



# Nonspecific immunomodulators for recurrent respiratory tract infections, wheezing and asthma in children: a systematic review of mechanistic and clinical evidence

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## Purpose of review

To provide an overview of the mechanistic and clinical evidence for the use of nonspecific immunomodulators in paediatric respiratory tract infection (RTI) and wheezing/asthma prophylaxis.

## Recent findings

Nonspecific immunomodulators have a long history of empirical use for the prevention of RTIs in vulnerable populations, such as children. The past decade has seen an increase in both the number and quality of studies providing mechanistic and clinical evidence for the prophylactic potential of nonspecific immunomodulators against both respiratory infections and wheezing/asthma in the paediatric population. Orally administered immunomodulators result in the mounting of innate and adaptive immune responses to infection in the respiratory mucosa and anti-inflammatory effects in proinflammatory environments. Clinical data reflect these mechanistic effects in reductions in the recurrence of respiratory infections and wheezing events in high-risk paediatric populations. A new generation of clinical studies is currently underway with the power to position the nonspecific bacterial lysate immunomodulator OM-85 as a potential antiasthma prophylactic.

## Summary

An established mechanistic and clinical role for prophylaxis against paediatric respiratory infections by nonspecific immunomodulators exists. Clinical trials underway promise to provide high-quality data to establish whether a similar role exists in wheezing/asthma prevention.

## Keywords

asthma, bacterial lysate, nonspecific immunomodulators, recurrent respiratory infection, wheezing

## INTRODUCTION

Despite being overwhelmingly viral in nature, respiratory tract infections (RTIs) are a major source of antibiotic misuse and create a significant burden of care [1–4,5<sup>\*</sup>]. Immunological immaturity and environmental factors (e.g. frequent social contacts, exposure to pollution and lack of breastfeeding) put children at increased risk of recurrent RTI (RRTI) [4,5<sup>\*</sup>,6,7,8<sup>\*\*</sup>]. RTIs early in life, and episodes of viral-induced wheezing in particular, are a significant risk factor for asthma in later life [4,6,7]. Patient interventions and parental education have a role in prevention of RRTI and its consequences, as does active immunization in cases where vaccines are available [5<sup>\*</sup>]. However, the difficulties inherent in effecting behavioural change and the lack of vaccines against most pathogenic organisms responsible for RTI create the need for other prophylactic strategies [5<sup>\*</sup>,9]. The

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## KEY POINTS

- Because of immunological immaturity and the increasing reliance of high-risk mixed social environments, recurrent RTIs cause a major burden of care in children.
- Despite their overwhelmingly viral cause, childhood RTIs are a significant source of antibiotic misuse and are associated with both direct costs and an increased risk of wheezing and asthma in later life.
- Prevention is key in order to reduce this burden of care and the associated increased risk of asthma and can be split into three fundamental aspects: parental education, active immunization (where available) and nonspecific immunomodulation.

use of nonspecific immunomodulation to boost the body's natural defences against infection offers a strategy with proven efficacy and tolerability in preventing RTIs in children [8<sup>\*\*\*</sup>].

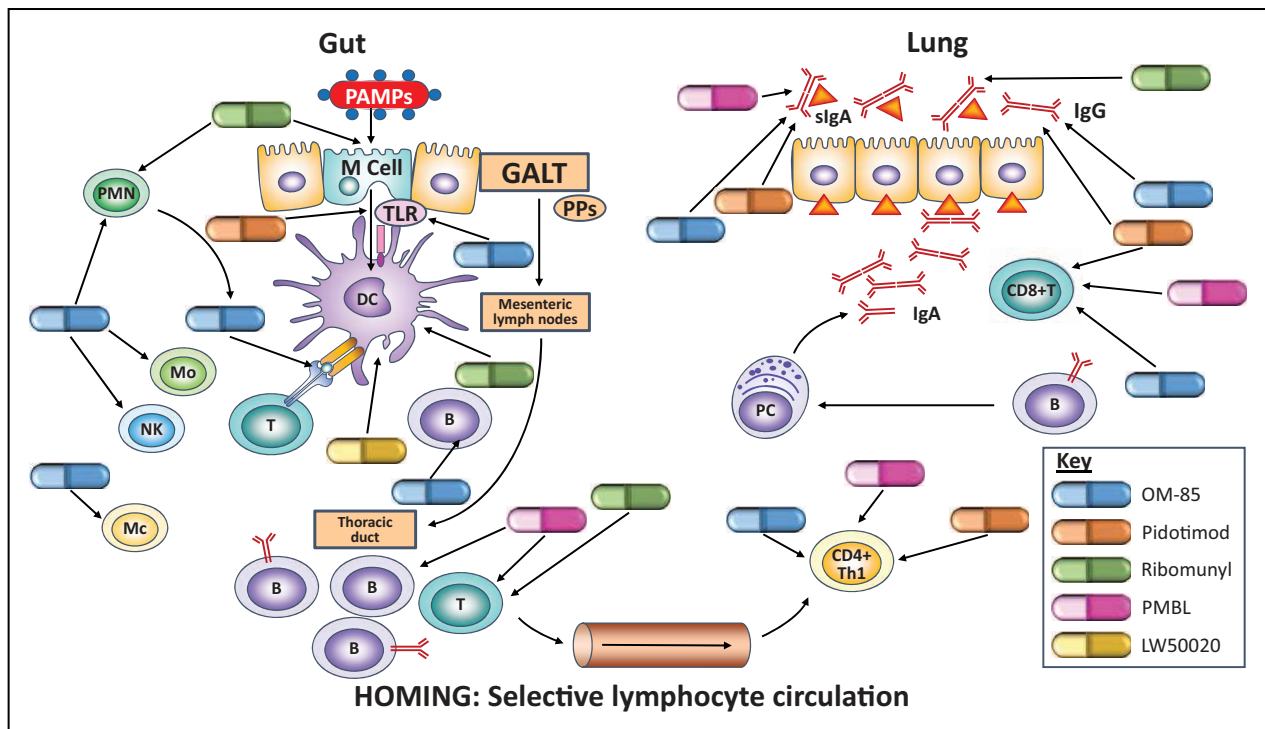
## AIM AND SEARCH STRATEGY

The aim of this publication was to summarize the mechanistic and clinical evidence for the use of nonspecific oral immunomodulators in the prevention of RTIs, wheezing and asthma exacerbations in

childhood. A systematic literature search was performed to identify articles with either mechanistic or clinical evidence on nonspecific immunomodulators between 1997 and 2017. Search terms and article disposition is shown in Supplementary Figure 1A, <http://links.lww.com/COAI/A15>. Only therapies with both mechanistic data and clinical data from paediatric double-blind randomized controlled trials were included in the analysis. A hand search of eligible articles and author expertise were used to supplement the included articles.

## RATIONALE FOR THE USE OF IMMUNOMODULATORS IN RESPIRATORY TRACT INFECTION, WHEEZING AND ASTHMA CONTROL

The empiric use of immunomodulators has over a century of clinical history, with publications investigating their efficacy dating back to at least the 1950s. The mechanistic rationale for the use of the orally administered immunomodulators for the prevention of respiratory conditions centres on the gut–lung immune axis (Fig. 1) [10]. Antigen sampling by M cells and dendritic cells resident in the Peyer's patches of the gut-associated lymphoid tissue leads to maturation of dendritic cells into an antigen-presenting cell phenotype [11]. The subsequent dendritic cell-initiated immune cascade



**FIGURE 1.** The gut–lung immune axis illustrating points of immunomodulator activity in RTI prophylaxis. B, B cell; GALT, gut-associated immune tissue; Mc, macrophage; Mo, monocyte; NK, natural killer cell; PAMPs, pathogen-associated molecular patterns; PC plasma cell; PMN, polymorphonuclear neutrophil; PPs, Peyer's patches; T, T cell. Based on [10].

involves homing of cells from both innate and adaptive branches of the immune system to the mucosal-associated lymphoid tissue of the lungs and subsequent antibody production.

Data suggest that immunomodulators may also act to aid maturation of the immune system in children, correcting T helper cell (Th) Th1/Th2 imbalance through activation of T regulatory (Treg) cells (for review, see Kearney *et al.* [12]). The correction of this Th2-oriented imbalance and other anti-inflammatory activity may reduce atopic responses related to wheezing and asthma. These effects combined with the reduced risk of RTIs, which predispose towards asthma and cause exacerbations, form the mechanistic framework for a reduced risk of wheezing events and asthma.

### MECHANISM OF ACTION FOR IMMUNOMODULATORS IN RESPIRATORY TRACT INFECTION

Five immunomodulators eligible for inclusion in this review had mechanistic data pertaining to the prophylaxis of RTIs: OM-85, pidotimod, ribomunyl, LW50020 and polyvalent mechanical bacterial lysate (PMBL) (Table 1) [13,14,15<sup>■</sup>,16<sup>■</sup>,17–20,21<sup>■</sup>,22–28,29<sup>■</sup>,30–36,37<sup>■</sup>,38–51].

#### OM-85

OM-85 is the product of alkaline lysis of 21 strains of common bacterial respiratory tract pathogens (Table 1) [14,52]. The active ingredients of OM-85 are resistant to gastric transit and cause maturation of mucosal dendritic cells in gastrointestinal Peyer's patches, a key step in orally induced respiratory immunity (Table 1; Fig. 1) [14,15<sup>■</sup>,17,22]. OM-85-induced dendritic cell activation occurs in a modulated manner, resulting in a putative prealert anti-infective state in the mucosal immune system (Table 1) [11,14,16<sup>■</sup>,22]. There are conflicting data on the identity of the dendritic cell-expressed pattern-recognition receptors (PRRs) activated by pathogen-associated molecular patterns comprising OM-85, possibly because of species differences (Table 1) [14,16<sup>■</sup>,18,19,22]. We identified a single eligible study reporting no dendritic cell maturation with OM-85 at concentrations below those affecting cell viability (<100 µg); however, these results conflict with other cell viability data [13,17].

Dendritic cells are the nexus of the innate and adaptive mucosal immune response, and OM-85-activated dendritic cells have been shown to directly activate cellular constituents of both immune-system branches (Table 1; Fig. 1) [14,22]. OM-85-

induced dendritic cells release chemokines that act on monocytes and natural killer (NK) cells, as well as proinflammatory chemokines which induce polymorphonuclear neutrophil migration (Table 1; Fig. 1) [14]. The downstream effects on OM-85 on the innate immune system include the release of antimicrobial peptides and the activation of macrophages resulting in expression of proinflammatory and antiviral cytokines (Table 1; Fig. 1) [16<sup>■</sup>,18–20,21<sup>■</sup>]. In line with these antiviral actions, OM-85 reduced rhinovirus infection of lung epithelial cells and cell death *in vitro* [21<sup>■</sup>]. Data also suggest that OM-85 causes more rapid neutrophil recruitment in response to viral infection, reducing viral load (Table 1) [15<sup>■</sup>].

OM-85-induced dendritic cells activate T cells *in vitro* and oral OM-85 increases antiviral CD8<sup>+</sup> T-cell response in the airways of mice following influenza infection (Table 1; Fig. 1) [15<sup>■</sup>,22,23]. In neonatal rats, oral OM-85 promotes immune system maturation by acting to correct the Th1/Th2 imbalance, and the release of antiviral Th1-related cytokines has been demonstrated both *in vivo* and *in vitro* (Table 1; Fig. 1) [14,25,26]. OM-85-induced dendritic cells also produce B-cell-related cytokines and OM-85 causes B-cell maturation *in vitro* [14,15<sup>■</sup>,23], leading to increases in serum and airway immunoglobulins (Ig) in both children and mice [16<sup>■</sup>,18,20,25,53] (Table 1; Fig. 1). In murine models of bacterial, viral and viral/bacterial respiratory infections, OM-85 reduced clinical symptoms and improved survival [15<sup>■</sup>,53]. However, one similar mouse study failed to show an effect on bacterial clearance, neutrophil recruitment or survival. The authors postulated that the virulence of the *Klebsiella pneumoniae* infection may have led to masking of the effect of OM-85 in this study [54].

#### Pidotimod

Unlike the other immunomodulators included in this review, pidotimod is a synthetic thymic dipeptide rather than a bacterial derivative [52,55] (Table 1). However, orally administered pidotimod appears to share a number of mechanistic similarities with bacterial immunomodulators. Pidotimod causes maturation of mucosal dendritic cells and increases antigen presentation [27,28,29<sup>■</sup>,30], likely via PRRs toll-like receptor 2 (TLR2) and TLR4 [29<sup>■</sup>,30,56] (Table 1; Fig. 1). Activated dendritic cells release cytokines and chemokines related to the innate immune response (Table 1) [28,29<sup>■</sup>]. Pidotimod-induced innate immune responses include increased expression of TLR2 in lung epithelial cells *in vitro*, increases in the release of antimicrobial peptides and improved mucociliary transport

**Table 1.** Characteristics of included immunomodulators and proposed mechanisms of action for infection prevention

Therapy	Constituents	Antigen-presenting cells	Innate immunity	Adaptive
OM-85	Alkaline lysis of 21 strains of eight species of respiratory tract pathogens: <i>Haemophilus influenzae</i> , <i>Streptococcus pneumoniae</i> , <i>Klebsiella pneumoniae</i> , <i>Klebsiella ozaenae</i> , <i>Staphylococcus aureus</i> , <i>Streptococcus pyogenes</i> , <i>Streptococcus viridans</i> and <i>Moraxella catarrhalis</i>	Maturation of mesenteric DCs [13, 14, 15*] Modulated activation suggesting prelerit anti-infective state [14, 16**] Innate and adaptive cytokine release [17] PRR yet to be determined [14, 16**, 18, 19]	Release of antimicrobial peptides [human beta-defensin-1 (hβD-1)] and C1q-R [20, 21*] ICAM downregulated in lung epithelium [21*] Rapid neutrophil recruitment in murine model of influenza infection [15*] Cytokines promoting NK-cells, monocytes, phagocytosis, neutrophils (CCL2, CCL3, CXCL1, CXCL5, CXCL6 and CXCL8) [14, 17] Macrophage activation (IL-1b, IL-6 and TNFα mRNA) [16**, 18, 19] Antiviral cytokine release (INFβ) [16**] Increased TLR2 expression in lung epithelial cells <i>in vitro</i> [31] Release of antimicrobial peptides (CAMP, LCN2, LTF and MPO) [29*] Improved mucociliary transport [32] Cytokines promoting macrophages, monocytes, NK cells and neutrophils (CCL3, CXCL1, CXCL2, IL-18 and IL-8) [29*, 33]	DC-induced T-cell activation [22, 23] Airway CD8 <sup>+</sup> T cells in murine influenza model [15*] Pro-B-cell cytokines (IL-6, BAFF and IL-10) [14, 23] Serum IgA/IgG (murine/human) [15*, 18, 20] B-cell maturation from mouse splenocytes [15*] Airway/salivary murine IgA/IgG [15*, 18, 24] Immune maturation (pro-INFγ and IgG2/anti-IL-4) [25] Release of antiviral cytokines INFα/INFγ [14, 21*, 25, 26]
Pidotimod	Synthetic thymic dipeptide (3-L-pyrroglutamyl-L-thiazolidine-4-carboxylic acid)	Mucosal DC maturation and increased antigen presentation [27, 28, 29*, 30] Increased TLR2 and TLR4 [29*, 30] Innate and adaptive cytokine release [28, 29*]	Activation of cytotoxic and helper T cells (CD3 <sup>+</sup> , CD4 <sup>+</sup> and CD4 <sup>+</sup> /CD8 <sup>+</sup> ) [34] Immune maturation (pro-IL-12, IFNγ, IL-10 and IL-18/anti-IL-4) [33–36, 37*, 38] Increased mucosal sIgA [39] Release of antiviral cytokines INFγ [39]	
Ribomunyl	Bacterial proteoglycans and ribosomes of common respiratory tract pathogens: <i>K. pneumoniae</i> (proteoglycans and ribosomes) and <i>K. pneumoniae</i> , <i>S. pneumoniae</i> , <i>S. pyogenes</i> and <i>H. influenzae</i> (ribosomes)	DC maturation [13, 40, 41] Innate and adaptive cytokine release [41]	Increased neutrophil adhesion molecules (+CD11c and +CD103) and phagocytosis [42, 43]	DCs-induced T cells activation causing release of antiviral INFγ (CD4 <sup>+</sup> ) [13, 41] Possible release of pro-TH1 cytokines (IL-12, IL-10) [13, 40] Increase in CD4 <sup>+</sup> and CD8 <sup>+</sup> T cells [44] B cell production (humoural, tonsils, mesenteric/cervical lymph nodes) [44] Salivary sIgA [45, 46] Serum IgA and IgG [44, 47, 48]
PMBL	Bacterial lysates of eight bacterial species: <i>S. aureus</i> , <i>S. viridans</i> , <i>S. pyogenes</i> , <i>K. pneumoniae</i> , <i>K. ozaenae</i> , <i>H. influenzae</i> serotype B, <i>M. catarrhalis</i> and <i>S. pneumoniae</i>	–	Putative macrophage activation (pro-IL-12) [49]	T cell activation (CD4 <sup>+</sup> and CD8 <sup>+</sup> ) [49] B cell activation [49] IgM memory B cell expansion [50] Immune maturation (+IL-2, +IL-10, IL-12 and +IFNγ) [49] Release of antiviral cytokines INFγ [49] Release of salivary sIgA [51]
LW50020	Bacterial lysates of seven bacterial species: <i>S. aureus</i> , <i>Streptococcus mitis</i> , <i>S. pyogenes</i> , <i>S. pneumoniae</i> , <i>K. pneumoniae</i> , <i>M. catarrhalis</i> and <i>H. influenzae</i>	DC maturation [13]		DC-induced T cells activation [13]

TNFα, tumour necrosis factor-alpha.

(Table 1; Fig. 1) [29<sup>■</sup>,31,32]. In a model of *Mycoplasma pneumoniae* infection, NK cell markers were down regulated; however, data suggest that this may improve resistance to further infection [34,57]. Furthermore, in a small group of adults with community acquired pneumonia, pidotimod reduced the number of cells producing tumour necrosis factor-alpha, a proinflammatory cytokine associated with a negative prognosis in this condition [30].

Pidotimod-induced dendritic cells promote proliferation of T cells and, along with induced monocytes, release cytokines promoting adaptive Th1-mediated immunity (Fig. 1; Table 1) [28,29<sup>■</sup>]. Pidotimod also directly increases levels of Th1-related cytokines and suppresses Th2 cytokines in various settings including in children with frequent infections (Fig. 1; Table 1) [29<sup>■</sup>,35,36,37<sup>■</sup>,38]. In addition, markers of both cytotoxic and helper T cells were elevated following the treatment of *M. pneumoniae* pneumonia though not in a study of combined treatment with loratadine for RRTI (Table 1; Fig. 1) [33,34]. However, we identified a single in-vitro study where pidotimod failed to promote differentiation of Th0 to Th1 [35]. Direct data showing pidotimod acting on B cells are lacking; however, increased production of nasopharyngeal and salivary secretory IgA (sIgA) in children with RTI has been demonstrated (Table 1; Fig. 1) [39]. Although, pidotimod therapy did not increase antibody titres in two studies on children with bacterial pneumonia or RRTI [33,34]. Finally, novel data suggest that pidotimod may have positive effects on the metabolic profile of children suffering RRTI [58].

### Ribomunyl

Ribomunyl is a mixture of bacterial proteoglycans and ribosomes which are delivered to lymphoid cells resident in Peyer's patches via uptake by mucosal M cells, resulting in dendritic cell maturation (Table 1; Fig. 1) [13,40,41,52,59,60]. Data on innate immune system effects are sparse, with studies showing increased expression of adhesion molecules and phagocytic activity in peripheral-blood neutrophils in response to ribomunyl [42,43] (Table 1; Fig. 1).

Ribomunyl-induced dendritic cells stimulate T cells causing antiviral interferon gamma (IFN- $\gamma$ ) release; however, there are conflicting data on ribomunyl-induced release of pro-Th1 cytokines (Table 1) [13,40,41]. Proliferation of T cells is evident in patients with otitis media treated with ribomunyl (Table 1; Fig. 1) [44]. Furthermore, oral administration causes expansion of constituent-specific B cells and sIgA production [45,46,61], and increased serum IgA and IgG in children with RRTI [44,47,48]. Increased sIgA concentrations in healthy volunteers were associated

with reduced adhesion of a constituent strain, *Streptococcus pneumoniae* (Table 1; Fig. 1) [46].

### Others

PMBL (Ismigen) is a sublingually delivered lysate made using a mechanical process that preserves the structure of the bacterial antigens [52]. It activates both T and B cells and causes release of pro-Th1 and macrophage activating cytokines *in vitro* [49] (Fig. 1; Table 1). PMBL induces memory B-cell expansion which correlates with RTI prophylaxis in patients suffering recurrence and sIgA response in healthy children and adults [50,51].

The immunomodulator LW50020 is an orally delivered bacterial lysate which induces dendritic cell maturation, and activated dendritic cells are capable of stimulating T lymphocytes (Table 1; Fig. 1) [13].

### Summary

The available mechanistic data on oral immunomodulators fit the proposed model of gut-mediated respiratory mucosal immunity. A relatively full mechanistic picture is available of OM-85 from activation of gut immunity, downstream activation of both innate and adaptive immune responses, trafficking of immune cells to the airway and release of airway sIg. Pidotimod appears to work via a similar mechanism derived from activation of mesenteric dendritic cell, leading to the activation of innate and adaptive immune branches and subsequent mounting of a response in the airway. The data on ribomunyl are more sparse particularly regarding innate immune action, though what data are available fit the current understanding of gut-lung immune axis. Little data on PMBL and LW50020 were available, though, importantly, effector activity in the lung has been demonstrated following oral immunization with PMBL.

## EFFICACY OF IMMUNOMODULATORS IN CHILDREN WITH RESPIRATORY TRACT INFECTION

All the above immunomodulators have evidence of efficacy in paediatric RTI-prophylaxis, to varying degrees.

### OM-85

OM-85 has demonstrated efficacy in a number of forms of paediatric RTI (Supplementary Table 1, <http://links.lww.com/COAI/A15>) [8<sup>■</sup>,62,63<sup>■</sup>]. Oral therapy reduced the incidence, prevalence and/or

duration of infections in children with a history of RRTI compared with placebo [64–67] and versus probiotic therapy [24]. In a study of children with recurrent tonsillitis, OM-85 prophylaxis improved outcomes in the majority of patients and, importantly, removed the need for surgery in a significant proportion of those treated [66]. In children with subacute sinusitis, OM-85 prophylaxis sped recovery and reduced infections [68], whereas children with chronic rhinosinusitis had a reduced symptom burden and a lower incidence of attacks [69]. OM-85 has also shown efficacy in high-risk environs, reducing the incidence and prevalence of infections in a Mexican orphanage [70].

Reductions in antibiotic and drug treatment following prophylactic therapy with OM-85 have also been demonstrated in children with a history of RRTI, subacute sinusitis and in high-risk environments (orphanages) [64,68,69]. OM-85 therapy reduced school absenteeism both in children with a history of RRTI and in those living within an orphanage [67,69]. Efficacy was unaffected by coadministration with antibiotic therapy or the influenza vaccine, with OM-85 conferring additional benefit in terms of absenteeism and prevalence of infections in both cases [67,68].

OM-85 is well tolerated with a frequency of adverse events comparable to that seen with placebo in clinical trials. Undesirable events are mainly mild and transient, with manageable risks. This safety profile appears to be stable in nature and frequency over long-standing use [24,64–67,69,70].

### Pidotimod

Research into the efficacy of pidotimod in the paediatric population has increased in recent years, particularly in the Russian Federation. The incidence and/or prevalence of infections was reduced in children with a history of RTI in a number of studies without an active control [32,71–74] versus another immunomodulator [75] and versus antibiotic therapy [37<sup>\*</sup>]. In children with RRTI, pidotimod reduced fever, cough and pulmonary rales [76], and duration of symptoms was also reduced compared with spleen amino peptide [36]. In children about to enter the high-risk day care environment, pidotimod showed nonsignificant reductions in RTI and antibiotic use. The lack of power in this study may have contributed to the failure to demonstrate significant efficacy [77].

Pidotimod prophylaxis also results in less antibiotic use [37<sup>\*</sup>,71,74], hospitalization and paediatric visits [71,72] and school absenteeism [72]. Where reported, adverse events were infrequent, mild and transient [71,72,75–77].

### Ribomunyl

In a number of trials on children with RRTI, including those with adenoiditis, pharyngotonsillitis and otitis media, ribomunyl reduced the incidence, prevalence and/or duration of infections [44,47,48,78,79]. The use of antibiotics/ancillary therapy [44,47,48,79], school absenteeism [44,47,79] and medical visits [48] was also reduced. In a comparison of ribomunyl prophylaxis for patients with more or less than five RTIs in the past year, only those with five or less showed a decrease in incidence of infection, and physicians did not rate a significant improvement in either group. Neither was there a difference in school absenteeism in this study [78]. Ribomunyl is generally well tolerated and treatment-related adverse events are uncommon.

### Other

LW50020 reduced clinical severity score, infection rates and duration of infections in children with RRTI compared with placebo [80]. Furthermore, the rate, duration and severity of RTIs, and the use of antibiotics reduced compared to pretreatment values in a dose comparison study in children with RRTI [81]. PMBL reduced the incidence of RTI and the use of both antibiotic and antiviral drugs, in children with a history of RRTI and was well tolerated [82]. Adverse drug reactions were infrequent, transient and nonserious with both therapies [81,82].

### Summary

The eligible immunomodulators demonstrated efficacy in preventing RTI in children with a history of RRTI, and in a number of specific upper RTI subtypes. Numerous definitions of RRTI were used and standardization of the definition of this condition is desirable. Although a quantitative assessment of trial quality was not undertaken, observations of reporting quality were in line with data from the 2012 Cochrane review suggesting articles assessing OM-85 were of higher quality [8<sup>\*\*</sup>]. Studies on pidotimod in particular lacked reporting of safety, control groups or information on the definition of RRTI, particularly in foreign language abstract-only publications.

### MECHANISM OF ACTION OF IMMUNOMODULATORS IN WHEEZING AND ASTHMA

Mechanistic data relating to OM-85, pidotimod, ribomunyl, PMBL in wheezing, asthma or related conditions were available.

**OM-85**

The Th2 immune response is key to the airway hyper-reactivity that occurs during asthma exacerbations. Data from mouse models show that orally administered OM-85 activates gut dendritic cells which induce trafficking of pro-Th1/anti-Th2 Treg cells to the lung (Table 2) [16<sup>■</sup>,18,37<sup>■</sup>,83<sup>■</sup>,84<sup>■</sup>,85–87,88<sup>■</sup>,90<sup>■</sup>,91–101]. OM-85 also downregulates Th2-associated markers on gut dendritic cells (Table 2) [16<sup>■</sup>]. In the lung, OM-85-induced Tregs inhibit the Th2-associated response, likely via modulation of the response of lung dendritic cells (Table 2) [83<sup>■</sup>,84<sup>■</sup>]. This immunoregulatory activity results in reduced allergen-induced airway inflammation and hyper-reactivity in sensitized mice over a time course which reflects OM-85’s cellular effects (Table 2) [83<sup>■</sup>,88<sup>■</sup>].

Shifting of the cytokine balance in a pro-Th1/anti-Th2 direction has been demonstrated in murine models of both asthma and allergy [17,19,85–87,88<sup>■</sup>], in human peripheral blood

mononuclear cells (PBMCs) [15<sup>■</sup>] and in children with asthma and related conditions [89,90<sup>■</sup>,91,102]. Notably, this anti-inflammatory effect is increased in the presence of proinflammatory mediators [15<sup>■</sup>]. In line with these changes in cytokine balance, OM-85 reduces the infiltration of proinflammatory cells in murine inflammatory models of asthma and allergic rhinitis [17,83<sup>■</sup>,84<sup>■</sup>,85,86,88<sup>■</sup>]; suppresses mucus metaplasia and hypersecretion [84<sup>■</sup>,85,88<sup>■</sup>]; and attenuates airway remodelling [88<sup>■</sup>].

The Th2 response is characterized by increased serum IgG1 and IgE, an effect inhibited by OM-85 in mouse models of allergic rhinitis [86] and asthma [18,84<sup>■</sup>,88<sup>■</sup>] (Table 2). This effect was not seen in all the studies we identified, however [83<sup>■</sup>,89]. Furthermore, in a low-dose study using murine asthma model, OM-85 did not reduce inflammatory cell infiltration, serum IgE or lung histopathologic findings, though proinflammatory cytokines were reduced and there was no increase in airway resistance in OM-85-treated mice [87]. In a response to

**Table 2.** Proposed mechanisms of action for the prevention of wheezing and asthma exacerbation

Therapy	Dendritic cells/monocytes	Th1-Th2 Balance	Airway inflammation	Immunoglobulins
OM-85	Increased T-reg-related CD103 <sup>+</sup> DCs in mesenteric lymph nodes [83 <sup>■</sup> ] Reduced Th2-associated markers on induced DCs (ICOSL) [15 <sup>■</sup> ] Accelerated resolution of airway DCs reaction to allergen in a mouse model of asthma [84 <sup>■</sup> ]	Trafficking of IL-10 producing Tregs from gut to airway [84 <sup>■</sup> ] Reduced CD4 <sup>+</sup> Th2-type cells and inflammatory cytokines (IL-4, IL-5, IL-6, IL-10 and IL-13) in lungs of sensitized mice [84 <sup>■</sup> ] Allograft of induced Tregs blocks Th2 and inflammatory cytokine production in sensitized mice (IL-5 and IL-13) [84 <sup>■</sup> ] Induces pro-Th1/anti-Th2 cytokine induction in mouse models of allergy/asthma (Pro-IFN-γ and IL-10/anti IL-1b, IL-4, IL-5, IL-13 and TGF-b1) [18,85–87,88 <sup>■</sup> ] Induced IL-10 release from human PBMCs increased under inflammatory conditions [15 <sup>■</sup> ] Pro-Th1 and anti-Th2 cytokine release in children with asthma (Pro-IL-10 IFN-γ/anti-IL-4, IL-17 and IL-1b) [16 <sup>■</sup> ,89,90 <sup>■</sup> ,91]	Blocks infiltration of eosinophils, neutrophils, macrophages and lymphocytes in mouse models of asthma/allergic rhinitis [83 <sup>■</sup> ,84 <sup>■</sup> ,88 <sup>■</sup> ] Allograft of induced Tregs blocks eosinophilia in sensitized mice [84 <sup>■</sup> ] Reduced mucus metaplasia, hypersecretion and tissue remodelling [83 <sup>■</sup> ,84 <sup>■</sup> ,88 <sup>■</sup> ]	Reduced specific-serum and nonspecific serum IgE and IgG1 in a mouse model of asthma and allergic rhinitis [16 <sup>■</sup> ,18,84 <sup>■</sup> ,85,86,88 <sup>■</sup> ]
Pidotimod	Upregulates anti-inflammatory NOD-like receptor NLRP12 in monocytes [92] Inhibits proinflammatory MCP-1 [92]	Downregulates Th2-associated CD-30 in cells from normal and atopic individuals [93]	–	Reduced IgE in a mixed group of patients with RRTI some of whom were atopic [37 <sup>■</sup> ]
Ribomunyl	–	Pro-Th1/anti-Th2 cytokine changes (pro-IFNγ/anti-IL-4, IL-5) [94,95]	–	–
PMBL	–	Anti-Th2 cytokine change (IL4) [96] Increased Treg cells [97]	–	–

DC, dendritic cell.

these results, it was suggested that reduced levels of the key eosinophil activator interleukin-5 may result in these cells being in a quiescent state and account for the absence of increased airway resistance [103].

## Other

Data on the other eligible immunomodulators related to wheezing, asthma or allergy were sparse. Pidotimod reduced inflammatory response to TLR ligands via the upregulation of a member of the nod-like receptor family of PRRs in human monocytes [92]. In PBMCs from children with or without atopic asthma, in-vitro pidotimod causes downregulation of a Th2-related marker, but does not appear to affect Th1/Th2 cytokine balance [37<sup>■</sup>,93]. In addition, pidotimod reduced serum IgE in 50% of a group of RTI patients, some of whom had atopy [37<sup>■</sup>]. However, in a recent study on the ovalbumin mouse model of asthma, pidotimod treatment leads to a significant increase in both IgE and eosinophil infiltration compared to mice treated with ovalbumin alone. This proinflammatory effect was reflected in increases in proinflammatory cytokine release and a failure to downregulate markers of asthma severity and airway remodelling [104].

Ribomunyl shifted the Th1/Th2 cytokine balance in favour of Th1 in two studies, although this was less marked and slower in patients with atopy than in those without [94,95]. In patients with allergic rhinitis who received PMBL, there was a decrease in IL-4, although IFN- $\gamma$  and IgE were not affected [96]. Finally, in children with partially controlled or uncontrolled asthma, PMBL treatment increased the numbers of CD8<sup>+</sup> cytotoxic cells, Treg cells and NK cells [97].

## Summary

There was a substantial gap in the depth of mechanistic data on wheezing/asthma between OM-85 and the other eligible immunomodulators. OM-85 appears to inhibit Th2-related inflammation via activation of gut dendritic cells and subsequent trafficking of Treg cells to the lung. A number of studies demonstrated anti-inflammatory effects in inflammatory or atopic physiological environments and reductions in cell infiltration and atopy-related immunoglobulins. The other immunomodulators showed some anti-inflammatory and proTh1 effects but lacked the data to obtain a clear mechanistic understanding of their potential influence on wheezing/asthma.

## EFFICACY OF IMMUNOMODULATORS IN WHEEZING AND ASTHMA

Studies into the efficacy of immunomodulators in wheezing and asthma were relatively sparse in

comparison to those studying RTIs in general; however, an increasing number of studies have been published over the last 10 years (Supplementary Table 2, <http://links.lww.com/COAI/A15>).

## OM-85

OM-85 prophylaxis reduced the duration and incidence of wheezing/asthma exacerbations in children with a history or recurrent wheezing or asthma [90<sup>■</sup>,91,105<sup>■</sup>,106], as well as hospitalizations related to asthma [89]. The reductions in exacerbations appear to be related to reduced incidence of RTIs in these studies [89,105<sup>■</sup>]. In line with this observation, OM-85 also reduced the incidence of RTI [21<sup>■</sup>,90<sup>■</sup>,91,105<sup>■</sup>,106] and antibiotic use [90<sup>■</sup>]. As expected, OM-85 was well tolerated in all the studies which reported safety data and its addition to corticosteroid therapy caused no apparent issues [21<sup>■</sup>,90<sup>■</sup>,105<sup>■</sup>].

## Pidotimod

The two studies investigating pidotimod in asthma and the related condition obstructive syndrome did not report data on asthma exacerbations; however, there were reductions in the incidence of RTI in both studies [39,107]. RTI duration was also reduced in children with allergic rhinitis and asthma [107].

## Polyvalent mechanical bacterial lysate

In an unpublished trial, PMBL reduced the incidence and prevalence of asthma exacerbations in children with atopic asthma [97]. In addition, PMBL improved symptoms in a mixed group of children and adults with allergic rhinitis [96].

## Summary

With some notable exceptions (e.g. Razi *et al.* [105<sup>■</sup>]), the quality of the identified studies on wheezing/asthma identified was low with important design and safety criteria frequently not reported. Trials currently underway are likely to provide higher quality data in the near future. Data available suggest that the reductions in exacerbations achieved were related to reductions in RTI. Again, future studies may provide insights on the contribution of the anti-inflammatory effects detailed herein towards prophylaxis.

## FUTURE RESEARCH

A search of the major clinical trial registries (EU Clinical Trials Register; Australian New Zealand



Clinical Trial Registry; ClinicalTrials.gov) revealed ongoing trials for OM-85 only.

### OM-85 in respiratory tract infection

A phase 4 trial (NCT03243565) investigating the efficacy of OM-85 in children with a history of RRTIs and symptoms of adenoid hypertrophy began recruiting in 2017. The primary outcome will be the number of RTIs, and secondary outcomes will include symptoms of adenoiditis [108].

### OM-85 in wheezing/asthma

Four trials investigating OM-85 in asthma and wheezing are currently ongoing. The OM-85 in Prevention of Asthma in Children (OMPAC) randomised controlled trial (RCT) (ACTRN12612000518864) will assess outcomes in infants who have a sibling with asthma/atopy, treated with OM-85 in two cycles during their first two winter seasons. Outcomes will include prevention of symptomatic lower RTIs, persistent asthma development and allergen sensitization [109]. Results are expected in June 2019. The Italian OMPeR RCT (EudraCT: 2016-002705-19) will investigate OM-85 for the prevention of upper respiratory tract infections (URTIs) in children with mild immunodeficiency (IgA and IgG), atopy or recurrent wheezing [110]. Standard and longer term dosing will be explored. The trial outcomes include URTIs prophylaxis, school days lost, use of antibiotics and wheezing, with results expected in 2018. In the BREATHE RCT (EudraCT: 2016-001213-24), adolescents and adults with uncontrolled asthma will receive OM-85 for two consecutive October–March winter seasons [111]. The primary outcome will be the incidence of asthma exacerbations. Trial results are expected in 2020.

The Oral Bacterial EXtracts for the prevention of wheezing lower respiratory tract illness (ORBEX) trial represents a step change in immunomodulator research [112<sup>\*\*\*</sup>]. This large, multicentre, National Institute of Health-funded RCT (NCT02148796) will enrol upwards of 1000 infants at high asthma risk due to having atopic eczema and/or parents or siblings with asthma. Participants will receive long-term OM-85 prophylaxis (3.5 mg/day for 10 days/month for 2 years). The primary outcome will be time to first wheezing episode in the third observational year when children are not receiving prophylaxis. Preliminary results of the ORBEX trial are expected by December 2022.

Alongside the above clinical outcomes, the effects of OM-85 on microbiota, immunological, inflammatory and genetic markers will be assessed in these trials [109–111,112<sup>\*\*\*</sup>].

## CONCLUSION

Mechanistic data, in particular for OM-85, support the rationale for use of immunomodulators in both prophylaxis against RTIs and wheezing/asthma exacerbations in children. The included immunomodulatory compounds appear to act on both adaptive and innate portions of the immune system conferring both immunoglobulin-related and cell-mediated immunity to the respiratory system. Maturation of the immune system via the redressing of the Th1/Th2 imbalance appears to be a route by which immunomodulators can both reduce RTIs and potentially reduce atopy. In addition, under inflammatory conditions, immunomodulators, particularly OM-85, appear to reduce inflammation via immunoregulatory mechanisms and reduce hyper-reactivity. Efficacy data in patients at risk of both RTI and asthma support the above mechanistic rationale, with reductions in both RTIs and asthma exacerbations. The large upcoming ORBEX study has the potential to verify the role of OM-85 as antiwheezing prophylactic.

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## Conflicts of interest

*There are no conflicts of interest.*

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