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INSIDE

Immunomodulation for Recurrent
Respiratory Tract Infections:
New Insights and Perspectives



IMMUNOMODULATION FOR RECURRENT RESPIRATORY TRACT INFECTIONS: NEW INSIGHTS AND PERSPECTIVES

A narrative summary of presentations from the 'Immunomodulation: New Insights and Perspectives' symposium held at the 1st World Association for Infectious Disease and Immunological Disorders (WAidid), Milan, Italy, 18th–20th February 2016

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MEETING SUMMARY

The 1st biennial WAidid Congress held in Milan, Italy, brought together academics and clinicians from the broad field of infectious diseases and immunology. The conference was founded in order to create a network connecting this diverse field and to allow the showcasing of data and therapeutic techniques amongst specialists concentrating on different age groups and organs. Prof Roth and Conference Chair Prof Esposito presented a symposium on the use of immunomodulation for prophylaxis against recurrent respiratory tract infections on Day 2 of the conference.

The symposium covered risk factors in the paediatric population and different treatment options for recurrent respiratory tract infections before focussing on the immunomodulatory prophylactic OM-85 (Broncho-Vaxom®, Broncho-Munal®, Ommunal®, Paxoral®, Vaxoral®). OM-85 is an orally administered immunomodulator, which has been shown to provide protection against respiratory infections of both viral and bacterial aetiologies in patients at high risk of recurrent infection. The symposium detailed the immunological mechanism of OM-85's protective effects as well as safety and efficacy data in various patient populations.

Keywords: Immunomodulation, recurrent respiratory tract infection (RRTI), asthma, allergy.

RISK FACTORS AND PATHOGENS IN CHILDHOOD RECURRENT RESPIRATORY TRACT INFECTION

Recurrent respiratory tract infections (RRTIs) are extremely common in the paediatric population.

In the absence of any underlying contributory pathological condition, an infection frequency of ≥ 8 episodes/year in infants and ≥ 6 episodes/year in children >3 years old is considered to represent recurrence.¹

Childhood itself, with its temporary immune system immaturity, may be said to be the primary cause of RRTI in the paediatric population.² However, numerous other modifiable and non-modifiable risk factors also contribute to the overall risk of recurrence. Modifiable risk factors include daycare attendance and passive smoking, while non-modifiable risk factors include prematurity, genetic predisposition, and atopy.³

Immunological immaturity is characterised by reduced neutrophil chemotaxis; reduced phagocytosis and reactive oxygen (RO₂) production; reduced CD4⁺, CD8⁺, CD19⁺, and natural-killer lymphocyte numbers; reduced production of the cytokines interleukin (IL)-12, IL-10, and interferon gamma (IFN-γ); decreased synthesis of immunoglobulin (Ig)M, IgA, and IgG; and reduced antigen response. In addition, polymorphisms of a number of genes (*TLR4*, *CCR5*, *IRAK4*, and *FcgRIII*) may contribute to impaired immunity, both during childhood and throughout life.⁴

Viruses are responsible for the vast majority of respiratory tract infections (RTIs; ≥80%). Common causal agents include human rhinovirus, respiratory syncytial virus, adenoviruses, and influenza virus.⁵ Bacteria spp. also represent aetiological agents, both alone and as bacterial superinfections, commonly following acute viral infections.⁶ Viral infections cause and contribute to serious respiratory conditions, which may result in hospitalisation. For example, in school-aged children, viral upper RTIs correlate with hospital admission for asthma.⁷

TREATMENT AND PROPHYLAXIS FOR RECURRENT RESPIRATORY TRACT INFECTION

Due to the preponderance of viral respiratory infections, antibiotics are only indicated in a limited number of specific conditions. However, antibiotic misuse is a worldwide healthcare issue, leading to a crisis of resistant pathogens and the threat of entering a post-antibiotic era. Therefore, there is a significant unmet need for additional antibiotic therapies and strategies to reduce infections. Prevention can be aimed at reducing modifiable risk factors or at protecting against non-modifiable risk factors by using active strategies in those at high risk.

Active, effective, and widespread immunisation remains the ultimate prophylactic strategy against

both bacterial (*Pneumococcus* [for example, the pneumococcal conjugate vaccine], *Haemophilus influenzae* type B, *Bordetella pertussis*, *Staphylococcus aureus*) and viral (measles and influenza) pathogens. Viral influenza is an important contributor to infant mortality particularly in young infants, and inoculation has significant benefits in reducing influenza and associated acute RTIs such as otitis media and pneumonia. In addition, vaccination controls transmission, resulting in indirect protection of other at-risk groups.^{8,9} For example, a Japanese childhood-vaccination programme produced dramatic effects on all-cause, influenza, and pneumonia-related deaths in all age groups when school-aged children were vaccinated (Figure 1).¹⁰

Alternative active-prevention strategies, such as proven effective immunomodulators, are useful and necessary, particularly where vaccinations are not available or in unvaccinated populations. Immunomodulatory agents include: bacterial lysates, pre/probiotics, immunological extracts, synthetic products, hormones and hormone derivatives, and natural/herbal products.

OM-85: AN ORALLY ADMINISTERED RESPIRATORY IMMUNOMODULATOR

OM-85 is an oral, bacterial, soluble extract comprising lysates derived from 21 different strains from five bacterial genera: *Haemophilus influenzae*, *Streptococcus* (*pneumoniae*, *sanguinis*, and *pyogenes*), *Klebsiella pneumoniae* (ssp. *pneumoniae* and ssp. *ozaenae*), *S. aureus*, and *Moraxella catarrhalis*.¹¹ Since its introduction in Switzerland in 1979, 94 million patients have been treated with OM-85, close to half of whom (46 million) were children.¹²

Bacterial exposure is known to induce immune system development and reduce allergic sensitisation. However, repeated infection can induce chronic inflammation, remodelling, and asthma in children, particularly in those with risk factors such as a family history of atopy. The broad effects of OM-85 may be viewed as a benign mirror of the effects of bacterial exposure: immune system activation that defeats bacterial infection, and immunoregulatory effects which reduce inflammation and the harmful consequences of immune system over activation.¹³

OM-85 therapy results in respiratory immunity and protects against both viral and bacterial

OM-85 IN CHRONIC INFLAMMATORY LUNG DISEASE

The majority of commonly used therapies for chronic inflammatory lung disease (CILD) (glucocorticoids, β 2-agonists, and phosphodiesterase inhibitors) target inflammation or bronchial muscle cells to reduce symptoms and have little or no effect on infections, which commonly drive the underlying disease and cause exacerbations. Anti-IgE therapies using humanised antibodies reduce IgE receptor activation, a common pathological consequence of CILD. However, data suggests cytokine specific humanised antibodies targeting IL-1, IL-4, IL-17, IL-5, IL-13, and CXCL-2 have limited efficacy or are likely to be efficacious only in certain subtypes of patients.¹⁸

A recent review of the mechanisms of CILD emphasised the central role of non-immune epithelial cells as the first cells that are exposed to inhaled bacteria or viruses.¹⁹ Epithelial cells are the primary target cells for most respiratory viruses and the site of viral replication, which occurs before the spread of infection to other cell types. These cells directly interact with macrophages, and in addition affect mesenchymal smooth muscle cells and related myofibroblasts, which are now recognised as a major source of proinflammatory stimuli and cytokines in CILD.

pathogens.^{14,15} Evidence from animal models suggests that lysate passes through the digestive system without being substantially modified and activates microfold cells in the Peyer's patches of the gut's mucosa-associated lymphoid tissue. Microfold cells are specialised to transport particles across the gut's epithelial barrier, delivering antigens to antigen-presenting cells, such as dendritic cells (DCs).¹⁶

OM-85 has been shown to directly activate the immune system via DCs. DCs act as the sentinels of the immune system and are key in shaping the immune response through their antigen-presenting function and the release of cytokines, which promote the maturation and activation of immune cells. OM-85 stimulates DCs through activation of pattern recognition receptors, resulting in the release of chemokines including: CXCL8, CXCL6, CCL3, CCL20, and CCL22 which, amongst many other functions, promote phagocytosis; IL-12, interferon (IFN) γ , and IFN α , which have antiviral activity (T helper [Th]-1 response); and IL-6, IL-10, and B cell Activating Factor (BAFF), which activate polyclonal antibody producing B cells, bypassing Th cells.^{11,13,17} Importantly, this cascade of cytokine production and cell activation provides mechanistic evidence from animal models for OM-85's ability to reduce both viral and bacterial infections through cytokine and antibody production.¹¹

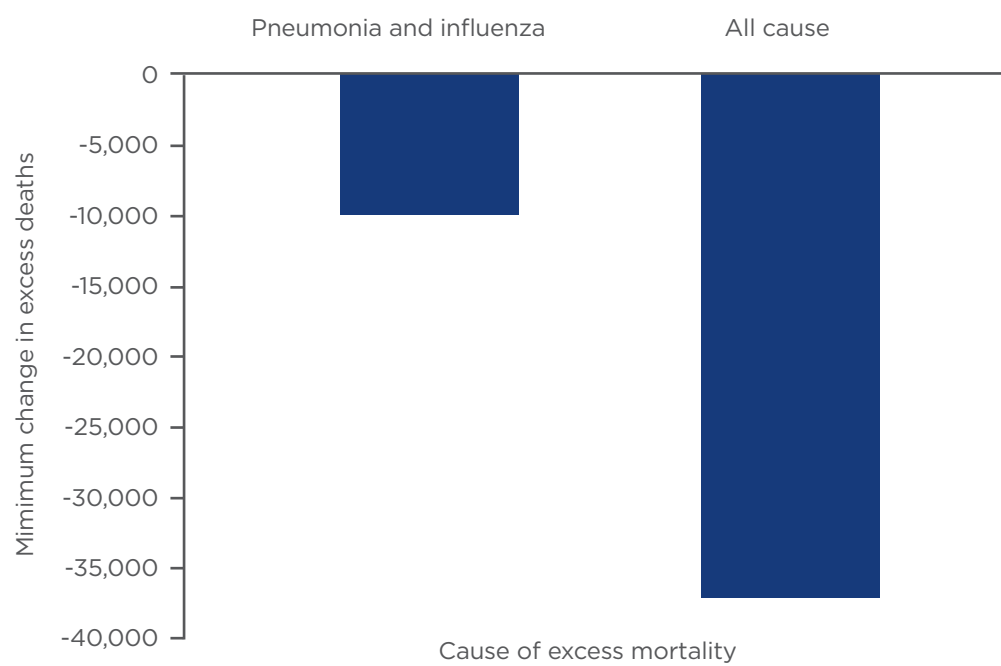


Figure 1: Average minimum change in excess deaths attributable to pneumonia and influenza, and all-causes, in Japan and the United States.¹⁰

Furthermore, epithelial cells interact with immune cells, including mast cells, B cells, and eosinophils, in response to infection. In addition, activation of DCs by viruses leads to downstream activation of both eosinophils and Th cells.¹⁹

A recent publication on asthma prevention highlighted the use of microbial products such as bacterial lysates in CILD to target infections.²⁰ OM-85 directly affects the action of macrophages and modifies the response of Th cells. Furthermore, OM-85 acts on mast cells and eosinophils, reducing eosinophil numbers. Macrophage activation by OM-85 was suggested to occur via Toll-like receptor (TLR)-2 and TLR-4. Researchers found an increase in proinflammatory cytokines IL-1 β , IL-6, and tumour necrosis factor- α (TNF)- α production also mediated via TLRs acting on both extracellular signal-regulated kinase (ERK)-1, ERK-2, and nuclear factor kappa B (NF- κ B) signalling pathways.²¹ While these data were obtained from macrophage cell lines and should be confirmed using primary myeloid cells, they indicate that OM-85 targets cell populations known to be important in CILD and the prevention CILD exacerbations. In DCs, OM-85 increased the release of the antiviral cytokine IFN- α , suggesting OM-85 therapy may induce a basal antiviral state. OM-85 was a weaker inducer of a number of proinflammatory factors (NF- κ B, TNF- α , IL-1 β , IL-6, and COX-2) than lipopolysaccharide (LPS), in DCs. The anti-inflammatory actions of OM-85 were particularly evident in the presence of a proinflammatory milieu (interferon gamma and LPS), where OM-85 resulted in a 3-fold increase in the release of anti-inflammatory IL-10. In addition, OM-85 induced neutrophil activating CXCL8 and proapoptotic and proinflammatory cytokine-activating factor caspase 1. This suggests the prophylactic properties of OM-85 may be partially mediated through increased apoptosis of infected cells and increased neutrophil activity. The above data provide putative mechanistic pathways for the viral and bacterial infection-prophylactic effects, and inflammation-reducing immune-regulatory effects of OM-85.¹⁷

Reduced infection rates have been demonstrated in a murine model of bacterial superinfection with the influenza virus and either *Streptococcus pneumoniae* or *Klebsiella pneumoniae*, following treatment with OM-85. The reduced infection rates were accompanied by lower viral load in lung tissues, reduced fever, reduced weight loss, and reduced overall disease score. The effects

appeared to be mediated by release of polyclonal antibodies effective in binding influenza virus, via activation of B cells, with DCs being the key to this process. Markers of DC activation were increased and inducible co-stimulator-ligand, which is known to be an important DC marker involved in allergy, was downregulated.¹¹ Numerous studies have demonstrated the direct effects of bacterial lysates on antibodies in CILD. OM-85 increases protective IgG and IgA.²²⁻²⁶ However, the mechanism by which OM-85 upregulates the expression of circulating IgG and IgA has yet to be fully determined.

Studies also suggest OM-85 reduces IgE expression via a shift from Th2 to Th1 cytokine profiles.^{27,28} Approximately 60% of asthma patients are of the allergic phenotype, where increased serum IgE is an important mediator of the response of immune cells and tissue forming cells.^{29,30} *In vitro* experiments indicate that reductions in IgE decrease the susceptibility of immune cells and tissue forming cells to asthma triggers.^{31,32} Interestingly, some of these IgE effects are independent of the presence of antigens and promote airway remodeling and tissue inflammation through high affinity IgE receptor binding. Therefore, reducing serum IgE through OM-85 therapy could have a beneficial effect during acute and non-acute asthma. The IgE reducing effect of OM-85 has been reported in human subjects and in animal models.^{27,28,33-35} Currently, the molecular mechanism by which OM-85 achieves a reduction in serum IgE remains speculative and needs further investigation.

In addition, OM-85 may inhibit IgE receptor function as it has been demonstrated with bacterial proteins.^{36,37} OM-85's theoretical interaction with IgE receptors and the possibility that this may reduce IgE binding on epithelial and mesenchymal smooth muscle cells, and thereby decrease the immune response to inhaled allergens and pathogens is currently being investigated (**Figure 2**).³⁸⁻⁴² These IgE related mechanisms provide a further theoretical framework for OM-85's amelioration of the inflammatory processes that exacerbate CILD.

In summary, mechanistic data are now available to account for an OM-85-derived reduction in viral and bacterial infections primarily through innate cellular immunity and adaptive cellular and humoral activity. In addition, the mounting of an adaptive immune response during viral infection and reductions in inflammation through inhibition of proinflammatory cytokines and

allergy-mediating IgE, have been demonstrated. These complementary mechanisms provide a viable explanatory pathway for OM-85-derived improvements in CILD outcomes.

BEYOND THE PREVENTION OF RECURRENT RESPIRATORY TRACT INFECTIONS: NEW HORIZONS FOR AN EFFECTIVE IMMUNOMODULATION

The goal of physicians using bacterial lysates such as OM-85 is to reduce infections in those at high risk of RRTI. OM-85 has been shown to overcome immune system immaturity in infants and create a state of immune alertness in patients at high risk of infection.

The efficacy of preventative therapy with OM-85 has been extensively studied in the paediatric population in nine main randomised trials and one long-term retrospective study. In order to identify those patients likely to benefit most from OM-85 therapy, the studies have covered conditions including acute sinusitis, chronic rhinosinusitis (CRS), recurrent acute RTI, recurrent tonsillitis, and recurrent wheezing.^{26,43-51}

EFFICACY OF OM-85 IN RECURRENT RESPIRATORY TRACT INFECTION

The overall efficacy of OM-85 in RRTI in the paediatric population was investigated in a systematic literature review in 2010. The study summarised data from eight randomised trials of OM-85 versus placebo (mean age 6.3 versus 6.4 years; n=435 and 416, respectively), many of which used the standard OM-85 treatment paradigm of 10 days/month for 3 months. Overall, there was a 26.2% reduction in recurrence (≥ 3 RTIs in 6 months) and a 35.5% reduction in acute RTI. The effect of OM-85 was proportional to the number of previous RTIs experienced and was greater in those of a younger age, indicating that OM-85 had the greatest benefit in those patients at highest risk.⁴⁸

The Cochrane collaboration performed a large meta-analysis on immunomodulatory therapies for paediatric RTIs. In general, the overall quality of trials in the meta-analysis was deemed poor; many trials were underpowered and included heterogeneous patient populations. OM-85 had the largest number of high quality trials overall and was the only bacterial lysate therapy with trials of

Grade A quality. OM-85 achieved an overall reduction in acute RTIs of 35.9% (95% confidence interval [CI]: -49.5 – -22.4) compared with placebo. Again the greatest effect was found in those patients with the highest burden in terms of recurrences.⁵²

OM-85's efficacy has also been assessed in a randomised placebo-controlled trial with a longer 12-month follow-up. Children (aged 1–12 years; N=54) with both upper and lower RRTIs were treated with two courses of OM-85 (10 days/month) for 3 months, beginning at Months 1 and 7. Kaplan-Meier analysis revealed a significant reduction ($p<0.001$) in OM-85-treated patients suffering RRTIs (≥ 6 acute events). The relative risk of RRTI was 0.37 (95% CI: 0.20–0.68) in favour of OM-85. The duration of acute RTI was also reduced in the OM-85 group compared with the placebo group (median days: 30.5 versus 55.0, respectively; $p<0.01$). In addition, there was significantly lower mean antibiotic consumption in the OM-85 group compared with the placebo group (2.46 courses versus 4.46, respectively; $p<0.001$).⁴⁹

Acute otitis media (AOM), tonsillitis, and rhinosinusitis are considered the archetypal ear, nose, and throat (ENT) conditions of childhood. OM-85 has been shown to reduce AOM by 68% ($p<0.001$) and 78% ($p<0.01$) in two randomised trials over 6 and 12 months, respectively (ages 6–13 years, N=200; ages 1–12 years, N=37, respectively).^{47,49} In a 5-year retrospective study of acute tonsillitis (ages 1–15 years; N=177), 51.2% of patients achieved a $>50\%$ reduction in acute episodes and 24.4% achieved a $\leq 50\%$ reduction with OM-85. In addition, none of those patients with a $>50\%$ reduction in acute episodes during follow-up required tonsillectomy, indicating that OM-85 can achieve a substantial reduction in the burden of illness for both patients and the healthcare system.⁵⁰

In a study of CRS during childhood (age 4–12 years; N=51), OM-85 was administered during the acute phase of illness followed by a prophylactic treatment phase. OM-85 achieved significant reductions in cough, nasal discharge, and nasal congestion from Day 15. Episodes of acute rhinosinusitis were reduced by 65% ($p<0.05$) and the duration of acute rhinosinusitis was also reduced (73%, $p<0.01$). Furthermore, OM-85-treated patients showed significant improvements in serum IgA values. Overall data suggest that OM-85 is both a curative and preventative treatment for CRS in the paediatric population.⁴³

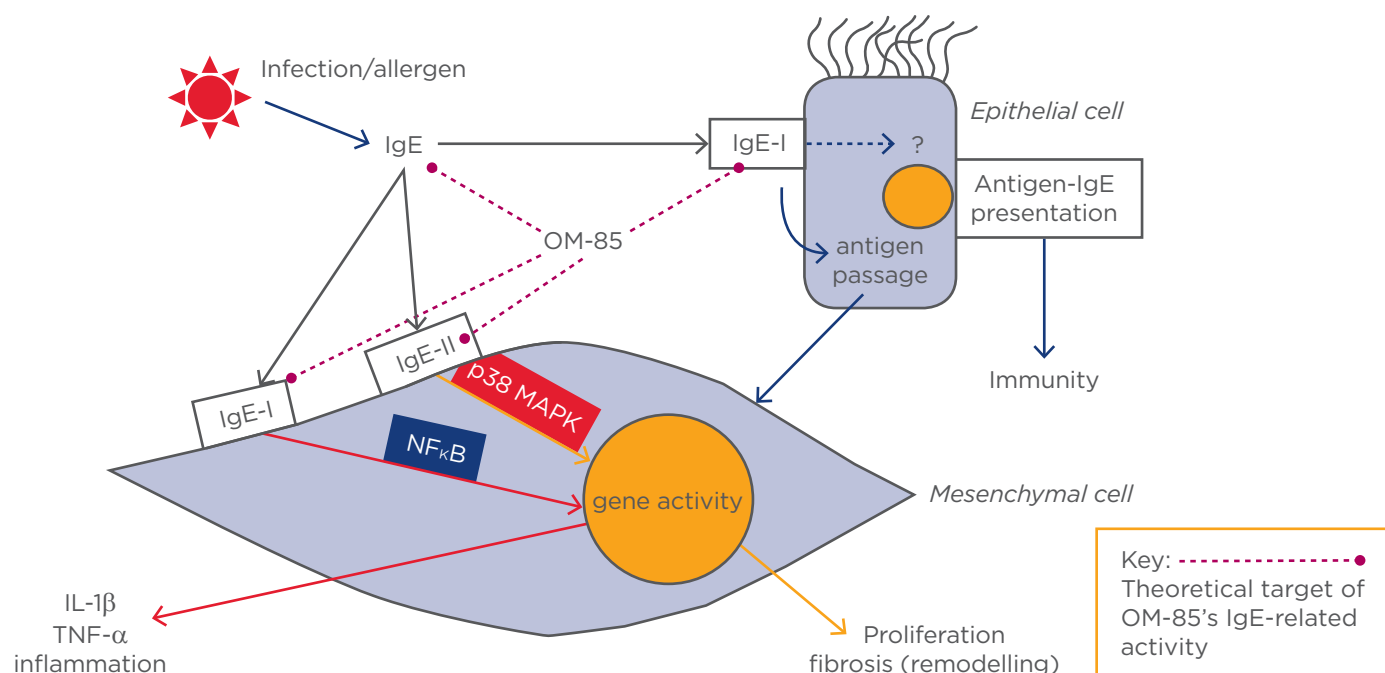


Figure 2: Theoretical mechanistic model of OM-85's effects on IgE-mediated cell activation.^{40,41}

IgE: immunoglobulin E; IL-1β: interleukin-1 beta; TNF-α: tumour necrosis factor alpha; NF_κB: nuclear factor kappa B; MAPK: mitogen-activated protein kinases.

Adapted from Palaniyandi et al.^{40,41}

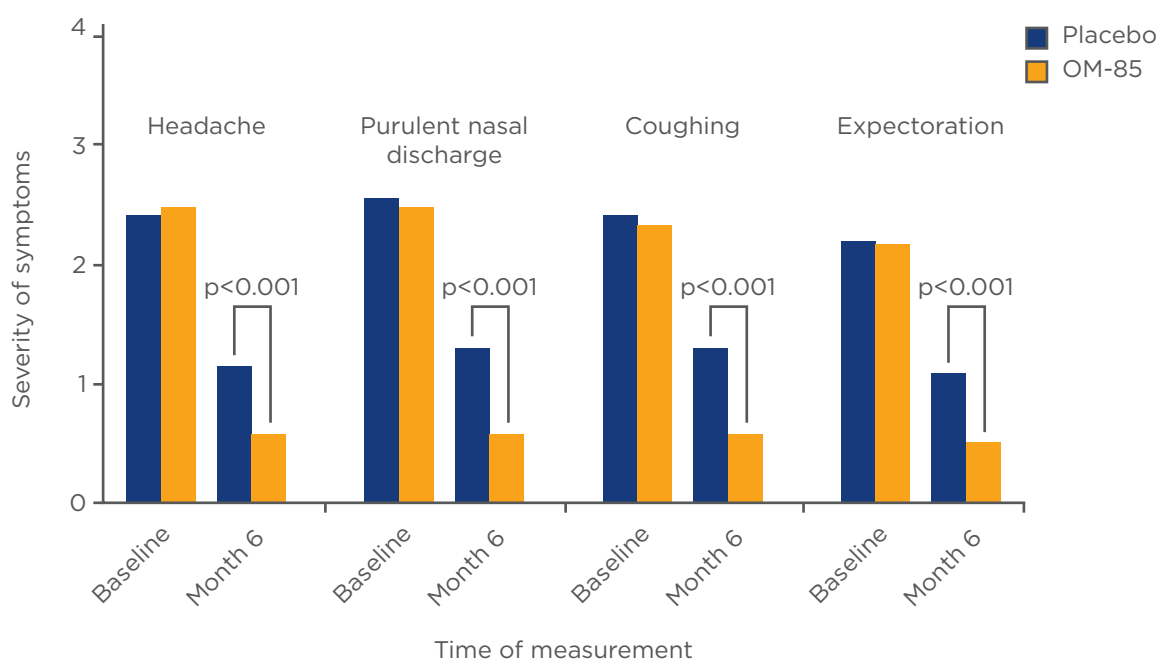


Figure 3: Symptom severity in chronic rhinosinusitis patients following OM-85 prophylaxis or placebo.⁵³

In a placebo-controlled trial of OM-85 added to amoxicillin/clavulanate therapy for subacute sinusitis (age 1.5–9 years; N=56), OM-85 therapy resulted in a faster mean time-to-improvement compared with placebo and antibiotics alone (5.5 days versus 10 days, respectively; p<0.05). In addition, fewer mean infections (1.5 versus 2.2;

p<0.05) and days of illness (14.5 versus 17.8; p<0.05) occurred in OM-85-treated patients compared with placebo-treated patients over the 6-month study. OM-85 therapy also reduced the use of antibiotics and drugs to treat symptoms, such as paracetamol and ibuprofen.⁴⁶

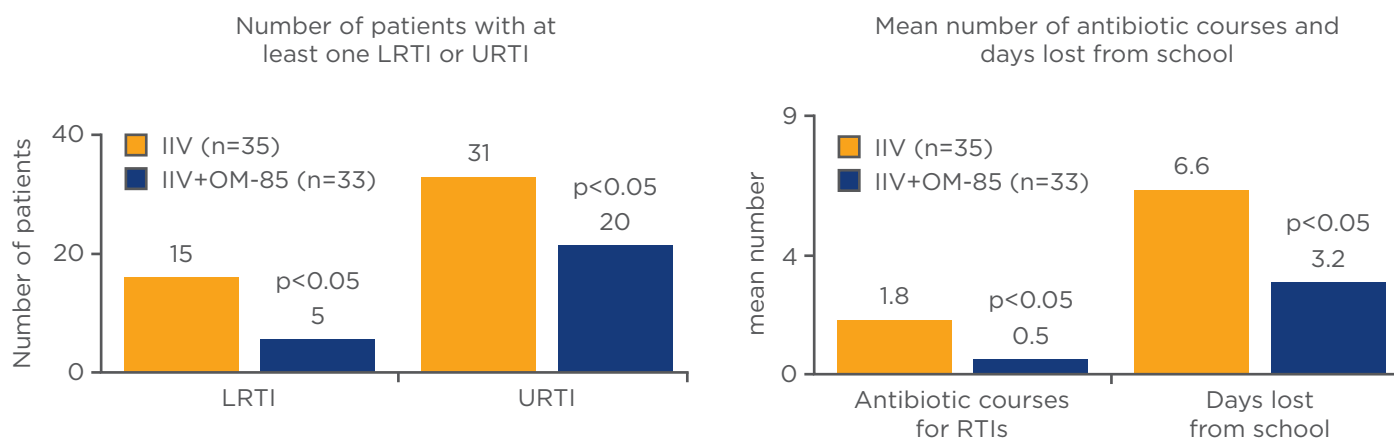


Figure 4: Combined OM-85 and inactivated influenza vaccine prophylaxis (OM-85+IVV) versus vaccine prophylaxis alone (IIV).⁵¹

LRTI: lower respiratory tract infection; URTI: upper urinary tract infection; RTIs: respiratory tract infections.

The efficacy of preventative therapy with OM-85 has also been investigated in adult patients, including those with CRS. In a 6-month placebo-controlled trial of patients >16 years of age (N=284), OM-85 achieved reductions in headache, purulent nasal discharge, coughing, and expectoration compared with placebo (Figure 3) from Month 1 onwards. In addition, OM-85 therapy resulted in a 45% reduction in the mean number of infections over 6 months and a 65% reduction in opaque sinuses, compared with placebo.⁵³ Based on this evidence, the 2012 European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) recommended OM-85 therapy be considered as an adjunct to standard therapy in adults with CRS and without nasal polyps, with an evidence Level Ib and Grade of recommendation A.⁵⁴

Persistent wheezing is an important issue in the paediatric population, and patients frequently present with both upper and lower RTIs. Preventative therapy using a 3 month course of OM-85 (10 days/month) in children (aged 1–6 years, N=75) suffering recurrent wheezing (≥3 episodes in 6 months) was assessed over 12 months. Patients treated with OM-85 achieved a significant reduction in wheezing beginning immediately after therapy (–30.4%; $p=0.013$) and persisting until the end of the study (–37.9%; $p<0.001$) compared with placebo. OM-85 therapy also reduced RTIs (–31.4%; $p<0.001$) and nasopharyngitis (–37.5%; $p<0.001$) to a similar extent over the 12 month study.²⁶

As noted previously, vaccination is an important prophylactic strategy against RRTI. A recent study

investigated the use of a combined preventative strategy with inactivated influenza vaccination and OM-85 (3 months, 10 days/month) in 68 children aged 36–59 months suffering RRTI (≥6 acute events/year). Combined prophylaxis achieved a significant reduction in both upper (–35%; $p<0.05$) and lower RTIs (–67%; $p<0.05$), as well as reductions in antibiotic use (–72%; $p<0.05$) and absenteeism (–52%; $p<0.05$), compared with influenza vaccination alone (Figure 4). The presence of differences in humoral and cellular immune response was also investigated, however, no between-group differences were found, indicating that there was no interference with vaccine antibody titres.⁵¹

SAFETY OF OM-85 IN RECURRENT RESPIRATORY TRACT INFECTION

OM-85 has shown good tolerability throughout individual studies.^{26,43–51,53} These individual study results are confirmed in the systematic review by Schaad and the Cochrane meta-analysis where adverse events were found to be mild and transient.^{48,52} OM-85 has 35 years of post-marketing surveillance data covering in excess of 94 million patients. Spontaneously reported adverse events from this expansive treated population again reflect a good tolerability profile. Adverse events were mild and gastrointestinal complaints, cough, and rash were the most common adverse drug reactions.

Another key aspect of prophylactic treatment is targeting the patient group that could benefit most from treatment with OM-85. The greatest effect is

likely to be achieved in those with immunological immaturity with the ideal time period of treatment directed towards high-risk events such as entrance to daycare.

COST EFFECTIVENESS OF OM-85

The above data make it clear that OM-85 is an effective prophylactic for patients at risk of RRTI. However, it is important to prove the cost effectiveness of prophylactic therapy, particularly when prescribing to patients who are at risk of a condition but not suffering from ongoing chronic disease. A recently published Italian pharmacoeconomic study using efficacy data from the Cochrane analysis demonstrated that the cost of treatment/patient was €20.40 for one cycle. Taking into account all-cost consequences the difference was of €1.29/month for each patient. However, this was more than balanced by community and healthcare service savings of €6.72/month and €30.50/month.⁵⁵

CONCLUSION

To conclude, when physicians act to reduce RRTI the first steps are to educate patients regarding risk factors, consider active immunisation, and utilise non-specific interventions with the aim of reducing overuse of antibiotics. The use of OM-85 is particularly effective in highly susceptible paediatric patients who are exposed to multiple risk factors for infection. In this group, OM-85 prophylaxis has been demonstrated to reduce the number, severity, and duration of RTIs; reduce antibiotic consumption; and reduce absenteeism from school and, as a consequence, of parents from work. The previously mentioned data demonstrate the efficacy of OM-85 in specific paediatric ENT conditions including recurrent tonsillitis, virus-induced rhinopharyngitis, and associated wheezing, as well as in CRS in adults. Furthermore, OM-85 demonstrated comparable tolerability to placebo. Further work investigating OM-85's efficacy is ongoing.

REFERENCES

- Gruppo di studio di Immunologia della società Italiana di Pediatria. [Le infezioni ricorrenti nel bambino: definizione ed approccio diagnostic]. Riv Immunol Allergol Pediatrica. 1988;2:127-34.
- Wheeler JG. Evaluating the child with recurrent infections - includes patient information sheet. 1996. Available at: http://www.drplace.com/Evaluating_the_child_with_recurrent_infections_-_includes_patient_information_sheet.16.22381.htm. Last accessed: 29 March 2016.
- Savitha MR et al. Modifiable risk factors for acute lower respiratory tract infections. Indian J Pediatr. 2007;74(5):477-82.
- Jesenak M et al. Recurrent respiratory infections in children - definition, diagnostic approach, treatment and prevention. 2011. Available at: <http://www.intechopen.com/books/bronchitis/recurrent-respiratory-infections-in-children-definition-diagnostic-approach-treatment-and-prevention>. Last accessed: 29 March 2016.
- Esposito S et al. Circulation of different rhinovirus groups among children with lower respiratory tract infection in Kiremba, Burundi. Eur J Clin Microbiol Infect Dis. 2012;31(11):3251-6.
- Hament JM et al. Respiratory viral infection predisposing for bacterial disease: a concise review. FEMS Immunol Med Microbiol. 1999;26(3-4):189-95.
- Johnston SL et al. The relationship between upper respiratory infections and hospital admissions for asthma: a time-trend analysis. Am J Respir Crit Care Med. 1996;154(3 Pt 1):654-60.
- Center for Disease Control and Prevention. Seasonal influenza vaccination resources for health professionals. Available at: <http://www.cdc.gov/flu/professionals/vaccination/>. Last accessed: 29 March 2016.
- Rapola S. National immunization program in Finland. Int J Circumpolar Health. 2007;66(5):382-9.
- Reichert TA et al. The Japanese experience with vaccinating schoolchildren against influenza. N Engl J Med. 2001;344(12):889-96.
- Pasquali C et al. Enhanced mucosal antibody production and protection against respiratory infections following an orally administered bacterial extract. Front Med. 2014;1:41.
- IMS sales data, 2015. Available at: <http://www.imshealth.com/>. Last accessed: 25 April 2016.
- Kearney SC et al. Immunoregulatory and immunostimulatory responses of bacterial lysates in respiratory infections and asthma. Ann Allergy Asthma Immunol. 2015;114(5):364-9.
- De Benedetto F, Sevieri G. Prevention of respiratory tract infections with bacterial lysate OM-85 bronchomunal in children and adults: a state of the art. Multidiscip Respir Med. 2013;8(1):33.
- Bessler WG, "The bacterial extract Broncho-Vaxom protects against respiratory infections - in vivo and in vitro studies," Mendez-Vilas A (ed.), Microbial pathogens and strategies for combating them: science, technology and education (2013) volume 3, Badajoz: Formatex Research Center, pp.1934-40.
- Mabbott NA et al. Microfold (M) cells: important immunosurveillance posts in the intestinal epithelium. Mucosal Immunol. 2013;6(4):666-77.
- Parola C et al. Selective activation of human dendritic cells by OM-85 through a NF- κ B and MAPK dependent pathway. PLoS One. 2013;8(12):e82867.
- Durham AL et al. Targeted anti-inflammatory therapeutics in asthma and chronic obstructive lung disease. Transl Res. 2016;167(1):192-203.
- Chung KF. Targeting the interleukin pathway in the treatment of asthma. Lancet. 2015;386(9998):1086-96.
- Beasley R et al. Risk factors for asthma: is prevention possible? Lancet. 2015;386(9998):1075-85.
- Luan H et al. OM85-BV induced the productions of IL-1 β , IL-6, and TNF- α via TLR4- and TLR2-mediated ERK1/2/NF- κ B pathway in RAW264.7 cells. J Interferon Cytokine Res. 2014;34(7):526-36.
- Schaad UB. OM-85 BV, an immunostimulant in pediatric recurrent

respiratory tract infections: a systematic review. *World J Pediatr.* 2010;6(1):5-12.

23. Sprenkle MD et al. Clinical efficacy of OM-85 BV in COPD and chronic bronchitis: a systematic review. *COPD.* 2005;2(1):167-75.

24. Navarro S et al. The oral administration of bacterial extracts prevents asthma via the recruitment of regulatory T cells to the airways. *Mucosal Immunol.* 2011;4(1): 53-65.

25. Steurer-Stey C et al. Oral purified bacterial extracts in acute respiratory tract infections in childhood: a systematic quantitative review. *Eur J Pediatr.* 2007;166(4):365-76.

26. Razi CH et al. The immunostimulant OM-85 BV prevents wheezing attacks in preschool children. *J Allergy Clin Immunol.* 2010;126(4):763-9.

27. Han L et al. A bacterial extract of OM-85 Broncho-Vaxom prevents allergic rhinitis in mice. *Am J Rhinol Allergy.* 2014;28(2):110-6.

28. Huber M et al. Th1-orientated immunological properties of the bacterial extract OM-85-BV. *Eur J Med Res.* 2005;10(5):209-17.

29. Redhu NS et al. IgE induces transcriptional regulation of thymic stromal lymphopoietin in human airway smooth muscle cells. *J Allergy Clin Immunol.* 2011;128(4):892-96.

30. Redhu NS et al. IgE induces proliferation in human airway smooth muscle cells: role of MAPK and STAT3 pathways. *Allergy Asthma Clin Immunol.* 2013;9(1):41.

31. Roth M et al. The role of IgE-receptors in IgE-dependent airway smooth muscle cell remodelling. *PLoS One.* 2013;8(2):e56015.

32. Roth M et al. Serum IgE Induced Airway Smooth Muscle Cell Remodeling Is Independent of Allergens and Is Prevented by Omalizumab. *PLoS One.* 2015;10(9):e0136549.

33. Ahrens B et al. Oral administration of bacterial lysates attenuates experimental food allergy. *Int Arch Allergy Immunol.* 2011;156(2):196-204.

34. Emmerich B et al. Local immunity in patients with chronic bronchitis and the effects of a bacterial extract, Broncho-Vaxom, on T lymphocytes, macrophages, gamma-interferon and secretory immunoglobulin A in bronchoalveolar

lavage fluid and other variables. *Respiration.* 1990;57(2):90-9.

35. Weiss S, Fux T. [Effect of Broncho-Vaxom on serum IgE and IgG levels in patients with bronchial asthma and chronic obstructive lung disease. A placebo-controlled double-blind study]. *Schweiz Med Wochenschr.* 1987;117(39):1514-8.

36. Kasakura K et al. Commensal bacteria directly suppress in vitro degranulation of mast cells in a MyD88-independent manner. *Biosci Biotechnol Biochem.* 2014;78(10):1669-76.

37. Vo TS et al. The role of peptides derived from *Spirulina maxima* in downregulation of FcεRI-mediated allergic responses. *Mol Nutr Food Res.* 2014;58(11):2226-34.

38. Campbell AM et al. Expression of the high-affinity receptor for IgE on bronchial epithelial cells of asthmatics. *Am J Respir Cell Mol Biol.* 1998;19(1):92-7.

39. Gounni AS et al. Human airway smooth muscle cells express the high affinity receptor for IgE (Fc epsilon RI): a critical role of Fc epsilon RI in human airway smooth muscle cell function. *J Immunol.* 2005;175(4):2613-21.

40. Palaniyandi S et al. Inhibition of CD23-mediated IgE transcytosis suppresses the initiation and development of allergic airway inflammation. *Mucosal Immunol.* 2015;8(6):1262-74.

41. Palaniyandi S et al. CD23-Dependent Transcytosis of IgE and Immune Complex across the Polarized Human Respiratory Epithelial Cells. *J Immunol.* 2011;186(6):3484-96.

42. Roth M, Tamm M. The effects of omalizumab on IgE-induced cytokine synthesis by asthmatic airway smooth muscle cells. *Ann Allergy Asthma Immunol.* 2010;104(2):152-60.

43. Zagar S, Löfler-Badzek D. Broncho-Vaxom in children with rhinosinusitis: a double-blind clinical trial. *ORL J Otorhinolaryngol Relat Spec.* 1988;50(6):397-404.

44. Paupe J. Immunotherapy with an oral bacterial extract (OM-85 BV) for upper respiratory infections. *Respiration.* 1991;58(3-4):150-4.

45. Collet JP et al. Economic impact of using an immunostimulating agent to prevent severe acute exacerbations in patients with chronic obstructive pulmonary disease. *Can Respir J.*

2001;8(1):27-33.

46. Gómez Barreto D et al. [Safety and efficacy of OM-85-BV plus amoxicillin/clavulanate in the treatment of subacute sinusitis and the prevention of recurrent infections in children]. *Allergol Immunopathol (Madr).* 1998;26(1):17-22.

47. Jara-Pérez JV, Berber A. Primary prevention of acute respiratory tract infections in children using a bacterial immunostimulant: a double-masked, placebo-controlled clinical trial. *Clin Ther.* 2000;22(6):748-59.

48. Schaad UB et al.; BV-Child Study Group. Immunostimulation with OM-85 in children with recurrent infections of the upper respiratory tract: a double-blind, placebo-controlled multicenter study. *Chest.* 2002;122(6):2042-9.

49. Gutiérrez-Tarango MD, Berber A. Safety and efficacy of two courses of OM-85 BV in the prevention of respiratory tract infections in children during 12 months. *Chest.* 2001;119(6):1742-8.

50. Bitar MA, Saade R. The role of OM-85 BV (Broncho-Vaxom) in preventing recurrent acute tonsillitis in children. *Int J Pediatr Otorhinolaryngol.* 2013;77(5): 670-3.

51. Esposito S et al. Impact of a mixed bacterial lysate (OM-85 BV) on the immunogenicity, safety and tolerability of inactivated influenza vaccine in children with recurrent respiratory tract infection. *Vaccine.* 2014;32(22):2546-52.

52. Del-Rio-Navarro BE et al. Immunostimulants for preventing respiratory tract infection in children. *Evidence-Based Child Health.* 2012;7(2): 629-717.

53. Heintz B et al. Clinical efficacy of Broncho-Vaxom in adult patients with chronic purulent sinusitis--a multicentric, placebo-controlled, double-blind study. *Int J Clin Pharmacol Ther Toxicol.* 1989;27(11):530-4.

54. Fokkens WJ et al. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. A summary for otorhinolaryngologists. *Rhinology.* 2012;50(1):1-12.

55. Ravasio R. Economic analysis of the immunostimulant OM-85 for the prevention of paediatric recurrent upper respiratory tract infections. *GRHTA.* 2015;2(3):117-62.