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Primary care experience on Stimunex[®] gocce in children with recurrent respiratory infections: a real-world study during the COVID-19 pandemic era

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Abstract

Background: Respiratory infections (RI) significantly burden society, mainly when there are recurrent respiratory infections (RRI). Thus, there is a need to prevent RI in clinical practice. In this regard, the modulation of the immune system and resolution of the inflammatory cascade could represent an ideal way to prevent RI. Stimunex[®] gocce, a multicomponent food supplement, contains *Sambucus nigra* extract, β-glucan, Zinc, and Vitamin D3. This study investigated its ability to prevent RRI in children using a real-world setting: the pediatric primary care.

Materials and methods: Two hundred and ninety-eight children with RRI were enrolled in the current study. The food supplement was randomly prescribed to 160 children with RRI daily for 4 months (Active group); the remaining 138 children with RRI were treated only with standard therapy for RI (Control group). The number and duration of RI, parental perception of symptom severity and treatment efficacy, use of medications, and school and working absence were evaluated.

Results: Children treated with Stimunex[®] gocce had significantly less RI than the Control group, both concerning upper and lower RI ($p < 0.001$ and 0.003 , respectively) during the follow-up period. Moreover, children in the Active group experienced shorter RI duration during the treatment and follow-up phases ($p < 0.001$ for both). In addition, parents of treated children perceived less severe symptoms and better treatment efficacy during the first and follow-up phases ($p < 0.001$ for all). The food supplement was well tolerated and there was no adverse event.

Conclusions: The current real-world study demonstrated that Stimunex[®] gocce supplementation in children with RRI might safely prevent RI episodes and reduce RI duration. These

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outcomes should be highlighted as obtained during the COVID-19 pandemic era, characterized by a dramatic reduction of RI.

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Introduction

Respiratory infections (RI) are the most common medical issue in childhood. Recurrent respiratory infections (RRI) affect pediatric morbidity and entails antibiotic use or overuse. Antibiotics can cause common adverse events, including rash, vomiting, and diarrhea; also, an indiscriminate use is associated with increased bacterial resistance.

The Italian Consensus on RRI has recently established inclusion and exclusion criteria to define a child with RRI.¹ Inclusion criteria depend on the age and encompass: (1) children aged 1-3 years old, with six or more RI yearly or two episodes of nonsevere pneumonia; (2) children aged 3-6 years old, with five or more RI yearly or two episodes of nonsevere pneumonia; and (3) children aged 6-12 years old, with three or more RI yearly or two episodes of nonsevere pneumonia.¹ Exclusion criteria include primary or secondary immunodeficiency, cystic fibrosis, primary ciliary dyskinesia, airways malformations, and localized RRI, for example, recurrent rhinosinusitis, otitis media, wheezing, and pharyngotonsillitis.¹

Many factors may promote and/or worsen RRI, including age (for the relative immaturity of the immune system), early attending at day care centers and preschool, air and home pollution, passive tobacco smoking, low socioeconomic level, microbial biofilm, and allergy.²⁻⁴

The RI treatment is generally based on antipyretic and anti-inflammatory medications (e.g., acetaminophen and ibuprofen) and antibiotics, although frequently prescribed empirically and inappropriately. However, this approach does not affect the recurrence of RI. Consequently, prevention of RI could be a fruitful activity in managing children with RRI.⁵ Many substances have been proposed to prevent RI, often leaning on immunomodulatory and anti-inflammatory activities.⁶ In this regard, Stimunex® gocce is a multicomponent food supplement containing *Sambucus nigra* extract, β -glucan Zinc, and Vitamin D3.

Sambucus nigra is a bush belonging to the *Caprifoliaceae* family and growing in wet woods, clearings, coppice, and hedges. The plant has small, white, pentamer, pot-like flowers grouped in corymbs emitting an aromatic smell; fruits are small drupes of black-purple color. The parts used in the traditional medicine are represented by dry fruits and flowers.^{7,8} The fruits contain mainly anthocyanosides, as cyanidin-3-O-glucoside and cyanidin-3-O-sambubioside, and lectins. The flowers are rich in flavonol glycosides, including isoquercitroside and rutin, and triterpenes, including ursolic acid derivatives and betulin. There is a body of evidence that demonstrated an anti-inflammatory activity exerted by *Sambucus nigra* extracts.⁹⁻¹³

β -glucans are natural polysaccharides found in the walls of yeasts, fungi, bacteria, algae, lichens, and food plants, including barley and oats. β -glucans have immunomodulatory activity and are employed as important

ingredients in food supplements, immunostimulants, and potential drugs.¹⁴ Glucans are recognized by various receptors, expressed by different immune cells, including macrophages, monocytes, dendritic cells, and NK cells.^{14,15} The interaction of glucans-receptors results in stimulating the immune system.¹⁴

Vitamin D (VD) is an essential hormone for humans as it exerts pleiotropic effects; many cells throughout the body express the VD receptor (VDR) and the enzyme 1α -hydroxylase.¹⁶ A relationship between VD status and the incidence and the severity of RI in children has been found in many observational studies; in particular, the link between severe deficiency and susceptibility to RI is prototypically represented by the high respiratory morbidity in children with rickets.¹⁷ Low VD status (<50 nmol/L) is an independent risk factor for treatment failure and delayed recovery from severe lower RI in children.¹⁸ VD supports the innate and adaptive immune response and plays a role in fighting pathogens, suggesting the need to guarantee an adequate status, particularly for patients with acute or chronic infections with profound VD deficiency. The benefit is notably greater in those receiving daily or weekly VD without additional bolus doses.¹⁹

Zinc is necessary for mounting an efficient and balanced immune response, mainly against pathogens.²⁰ Zinc also affects hematopoiesis, including differentiation and maturation into immune cell subtypes.

Based on this background, a recent *in vitro* study reported a relevant immunoregulatory activity exerted by the multicomponent Stimunex® gocce. Stimunex® gocce could prevent RI from acting on different steps of the immune response. The current real-world study aimed to evaluate the preventing activity of Stimunex® gocce in children prone to RI and managed in a primary care setting.

Materials and methods

Two hundred and ninety-eight children with RRI were enrolled in the current study. A primary care pediatrician evaluated the patients. The inclusion criteria were: (1) age between 2 and 6 years, (2) both sexes, and (3) history of RRI in the past years. The exclusion criteria were: (1) congenital or acquired immunodeficiency, (2) craniofacial abnormalities, (3) Sleep apnoea syndrome, (4) Down syndrome, (5) chronic disease (including metabolic disorders, cystic fibrosis, cancer, etc.), (6) clinically relevant passive smoking, and (7) previous (last 3 months) or current administration of drugs able to interfere with the study (e.g., immunomodulators, probiotics, vitamins, oligo-elements, or systemic corticosteroids for at least two consecutive weeks).

According to the Helsinki Conference Document and the parents or legal tutors, the study was conducted after

receiving complete information on the study and giving their written informed consent to participate. The local Ethics Committee approved the study.

All children were treated with standard treatment for any infection that occurred during the observation period. The children were randomly (ratio 1:1) and consecutively subdivided into two groups at baseline. The first group was supplemented with Stimunex[®] gocce 1 drop/kg/BW daily for the first month, then for 15 consecutive days monthly for 3 months and considered as the active group. The second group was treated only as needed for RI with the standard therapy and considered the control group.

Stimunex[®] gocce is a multicomponent food supplement, available as an oral solution, containing *Sambucus nigra* extract, standardized in polyphenols and anthocyanins, β -glucan, Zinc, and Vitamin D3.

The primary outcome was the total number of RI observed during the study period. Respiratory infection was diagnosed based on the symptoms reported by the parents, as previously described in detail.²² Briefly, the RI diagnosis was made when at least two symptoms or fever (axillary temperature $\geq 38^\circ\text{C}$), in addition to one other symptom (see below), were present for at least 48 h. The considered symptoms were: mucopurulent rhinorrhoea, stuffy or dripping nose or both, sore-throat, cough (dry or productive), otalgia, fever, dyspnoea, and mucopurulent phlegm. RI was classified as an upper respiratory infection (URI), including common cold, rhinosinusitis, pharyngitis, otitis, laryngitis, or lower respiratory infection (LRI), including tracheitis, bronchitis, and pneumonia.

Secondary outcomes were: (1) the number of URI and LRI during the study period, (2) the use of antibiotics (number of cycles), and symptomatic drugs, such as antipyretic and anti-inflammatory medications, evaluated as number of cycles, (3) the duration of RI, expressed in days; (4) the severity of RI and the effectiveness of treatments perceived by the parents, measured by the visual analogue scale (VAS) according to the methods described in a previous study,²³ and (5) the number of days lost for school attendance or working days by the parents.

All children were visited at baseline (Visit 1), after the 4-month treatment period (Visit 2), and after a 4-month follow-up (Visit 3). The study was conducted between September 2020 and June 2021.

Continuous variables were summarized as mean with standard deviation. The significance of differences between groups was assessed with independent sample *t*-tests for normally distributed variables or by Mann Whitney U test, as appropriate. Results refer to two-tailed *p*-value, $\alpha=0.05$. All analyses were performed using SPSS[®] version 25.0 (IBM Corp., USA).

Results

Table 1 reports the demographic characteristics in the two groups at baseline (Visit 1). Globally, 298 children completed the study and were included in the statistical analysis: 160 in the active group and 138 in the control group. The study population included 153 females and 145 males; the mean age was 4.4 years. There was no statistical difference between the groups.

Table 1 Demographic characteristics at Visit 1.

			Treatment		
			Total	No treatment	Stimunex [®] gocce
Sex	Female	n	153	71	82
		%	51.3	51.4	51.2
	Male	n	145	67	78
		%	48.7	48.6	48.8
Age, years	Valid N		298	138	160
	Mean		4.4	4.4	4.4
	Standard deviation		1.75	1.73	1.77

Concerning the primary outcome, children treated with Stimunex[®] gocce experienced significantly ($p<0.001$) less RI than control subjects during the follow-up period, whereas there was no difference during the treatment period (**Figure 1**, **Tables 2** and **3**). In addition, children of the active group had significantly fewer upper and lower airway infections during the follow-up period ($p<0.001$ and 0.003 , respectively), but there was no significant difference in the first phase.

About the duration of RI episodes, children actively treated with the food supplement had a significantly shorter duration of RI both during the treatment period and follow-up period ($p<0.001$ for both).

The parents of the active group children perceived less severe symptoms of their children than parents of the control group both during the treatment phase and follow-up phase ($p<0.001$ for both), as reported in **Tables 2** and **3**, and **Figure 2**. Consistently, the parents of the active group children perceived greater efficacy of their children's treatments than parents of the control group both during the treatment phase and follow-up phase ($p<0.001$ for both), as reported in **Tables 2** and **3**, **Figure 2**.

In addition, the assessment of intragroup changes between Visit 2 and Visit 3 (Δ is-V3) showed that children in the active group had a lower total number of RI ($p=0.001$), less URI ($p<0.001$), lower duration of infections ($p=0.011$), and less cycles of antibiotics ($p=0.002$) than the control group children (**Figure 3**).

About the missed school and workdays, there were no significant differences between both groups during the treatment period and the follow-up period (**Tables 2** and **3**).

No clinically relevant adverse event was reported in children supplemented with Stimunex[®] gocce.

Discussion

Respiratory infections, mainly if recurrent, significantly burden the child, family, doctor, and society. Moreover, RI represents the first reason for antibiotic prescription, parental absence from work to take care of the ill child, and frequent outpatient doctor and emergency room visits. As a result, preventive strategies to reduce this RI impact are warranted.

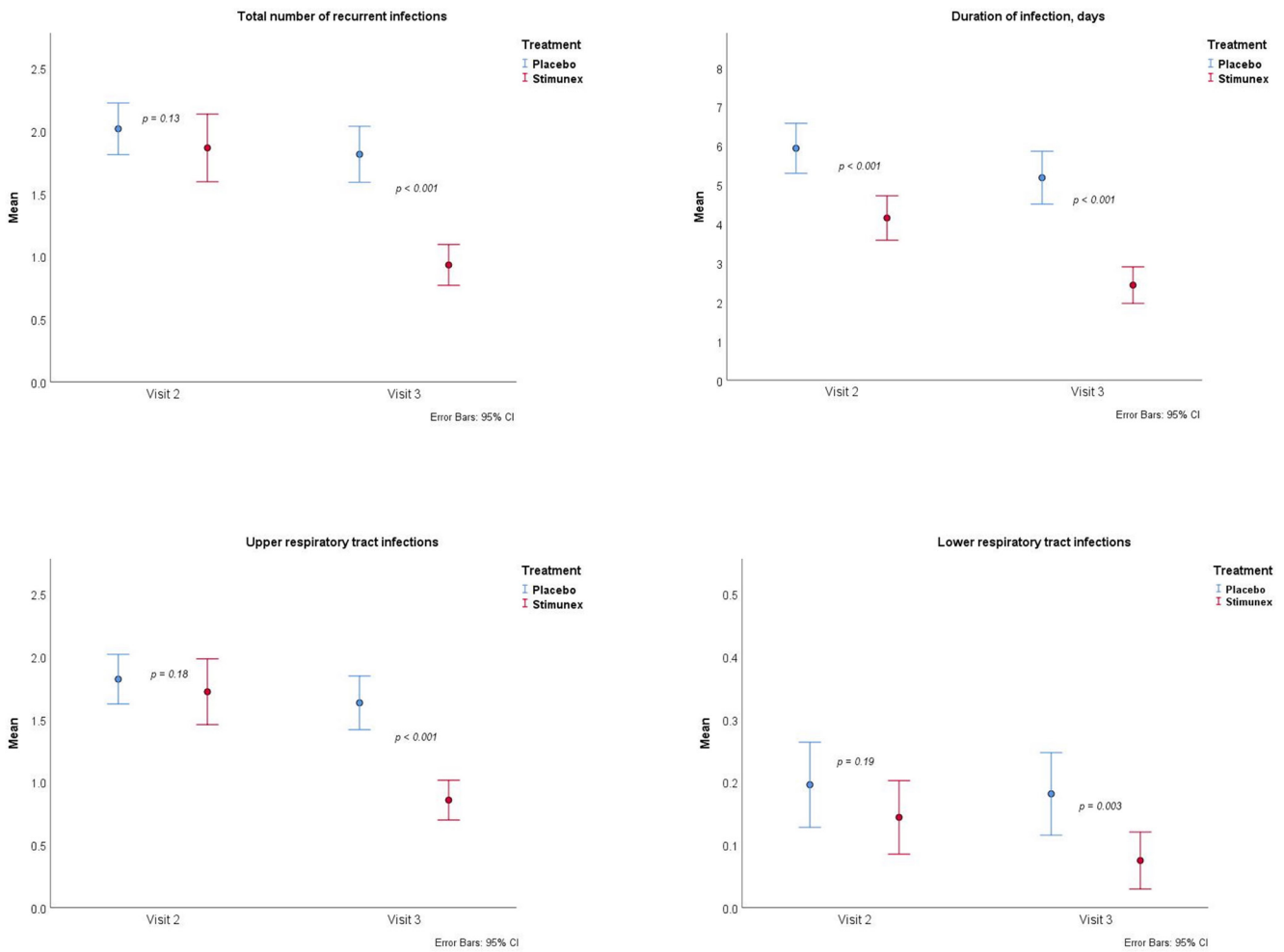


Figure 1 Upper left quadrant: mean total number of RI in control and treated groups. Upper right quadrant: mean duration (days) of RI in the two groups. Lower left quadrant: mean number of upper RI in control and treated groups. Lower right quadrant: mean number of lower RI in control and treated children. Data concerned Visit 2 and 3.

Table 2 Assessments at Visit 2.

	Treatment				p
	No treatment		Stimunex® gocce		
	Mean	St.dev	Mean	St.dev	
Total number of recurrent infections	2.0	1.21	1.9	1.70	0.13
Upper respiratory tract infections	1.8	1.16	1.7	1.66	0.18
Lower respiratory tract infections	0.2	0.40	0.1	0.37	0.19
Duration of infection, days	5.9	3.76	4.2	3.59	<0.001*
VAS symptoms	4.8	2.62	3.0	2.65	<0.001*
VAS efficacy	2.9	2.05	5.3	3.38	<0.001*
Cycles of antibiotics	0.6	0.82	0.8	0.99	0.13
Cycles of antipyretics	0.6	0.63	0.5	0.53	0.97
Days of school loss	3.4	4.73	3.4	3.62	0.44
Days of parental job loss	2.3	3.07	2.0	2.51	0.67

VAS: visual analog scale.

Table 3 Assessments at Visit 3.

	Treatment				p
	No treatment		Stimunex® gocce		
	Mean	Std.dev	Mean	Std.dev	
Total number of recurrent infections	1.8	1.31	0.9	1.03	<0.001*
Upper respiratory tract infections	1.6	1.26	0.9	1.00	<0.001*
Lower respiratory tract infections	0.2	0.39	0.1	0.29	0.003*
Duration of infection, days	5.2	3.97	2.4	2.96	<0.001*
VAS symptoms	4.5	2.60	2.5	2.97	<0.001*
VAS efficacy	3.3	2.49	6.2	3.04	<0.001*
Cycles of antibiotics	0.4	0.72	0.2	0.49	0.11
Cycles of antipyretics	0.4	0.62	0.4	0.56	0.83
Days of school loss	2.2	3.42	1.8	3.34	0.31
Days of parental job loss	1.6	2.47	1.5	3.23	0.28

VAS: visual analog scale

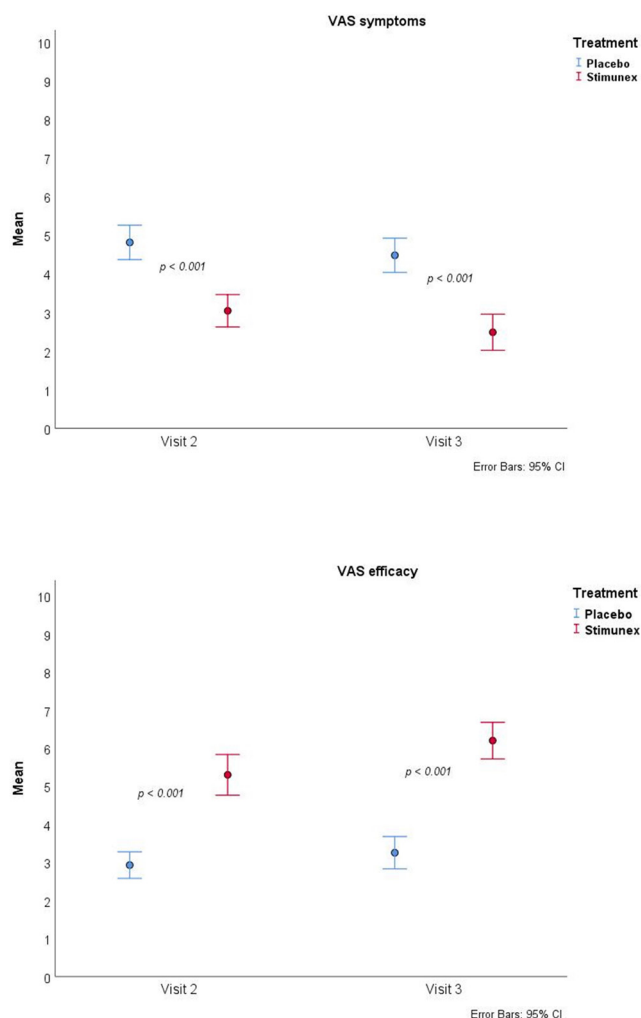


Figure 2 Upper quadrant: visual analog scale (VAS) concerning the parents' perception of symptom severity in the two groups at Visit 2 and Visit 3. Lower quadrant: VAS concerning the parents' perception of treatment efficacy in the two groups at Visit 2 and Visit 3.

Respiratory infections engage the immune system, involving the innate and the adaptive response with humoral and cellular signaling. An efficient immune response should clear the pathogens and resolve the associated inflammation. However, if the immune system is impaired, RI tends to recur. Therefore, manipulating the immune response could be a therapeutic goal to prevent RI.

Based on this background, we tested the hypothesis that Stimunex[®] gocce, a multicomponent food supplement, could modulate immune response reducing the impact of RI in children prone to recurrence. In addition, we chose a real-world setting, such as pediatric primary care, as it mirrors what occurs in daily clinical practice.

The findings showed that Stimunex[®] gocce supplementation significantly reduced the number of RI episodes during the follow-up period. In particular, both upper and lower RI significantly diminished after the multicomponent supplementation. Namely, children halved the RI episodes after a 4-month course. Consistently, the duration of RI episodes was less than half in treated children compared with control subjects; the antibiotic use also diminished in

treated children. Also, the parents' perception of symptom severity and treatment efficacy was better in the active group than in the control group. Notably, the food supplement significantly reduced the RI duration and affected the parental perception already during the treatment phase. On the contrary, the food supplement did not affect the use of antibiotics and symptomatic drugs. A slight, but not significant, reduction of missed days, both concerning school attendance and work, was observed in the active group.

These findings, mainly concerning the effects achieved during the follow-up, could be explained by the complex mechanism of action of Stimunex[®] gocce. Two main mechanisms may be conceived: modulation of the immune system, exerted mostly by β -glucan, Zinc, and VD, and anti-inflammatory activity, exerted mainly by *Sambucus nigra* extract. The first mechanism may strengthen the immune response to pathogens; the latter may dampen the amplification of the inflammatory cascade associated with infection. These positive effects may reduce the number, duration, and severity of RI and consistently impact the parental esteem.

The elder's flowers and berries are widely used in phytotherapy to alleviate respiratory symptoms. *Sambucus nigra* extracts significantly reduce proinflammatory cytokines release, promoting the resolution of inflammatory events related to respiratory infection.²¹

β -glucans modulate the immune response stimulating the antigen-presenting machinery reinforcing type 1 response.^{24,25}

VD induces the expression of two human antimicrobial peptides: cathelicidin and β 2-defensin. These proteins belong to a group of small, multifunctional polypeptides with potent antimicrobial activity; and resistant to proteolysis microbes do not develop resistance to them.²⁶ In addition, VD modulates alarmin production, resolves inflammation, and repairs damaged tissues.²⁷ Therefore, VD reinforces the immune function improving the resistance to infection. Adequate Zinc supplementation is required for a physiological immune response.²⁸ Indeed, Zinc deficiency is associated with an impaired immune response against pathogens. As a result, Zinc supplementation contributes to supporting the immune defense.

Considering these complex mechanisms, it is reasonable that this multicomponent food supplement requires an adequate time, such as a 4-month course, to exhibit its effectiveness. Even if Stimunex[®] gocce may shorten RI duration and positively affect the parental perception of RI, the full effects are expected during the follow-up phase.

Another aspect deserves attention: this study was performed during the COVID-19 pandemic era, in particular throughout the second and third waves. There is impressive evidence that COVID-19 dramatically abolished the incidence of RI, probably because of preventive measures, including social distancing, facial masks, handwashing, and lockdown.^{29,30} This fact contributes to conveying a greater emphasis to the reported outcomes. Furthermore, untreated children experienced only four RI episodes during the study, which is very low for that age group. A recent study, conducted in the same geographic area before the COVID-19 pandemic, reported a mean of seven respiratory infection episodes per year.³¹ As a consequence, the Stimunex[®] gocce preventive effects could be even more remarkable.

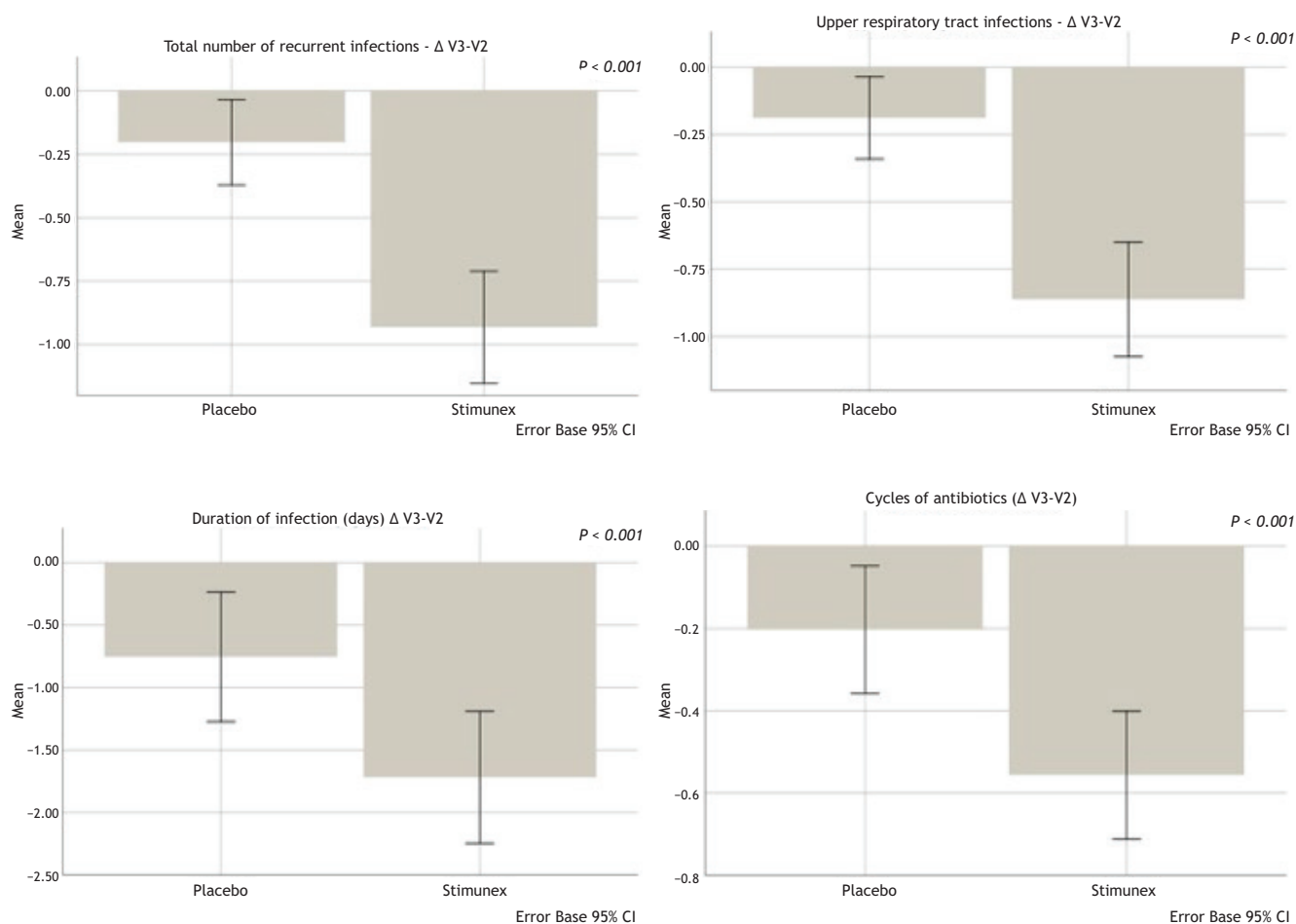


Figure 3 Upper left quadrant: Δ changes of the total number of RI in control and treated groups. Upper right quadrant Δ changes of the mean duration (days) of RI in the two groups. Lower left quadrant: Δ changes of the mean number of upper RI in control and treated groups. Lower right quadrant: Δ changes of cycles of antibiotics in control and treated children. Data concerned Visit 2 and Visit 3.

However, the present study has some limitations, including the open design, the lack of documented infections diagnosis and mediator measurement. Also, the current study cannot define the real mechanisms of action involved in the obtained outcomes. Furthermore, as Stimunex® gocce is a multicomponent food supplement, and there is no possibility of identifying each component's single activity. Therefore, the findings could not allow for drawing definitive conclusions about the exact mechanisms of action. Thus, further studies should be designed to answer these unmet needs. On the other hand, the current study was performed in a real-world setting, such as pediatric primary care. The real-world studies are actual as they may provide information more adherent to the daily practice that randomized controlled trial involving selected patient populations that rarely mirror the real situation.³²

Conclusions

The current real-world study demonstrated that Stimunex® gocce supplementation in children might safely prevent and reduce the RI clinical burden.

Conflict of interest

The authors state that there was no conflict of interest.

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