

LETTERS TO THE EDITOR

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Role of *S. salivarius* K12 in the prevention of URTI and AGE in nursery-aged children

Acute upper respiratory tract infections (URTIs) in children are a major cause of morbidity, absence from daily life and are among the most common reasons for pediatrician visits.^{1,2} Any intervention that could prevent them would deliver important life-saving and cost-effective impacts. Despite their wide clinical use, the evidence-based indications of probiotics are narrow and mostly focus on the treatment of acute gastroenteritis (AGE).³ Indeed, the potential ability of probiotics to influence and stabilize the gut microbiota, improving its resistance to colonization, supports their rational use.⁴ Although the evidence for ability of probiotics to also modulate immune functions is thought to be modest, it should nonetheless make the case for probiotics to play a possible role in preventing and/or reducing the symptoms of upper respiratory diseases.⁵ To date, strains from *Lactobacillus* and *Bifidobacterium* spp. are the most common probiotics used to treat a wide range of diseases, ailments and conditions that affect humans and animals.⁶ Much less common is the possibility of resorting to different bacterial species, such as *Enterococcus faecium*, endowed with well-documented clinical anti-URTIs and anti-AGE properties.⁷ Among the species less widely used as probiotics, the oral commensal *Streptococcus salivarius* (Ss) is among the best studied, with particular reference to the K12 strain.⁸ This strain has been widely investigated, especially for its effective action in fighting ear, oral, pharyngeal, and tonsillar infections caused by *S. pyogenes*, *S. pneumoniae*, *M. catarrhalis*, and/or *H. influenzae*.⁹ The effectiveness of the Ss K12 is more commonly traced back to its ability to release two antibiotics (Salivaricin A2 and Salivaricin B), which are effective at damaging the membrane of the target bacteria.¹⁰ However, the capacity of Ss K12 to counteract bacterial antagonists is not limited to the release of bacteriocins. Other microbial species, non-sensitive to salivaricins A2 and B, including oral-pharyngeal viruses (syncytial virus, adenovirus, rhinovirus), fungi such as *Candida*, or Gram-negative bacteria such *Aggregatibacter*, *Fusobacterium*, or *Porphyromonas*, are effectively opposed by the Ss K12 strain within

the oral-pharyngeal environment through mechanisms such as the development of a local response mediated by interferons or more simply of mechanical antagonism and/or environmental competition.^{11, 12} Finally, probably as a result of its ability to transfer from the oral cavity to the lung tissue, Ss K12 has also recently demonstrated anti-COVID-19 action on both children and adults.^{13, 14}

Despite the large number of clinical studies carried out, the K12 strain has never been investigated for safety and efficacy in very young children under 3 years of age. This is despite the existence of a nutraceutical preparation developed precisely to be administered to babies as young as a few months old (Bactobli Infant[®]; notification to Italian minister of health: I.5.i.h.2/2018/95881). Our study therefore evaluated the action of this nutraceutical preparation by retrospectively analyzing the results obtained in children attending several kindergartens in the province of Milan (Italy). The analysis involved 287 children attending the first or second year of kindergarten who had been treated (N.=186) for at least 90 days (from January to March 2022, or from October to December 2022) by their pediatrician with Ss K12. Untreated children (N.=101), attending the same kindergartens at the same time, were used as controls. This retrospective, controlled, observational and open-label analysis has been registered on www.clinicaltrials.gov (identifier: NCT05840926) and approved by the Ethics Committee for Clinical Trials (Protocol number: 70; July 20th, 2023). Informed written consent was obtained from all parents of the children considered in the analysis.

All findings are shown in Table I. The two groups were superimposable as regards to age, years of kindergarten attendance, birth weight, gestational age, type of feeding, and number of siblings. The results showed that per child, probiotic treatment generally reduced all the rates of infection, with particular reference to the episodes of bacterial bronchitis and tracheobronchitis, bacterial sinusitis and rhinosinusitis, viral infections, as rhinitis, laryngitis, tracheitis and Covid-19, as well as gut symptoms of gastroenteritis. A lower rate of infections among the children treated with the probiotic can also be deduced from the significantly lower prescription of antibiotics. The parental report given to the respective pediatricians also describes the product – a powder preserved in capsules that can be opened and rubbed onto the child's gums using a fingertip or administered via a pacifier – as well-tolerated and free of side effects, at least as regards those specifically attributable to the probiotic and therefore not observed in the control group (data not shown).

The results of our analysis, extended in this study to a different age range than that usually verified, confirm

TABLE I.—Children's features, relative prevention of URTI and AGE (both calculated as number of episodes per child) and use of antibiotics (number of therapies per child) in nursery-aged children treated (N.=186) or not treated (N.=101) with *S. salivarius* K12.

Parameter	<i>S. salivarius</i> K12	Control	P value
Age (months)	19.8±8.1	17.7±7.7	NS
Birth weight (kg)	3.1±0.6	3.2±0.6	NS
Gestational age (weeks)	38.7±2.2	38.3±4.3	NS
Type of feeding (B/A/M)	75/62/49	45/34/22	NS
N. of siblings	0.4±0.5	0.5±0.5	NS
Nursery attendance (years)	1.3±0.5	1.2±0.4	NS
Bronchitis/tracheobronchitis	0.22±0.45	0.41±0.72	0.035
Acute otitis media	0.16±0.36	0.39±0.68	0.015
Pharyngitis/tonsillitis	0.08±0.27	0.13±0.37	NS
Tracheobronchitis/bronchiolitis	0.03±0.18	0.07±0.26	NS
Laryngotracheitis/tracheitis	0.02±0.15	0.06±0.24	NS
Rhinosinusitis	0±0	0.02±0.14	NS
Adenoiditis	0±0	0.01±0.10	NS
Sinusitis/rhinosinusitis	0±0	0.03±0.17	0.018
Gastroenteritis	0.1±0.31	0.27±0.44	0.001
Rhinitis/laryngitis/tracheitis	0.63±0.07	1.60±0.10	0.001
COVID-19	0.02±0.15	0.09±0.29	0.001
Amoxicillin	0±0	0.68±0.85	0.001
Macrolides	0±0	0.14±0.40	0.001
Cephalosporins	0±0	0.16±0.54	0.001
All antibiotics	0±0	0.98±1.03	0.001

All values, except type of feeding, that are given as 'number of children', are given as mean±SD. All statistics have been calculated by Wilcoxon test.

B: breastfeeding; A: artificial; M: mixed feeding; NS: not significant.

that *Ss* K12 is a safe and effective probiotic. The results show that routine use of *Ss* K12 could significantly reduce both infection rates in children attending the first two years of kindergarten and the frequency of antibiotic therapy to treat these infections.

Obviously, our study has the usual limitations of retrospective analyses (no placebo and no blind conditions). However, it was performed on a non-small number of subjects and in an acceptably controlled manner and reports for the first time, to our knowledge, the safety and efficacy profiles of the K12 strain in children under 3 years of age.

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Conflicts of interest

Francesco Di Pierro is a member of the Scientific Board of Pharmextracta. Alexander Bertuccioli and Maria Colombo are currently working as consultants for Pharmextracta. All other authors have no conflicts of interest.

Authors' contributions

All authors read and approved the final version of the manuscript.

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