# PREVENZIONE DELLE INFEZIONI RESPIRATORIE RICORRENTI

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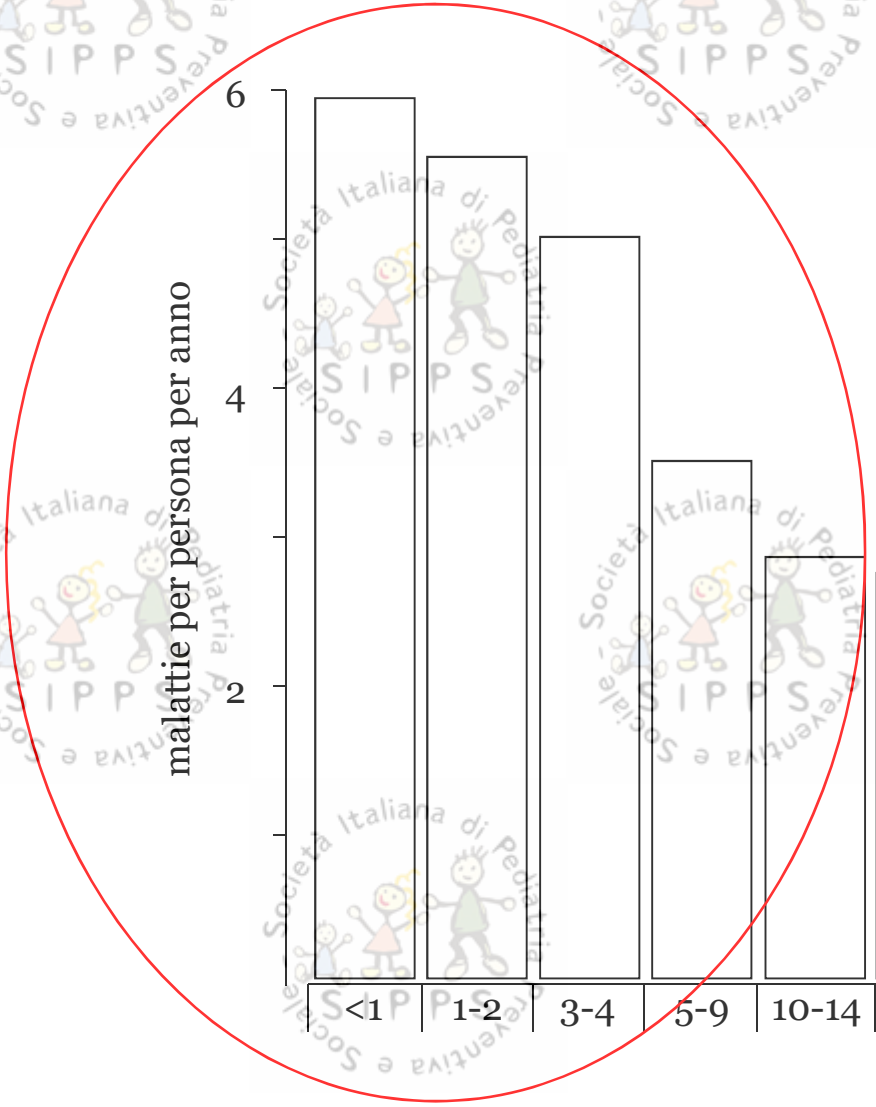
**Sofia ha 3 anni e mezzo**
**Milano, 23 novembre 2015**
**I visita**

**la mamma racconta:**

- **6 - 8 episodi di otite (ultimo a giugno 2015)**
- **raffreddore persistente da inizio settembre**
- **due episodi di bronchite asmatica in inverno**
- **una rinosinusite a marzo 2015**
- **frequenta la scuola materna a tempo pieno**
- **ha un fratello di 6 anni**
- **usa il ciuccio**
- **cresce bene;  mai ricoveri**

# incidenza annuale media di infezioni respiratorie per classe di età

**Heikkinen T & Järvinen A. Lancet 2003; 361: 51-59**




Fino al 25% dei bambini di età inferiore a 5 anni nei paesi industrializzati hanno infezioni respiratorie ricorrenti
(non è una malattia rara)

Dipartimento di Pediatria
Università di Firenze

# Infezioni respiratorie ricorrenti (IRR) : diverse definizioni

- ≥ 6 infezioni respiratorie in un anno
- ≥ 1 infezione delle alte vie al mese da settembre ad aprile
- ≥ 3 infezioni delle basse vie in un anno

(Gruppo di Studio di Immunologia della Società Italiana di Pediatria, 1988)

| | |
|---|---|
| **Età < 3 anni** | **ñ 8 IVAS /anno** |
| **Età ≥ 3 anni** | **ñ 6 IVAS/anno** |
| **Tutte le età** | **ñ 2 IVAI/anno** |

In assenza di condizioni patologiche di base che possano giustificare la ricorrenza

*Korppi M, Pediatr. Pulmonol. 1997*
*De Mattia D, Immunopharmacol. Immunotoxicol. 1993*
*Valleron AJ, Develop. Biol. Standard 1992*
*A.Ugazio. Il bambino con infezioni ricorrenti. 2003*

Necessita’ di anamnesi accurata supportata da:

- dati clinici documentati ed oggettivi
- criteri diagnostici “rigorosi” (attenzione soprattutto a otite media acuta e rinosinusite)

In mancanza di anamnesi: follow-up per 2-4 mesi (deve essere escluso dalla definizione di IRR il bambino che presenta solo una breve serie di ricorrenze limitate nel tempo)

# EZIOLOGIA DELLE INFEZIONI RESPIRATORIE RICORRENTI

- I virus (RVS, Rhinovirus, virus influenzali, adenovirus, parainfluenzali, metapneumovirus ma non solo … enterovirus emergenti) sono i principali agenti eziologici delle infezioni respiratorie ricorrenti (80%)

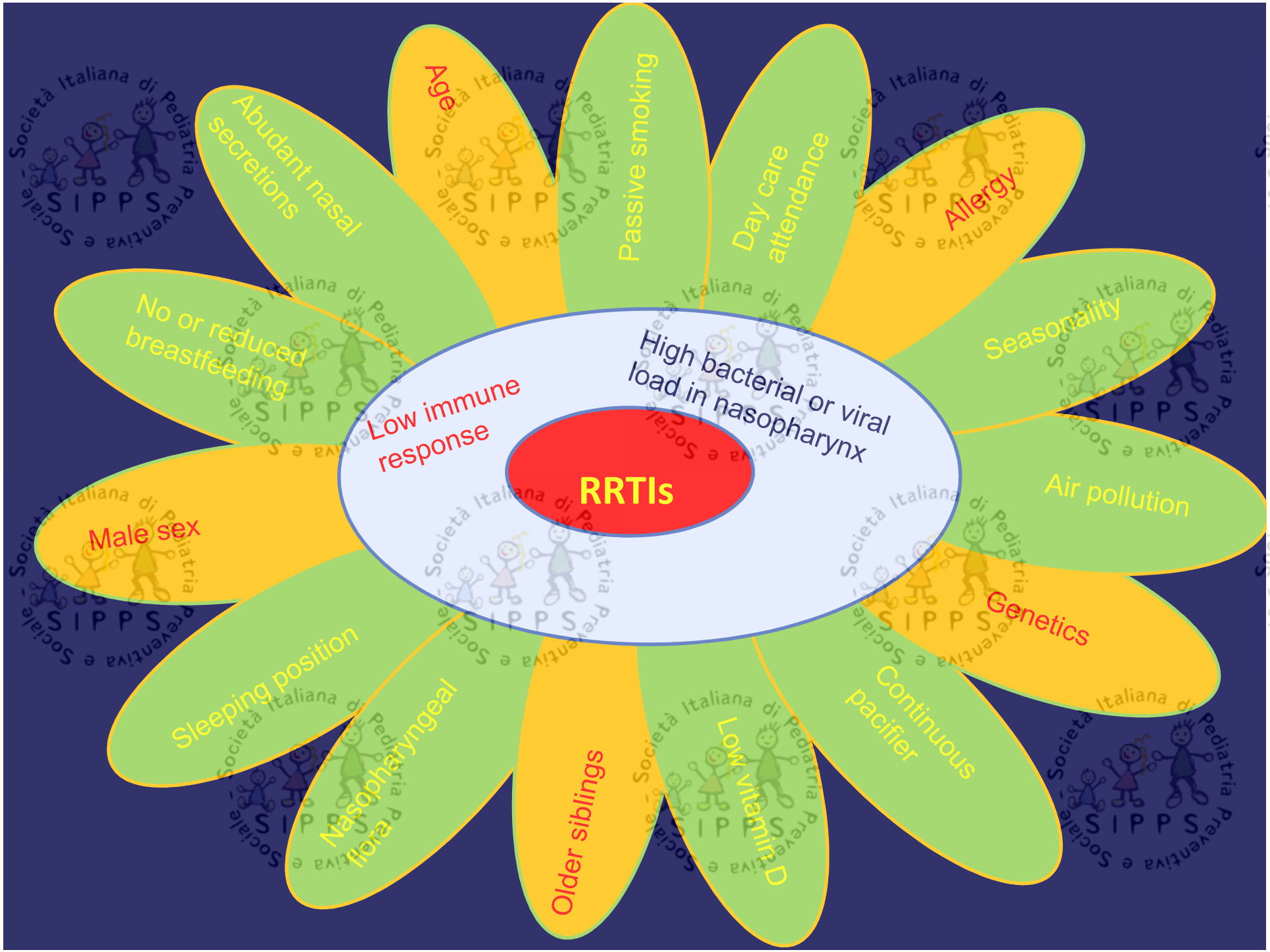
- Alcuni patogeni respiratori batterici quali Streptococcus pneumoniae (principale agente eziologico della CAP), Mycoplasma pneumoniae, Haemophilus influenzae e Streptococcus pyogenes possono giocare un ruolo di rilievo

# L'impatto negativo delle infezioni respiratorie ricorrenti

- malessere fisico del bambino in fase acuta di malattia
- uso inappropriato di antibiotici (aumento resistenze e effetti collaterali)
- uso inappropriato di altri farmaci (mucolitici, steroidi, decongestionanti, terapie alternative)
- consulti di specialisti (ORL, allergologi) e NON
- accessi in PS (20% delle consultazioni mediche)
- ospedalizzazioni frequenti
- alterata qualità di vita per la conseguente medicalizzazione
- possibile disturbo dell'evoluzione psicologica (meno giochi all'aperto!)
- malessere psicologico della famiglia
- conseguenze economiche per la famiglia e la società per le assenze da scuola e perdita di lavoro dei genitori (costo stimato di un episodio 150-200 euro in Italia)

# What can be done?

- Treatment
  - → controversial role of antibiotics
  - → role of symptomatic measures
- PREVENTION
  - → Firstly, based on risk factors
  - → Secondly, based on past history


RRTIs
High bacterial or viral load in nasopharynx
Low immune response
Abudant nasal secretions
Age
Passive smoking
Day care attendance
Allergy
No or reduced breastfeeding
Seasonality
Male sex
Air pollution
Sleeping position
Genetics
Nasopharyngeal flora
Older siblings
Low vitamin D
Continuous pacifier

# Immunisation

- ACTIVE effective IMMUNIZATION
  ⇨ ultimate objective

- Viral vaccines: Influenza, measles
  (RSV, rhinovirus)

- Bacterial vaccines: *Pneumococcus* (PCV), *Haemophilus influenzae* type b, *Bordetella pertussis* (*Staph. aureus*)

# Influenza vaccination of healthy children

## Objectives

- Protection of children against
  - influenza
  - otitis media
  - Pneumonia
- Control of transmission
  - indirect protection of other at-risk persons

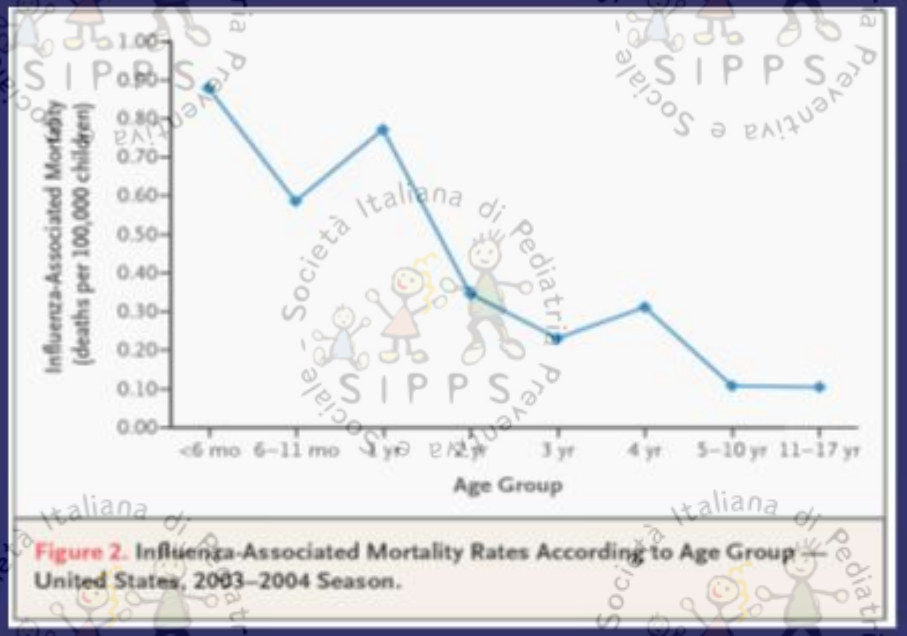
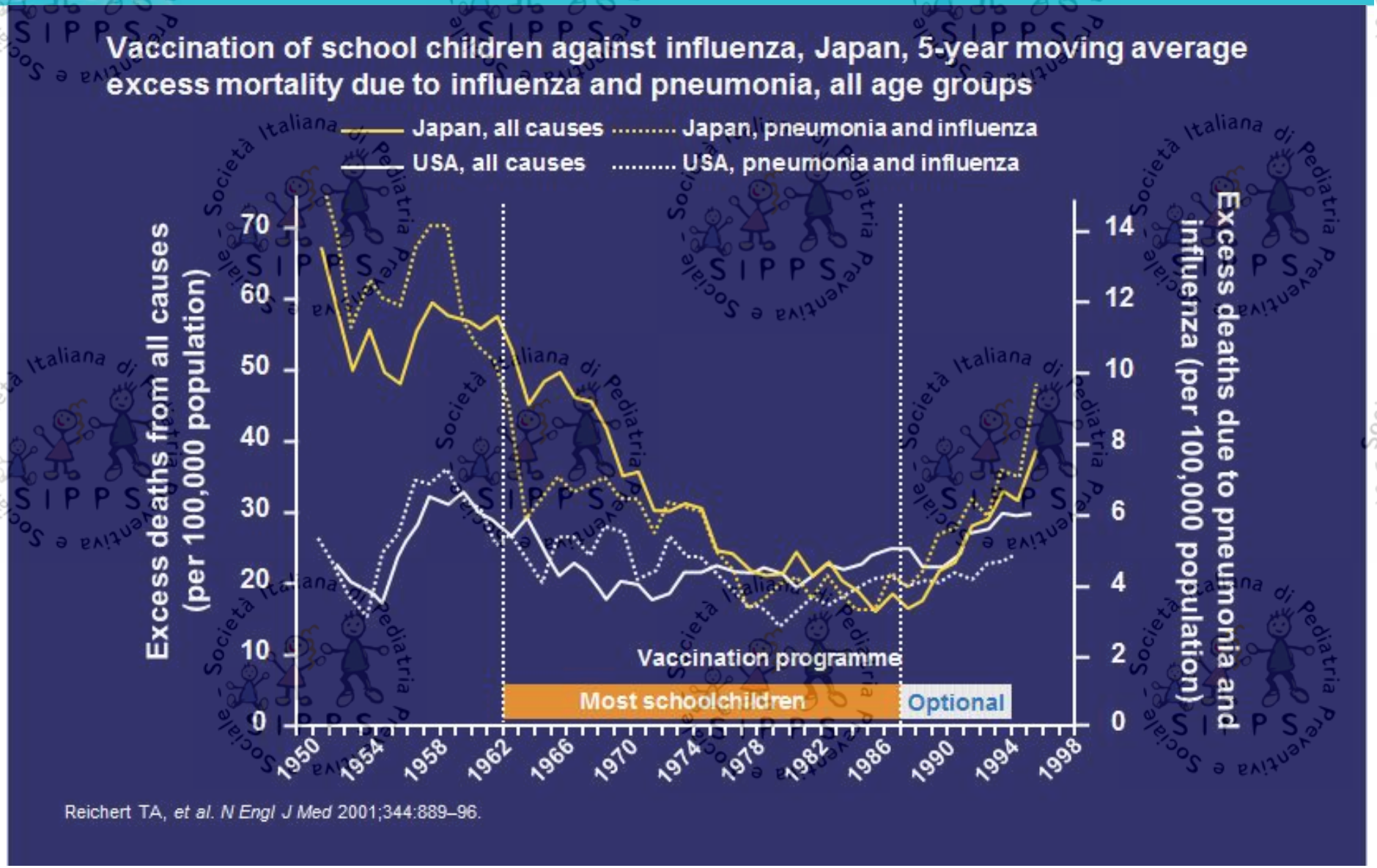



Figure 2. Influenza-Associated Mortality Rates According to Age Group — United States, 2003–2004 Season.



1. www.cdc.gov 2. ESWI. 2006 3. Rapola S. *Int J Circumpolar Health* 2007;66:382-9

# Impact of the community of childhood influenza vaccination in Japan and USA



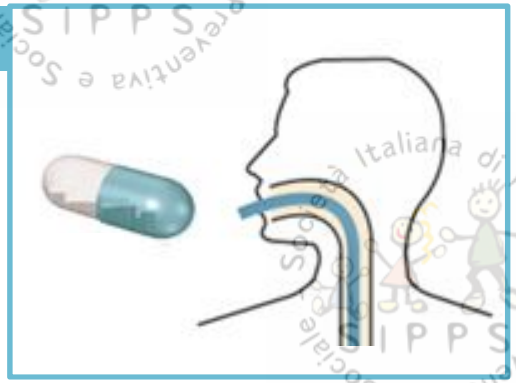
# Immunostimulants

- ✓ Bacterial lysates (1st and 2nd generation)
- ✓ Bioactive polysacharides (Glucans)
- ✓ Transfer factor (human leukocytes)
- ✓ Isoprinosine (Metisoprinol)
- ✓ Thymic hormones and derivatives
- ✓ Prebiotics, Probiotics and Nucleotides
- ✓ Echinacea extract, Ginseng, Propoleum

www.intechopen.com/books/bronchitis/recurrent-respiratory-infections-in-children-definition-diagnosticapproach-treatment-and-prevention

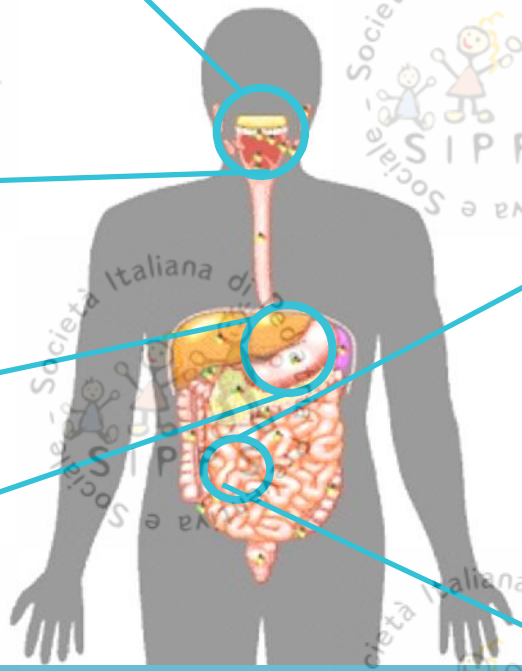
# OM-85 is an oral immunomodulator

1



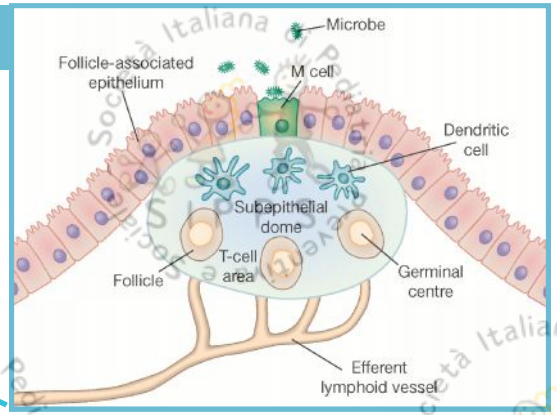
OM-85 is administered orally

2 It passes the stomach



Through M cells it activates selectively the Peyer's patches, thus the mucosal associated lymphoid tissue (immune system)[1,2]

3



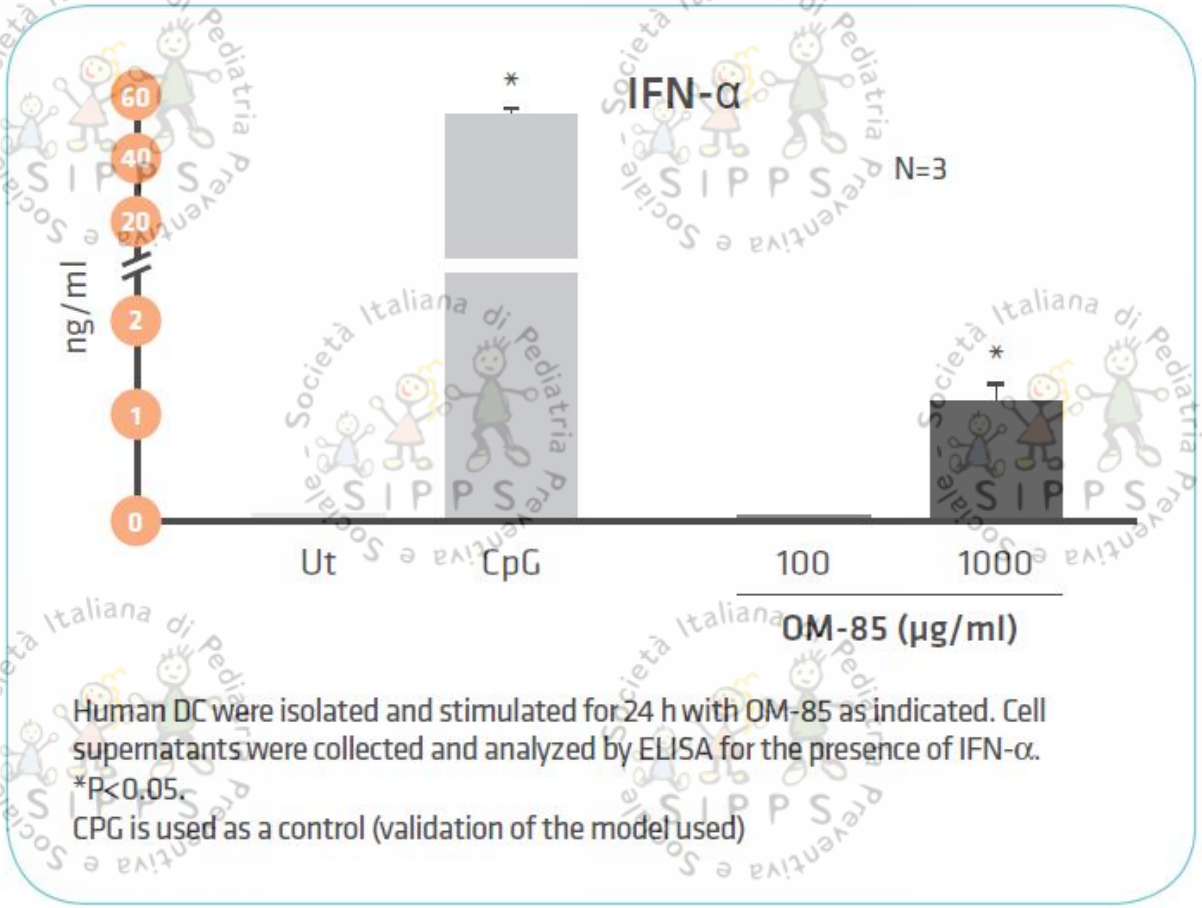

Intestinal mucosa

It has been shown to modulate the immune response to protect the host against viral and bacterial pathogens

1. De Benedetto et al. Multidiscip Resp Med 2013; 2. Bessler et al. Microbial pathogens and strategies for combating them: science, technology and education vol. 3, 2013

# OM -85 induces a selective activation of human DC and production of anti-viral IFNα

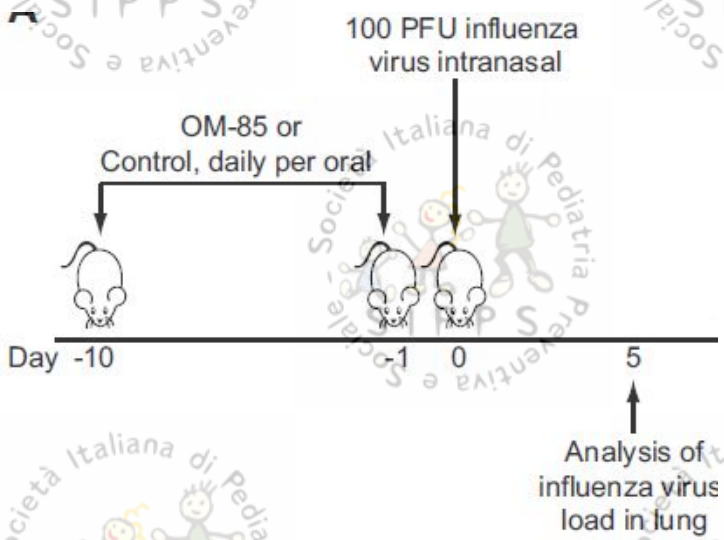
**Most important cytokine for the defense against viral infections OM-85 may help to set up a basal antiviral state**



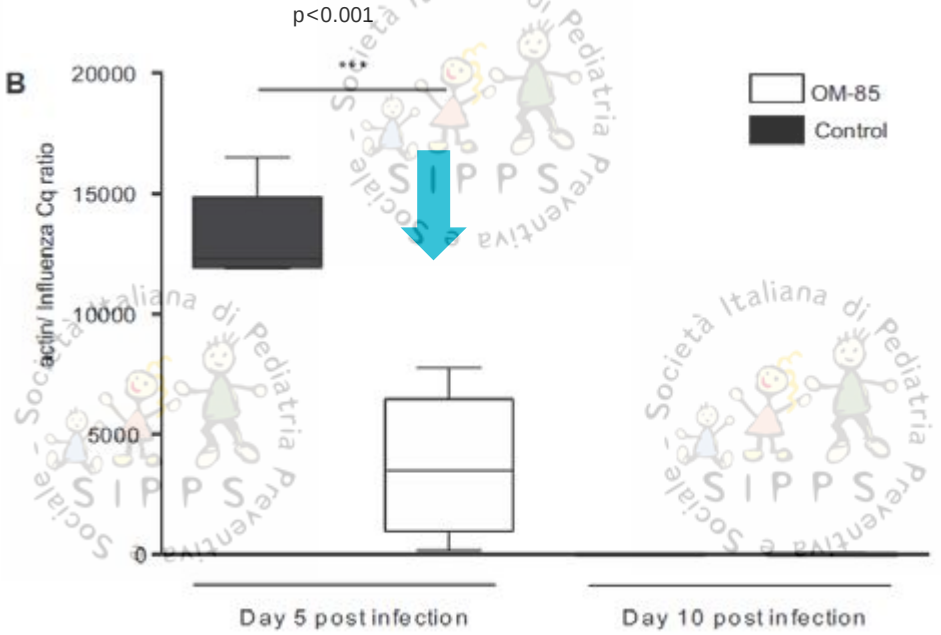

Human DC were isolated and stimulated for 24 h with OM-85 as indicated. Cell supernatants were collected and analyzed by ELISA for the presence of IFN-α.
*P<0.05.
CPG is used as a control (validation of the model used)

1. Parola et al. PLoS One 2013

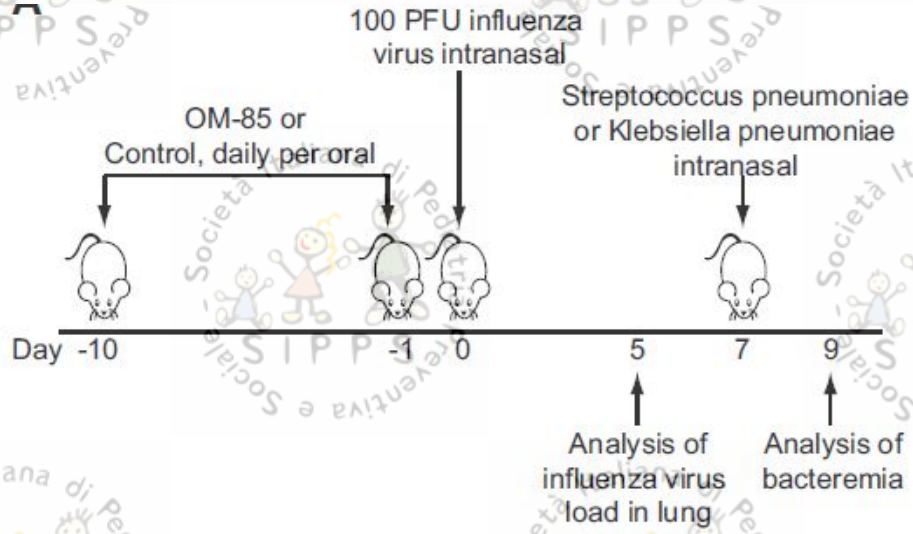
# In mice OM-85 protects against influenza virus

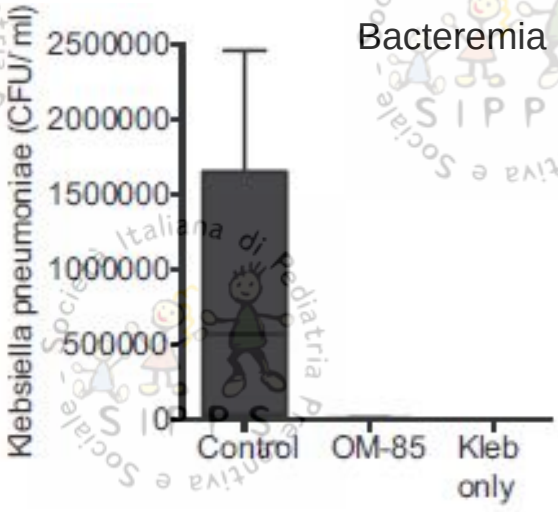


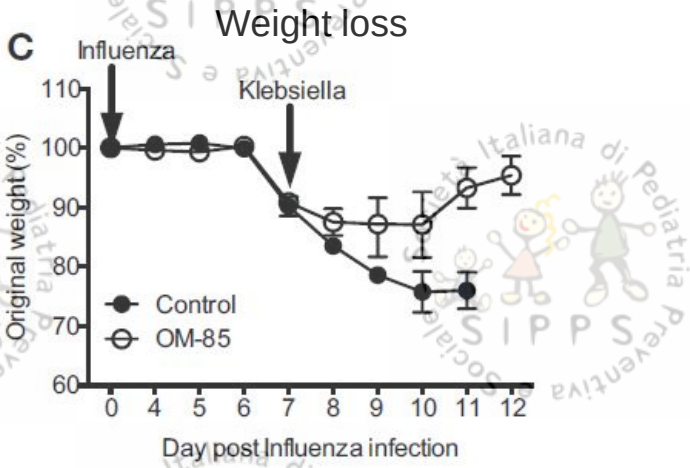

OM-85 enhances innate immune response, resulting in more rapid control of the infection and a reduced viral H1N1 load in the lungs

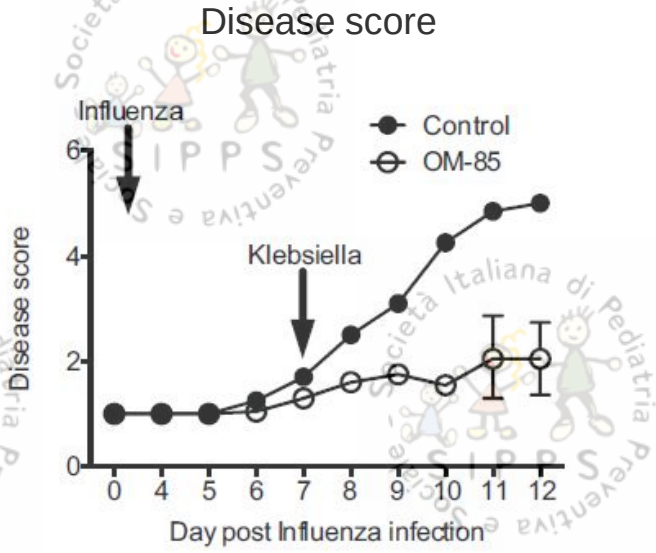


# OM-85 pre-treated mice were protected from secondary bacterial infection



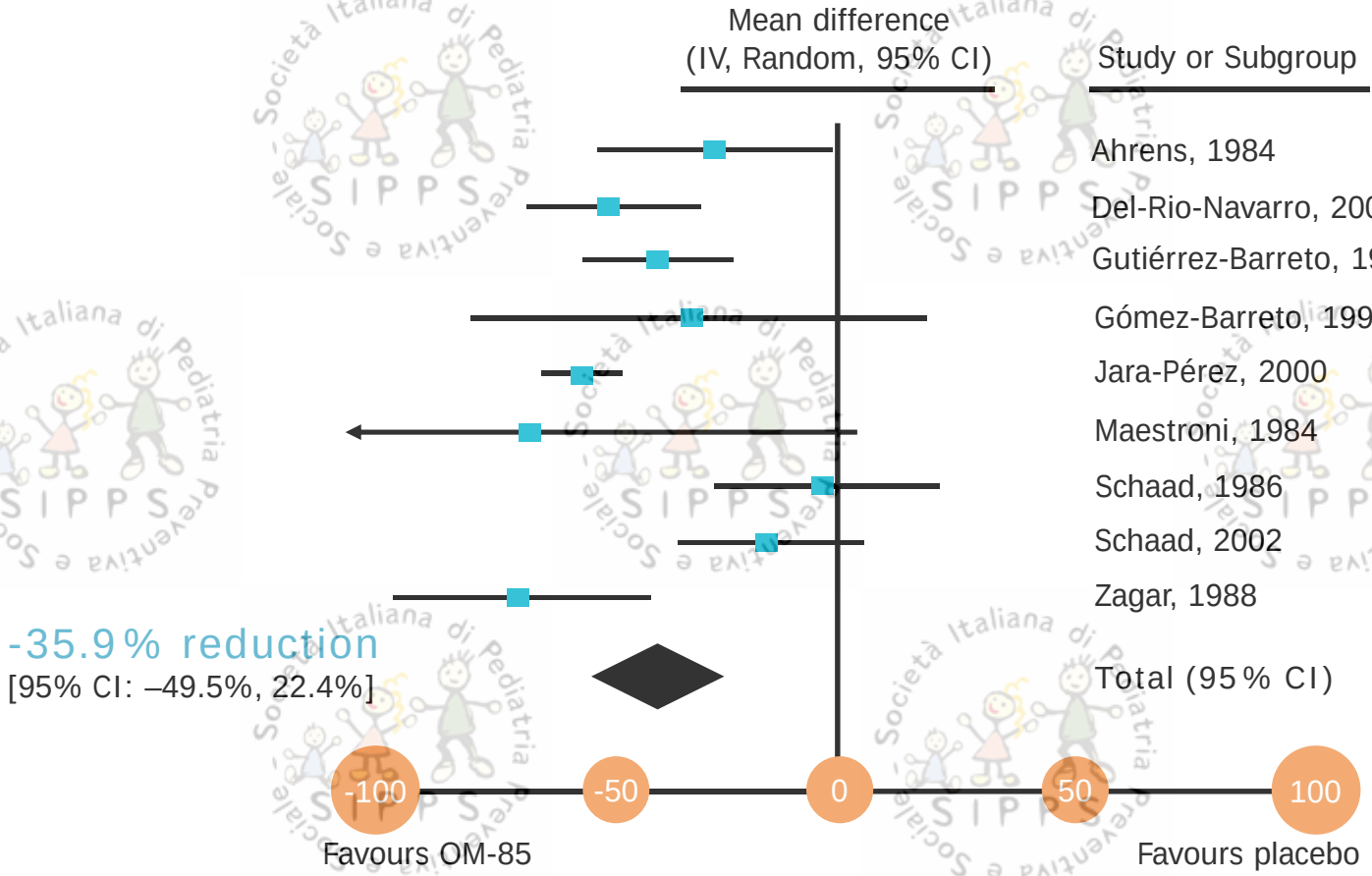




Pasquali et al. 2014 Front Med (Lausanne). 1:41 (doi: 10.3389/fmed.2014.00041)

# OM-85 reduce total number of ARTIs in children: a Cochrane meta-analysis

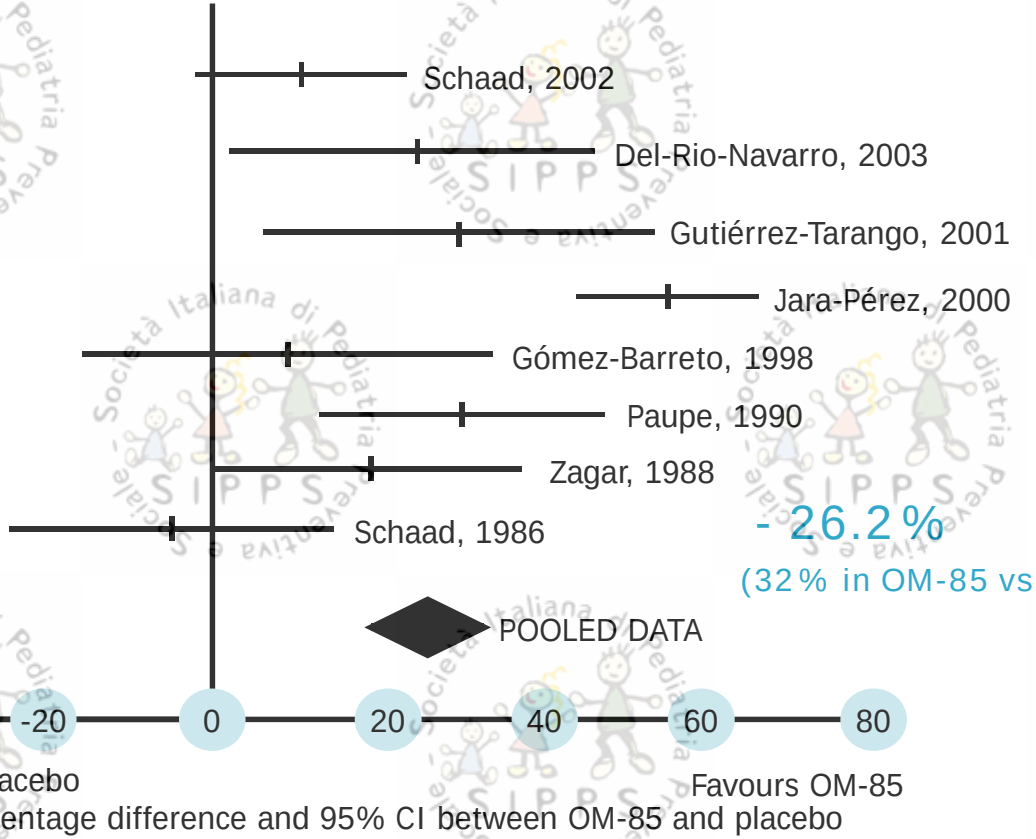



Percentage difference and 95% CI between OM-85 and placebo

Del-Rio-Navarro et al. Cochrane Database Syst Rev 2012

# 26.2% fewer patients with rRTIs (≥3 RTIs in 6 months) vs placebo

Mean number of RTIs was reduced in verum group by 35.5%

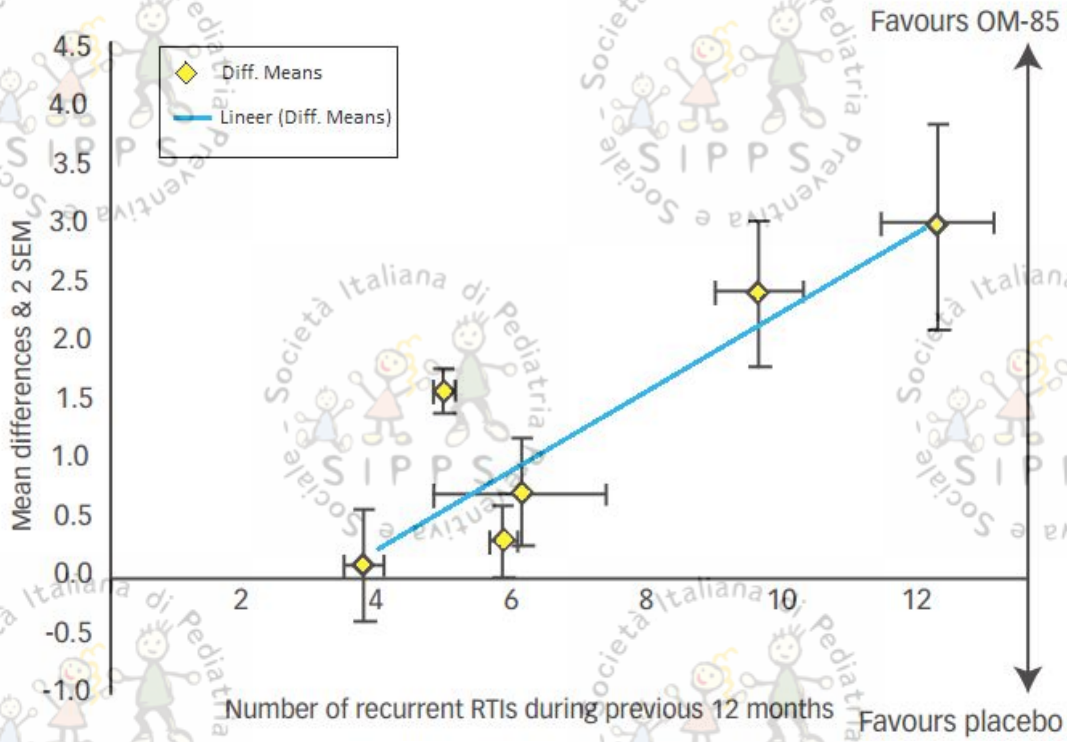



- 26.2%

(32% in OM-85 vs 58.2 % in PB)

Schaad UB et al. World J Pediatr 2010;6(1):5-12

# Higher the risk, higher the benefit

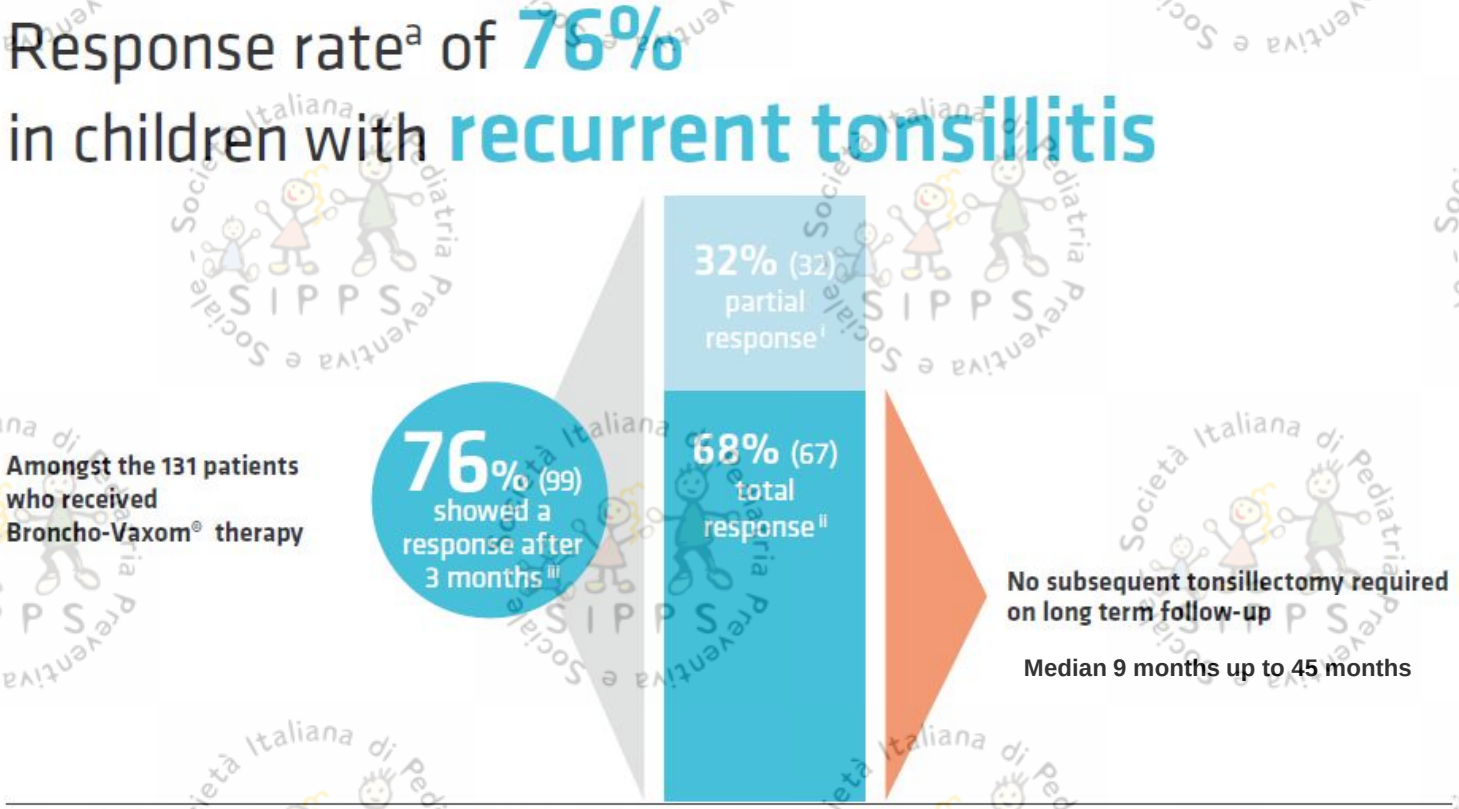



This beneficial effect is proportional to the number of RTIs in the previous 12 months and is larger in younger children [a]

Schaad UB et al. World J Pediatr 2010;6(1):5-12

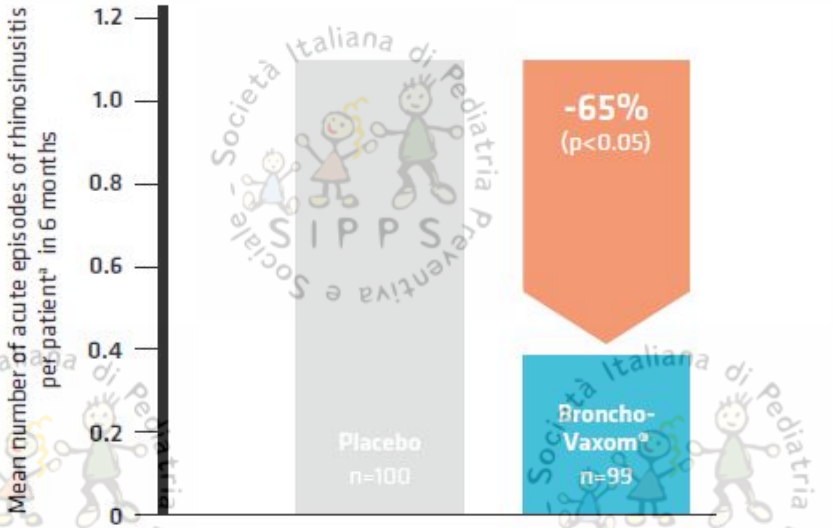
a= data not shown

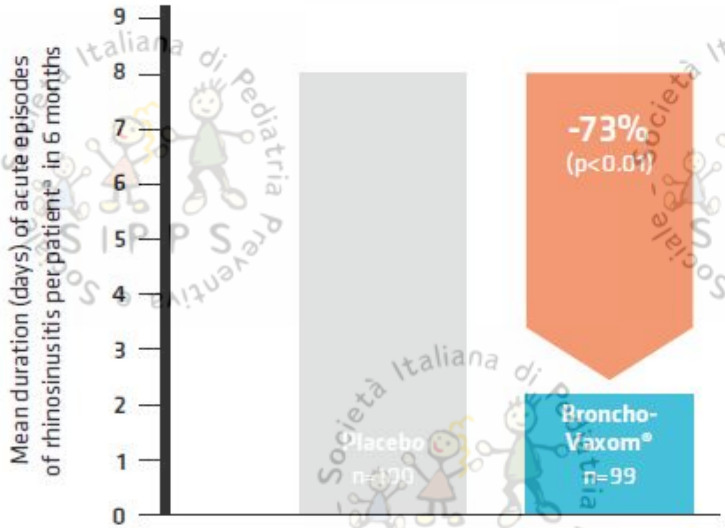
# Responders patients had a good prognosis: no tonsillectomy over 5 yrs




Bitar MA et al. Int J Pediatr Otorhinolaryngol 2013;77:670-673

# Significantly fewer and shorter acute episodes of rhinosinusitis

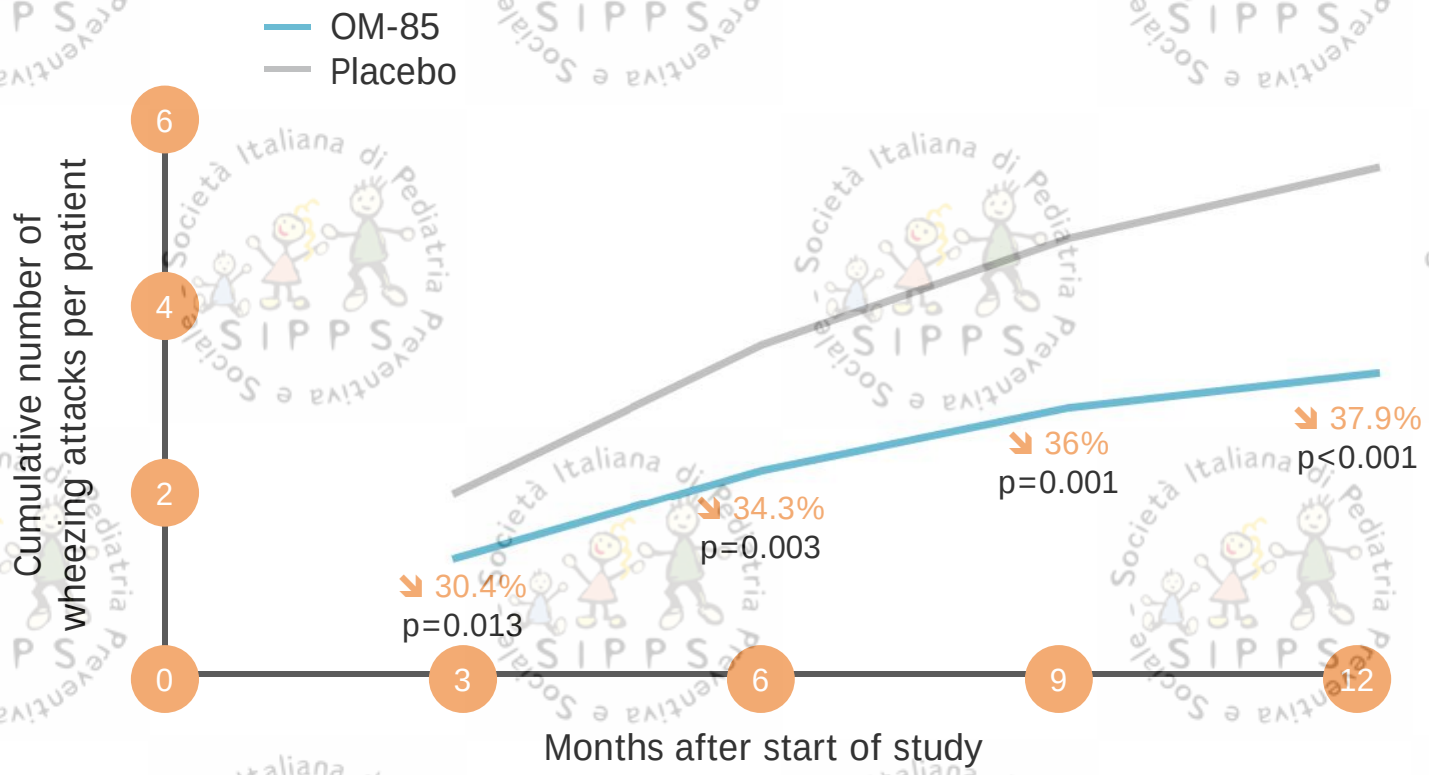



From a double-blind, placebo-controlled study in 51 children (4-12 years), presenting with an acute episode of rhinosinusitis. Their mean rate episodes in the last 12 months was 6. Adapted from Zagar S. et al. 1988.

Zagar S and Lofler-Badzek D.ORL;1988;50:1-8

# OM-85 prevents wheezing attacks in pre-school children

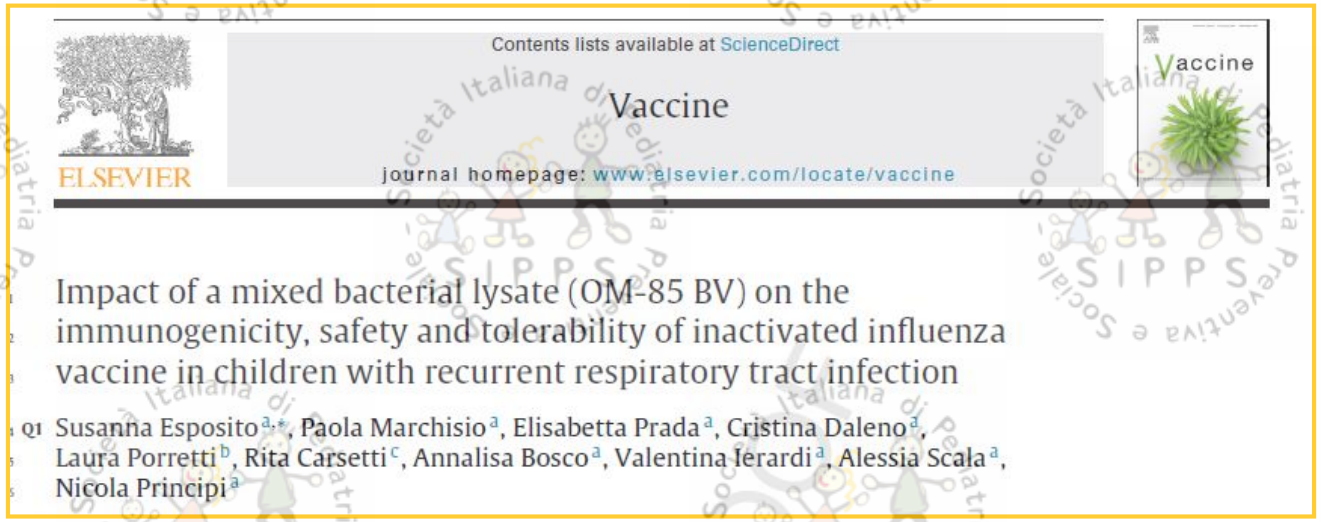



The cumulative difference in wheezing attacks between the 2 groups was 2.18 wheezing attacks per patient in 12 months; there was a 37.9% reduction in the group given OM-85 compared with the group given placebo (P < 0.001)

# OM-85 in prevention of RTIs* in combination with IIV

- Assess the immune response towards a combined prevention (IIV and OM-85) and IIV only

- Evaluate efficacy and tolerability of combined preventative strategies



Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Impact of a mixed bacterial lysate (OM-85 BV) on the immunogenicity, safety and tolerability of inactivated influenza vaccine in children with recurrent respiratory tract infection

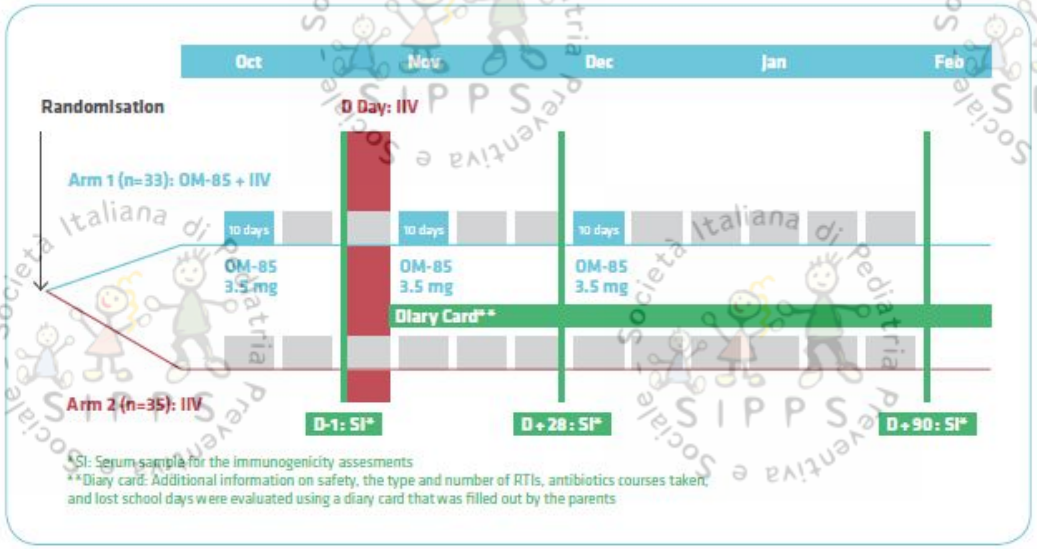
Susanna Esposito[a,*], Paola Marchisio[a], Elisabetta Prada[a], Cristina Daleno[a], Laura Porretti[b], Rita Carsetti[c], Annalisa Bosco[a], Valentina Ierardi[a], Alessia Scala[a], Nicola Principi[a]

*Both URTIs and LRTIs

Esposito S et al. Vaccine 2014;32:2546-2552

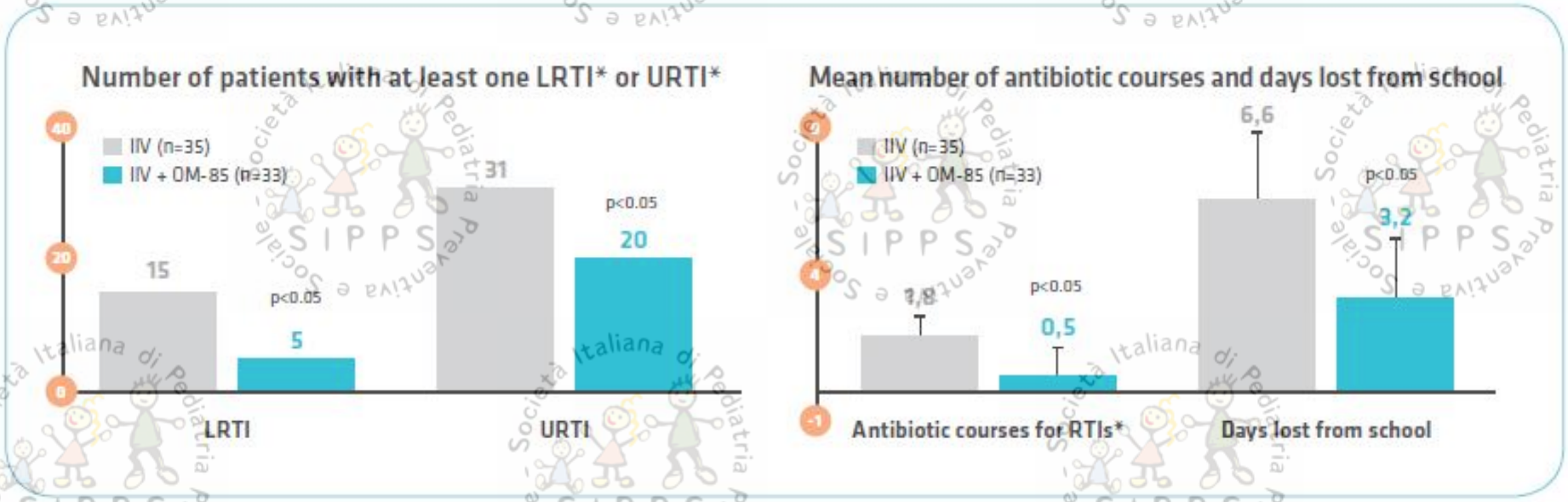
# Study design

- Prospective randomized single blind study (1 October 2012 and 31 March 2013)
- 68 children included (36-59 months)
- ≥6 practitioner-attended episodes in 1 years
- At least 1 previous IIV
- Single-blind: the patients and their parents were asked not to mention the treatment assignment to their pediatricians




Esposito S et al. Vaccine 2014;32:2546-2552

# Higher reduction in RTIs and Ab use in OM-85 and IIV group




Significant reduction in:

- number of patients with at least one URTI* (-35% vs. IIV)
- number of patients with at least one LRTI* (-67% vs. IIV)
- mean number of antibiotics courses (-72% vs. IIV)
- mean number of days lost from school (-52% vs. IIV)

Esposito S et al. Vaccine 2014;32:2546-2552

# Humoral and cellular immune response to IIV was not affected

- No between-group differences in the humoral (antibodies against each of the three influenza strains) and cellular (dendritic and memory B cells in peripheral blood) immune responses
  - Low dose of administration compared to that used in the mouse model
  - Measurement in blood (i.e. BAL measurements more relevant but limited in young children)

Administration of IIV about 15 days after the start of the first course of OM-85 does not affect humoral or cell-mediated immunity to the vaccine

Esposito S et al. Vaccine 2014;32:2546-2552

# Impact of a OM-85 on the immunogenicity, safety and tolerability of inactivated influenza vaccine in children with rRTI

Table 4.

Summary of local and systemic reactions in the 14 days following vaccination with an inactivated influenza vaccine (IIV) in children in children treated with OM-85 BV and untreated controls.

| Adverse events | Treated with OM-85 BV and vaccinated with IIV ($n$ = 33) | Only vaccinated with IIV ($n$ = 35) |
|---|---|---|
| Local reactions, no. (%) | | |
| Erythema | 1 (3.0) | 1 (2.9) |
| Swelling/induration | 3 (9.0) | 5 (14.2) |
| Pain | 1 (3.0) | 1 (2.9) |
| At least one local event | 4 (12.1) | 6 (17.1) |
| Systemic reactions, no. (%) | | |
| Fever ≥38 °C | 1 (3.0) | 2 (5.7) |
| Irritability | 2 (6.0) | 3 (8.6) |
| Sleepiness | 1 (3.0) | 1 (2.9) |
| Vomiting | 0 (0.0) | 1 (2.9) |
| Diarrhoea | 1 (10.0) | 0 (0.0) |
| At least one systemic event | 2 (6.0) | 4 (11.4) |
| At least one local or systemic event | 5 (15.2) | 7 (20.0) |
| Requiring drugs for local or systemic events | 4 (12.1) | 5 (14.2) |
| Serious adverse events | 0 (0.0) | 0 (0.0) |

No statistically significant difference.

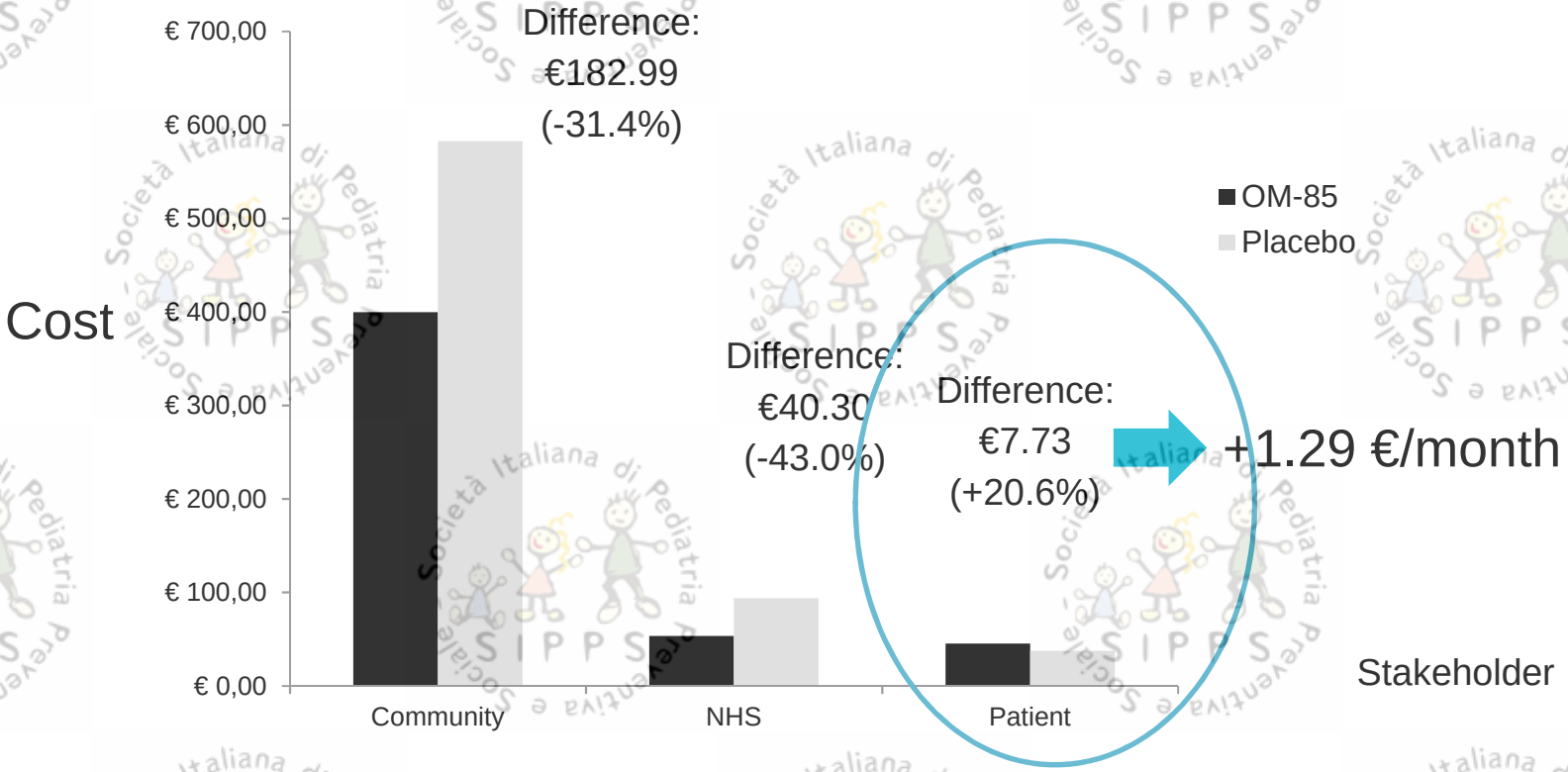
The administration of both Broncho-Vaxom® and IVV in a short period of time appeared to be safe and well tolerated

Esposito S et al. Vaccine. 2014 May 7;32(22):2546-52.

# DATA FROM THE POST-MARKETING SAFETY AND PEDIATRIC TRIALS

- A long (30 years) post-marketing experience, many pediatric trials
- 3.6 million patients treated per year worldwide (adults and children)
- Very low incidence of adverse events identified/observed in post-marketing experience: approximately 3 cases per 100'000 patients treated
- Good tolerance
- AEs mainly non serious (gastrointestinal, skin)

# Results on costs based on therapeutic options and probabilities




- Cost of OM-85 for one cycle: Euro 20.99 Euro
- This is largely compensated by the societal cost saving
- Saving for HCS will be sufficient to cover also OM-85 price

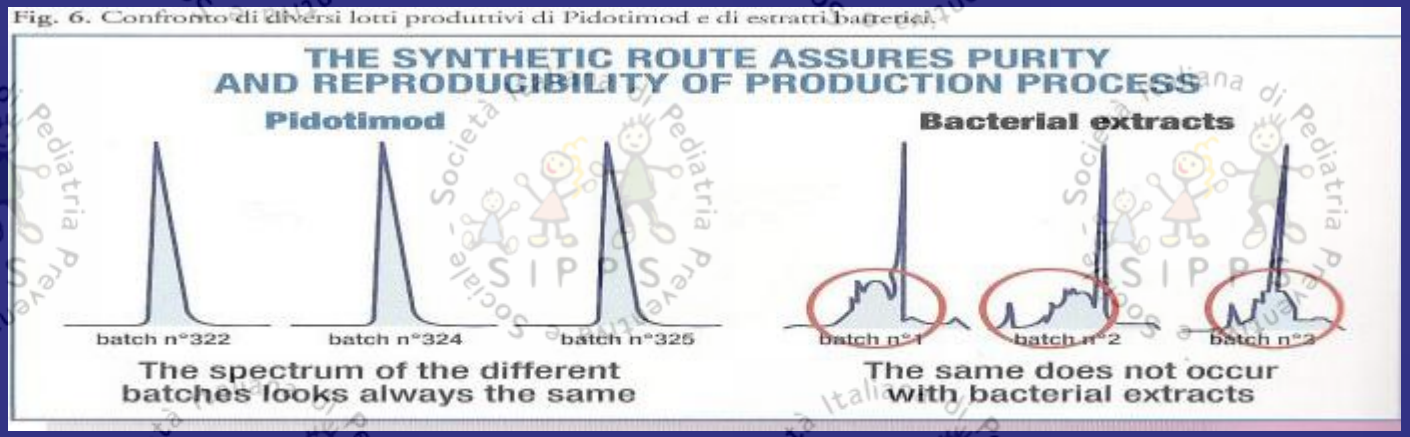
**OM-85 is cost effective for Society… and for HCS**

Ravasio R. *Global & Regional Health Technology Assessment 2015 ; 0 (0): 00—00 DOI: 10.5301/GRHTA.5000200*

# PIDOTIMOD

**Tipo di molecola:** dipeptide sintetico

Essendo un composto di sintesi è puro, la sua struttura è identica in tutti i lotti di produzione



Zuccotti and Mameli *Italian Journal of Pediatrics* 2013, **39**:75
http://www.ijponline.net/content/39/1/75

ITALIAN JOURNAL OF PEDIATRICS

COMMENTARY Open Access

# Pidotimod: the past and the present

Gian Vincenzo Zuccotti* and Chiara Mameli

**THE PAST**

| Autore | Tipologia | Pazienti | Trattamento | Conclusioni |
|---|---|---|---|---|
| Burgio GR. Arzneimittelforschung. 1994 | RTC doppio cieco con placebo multicentrico | 101 bambini (2-13 anni) | 400 mg/die per 60 gg | Riduzione del numero di pz con sintomi di IR delle alte e basse vie |
| Motta G. Arzneimittelforschung. 1994 | RTC doppio cieco con placebo | 235 bambini (3-14 anni) | 800 mg/die per 15gg poi 400 mg/die per 60 gg | Riduzione del numero di tonsilliti |
| Passali D. Arzneimittelforschung. 1994 | RTC doppio cieco con placebo multicentrico | 416 bambini (3-14 anni) | 400 mg/die per 60 gg | Riduzione dei giorni di febbre, della severità degli episodi acuti, nel numero di ATB e dell'assenteismo. |
| Caramia G. Arzneimittelforschung. 1997 | RTC doppio cieco con placebo multicentrico | 120 bambini (2-8 anni) | 400 mg per 2 volte al giono per 15 gg, 400 mg/die per 60 gg | Più rapido miglioramento clinico, riduzione delle ospedalizzazioni, delle ricadute e dell'uso di ATB. In caso di ricaduta risposta clinica più rapida |
| Careddu. Arzneimittelforschung. 1994 | RTC doppio cieco con placebo multicentrico | 748 bambini (3-14 nni) | 400 mg/die per 60 gg | Riduzione del numero di IRR, dell'uso di ATB e di farmaci sintomatici. Meno assenteismo |

| Autore | Tipologia | Pazienti | Trattamento | Conclusioni |
|---|---|---|---|---|
| La Mantia. J Chemother 1999 | Pz trattati vs nn trattati | 14 bambini con Sindrome di Down (3-13 anni) | 400 mg/die per 60 gg | Riduzione del numero di gg di febbre, delle severità delle IR, dell'uso di ATB e di antipiretici |

# Due schemi di prevenzione delle IRR con pidotimod

- 400 mg/die per uno – due mesi in autunno
- 400 mg x 2/die per 10 giorni al mese da ottobre ad aprile

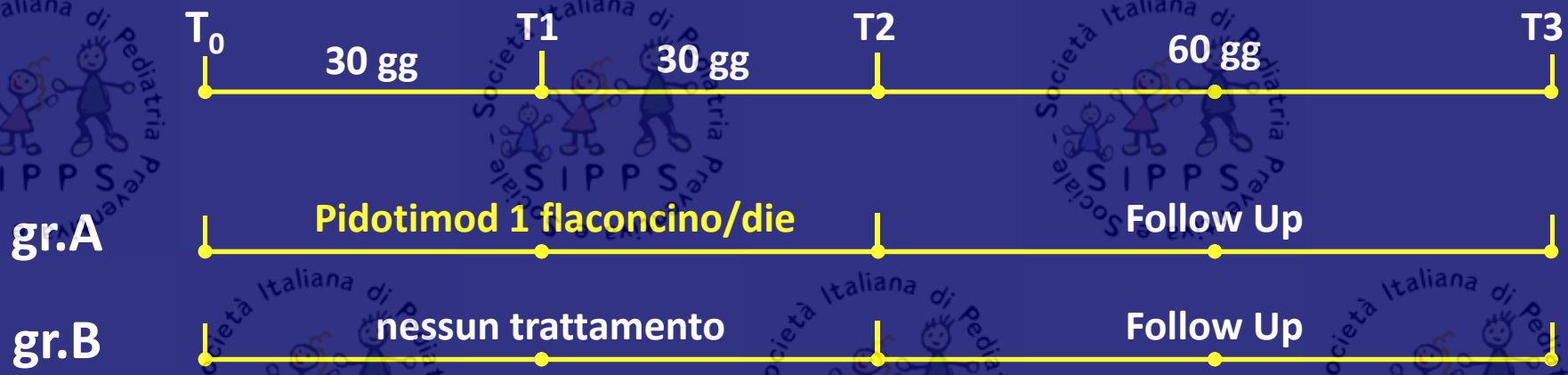
Minerva Pediatr. 2014 Oct;66(5):363-7.

# Pidotimod may prevent recurrent respiratory infections in children.

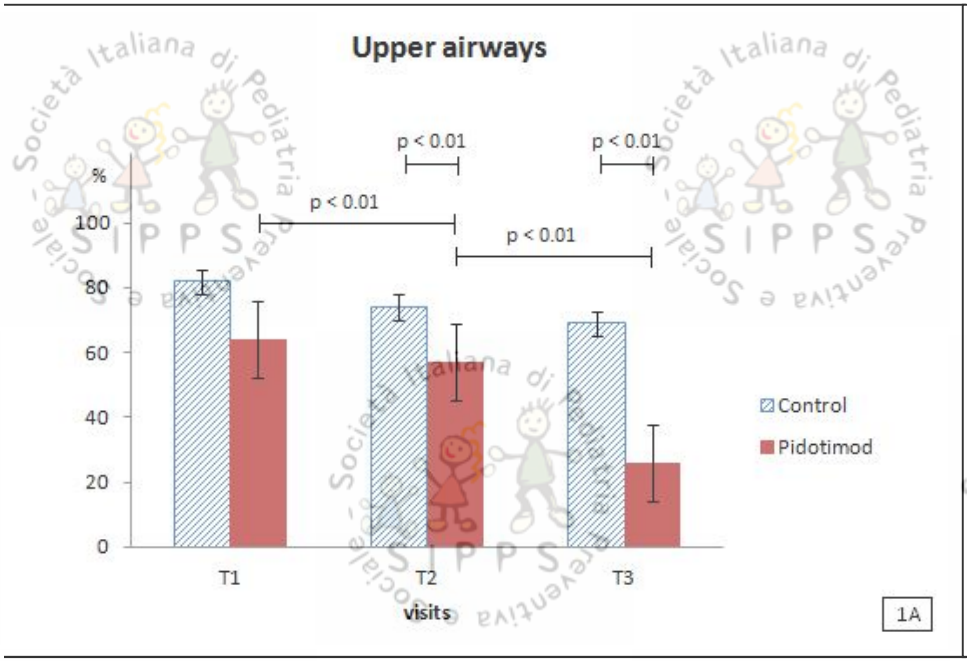
Licari A[1], De Amici M, Nigrisoli S, Marseglia A, Caimmi S, Artusio L, Marseglia GL.

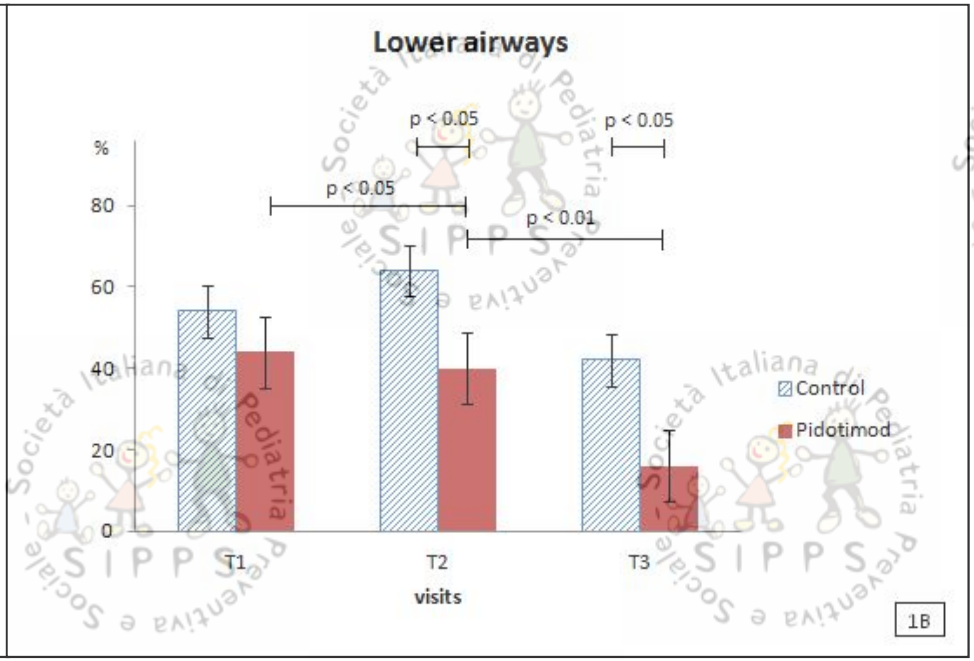
- **Studio prospettico randomizzato a gruppi paralleli** ***gruppo Trattati ( 45 bambini , 400 mg/die) vs gruppo non Trattati (44 bambini) (età 4.9 anni, range 3- 10 anni)***

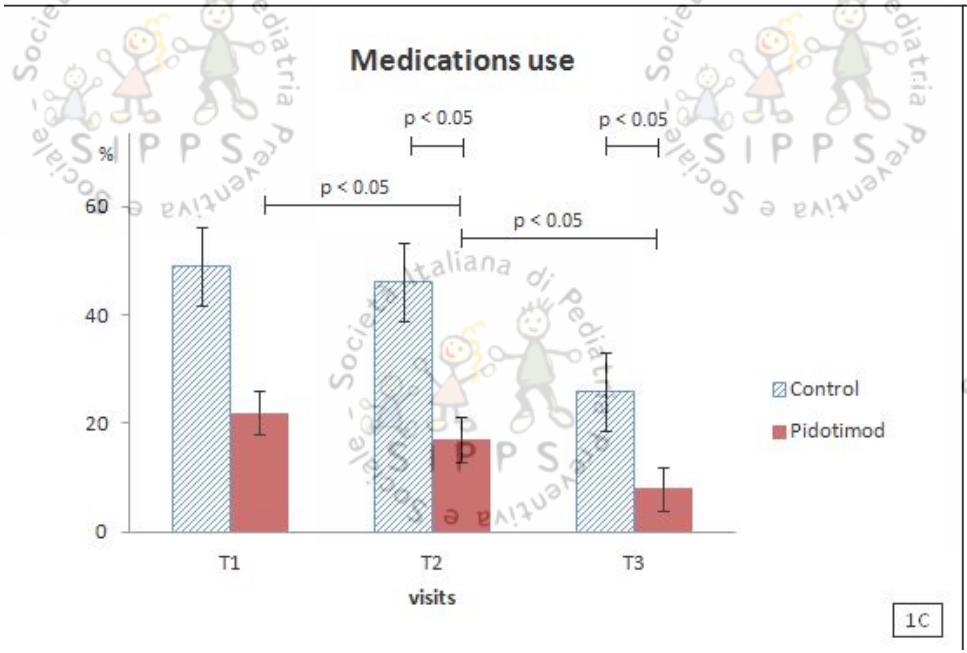
- **Schema di trattamento:**

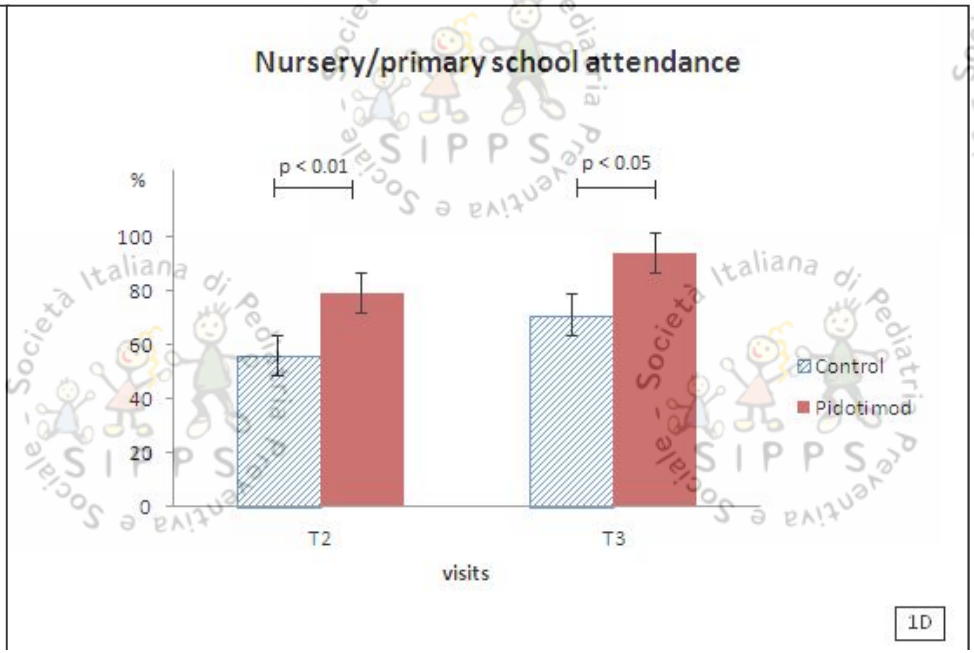



- **Periodo di studio: novembre – febbraio**


Upper airways
%
100
80
60
40
20
0
p < 0.01
p < 0.01
p < 0.01
p < 0.01
T1
T2
T3
visits
Control
Pidotimod
1A


Lower airways
%
80
60
40
20
0
p < 0.05
p < 0.05
p < 0.05
p < 0.01
T1
T2
T3
visits
Control
Pidotimod
1B


Medications use
%
60
40
20
0
p < 0.05
p < 0.05
p < 0.05
p < 0.05
T1
T2
T3
visits
Control
Pidotimod
1C


Nursery/primary school attendance
%
100
80
60
40
20
0
p < 0.01
p < 0.05
T2
T3
visits
Control
Pidotimod
1D

# Immunomodulatory activity of pidotimod administered with standard antibiotic therapy in children hospitalized for community-acquired pneumonia

JOURNAL OF TRANSLATIONAL MEDICINE

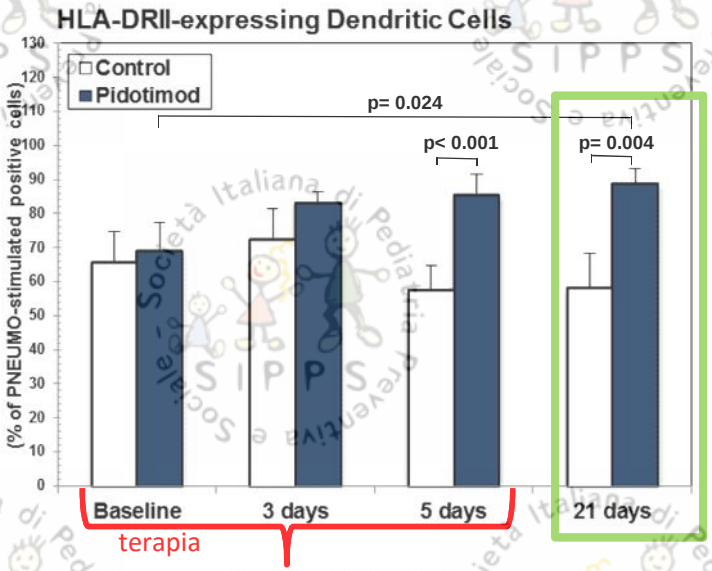
Susanna Esposito[1*], Micaela Garziano[2], Veronica Rainone[2], Daria Trabattoni[2], Mara Biasin[2], Laura Senatore[1], Paola Marchisio[1], Marta Rossi[3], Nicola Principi[1] and Mario Clerici[4,5]

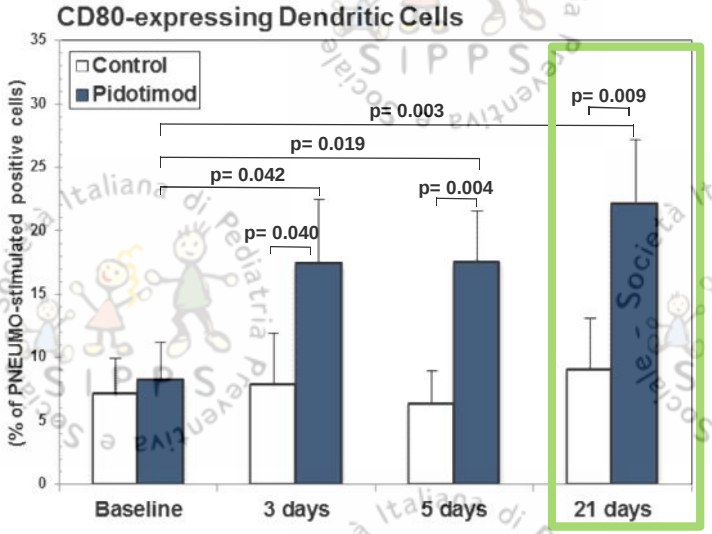
## OBIETTIVI

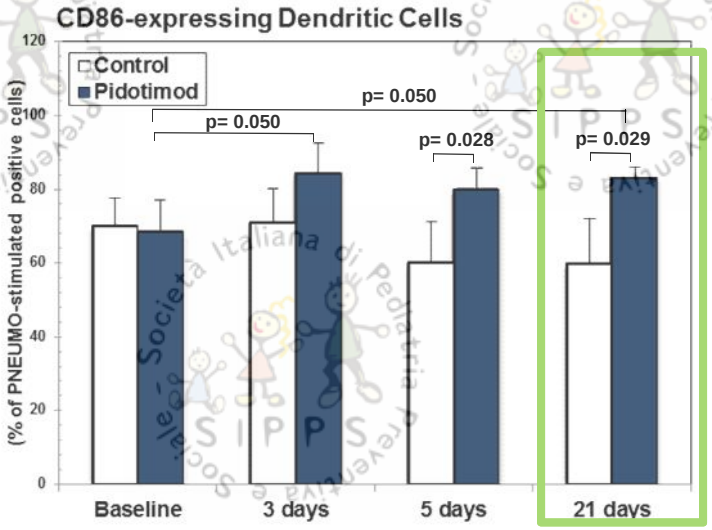
In bambini con CAP trattati solo con terapia antibiotica rispetto a bambini con CAP trattati con PIDOTIMOD in aggiunta alla terapia antibiotica:

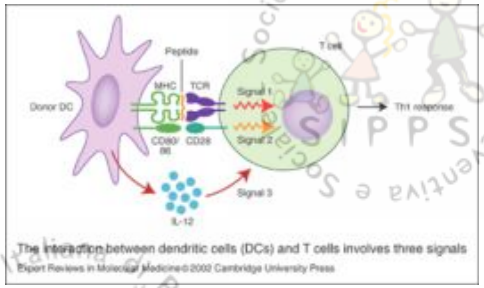
- valutare la risposta clinica, in termini di raggiungimento della stabilità;
- valutare gli effetti clinici del trattamento con PIDOTIMOD in aggiunta alla terapia antibiotica sui marker infiammatori (PCR, PCT);
- analizzare gli effetti immunomodulatori del PIDOTIMOD in aggiunta alla terapia antibiotica in pazienti affetti da CAP.

# PIDOTIMOD up-regola l'espressione di molecole co-stimolatorie CD80 e CD86 e la maturazione delle Cellule Dendritiche



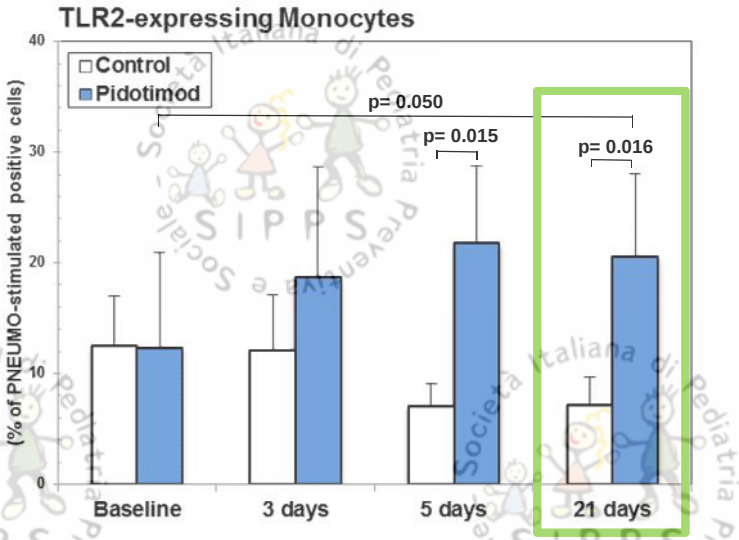



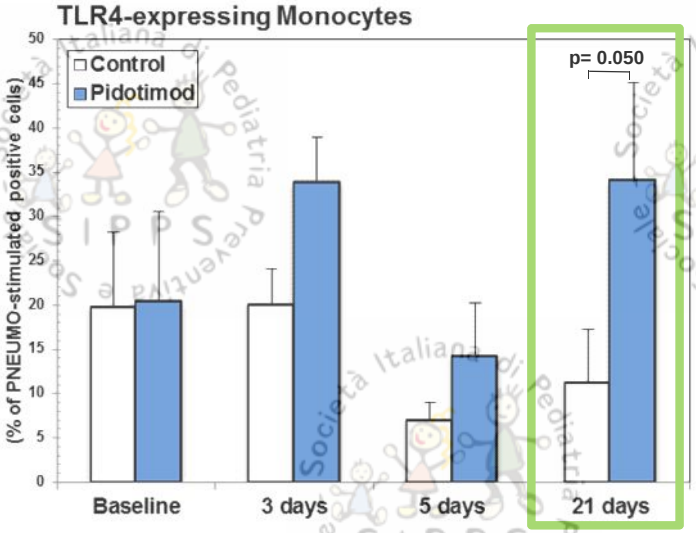



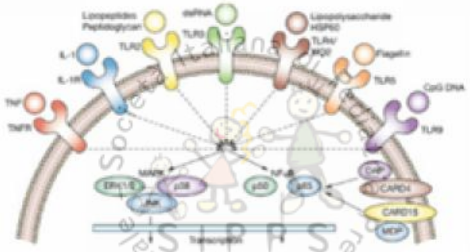




**Stimolazione con pool di peptidi di pneumococco (antigeni specifici per CAP)**

# PIDOTIMOD up-regola l'espressione di TLR2 e TLR4 in monociti

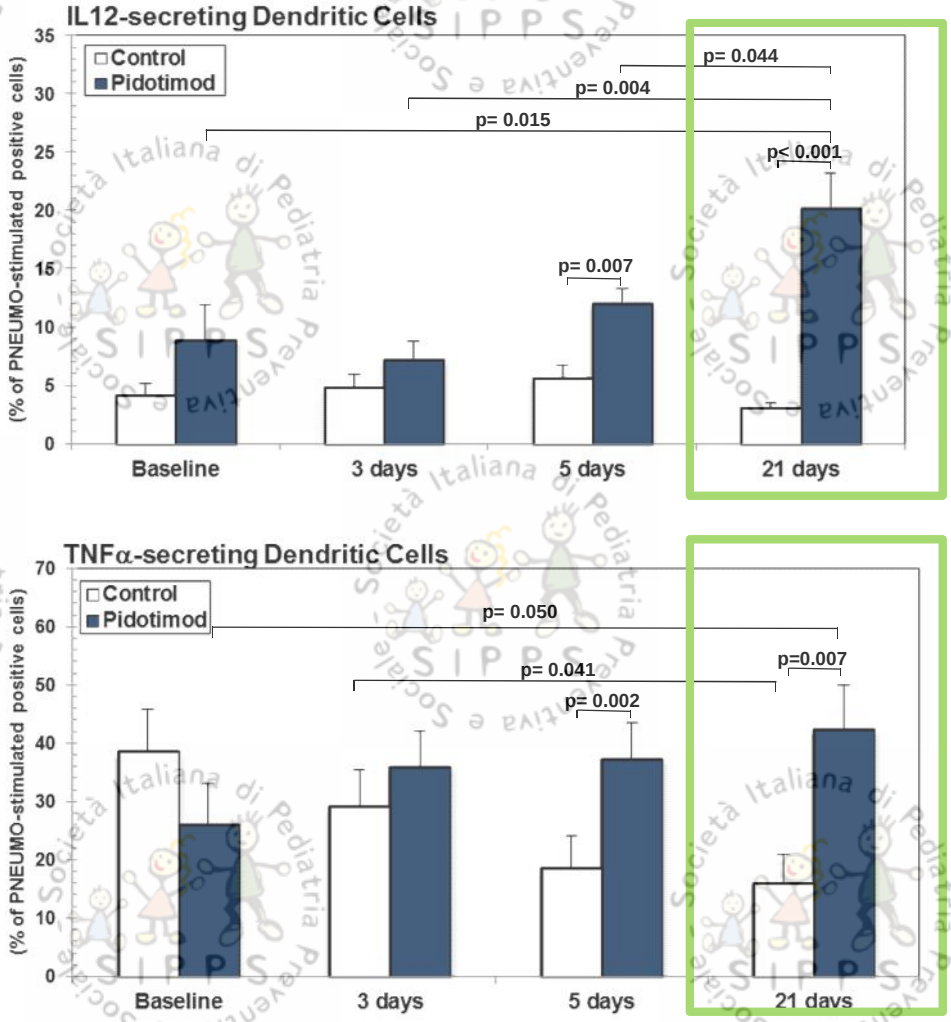


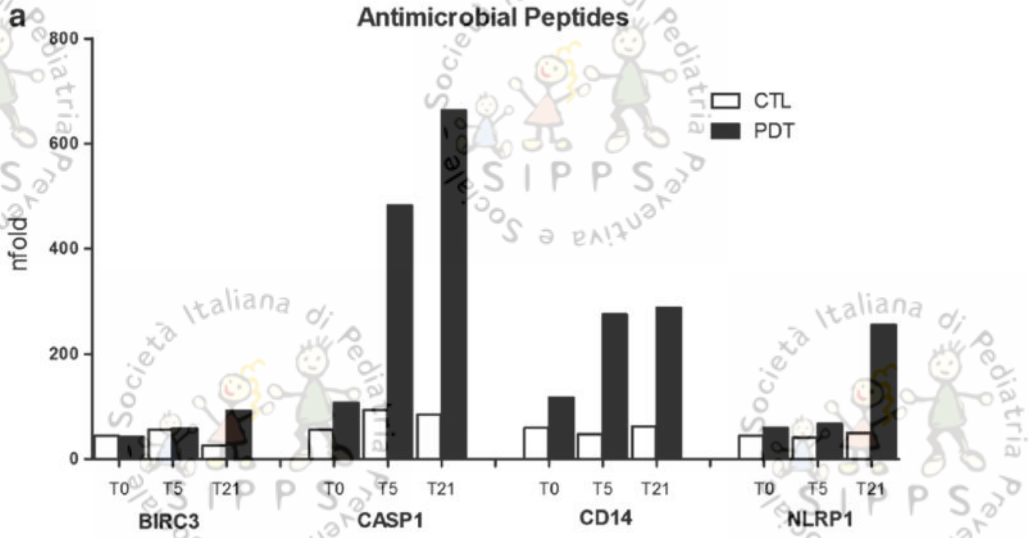



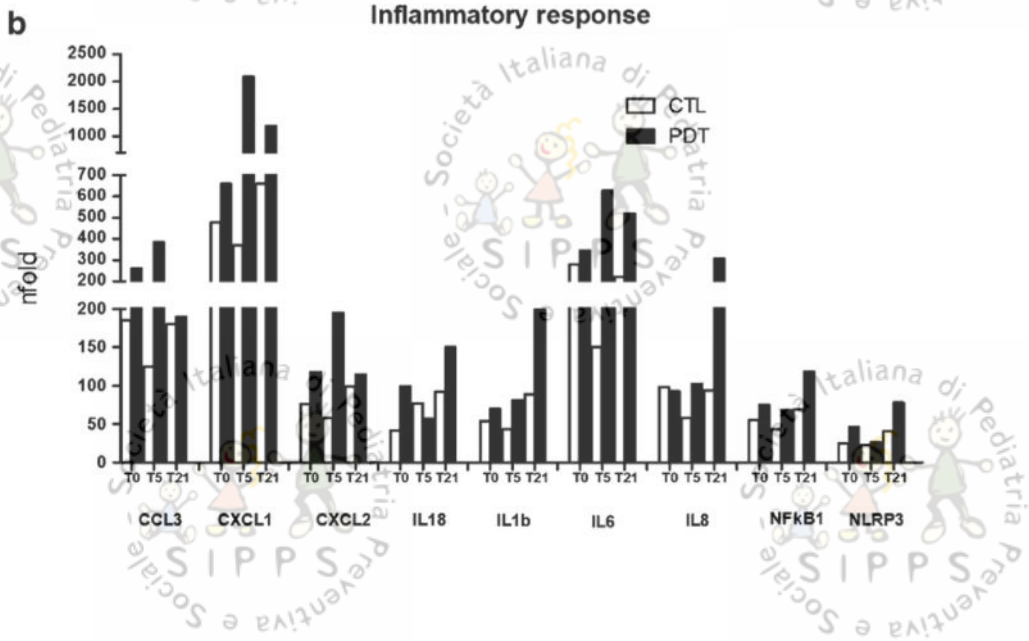
**TLR : «allerta» per riconoscimento patogeni**

# PIDOTIMOD stimola la produzione di IL-12 e TNF-α* in cellule dendritiche stimolate da pneumo




*** indirizzano la maturazione dei linfociti verso differenziazione Th1**




# SEGNALI DI RISPOSTA ANTIBATTERICA: AUMENTO DELLA SINTESI DI PEPTIDI ANTIMICROBICI E DELLA RISPOSTA INFIAMMATORIA

# Immunomodulatory activity of pidotimod administered with standard antibiotic therapy in children hospitalized for community-acquired pneumonia

JOURNAL OF TRANSLATIONAL MEDICINE

Susanna Esposito[1*], Micaela Garziano[2], Veronica Rainone[2], Daria Trabattoni[2], Mara Biasin[2], Laura Senatore[1], Paola Marchisio[1], Marta Rossi[3], Nicola Principi[1] and Mario Clerici[4,5]

## Conclusions

This study demonstrates for the first time that PDT administration together with standard antibiotic therapy is associated with a favorable persistent immunomodulatory effect in children with CAP, suggesting that it could reduce the risk of early recurrences.

JOURNAL OF BIOLOGICAL REGULATORS & HOMEOSTATIC AGENTS Vol. 27, no. 1, 0-0 (2013)

*LETTER TO THE EDITOR*

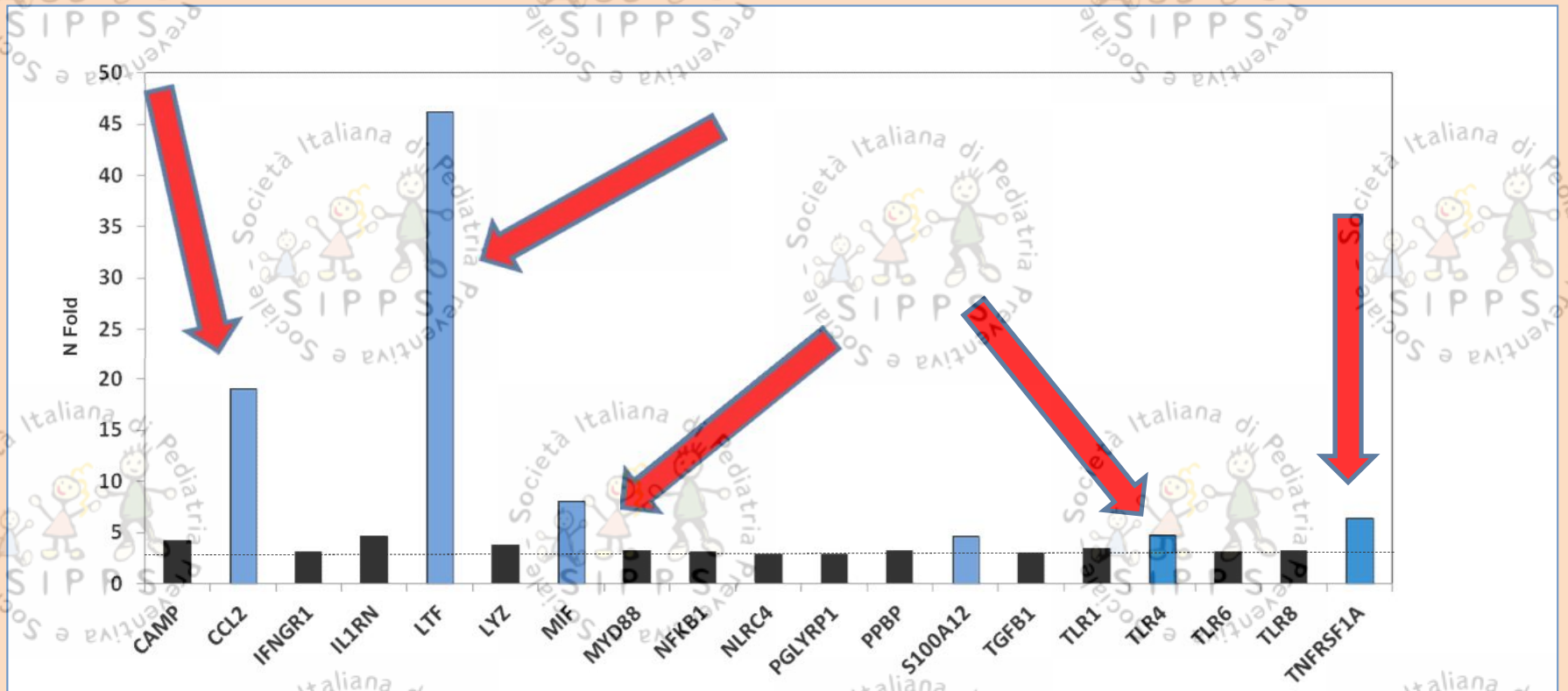
# IMMUNOMODULATING ACTIVITY OF PIDOTIMOD IN CHILDREN WITH DOWN SYNDROME

G.V. ZUCCOTTI[1], C. MAMELI[1], D. TRABATTONI[2], S. BERETTA[1], M. BIASIN[2], L. GUAZZAROTTI[1] and M. CLERICI[3]

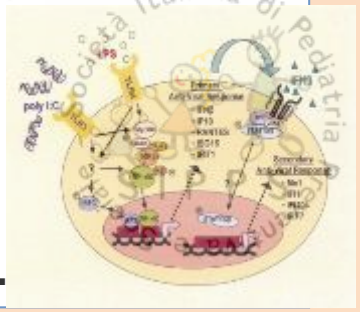
Valutare la capacità di PIDOTIMOD di modulare le risposte immuni in bambini con sindrome di Down vaccinati con vaccino influenzale stagionale (2011-2012)

- Studio randomizzato controllato: 35 bambini affetti da Sindrome di Down, età: 3-10 anni, randomizzati (1:1) a ricevere **Pidotimod 400 mg, somministrato oralmente 1/die per 90 giorni o placebo.**
- Al baseline vaccinazione con una singola dose di vaccino anti-influenzale virosomiale-adiuvato.
- Le risposte immuni innate ed adattative sono state valutate al baseline e 3 mesi dopo l'arruolamento.

# RISULTATI: Espressione di geni delle risposte immuni innate e adattative




**PIDOTIMOD induce una significativa up-regolazione di geni coinvolti nella chemiotassi, nell'attività antimicrobica e nell'infiammazione. PIDOTIMOD modula positivamente le risposte immuni innate determinando un più efficace controllo delle fasi iniziali dell'infezione.**




# ALTRI IMMUNOMODULANTI

## LATTOFERRINA

Antivirale
Antibatterico
Immunomodulante
Anti-infiammatorio

## RESVERATROLO

Blocca la replicazione virale
Inibisce alcuni mediatori dell'infiammazione
Stimola la funzione immunitaria
Potente antiossidante

## ECHINACEA

Immunomodulante

Proliferazione delle cellule del Sistema Immunitario, stimolazione della fagocitosi granulocitaria, aumentano la produzione di Citochine infiammatorie (in particolare TNFα, IL-1, IL-6, Interferon-β, NO

Anti-infettivo

## ZINCO

Essenziale per il funzionamento di molti enzimi e mediatori cellulari
Contribuisce alla stabilizzazione della MB cellulare
Regola l'apoptosi dei linfociti
Coinvolto in molti meccanismi immunitari

## PROBIOTICI

Immunoesclusione, immunoregolazione, immunoeliminazione a livello locale

## VITAMINA D

Ruolo nell'omeostasi del sistema immunitario regolando direttamente e indirettamente la proliferazione, la differenziazione e la funzione delle cellule immunitarie

# EFFICACY AND SAFETY OF ECHINACEA PURPUREA IN TREATING URTIs IN CHILDREN

Taylor JA et al. JAMA 2003;290:2824-30

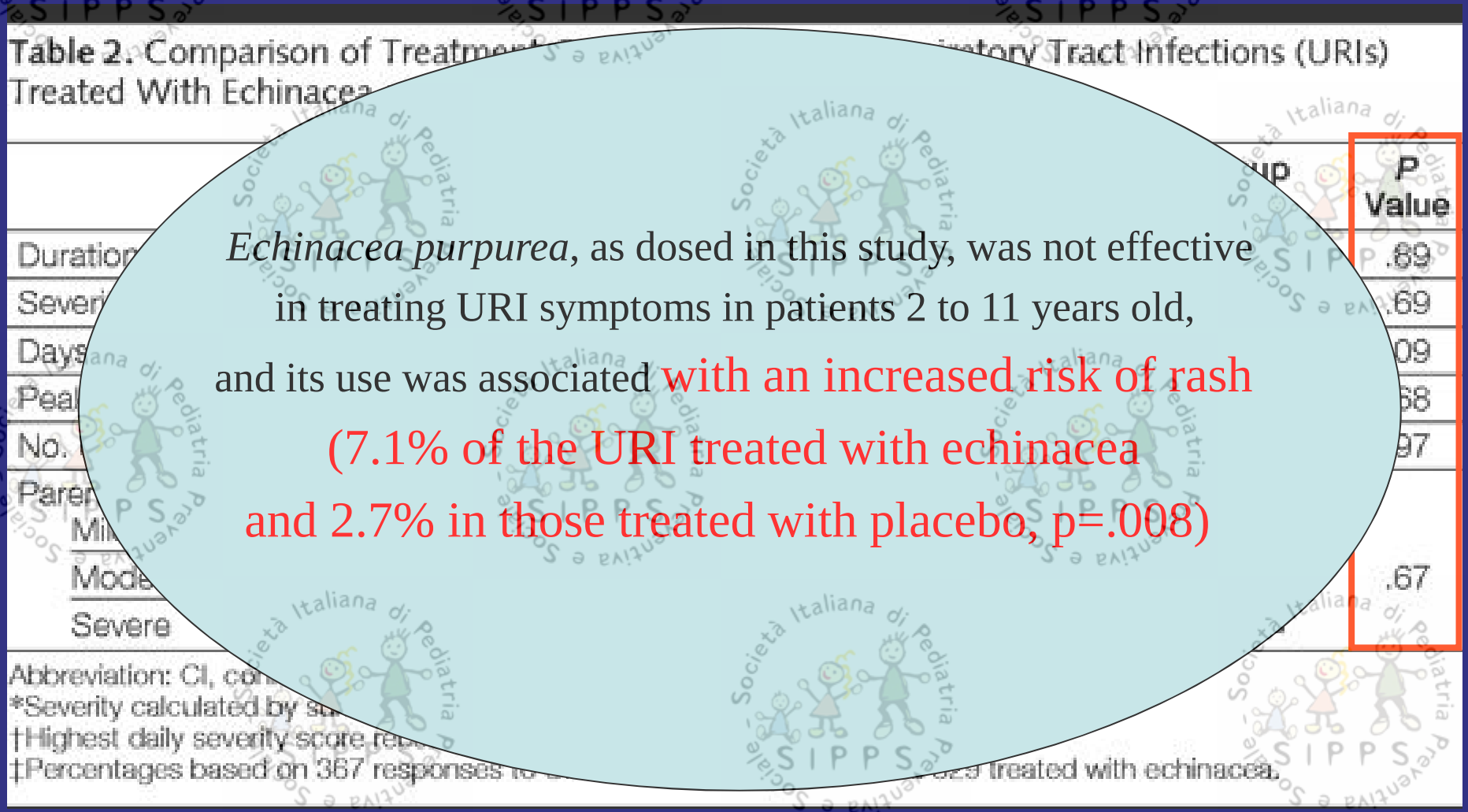


Table 2. Comparison of Treatment [illegible] Tract Infections (URIs) Treated With Echinacea

| | | | | P Value |
|---|---|---|---|---|
| Duration | | | | .89 |
| Severi | | | | .69 |
| Days | | | | 09 |
| Peal | | | | 68 |
| No. | | | | 97 |
| Paren | | | | |
| | Mi | | | |
| | Mode | | | .67 |
| | Severe | | | |

Abbreviation: CI, co
*Severity calculated by st
†Highest daily severity score rec
‡Percentages based on 367 responses fo [illegible] 323 treated with echinacea.

*Echinacea purpurea*, as dosed in this study, was not effective in treating URI symptoms in patients 2 to 11 years old, and its use was associated with an increased risk of rash (7.1% of the URI treated with echinacea and 2.7% in those treated with placebo, p=.008)

JAMA Clinical Evidence Synopsis

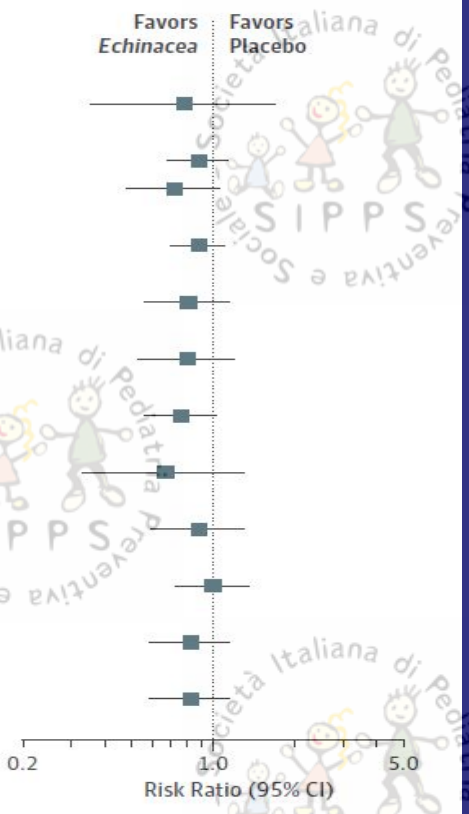
# *Echinacea* for Preventing and Treating the Common Cold

Marlies Karsch-Völk, MD; Bruce Barrett, MD, PhD; Klaus Linde, MD

JAMA February 10, 2015 Volume 313, Number 6

Figure. Risk Ratios for Participants With at Least One Cold Episode In the Prevention Trials

| Study by *Echinacea* product | *Echinacea* No. With Outcome | *Echinacea* Total No. of Participants | Placebo No. With Outcome | Placebo Total No. of Participants | Risk Ratio (95% CI) |
|---|---|---|---|---|---|
| *E purpurea* herb | | | | | |
| Hall, 2007 | 7 | 18 | 7 | 14 | 0.78 (0.36-1.70) |
| *E purpurea* herb pressed juice | | | | | |
| Grimm, 1999 | 35 | 54 | 40 | 54 | 0.88 (0.68-1.13) |
| Sperber, 2004 | 14 | 24 | 18 | 22 | 0.71 (0.48-1.05) |
| *E purpurea* dried plant extract | | | | | |
| O'Neill, 2008 | 22 | 28 | 27 | 30 | 0.87 (0.70-1.10) |
| *E purpurea* root extract | | | | | |
| Zhang, 2003 | 25 | 54 | 33 | 57 | 0.80 (0.56-1.15) |
| *E purpurea* root alcoholic extract | | | | | |
| Melchart, 1998 | 29 | 99 | 33 | 90 | 0.80 (0.53-1.20) |
| *E purpurea* root and *E angustofolia* root | | | | | |
| Tiralongo, 2012 | 37 | 85 | 49 | 85 | 0.76 (0.56-1.02) |
| 4% phenolic extract of *E purpurea* and *E angustifolia* | | | | | |
| Turner, 2000 | 11 | 55 | 14 | 46 | 0.66 (0.33-1.30) |
| *E angustifolia* root alcoholic extract | | | | | |
| Melchart, 1998 | 32 | 100 | 33 | 90 | 0.87 (0.59-1.29) |
| *E angustifolia* root extract with $CO_2$ | | | | | |
| Turner, 2005 | 25 | 45 | 58 | 103 | 0.99 (0.72-1.35) |
| *E angustifolia* root extract with 60% ethanol | | | | | |
| Turner, 2005 | 24 | 52 | 58 | 103 | 0.82 (0.58-1.15) |
| *E angustifolia* root extract with 20% ethanol | | | | | |
| Turner, 2005 | 24 | 52 | 58 | 103 | 0.82 (0.58-1.15) |




associated with a lower rate of colds, 285 of 666 patients in the *Echinacea* group vs 279 of 501 patients in the placebo group (risk ratio, 0.83 [95% CI, 0.75-0.92]; $P < .001$).

Men: 1640 (42%) Women: 2294 (58%) (sex not reported in 5 trials)

Race/ethnicity: Unavailable

Age, mean: 27.9 years (age not reported in 5 trials)

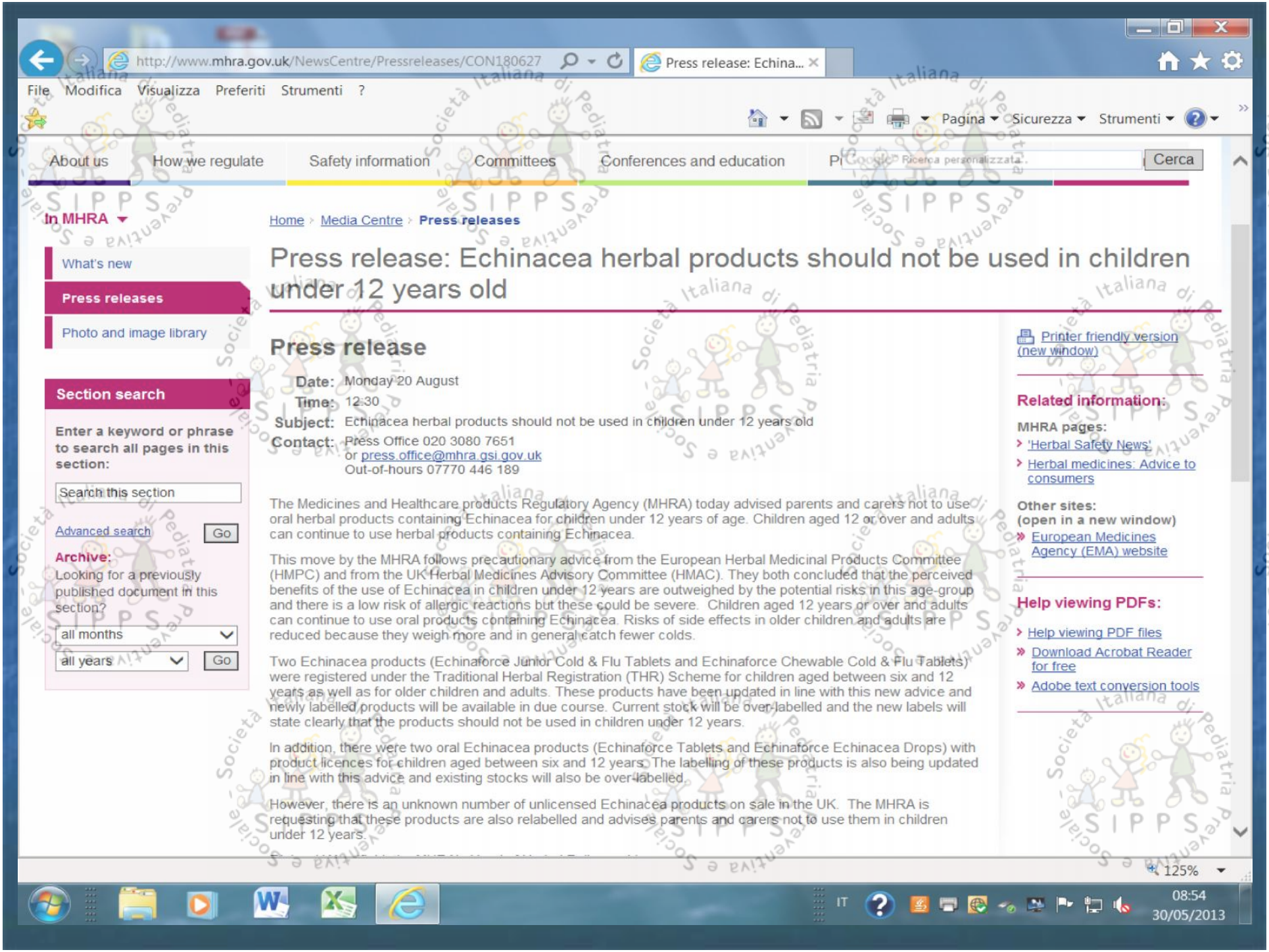
# Effectiveness of an Herbal Preparation Containing Echinacea, Propolis, and Vitamin C in Preventing Respiratory Tract Infections in Children

*A Randomized, Double-blind, Placebo-Controlled, Multicenter Study*

*Herman A. Cohen, MD; Itzchak Varsano, MD; Ernesto Kahan, MD, MPH; E. Michael Sarrell, MD; Yosef Uziel, MD*

## Table 2. Incidence of Respiratory System Infection

| Diagnosis | No. (%) Chizukit* (n = 160) | No. (%) Placebo (n = 168) | Reduction, % | *P* Value† |
|---|---|---|---|---|
| Upper respiratory tract infection | 79 (47.4) | 158 (94.0) | 50 | <.001 |
| Acute otitis media | 31 (19.4) | 73 (43.5) | 68 | <.001 |
| Pneumonia | 13 (8.1) | 38 (22.6) | 66 | <.001 |
| Tonsillopharyngitis | 10 (6.3) | 25 (14.9) | 60 | .01 |


http://www.mhra.gov.uk/NewsCentre/Pressreleases/CON180627
Press release: Echina...
File Modifica Visualizza Preferiti Strumenti ?
Pagina Sicurezza Strumenti
About us
How we regulate
Safety information
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Advanced search
Go
Archive:
Looking for a previously published document in this section?
all months
all years
Go
Press release: Echinacea herbal products should not be used in children under 12 years old
Press release
Date: Monday 20 August
Time: 12:30
Subject: Echinacea herbal products should not be used in children under 12 years old
Contact: Press Office 020 3080 7651
or press.office@mhra.gsi.gov.uk
Out-of-hours 07770 446 189
The Medicines and Healthcare products Regulatory Agency (MHRA) today advised parents and carers not to use oral herbal products containing Echinacea for children under 12 years of age. Children aged 12 or over and adults can continue to use herbal products containing Echinacea.
This move by the MHRA follows precautionary advice from the European Herbal Medicinal Products Committee (HMPC) and from the UK Herbal Medicines Advisory Committee (HMAC). They both concluded that the perceived benefits of the use of Echinacea in children under 12 years are outweighed by the potential risks in this age-group and there is a low risk of allergic reactions but these could be severe. Children aged 12 years or over and adults can continue to use oral products containing Echinacea. Risks of side effects in older children and adults are reduced because they weigh more and in general catch fewer colds.
Two Echinacea products (Echinaforce Junior Cold & Flu Tablets and Echinaforce Chewable Cold & Flu Tablets) were registered under the Traditional Herbal Registration (THR) Scheme for children aged between six and 12 years as well as for older children and adults. These products have been updated in line with this new advice and newly labelled products will be available in due course. Current stock will be over-labelled and the new labels will state clearly that the products should not be used in children under 12 years.
In addition, there were two oral Echinacea products (Echinaforce Tablets and Echinaforce Echinacea Drops) with product licences for children aged between six and 12 years. The labelling of these products is also being updated in line with this advice and existing stocks will also be over-labelled.
However, there is an unknown number of unlicensed Echinacea products on sale in the UK. The MHRA is requesting that these products are also relabelled and advises parents and carers not to use them in children under 12 years.
Printer friendly version (new window)
Related information:
MHRA pages:
'Herbal Safety News'
Herbal medicines: Advice to consumers
Other sites:
(open in a new window)
European Medicines Agency (EMA) website
Help viewing PDFs:
Help viewing PDF files
Download Acrobat Reader for free
Adobe text conversion tools
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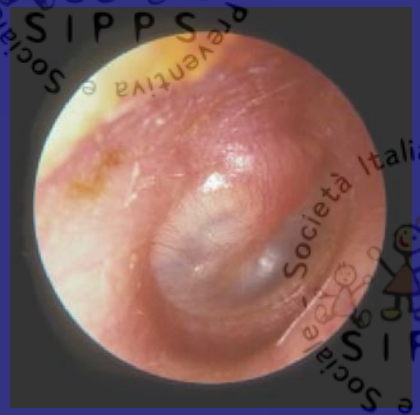
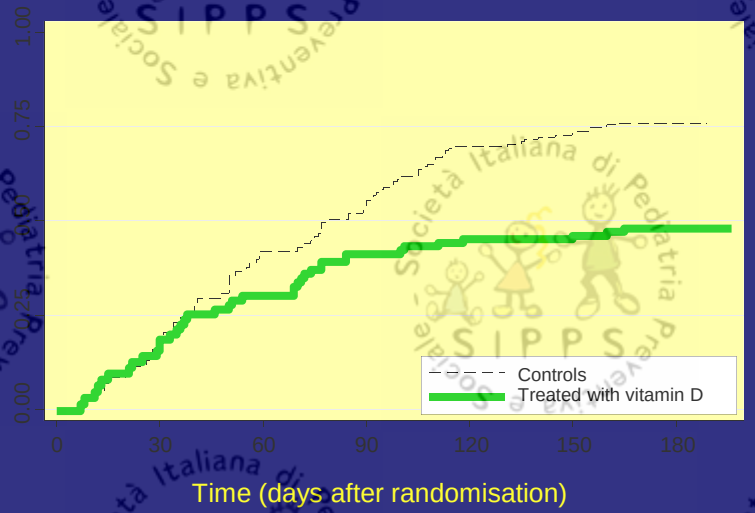
30/05/2013

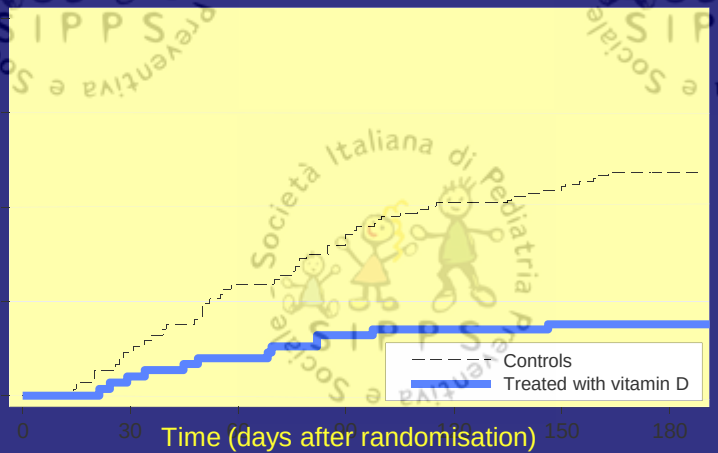
# Efficacy of vitamin D3 1000 U/day in children 1 – 5 yrs with a history of rAOM

ALL episodes

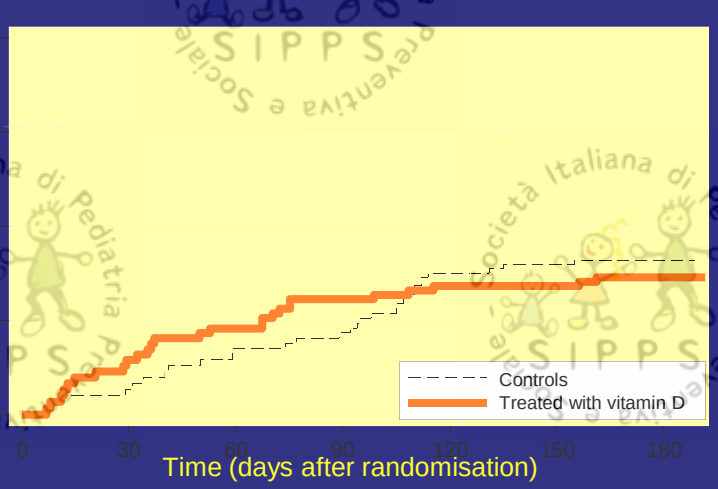





uncomplicated AOM episodes




complicated with othorrea AOM episodes




Marchisio P et al. PIDJ 2013

# Vitamin D and Respiratory Tract Infections: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

PLoS ONE 8(6): e65835. doi:10.1371/journal.pone.0065835

Peter Bergman[1,2], Åsa U. Lindh[3], Linda Björkhem-Bergman[4*], Jonatan D. Lindh[4*]

2013

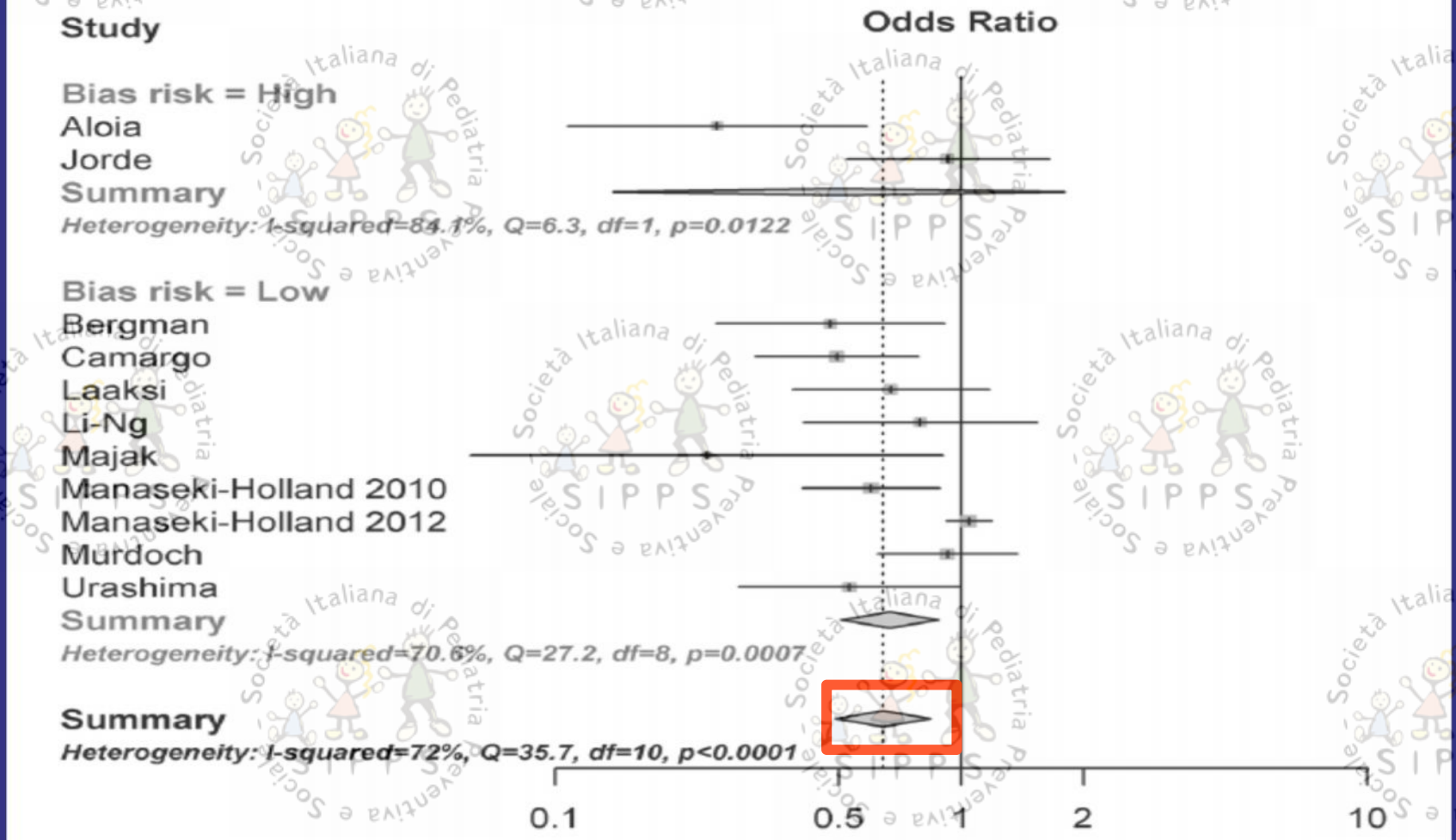


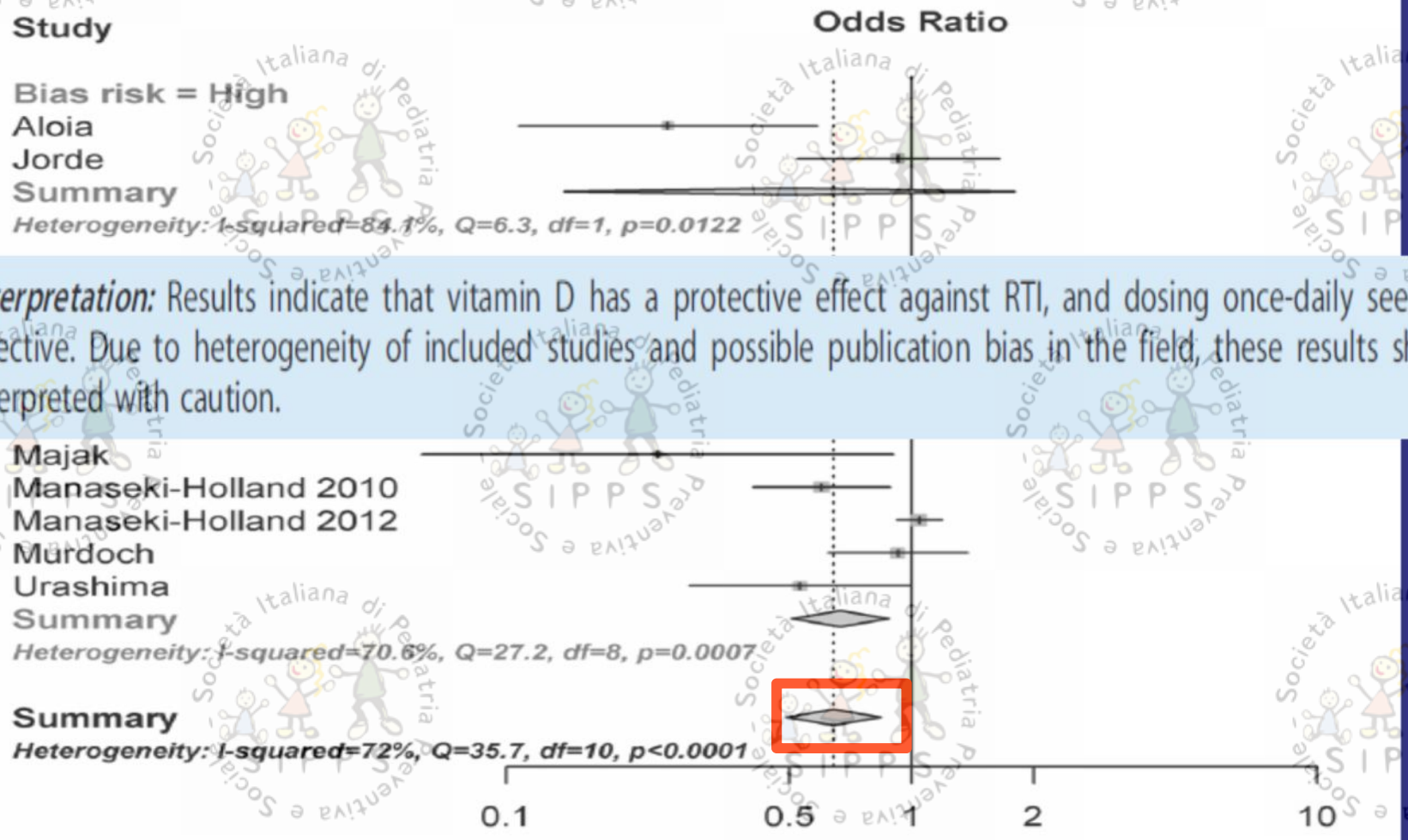

**Figure 2. Efficacy of vitamin D for prevention of respiratory tract infections.**

# Vitamin D and Respiratory Tract Infections: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

PLoS ONE 8(6): e65835. doi:10.1371/journal.pone.0065835

Peter Bergman[1,2], Åsa U. Lindh[3], Linda Björkhem-Bergman[*], Jonatan D. Lindh[*]

2013




*Interpretation:* Results indicate that vitamin D has a protective effect against RTI, and dosing once-daily seems most effective. Due to heterogeneity of included studies and possible publication bias in the field, these results should be interpreted with caution.

**Figure 2. Efficacy of vitamin D for prevention of respiratory tract infections.**

# S.salivarius 24SMB characterization

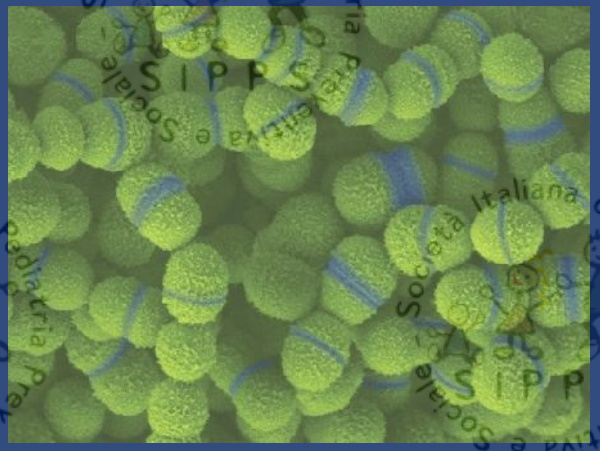
- S.salivarius 24SMB (Patent number DSM 23307), an α haemolitic strain derived from oral/nasopharyngeal swabs from healthy children, was selected as a potential probiotic possessing desirable characteristics for *bacteria-therapy*

- Molecular identification by sequencing of the *sodA* gene

- Bacteriocin-like inhibitory substances (BLIS) activity against potential pathogens involved in AOM

- in vitro *safety assessment*

i) metabolic activity
ii) detection of virulence genes
iii) susceptibility testing



Santagati et al. FEMS Immunol Med Microbiol. 2012; 65:23-31

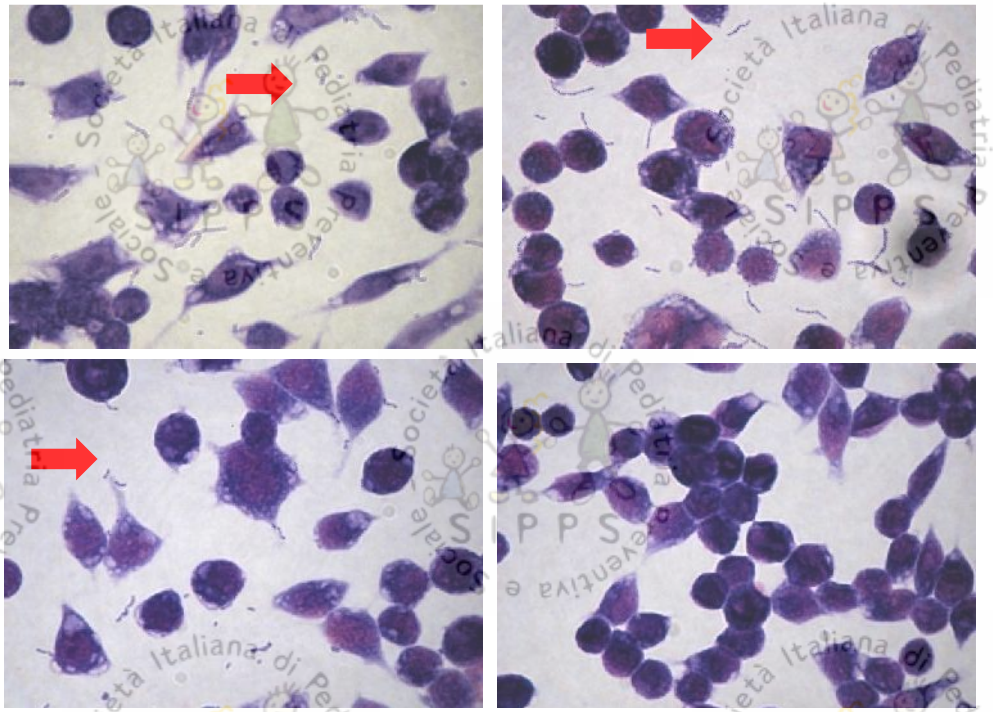
# Bacterial adhesion to HEP-2 cell layer by microscopic examination

| A Species | Strain | *Adl |
|---|---|---|
| *Streptococcus salivarius* | K12 | 1,059 |
| *Streptococcus salivarius* | 24SMB | 1,362 |
| *Streptococcus salivarius* | 4SMB | 500 |

•Adhesion indexes: number of bacteria /100 Hep-2 cells

Test of adhesion of *Streptococcus salivarius* to HEp-2 cell lines (ATCC CCL23- Human larynx carcinoma squamous cell) by microscopic examination

*S. salivarius* K12 *S. salivarius* 24SMB



*S. salivarius* 4SMB negative control

Santagati et al; FEMS Immunol Med Microbiol. 2012;

# Utilizzo di S. Salivarius 24SMBc in bambini con storia di otite media acuta ricorrente

1. **Pazienti di età compresa tra 12 e 72 mesi;**
2. **Anamnesi positiva per OM acuta recidivante non complicata o complicate:**
   - almeno 3 episodi nei 6 mesi precedenti OPPURE
   - almeno 4 episodi nei 12 mesi precedenti;
3. **Precedenti episodi di OMA documentati nella cartella clinica e trattati con adeguata terapia antibiotica;**
4. **Consenso scritto da parte di ENTRAMBI i genitori/tutori**

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

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Eur J Clin Microbiol Infect Dis
DOI 10.1007/s10096-015-2491-x

100 bambini arruolati

50 randomizzati a trattamento con *S. salivarius* 24SMB

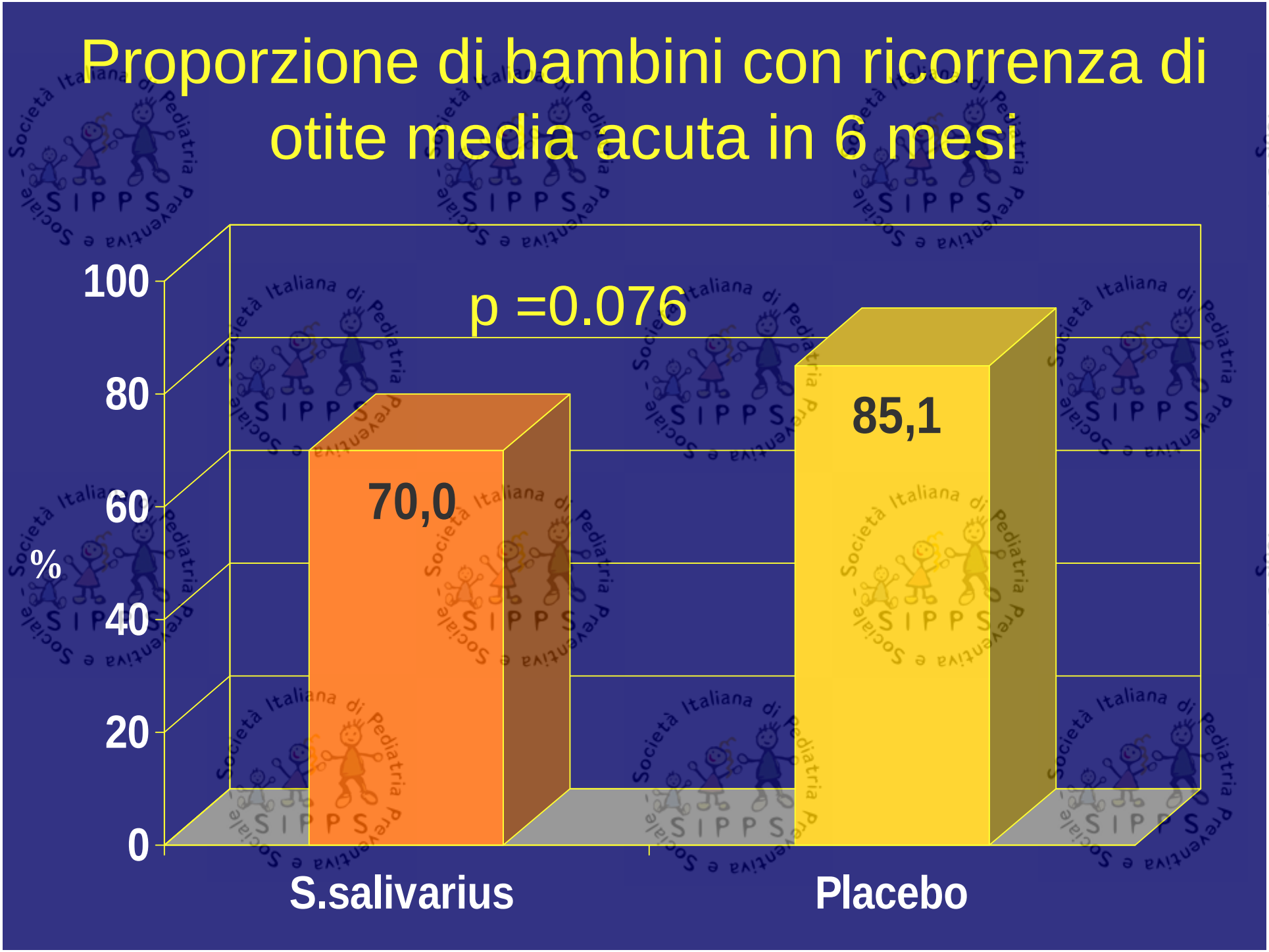
47 randomizzati nel gruppo placebo


KIT SPERIMENTALE:
La sospensione ricostituita si somministra attraverso uno spray nasale che nebulizza 5 MLD di *S. salivarius* 24SMB per dose **oppure** soluzione salina isotonica del tutto indistinguibile

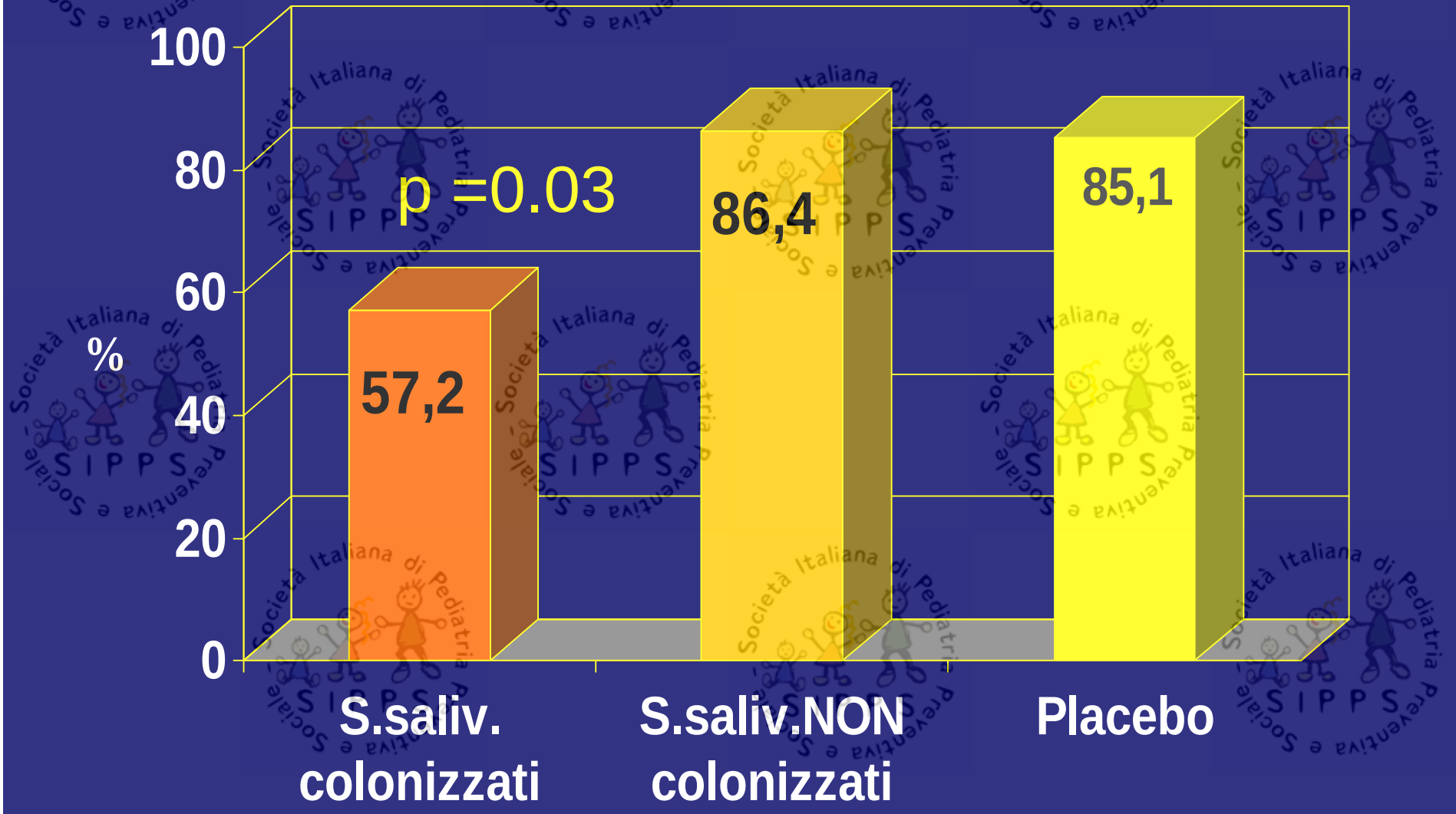
# Caratteristiche epidemiologiche della popolazione in studio

| | S.salivarius 24SMBc N (%) | Placebo N (%) | P |
|---|---|---|---|
| Pazienti, totali | 50 (100) | 47 (100) | |
| Età (anni), media (DS) | 2.7 ± 1.1 | 3.1 ± 1.2 | 0,07 |
| Caucasici | 50 (100,0) | 47 (100,0) | 1,00 |
| Allattamento materno ≥ 3 mesi | 42 (84,0) | 38 (80,9) | 0,68 |
| Uso regolare del ciuccio | 21 (42,0) | 23 (48,9) | 0,49 |
| Presenza di fratello maggiore | 30 (60,0) | 28 (59,6) | 0,25 |
| Esposizione al fumo passivo | 12 (24,0) | 12 (25,5) | 0,86 |
| Frequenza dell'asilo | 44 (88,0) | 42 (89,4) | 0,83 |
| Vaccino antipneumococcico | 43 (86,0) | 41 (87,2) | 0,86 |
| IgE elevate | 23 (39,7) | 21 (36,2) | 0,70 |

# Proporzione di bambini con ricorrenza di otite media acuta in 6 mesi



# Proporzione di bambini con ricorrenza di otite media acuta in 6 mesi in rapporto a colonizazzazione



THE FIRST CAUSE OF RECURRENT INFECTIONS IN CHILDREN IS...

CHILDHOOD ITSELF

(J.G. Wheeler 1996)

From

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PEDIATRIC , WEIGHED AND SHARED EVIDENCE MEDICINE

Grazie per l’attenzione