INTRODUCTION

Respiratory tract infections (RTIs) are a major burden in the paediatric population. RTIs are more frequent in children <5 years of age and affect 50% of patients in a given year. In children <1 year of age, 60% will experience an RTI each year. Lower respiratory tract infections (LRTIs) are also common in children, as are their associated complications, including bronchiolitis/bronchitis, pneumonia, and recurrent wheeze/asthma. In addition, less common but serious conditions such as bronchiectasis and post-infectious bronchiolitis obliterans may result from LRTIs in the paediatric population.

Bronchiolitis and bronchitis, essentially inflammation of the bronchioles or bronchial tube portions of the LRT, are common in childhood and have many causal agents. Human rhinovirus (hRV) is associated with 73% of respiratory infections during the first year of life in otherwise healthy children. Despite being frequently considered as primarily upper respiratory tract pathogens, hRV serotypes are now recognised as important pathogens in many cases of bronchiolitis. Furthermore, hRV may be associated with a wide range of symptom severity and is also the most common cause of mild-to-moderate wheezing symptoms in high-risk infants, as well as being a significant pathogen in severe infections. Respiratory syncytial virus (RSV) is the second most common upper respiratory tract pathogen detected during the first year of life (11%) in otherwise healthy children. The prevalence of
RSV increases in parallel with the RTI symptom severity.\(^4\) RSV is a significant contributor to severe infections in infants at high risk of developing wheezing and asthma, is the most common pathogen in LRTI in premature babies (particularly in cases of severe infection), and is the most common cause of bronchiolitis in general.\(^3\)-\(^5\)

Pneumonia is a frequent disease in early life and is defined as inflammation of the lung alveoli caused by infectious disease. A prospective study in the USA revealed community-acquired pneumonia requiring hospitalisation to be relatively common, affecting around 45% of children aged <2 years and 25% of children aged 2–4 years, with the incidence decreasing steadily with age. Most cases were viral, with RSV most commonly detected followed by hRV. The incidence of bacterial infections did, however, increase with age.\(^6\)

Wheeze is a common symptom of LRTIs such as bronchiolitis and pneumonia. Almost half (47%) of all children in Latin America experience one bout of wheezing during the first year of life, with 21% suffering from recurrent wheezing (≥3 bouts).\(^7\) There are three main wheezing aetiologies during childhood: transient wheezing, virus-associated wheezing, and atopic wheezing.\(^8\),\(^9\) Early transient wheezing may affect any child and usually resolves spontaneously or becomes less frequent after 3 years of age. The main risk factors for transient wheezing are premature birth and parental smoking, and the condition does not appear to increase the risk of developing asthma. Virus-associated wheezing is episodic, with symptoms concomitant to RTI but otherwise absent. Patients display bronchial hyperreactivity, with wheezing following viral bronchitis and no history of atopy. Children with virus-associated wheezing respond well to bronchodilators. Atopic wheezing is characterised by intermittent symptoms related to sensitisation by, and exposure to, aerial allergens. Patients display high IgE levels, with positive skin sensitivity and pulmonary function tests also commonly seen.

A recent report by the Argentinean Pediatrics Society suggests that wheezing incidents occurred in almost half of children during the first 6 years of life, with 20% experiencing early transient wheezing, 14% persistent wheezing, and 15% late-onset wheezing.\(^10\) Wheezing bouts during childhood may be associated with the development of asthma, a serious condition with 250,000 exacerbation-related deaths per year worldwide.\(^11\) Many of these deaths are avoidable and caused by misdiagnosis, treatment errors, or patients failing to seek medical attention, with the majority occurring in patients with advanced disease.

**RISK FACTORS FOR PAEDIATRIC INFECTION AND ASTHMA**

Anatomical, immunological, and societal factors all contribute to the higher frequency of RTI in children. Anatomical risk factors include differences in growth as well as tubaric dysfunction, while functional immaturity of the immune system is the major immunological risk factor in the paediatric population (described in more detail below). The majority of children in Latin American countries, such as Brazil (80%), and around the world now attend day-care centres, which alters the pattern of early-life infections. Rates of 6–7 infections per year are common in children, particularly if they go to day-care centres or have siblings who attend school, and the tools available to physicians are relatively limited.

Viral LRTIs and sensitisation to allergens are important risk factors for developing asthma. There is a strong body of evidence for hRV-associated asthma risk, and data also suggest an RSV-associated risk. Children with dual viral/allergen exposure exhibit the greatest risk of developing asthma, suggesting a synergistic relationship. In children <3 years of age, 95% of asthma exacerbations are associated with viral infections; in school-age children, 85% of exacerbations are associated with viruses, and in adults the figure is 80%. In this regard, asthma can be understood as an allergic disease driven by exaggerated responses to viral infections.

**FUNCTIONAL IMMATURITY IN THE IMMUNE SYSTEM AND INCREASED RISK OF INFECTION AND ALLERGY**

Functional immaturity of the immune system is a major driver of infection and allergy in children. In utero, the fetal immune system is in a quiescent state favouring the Th2 cytokine interleukin (IL)-4, with the Th1 response limited in order to protect the placenta from the toxic effects of interferon gamma (INF\(\gamma\)). Th2 continues to predominate during the early neonatal period via mechanisms such as temporary hypermethylation of the INF\(\gamma\) promoter in Th cells. Conversely, IL-17, which acts to protect the early neonatal immune system and
placenta, reaches a peak in the neonatal period before declining with age. Th2 maturation is evident from the fourth month of life, while Th1 function and INFγ production are delayed until 18 months. INFγ concentrations then gradually increase with age until reaching adult levels, although lower INFγ levels are common in patients with a history of atopy and recurrent respiratory tract infections (rRTIs). The Th1/Th2 imbalance during the neonatal period may predispose neonates to infection and allergic disease.12

A number of factors other than Th1/Th2 imbalance contribute to immune system immaturity continuing beyond the neonatal period into the early years of life. The activation of CD14+ monocytes involved in innate immunity varies with age, with different cytokines (IL-12, IL-6, IL-10, IL-18, IL-3, and tumour necrosis factor alpha [TNFα]) produced in response to stimulation by both INFγ and bacterial lipopolysaccharide. Furthermore, dendritic cell (DC) numbers are inversely proportional to the frequency of RTIs during the first year of life, suggesting that fewer cells increase susceptibility to infection. In addition to circulating DCs, mucosa-associated DCs and the T cells that regulate their activity also show a deficiency in early life.12

In summary, susceptibility to infections is at a maximum during early life, with the risk of atopy running in parallel. Immune system deficiencies are widespread and affect all aspects of immune function. The Th1/Th2 imbalance, attenuated monocyte function, and deficiencies in circulating and mucosal DC populations all contribute to immune system immaturity. In addition, there is a decrease in the regulatory T cells that control the activation of mucosal DCs.

**IMMUNOMODULATOR PROPHYLAXIS IN THE PAEDIATRIC POPULATION**

The increased risk of infection during childhood predisposes children to complications, including allergic conditions such as asthma. In addition, functional immaturity of the immune system, which is in itself a risk factor for increased infection, directly predisposes children to allergic disease. These interrelated factors make immunomodulation an attractive therapeutic option in children due to both infection prophylaxis and immunomodulatory effects, which may rebalance the immune system away from chronic conditions such as asthma or allergy.

OM-85 is a bacterial lysate therapy composed of immunomodulatory fractions from 21 of the most common strains of respiratory pathogen. Despite solely being composed of bacterial extracts, OM-85 has been shown to increase the concentration of the anti-viral cytokine INFα via the activation of DCs. In addition, increases in IL-6 and B-cell activating factor offer a further mechanism through which OM-85 may prevent a broad spectrum of viral and bacterial infections via the production of polyclonal antibodies.13 Indeed, OM-85 was shown to reduce mortality in mice infected with both *Salmonella typhimurium*, a bacterial strain not used in the OM-85 manufacturing process, and the H1N1 strain of viral influenza, in a recent in vivo study.14 Furthermore, in vivo efficacy against viral/bacterial co-infection (H1N1 followed by *Streptococcus pneumoniae* or *Klebsiella pneumoniae*) was shown in mice, with associated increases in CD8+ cytotoxic T cell activity and activation of B cells. The production of polyclonal antibodies was also confirmed, including the production of influenza-specific IgA and RSV specific IgG in the airways of naive mice,15 confirming a mechanism via which OM-85 may protect infants from these key drivers of infection-related respiratory complications. These data illustrate mechanistic pathways through which OM-85 may reduce both viral and bacterial infections in the paediatric population.

The data described above offer a rationale for prophylaxis against a broad range of infection types and the consequent possibility of reducing resultant complications such as asthma. In addition, the immunomodulatory effects of OM-85 may directly address aspects of immune system immaturity that predispose to allergy. OM-85 increases IgG2b, a Th1-related immunoglobulin isotype, in neonatal rats and upregulates INFγ while downregulating Th2-specific IL-4 in a mouse model of asthma.16,17 OM-85-induced reductions in Th2-related IgE, IgG1, and IL-4 have also been demonstrated in a mouse model of allergic rhinitis.18 All these changes are indicative of a potential to rebalance the Th2 bias found in the neonatal immune system and in allergic conditions. Similar changes have been confirmed in humans, where OM-85 increased INFγ (Th1) and reduced IL-4 (Th2) in addition to increasing the anti-inflammatory and pro-Th1 cytokine IL-10.19
Acute otitis media (AOM), tonsillpharyngitis, and rhinosinusitis are three of the most common forms of RTI affecting children. OM-85 has demonstrated efficacy in reducing recurrent upper respiratory tract infection (rRTI) and recurrent AOM in children in both 6 and 12-month randomised trials. Prophylaxis with OM-85 resulted in significant reductions in infections over both the 6-month (68%, p<0.001) and 12-month (75%, p<0.01) time periods, and reduced antibiotic use in both trials.20,21 In a 6-month randomised trial in children with recurrent tonsillitis, the majority of participants (76%) treated with OM-85 experienced a reduction in the frequency of recurrence. In addition, there was a dramatic reduction (68%) in the need for surgery in the 3-month responder group during the follow-up period.22 In a 6-month randomised trial conducted in children with chronic rhinosinusitis, both the incidence and the duration of recurrences were reduced (~65% [p<0.05] and ~73% [p<0.01], respectively) in conjunction with a significant reduction in antibiotic use.

Meta-analyses and systematic reviews offer the highest quality evidence available for physicians considering the efficacy of therapeutic interventions. A recent systematic review assessed OM-85 in paediatric rRTIs as a whole. Pooled data from 8 well-designed and well-conducted studies including 851 participants were analysed; mean age was 6.3 and 6.4 years for OM-85 and placebo-treated patients, respectively. There were 25.2% fewer RTIs in the OM-85-treated group compared with the placebo group, and the effect was greater in patients who were at increased risk of recurrent infection.23 Similar results were found in a systematic review of four meta-analyses, which found that bacterial lysate therapy reduced recurrences of RTIs and the need for antibiotics while producing no significant adverse effects.24 Finally, in a recent Cochrane Review on the efficacy of immunomodulators for the prevention of acute RTI in children with a history of rRTI, pooled data (N=852) revealed a highly significant 35% reduction (95% confidence interval: −49.46 to −22.35) in the prevalence of acute RTI.25

OM-85 IMMUNOMODULATION FOR PAEDIATRIC WHEEZING AND ASTHMA

Razi and colleagues26 assessed the efficacy of OM-85 in a randomised, placebo-controlled study in preschool children aged 1–6 years with recurrent wheezing. Although participants were not on asthma medication at the start of the study, they all began taking it during the study, suggesting that the data may be extrapolated to patients with asthma and persistent wheezing. OM-85 treatment reduced wheezing attacks by 2.18 per patient/year and by 38% overall (p<0.001) (Figure 1). OM-85 also achieved a reduction in the incidence of RTIs by 31% (p<0.001). A reduction in the duration of
wheezing was also noted, as were decreases in airway inflammation and structural alterations.

Multiple linear regression analyses revealed the main difference between the two groups was a reduction in the number of acute RTIs. Cases of nasopharyngitis were reduced by an extent (38%) similar to the reduction in wheezing events and overall RTIs. OM-85 was well tolerated and the authors concluded that treatment achieved a clinically significant reduction in recurrent virus-induced wheezing in preschool children and may be a useful complementary therapy alongside current treatments for wheezing.  

A recent study investigated the effect of OM-85 on human beta-defensin-1 (hβD-1) and IgG levels in children with asthma and rRTI. hβD-1 is found in lung bronchi mucus and acts as an antimicrobial agent as part of the innate immune system. The study was a double-blind, placebo-controlled trial in children with asthma and rRTI (N=62). There was a significant clinical benefit in terms of the frequency of infections at both 6 and 12 months (p<0.05) and levels of hβD-1, IgA, and IgG were significantly increased (p<0.05). 26 As previously noted, OM-85 has been shown to modulate the cytokine profile in children with asthma 19 In this same study, children treated with OM-85 in conjunction with an inhaled steroid versus steroid therapy alone showed a reduced incidence of asthma attacks and RTIs, as well as a reduction in antibiotic use. 19 The above data suggest that OM-85 has efficacy both in children at risk of developing asthma and in those already living with the condition.

IgG subclass deficiencies are defined as a selective and persistent reduction in ≥1 IgG subclass, with normal total IgG concentration and normal B cell counts. 29 Patients are frequently asymptomatic, with a minority showing poor antibody response to specific antigens and recurrent viral and bacterial infections. 30 The efficacy and safety of OM-85 in children aged 3–6 years with IgG subclass deficiency and rURTI was tested in a prospective, randomised, placebo-controlled trial. Despite conflicting data from other human and animal studies, there was no significant change in the IgG subclass levels following therapy, possibly due to drug dose or species differences. 27,31-34 From a clinical perspective, however, OM-85-treated patients showed an almost 50% reduction in the number of acute RTIs compared with placebo-treated patients (2.8 versus 5.2; p<0.001). Adverse events were mild and similar in number in both groups. 34 IgA deficiency with the risk of autoimmunity is the most common primary immune deficiency.

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**OM-85 IMMUNOMODULATION IN PAEDIATRIC PATIENTS WITH IMMUNODEFICIENCIES**

Data from the registry of the Latin American Group for Primary Immunodeficiency Diseases for the year 2007 showed that more than half of the immunodeficiencies in the region were predominantly antibody-related (Figure 2), similar to the pattern seen worldwide. More than half (55%) of these antibody deficiencies were of the heavy-chain class or isotype, which includes IgG subclass and IgA deficiencies. 26

**Figure 2: Primary immunodeficiency diseases in Latin America.** 28
Two-thirds of patients are asymptomatic, but IgA deficiency increases the risk of rRTI. Allergic diseases such as rhinitis, asthma, and conjunctivitis, as well as autoimmune conditions such as purpura, arthritis, systemic lupus erythematosus, and vitiligo may also be manifest in these patients.

Given the ability of OM-85 to modulate immune responses, and the risk of cross-reactivity with host antigens through molecular mimicry with antigens in the bacterial lysate, the possibility of adverse events in patients at risk of autoimmunity must be considered. Karaca et al. assessed these risks in a placebo-controlled trial of 64 children (aged 4–17 years) with IgA deficiency and rRTI. Over the lengthy follow-up (mean: 4 years) there were no signs of clinical autoimmunity and no differences in the number of infections (mean: 6.2/year). Both groups showed signs of serological autoimmunity, but there were no between-group differences. Overall, the data suggest that patients with an IgA deficiency have a predisposition to develop autoimmunity, but OM-85 did not increase this risk.

**Figure 3: Number of patients suffering a lower respiratory tract infection (LRTI) or upper respiratory tract infection (URTI) following treatment with OM-85 + inactivated influenza vaccine (IIV) versus IIV alone.**

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<th>IIV (n=35)</th>
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<td>LRTI Frequency</td>
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<td>URTI Frequency</td>
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The use of OM-85 as a complementary prophylactic was recently assessed in a prospective, randomised, single-blind study (N=68) comparing an inactivated influenza vaccine (IIV) alone and in combination with OM-85 for the reduction of rRTIs in children aged 2–5 years. Participants had ≥6 practitioner-attended episodes in 1 year and had received an IIV previously. There was a marked reduction in the incidence of both URTIs (−35%) and LRTIs (−67%) in patients treated with combination therapy versus IIV alone (Figure 3). In addition, children who received OM-85 and IIV had a lower mean number of antibiotic courses (−72%) and lower school absenteeism (−52%). IIV-induced humoral immunity was not affected by OM-85 and the combination therapy was well tolerated.

**Cost-effectiveness of OM-85 in children**

A study was carried out to assess the cost-effectiveness of OM-85 in children at risk of rURTIs using data from four randomised clinical trials. Cost savings per family based on one prevention cycle were €107.42 (41%) over 6 months, and €196.05 (31%) over 1 year with two prevention cycles. Societal savings were €231.26 (45%) over 6 months and €422.02 (34%) over 1 year, and savings...
to the healthcare system were €48.52/patient over 6 months. The data showed that one cycle of therapy with OM-85 prevented a mean of 1.60 episodes/child. The authors concluded that OM-85 was a cost-effective option for the treatment of rURTIs in children.37

A REAL-WORLD CASE STUDY OF PAEDIATRIC RECURRENT RESPIRATORY INFECTION

A 12-month-old male infant presented with a history of three episodes of LRTI with concurrent wheeze and family history of mild asthma. Born prematurely at 29 weeks, weighing 1,220 g, the patient required mechanical ventilation for 10 days and supplemental oxygen for 35 days. He was discharged in September and returned to the hospital with severe bronchiolitis in December. The patient suffered two further wheezing episodes in March and April and was diagnosed with respiratory RSV infection.

Treatment options included: RSV monoclonal antibody (palivizumab); inhaled steroids; montelukast; environmental prophylaxis such as good hand hygiene, limiting contact with other children and adults with RTIs, avoidance of tobacco smoke, breastfeeding, and removal from day care; and OM-85 prophylaxis. Data suggest that palivizumab reduces the number of wheezing incidents during the first year of life in preterm infants.38 Experts suggest that inhaled steroids should not be used in children <2 years of age due to the scant evidence of efficacy and risk of interference with lung development. In comparison, OM-85 is a well-tolerated option in the paediatric population and has shown efficacy in reducing rRTI in high-risk populations. Combined treatment using palivizumab and OM-85 may be a viable therapeutic option for the patient.

CONCLUSION

Children are at high risk of RTIs and associated complications due to changes in child care and anatomical changes associated with growth. In addition, the functionally immature immune system predisposes children to both RTIs and allergic conditions. The immunomodulatory properties of the immunomodulator OM-85 act to both reduce the risk of infection and rebalance the functional Th2 bias that predisposes children to allergy. OM-85 has shown efficacy in reducing recurrent infection in the overall paediatric population and in special paediatric populations without increasing the risk of autoimmunity in high-risk patient groups.

REFERENCES


17. Huber M et al. Th1-oriented...