Expert consensus on the role of OM-85 in the management of recurrent respiratory infections: A Delphi study

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ABSTRACT

Recurrent infections of upper and lower respiratory tract have an important clinical and economic impact, which can be reduced through appropriate preventive measures, including the use of immunomodulating agents, such as OM-85, which proved to be effective and safe in both adults and children. Although OM-85 can be useful for the prevention of respiratory tract infections, it is still underused in clinical practice. In order to evaluate the level of awareness of the disease burden of recurrent respiratory infections in adults and children and to assess the level of agreement on the prophylactic and therapeutic approach to the disease, including the use of immunomodulants, a Delphi study was performed. A board of six experts in the field of respiratory infections was appointed to elaborate a series of statements covering four main topics (disease, prevention, OM-85, and future strategies), which were thereafter voted by a panel of 30 experts. Results showed that prevention is unanimously recognized as the most important intervention to reduce disease burden, and the use of immunomodulation to improve the effectiveness of vaccination is gaining increasing favor among clinicians. In this respect, OM-85 is recognized as the most studied immunomodulating agent currently available, whose efficacy and safety make it a valuable tool to optimize the management of recurrent respiratory infections in both adults and children. In particular, the combined use of OM-85 and influenza vaccine was recognized as an effective and safe approach to improve the current prevention strategies in order to reduce the burden of recurrent respiratory infections.

Introduction

Respiratory tract infections (RIs) represent one of the most serious health problems all over the world. In 1998, the World Health Organization (WHO) defined RIs, either acute or recurrent, as “the forgotten pandemic.”\textsuperscript{1} RIs are the primary cause of morbidity in high-income countries (the USA, Canada, and Western Europe) and account for 20% of physician consultations, 30% of lost working days, and 75% of antibiotic prescription. The economic burden of RIs in industrialized countries is very high: for example, in the USA, 500 million episodes of non-influenza RIs have occurred yearly between 2000 and 2002, with a cost of about 40 billion USD/year, including both direct (17 billions/year) and indirect (22.5 billions/year) costs.\textsuperscript{2}

In the adult population, RIs consist primarily of acute exacerbations of chronic bronchitis or chronic obstructive pulmonary disease (COPD), as well as of recurrent respiratory infections (RRI).\textsuperscript{3} RRI can affect upper or lower respiratory tract and can be caused by a wide range of microorganisms: the primary cause of the infections is generally a virus (influenza and parainfluenza virus, adenovirus, or rhinovirus), whereas recurrent episodes are often caused by bacterial agents (\textit{Acinetobacter} spp., \textit{Chlamydia pneumoniae}, \textit{Enterobacteriaceae}, \textit{Haemophilus influenzae}, \textit{Legionella pneumophila}, \textit{Moraxella catarrhalis}, \textit{Mycoplasma pneumoniae}, \textit{Nocardia asteroides}, \textit{Pasteurella multocida}, \textit{Pseudomonas aeruginosa}, \textit{Staphylococcus aureus}, \textit{Stenotrophomonas maltophilia}, \textit{Streptococcus pneumoniae}, or \textit{Streptococcus pyogenes}).\textsuperscript{3}

Large evidences from epidemiological studies show that RIs are the main cause of mortality and morbidity in children. Up to 25% of children aged <1 y and about 18% of those aged 1–4 y develop RRI in industrialized countries, with an incidence of 3–8 episodes/year, although 10–15% of children develop up to 12 infections/year.\textsuperscript{4} In developing countries, RRI caused 1.9 million deaths among children in the year 2000, 70% of which were in Africa and South-East Asia.\textsuperscript{5} Upper respiratory tract infections, including rhinitis, pharyngotonsillitis, laryngitis, and acute otitis media, represent about 90% of all infections.\textsuperscript{4} At least 80% of RIs in children are caused by viruses (rhinovirus, respiratory syncytial virus, adenovirus, or influenza virus).\textsuperscript{5} Several studies demonstrated that RIs in pediatric patients are more frequent in the presence of risk factors, such as tobacco smoke exposure, environmental...
pollution, lack of breast feeding, and daily care attendance. The role of these predisposing factors was confirmed by the protective effect exerted by the restrictive measures imposed by the pandemic situation: a recent Italian study reported a reduction of the need for previously prescribed tonsillectomy interventions as a consequence of a disease improvement associated with a lower stimulation by infectious agents. RRs in children are responsible for most days of absence for illness from school and have a huge social and economic impact, caused by a higher number of medical consultations, healthcare costs, and absence of parents from work. Moreover, RRs are associated with decline in pulmonary function, antibiotic overuse, and quality of life (QoL) impairment, both for patients and their families. A study performed on 420 children aged 2–4 y showed that children with RRs have a worse functioning compared with healthy mates in terms of physical fitness, emotional development, and school performance. Another negative consequence of RRs in children is antibiotic overuse, with related adverse effects (i.e., development of antibiotic resistance and microbiota alteration). Similarly, RRs cause an increase in corticosteroid (systemic or inhaled) use in children with post-viral wheezing, which however proved to be ineffective in modifying the clinical course of the disease and its progression toward asthma.

The currently recommended strategy to limit the burden of RRs is the elimination of environmental triggering factors (which is actually not feasible) and the systematic use of available vaccines. The number of effective vaccines against respiratory pathogens has increased in recent years, and most of them are recommended in both adults and children based on the positive results of several clinical trials evaluating their efficacy and safety in preventing RRs. In particular, the use of vaccines against influenza, pneumococcus, pertussis, and measles proved to be crucial to reduce the burden of RRs, and they are currently included in the vaccination plans of most countries worldwide (with different indications in individual countries). Conversely, the use of antibiotics to prevent and treat RRs is inappropriate, considering their prevalent viral etiology, and should be discouraged. However, the still insufficient vaccination coverage, the partial efficacy of vaccines in children, and the progressive increase in MDR bacteria require new therapeutic and preventive approaches that need to be both effective and safe. Too much attention is often paid to symptom relief, whereas a stronger effort is needed to optimize preventive approaches in order to limit disease burden and avoid antibiotic overuse.

An additional preventive measure against RRs may be a broader use of immunomodulating agents, which proved to be effective in both adults and children. Among the immunomodulating agents, only OM-85 has a sufficient body of evidence supporting its routine clinical use. OM-85 is a lysate of 21 strains of bacterial pathogens derived from the 8 major species and subspecies that are a common cause of RRs (Haemophilus influenzae, Streptococcus pneumoniae, Klebsiella pneumoniae, Klebsiella ozaenae, Staphylococcus aureus, Streptococcus pyogenes Streptococcus sanguinis, and Moraxella catarrhalis). Several studies have demonstrated that OM-85 can act on both innate and adaptive immunity, thereby inducing dendritic cell maturation in gastrointestinal Peyer’s patches, resulting in the increase of the immune defenses also in the lung mucosa. In addition to defending against viral and bacterial infections, OM-85 treatment was shown to control inflammation and also reduce tissue damage in the presence of chronic inflammatory conditions, such as chronic rhinosinusitis, through the reduction in pro-inflammatory cytokines (e.g., IL-1β) and the increase in anti-inflammatory cytokines (e.g., IL-10). Through these actions, OM-85 exerts a modulating effect, which induces a pre-activation of the immune system, warranting an early protection against infectious agents, as well as a control of the inflammatory state, through the balanced release of anti-inflammatory cytokines and factors. Nonspecific immune modulation obtained with OM-85 bacterial lysate amplifies natural defenses against infections and reduces respiratory tract inflammation induced by infections and allergens, thereby representing a possible strategy for the management of recurrent respiratory infections in at-risk individuals. Since RRs are caused by both viruses and bacteria, the combined action of OM-85 against both types of microorganisms can explain its efficacy in the prevention of RRs. OM-85 is the most studied immunomodulating agent for infection prevention. The first important randomized, double-blind, placebo-controlled study performed in 396 patients with chronic bronchitis demonstrated a 28% reduction in RRs in patients treated with OM-85 (p < .05), associated with a reduction in antibiotic prescriptions (p < .05), and no increase in adverse events. In another randomized, double-blind, placebo-controlled 6-month study performed in 381 patients with severe COPD and a long smoking history, OM-85 induced a 55% reduction in the number of hospitalization days for respiratory diseases vs. placebo (p = .037). In a subsequent randomized, double-blind, placebo-controlled trial performed in 273 patients aged >40 y with recently diagnosed chronic bronchitis or COPD and current exacerbation, exacerbation rate was reduced by 29% with OM-85 vs. placebo (0.61 vs. 0.86, respectively; p = .03). Such reduction was more pronounced in patients who were smokers or ex-smokers, showing a 40% lower mean rate of exacerbation vs. placebo (0.62 vs. 1.04, respectively; p < .01). No serious drug-related adverse event was recorded, as well as abnormalities in laboratory parameters. A more recent study demonstrated the ability of OM-85 to protect COPD patients from exacerbations by significantly reducing the percentage of patients with exacerbations after 12 weeks of treatment and maintaining its beneficial effect until 22 weeks, with a positive tolerability profile. Based on the available evidences, the use of OM-85 was recognized by various scientific societies as a valuable tool to prevent RRs: the European Rhinologic Society (ERS) recommended the use of OM-85 to treat chronic rhinosinusitis, in association with standard medical therapy, whereas the 2021 GOLD guidelines for the management of COPD cited two studies performed with OM-85 in COPD patients, showing that the use of immunomodulators in the management of COPD induces a reduction in number and severity of exacerbations.
Thanks to its long-term efficacy and good safety profile, OM-85 can be recommended as first-choice prophylactic treatment also for the prevention of respiratory tract infections in children, especially those with high risk of recurrence, since the protective effect of OM-85 was shown to be proportional to the number of RIs, being highest in younger children (<6 y). The use of OM-85 for 10 consecutive days every month for 3 months was shown to be able to reduce the risk of RRs in children, with a favorable safety profile. The protective effect was highest in children with highest risk, suggesting that OM-85 administration might be particularly useful and should be recommended in these subjects. The use of OM-85 was effective in reducing the incidence of RRs also after a second year of treatment, confirming that a second yearly course of lysozyme administration can be useful to maintain protection, particularly when the diagnosis of RRs is made in younger children, for whom it is likely that definitive maturation of the immune system still requires a long time. Based on the available evidences, a recent consensus statement of the World Association of Infectious Diseases and Immunological Disorders (WAidid) stated that OM-85 should be recommended for the prevention of RRs in high-risk children starting from 6 months of age, although further studies on detection of biomarkers able to support the identification of best responder profile and a precise host-tailored medicine are needed. Since the currently available preventive measures are not fully effective in reducing the incidence of RRs in both adults and children when used individually, their combined use may be useful to reduce disease burden and avoid antibiotic overuse. A prospective, randomized, single blind study, performed in 68 children aged 36–59 months treated with OM-85 for 3 months with 10-d cycles and receiving influenza vaccine 15 d after the first cycle, demonstrated a more pronounced reduction of upper and lower respiratory tract infections. Moreover, a reduction of antibiotic use and of the number of missed school-days was recorded, with no interference of OM85 on the immune response against the influenza vaccine and no increase of adverse events. These results support the efficacy and safety of such approach to reduce the impact of RRs in the pediatric population. The safety of the combined use of OM-85 and influenza vaccine was confirmed also by two subsequent studies in the long term (2 y): in these studies, the combined administration of OM-85 and influenza vaccine was well tolerated and was not associated with any increase in local or systemic adverse events or occurrence of severe adverse events. These evidences support the contemporary administration of OM-85 and influenza vaccine to optimize the efficacy of preventive strategies for RRs in the pediatric population.

Aims

The aim of the present study was to evaluate the level of awareness of the disease burden of RRs in adults and children and to assess the level of agreement on the prophylactic and therapeutic approach to the disease in order to define expert recommendations which, in the absence of specific treatment guidelines, may be of use for physicians in everyday clinical practice to optimize treatment and possibly improve outcomes. In this respect, the aim of the study was also to define possible strategies based on the combined use of OM-85 and currently available vaccines, which might maximize protection against RRs in the current pandemic situation.

Methods

A Delphi method was used to reach the abovementioned aims. It represents an indirect, anonymous, iterative process aimed at achieving consensus among experts on specific topics, especially regarding disease management and drug therapy.

A board of six experts in the field of respiratory tract infections (one pediatrician, two otolaryngologists, one pneumologist, one allergologist, and one general practitioner) was appointed as a scientific committee in charge of designing and supervising the study.

A panel of 30 experts in the field of respiratory tract infections (pediatrics, allergology, pneumology, otolaryngology, and primary care) was thereafter selected by the board, on the basis of their skills in research and/or clinical experience, as members of the voting panel.

A total of 40 statements were elaborated and shared by the scientific committee, covering four main topics identified on the basis of clinical experience and available literature: (i) Disease (burden of disease in the adult and pediatric populations); (ii) Prevention (current strategies and unmet needs); (iii) OM-85 (mechanism of action, efficacy and safety in the adult and pediatric populations, and rationale for its use in clinical practice); (iv) Future strategies (combined use of OM-85 and vaccines and possible vaccination schedules).

Statements were uploaded to a dedicated online platform to be voted by the panel of experts using a 5-point Likert scale (from 1 = complete disagreement to 5 = complete agreement). Median (SD) of the achieved agreement was calculated for each statement. According to the most frequently adopted Delphi method, the definition of consensus was set at least 75% agreement for 4 + 5 scores.

Results

A total of 24 out of 30 members of the expert panel (80%) participated to the voting phase. By applying the predefined criteria for the definition of consensus (at least 75% agreement for 4 + 5 scores), 31 out of the 40 proposed statements reached consensus after the first round of voting. No further rounds were performed.

Results for individual statements reaching or not reaching consensus are reported in Tables 1 and 2, respectively. Consensus was reached by 8 out of 11 (73%) statements regarding disease burden, 6 out of 6 (100%) statements regarding prevention, 14 out of 19 (74%) statements regarding OM-85, and 3 out of 4 (75%) statements regarding future strategies.

Among statements on disease, 3 out of 8 statements reaching consensus recorded 100% agreement (statements 4, 8 and 11), 3 recorded agreement ≥92%, and 2 ≥83 (Table 1). A lack of
Table 1. Statements reaching consensus during the first round of voting.

| Statement | Disease | % agreement (scores 4 + 5) | Mean score (SD) |
|-----------|---------|----------------------------|-----------------|
| 1. Acute respiratory infections are the primary cause of morbidity in high-income countries (the USA, Canada, and Western Europe). | | 88 | 4.0 (0.9) |
| 2. Respiratory tract infections are the most frequent cause of visit to the General Practitioner’s Office in autumn and winter. | | 83 | 4.4 (0.9) |
| 4. Most respiratory tract infections in children are caused by viruses (rhinovirus, respiratory syncytial virus, adenovirus, and influenza virus). | | 100 | 4.7 (0.5) |
| 5. Primary risk factors for respiratory tract infections in pediatric patients include tobacco smoke exposure, environmental pollution, no breast feeding, and daily care attendance. | | 96 | 4.6 (0.6) |
| 6. Recurrent respiratory tract infections have a huge social and economic impact, caused by a higher number of medical consultations, health-care costs, school absenteeism, and absence of parents from work. | | 96 | 4.6 (0.6) |
| 7. Recurrent respiratory tract infections are associated with decline in pulmonary function, antibiotic overuse, and quality of life impairment, both for patients and their families. | | 92 | 4.3 (0.6) |
| 8. Recurrent respiratory tract infections cause an increase in corticoid (systemic or inhaled) use in children with post-viral wheezing. | | 100 | 4.5 (0.5) |
| 11. A significant reduction in the number of recurrent respiratory tract infections is an important therapeutic target to reduce the social and economic burden of the disease, as well as to improve the QoL of children and their families and to limit the risk to develop chronic diseases with recurrent exacerbations. | | 100 | 4.6 (0.5) |

Prevention

| Statement | Disease | % agreement (scores 4 + 5) | Mean score (SD) |
|-----------|---------|----------------------------|-----------------|
| 12. The currently recommended strategy to limit the burden of recurrent respiratory infections is the elimination of environmental triggering factors and the systematic use of available vaccines. | | 96 | 4.6 (0.6) |
| 13. The use of vaccines against influenza, pneumococcus, pertussis, and measles is crucial to reduce the burden of respiratory tract infections. | | 96 | 4.7 (0.6) |
| 14. The use of antibiotics to prevent and treat recurrent respiratory infections is inappropriate, considering their prevalent viral etiology. | | 96 | 4.6 (0.6) |
| 15. The partial efficacy of vaccines in children and the progressive increase of MDR bacteria require new therapeutic and preventive approaches, which need to be both effective and safe. | | 79 | 4.0 (0.8) |
| 16. The complete removal of environmental factors responsible for recurrent infections is actually impossible, although practices such as face masks, social distancing, and frequent handwashing during the current pandemic have reduced the incidence of recurrent respiratory infections. | | 92 | 4.5 (0.8) |
| 17. Although influenza vaccination use has increased in recent years, its coverage is still far from recommended targets in at-risk categories (75% minimum and 95% optimal). | | 92 | 4.4 (0.7) |

OM-85

| Statement | Disease | % agreement (scores 4 + 5) | Mean score (SD) |
|-----------|---------|----------------------------|-----------------|
| 18. OM-85 exerts a modulation effect which induces a pre-activation of the immune system, warranting an early protection against infectious agents, as well as a control of the inflammatory state, through the balanced release of anti-inflammatory cytokines and factors. | | 92 | 4.2 (0.6) |
| 19. OM-85 is the most studied immunomodulating agent for infection prevention. | | 92 | 4.3 (0.6) |
| 20. OM-85 was shown to be effective in reducing the number of recurrent respiratory tract infections in smokers and in patients with COPD and chronic rhinosinusitis. | | 88 | 4.3 (0.7) |
| 22. Orally administered OM-85 (10 d/month for 3 months) is effective in reducing the risk of new infections in children with recurrent respiratory infections aged 1–13 y, with a good safety and tolerability profile. | | 88 | 4.3 (0.8) |
| 23. Treatment with OM-85 reduces the frequency of recurrent upper and lower respiratory tract infections in children, with a higher protective effect in subject with an increased recurrence risk. | | 92 | 4.3 (0.8) |
| 24. In children with respiratory tract infections, treatment with OM-85 reduces the number of recurrences, the use and duration of antibiotic therapy, days of illness, and school absenteeism. | | 88 | 4.3 (0.9) |
| 25. In children with respiratory tract infections and post-viral wheezing, treatment with OM-85 reduces the number of nasopharyngitis and wheezing episodes, as well as antibiotic use over 12 months. | | 88 | 4.2 (0.8) |
| 29. OM-85 protective effect is maintained after a second yearly course of administration, with unchanged tolerability profile | | 79 | 4.0 (0.8) |
| 30. OM-85 is well tolerated and safe, and it is not associated with severe adverse events and has shown a good compliance level. | | 100 | 4.4 (0.5) |
| 31. Efficacy and safety of OM-85 have been demonstrated also in association with influenza vaccine. | | 87 | 4.2 (0.8) |
| 32. OM-85 was shown to be well tolerated and effective in reducing the number and duration of recurrent infections of upper respiratory tract (otitis, tonsillitis, and sinusitis) in children, favoring the reduction of antibiotic use, time devoted to medical treatment, and school absenteeism. | | 92 | 4.2 (0.7) |
| 34. Non-specific immunomodulation obtained with OM-85 bacterial lysate amplifies natural defenses against infections and reduces respiratory tract inflammation induced by infections and allergens, thereby representing a possible strategy for management of recurrent respiratory infections in at-risk individuals. | | 83 | 4.1 (0.8) |
| 35. OM-85 efficacy in improving the immune response against recurrent viral infections of respiratory tract in children may be particularly useful in the current COVID-19 pandemic situation. | | 75 | 3.8 (0.8) |
| 36. Thanks to its long-term efficacy and good safety profile, OM-85 can be recommended as first-choice prophylactic treatment for the prevention of respiratory tract infections in children, especially those at high risk of recurrence. | | 92 | 4.0 (0.6) |

Future strategies

| Statement | Disease | % agreement (scores 4 + 5) | Mean score (SD) |
|-----------|---------|----------------------------|-----------------|
| 37. The simultaneous administration of OM-85 and influenza vaccine does not affect the immune response against influenza virus and is not associated with increased adverse events, representing an effective and safe approach to reduce the burden of recurrent respiratory tract infections in children. | | 96 | 4.3 (0.6) |
| 39. OM-85 and influenza vaccine exert a synergistic effect on the reduction of recurrent respiratory tract infections. | | 83 | 4.0 (0.9) |
| 40. Since the incidence of new recurrences of respiratory tract infections is highest during winter and several courses of treatment with OM-85 are needed to obtain the highest protective effect, it is recommended to start OM-85 administration early in autumn, a few weeks before influenza vaccination. | | 96 | 4.4 (0.7) |
consensus was recorded for statements 3, 9, and 10, reaching 62%, 67%, and 66% agreement, respectively (Table 2). Among statements on prevention (all of which reached consensus), percent agreement ranged from 79% (statement 15) to 96% (statements 12, 13, and 14) (Table 1). Among statements on OM-85, 6 out of 14 statements reaching consensus achieved agreement ≥92%, 6 ≥83%, and 2 ≥75% (Table 1). A lack of consensus was recorded for statements 21, 27, 28, and 33, whose agreement ranged from 62% to 67% (Table 2). Among statements on future strategies, two out of three statements reaching consensus achieved agreement ≥96% and 1 ≥83% (Table 1). A lack of consensus was recorded for statement 38, reaching 71% agreement (Table 2).

## Discussion

Most of the proposed statements reached consensus in the first round of the Delphi survey (Table 1), suggesting a generally homogeneous approach to RRI management among involved clinicians.

In particular, most statements regarding disease issues (statements 1–11) achieved a very high level of consensus (percent agreement 88–100%) (Table 1), suggesting a high level of awareness on the clinical and socio-economic impact of RRIs in both adults and children. In particular, a full (100%) consensus was reached for statements 4 and 8, regarding the mostly viral etiology of RRIs, and the associated risk of increased corticoid use, which however is inappropriate, being ineffective in modifying the clinical course of the disease, while causing well-known sideeffects. A full consensus was also reached for statement 11, regarding the awareness that a significant reduction in the number of RRIs is an important therapeutic target, to reduce the social and economic burden of the disease, as well as to improve the QoL of children and their families and to limit the risk to develop chronic diseases with recurrent exacerbations. Indeed, occurrence of RRIs early in childhood is an important risk factor for the development of asthma later in life. The lack of agreement observed for a few statements regarding the disease burden (statements 3, 9, and 10) (Table 2) suggests a not fully achieved awareness of the important implications of RRIs for affected patients, in terms of mortality, morbidity, and adverse events associated with inappropriate treatment (percent agreement 62%, 67%, and 66%, respectively).

All statements on prevention (statements 12–17) reached consensus (percent agreement 92–96%) (Table 1), suggesting that advantages and limits of currently available preventive measures are well known and widely shared by clinicians. In particular, it is well known that the complete removal of environmental factors responsible for recurrent infections is actually impossible, although practices such as face masks, social distancing, and frequent handwashing during the current pandemic have reduced the incidence of RRIs. Moreover, as far as vaccination is concerned, currently available vaccines are only partially effective: influenza vaccines are effective in 80% of vaccinated children, and currently available antipneumococcus vaccines protect against 13 serotypes, whereas pathogenic serotypes are more than 90. As far as pertussis vaccine is concerned, the use of the acellular preparation does not induce any immune response at the mucosal level, favoring persistent colonization and pathogen transmission. Protective immunity seems to vanish a few years after vaccination, which could explain the increase in pertussis incidence recorded in Europe since 2011 and the need of booster doses throughout life. In the case of measles vaccine, although mandatory vaccination was introduced in most countries almost 20 y ago, vaccination coverage is still poor in Europe, as documented by the frequent development of several infection foci (over 1,500 cases in 17 countries have been reported in 2019). Although vaccination is considered an effective approach to
the prevention of infectious diseases, vaccination coverage showed a decrease between 2013 and 2016, far below the recommended 95% cut off considered by the WHO as the optimal coverage to limit the circulation of microorganisms in the community and obtain the so-called herd immunity.\textsuperscript{31} Vaccination coverage showed a new increase in 2017, and this trend was confirmed in 2018, with 95% coverage for pertussis vaccine, 93% for pneumococcus, and 92% for measles. Vaccination coverage for influenza is still limited, having reached 17% during the 2019–2020 season, with a higher percentage (55%) recorded in the elderly population.\textsuperscript{31} However, during the current pandemic, a decrease in vaccination coverage was observed almost everywhere.\textsuperscript{32,33} In order to significantly reduce influenza morbidity, complications, and mortality, further efforts are needed to meet the WHO recommendations (confirmed by the National Vaccine Prevention Plan) of 75% coverage as the minimum and 95% as the optimal target in at-risk patients and in subjects aged >65 y.\textsuperscript{31} On the other hand, antibiotics are becoming less effective in recent years, as a consequence of excessive and inappropriate use causing the development of resistance by common respiratory pathogens.\textsuperscript{3}

Also for statements on OM-85 (statements 18–36), a high level of consensus was achieved for most issues (percent agreement 75–100\%\textsuperscript{47}) (Table 1), confirming that its mechanism of action and the potential benefits of its use in association with vaccination are well known by clinicians: this makes the implementation of more effective preventive measures based on OM-85 use feasible in the near future, both in adults and children. The complete agreement (100\%) achieved for statement 30, regarding the efficacy and tolerability of OM-85, suggests a high level of confidence by clinicians with the use of this immunomodulating agent, supported by available evidences. In several studies, OM-85 proved to be effective in reducing the number and duration of RRIs,\textsuperscript{34} limiting school and work absenteeism,\textsuperscript{35} and showed a favorable safety profile, with mild and transient adverse events, which can be easily managed.\textsuperscript{17} The reduced use of antibiotic is a further benefit of OM-85, warranting its use in the management of RRIs.\textsuperscript{3}

A high level of agreement (92\%) was achieved for statements 23 and 36, regarding the efficacy of OM-85 in reducing the frequency of recurrent upper and lower respiratory tract infections in children, with a higher protective effect in subjects with an increased recurrence risk. This reflects available evidences: several clinical trials have evaluated whether immunomodulation through OM-85 administration could reduce the risk of new infectious episodes in children with RRIs, without causing adverse effects.\textsuperscript{17} Oral administration of OM-85 for 3 months (10 d/month) was shown to be effective in reducing RRIs in high-risk children, with a good tolerability profile.\textsuperscript{6} In a randomized, double-blind placebo-controlled study performed in patients aged 6–13 y with ≥3 acute episodes of RRIs in the 6 months before enrollment, treatment with OM-85 for 6 months induced a 52\% reduction in the number of infections vs. placebo. Moreover, OM-85 use was associated with a reduction in antibiotic use, days of illness, and school absenteeism (p < .001), with no increase in adverse events.\textsuperscript{35} A randomized, double-blind placebo-controlled study performed in 75 pre-school children with a history of frequent wheezing episodes (≥3 events in the previous 6 months) demonstrated that a single OM-85 course reduced by 38\% both rhinopharyngitis and wheezing episodes over 12 months, with a significant reduction in the cumulative frequency of wheezing episodes vs. placebo (−22.4 d/y; p < .001) and in the percentage of patients using antibiotics (−44\%).\textsuperscript{36} In patients aged 1–12 y (n = 54), with a high number of exacerbations in the previous 12 months, administration of two courses (with a 6-month interval) of OM-85 significantly reduced the median number of RRIs per patient vs. placebo (5.0 vs. 8.0; p < .001), as well as the percentage of patients without exacerbations (<6 acute episodes), with a 70\% reduction with OM-85 vs. 20\% with placebo (p < .001). Treatment with two OM-85 courses significantly reduced the median duration of exacerbation episodes vs. placebo (30.5 vs. 55.0 d, respectively; p < .001), as well as the median number of antibiotic cycles prescribed in the same period (1.5 vs. 4.0 respectively; p < .001). Safety profile was good, with a similar number of adverse events in the two groups.\textsuperscript{37} The efficacy and safety of OM-85 in patients with RRIs demonstrated in clinical trials were confirmed in clinical practice by a recent retrospective study performed in 200 children aged 3–6 y with RRIs, showing that OM-85 administration before winter significantly reduced the risk for new RRIs, limiting the number of wheezing episodes and of antibiotic cycles vs. control group.\textsuperscript{27} The protective efficacy of OM-85 was maintained also after a second course administered the next year, demonstrating its beneficial effect in particular in younger children, whose immune system is still immature, and was well tolerated, being associated with no severe adverse events.\textsuperscript{27} A systematic review including only randomized and placebo-controlled studies (n = 8) reported a lower frequency of recurrent infections of upper and lower respiratory tract in patients treated with OM-85 vs. placebo (32\% vs. 52\%, 35.5\% reduction; p < .001), with a higher protective effect in patients at higher risk for exacerbations.\textsuperscript{38} A high level of agreement was achieved also for statements 24 (88\%) and 32 (92\%), regarding the efficacy of OM-85 in reducing the number of recurrences (including infections of the upper respiratory tract, such as otitis, tonsillitis, and sinusitis), the use and duration of antibiotic therapy, as well as school-related absenteeism. In this respect, a large meta-analysis, including 4851 patients, showed a 52\% lower RI frequency in patients treated with OM-85 vs. controls. Moreover, the duration of antibiotic therapy in the OM-85 group was significantly shorter than in the control group (−42\%), as well as the duration of infection (−45\%) and of fever, cough, and dyspnea (−49\%).\textsuperscript{39} A more recent meta-analysis including 14 studies for a total of 1859 children (of whom 890 received OM-85) demonstrated that the use of OM-85 is associated with a lower frequency of RIs (−1.16; p < .001), a shorter duration of such episodes (MD, −19.51; p < .001), a lower number of antibiotic cycles (MD, −1.40; p = .03), with no increase in the frequency of adverse events (OR, 1.02; p = .94).

However, the lack of agreement regarding a few items on OM-85 demonstrates that the use of immunomodulants in adults in general and of OM-85 in particular is still not fully implemented in clinical practice, despite the available data on its
efficacy and safety. A lack of consensus was recorded in particular on the use of OM-85 in patients with chronic rhinosinusitis (statements 21 and 33, percent agreement 63% both), chronic tonsillitis (statement 27, percent agreement 63%), and ORL infections (statement 26, percent agreement 67%), which represent conditions that can potentially benefit from the use of immunomodulation (Table 2). In this respect, in a multicentric, randomized, double-blind, placebo-controlled study, OM-85 significantly reduced the number of reinnfection episodes in patients with chronic rhinosinusitis, as well as the severity of associated symptoms.\textsuperscript{10} OM-85 was shown to be effective also in the prevention of ORL infections when associated with antibiotic therapy in children with subacute sinusitis and RRs, reducing time to recovery (15.4 vs. 20.3 d; \( p < .05 \)) and number of recurrences (1.6 vs. 2.2; \(-33\%\); \( p < .05 \)).\textsuperscript{41} Further studies have assessed OM-85 effect in the prevention of acute episodes of chronic rhinosinusitis, showing that treatment with OM-85 can be used to relieve cough and nasal obstruction/congestion and secretion and reduce the time of medical care, as well as the number and duration of subsequent exacerbation.\textsuperscript{42,43} In children with recurrent tonsillitis, treatment with OM-85 reduces the number of tonsillectomies, avoiding the risks associated with such invasive procedure and related costs. A retrospective observational study performed in 131 children aged 1–15 y, with recurrent tonsillitis \( \geq 3 \) episodes/y reported a partial (reduction of tonsillitis episodes \( \leq 50\% \)) or complete (reduction of tonsillitis episodes \( > 50\% \)) response to OM-85 in 2/3 of treated subjects after a 3-month course. Such effect translated into a relevant reduction of the number of tonsillectomies.\textsuperscript{44} In this respect, it should be noted that recommendations for the use of OM-85 in ORL infections are poor and still not shared among clinicians: multidisciplinary working groups should be created in order to favor the implementation of most recent guidelines into clinical practice.

Poor consensus was recorded also for the persistence of OM-85 protective effect after the first course of administration (statement 28, percent agreement 62%) (Table 2), suggesting a still incomplete awareness on the long-term benefits of its use in the management of RRs. A recent randomized, double-blind placebo-controlled study performed in 288 children aged 1–6 y with RRs, treated with OM-85 or placebo for 3 or 6 months, demonstrated a significantly lower number of RRs with OM-85 vs. placebo, as well as a reduced number of days of absence from school of children and from work of their patients. In this study, no difference was observed in the incidence of RRs between patients treated with OM-85 for 3 or 6 months, suggesting that the protection induced by a shorter prophylactic course with OM-85 is maintained over several months after the end of treatment. Moreover, OM-85 was well tolerated and safe, with a good compliance level and was never discontinued because of occurrence of severe adverse events.\textsuperscript{14}

Finally, statements on future strategies (statements 37–40) reached a high degree of consensus (percent agreement 83–96%) (Table 1), suggesting the possibility to generate a unified approach to the prevention of RRs. In particular, the combined use of OM-85 and influenza vaccine was recognized as a an effective and safe approach to reduce the burden of recurrent respiratory tract infections in children: since the incidence of new recurrences of respiratory tract infections is highest during winter and several courses of treatment with OM-85 are needed to obtain the highest protective effect, it is recommended to start OM-85 administration early in autumn, a few weeks before influenza vaccination, so that the immune stimulation exerted by OM-85 can amplify the antibody response induced by vaccination.\textsuperscript{26} No complete consensus was reached for the possible benefits in reducing COVID-19 incidence with the combined use of OM-85 and COVID-19 vaccination (statement 38, percent agreement 71%) (Table 2), suggesting the need for more robust data supporting this possible indication. In fact, OM-85 efficacy in improving the immune response against recurrent viral infections of respiratory tract in children may be particularly useful in the current COVID-19 pandemic situation, potentially increasing the protective effect of vaccines against SARS-CoV-2.\textsuperscript{34} However, specific studies to confirm such hypothesis are needed.

The main strength of the present study derives from the fact that the list of consensus statements was derived from the existing clinical literature and formulated by a board of international experts with strong expertise in the field, warranting the scientific and clinical value of the issues addressed. Another strength lies in the diversified composition of the expert panel, including clinicians belonging to different therapeutic areas (pediatrics, allergology, pneumology, otolaryngology, and primary care), as well as in the applied method (Delphi process), warranting anonymous contributions: both aspects add value to the wide consensus recorded and contribute to the reliability of the results.

However, the present study also has limitations, mainly associated with the applied methodology: being a consensus study, the results obtained mainly reflect the current knowledge and clinical expertise of the involved clinicians, rather than adding evidences to the already wide bulk of studies performed to demonstrate the efficacy of OM-85 in improving the control and reducing the burden of the disease. The results obtained are anyway important to support clinicians in their everyday clinical practice in order to optimize treatment and possibly improve outcomes. A further criticism may derive from the fact that a single round of voting was performed; however, in line with previously published Delphi studies,\textsuperscript{45} being the achieved percentage of consensus quite high after the first round for most statements covering all the proposed issues, the contribution of further voting rounds was considered of poor relevance.

**Conclusions**

RRs are associated with a relevant mortality and morbidity risk in both adults and children, with a significant impact on QoL and health-care costs. According to the results of the present Delphi study, prevention is unanimously recognized as the most important intervention to reduce disease burden, and the use of immunomodulation to improve the effectiveness of vaccination is gaining increasing favor among clinicians. In this respect, OM-85 is recognized as the most studied immunomodulating agent currently available, whose efficacy and safety profile makes it a valuable
tool to optimize the management of RRIs in both adults and children. In particular, the combined use of OM-85 and influenza vaccine was recognized as an effective and safe approach to improve the current prevention strategies in order to reduce the burden of RRIs in children.

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