

# The relationship between respiratory syncytial virus infections and the development of wheezing and asthma in children

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## Purpose of review

The relationship between respiratory syncytial virus lower-respiratory-tract infections in early childhood and asthma has been the subject of much debate. Most, but not all, previous cohort studies have failed to identify a link between early respiratory syncytial virus infection and atopic asthma. Recent studies have helped clarify some apparently contradictory findings.

## Recent findings

Cohort studies focusing on wheezing in early childhood have indicated that this is associated with an increased incidence of atopic asthma but that this risk is not increased by respiratory syncytial virus infection. Indeed, wheeze associated with rhinovirus infection may be a better marker for possible asthma. In contrast, there is no increased risk of atopic disease in infants with respiratory syncytial virus 'acute bronchiolitis', a phenotype characterized by widespread crepitation. Post-bronchiolitic symptoms are associated with intercurrent viral infections in particular and the incidence of symptoms falls rapidly during infancy.

## Summary

These studies confirm earlier suggestions that the phenotype of respiratory illness and hence the host response rather than the infecting organism is the best predictor of the future pattern of respiratory illness. Such considerations must be central to the design of any future intervention or cohort studies.

## Keywords

acute bronchiolitis, asthma, atopy, respiratory syncytial virus

## Introduction

It is clear that the respiratory syncytial virus (RSV) is, like many other respiratory viruses, able to precipitate an exacerbation in asthmatic subjects [1,2] and, as is also the case for many respiratory viruses, is able to induce wheeze in very young children [3,4<sup>•</sup>–7<sup>•</sup>]. However, its possible role in the induction of atopic disease has been the focus of much debate and research over the past three decades. In order to try and understand the long-standing and often passionate debate regarding the role or otherwise of the RSV infection in early childhood in the induction of asthma and/or atopy it is necessary to review the background to this debate before moving on to look at more recent publications that should help to finally resolve the issues.

The RSV is probably the most successful of all viruses, causing annual epidemics of respiratory illness throughout the world [8,9]. In temperate climates these epidemics last 3–5 months, peaking in mid-winter. The annual epidemics are remarkably consistent in timing across continents and from year to year. The virus was first isolated nearly 50 years ago from chimpanzees but it quickly became apparent that this was the virus largely responsible for the annual epidemics of respiratory illness observed in young infants. Between 0.5 and 2% of all infants are admitted to hospital with airways obstruction due to RSV infection and it remains the commonest reason for hospitalization in infancy [8]. The majority of those admitted to hospital are diagnosed as having 'acute bronchiolitis' and it has been known for many decades that such infants experience increased levels of recurrent respiratory symptoms in subsequent years [10,11]. This led to the suggestion that there may be a link between acute bronchiolitis and asthma and since the organism most commonly responsible for acute bronchiolitis is RSV attention subsequently focused on this virus as having a possible role in the development of atopic asthma. An enormous amount of time and effort has been devoted in subsequent decades to trying to determine whether such a link exists [3,4<sup>•</sup>–6<sup>•</sup>,12–19,20<sup>•</sup>,21,22<sup>•</sup>,23,24,25<sup>•</sup>,26]. While the majority of cohort and epidemiological studies have failed to support the contention that RSV infection in infancy increases levels of atopy [3,4<sup>•</sup>–6<sup>•</sup>,12–19,20<sup>•</sup>,21,22<sup>•</sup>] those who have pursued this theory with enthusiasm have been bolstered by the results of rodent experiments and occasional clinical studies [25<sup>•</sup>,26]. More recent studies appear to provide an explanation for the occasional result that appears to be at variance with the majority.

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## Abbreviation

**RSV** respiratory syncytial virus

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## The respiratory syncytial virus

RSV is closely related to paramyxoviruses but resides in a small group of viruses, which include the human, bovine and ovine forms of RSVs. The only natural host for the human form of RSV appears to be humans themselves. As noted above it appears an extraordinarily successful virus causing annual epidemics of disease throughout the world. While its importance in causing respiratory illness in early childhood has been recognized for many decades its importance in the elderly has only been fully recognized in recent years [27–29], with epidemiological studies linking epidemics of RSV to increased mortality and increased hospitalization rates with respiratory disease in the elderly and, in particular, those with chronic obstructive airways disease. Data would suggest that in most years it is probably at least as important a pathogen as influenza. Lack of recognition of its importance in the elderly and in chronic obstructive pulmonary disease in the past has been in part due to lack of awareness and in part due to difficulty in isolating the virus from the upper airways of adults. Interestingly it is more readily isolated from the lower airways.

The reason for the virus' success is unclear. There are suggestion that antigenic shift and the co-circulation of different strains are significant factors [30] but it seems likely that poor immunity following infection is probably more important. Antibody responses are often poor or undetectable while an experimental infection study demonstrated repeated infections with the same strain of virus within months of a natural infection in the majority of participating subjects [31]. During each epidemic approximately 30% of the population are infected, indicating that re-infection is common throughout life, while the infection rate in infants is in excess of 60% with all infants having been infected by the age of 2 years and many having been re-infected by this age [32,33]. Poor maternal immunity results in low levels of neutralizing antibodies in infants and it has been shown that there is an inverse relationship between risk of infection and passively acquired neutralizing antibody levels. To date the trigger for the epidemics of RSV infections has not been identified; nor has the disappearance of the virus in early spring been explained [34].

## Phenotypes of respiratory disease

The RSV is responsible for a variety of clinical illnesses. The most common in the general population is an upper respiratory infection, usually manifest as an unpleasant coryzal illness, often accompanied by a bronchitic cough. In children in particular, it also commonly causes otitis media. As noted above, many studies have implicated RSV in exacerbations of asthma in both children and adults though it is not as commonly identified as rhinovirus. It is certainly the most important cause of lower-respiratory-tract infection in the very young and a major

cause in the elderly, although RSV pneumonic illnesses are also well described in young adults in institutions. The most common form of lower-respiratory-tract illness noted in infants is 'acute bronchiolitis' [1,35]. In addition it remains the commonest cause of pneumonia and virus-associated wheeze in the under 2-year-olds and may also cause croup. The overlap with other viruses is considerable, with viruses such as rhinovirus, metapneumovirus, parainfluenza and influenza all being capable of inducing any of the clinical phenotypes noted above [6<sup>•</sup>,7<sup>•</sup>,36,37]. While metapneumovirus is increasingly recognized as a cause for acute bronchiolitis RSV still accounts for more than 60% of cases. That RSV remains the commonest cause of acute bronchiolitis year in year out probably reflects the success of the virus in infecting such a large proportion of the infant population, with those being hospitalized being the 'tip of the iceberg'.

A fundamental difficulty encountered when attempting to interpret studies involving children with 'bronchiolitis' is the definition of this term [8]. The majority of paediatricians in the UK, Australia and parts of Europe will use this term to refer to patients showing signs of viral upper-respiratory-tract viral infection together with lower-respiratory-tract inflammation characterized by widespread crepitations. These infants may wheeze at some point during the acute illness. The term 'acute bronchiolitis' in North America and other parts of Europe is frequently used to describe infants with their first wheezing episode associated with a viral upper-respiratory-tract infection and as such is likely to include phenotypes such as early asthma and 'wheezy bronchitis', in whom a quite different pathophysiology may be superimposed on the normal host–virus interaction. Many of those included in a North American study would be considered to have virus-induced wheeze ('wheezy bronchitis') in the UK while many viewed as having bronchiolitis in the UK might be labelled as having pneumonia in the USA based on chest X-ray findings and absence of wheeze.

There are clearly difficulties in trying to precisely determine phenotypes of disease and these are largely attributable to the lung's limited repertoire of responses. Insults may lead to airways obstruction by precipitating smooth muscle contraction, bronchial wall oedema or increased airway secretions. These may lead to noisy breathing with wheeze and/or rattles and abnormal, added sounds on auscultation. Cough is common to most forms of airway inflammation though the nature of the cough may vary. Within the cohort of young children who genuinely wheeze with RSV infections will be a group experiencing an early exacerbation of asthma and others who are prone to developing virus-induced wheeze in whom the index illness happens to be attributable to an infection with RSV. It should also be noted that the use of the term

'wheeze' by parents and physicians is frequently imprecise and adds a further level of uncertainty when reviewing studies [38,39].

In trying to unravel the RSV literature it is important when reviewing cohort studies to determine whether entry criteria are based on organism, a clinical diagnosis of 'acute bronchiolitis', the presence or absence of wheeze or a combination of these. It seems likely that the outcomes of cohort studies based on children with 'bronchiolitis' or RSV infection in infancy are probably significantly influenced by the phenotype of the initial illness and reflect host rather than virus factors. More recent studies reviewed below appear to support this suggestion.

### **The immunopathology of respiratory syncytial virus 'acute bronchiolitis'**

In the early 1970s it was suggested that 'acute bronchiolitis' might be due to an a specific form of immunopathology. This was based on the observation the majority of infants admitted to hospital with RSV bronchiolitis were less than 6 months of age, a time when maternal antibody levels should provide some protection and on the disturbing results of a vaccine study in which infants who received a formalin-inactivated vaccine had more severe disease when subsequently infected with RSV [40]. This gave rise to the suggestion that 'acute bronchiolitis' was due to an immune-complex disease. Though this suggestion quickly fell from favour it was the first in a line of hypotheses which tried to link the acute illness seen in hospital with a specific immunopathology [8]. Moreover, the two most influential suggestions also tried to provide a link between the acute illness and the suggestion that RSV infection in infancy promotes the development of asthma and atopic disease.

The first to implicate IgE was a suggestion that the acute illness was a type 1 allergic reaction in those already having been exposed to the virus earlier in the season, but the pattern of epidemics and age of the acute illness soon led to the fall from favour of this theory. Subsequently a group from Buffalo, New York, implicated an RSV-specific response in the severity of the acute illness and in subsequent symptoms [41,42] but the effect appeared to disappear by the end of the first decade [43]. While some groups have supported the finding others have been unable to replicate these results and their significance remains unclear. A refinement of this suggested that the inflammatory process during the acute illness was weighted towards a Th2 response and that this influenced the response to other potential allergens. Support for this came from a number of experiments using rodents in which RSV infection appeared to promote an IgE-mediated response to allergens such as ovalbumin [44], and other experiments in which eosinophilic responses could be induced in rodents that

had been previously primed to produce such a response [45]. However, rodents do not develop a bronchiolitic illness when infected with RSV and the relevance of these studies to humans is far from clear [46]. Data obtained in humans have been contradictory with some studies appearing to support the suggestion and others failing to find any such tendency [47–51,52<sup>\*</sup>]. It is possible that such discrepancies are due to different responses in different groups of patients or reflect methodological challenges involved in studying events in the lungs of very young infants.

There have been a number of difficulties with these theories which suggest that the virus itself induces an aberrant response in some individual leading to hospitalization with acute bronchiolitis and/or is responsible for inducing atopic asthma. Perhaps most taxing is the observation that the vast majority of studies have failed to find increased expression of atopy in cohorts of children followed up after RSV infection in early childhood. Moreover, it needs to be remembered that those admitted to hospital are the tip of an iceberg with a continuum of disease severity from mild upper-respiratory-tract infection to severe lower-airways obstruction. Approximately 25% of all infants with RSV infection develop lower-respiratory-tract symptoms but it is only the most severe 10% of these who are hospitalized. While factors such as infecting dose may play a role in determining disease severity, the most important factors in determining hospitalization are gestational age, postnatal age and pre-existing risk factors such as chronic lung disease. Passive immunity also appears to play a role in disease severity but is more difficult to quantify. This would suggest that intrinsic risk factors rather than aberrant inflammatory response are more important in determining which infants are hospitalized. Community-based studies would suggest that mild, non-hospitalized RSV lower-respiratory-tract infections are as likely to be associated with subsequent symptoms as those leading to hospitalization, again suggesting a spectrum of disease severity rather than discontinuous populations [18].

It is now recognized that the inflammatory process in the airways of infants with RSV bronchiolitis is dominated by an intense neutrophil influx in both the lower and upper airway [53–56] and that neutrophil products such as myeloperoxidase and neutrophil elastase are released into the airways [56]. The neutrophil influx is driven by the release of interleukin-8 and other cytokines by infected inflammatory cells [52<sup>\*</sup>,56]. Leukotrienes do appear to be released [57] but unbound neutrophil elastase is found in excess of its inhibitors in the airways of infants with acute bronchiolitis and accounts for the majority of protease activity present in the airways. It is still unclear whether these cells participate in clearance of virus. A number of studies suggest that viral titres fall before the symptoms

are at their most florid, suggesting that control of inflammation rather than antiviral therapies are required once patients are symptomatic.

### Cohort studies

It has been evident for many decades that there is an association between RSV LRIs in infancy and increased respiratory morbidity in the early childhood. Opinions tended to polarize between those who believe that symptomatic RSV lower-respiratory-tract infections in early life induce, or are a marker for, an atopic asthmatic phenotype and those who believe that non-atopic mechanisms contribute to both the acute illness and subsequent respiratory morbidity. The progressive reduction in prevalence of symptoms through the first decade noted in all these studies is quite different to the natural history of the respiratory morbidity associated with atopic asthma. As noted in the introduction the overwhelming weight of published data from human studies would argue against the proposition that RSV plays a role in inducing atopic asthma [3,4<sup>•</sup>–6<sup>•</sup>,12–19,20<sup>•</sup>,21,22<sup>•</sup>] but a few have found evidence for such a link. These studies suggest that the impact of RSV can be discerned more clearly in the early years of life and that its relative impact on the overall prevalence of atopy wanes over time [26]. An alternative explanation lies in the phenotype of subject recruited in the study in that all the studies reporting an increase in RSV-specific IgE responses [41–43] or a general increase in atopy [23–26] have used wheeze as a necessary criterion for entry and this may be a critical factor in explaining why their results should differ from those recruiting patients with bronchiolitis defined by the presence of crepitations.

### The importance of disease phenotype

A number of recent studies appear to have helped clarify the debate on the importance of disease phenotype. A key issue appears to be the phenotype of the initial illness. Among infants hospitalized with RSV infections 'acute bronchiolitis' is much more common than virus-associated wheeze and recent studies suggest that these groups have different outcomes that are more dependent upon the type of illness than the virus responsible for generating these symptoms. Several studies have indicated that a virus-associated illness in infancy or early childhood characterized by wheeze carries an increased risk of asthma in later life and that RSV itself is not an independent risk factor [3,4<sup>•</sup>–6<sup>•</sup>,58]. Indeed a number of studies appear to show that wheeze associated with viruses such as rhinovirus in infancy or early childhood are more likely to be associated with later asthma than episodes associated with RSV infection [3,4<sup>•</sup>–6<sup>•</sup>]. In a study from our group (H Elphick, S Ritson, ML Everard, unpublished work) in which infants with RSV were allocated to a phenotype of 'wheeze' or 'bronchiolitis' at admission it was found those with RSV-induced

wheeze had much higher levels of atopy and health-care utilization (including the use of inhaled corticosteroids and visits to primary care physicians with respiratory illness) than controls while those with RSV bronchiolitis did not have an increase in atopy and their symptoms were limited to relatively mild virus-induced exacerbations with little in the way of interval symptoms. This study was consistent with a recent study that suggested that 'post-bronchiolitic' symptoms were closely linked to intercurrent viral infections [59].

A consistent finding among cohort studies including infants admitted with acute RSV-induced 'bronchiolitis' (characterized by widespread crepitations on auscultation) is the observation that such infants do not have an increased family history or personal history of atopy, either prior to the acute illness or at follow up. Assuming that RSV bronchiolitis does not protect individuals from either atopy or asthma one would anticipate that the incidence of these will be similar to the general population, which is indeed the conclusion of most studies. The implication of these studies is that it is the host's response rather than the virus itself that influences the phenotype of both the clinical illness and pattern of subsequent symptoms.

When discussing post-bronchiolitic symptoms it is important to distinguish those in the immediate aftermath of the acute illness and the subsequent recurrent symptoms. There have been suggestions that leukotrienes may play an important role in the immediate post-bronchiolitic symptoms [60], although the results of further studies are required for this to be clarified and again it may transpire that the phenotype of disease may influence the response to anti-leukotriene therapy and indeed other forms of therapy.

If allergic sensitization does not account for the respiratory morbidity following RSV bronchiolitis then we need to look elsewhere for an explanation. Do children with RSV lower-respiratory-tract infection in early childhood have pre-existing abnormalities of airways function that manifests itself during the initial illness or does the lower-respiratory-tract infection itself produce changes in the lower airways that predispose the infant to further problems? Further clinical studies involving infants and young children will be required if a definitive answer is to be obtained. Previous cohort studies involving children with RSV bronchiolitis or 'lower respiratory tract disease' have described reduced lung function associated with increased bronchial responsiveness when children are seen at school age [14,18,19,22<sup>•</sup>]. However, none of these studies explored the possibility that anti-inflammatory therapy would have a significant impact on these symptoms. As noted above the frequency and severity of symptoms declines rapidly in the first few years of life.

## Conclusion

In 1963 Reynolds and Cook [61] observed that there were probably two groups of patients among those admitted with 'acute bronchiolitis': those in whom airways obstruction was largely attributable to oedema of the airways and secretions and a second group with a predisposition to asthma. He observed that they cannot be easily distinguished and that most are in the former group. As with many other aspects of respiratory disease in early childhood we appear to have come full circle. While RSV undoubtedly can precipitate an exacerbation of asthma and induce wheezing in infants prone to 'virus-induced wheeze' it does not of itself appear to either precipitate asthma or induce atopy. The long-term outcome can in part be predicted by the phenotype of the initial illness, with those in whom wheeze is the dominant symptom having a much greater likelihood of having asthma later in life than those with classical bronchiolitis or other forms of lower-respiratory-tract disease. Within a cohort of wheezing children factors such as a family and personal history of atopy and eosinophilia appear to be the best guide to predicting which subjects will be exhibiting early asthmatic symptoms and which are likely to have simple virus-induced wheeze. In the group with acute bronchiolitis there is an excess of symptoms compared with controls but these appear to have a much better prognosis, with prevalence falling rapidly through early childhood. They are generally associated with intercurrent viral infections. The implication of these findings is that the phenotype of the disease is probably more important than the causative organism and this must be considered when designing future studies, be it a cohort study, assessment of the inflammatory process or an intervention study.

## References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 72–73).

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