3 Long-term consequences of respiratory syncytial virus (RSV) bronchiolitis

L Bont, WMC van Aalderen, JLL Kimpen

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Despite differences in study design, follow-up studies consistently show that approximately half of the patients with respiratory syncytial virus (RSV) lower respiratory tract infection (LRTI) during infancy go on to have recurrent wheezing episodes during childhood. Respiratory symptoms are associated with abnormal lung function, including bronchial hyperresponsiveness. Wheezing symptoms following RSV LRTI gradually decrease and it appears that during school age airway morbidity is no longer related to RSV LRTI during infancy. Mechanisms underlying the association between RSV LRTI and long-term airway morbidity are poorly understood. On the one hand, abnormal airway function that is congenitally present or acquired before RSV LRTI occurs could be the cause of both RSV LRTI and subsequent recurrent wheezing. On the other hand, it is possible that RSV LRTI causes changes in the lower airways or the immune system that result in long-term airway morbidity. Animal models suggest RSV infection can promote the development of allergic sensitisation, but most studies in humans do not indicate a role for atopy in the development of recurrent wheezing following RSV LRTI.

3.1 Abstract

Despite differences in study design, follow-up studies consistently show that approximately half of the patients with respiratory syncytial virus (RSV) lower respiratory tract infection (LRTI) during infancy go on to have recurrent wheezing episodes during childhood. Respiratory symptoms are associated with abnormal lung function, including bronchial hyperresponsiveness. Wheezing symptoms following RSV LRTI gradually decrease and it appears that during school age airway morbidity is no longer related to RSV LRTI during infancy. Mechanisms underlying the association between RSV LRTI and long-term airway morbidity are poorly understood. On the one hand, abnormal airway function that is congenitally present or acquired before RSV LRTI occurs could be the cause of both RSV LRTI and subsequent recurrent wheezing. On the other hand, it is possible that RSV LRTI causes changes in the lower airways or the immune system that result in long-term airway morbidity. Animal models suggest RSV infection can promote the development of allergic sensitisation, but most studies in humans do not indicate a role for atopy in the development of recurrent wheezing following RSV LRTI.
Long-term consequences of respiratory syncytial virus (RSV) bronchiolitis

Maimonides wrote in 1170 A.D.: “I conclude that this disorder (asthma) starts with a common cold, especially in the rainy season, and that the patient is forced to gasp for breath day and night”[1]. This observation might well be the first description of the relation between bronchiolitis and recurrent wheezing. Infants who recover from respiratory syncytial virus (RSV) lower respiratory tract infection (LRTI) have an increased risk for the subsequent development of recurrent wheezing during early childhood[2;3]. Recurrent wheezing is accompanied by functional abnormalities of the airways, such as bronchial hyperresponsiveness[4;5]. Although knowledge on clinical, infectious and immunological factors in the pathogenesis of RSV LRTI increases rapidly, mechanisms by which RSV LRTI results in long-term airway morbidity are still poorly understood. Insight in these mechanisms is required in order to develop innovative intervention strategies to prevent or treat long-term airway morbidity following RSV LRTI. The aim of this article is to provide an overview of clinical and experimental studies on the relation between RSV LRTI and long-term consequences.

During the last 40 years a number of prospective follow-up studies have focused on the relation between RSV LRTI and subsequent airway morbidity[2-16]. Although these studies have generally confirmed that such a relation exists, differences in the incidence of long-term airway morbidity following RSV LRTI and differences in the magnitude of involved risk factors were found. These differences may be explained, at least partially, by the study design used to investigate the relation between RSV LRTI and subsequent airway morbidity. Moreover, the definitions used for the different disease entities that have been used in the studies may be confusing. Definitions used in this article are shown in table 3.1.

A number of large-scale follow-up studies were performed before immunofluorescence for RSV became generally available for RSV diagnosis (table 3.2). In these studies, which are still cited in current literature, bronchiolitis patients were included regardless of the infectious agent. It can not be excluded that even patients with bacterial infections have been included.

Historical (retrospective) follow-up studies have shown the possible epidemiological relation between RSV LRTI and childhood asthma. Since childhood asthma is a heterogeneous disease, longitudinal follow-up studies were required to obtain more valid information. In addition, well defined (matched) control children were needed to estimate the relative risk for airway morbidity following RSV LRTI.

Another explanation for the observed differences in outcome variables in the studies on long-term airway morbidity following RSV bronchiolitis is that severity of the initial RSV LRTI differs between the studies. Most studies focus on hospitalised infants. Only recently, new data of long term consequences of RSV LRTI in non-hospitalised infants have been published[16]. The presence of respiratory wheeze is required in studies focusing on classical RSV bronchiolitis, in other studies any sign of LRTI is sufficient for inclusion. For example, “chest cough” as the sole symptom of LRTI caused by RSV in a 3-year-old child, was sufficient for inclusion in a recently published large longitudinal study on
For practical reasons mechanically ventilated infants are usually excluded. Therefore, little data are available on long term consequences of this group of patients. It may well be that the severity of the initial disease influences the outcome in the long term.

Two types of outcome parameters for airway morbidity can be distinguished: airway symptoms and lung function. To date, most follow-up studies have used standardised questionnaires focusing on airway symptoms. However, bias can occur when questionnaires are filled out by parents. Most importantly, parents might in retrospect forget the occurrence of symptoms that are related to the respiratory state of their child (recall bias) or over-report in a certain time-frame. Parents might not understand the questions when they are not put very simple or they might not report the occurrence of events in the past because it is socially unaccepted (for example exposure to cigarette smoke).

Airway symptoms as experienced by the infants or parents are probably best assessed using daily diaries for airway symptoms, because it is a chronological report of symptoms as they are experienced. It is time-consuming to note airway symptoms in a diary for a long period of time, which allows for more non-compliance and dropouts during follow-up. Our experience is that regular contact with parents is time consuming for investigators but can provide parental motivation to note the presence or absence of simple airway symptoms (runny nose, cough, wheeze) in a diary for at least up to two years (Bont and colleagues, submitted for publication).

In addition to symptoms, lung function can be assessed as an objective outcome parameter. Since RSV LRTI is related to airway morbidity up to the age of 6 years, lung function abnormalities are predominantly expected during these years. However, at the age of 0-4

### Table 3.1 Terms and definitions used throughout the article

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma[64]</td>
<td>an inflammatory disease of the airway of the lung, characterised by intermittent airway narrowing and variable symptoms of chest tightness, wheeze and shortness of breath</td>
</tr>
<tr>
<td>Airway hyperresponsiveness[64]</td>
<td>Characteristic physiological abnormality in asthma with exaggerated airway narrowing in response to bronchoconstrictor stimuli</td>
</tr>
<tr>
<td>Allergy[64]</td>
<td>Th2-associated immune reactions to allergens</td>
</tr>
<tr>
<td>Atopy[64]</td>
<td>Familial syndrome of asthma, ecema and hay fever. Can be recognised by elevated serum IgE levels, and positive skin prick tests or ELISA tests which detect IgE directed against allergens. Virtually synonymous with allergy.</td>
</tr>
<tr>
<td>RSV bronchiolitis[65]</td>
<td>Lower respiratory tract infection with characteristic expiratory wheeze caused by RSV in young infants without history of wheezing respiration.</td>
</tr>
<tr>
<td>Lower respiratory tract infection[16]</td>
<td>Infectious disease of the airway of the lung, characterised by shortness of breath, wheezing or severe cough</td>
</tr>
</tbody>
</table>
years only non-conventional techniques for lung function measurement are available. Tidal breathing analysis can be used to assess airway resistance [17;18]. Bronchial hyperresponsiveness can be assessed using trachea auscultation to determine the methacholine concentration to induce wheezing[19]. However, the validity and reliability of these techniques have not yet been fully established. To study airway resistance and compliance, most techniques analyse tidal breathing. In addition, these techniques can measure the effect of bronchodilators. Improvement of lung function analysis techniques during early childhood will enable investigators to focus on the evolution of airway function abnormalities following RSV LRTI on the long term.

Table 3.2 Study design and inclusion criteria used in 13 RSV follow-up studies

<table>
<thead>
<tr>
<th>Year</th>
<th>Reference</th>
<th>Prospective</th>
<th>Controls</th>
<th>Hospitalisation</th>
<th>RSV diagnosis</th>
<th>Bronchial obstruction</th>
<th>Age (months)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>1963</td>
<td>Eisen[2]</td>
<td>no</td>
<td>no</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>&lt;24</td>
<td>248</td>
</tr>
<tr>
<td>1978</td>
<td>Sims[3;24]</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>&lt;12</td>
<td>35</td>
</tr>
<tr>
<td>1982</td>
<td>Pullan[5]</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>&lt;12</td>
<td>130</td>
</tr>
<tr>
<td>1984</td>
<td>McConnachie[7]</td>
<td>no</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>yes</td>
<td>&lt;24</td>
<td>177</td>
</tr>
<tr>
<td>1984</td>
<td>Hall[6]</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>&lt;24</td>
<td>29</td>
</tr>
<tr>
<td>1986</td>
<td>Welliver[11;23]</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>&lt;6</td>
<td>38</td>
</tr>
<tr>
<td>1989</td>
<td>Sly[10]</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>&lt;12</td>
<td>48</td>
</tr>
<tr>
<td>1992</td>
<td>Murray[22]</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>&lt;12</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>1995</td>
<td>Sigurs[12]</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>&lt;12</td>
<td>52</td>
</tr>
<tr>
<td>1997</td>
<td>Dezateuz[66]</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>&lt;12</td>
<td>29</td>
</tr>
<tr>
<td>1997</td>
<td>Renzi[14]</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>&lt;12</td>
<td>26</td>
</tr>
<tr>
<td>1999</td>
<td>Steim[16]</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>&lt;36</td>
<td>207</td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>Bont[40]</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>&lt;12</td>
<td>50</td>
</tr>
</tbody>
</table>

n: number of RSV patients

3.4 Relation RSV bronchiolitis and airway morbidity

An overview of relevant epidemiological studies analysing the relation between RSV LRTI and airway morbidity is shown in table 3.3. Wheezing episodes following RSV LRTI are found in 42-71% of patients. It is generally assumed that wheezing episodes following RSV LRTI are associated with viral upper respiratory tract infections[5], and not allergen exposure in contrast to children who suffer allergic asthma. This is in line with data from a community based longitudinal study (not focused on RSV) that showed that viral URTI also have been associated with asthma episodes in asthmatic school children[20;21]. Infants who will go on to have wheezing episodes will do so within 12-24 months after the first episode of RSV LRTI[3]. Less than 10% of children with recurrent wheezing following RSV LRTI began to have wheezing episodes after they were 2 years old.

A large number of studies attempted to identify clinical risk factors that determine the development of airway morbidity following RSV bronchiolitis. To date, these risk factors are not well understood. Disease severity and age at the moment of RSV LRTI could not
be related to subsequent airway morbidity[3;5;6;22]. Male sex appeared to be a risk factor for recurrent wheezing following RSV LRTI in some, but not all studies[7;23;24]. It has been shown by Martinez and colleagues that pre-existent lower levels of lung function in newborns are associated with subsequent incidence of lower respiratory tract illness with or without wheezing in the first year of life[17]. In line with this finding, it has been suggested that infants with recurrent wheezing following RSV LRTI have lower lung function early in infancy, before any respiratory tract infection has occurred[16]. However, this hypothesis needs to be confirmed. In addition to premorbid lung function, atopy is a possible risk factor, that was studied extensively, but results were inconclusive (table 2). Another risk factor for recurrent wheezing is exposure to cigarette smoke.

### Table 3.3  Relation between RSV LRTI during infancy and subsequent development of airway morbidity and atopy

<table>
<thead>
<tr>
<th>First author</th>
<th>Main outcome parameter</th>
<th>Duration follow-up (years)</th>
<th>Main finding</th>
<th>Percentage wheeze</th>
<th>Lung function performed</th>
<th>Relation with atopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eisen[2]</td>
<td>Questionnaire</td>
<td>14</td>
<td>Bronchiolitis related to recurrent wheeze</td>
<td>49</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Sims[3]</td>
<td>Questionnaire</td>
<td>8</td>
<td>Atopy not related to wheeze following RSV</td>
<td>56</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Gurwitz[4]</td>
<td>Bronchial reactivity</td>
<td>8</td>
<td>Hyperresponsiveness after bronchiolitis</td>
<td>52</td>
<td>yes</td>
<td>–</td>
</tr>
<tr>
<td>Pullan[5]</td>
<td>Lung function</td>
<td>10</td>
<td>RSV related to subsequent wheeze and low lung function</td>
<td>42</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>McConnachie[7]</td>
<td>Questionnaire</td>
<td>8</td>
<td>9.4% of wheeze in children related to RSV</td>
<td>44</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Hall[6]</td>
<td>Physician diagnosed wheeze</td>
<td>8</td>
<td>wheeze after RSV related to low lung function, but not atopy</td>
<td>45</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Welliver[11;67]</td>
<td>Physician diagnosed wheeze</td>
<td>2.0</td>
<td>Nasal RSV-specific IgE predicts wheeze</td>
<td>53</td>
<td>yes</td>
<td>–</td>
</tr>
<tr>
<td>Sly[10]</td>
<td>Questionnaire</td>
<td>5</td>
<td>Family atopy not related to wheeze after RSV</td>
<td>71</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Murray[22]</td>
<td>Wheeze</td>
<td>5.5</td>
<td>Personal atopy not related to wheeze after RSV</td>
<td>43</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Sigurs[12]</td>
<td>Skin prick test, allergen-specific IgE</td>
<td>3</td>
<td>RSV risk factor for allergy</td>
<td>60</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>Renzi[14]</td>
<td>Diary</td>
<td>0.25</td>
<td>Th2 cytokine profile predict wheeze</td>
<td>65</td>
<td>no</td>
<td>–</td>
</tr>
<tr>
<td>Dezateux[66]</td>
<td>Lung function</td>
<td>0.7</td>
<td>Diminished t_{min} ratio after RSV</td>
<td>55</td>
<td>yes</td>
<td>–</td>
</tr>
<tr>
<td>Stein[16]</td>
<td>Questionnaire</td>
<td>13</td>
<td>Wheezing after RSV up to age 11, not at age 13 no relation with atopy</td>
<td>1</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Bont[40]</td>
<td>Wheeze (diary)</td>
<td>1.0</td>
<td>Monocyte IL-10 related to recurrent wheeze after RSV</td>
<td>58</td>
<td>no</td>
<td>no</td>
</tr>
</tbody>
</table>

(1) Odd’s ratio at age 6 for frequent and infrequent wheeze: 4.3 and 3.2, respectively
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before or after RSV LRTI[3;6;7]. Cigarette smoke has also been shown to be a risk factor for airway morbidity in childhood in the general population[25;26]. Because maternal smoking during pregnancy is a determinant of lung function during early infancy, smoke exposure could contribute to the risk for both hospitalisation for RSV LRTI and the subsequent development of airway morbidity[25]. Parental history of asthma, in particular maternal asthma, has been mentioned as a risk factor for childhood asthma[27;28]. Although parental history of asthma has been associated with RSV bronchiolitis[22], to our knowledge the predictive value of parental history of asthma for recurrent wheezing following RSV LRTI has not yet been investigated.

A few studies have followed infants for more than 10 years to study the evolution of symptoms or lung function abnormalities following RSV LRTI[2;5;16]. These studies generally show that the risk for wheezing following RSV LRTI decreases with age. Stein and colleagues recently published the first prospective longitudinal study of a large cohort that was drawn from the community. Infants were followed for 13 years[16]. They compared infants with RSV LRTI with infants without any LRTI during the first three years of life. The presence of recurrent wheezing was assessed using standardised questionnaires when children in the study were 6, 8, 11 and 13 years old. In addition, lung function tests were performed when children were 11 years old. These lung function tests included assessment of the response to inhaled salbutamol. Frequent wheeze (≥4 wheezing episodes during the last year) and infrequent wheeze (<4 wheezing episodes during the last year) were found more frequently at age 6 in infants with RSV LRTI than in infants without LRTI (relative risk 4.3). Subsequently, the risk decreased markedly and was not significant when infants were 13 years old. Forced expiratory volume in 1 second (FEV1) at age 11 was significantly lower in infants who suffered from RSV LRTI in the past than in infants without LRTI, but this difference was not observed after salbutamol inhalation, suggesting reversible airflow limitation.

Several studies investigated whether treatment of initial RSV bronchiolitis can influence the long-term outcome. The use of ribavirin during initial RSV have been found to reduce the occurrence of wheezing following RSV bronchiolitis by some investigators[29]. However, these data could not be confirmed by others[30]. Similar to the use of ribavirin during RSV bronchiolitis to prevent recurrent wheezing, conflicting data have been reported in the use of inhaled corticosteroids[31;32].

Palivizumab is a humanized monoclonal antibody that reduces hospitalisation rates from 10.6% to 4.8% in preterm infants with and without chronic lung disease[33]. Of interest would be follow-up data of airway symptoms of infants from the trial with palivizumab.

These follow-up data may provide evidence whether prevention of RSV also results in the prevention of long-term airway morbidity. This would support the idea that RSV LRTI results from pre-morbid pathology, at least in this specific high-risk group.

3.5 Pathophysiology of airway morbidity following RSV LRTI

3.5.1 Human studies

It has been suggested that children with RSV LRTI in early childhood have pre-existing abnormalities of lung function that manifest during the initial illness and again during recurrences of wheezing episodes[16]. An alternative explanation for the association between RSV LRTI and the subsequent development of recurrent wheezing is that RSV
itself causes changes in the lower airways or caused changes in the immune system that result in long-term airway morbidity. In line with this latter hypothesis, it has been suggested that RSV results in allergy, which subsequently leads to allergic asthmatic symptoms.

Airway damage during RSV LRTI might well be a factor in the pathogenesis of long-term airway morbidity. It is likely that severity of disease during RSV LRTI is related to the magnitude of destruction of airway epithelium. Therefore, studies have attempted to find an association between severity of disease during RSV LRTI and subsequent long-term airway morbidity, but this was not found[3;5]. In a prospective cohort study, we found that mechanically ventilated infants with RSV LRTI without pre-existing airway disease have no larger risk for recurrent wheeze or physician diagnosed asthma than other hospitalised infants with RSV LRTI (unpublished data). This suggests that other mechanisms than destruction of airway epithelium during RSV LRTI are important in the pathogenesis of long-term airway morbidity following.

Allergy is a Th2-driven syndrome of which IgE-mediated disease manifestations are a hallmark (table 1). Considering the clinical similarities between recurrent wheezing following RSV and allergic asthma, the relationship between allergy-related immune responses and recurrent wheezing following RSV LRTI has been studied. For long, it has been believed that RSV bronchiolitis and subsequent airway morbidity are associated with the same or similar pathogenetic mechanisms that cause atopy and allergy. In a prospective cohort study with 47 infants with RSV bronchiolitis in the first year of life and 94 matched controls, Sigurs and colleagues analysed the risk to develop a positive skin prick tests and increased serum IgE against common inhalant and food allergens at age 3 years as signs of atopy[12]. Signs of atopy were found in 32% of infants with a history of RSV bronchiolitis and in 9% of controls. This apparent risk for allergic sensitisation following RSV bronchiolitis was independent of family history of atopy. Contrasting data were found in the study by Stein and colleagues, in which it was shown that RSV LRTI before the fourth birthday is no risk factor for positive skin prick test for common food or inhalation allergens or increased serum IgE after age 6[16;352].

Eosinophils play a clear role in allergic asthma. Therefore, eosinophils and eosinophil activity during RSV LRTI have been studied in relation to the development of recurrent wheezing. In two different studies, Reijonen and Koller found that eosinophilic cationic protein (ECP) levels during bronchiolitis in nasopharyngeal secretions (NPS) and serum, respectively, were associated with recurrent wheezing in the first year of life[13;34-36]. However, in these studies RSV infection was not required for inclusion. A prospective follow-up study by Ehlenfield and colleagues showed that eosinophilia during RSV bronchiolitis is associated with persistent wheezing after 6 years of age, but not with transient wheezing in early childhood[37].

Similar to allergic asthma, Th2-like cytokine responses have been put forward as a potential mechanism by which RSV results in long-term airway morbidity. Renzi showed that peripheral blood lymphocytes of 26 bronchiolitis infants, produced less IFNγ in response to IL-2 and more IL-5 in response to Dermatophagoides farinae five months after the acute bronchiolitis in children who developed recurrent wheezing[14], indicating a blunted Th1 response in confirmation with Th2 predominance. However, RSV was diagnosed in only half of the infants. In a different study decreased ex vivo IFNg/IL-4 ratios in response to non-specific stimuli were found during RSV LRTI[15]. However, from this
study no follow-up data are available. In contrast with the previous 2 studies, we have recently shown that \textit{ex vivo} IFN\(\gamma\)/IL-4 ratios in a whole blood culture system stimulated with phytohemaglutinin (PHA) during RSV LRTI was comparable with normal controls. In addition, IFN\(\gamma\)/IL-4 ratios were not associated with recurrent wheezing during one year follow-up. These apparent differences found in our study may be explained by different inclusion criteria and different culture assays.

During RSV LRTI RSV-specific IgE is secreted in the respiratory tract and correlates with disease severity\cite{38,39}. In addition, it was shown in a cohort of 38 infants that peak titres of RSV-specific IgE in nasopharyngeal secretion (NPS) during RSV LRTI predicted wheezing during a 48 months follow-up period\cite{23}. RSV-specific IgE in NPS are not related to allergic sensitisation during the follow-up period. Thus, the production and release of RSV-specific IgE in the respiratory tract appears to be regulated by mechanisms that are unrelated to atopy. More research is required to investigate the potential role of RSV-specific IgE in airway morbidity following RSV LRTI.

Recently, we have shown that monocyte cytokine profiles in the blood during RSV LRTI are related to disease severity, and also to subsequent airway morbidity\cite{40,41}. In a group of 30 RSV infected infants requiring mechanical ventilation, IL-12 production in whole blood cultures at initiation of mechanical ventilation had predictive value for duration of respiratory insufficiency\cite{41}. In a different study, we investigated whether monocyte cytokine responses during RSV LRTI are also associated with subsequent long-term airway morbidity\cite{40}. Results showed that monocyte IL-10 production 3-4 weeks after hospitalisation was associated with recurrent wheezing during a one year follow-up period and with physician diagnosed asthma. Sherran and colleagues have shown that IL-10 concentrations in NPS are increased during LRTI RSV but no attempt was made to relate IL-10 levels in NPS to subsequent airway morbidity\cite{42}. Further study is required to elucidate by what mechanism monocyte IL-10 responses during RSV may contribute to recurrent wheezing.

### 3.5.2 Animal studies

In studies of experimental infection with RSV, replication of the virus within the lung has been demonstrated in several animals, including monkey species, mice, rats and guinea pigs\cite{43-46}. None of these animals develop signs of respiratory illness resembling human RSV bronchiolitis. For this reason, discussion persists as to whether animal models are relevant for human RSV infection. Murine RSV infection is the animal model that has been studies most extensively. Signs of illness in mice include weight loss and decreased activity\cite{47}. Objective evidence of respiratory illness was observed in RSV infected BALB/c mice using whole body plethysmography\cite{48}. With this method increased respiration rate and abnormal breathing patterns were observed. Increased responsiveness to methacholine following RSV infection was seen in mice, rats and guinea pigs\cite{48-50}. Consequently, these animals could be suitable models, since increased hyperresponsiveness is also seen in infants with airway morbidity following RSV infection\cite{4}. The major limitation of animal models to study long-term airway morbidity following RSV infection is that persistence of abnormal lung function has not yet been established. Therefore, the major challenge for animal studies in the future is to establish the relevance for the human situation.
From experiments in the mouse model, it has been suggested that RSV infection may interact with immunological mechanisms involved in the development of Th2-like immune responses, including allergic sensitisation[51-57]. In mice who were sensitised to the G protein, RSV infection enhances allergic airway sensitization, resulting in lung eosinophilia and in airway hyperresponsiveness[34;58]. It was shown that transfer of T cells, in particular CD8+ cells, of RSV infected mice into naïve mice result in increased eosinophil influx and production of Th2 cytokines following challenge with ovalbumine[59]. In order to reduce morbidity caused by RSV in the animal model, experiments have been designed to induce Th1-like immune responses during RSV infection[60]. Treatment with IL-12 of BALB/c mice, primed with RSV G protein, reduced lung eosinophilia and the production of Th2 cytokines following RSV infection, but did not reduce acute illness, as assessed by weight loss. The latter experiment nicely shows that immune responses can be modified, but indicates that morbidity caused by RSV is much more complex. In addition, we note that most studies were performed in BALB/c mice, which have a genetic predisposition to develop Th2-like immune responses. Further study is required to investigate the interaction between RSV infection and the development of allergy in animal models without a predisposition for Th2-like immune responses.

Animal models have indicated that also non-immune mechanisms could be involved in the pathogenesis of airway hyperresponsiveness following RSV infection. The increased responsiveness to bronchodilators following RSV LRTI observed by Stein and colleagues can not easily be explained by aforementioned immune-mediated mechanisms that might be involved in airway morbidity following RSV LRTI. In different animal models persistent alterations in the development of non-adrenergic non-cholinergic inhibitory neural pathways were seen following RSV infection[61-63]. This change was associated with increased contractility of airway smooth muscle. To test the relevance of these models for humans, future studies on neural regulation of airway tone in humans following RSV are required.

3.6 Conclusions

In the present article we reviewed clinical and experimental data on the relation between RSV LRTI and long-term airway morbidity. Remarkable differences in design, inclusion criteria and measures of clinical outcome exist between follow-up studies. However, most studies show that approximately half of infants with RSV LRTI will have recurrent episodes of wheezing during early childhood. Both early and more recently published data indicate that airway morbidity following RSV LRTI is transient and subsides during school age.

The pathogenesis of recurrent wheezing following RSV bronchiolitis is still poorly understood. Present studies focus on pre-existing lung function defects as the major cause of both RSV bronchiolitis and long-term airway morbidity. Although it appears that atopy does not play a large role in the development of airway morbidity following RSV bronchiolitis, immunological studies on the role of Th2 cytokine responses are still subject of conflict. Immunological research needs to focus on alternative mechanisms in the pathogenesis of airway morbidity following RSV bronchiolitis. Potentially, antigen presenting cells as well as epithelial cells play an important role in the development of airway
morbiditv following RSV bronchiolitis. Animal studies provide the opportunity to obtain detailed observations of pathogenetic changes in immune responses and pulmonary function following RSV infection. However, it is urgently required that the relevance of different animal models for human RSV bronchiolitis are established. Better knowledge of the pathogenesis of long-term consequences of RSV bronchiolitis will facilitate the development of innovative intervention strategies to prevent or treat long-term airway morbidity following RSV bronchiolitis.

References

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