A low-dose multicomponent medication as a new approach in prevention and early add-on treatment of recurrent respiratory infections in children: a Delphi Consensus

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ABSTRACT. – OBJECTIVE: Recurrent respiratory infections (RRIs) represent a demanding challenge in pediatricians' clinical practice. A previous Inter-Society Consensus defined criteria for identifying children with RRIs and assessed the available treatments, considering the evidence grade.

MATERIALS AND METHODS: The present Delphi consensus proposed a series of statements concerning the practical use of Citomix, a multicomponent low-dose medication. The participants should be primary care, private practice, and hospital/university pediatricians with extensive experience using this product to manage children with RRIs. One hundred twelve Italian pediatricians voted for the statements.

RESULTS: The agreement grade was high for all statements (ranging from 69.6% to 99.1%). The participants expressed their satisfaction with using this medication, which may represent a valuable and safe option for preventing and adding on treating children with RRIs. These statements reflected their personal opinions based on daily clinical practice.

CONCLUSIONS: The results of this Delphi consensus represented an input for further evidence-based studies highlighting the effectiveness of low-dose medications for both the prevention and treatment of RRIs.

Key Words:
 Recurrent respiratory infections, Prevention, Treatment, Children, Low-dose multicomponent medication, Citomix.

Introduction

Recurrent Respiratory Infections (RRIs) are a common problem in childhood, as about 25% of children younger than one year and 6% of children during the first six years of life present RRIs[1-4]. The upper respiratory tract is usually more affected by infections than the lower tract, and some children can exclusively experience RRIs in this site[5].

The social and economic impact of RRIs is global, requiring frequent medical care and often resulting in the prescription of inappropriate or unvalidated treatments[6,7].

Although children experience many respiratory infections throughout childhood, clinicians have not been given clear guidance on managing recurrent conditions for decades. In 2021, an Italian Inter-Society Consensus established age-related criteria for defining RRIs, which encompass: (i) children aged 1-3 years old, with $\geq$ 6 RIs in a year or two episodes of mild pneumonia; (ii) children aged 3-6 years old, with $\geq$ 5 RIs in a year or two episodes of mild pneumonia; and (iii) children aged 6-12 years old, with $\geq$ 3 RIs in a year or two episodes of mild pneumonia[7]. Exclusion criteria include primary or secondary immunodeficiencies, cystic fibrosis (CF) and/or cystic fibrosis transmembrane conductance regulator (CFTR) protein diseases, primary ciliary

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dyskinesia (PCD), non-CF-related bronchiectasis, genetic disorders, cardio-respiratory malformations, neuromuscular disorders, preexisting chronic lung diseases, and localized RRIs, e.g., recurrent rhinosinusitis, otitis media, and pharyngotonsillitis[7].

Moreover, RRIs present typical seasonality, with the highest rate occurring between autumn and winter. Although the etiological agents are not always detected, viruses constitute the common cause of infections, and rhinoviruses, adenoviruses, metapneumovirus, bocavirus, respiratory syncytial virus (RSV), coronaviruses, and herpesvirus-6 are the most frequently isolated agents[8]. Each virus may lead to a specific clinical manifestation, e.g., RSV principally involved in bronchiolitis and rhinoviruses in the common cold[8]. Although these conditions often improve significantly by around 12 years of age, the real challenge for pediatricians is distinguishing which cases require comprehensive diagnostic evaluations and targeted treatments from those that do not[4,7].

The personal and family medical history and a careful clinical examination are usually sufficient to identify patients with suspected underlying diseases, such as CF, immunodeficiency syndromes, or congenital anomalies of the airways, who need prompt investigations[7,10]. Several risk factors may be associated with RRIs, including prematurity, early exposure to infectious agents, limited breastfeeding, living in a large family unit, immune system immaturity, exposure to parental smoking and air pollution, atopy and allergy, incorrect diet, and low socio-economic status[10-12]. Furthermore, the incidence of RRIs seems to be higher, and RIs can present a more severe clinical course in some particular populations, such as children with Down syndrome[13]. Severe infections, ineffective response to usual therapy, and isolation of atypical or opportunistic pathogens in children with recurrent infective episodes are red flags for non-benign RRIs[14].

Regarding the possible preventive treatment of RRIs, the previous Inter-Society Consensus reported that practically all used remedies had weak or strong negative recommendations[7]. Only one lysate bacterial extract and pidotimod had weak positive recommendations for selected subjects[8].

Nevertheless, many doctors use immunomodulators in real-world practice to offer a solution to parents who need help with their children's health problems. In this scenario, low-dose pharmacology might represent a new possible solution.

Low-dose pharmacology is based mainly on administering physiologically low doses of signaling molecules (cytokines, hormones, neuropeptides, and growth factors) orally[15,16]. Low-dose signaling molecules act at their physiological working range between micrograms and femtograms, i.e., from 10^{-6} to 10^{-15} M[17,18]. Low-dose cytokine activity involves specific intracellular transduction pathways and enhances the biological function of the cell, contributing to the intercellular crosstalk[17]. Their low concentration triggers receptors' activation, avoiding saturation phenomena and possible receptors' freezing[18].

Evidence[19-21] shows that oral cytokine intake can effectively modulate immune response. Because of its excellent accessibility, the oral mucosa is a potential elective interface for the administration of active molecules, mainly of a peptidic nature[22]. The mechanism of action for orally administered peptides involves the antigen-presenting cells (APCs) at the oral mucosal epithelium level. Signaling molecules are detected by APCs directly in the oral mucosa and presented to immunocompetent T cells within oropharyngeal lymph nodes, inducing a specific immune response[23].

Since 2009, preclinical and clinical research[16,18,24-32] have shown the effectiveness and safety of low-dose pharmacology.

Citomix (Guna S.p.a., Milan, Italy) is a multicomponent low-dose medication for oral administration that contains herbals (concentration 10^{-3} M), substances of animal origin (swine derivatives, concentration: 10^{-9} M), and signaling molecules such as growth factors, interleukins, and interferons (concentration 10^{-9} M and below). Citomix's composition has been designed to activate innate and adaptive cell-mediated immunity and simultaneously modulate inflammatory processes.

Citomix is characterized by three groups of compounds: herbal, biological/biotechnological, and animal, as summarized in Figure 1.

Herbal components include *Ananassa sativa* (with high bromelain contents), which is traditionally used to treat a wide range of inflammatory conditions[33], *Centella asiatica*, which has immunomodulatory and anti-inflammatory activity[34], and *Vaccinum vitis*, with its flavonoid composition, which is considered a powerful antioxidant and anti-inflammatory agent[35].

Biological/biotechnological components (signaling molecules) perform modulatory activity on the immune system. These molecules include G-CSF, IFN-γ, IL-1β, IL-2, IL-4, and IL-6.
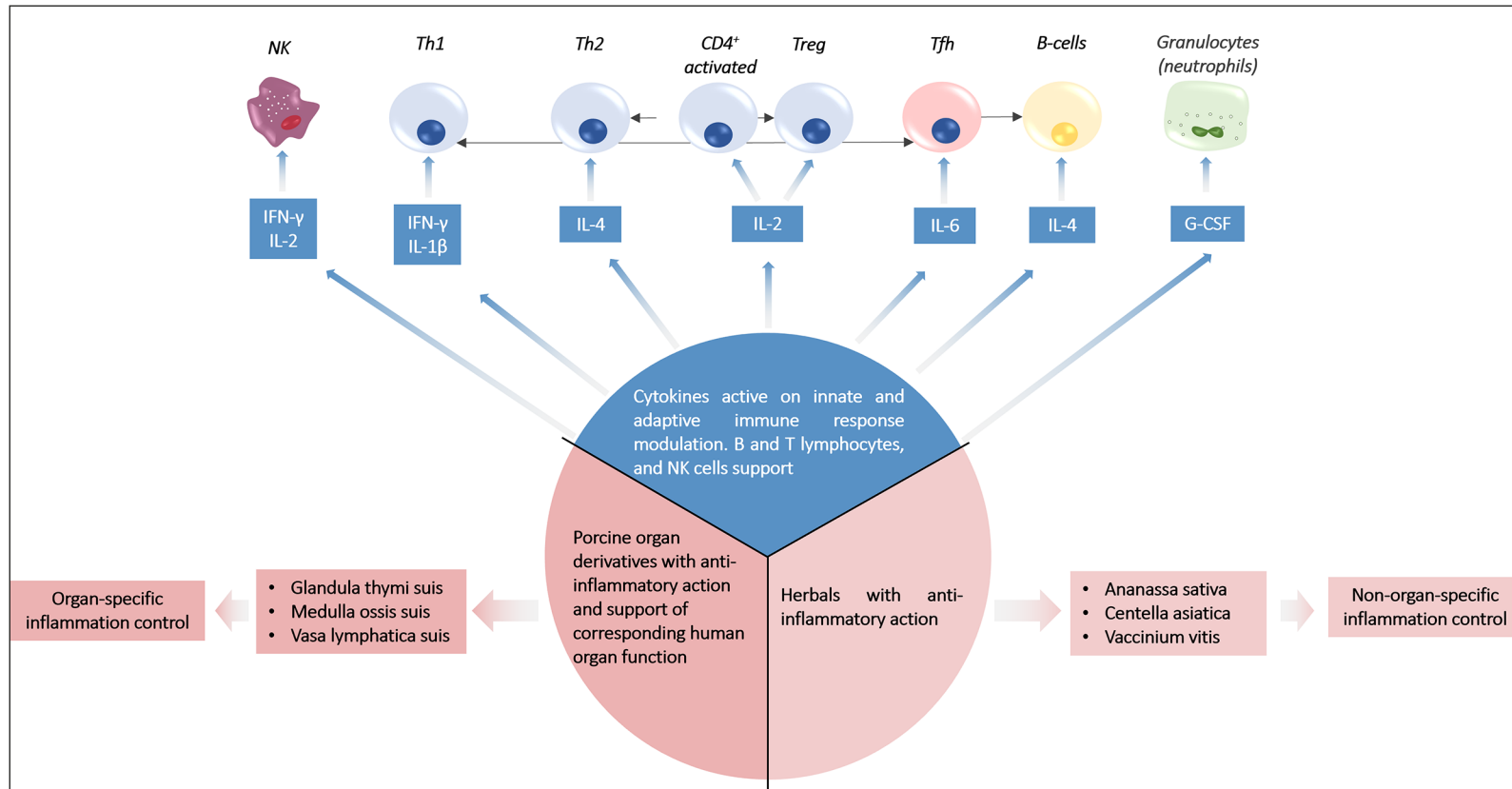
Figure 1. Graphical representation of Citomix mode of action and description of specific cellular activities promoted by Citomix's cytokines pool. NK: Aspecific cytolysis of infected cell; Th1: Cell-mediated immune response (activation of CD8+ in T-cytotoxic cell *via* IFN-γ), defense against bacteria and viruses; Th2: Humoral immune response (activation of B cells *via* IL-4), defense against parasites; Treg: Immune tolerance and immunoregulation; Tfh: B cell maturation; B-cells: Antibody response activation; Granulocytes (neutrophils): Immune response activation.

Granulocyte Colony Stimulating Factor (G-CSF) is a pleiotropic hematopoietic growth factor that regulates the proliferation and differentiation of progenitor cells in the bone marrow and the release of mature neutrophils in peripheral blood. It also increases Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC) and the production of superoxide anions[36].

Interferon-γ (IFN-γ) exerts a powerful immunoregulatory action on various cells, guides the differentiation of T-naïve cells into Th1, induces the maturation of CD8+ cells and the activation of macrophages, and promotes cytotoxicity from part of NK cells. IFN-γ is also essential for the immune reaction against intracellular pathogens and exerts a powerful phagocyte-activating effect[37].

Interleukin-1β (IL-1β) drives the onset of pro-inflammatory responses, triggering innate immunity and activating B and T lymphocytes[38].

Interleukin-2 (IL-2) is a pleiotropic growth factor for T and B lymphocytes. Together with IL-12, it increases NK cell cytotoxicity[39].

Interleukin-4 (IL-4) drives the expansion of B lymphocytes and activates the macrophage response[40].

Interleukin-6 (IL-6) promotes infection response, contributes to acute phase protein synthesis, and drives B lymphocyte maturation[41].

Components of animal origin are three porcine organ derivatives (*Glandula Thymi suis*, *Medulla ossis suis*, *Vasa lymphatica suis*), which act immunologically at the level of the corresponding human organs, contributing to the modulation of inflammatory phenomena[42,43].

In 2018, a preclinical study highlighted that Citomix could significantly increase the expression of B memory cells, IFN-γ, IL-6, IgA, and IgM (decreasing IgG for isotype switching) and modulate IL-10 expression[31]. These *in vitro* outcomes suggested a potential clinical use in the early immune response against pathogens[31].

Based on this background, a Delphi consensus on the management of RRIs using this multicomponent low-dose medication involved a large group of Italian primary care, private practice, and hospital/university pediatricians.

Materials and Methods

Delphi Method

A modified Delphi method aimed to reach a consensus among Italian pediatricians on RRI management in real-world experience.

A restricted group of independent experts constituted the steering committee that drafted a list of statements to be voted on. The first round of the Delphi process involved anonymous and interactive feedback and voting, allowing a panel of primary care, private practice, and hospital/university pediatricians (Consensus Panel), deeply involved in managing children with RRIs, to express their agreement grade for each statement.

The involved pediatricians acquired extensive experience in the use of Citomix in clinical practice (at least 15 years) and specialization in pediatrics. In addition, a preliminary questionnaire (pretest) has been submitted to correctly design both statements and the Delphi consensus structure.

The Delphi consensus process was conducted between January 2024 and March 2024. The web-based multiple-choice questionnaire was sent to the Consensus Panel to gather specific information about the Delphi process's content area. The Voting Consensus Panel consisted of 112 Italian pediatricians.

The Delphi consensus panel was requested to rate their agreement with each questionnaire statement using a 5-point Likert scale, ranging from 1 (strongly disagree) to 5 (strongly agree). Each expert provided individual and anonymous feedback on the statements, considering the personal routine RRI practice and clinical evidence. The number and percentage of participants scoring each item as 1-2 (disagreement) or 4-5 (agreement) was calculated (Table I).

The steering committee then discussed the results in a virtual meeting. For each questionnaire statement, consensus was considered to have been achieved based on the agreement of at least 66.6% of the Consensus Panel and the acceptance of the steering committee. To increase the response rate, periodic reminders of the pending survey have been sent to the panelists by e-mail.

Statements

The statements encompass two main topics: the first concerns RRI definitions, and the second concerns RRI management using the multicomponent low-dose medication. Table II summarizes the 18 statements.

Software

A software customized web application (developed by PHP ver 8.0, Db MySql, Front end HTML5/CSS3/ JAVASCRIPT) was used to conduct the Delphi survey/questionnaire.

Table I. Statements summary.

Topic A: RRIs Definitions

1. Recurrent Respiratory Infections (RRIs) are a clinical condition of frequent observation in children and are the main causes of morbidity in high-income countries. Therefore, RRIs represent an important challenge for pediatricians. In addition, RRIs have a significant social and economic impact consequent to high access to medical care, school absenteeism and absence from work for parents.
2. Among individual risk factors, immunological inexperience plays a key role along with early community entry, passive smoking and environmental pollution, low birth weight or prematurity and/or the presence of atopy.
3. The first diagnostic step for RRIs is basically based on excluding chronic pathological conditions, such as recurrent infections exclusively in a site (e.g., recurrent rhinosinusitis, recurrent otitis media, recurrent pharyngo-tonsillitis), known primary or secondary immunodeficiencies (including IgA deficiency), cystic fibrosis and/or CFTR-protein disorders, primary ciliary dyskinesia, non-cystic fibrosis-related bronchiectasis, genetic pathologies, known malformations of the cardio-respiratory system, neuromuscular pathologies, and other pre-existing chronic lung diseases.
4. The criteria for defining a child with RRIs in pediatric age are:
   • 1-3 years: 6 or more respiratory tract infections (1 of which may be pneumonia, including severe pneumonia) in a year or 2 mild cases of pneumonia confirmed by clinical criteria and/or x-ray in a year
   • 3-6 years: 5 or more respiratory tract infections (1 of which may be pneumonia, including severe pneumonia) in a year or 2 mild cases of pneumonia confirmed by clinical criteria and/or x-ray in a year
   • 6-12 years: 3 or more respiratory tract infections (1 of which may be pneumonia, including severe pneumonia) in a year or 2 mild cases of pneumonia confirmed by clinical criteria and/or x-ray in a year
5. Most respiratory infections in children are caused by viruses (e.g., rhinovirus, respiratory syncytial virus, adenovirus, influenza virus)
6. RRIs may be associated with worsened respiratory function, abuse and misuse of antibiotics, and deterioration of the quality of life not only of the child but of the entire family

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Topic B: RRIs Treatment and Prophylaxis

7. RRIs treatment is generally based on symptomatic drugs (e.g., ibuprofen, paracetamol, and inhaled or systemic corticosteroids) and antibiotics, often inappropriately.
8. Effective RRIs prevention strategy should be a primary objective in clinical practice. For this purpose, conventional immunomodulants for RRIs prophylaxis are commonly used in daily practice.
9. A recent Inter-Society Consensus recognized as weakly effective the RRIs prophylaxis based on the use of:
   • Biological Response Modifiers (BRMs)
   • Probiotics, prebiotics, symbiotics, postbiotics
   • Lysates and bacterial extracts
   • Vitamins and trace elements
   • Vaccination against flu and pneumococcus
   • Nasal lavages with hyaluronic acid, thermal waters, resveratrol
   • Reduction of risk factors
   • Adeno/tonsillectomy
   • Antibiotic prophylaxis
10. Complementary or alternative immunomodulation interventions for RRIs prophylaxis might be instead an option.
11. Oral administration of cytokines has been shown to be effective in modulating the immune response.
12. Citomix is a low-dose multicomponent product based on cytokines and components of natural origin that can modulate the immune response by acting on both innate and adaptive immunity.
13. Citomix has a good safety and tolerability profile.
14. Citomix could improve the early response to pathogens.
15. Citomix could be considered in RRIs management.
16. In RRIs prophylaxis, the recommended dosage of Citomix is 5 granules per day for 12 weeks.
17. Citomix could be added in the early treatment of acute RRIs.
18. In the early treatment of the acute episode of RRIs, the recommended dosage of Citomix is 10 granules per day 2 times per day for 2-3 days, continuing with 5 granules 2 times per day for 5-7 days.

Results

One hundred twelve pediatricians, experts in RRI care, evaluated the 18 statements and reached a consensus on all 18. The participants were 64% primary care pediatricians, 27% private practice pediatricians, and 9% hospital/university pediatricians. The consensus was reached after the first round.

Topic A: RRIs (Statements 1-6)

As detailed in Figure 2, the statements regarding RRIs as a disease showed high levels of

Table II. Voting results agreement for each individual statement in the Delphi consensus.

	1) Strongly disagree	2) Disagree	3) Undecided	4) Agree	5) Strongly agree	Sum of votes 4-5	Consensus reached if ≥ 66.6%
Topic A: RRIs							
Statement 1	1/112	0/112	1/112	45/112	65/112	110	98.2%
Statement 2	1/112	0/112	1/112	38/112	72/112	110	98.2%
Statement 3	1/112	3/112	5/112	56/112	47/112	103	92%
Statement 4	1/112	2/112	4/112	59/112	46/112	105	93.8%
Statement 5	1/112	1/112	3/112	46/112	61/112	107	95.5%
Statement 6	1/112	1/112	1/112	58/112	51/112	109	97.3%
Topic B: RRIs treatment and prophylaxis							
Statement 7	2/112	12/112	5/112	60/112	33/112	93	83%
Statement 8	1/112	7/112	9/112	66/112	29/112	95	84.8%
Statement 9	2/112	15/112	17/112	52/112	26/112	78	69.6%
Statement 10	0/112	1/112	2/112	62/112	47/112	109	97.3%
Statement 11	0/112	1/112	3/112	56/112	52/112	108	96.4%
Statement 12	0/112	0/112	2/112	59/112	51/112	110	98.2%
Statement 13	0/112	0/112	1/112	54/112	57/112	111	99.1%
Statement 14	0/112	0/112	1/112	61/112	50/112	111	99.1%
Statement 15	0/112	0/112	2/112	55/112	55/112	110	98.2%
Statement 16	0/112	0/112	7/112	59/112	46/112	105	93.8%
Statement 17	0/112	0/112	10/112	57/112	45/112	102	91.1%
Statement 18	0/112	2/112	8/112	63/112	39/112	102	91.1%
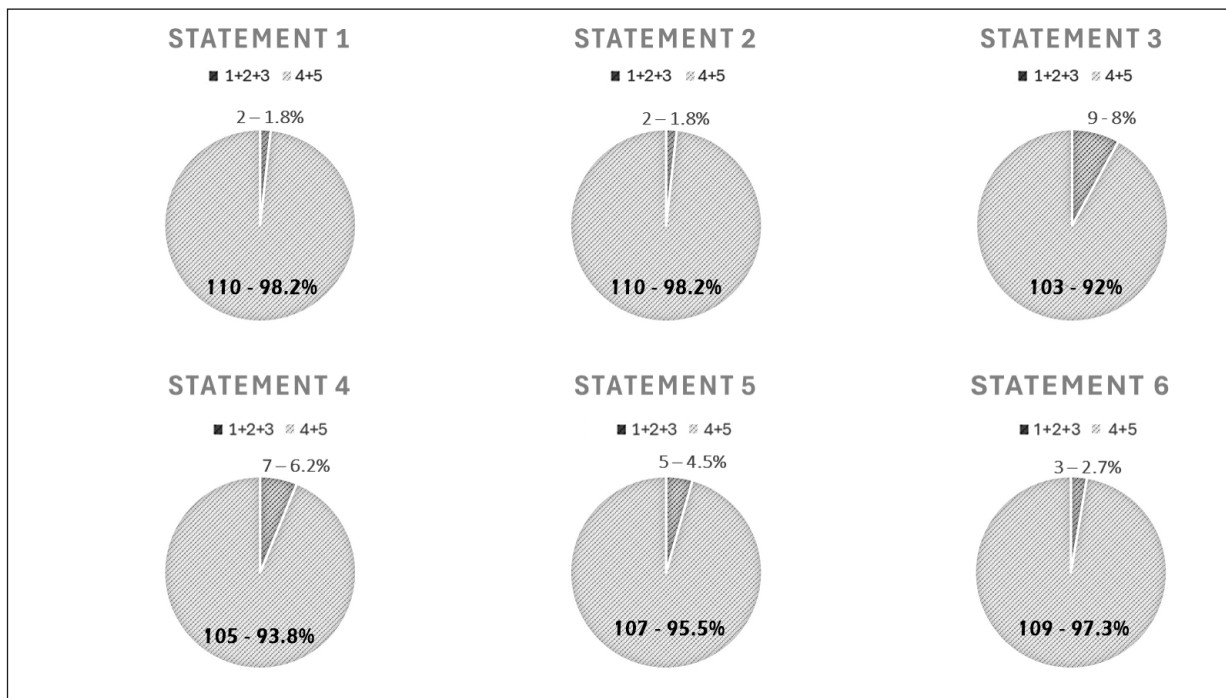
Figure 2. Graphical representation of voting result agreement for each individual statement referred to Topic A: RRIs (statements 1-6) in the Delphi consensus. Reported results are the sum of votes obtained by each statement, according to the five-option scheme adopted for the consensus (1: strongly disagree; 2: disagree; 3: undecided; 4: agree; 5: strongly agree). Results are aggregated and expressed in absolute value and percentage.

agreement, with consensus ranging from 92.0% to 98.2%.

Statement 1 established that RRIs are a clinical condition that requires frequent observation in children and are the leading cause of morbidity in high-income countries. Therefore, RRIs represent an essential challenge for pediatricians. In addition, RRIs have a significant social and economic impact, consequent to high access to medical care, school absenteeism, and absence from work for parents. This statement received 98.2% agreement.

Statement 2 reported that immunological inexperience plays a key role among individual risk factors, along with early community entry, passive smoking and environmental pollution, low birth weight or prematurity, and/or the presence of atopy. This statement obtained 98.2% agreement.

Statement 3 declared that the first diagnostic step for RRIs is based on excluding chronic pathological conditions, such as recurrent infections exclusively in a site (e.g., recurrent rhinosinusitis, recurrent otitis media, recurrent pharyngo-tonsillitis), known primary or secondary immunodeficiencies (including IgA deficiency), cystic fibrosis and/or CFTR-protein disorders, primary ciliary dyskinesia, non-cystic fibro-

sis-related bronchiectasis, genetic pathologies, known malformations of the cardio-respiratory system, neuromuscular pathologies, and other pre-existing chronic lung diseases. This statement reached 92% agreement.

Statement 4 stated that the criteria for defining a child with RRIs in pediatric age are as follows. For children 1-3 years old: 6 or more respiratory tract infections (1 of which may be pneumonia, including severe pneumonia) in a year or two mild cases of pneumonia confirmed by clinical criteria and/or x-ray in a year, for 3-6 years: 5 or more respiratory tract infections (1 of which may be pneumonia, including severe pneumonia) in a year or two mild cases of pneumonia confirmed by clinical criteria and/or x-ray in a year, and for 6-12 years: 3 or more respiratory tract infections (1 of which may be pneumonia, including severe pneumonia) in a year or two mild cases of pneumonia confirmed by clinical criteria and/or x-ray in a year. This statement had 93.8% agreement.

Statement 5 established that most respiratory infections in children are caused by viruses (e.g., rhinovirus, RSV, adenovirus, influenza virus). The statement had 95.5% agreement.
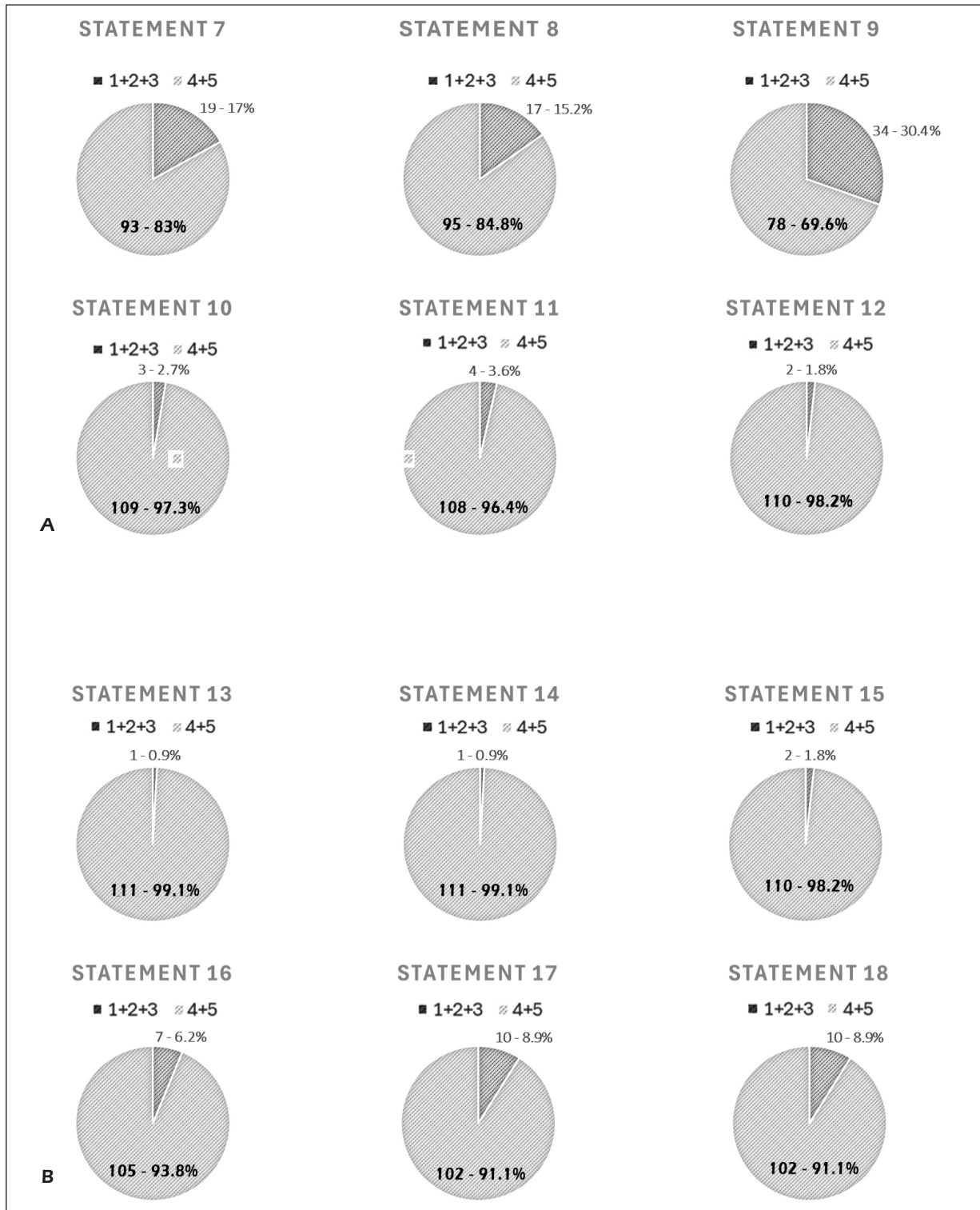
Figure 3. Graphical representation of voting result agreement for each individual statement referred to Topic B: RRIs treatment and prevention [(**A**) statements 7-1; (**B**) statements 13-18] in the Delphi consensus. Reported results are the sum of votes obtained by each statement, according to the five-option scheme adopted for the consensus (1: strongly disagree; 2: disagree; 3: undecided; 4: agree; 5: strongly agree). Results are aggregated and expressed in absolute value and percentage.

Statement 6 reported that RRIs may be associated with worsened respiratory function, abuse and misuse of antibiotics, and deterioration of the quality of life not only of the child but of the entire family. The statement had 97.3% agreement.

Topic B: RRIs Treatment and Prevention (Statements 7-16)

The statements regarding the RRIs treatment and prophylaxis showed high levels of agreement, with consensus ranging from 69.6% to 99.1%, as reported in Figure 3.

Statement 7 stated that RRI treatment is generally based on symptomatic drugs (e.g., ibuprofen, paracetamol, inhaled or systemic corticosteroids) and antibiotics, often inappropriately. The agreement was 83%.

Statement 8 declared that an effective RRI prevention strategy should be a primary objective in clinical practice. Conventional immunomodulants for RRI prophylaxis are commonly used in daily practice for this purpose. The statement obtained 84.8% agreement.

Statement 9 stated that a recent Inter-Society Consensus recognized as weakly effective the RRIs prevention based on the use of biological response modifiers (BRMs), probiotics, prebiotics, symbiotics, postbiotics, lysates and bacterial extracts, vitamins and trace elements, vaccination against flu and pneumococcus, nasal lavages with hyaluronic acid, thermal waters, resveratrol, reduction of risk factors, adeno/tonsillectomy, and antibiotic prophylaxis. This statement reached 69.6% agreement.

Statement 10 established that complementary or alternative immunomodulation interventions for RRI prophylaxis might be instead an option. There was 97.3% agreement.

Statement 11 reported that oral administration of cytokines has been shown to be effective in modulating the immune response. This statement was in 96.4% agreement.

Statement 12 reported that Citomix is a low-dose multicomponent product based on cytokines and components of natural origin that can modulate the immune response by acting on both innate and adaptive immunity. The agreement was 98.2%.

Statement 13 stated that Citomix has a good safety and tolerability profile. This statement reached 99.1% agreement.

Statement 14 reported that Citomix could improve the early response to pathogens. This statement obtained 99.1% agreement.

Statement 15 established that Citomix could be considered in RRI management. The agreement was 98.2%.

Statement 16 defined the recommended dosage of Citomix for RRI prevention as five granules per day for 12 weeks. The statement was agreed upon by 93.8%.

Statement 17 stated that Citomix could be added in the early treatment of acute RIs. The agreement was 91.1%.

Statement 18 declared that in the early treatment of acute episodes of RIs, the recommended dosage of Citomix is 10 granules per day, two times per day for 2-3 days, continuing with 5 granules twice daily for 5-7 days. The agreement was 91.1%.

Discussion

The present Delphi consensus collected the agreement grade expressed by a large panel of primary care, private practice, and hospital/university pediatricians who developed a robust experience using Citomix to manage children with RRIs. The high level of agreement for all statements supports the endorsement of these recommendations. In particular, the statements regarding the RRI definitions (Statements 1-6) reached high levels of agreement, with consensus ranging from 92.0% to 98.2%.

Respiratory infections, mainly in children, are a demanding challenge for physicians. Commonly, a relative immune defect sustains their recurrence. Currently, there is no standardized treatment for their prevention, which should act on the immune system. Recurrent respiratory infections are a prevalent clinical condition in childhood, and they have an essential social and economic impact. Namely, RRIs represent one of the most common reasons for pediatric medical visits in the early years of life[7].

Many factors may be involved in promoting and/or causing RRIs, including age (for a relative immaturity of the immune system), early attendance at nursery school, air and home pollution, passive smoking, low socio-economic level, and atopy. In addition, virus infections may increase the probability of contracting frequent respiratory infections because of the high number of circulating viruses and the numerous sub-types. Viral infections are predominant, but bacterial super-infections may also appear. Consequently, there is an overuse/misuse of antibiotics that, in turn,

induces antibiotic resistance[44]. Moreover, biofilm causes frequent antibiotic unsuccess[45].

The diagnosis of RRIs is frequently a diagnosis of exclusion of other chronic conditions, mainly including genetic pathologies, cystic fibrosis, congenital immunodeficiencies, malformities, and chronic respiratory diseases.

Also, the statements regarding the RRI treatment and prevention (Statements 7-18) showed high levels of agreement, with consensus ranging from 69.6% to 99.1%.

In general, practical RRI treatment consists of symptomatic drugs (e.g., acetaminophen and ibuprofen) and antibiotics administration, but frequently without precise indication. At present, prevention and early treatment of RRIs should be a goal in clinical practice. However, a recent Inter-Society Consensus established that most remedies used for preventing RRIs had a weak (if any) level of recommendation[7]. This document actually does not reflect what happens in everyday clinical practice. Indeed, many parents of children with RRIs ask their pediatrician for a remedy that can reduce the number of infections. As a result, immunomodulants are widely used in the standard practice.

The class of immunomodulators is extensive, including herbal compounds, vitamins, oligo-elements, probiotics and derivatives, and biological and small molecules. In this regard, there is experimental evidence that low-dose cytokine oral intake may be adequate in modulating immune response[46]. A possible mechanism of action for orally administered peptides may involve M cells at the intestinal epithelium level[47]. Signaling molecules are detected by M cells directly in the intestinal lumen and presented to immune T cells within Peyer's patches lymph nodes, inducing a specific immune response. The same mechanism has also been described for the oropharyngeal lymph nodes. However, a possible pitfall of signaling molecules (and peptides in general) oral administration, even more so when used in low doses, is represented by their low bioavailability (typically less than 1-2%): for this reason, an effective drug delivery system is requested to overcome this problem.

Citomix is a low-dose multicomponent compound that can modulate the immune response, promoting an optimal anti-infective immune response. In this regard, Citomix *in vitro* increased IL-6 and IFN-γ release, IgA and IgM production, and memory B cell subpopulations, and, in turn, decreased the early IL-10 production[31].

This potential effect could, in theory, be fruitful in preventing infection, mainly concerning the increased production of the "protective" IgA and the early immune response to pathogens, the prerogative of IgM.

The concentrations of the signaling molecules in Citomix should permit them to act within the complex network of signals, supporting their overall response and maintaining system homeostasis. Low concentrations of signaling molecules should guarantee a safe pharmacological profile, which is fundamental for the clinical applications of Citomix.

Citomix may represent a valuable option for preventive therapy, acute event add-on treatment, and relapse prevention. The absence of side effects, good compliance, and the results obtained justify the large-scale use of the product as initially demonstrated by a clinical trial[48].

The results of the preclinical research on Citomix are consistent with the data of the first clinical observations on children with recurrent upper respiratory tract infections (URTI) who, following cycles of prophylaxis with Citomix, have significantly decreased the number of URTI episodes, the days of fever and absence from school, and have been treated much less frequently with antibiotics[48]. The latter data is consistent with the most current recommendations for the lesser use of antibiotics, especially in the early years of life, motivated mainly by the increase of bacterial resistance phenomena[49].

Limitations

This study has some limitations related to the Delhi methodology: as it was a consensus study, the obtained results were linked to the skills and knowledge of the involved MDs rather than adding new evidence of Citomix's efficacy. Further criticism may be derived from the fact that a single round of voting was performed. This choice was justified by the high percentage of consensus obtained after the first round; for this reason, the contribution of further voting rounds was considered of poor relevance.

Conclusions

The present Delphi consensus collected the agreement grade expressed by a large panel of primary care, private practice, and hospital/university pediatricians who have developed robust experience using Citomix to manage children with RRIs. The high level of agreement could endorse the use of Citomix in clinical practice for preven-

tion and early add-on treatment of RRIs. It is opportune to highlight that the opinions expressed by the panelists are derived both from their experience, acquired by daily practice, and from the evidence derived from preclinical studies and an observational study. In conclusion, according to the present Delphi consensus, Citomix appears to be a valid opportunity for the prevention and early add-on treatment of RRIs. Nevertheless, there is a need to endorse these opinions by conducting further studies that should be performed according to robust evidence-based methodology.

Conflict of Interest

Ethics Approval

Not applicable.

Informed Consent

Not applicable.

AI Disclosure

The authors declare that no artificial intelligence software or applications were used to manage data or write the manuscript.

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Authors' Contributions

Massimo Agosti: conception of the study, supervision.
Antonello Arrighi conception of the study, discussion.
Sergio Bernasconi: conception of the study, supervision.
Gianni Bona: conception of the study, supervision.
Giorgio Ciprandi: drafting, writing, and editing the article.
Salvatore Leonardi: conception of the study, supervision.
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Data Availability
The data are available upon request from the corresponding author.

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