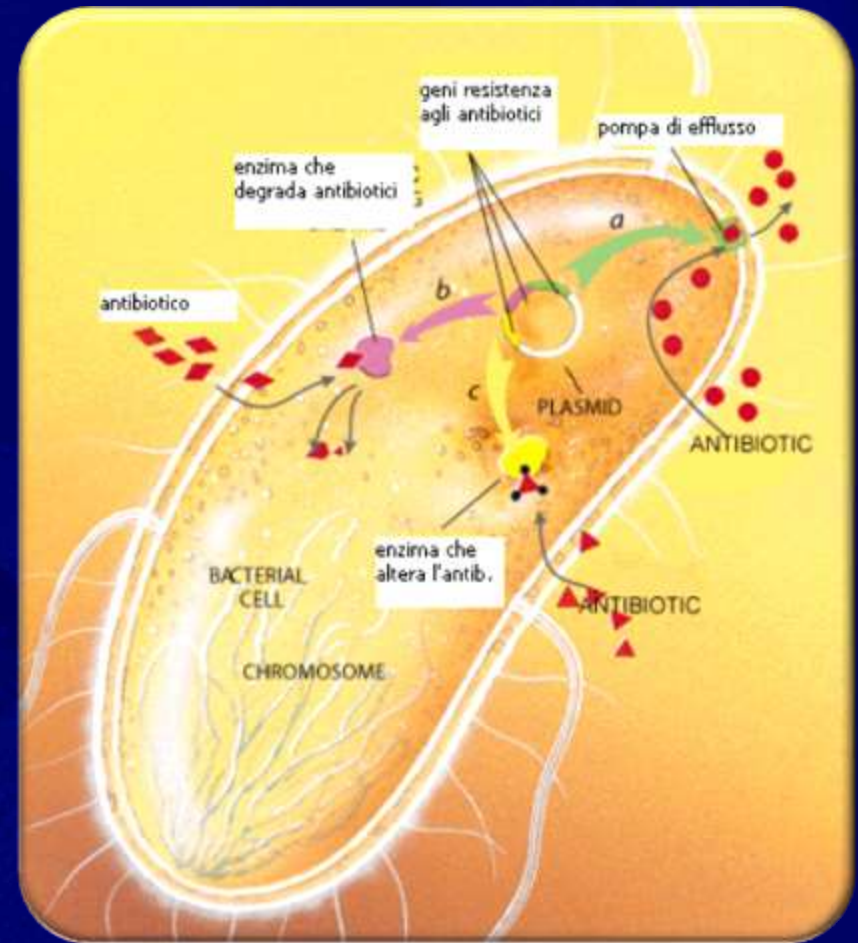




BATTERIOTERAPIA

MOTIVAZIONI

L'emergenza mondiale della resistenza dei batteri agli antibiotici ha prodotto la necessità di individuare metodi alternativi nella lotta contro le infezioni batteriche.



FARMACO-RESISTENZA



BACTERIOTERAPIA COME ?



PROBIOTICI

Sfruttano il meccanismo di competizione.
(L'organo target in questo caso è l'intestino)

I microrganismi devono essere:



Pasteur
1877



Metchnikoff
1907





BATTERIOTERAPIA

In ORL

OGGI DOVE SIAMO

?



Probiotici in ORL

S.Salivarius M18



Potenzialmente anticarie

S.Salivarius TOVE-R



Potenzialmente anticarie

S.Salivarius K58



Potenzialmente anticarie, ma instabile

S.Salivarius ST3



Potenzialmente compete con il pyogenes

Micrococcus luteus Q24



Potenzialmente compete con specie responsabili di infezioni cutanee

Lactobacillus



Potenzialmente compete con la candida

S.Salivarius 24 SMBc

S.Oralis 89a



NASALI

Competono con:

**S.pneumoniae, M. catarrhalis ,
H.influenzae**

Hanno notevoli proprietà adesive



BATTERIOTERAPIA

ORALE



S.SALIVARIUS K12

INDICAZIONI

- Uno dei commensali predominanti della cavità orale.
- Usato negli squilibri del microbiota nel cavo orale.
- Introdotto per contrastare le infezioni dello *S.pyogenes*, vanta altre applicazioni (alitosi e carie dentale).
- Altre potenziali applicazioni: contro le infezioni virali respiratorie e la candidosi orale.

Future Microbiol. 2012;7(12):1355-1371

Philip A Wescombe; John DF Hale; Nicholas CK Heng; John R Tagg



BATTERIOTERAPIA

NASALE



BACTERIOTERAPIA Nasale

LA BACTERIOTERAPIA NASALE SFRUTTA
I NATURALI MECCANISMI DI COMPETIZIONE
BATTERICA
CON PROBIOTICI SELEZIONATI
CHE IMPEDISCONO AI PATOGENI,
CON I QUALI CONDIVIDONO
LO STESSO ECOSISTEMA ABITATIVO, DI
PREVALERE.



BACTERIOTERAPIA

NASALE

S.Salivarius 24
SMBc

S.Oralis 89a



S.ORALIS 89a

Studi dimostrano la sua efficacia nel competere con *S.pneumoniae*, *M. catarrhalis*, *H.influenzae*



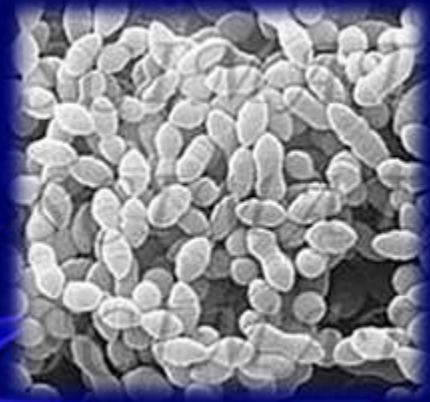
Spray bacteriotherapy decreases middle ear fluid in children with secretory otitis media

This is the first study to show a beneficial effect of bacterial spray treatment in children with established secretory otitis media.

Arch Dis Child 2009;94:92-98
S Skovbjerg,¹ K Roos,² S E Holm et Al.



S.SALIVARIUS 24 SMBc



ISOLATO DAI
TAMPONI
NASALI

- È un normale saprofita
- NON ha geni di virulenza
- NON è assolutamente patogeno
- NON ha resistenza agli antibiotici
- Produce batteriocine contro ceppi anche iper-virulenti di *S.pyogenes* e *S.pneumoniae*.

RESEARCH ARTICLE

Bacteriocin-producing oral streptococci and inhibition of respiratory pathogens

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DOI: 10.1111/j.1574-695X.2012.00928.x

Editor: Patrick Brennan

Keywords

Streptococcus salivarius; oral probiotics; BLS activity.

Abstract

The use of bacteria as probiotics is in continuous development, thanks to their capacity to maintain or restore a host's natural microbiome by interference with and/or inhibition of other microorganisms mediated by antimicrobial peptide production such as bacteriocins. In the oral cavity, *Streptococcus salivarius*, a non-pathogenic and predominant oral species, is one of the major bacteriocin producers that is able to coexist in this environment and reduce the frequency of colonization of the main pathogens involved in upper respiratory tract infections. The aim of this study was to screen oral bacteria colonizing healthy children for their use as potential oral probiotics. Eighty-one α -hemolytic streptococci isolated from nasal and/or pharyngeal swabs of 31 healthy children aged between two and twelve years were isolated. Among them, 13 α -hemolytic streptococci were selected for their bacteriocin-like inhibitory activity against potential pathogens. These strains were tested for bacteriocin production and assayed for their capacity to adhere to HEp-2 cell lines. Our data showed that 13 bacteriocin producer strains were able to inhibit different gram-positive pathogens. Among them one strain, *S. salivarius* 24SMB, deposited as DSM 23307, was selected as a potential oral probiotic, thanks to its safety assessment, ability to inhibit *Streptococcus pneumoniae* and the absence of virulence and antibiotic resistance genes.

Introduction

The microorganisms that inhabit the human oral cavity have been designated as the oral microflora or more recently, as the oral microbiome; the microbiome is the ecological community of commensal, symbiotic, and pathogenic microorganisms that colonize different sites in the human body. The Human Microbiome Project states that an understanding of human health and disease is impossible without understanding the human microbiome (Dewhirst *et al.*, 2010). More than 700 bacterial species are present in the oral cavity and, maintaining the bacterial communities unaltered, has a significant impact on general health by either preventing or causing infections. It has been suggested that changes in the structure of this complex community could contribute to a shift in the balance of the resident microflora to a disease-associated species composition (Marsh, 1991; Aas *et al.*, 2005;

Caglar *et al.*, 2005). Bacterial interference, such as antagonism, has a fundamental role in keeping the balance of the microbial ecology associated with the ability of bacterial species to interfere during surface colonization. This phenomenon represents an interesting mechanism of defense because of the capability of endogenous microflora to interfere or inhibit the growth of potential pathogens (Falagas *et al.*, 2008). Clinical evidence of bacterial interference in the treatment of halitosis and/or *Streptococcus pyogenes* infection has been reported by J. R. Tagg and co-workers, attributing this ability to the presence of *Streptococcus salivarius* K12 belonging to the normal commensal flora of the nasopharynx as it is a *salA* bacteriocin producer strain able to interfere with *S. pyogenes* species (Burton *et al.*, 2006a, b; Power *et al.*, 2008). *Streptococcus salivarius*, a non-pathogenic species and predominant colonizer in the oral microbiome, is one of the major producers of a variety of bacteriocin-like inhibitory

Colonization, safety, and tolerability study of the *Streptococcus salivarius* 24SMBc nasal spray for its application in upper respiratory tract infections

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Abstract *Streptococcus salivarius*, a non-pathogenic species and the predominant colonizer of the oral microbiota, finds a wide application in the prevention of upper respiratory tract infections, also reducing the frequency of their main pathogens. In this pilot study, the primary objective was to evaluate the safety and tolerability of a nasal spray, *S. salivarius* 24SMBc, as a medical device in a clinical study involving 20 healthy adult subjects. The secondary aim was to determine the ability of colonization assessed by molecular fingerprinting. Twenty healthy adult subjects, aged between 30 and 54 years, without a medical history of recurrent otitis media, were enrolled. All patient characteristics fulfilled the inclusion criteria. All subjects were treated daily for 3 days with the nasal spray containing *S. salivarius* 24SMBc at a concentration of 5×10^9 colony-forming units (CFU)/ml. The persistence of *S. salivarius* in the nasopharynx was investigated by the antagonism test and random amplified polymorphic DNA polymerase chain reaction (RAPD-PCR). The tolerability and safety were clinically assessed by clinical examinations during treatment. Our results demonstrate the capability of *S. salivarius* 24SMBc to colonize the rhinopharynx tissues in 95 % of subjects and persist in 55 % of them after 6 days from the last dose of the formulation, maintaining a concentration of 10^5 CFU/ml. The treatment was well tolerated by all healthy patients and no adverse effects were found. The

topical application of streptococcal probiotics is a relatively undeveloped field but is becoming an attractive approach for both prevention and therapy, especially for pediatric age patients. *S. salivarius* 24SMBc possess characteristics making this strain suitable for use in bacteriotherapy.

Introduction

In recent years, there has been increasing evidence indicating beneficial effects of probiotics in the prevention and treatment of many diseases, especially in the gastrointestinal tract, preserving intestinal epithelium by maintaining its microbiota and modulating immune response [1–4]. Until now, few studies have been addressed to the use of probiotic strains in upper respiratory tract infections (URTIs) and some studies suggested clinical advantages for the host after probiotic administration [5–7]. The strategy of using a bacterial species belonging to the healthy human oral microbiota as an oral probiotic for URTIs offers great benefits for the host, contributing to the recolonization process, re-establishing microbial balance, and reducing the level of potential pathogens. As regards to potential pathogens, *Streptococcus salivarius* species is considered the predominant “safe” colonizer, capable of fostering a more balanced, health-associated oral microbiota, interfering with potential pathogens; thanks to these characteristics, it is suitable for use as an oral probiotic [8]. Nasopharyngeal colonization plays an essential role in the pathogenesis of URTIs and, in particular, in recurrent acute otitis media (rAOM), acting as a reservoir for mainly respiratory pathogens, such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* [9, 10]. Rebalance of the nasopharyngeal microbiota is a new strategy for the prevention of AOM based on the interaction and competition between potentially pathogenic and commensal bacteria. The

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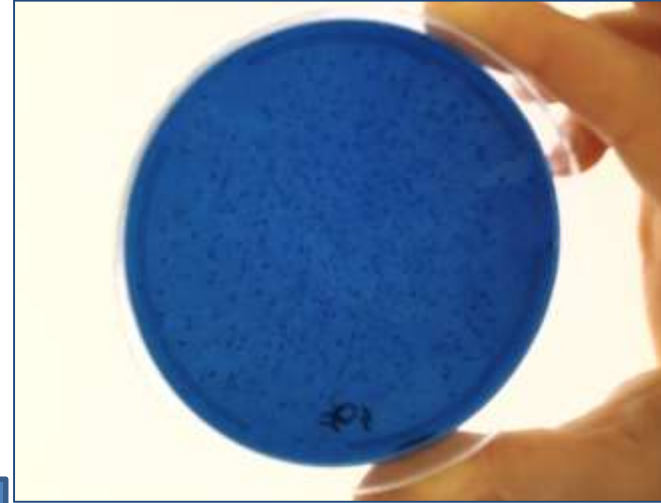
¹ LabMMAR, Department of Biomedical and Biotechnological Sciences, Section of Microbiology, University of Catania, Via Androne 81, 95124 Catania, Italy

² Department of Medical Sciences, Surgical and Advanced Technologies, GF Ingrassia, University of Catania, Catania, Italy

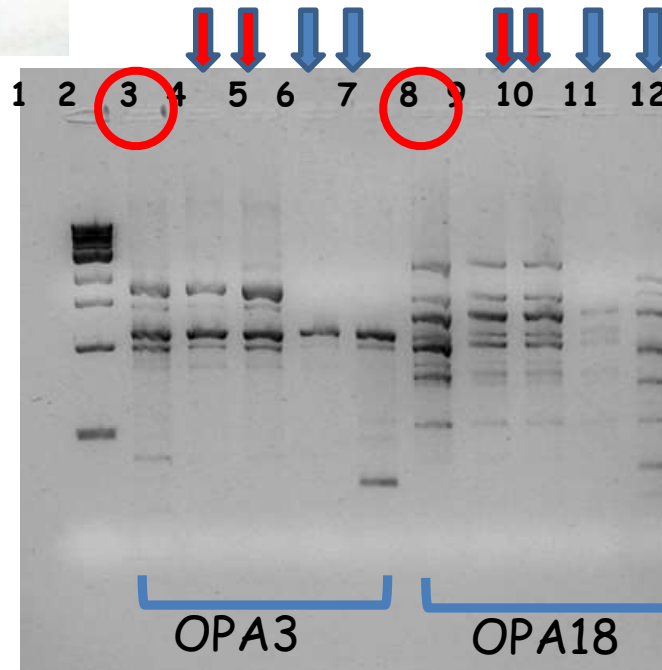
The microbiological objective consisted in the evaluation of the ability to colonize the nasal pharynx by plating in blood agar and selective medium and molecular fingerprinting using the RAPD (Random Amplified Polymorphic DNA) method



Blood agar



Nasal swabs plated onto Mitis Salivarius agar (MSA).



Marker 1Kb.

2; 7: *S. salivarius* 245MBc

3;8: *S. salivarius* from patient 3

4;9: *S. salivarius* from patient 4

5;10: *salivarius* from patient 6

6;11: *salivarius* from patient 1

12: Marker 100 bp.



***Streptococcus salivarius* 24SMB administered by nasal spray for the prevention of acute otitis media in otitis-prone children**

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M. Fattizzo¹ · C. Rosazza¹ · S. Stefani² · S. Esposito¹ · N. Principi¹

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Abstract This paper reports the results of the first study in which *Streptococcus salivarius* 24SMB, a safe α -haemolytic strain capable of producing bacteriocin-like substances with significant activity against acute otitis media (AOM) pathogens, was intranasally administered in an attempt to reduce the risk of new episodes of AOM in otitis-prone children. In this prospective, randomized, double-blind, placebo-controlled study, 100 children aged 1–5 years with histories of recurrent AOM were randomized 1:1 to receive an intranasal *S. salivarius* 24SMB or placebo twice daily for 5 days each month for 3 consecutive months. Fifty treated children and 47 who received placebo who were compliant with study protocol were followed monthly for 6 months. The number of children who did not experience any AOM was higher among the children treated with the *S. salivarius* 24SMB preparation than among those in the placebo group (30.0 vs 14.9 %; $p=0.076$). Moreover, the number of children who received antibiotics during the study period was lower among the children treated with *S. salivarius* 24SMB than among those who received placebo (70 vs 83.0 %; $p=0.13$). Compared with the children who were not colonized by *S. salivarius* 24SMB after treatment, the number of colonized children who experienced any AOM was significantly lower (42.8 vs 13.6 %; $p=0.03$). Similar results were observed when

the children treated with antibiotics for AOM were analysed (67.8 vs 95.5 %; $p=0.029$). This study revealed the ability of intranasally administered *S. salivarius* 24SMB to reduce the risk of AOM in otitis-prone children.

Introduction

The prevention of further episodes of acute otitis media (AOM) in otitis-prone children is recommended by all experts to reduce the risk of complications, medical costs, and social and family problems that are strictly related to recurrent AOM [1, 2]. The control of environmental risk factors, antibiotic administration, immunoprophylaxis, vitamin D supplementation, probiotics, surgery, and alternative medicine has been proposed as a series of prophylactic measures [1, 2]. However, none of these measures is completely effective. Compared with controls, the majority of studies have observed reductions in the total numbers of episodes in treated children; however, even when various methods are applied simultaneously, a considerable number of children receive no benefit and continue to experience AOM. Furthermore, the use of some of these measures is widely questioned [1–4]. Long-term prophylactic antibiotic administration is associated with an increased risk of side effects and the emergence of resistant bacteria [3]. Similarly, the safety and tolerability of most alternative medicine remedies are not precisely defined [4].

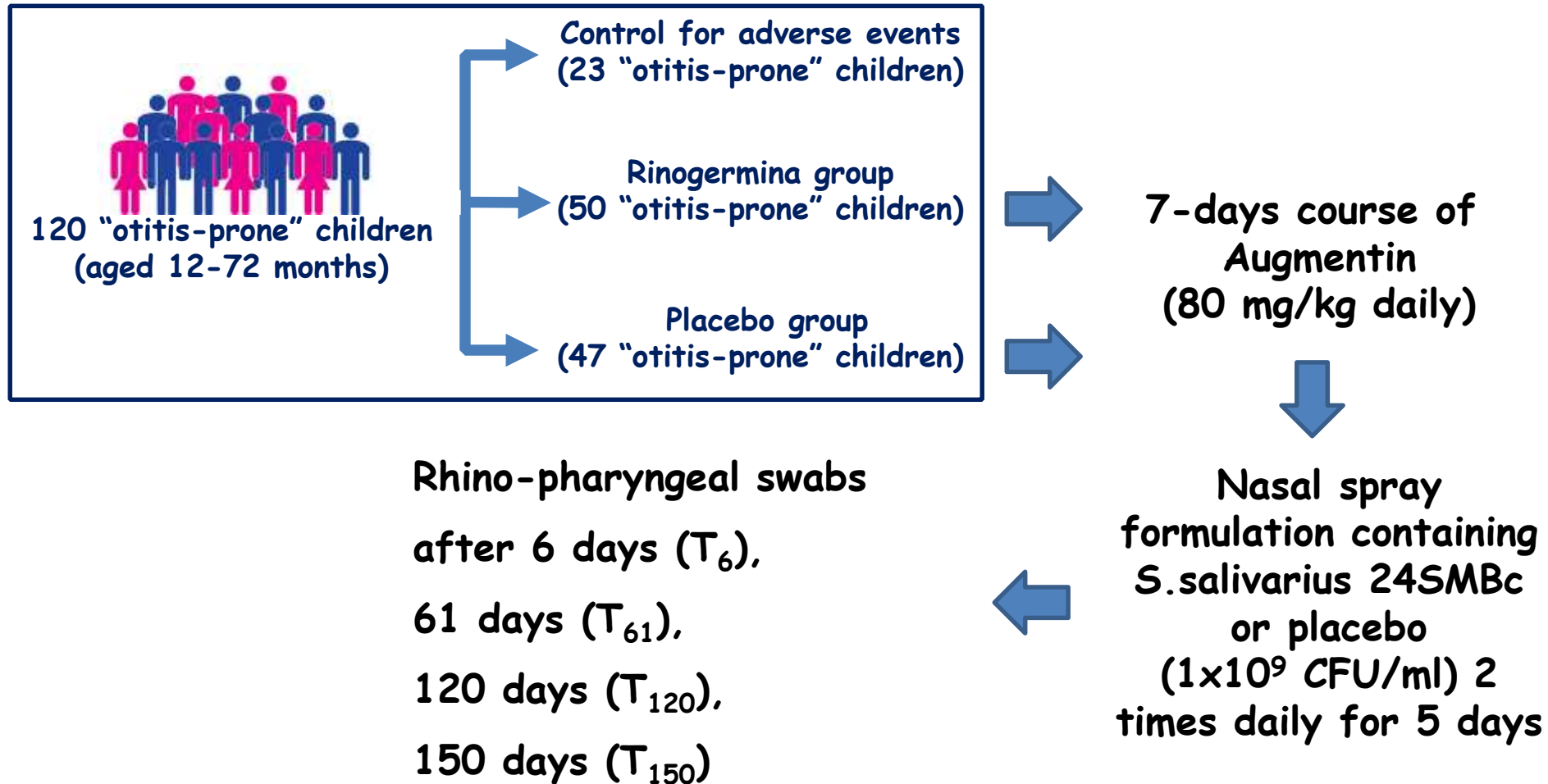
Some years ago, a number of studies reported evidence that the normal nasopharyngeal flora inhibits the growth of common otopathogens [5] and thus could play a relevant role in the prevention of upper respiratory tract infections, including AOM [6, 7]. Specifically, it has been reported that the numbers of α -streptococci colonizing the nasopharynx are significantly lower in otitis-prone children than in healthy children,

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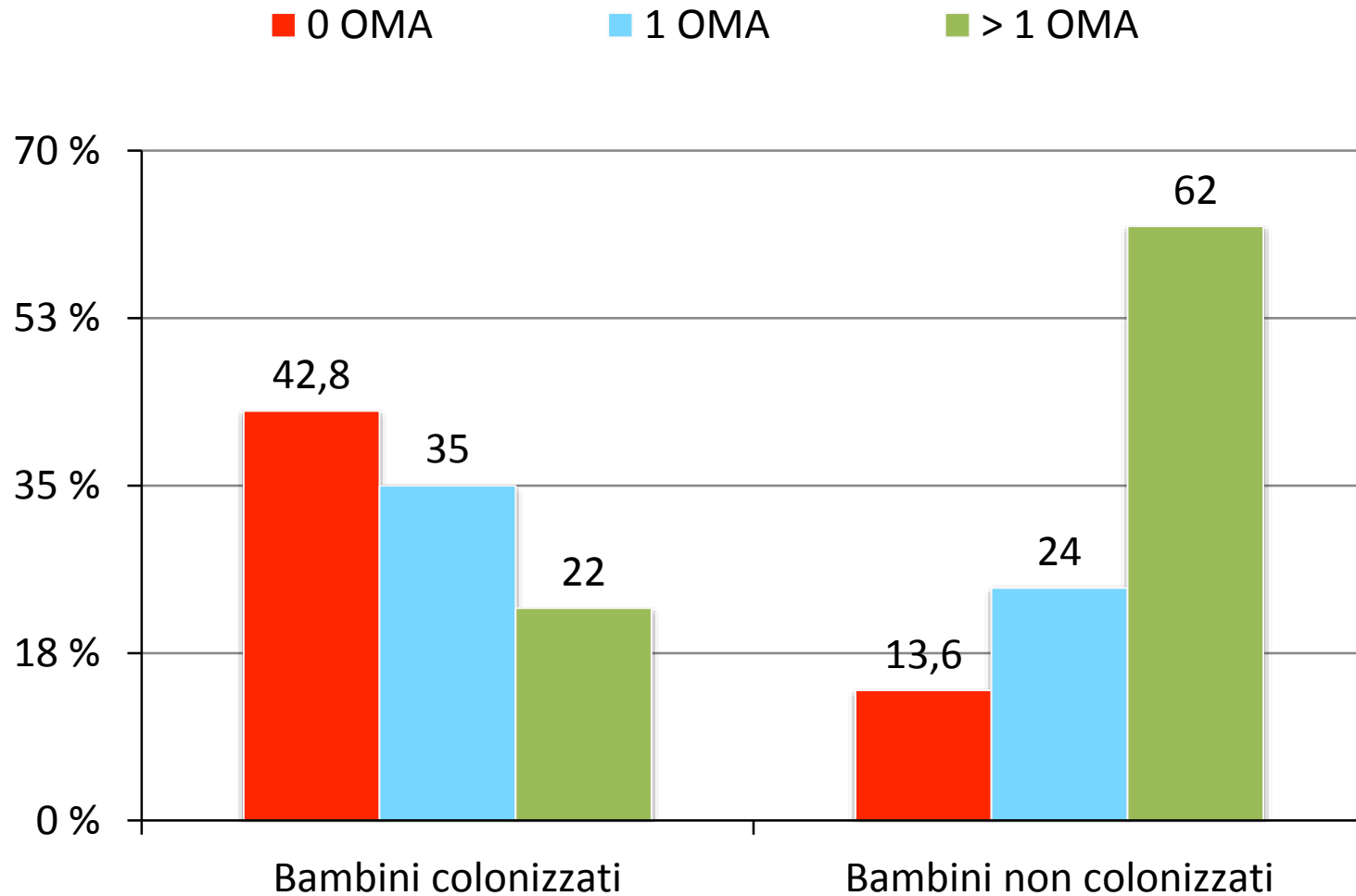
¹ Pediatric Highly Intensive Care Unit, Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Via Comenda 9, 20122 Milano, Italy

² Department of Biomedical and Biotechnological Sciences, MMAR Laboratory, University of Catania, Catania, Italy

Clinical evaluation of *S.salivarius* 24SMBc in a paediatric randomized, placebo-controlled, double-blind trial

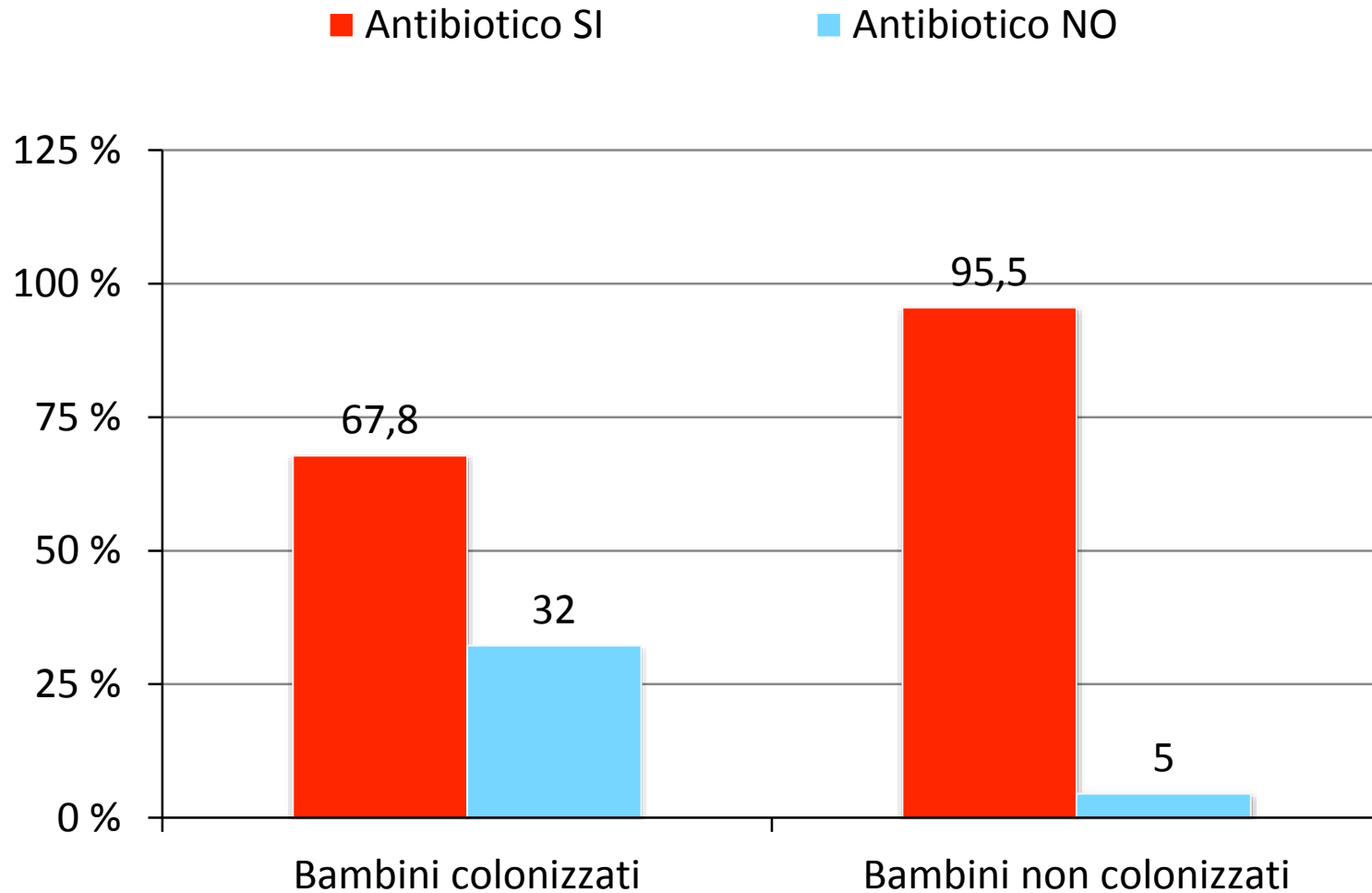


Rapporti tra colonizzazione con *S. salivarius* 24SMBc e insorgenza di OMA



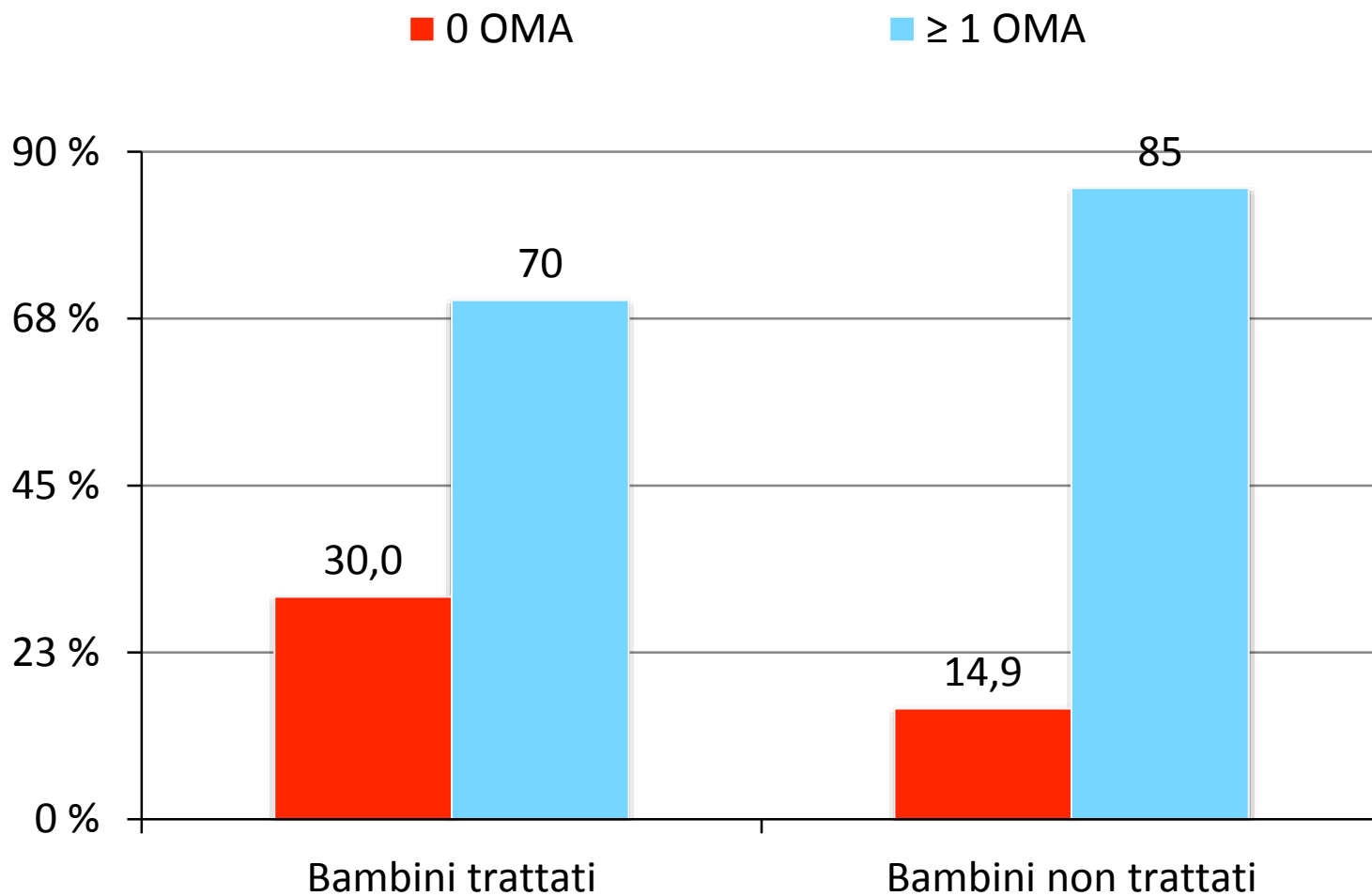
$p < 0.05$

Rapporti tra colonizzazione con *S. salivarius* 24SMBc ed utilizzo di antibiotici



$p < 0.05$

Rapporti tra trattamento e insorgenza di OMA



$p = 0.07$

...Thanks to...

Nicola Principi, Susanna Esposito, Paola Marchisio

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Università degli Studi di Milano

Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico

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resistenza (LMMAR) Dipartimento di Scienze Bio-mediche Università
degli Studi di Catania

Ignazio La Mantia

U.O.C. Otorinolaringoiatria

P.O Acireale

HOME-MESSAGE

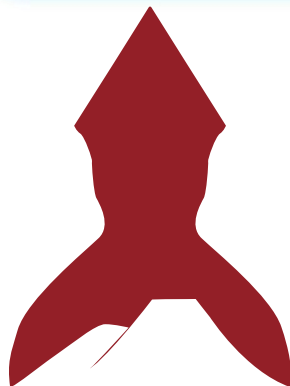
- Il microbiota nasale ha un ruolo fondamentale nell'eziopatogenesi dell'otite media acuta ricorrente (IRR)
- L'uso di probiotici in spray nasale sembra influenzare il microbiota nasale con un ruolo preventivo nei confronti dell'otite media acuta
- L'uso di probiotici nasali è sicuro e ben tollerato



MASTER-VAS di AIVAS



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Le Guide del Quartiere: Susy



Le “Mamme” del Quartiere



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l'umanesimo
è diventato
umanità
Per non morire!



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Grazie