



# I modificatori della reattività biologica: aspetti pratici di medicina traslazionale.

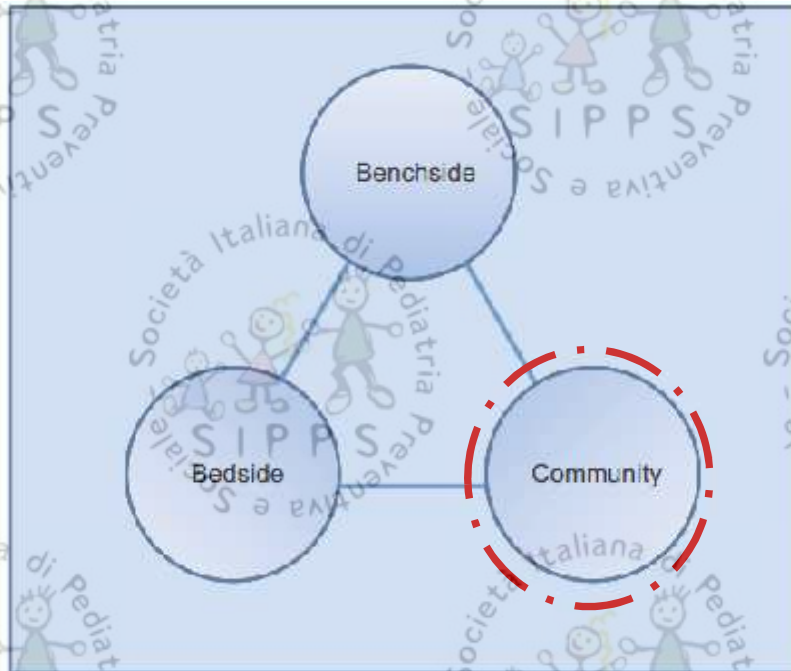
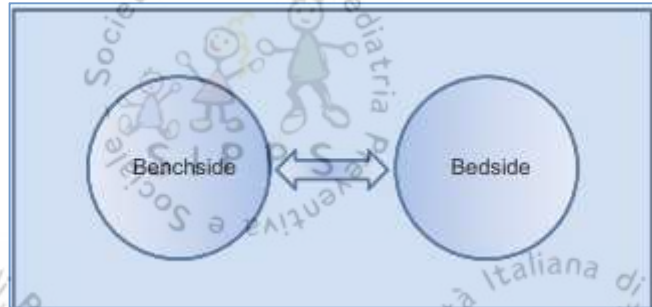
Francesca Santamaria

P. I. Pneumologia Pediatrica  
A. O. U. Federico II, Napoli



DIPARTIMENTO DI SCIENZE MEDICHE TRASLAZIONALI  
UNIVERSITÀ DEGLI STUDI DI NAPOLI - FEDERICO II

# I modificatori della reattività biologica: aspetti pratici di **Medicina Traslazionale**.



**Translational Medicine (TM)** is an interdisciplinary branch of the biomedical field supported by three main pillars: benchside, bedside and community.

The goal of TM is **to combine** disciplines, resources, expertise, and techniques within these pillars to promote enhancements in prevention, diagnosis, and therapies.





# Recurrent Respiratory Infections (RRTIs): definition

Criteri per definire il bambino affetto da Infezioni Respiratorie Ricorrenti (IRR) in età pediatrica <sup>a, b</sup>.

- **1-3 anni:**
  - 6 o più infezioni delle vie respiratorie (delle quali 1 può essere polmonite, anche grave) in un anno o
  - 2 polmoniti non gravi <sup>d</sup> confermate da criteri clinici e/o radiologici in un anno
- **3-6 anni:**
  - 5 o più infezioni delle vie respiratorie (delle quali 1 può essere polmonite, anche grave) in un anno o
  - 2 polmoniti non gravi <sup>d</sup> confermate da criteri clinici e/o radiologici in un anno
- **6-12 anni:**
  - 3 o più infezioni delle vie respiratorie (delle quali 1 può essere polmonite, anche grave) in un anno o
  - 2 polmoniti non gravi <sup>d</sup> confermate da criteri clinici e/o radiologici in un anno

## Consensus Statement Intersocietario sulle Infezioni respiratorie Ricorrenti (IRR) in Pediatria 2019

### Società Scientifiche:

SIP A.Villani  
SIMRI G.Piacentini  
SIAIP GL.Marseglia  
SIPPS G.Di Mauro  
SITIF G.Castelli Gattinara  
SICUPPP Becherucci  
FIMP P.Biasci  
SIO C.Vicini  
SIOP S.Bottero  
SIM MT.Palamara  
SIC A.Novelli

### Responsabili di Progetto:

R.Cutrerà  
E.Chiappini  
L.Galli  
P.Marchisio  
G.L.Marseglia  
F.Santamaria

.....aspetti pratici  
di **Medicina**  
**Traslazionale.**

# RRTIs in children

1. How big is the problem in the real life?
2. Why children develop RRTIs?
3. How to reduce RRTi?



# RRTIs in children

## How big is the problem in the real life?

At least 6% of Italian children < 6 yr have RRTIs.

*de Martino, PAI 2007*

Incidence in Finland: 10%

*Toivonen, 2016*

Incidence in China: ~18%

*Liu, J Cap Med Univ 2011*

## A major point

No epidemiological data from Italy

# RRTIs in children

1. How big is the problem in the real life?

2. Why children develop RRTIs?

3. How to reduce RRTIs?



# Risk factors for RRTIs

- day-care attendance
- large family size, overcrowding
- school-aged siblings
- missed vaccination

*“Attending a daycare centre is the most important risk factor for RRTIs in children 2-5 years”*

*Forssel, Scand J Prim Health care 2001*

**Table 1. Risk factors for recurrent pneumonia in children.**

Condition	Proposed Underlying Mechanisms
Prematurity/bronchopulmonary dysplasia	Inadequate immunity due to low maternal antibodies levels Impaired lung function Altered innate immunoregulatory response of the lungs to respiratory pathogens secondary to neonatal hyperoxia
Atopy	Defective innate immune response of epithelial cells Interleukin 13-dependant reduced mucociliary clearance
Tobacco smoke exposure	Neonatal low lung volume and impaired toll-like receptor-mediated immune response Suppressed phagocytic activity of neutrophils and monocytes/macrophage cells secondary to reduced production of oxygen radicals Increased bacterial adherence Impaired lung function
Over-crowding	Increased exposure to respiratory pathogens
Indoor and outdoor pollution	Distal bronchial and alveolar inflammation

*Montella, Int. J. Mol. Sci. 2017*

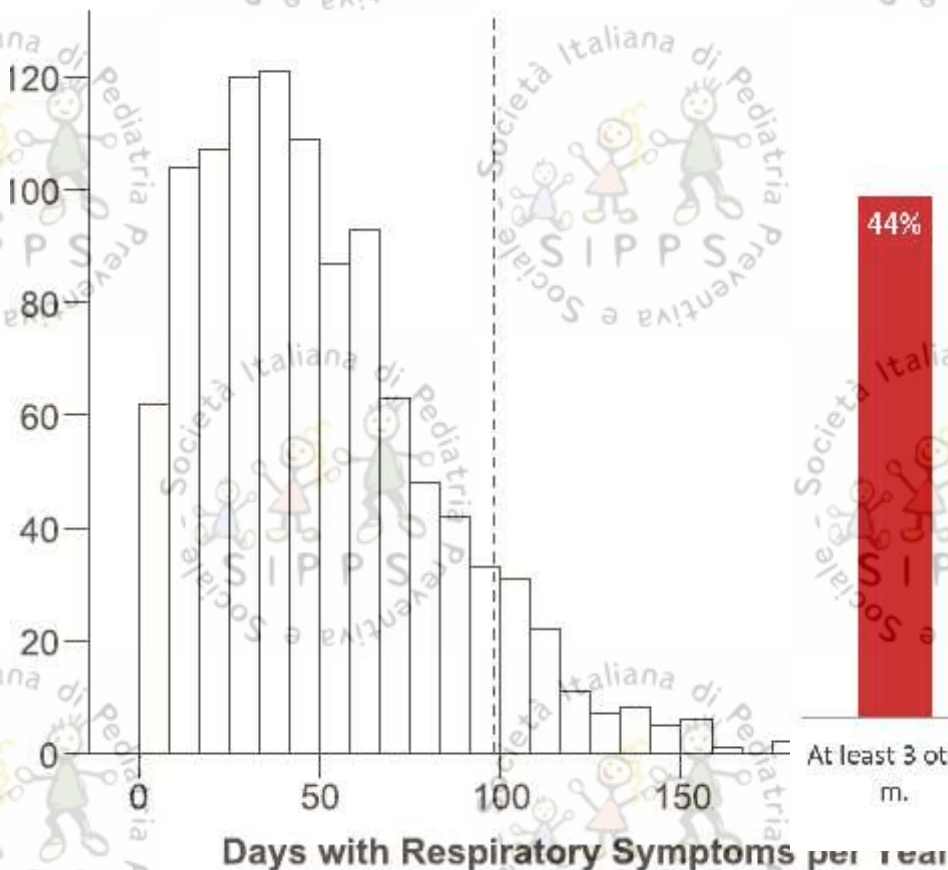
# Burden of RRTI in Children: A Prospective Cohort Study. *Toivonen, 2016 (Finland)*

The Pediatric Infectious Disease Journal

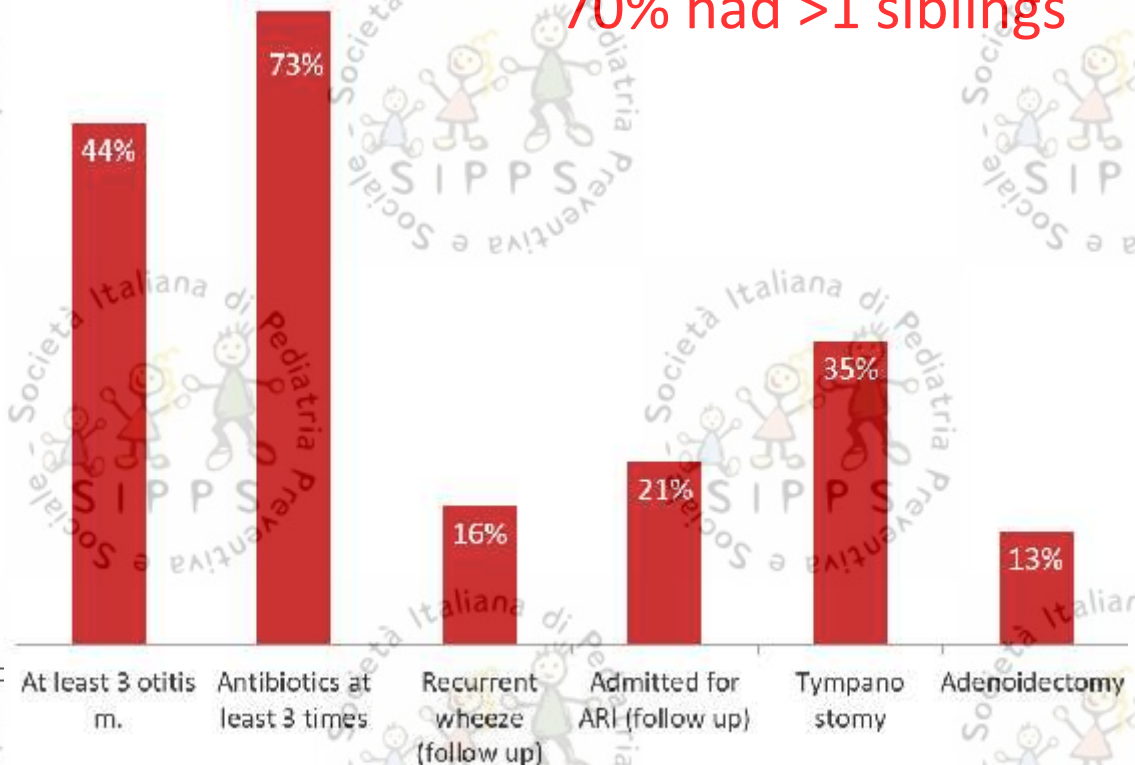
A prospective study of 1089 ch. from birth to 2 yrs (Jan 2008- April 2010)

- 98 days = n<sup>o</sup> of airways illness days/yr = 90<sup>th</sup> centile
- Children > this limit (= 109): median of 9.6 ARI/yr.

N<sup>o</sup> of children



70% had >1 siblings



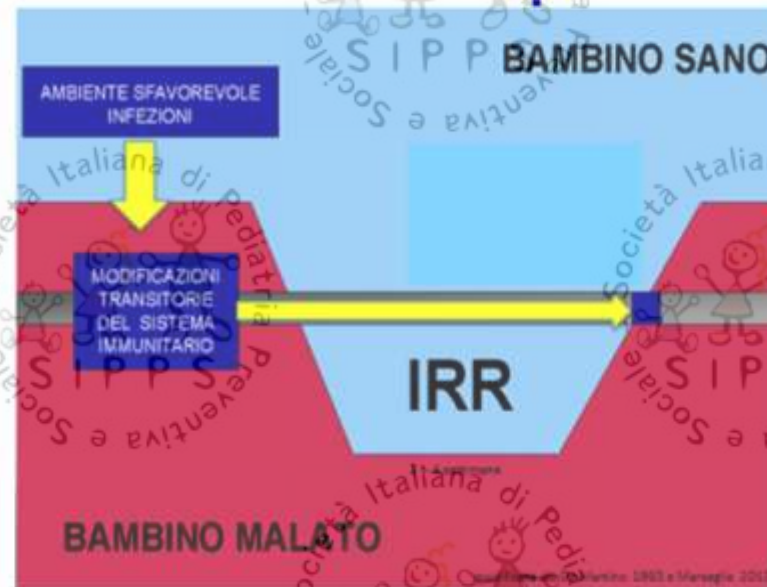


# RRTIs in children

1. How big is the problem in the real life?

2. Why children develop RRTIs?

Cortesia di Prof Marchisio



No significant alterations in immunity, but **mild transient** ID

- ✓ decreases in CD4+ T lymphocytes
- ✓ alterations in cytokine responses and neutrophil chemotaxis
- ✓ partial IgA defects, and altered IgG subclasses

# RRTIs in children

1. How big is the problem in the real life?

2. Why children develop RRTIs?

3. How to reduce RRTIs?



# RRI in children

## How to reduce RRI?

1. Limit the exposure to circulating pathogens (crowding)
2. Limit the exposure to passive smoke or allergens
3. **Improve the immaturity of the immune system**



## Immunomodulators

- Probiotics, prebiotics and symbiotics
- Bacterial lysates and extracts
- Synthetic molecules (pidotimod, methisoprinol, levamisole)
- Trace elements and vitamins
- Others

## Asthma: NHLBI Workshop on the Primary Prevention of Chronic Lung Diseases

Ann ATS 2014

Daniel J. Jackson<sup>1</sup>, Tina V. Hartert<sup>2</sup>, Fernando D. Martinez<sup>3</sup>, Scott T. Weiss<sup>4</sup>, and John V. Fahy<sup>5</sup>

Interventions in

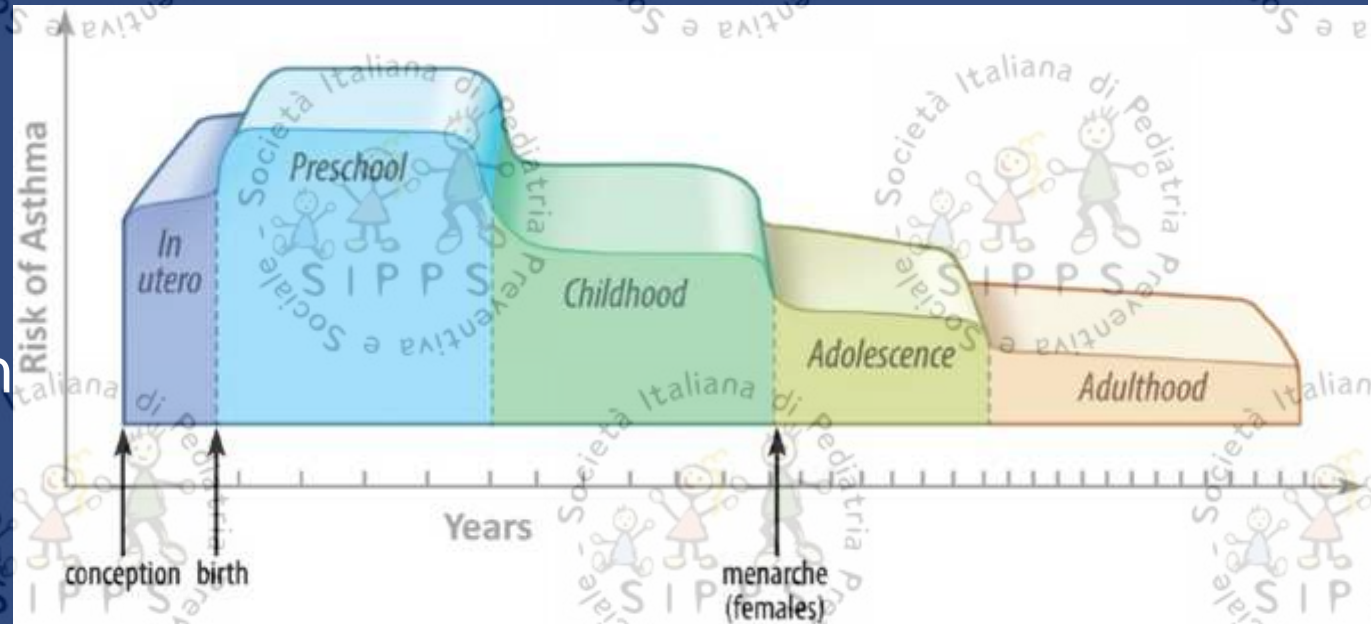
Early postnatal life



Immune modulation



The rationale is



Dendritic cell maturation

expression of TLR e class II HLA on dendritic cell surface

IL1, IL6 & IL12 synthesis

T lymphocytes differentiation → Th<sub>1</sub>



# Immunomodulators

# PROBIOTICS

- 8 pediatric RCTs
  - 7: daycare/healthy
  - 1: **nosocomial** GI/airway infections
- May **slightly** reduce school absence & antibiotics

**Large, multicenter, double-blind CTs are needed**



Cochrane  
Library

2015



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

09 September 2019  
EMA/502527/2019

*Settembre 2019*

## Bacterial lysate medicines for respiratory conditions to be used only for prevention of recurrent infections

On 27 June 2019, EMA recommended that bacterial lysate medicines authorised for respiratory conditions should only be used for the prevention of recurrent respiratory infections, with the exception of pneumonia. This followed a review that concluded that there are no robust data showing that these medicines are effective at treating existing respiratory infections, or for the prevention of pneumonia, therefore they should not be used for these purposes.

In the review, EMA's human medicines committee (CHMP) considered the results of clinical studies, data on side effects reported with these medicines, and advice from an expert group on infectious diseases.

Although data are limited, the review found some evidence of effectiveness of these medicines in the prevention of recurrent respiratory tract infections and the safety profile is in line with what is expected for this type of product. The CHMP therefore recommended that use of the medicines for prevention can continue, but the companies must provide further data on safety and effectiveness from new clinical studies by 2026.

### Information for patients

- Bacterial lysate medicines should not be used to treat existing infections of the airways or to prevent pneumonia (a lung infection) because there are not enough data to show that they work for these uses.
- Bacterial lysate medicines can continue to be used to prevent infections of the airways (except pneumonia) from coming back in patients who regularly get infections.
- If you have an infection and are taking a bacterial lysate medicine to treat it, or if you are taking one of these medicines to prevent pneumonia, contact your doctor or pharmacist for advice on alternatives.
- If you have any questions or concerns about your medicine, discuss them with your doctor or pharmacist.

### Information for healthcare professionals

- The indications of bacterial lysate medicines have been restricted to prophylaxis of recurrent respiratory tract infections, with the exception of pneumonia. Bacterial lysate medicines should not

- Synthetic molecules (pidotimod, methisoprinol, levamisole)
- Probiotics, prebiotics and symbiotics
- Bacterial lysates and extracts
- Trace elements and vitamins
- Others

**L' Agenzia Europa per i Medicinali (EMA) raccomanda che i medicinali a base di lisati batterici autorizzati per le malattie respiratorie siano utilizzati soltanto per la prevenzione delle IRR, con l'esclusione della polmonite**



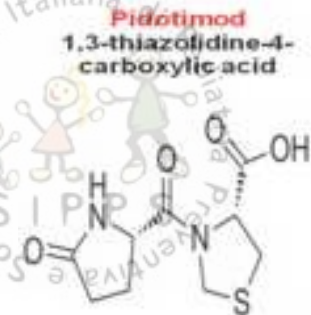
# Immunomodulators

## Pidotimod

- Synthetic molecules (pidotimod)
- Probiotics, prebiotics and symbiotics
- Bacterial lysates and extracts
- Trace elements and vitamins
- Others

- Immunomodulatory activity on innate/adaptive immune response
- Induces dendritic cell (DC) maturation
- Upregulates the expression of HLA-DR & co-stimulatory CD83 and CD86
- Stimulates DCs to release pro-inflammatory molecules (*driving T cell towards Th1 phenotype*)
- Enhances natural killer cell functions
- Inhibits thymocyte apoptosis & promotes phagocytosis

Rapidly absorbed by GI tract  
(bioavailability 45%)



*Pharmacol Res. 1992; Intern Immunopharmacol 2019*

# Pidotimod & clinical research on pediatric RTIs.....

- ***Mameli C, Pharmacol Res. 2015.***

Pidotimod for the prevention of **acute respiratory infections** in healthy children entering into daycare.

- ***Esposito S, J Transl Med. 2015.***

Immunomodulatory activity of pidotimod administered with standard antibiotic therapy in **children hospitalized for CAP.**

- ***Licari A, Minerva Pediatr. 2014***

Pidotimod may prevent **recurrent respiratory infections** in children.

- ***Zuccotti GV, J Biol Regul Homeost Agents. 2013***

Immunomodulating activity of Pidotimod in **ch. with Down syndrome**





2019

International Immunopharmacology

Journal homepage: [www.elsevier.com/locate/intimp](http://www.elsevier.com/locate/intimp)

523 → 29 RCT

Review

Pidotimod, an immunostimulant in pediatric infections: A meta-analysis

Hui Niu, Rui Wu

## Pidotimod

Reduces relapses & need of antibiotics  
Increases serum Ig levels

RR of relapse

High-quality evidence and universally accepted standard from RCT are required

0.1 0.2 0.5 1 2  
Favours [control]

Favours PDT

0.1 0.2 0.5 1 2  
Favours [control]

IgA

Favours PDT

# Pidotimod & clinical research on pediatric RTIs.....

Pidotimod for the prevention of acute respiratory infections in healthy children entering into daycare: A double blind randomized placebo-controlled study

Chiara Mameli<sup>a</sup>, Angela Pasinato<sup>b</sup>, Marina Picca<sup>c</sup>, Giorgio Bedogni<sup>d</sup>, Stefania Pisanelli<sup>e</sup>, Gian Vincenzo Zuccotti<sup>a,\*</sup>, for the AX-Working group<sup>f</sup>

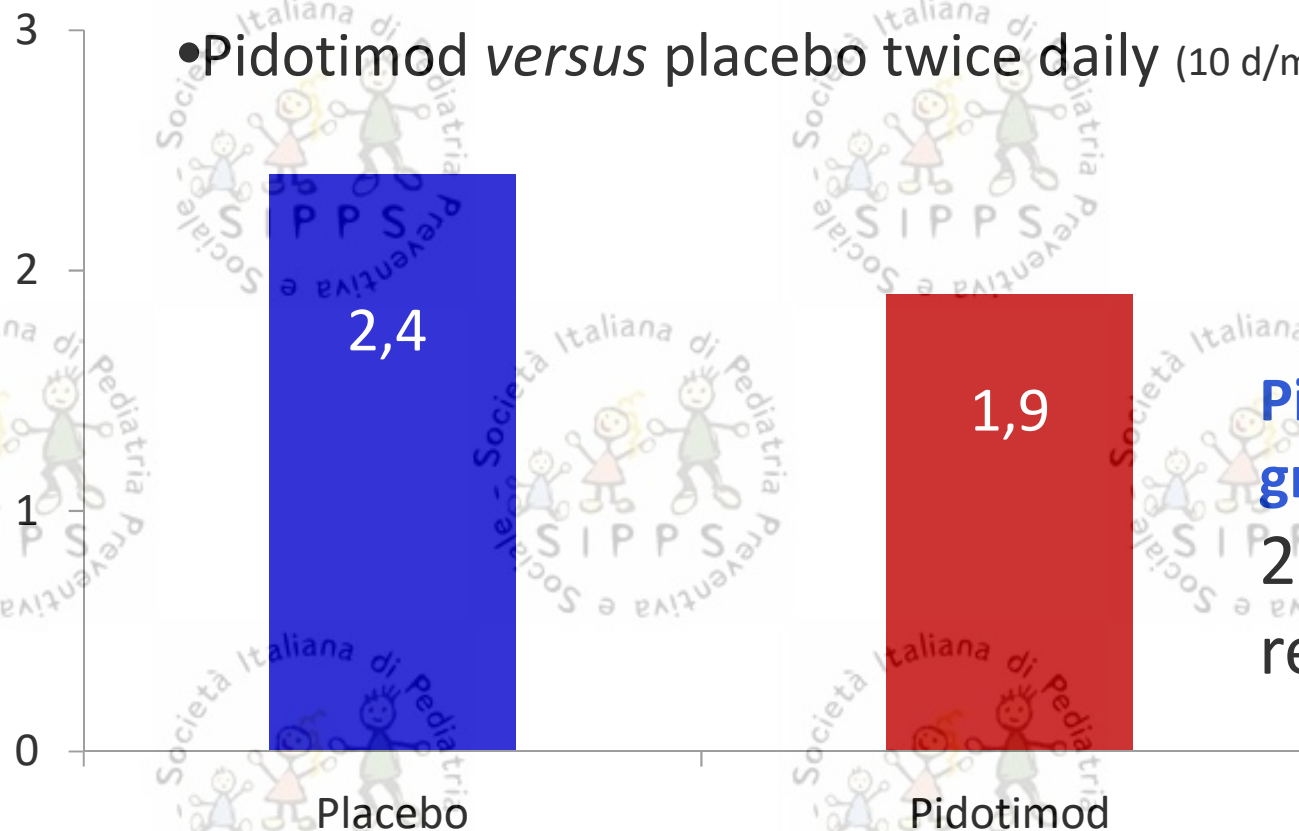
Pharmacological Research 97 (2015) 79–83

## Double-blinded RCT

- **49 healthy 3-yr-old ch.** not yet attending day-care

- **Pidotimod *versus* placebo** twice daily (10 d/mo, Oct-April).

Infections  
rate

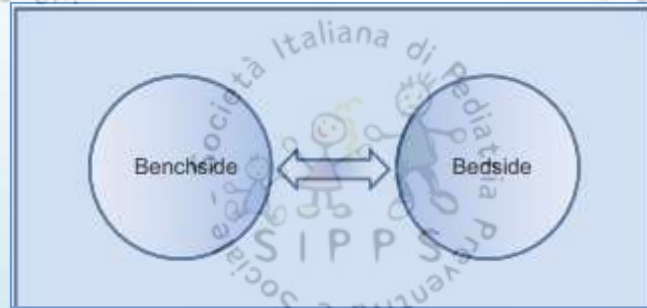


**Pidotimod  
group:  
22%  
reduction**



# Pidotimod: the Clinical Trials in children

## The airways microbial dysbiosis



# ...how to study dysbiosis?

## Dysbiosis

Changes in microbial composition/function in the airways and the gut likely linked to alterations in immune responses and to the development of lung diseases

# Pidotimod: the Clinical Trials in children

...how to study dysbiosis?

## METABOLOMICS ANALYSIS

Metabolomics systematically identify and quantify the set of metabolites in biological specimens by NMR or liquid chromatography mass spectrometry.

*Fanos, 2013   Hasegawa, 2016   Carraro, 2018*

Can metabolomics be used in the diagnosis of airways infection?



# Metabolomics and Inflammatory/Infectious Chest Diseases

IRCCM, 2014

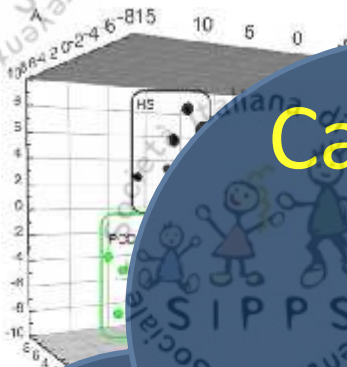
Pozzuoli

Can metabolomics be used in the diagnosis of airways infection?

Metabolomics have the potential to become a diagnostic aid in airway infections.

Metabolites distinct in pneumoniae and other pathogens.

*Stringer, Front Immunol. 2016*



# Pidotimod: the Clinical Trials in children

## METABOLOMICS ANALYSIS and RRI



- Can metabolomics discriminate healthy ch. from those with RRI?
- If yes, can the “dysregulated” metabolic profile of RRI be due to different microbiome?
- If yes, can immunomodulators modify the “dysregulated” metabolic profile of RRI ?



# Pidotimod & clinical research on pediatric RTIs.....

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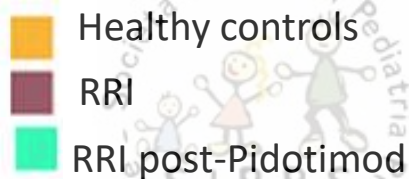
- ***Bozzetto S, Pharmacol Res. 2017***

Metabolomic profile of children with **recurrent respiratory infections**

# Pidotimod & clinical research on pediatric RTIs.....

## Metabolomic profile of ch. with RRI

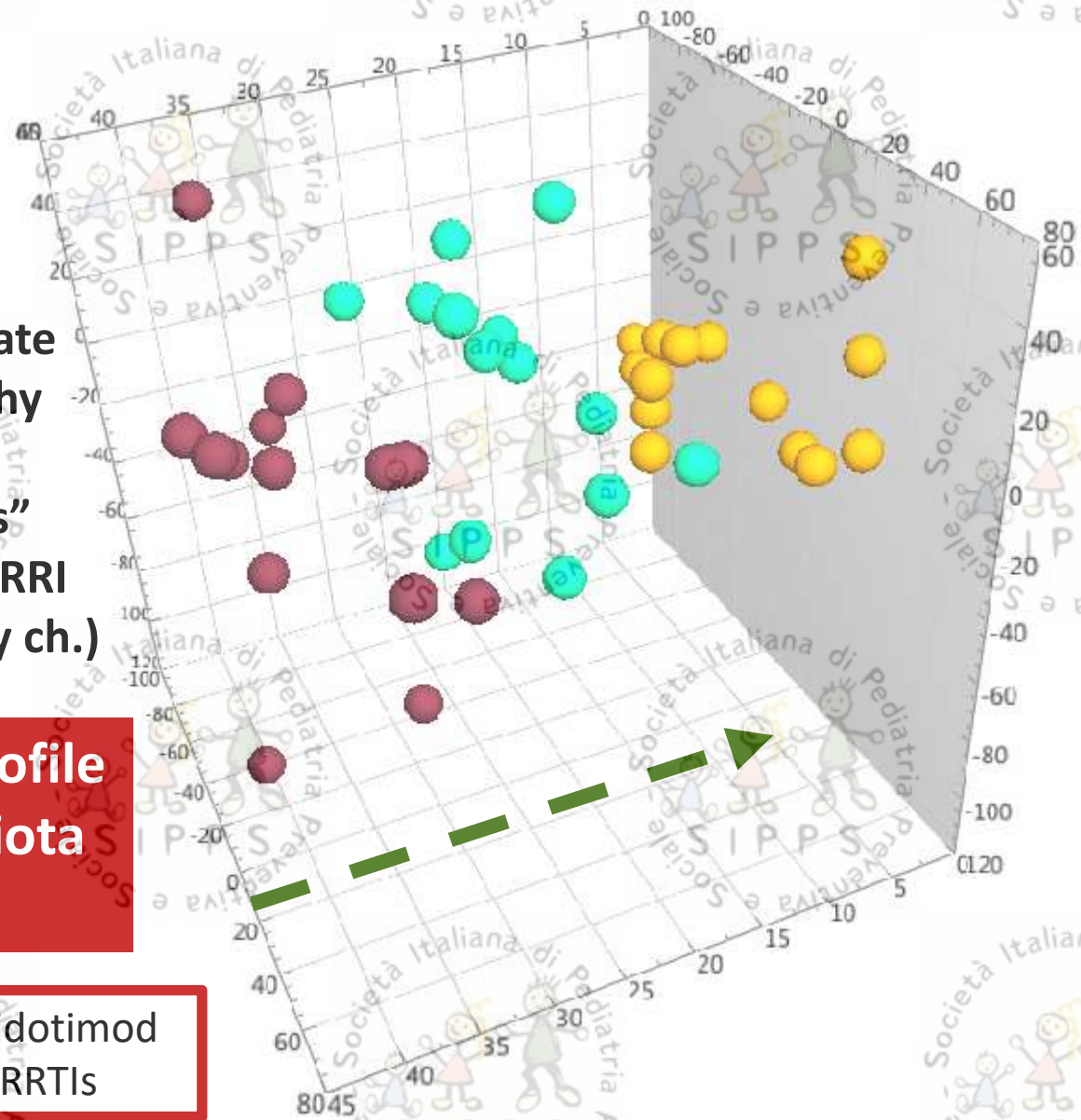
Bozzetto, 2017



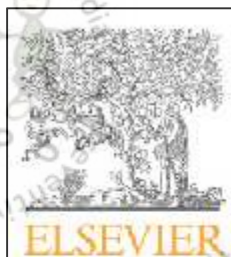
1. Metabolomics can discriminate children with RRI from healthy ctrls
2. Pidotimod partially “restores” the metabolome of ch. with RRI (=NOT different from healthy ch.)

**Dysregulated metabolic profile due to an altered microbiota composition in RRTIs?**

No study compared the effect of pidotimod *plus* probiotics in children with RRTIs







Contents lists available at ScienceDirect

## Pulmonary Pharmacology & Therapeutics

journal homepage: [www.elsevier.com/locate/ypupt](http://www.elsevier.com/locate/ypupt)

2019



Effects of pidotimod and bifidobacteria mixture on clinical symptoms and urinary metabolomic profile of children with recurrent respiratory infections: a randomized placebo-controlled trial

Francesca Santamaria<sup>a,\*</sup>, Silvia Montella<sup>a,\*</sup>, Matteo Stocchero<sup>b</sup>, Paola Pirillo<sup>b,c</sup>, Sara Bozzetto<sup>b</sup>, Giuseppe Giordano<sup>b,c</sup>, Marco Poeta<sup>a</sup>, Eugenio Baraldi<sup>b,c</sup>

**Primary clinical endpoint**      **Secondary metabolomic endpoint**

Symptom-free days

Any change in the urine

Days with common cold

metabolomic profile.

**before and after treatment with pidotimod and bifidobacteria mixture**

Children with RRTIs aged 3–6 years attending nursery school/kindergarten

Inclusion  
criteria

A four-arm, exploratory, prospective, RCT  
(2 autumn seasons, in 2 consecutive yrs)

### Group A

pidotimod  
(1 vial 400  
mg/d)

+

bifidobacteria  
mixture  
(1 sachet 3 g/d)

### Group B

pidotimod +  
placebo of  
bifidobacteria  
mixture

### Group C

placebo of  
pidotimod +  
bifidobacteria  
mixture

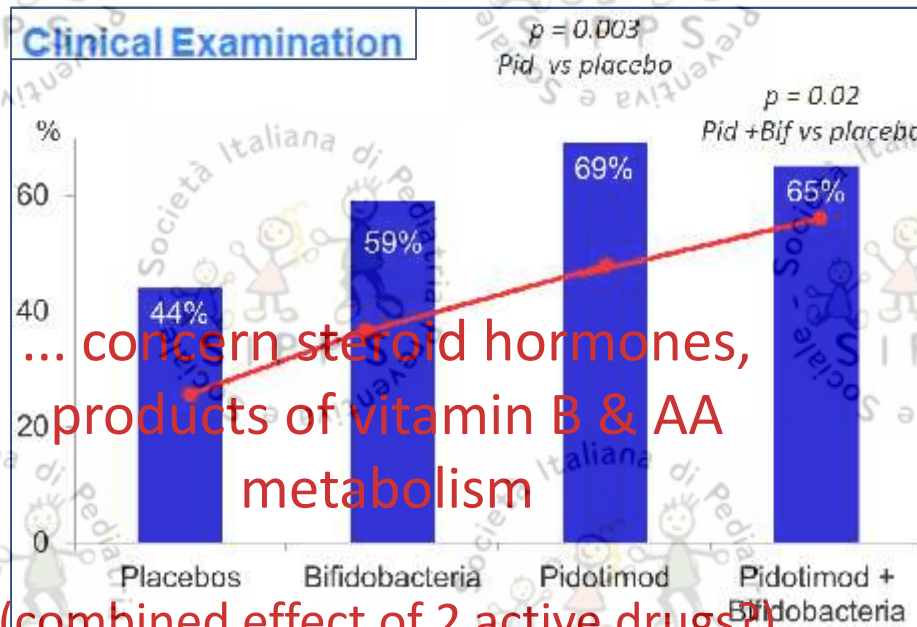
### Group D

placebo +  
placebo

- active drugs and/or placebo in the first 10 days, each month, for 4 months
- follow-up for 2 additional months.



# Results

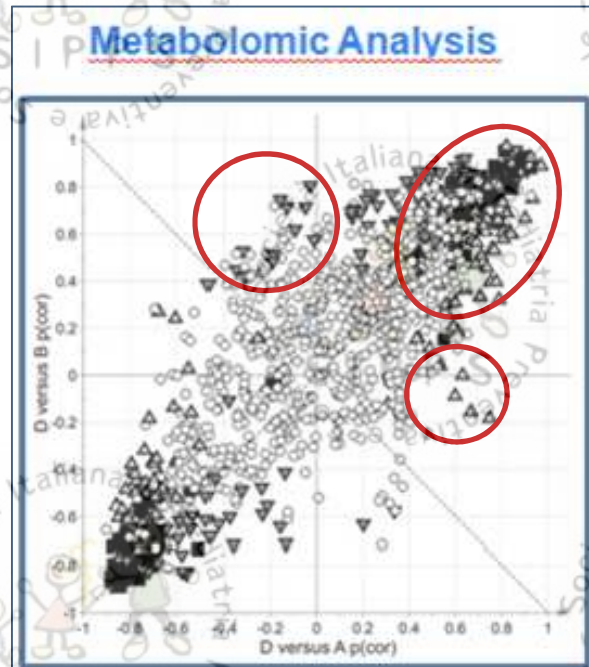


... concern steroid hormones,  
products of vitamin B & AA  
metabolism

(combined effect of 2 active drugs?)

**Symptom-free days (%)**

(associated with microbiota  
composition?)



Significant differences in

- cases treated with **PIDO + Bifidobact** vs placebos
- cases treated with **PIDO + placebo of Bifidobact** vs placebos

No significant differences

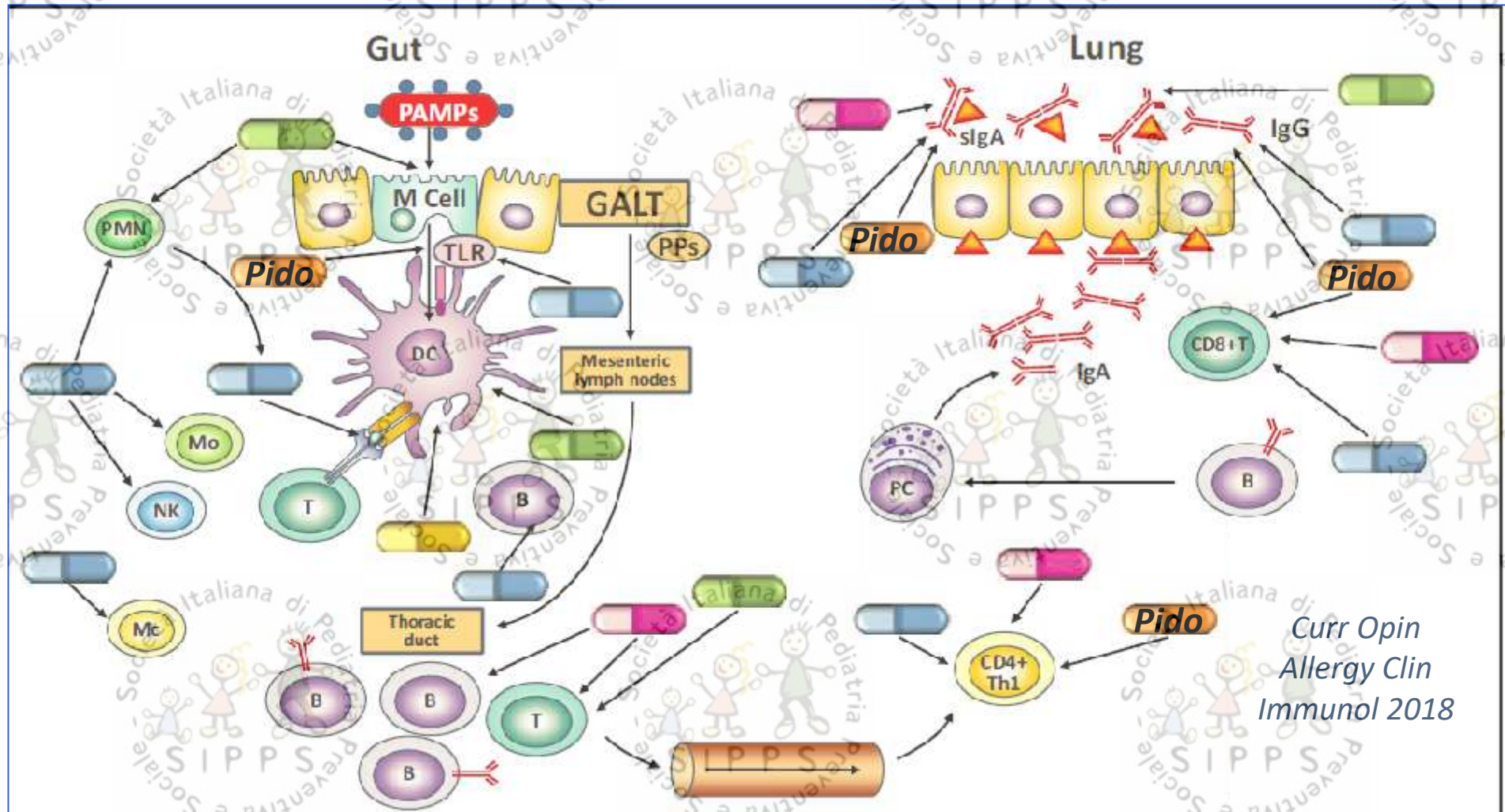
- in cases treated with **Bifidobact + placebo of PIDO** vs placebos

# TAKE HOME MESSAGES

1. First exploratory prospective RCT on clinical efficacy and effects on the urine metabolomic profiling of the combined use of an immunostimulant & probiotics
2. Pidotimod, administered alone or combined with bifidobacteria, is safe and effective for preventing RRI in preschool children
3. Metabolomics can be used in the field of infectious diseases



# TAKE HOME MESSAGES



*Curr Opin  
Allergy Clin  
Immunol 2018*

*...there is potential for manipulation of the gut microbiota in the treatment of lung diseases.*

*Budden, Nat Rev Microbiol. 2017*

# SPECIAL THANKS TO THE PRIMARY CARE PEDIATRICIANS



DIPARTIMENTO DI SCIENZE MEDICHE TRASLAZIONALI  
UNIVERSITÀ DEGLI STUDI DI NAPOLI - FEDERICO II

&

Dipartimento di Salute  
della Donna e del  
Bambino  
Università di Padova

*Eugenio Baraldi*  
*Matteo Stocchero*  
*Giuseppe Giordano*  
*Sara Bozzetto*

## ...AND TO CHILDREN'S PARENTS

Abete Antonio  
Amendola Emilia  
Amoroso Riccardo  
Cecere Gaetano  
Ciampa Paola  
Crisanti Angela Francesca  
Di Lorenzo Raffaele  
Donnarumma Maria  
Ecuba Paola  
Emilia Finelli  
Ercolini Paola  
Fasano Antonietta  
Gaetaniello Lucia  
Giaccio Giuliana  
Habetswallner Daniela  
Lettera Patrizia  
Mayer Marina  
Micillo Maria  
Musto Anna  
Pastore Imma  
Santangelo Maria Teresa  
Wanderlingh Paola



# RRTIs in children

2019



*Consensus  
Statement  
Intersocietario  
sulle*  
**Infezioni  
Respiratorie  
Ricorrenti  
in Pediatria**





# RRI in children

## How to reduce RRI?

1. Limit the exposure to circulating pathogens (crowding)
2. Limit the exposure to passive smoke or allergens
3. **Improve the immaturity of the immune system**



## Immunomodulators

- Probiotics, prebiotics and symbiotics
- Bacterial lysates and extracts
- Synthetic molecules (pidotimod, methisoprinol, levamisole)
- Trace elements and vitamins
- Others

## RRI in children

- Probiotics, prebiotics and symbiotics
- Bacterial lysates and extracts
- Synthetic molecules (pidotimod, methisoprinol, levamisole)
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## Effects of bovine colostrum on recurrent respiratory tract infections and diarrhea in children

Saad, Medicine, 2016

Assessment parameters at baseline and changes at 2 and 6 months after bovine colostrum therapy.					
Parameter (mean±SD)	Baseline <sup>†</sup>	After 2 months	After 6 months	P1 <sup>†</sup>	P2 <sup>‡</sup>
Total number of infections	8.6±5.1	5.5±1.2	5.7±1.6	<0.001	<0.001
Upper respiratory tract infection	8.2±3.3	3.6±2.2	3.8±3.1	<0.0001	<0.001
Diarrhea	6.1±2.0	3.7±2.5	3.9±2.7	<0.001	<0.001
Other infections	1.9±3.3	1.1±1.7	1.2±1.8	0.01	<0.05
Hospital admission	2.2±1.5	0.9±0.8	1.1±0.8	<0.001	<0.001

**Conclusion:** BC is effective in the prophylaxis of recurrent URTI and diarrhea as it reduces the number of episodes and the hospitalization due to these infections. Results of this study suggest that BC could be provided as a therapeutic option for children with recurrent URTI and diarrhea.

*Open study*



# RRI in children

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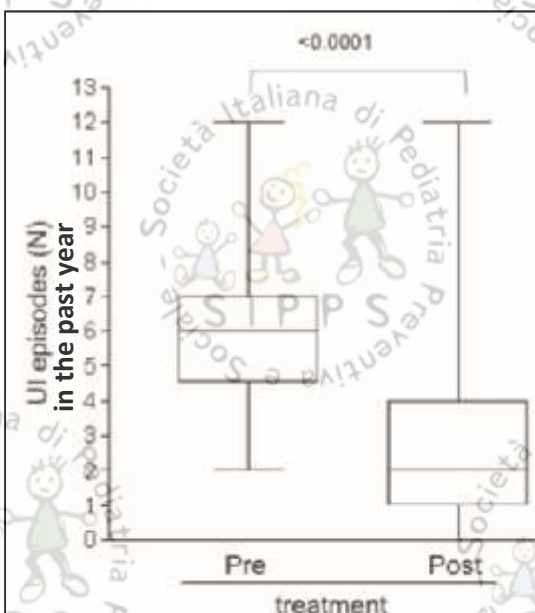
European Review for Medical and Pharmacological Sciences

2019; 23(1 Suppl): 39-43

## Bacteriotherapy in children with recurrent upper respiratory tract infections

*Open study*

V. TARANTINO<sup>1</sup>, V. SAVAIA<sup>1</sup>, R. D'AGOSTINO<sup>1</sup>, M. SILVESTRI<sup>2</sup>, F.M. PASSALI<sup>3</sup>,  
S. DI GIROLAMO<sup>3</sup>, G. CIPRANDI<sup>4</sup>



Nasal spray containing *Streptococcus salivarius* 24SMB & *Streptococcus oralis* 89a (2 puffs/nostril twice day for 1 week, repeated for 3 mo).

Bacteriotherapy nasal spray could prevent recurrent URTI in children.