

**Abbiamo fatto progressi nella
prevenzione delle riacutizzazioni
nel bambino con condizioni
respiratorie croniche di base?**

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AGENDA

- **Epidemiologia delle riacutizzazioni respiratorie**
- **Fattori di rischio e possibilità di prevenzione**
- **Ruolo degli immunostimolanti**



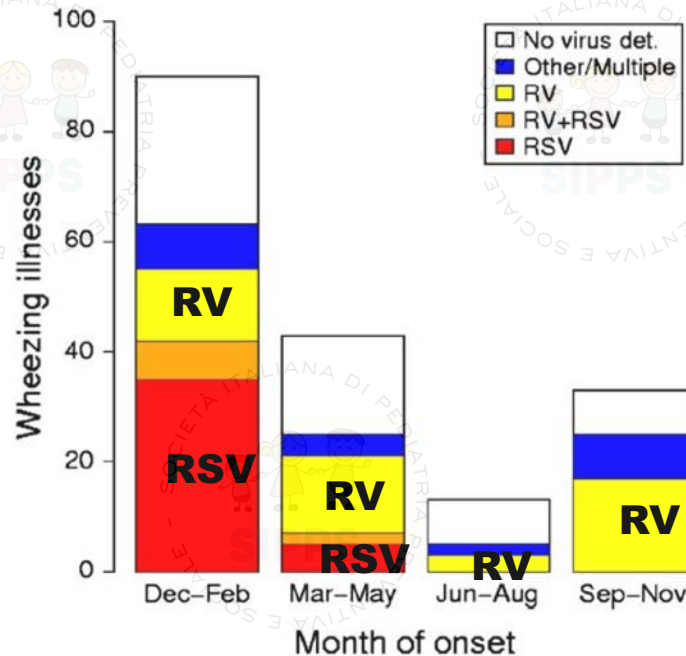
Burden of wheezing and asthma

20% of all children have at least 1 episode of LRI associated with wheezing in the first year of life

70% of these are associated with viral infections

Wright AL. Lower respiratory tract illness in the first year of life. Am.J.Epidemiol. 1996

SEASONALITY AND ETIOLOGY OF WHEEZING EPISODES IN 285 CHILDREN IN THE 1ST YEAR OF LIFE



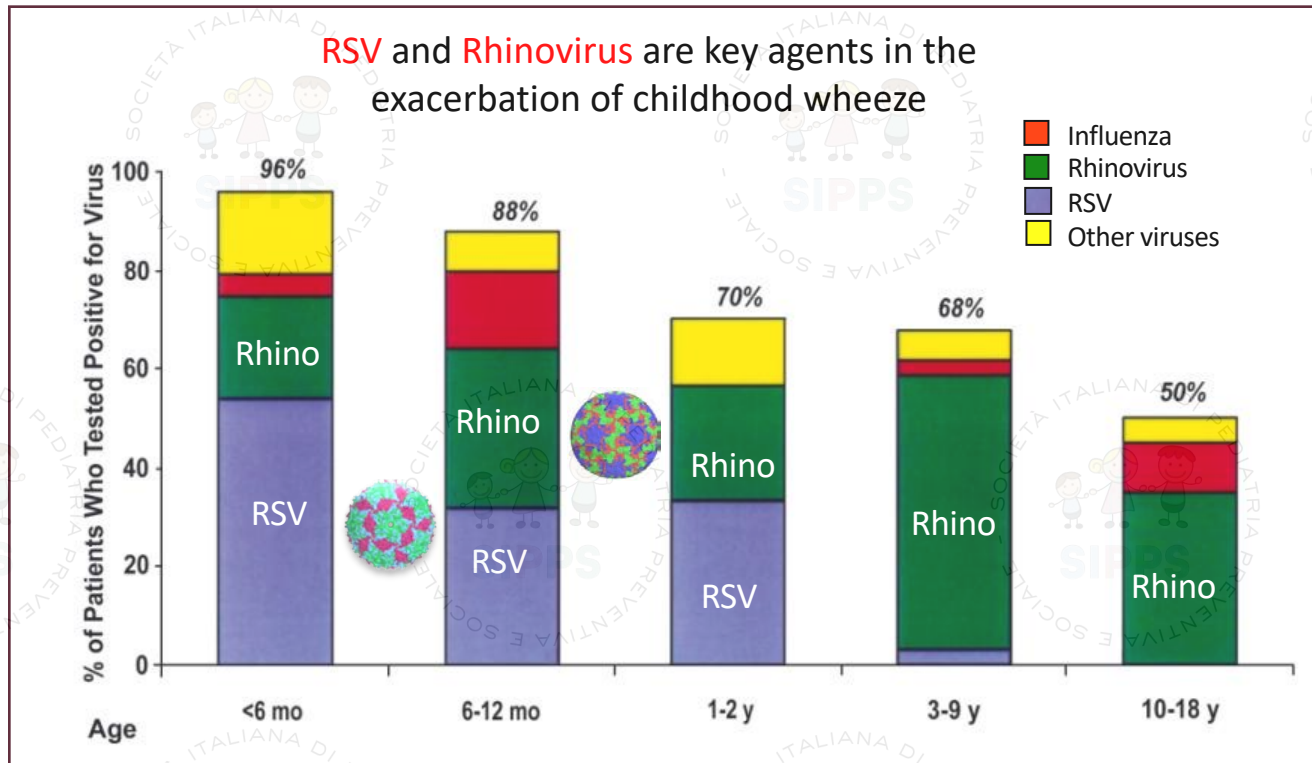
HRV-A, HRV-B and HRV-C are very widespread and continuously co-circulating on all continents throughout the world

Gern JE. JACI 2006;117:72-8.

Courtesy of Giovanni A. Rossi

VIRAL PATHOGENS IN CHILDREN HOSPITALIZED FOR WHEEZING

Courtesy of Giovanni A. Rossi

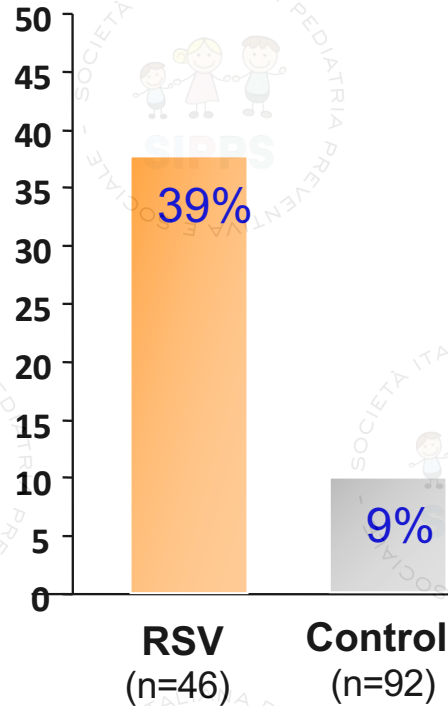


Heymann PW. Viral pathogens in nasal secretions among children hospitalized for wheezing in relation to age. JACI 2004; 114: 239-47

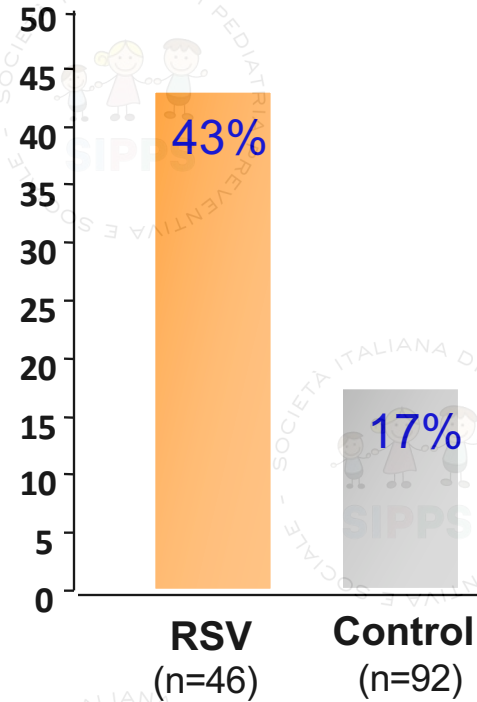
Infants hospitalized for RSV bronchiolitis: 18 years follow-up



Asthma & recurrent wheeze



Atopy



Sigurs, Thorax 2010

Host Factors?

↓ antiviral responses
↓ lung function
Genetic polymorphisms



Asthma



Abnormal Host



RISK FACTORS FOR RECURRENT RESPIRATORY INFECTIONS IN CHILDREN

- day-care attendance,
- early socialization,
- large family size, overcrowding,
- positive family history on atopic diseases,
- school-aged siblings,
- prematurity,
- low bodyweight infants,
- reduction of breast-feeding,
- climate and environmental factors (indoor and outdoor pollutions exposure),
- home dampness,
- pets at home (especially cats and dogs),
- parental smoking and smoking in pregnancy,
- anatomic or functional alterations of the upper or lower airways,
- allergy/atopy,
- gastroesophageal reflux,
- male gender,
- poor socio-economic conditions with malnutrition,
- intense training and physical stress,
- missed vaccination.

Savitha MR, Nandeeshwara SB, Pradeep Kumar MJ, ul-Haque F, Raju CK. Modifiable risk factors for acute lower respiratory tract infections. Indian J Pediatr. 2007 May;74(5):477-82.

WHAT CAN BE DONE?

- **Treatment**

- **limited role of antibiotics**

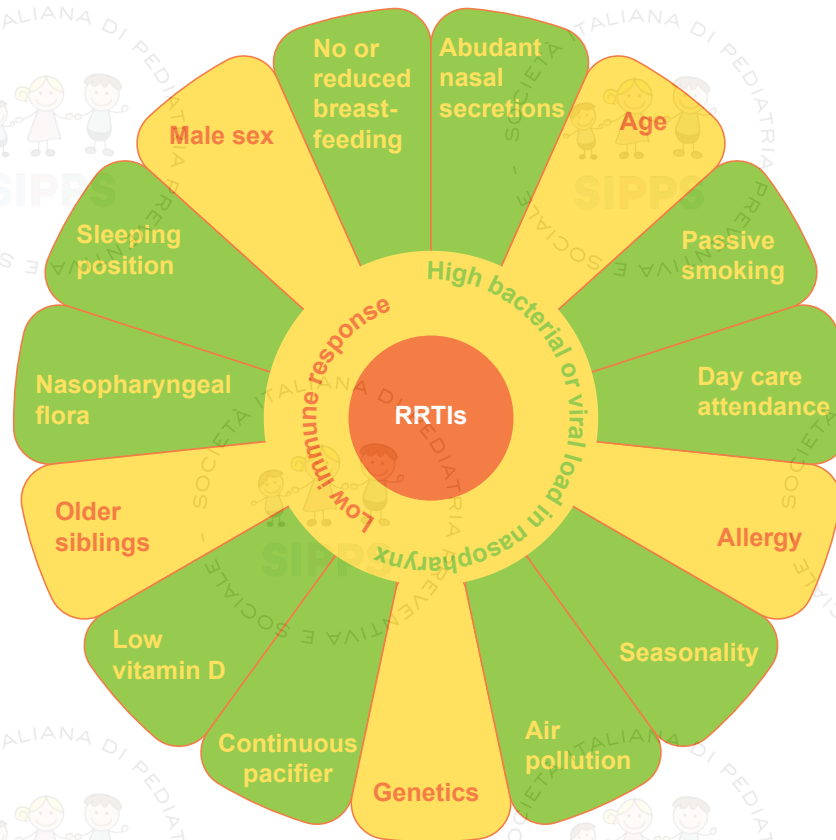
- **role of symptomatic measures**

- **PREVENTION**

- **Firstly, based on risk factors**

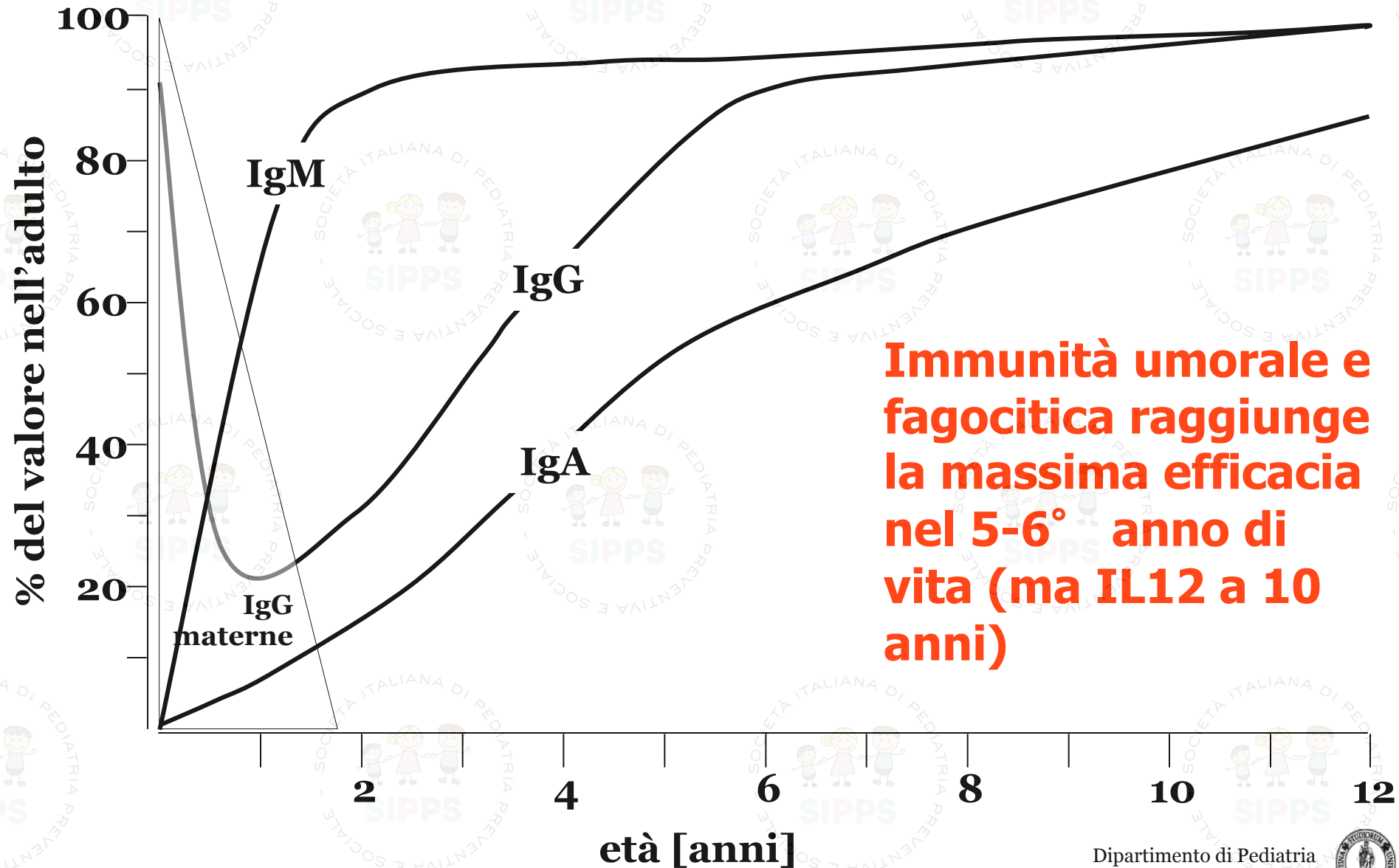
- **Secondly, based on past history**

HIGH BACTERIAL OR VIRAL LOAD IN NASOPHARYNX



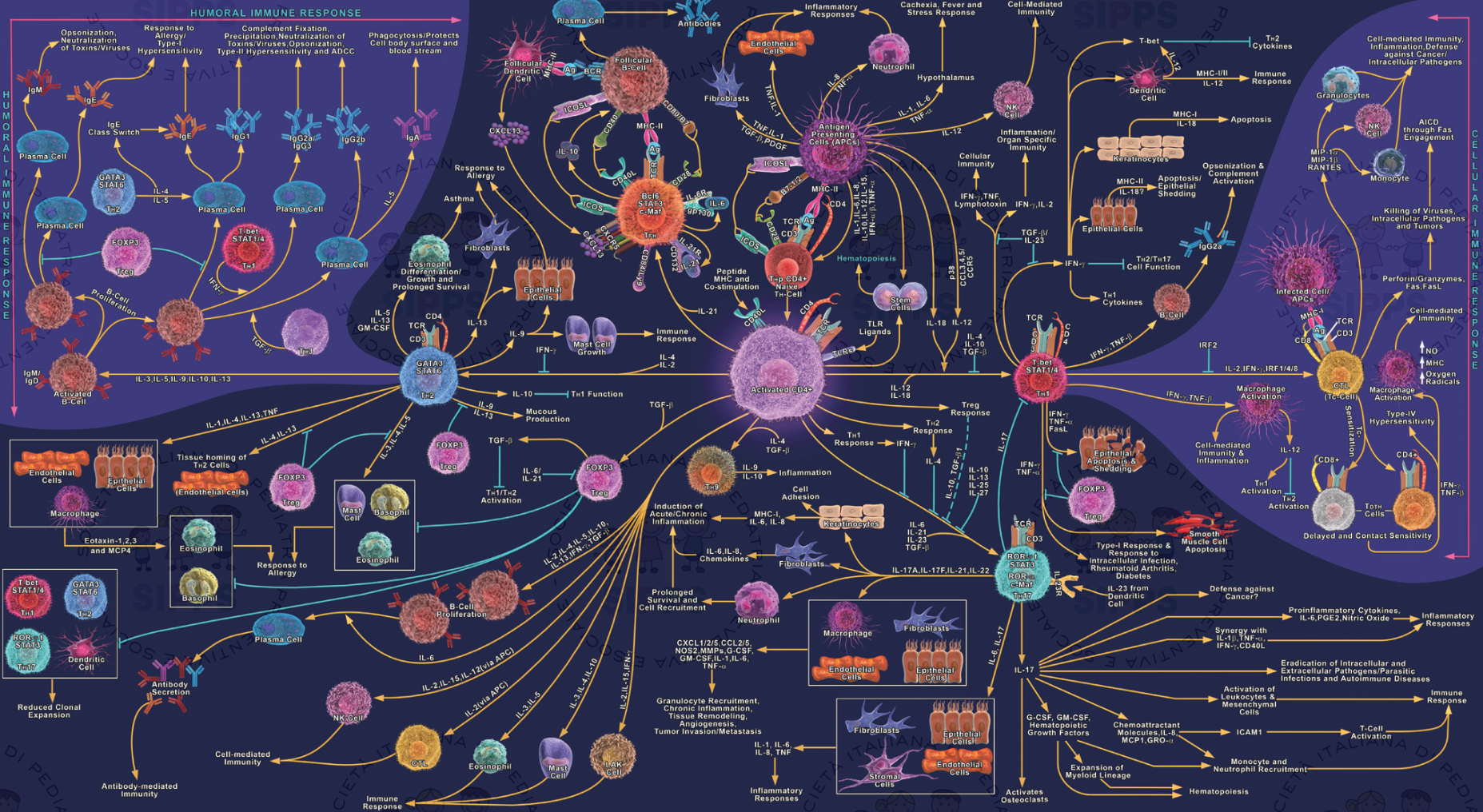
classi immunoglobuliniche per età

Chiappini E & de Martino M. *Immunity development*. In [Nicoletti I & Tanner JM Eds] *Physiological and Pathological Auxology*. Nicomp L.E. Publ: London 2004



Immunità umorale e fagocitica raggiunge la massima efficacia nel 5-6° anno di vita (ma IL12 a 10 anni)

Immunologic Networks 2009



www.biolegend.com

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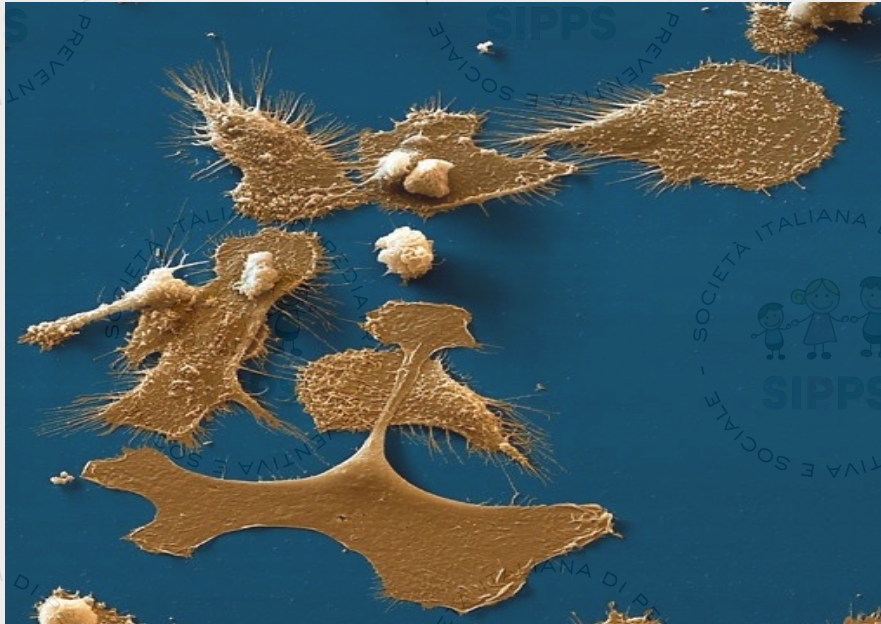
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We would like to thank *Dr. Vijay K. Kuchroo* of Harvard Medical School for his contributions to this poster.

Created by ProteinLounge.com in April 2009

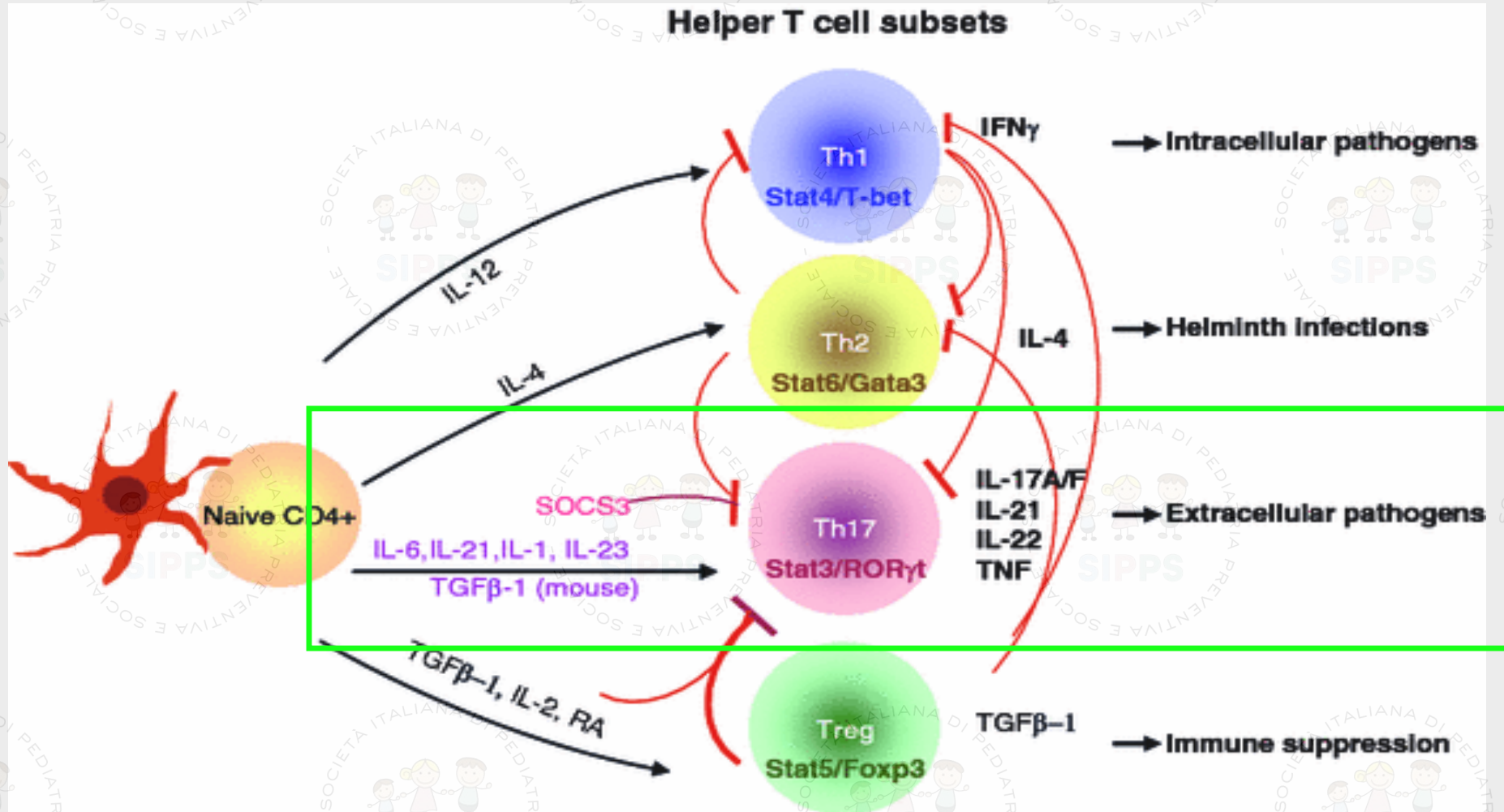
I sistemi dell'immunità innata ed adattativa sono strettamente integrati tra loro a livello cellulare e molecolare

Cellule dendritiche

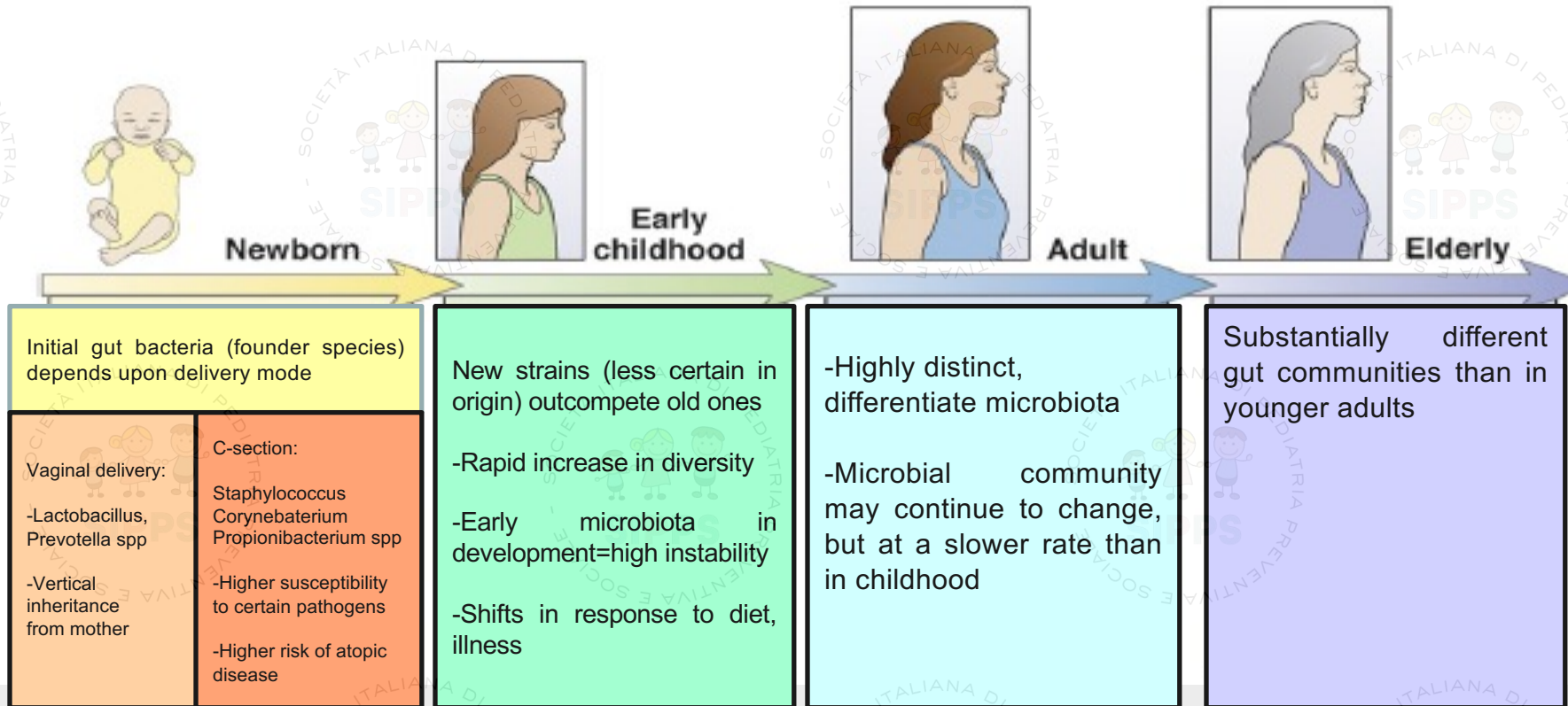


Ponte tra immunità innata e acquisita

New complexities in CD4+ T cell differentiation



Development of the Human Gastrointestinal Microbiota and Insights From High-Throughput Sequencing



Antibiotic overuse: Stop the killing of beneficial bacteria

Blaser; Nature, 2011, Vol 476: 393-394

- Evidence is accumulating that **our welcome residents do not recover completely from antibiotics or are replaced in the long term by resistant organisms**
- Overuse of antibiotics could be fueling the dramatic increase in conditions such as obesity, type 1 diabetes, inflammatory bowel disease, allergies and asthma, which have more than doubled in many populations



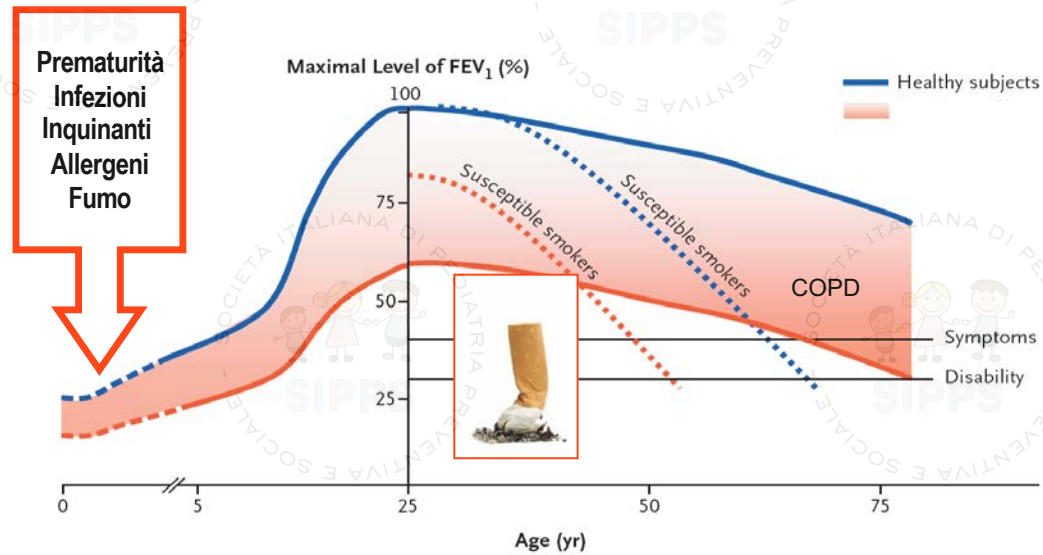
David up: could excessive prescription of antibiotics be hampering children's ability to fight disease?

Stop the killing of beneficial bacteria

Concerns about antibiotics focus on bacterial resistance — but permanent changes to our protective flora could have more serious consequences, says Martin Blaser.

“Fetal programming” e maturazione polmonare

Tutti i fattori che espongono ad un'alterata maturazione polmonare nei primi 5 anni di vita determinano un maggiore rischio di sviluppare asma infantile e BPCO precoce nell'adulto



Inquinamento ambientale ed infezioni respiratorie in età pediatrica

I bambini più a rischio sono quelli con familiarità per atopia o che soffrono di wheezing ricorrente o asma:

Esposito et al. *BMC Pulmonary Medicine* 2014, **14**:130
<http://www.biomedcentral.com/1471-2466/14/130>


BMC
Pulmonary Medicine

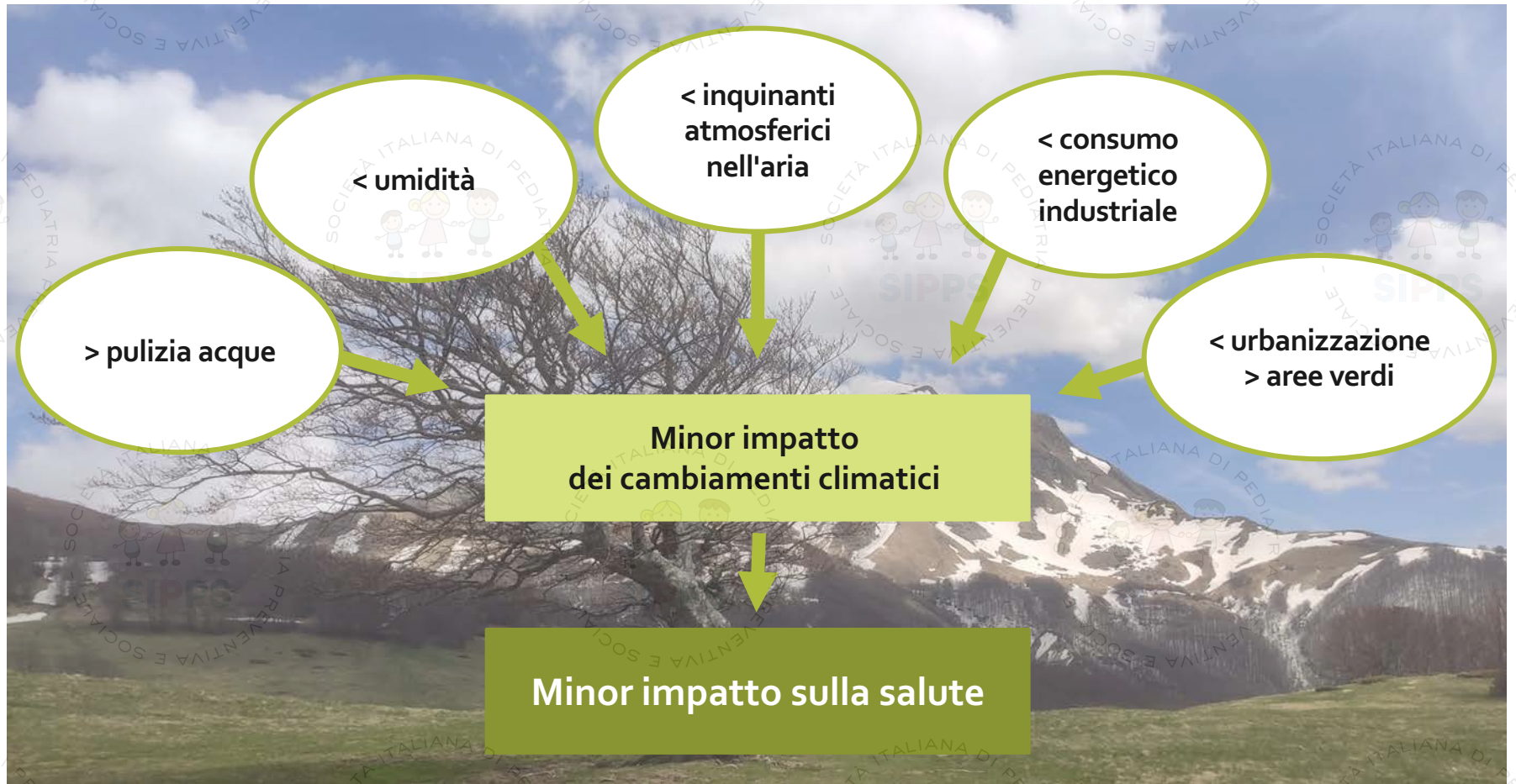
RESEARCH ARTICLE

Open Access

Impact of air pollution on respiratory diseases in children with recurrent wheezing or asthma

Susanna Esposito^{1*}, Carlotta Galeone², Mara Lelii¹, Benedetta Longhi¹, Beatrice Ascolese¹, Laura Senatore¹, Elisabetta Prada¹, Valentina Montinaro¹, Stefano Malerba³, Maria Francesca Patria¹ and Nicola Principi¹

VIVERE NELL'APPENNINO EMILIANO-ROMAGNOLO



(Dati arpae.it 2019)

VITAMIN D SUPPLEMENTATION AND PREVENTION OF RTIs IN PEDIATRIC AGE

	Number of trials	Proportion of participants in the intervention group with one or more events	Proportion of participants in the control group with one or more events	Odds ratio (95% CI)	I ²	p value for heterogeneity
Efficacy outcomes						
Upper respiratory infection*	29	8578/14 569 (58.9%)	8475/14 115 (60.0%)	0.96 (0.91-1.02)	1.2%	0.45
Lower respiratory infection*	15	3930/13 243 (29.7%)	3956/13 108 (30.2%)	0.98 (0.93-1.04)	0	0.63
Emergency department attendance, hospital admission due to an ARI, or both	19	139/10 963 (1.3%)	149/10 850 (1.4%)	0.90 (0.71-1.14)	0	1.00
Death due to ARI or respiratory failure	34	14/14 688 (0.1%)	11/14 139 (0.1%)	1.04 (0.61-1.77)	0	1.00
Use of antibiotics to treat an ARI*	14	2056/8638 (23.8%)	2109/8504 (24.8%)	0.92 (0.83-1.01)	9.0%	0.35
Absence from work or school due to ARI	10	378/1527 (24.7%)	364/1044 (34.9%)	0.91 (0.69-1.20)	35.3%	0.13
Safety outcomes						
Serious adverse event of any cause*	36	567/14 937 (3.8%)	585/14 407 (4.1%)	0.97 (0.86-1.07)	0	0.99
Death due to any cause	35	129/14 930 (0.9%)	110/14 374 (0.8%)	1.13 (0.88-1.44)	0	1.00
Hypercalcaemia	22	51/10 370 (0.5%)	41/10 000 (0.4%)	1.18 (0.80-1.74)	0	1.00
Renal stones	21	117/12 616 (0.9%)	136/12 219 (1.1%)	0.85 (0.67-1.11)	0	1.00

Jolliffe et al. Lancet Diabetes Endocrinol. 2021

Prevenzione e controllo dell'influenza: raccomandazioni per la stagione 2022-2023

Persone ad alto rischio di complicanze o ricoveri correlati all'influenza:

- Donne che all'inizio della stagione epidemica si trovano in gravidanza e nel periodo "postpartum".
- Soggetti dai 6 mesi ai 65 anni di età affetti da patologie che aumentano il rischio di complicanze da influenza:
 - a) *malattie croniche a carico dell'apparato respiratorio (inclusa l'asma grave, la displasia broncopolmonare, la fibrosi cistica e la broncopatia cronico ostruttiva-BPCO);*
 - b) *malattie dell'apparato cardio-circolatorio, comprese le cardiopatie congenite e acquisite;*
 - c) *diabete mellito e altre malattie metaboliche (inclusi gli obesi con indice di massa corporea BMI >30);*
 - d) *insufficienza renale/surrenale cronica;*
 - e) *malattie degli organi emopoietici ed emoglobinopatie;*
 - f) *tumori e in corso di trattamento chemioterapico;*
 - g) *malattie congenite o acquisite che comportino carenza produzione di anticorpi, immunosoppressione indotta da farmaci o da HIV;*
 - h) *malattie infiammatorie croniche e sindromi da malassorbimento intestinali;*
 - i) *patologie per le quali sono programmati importanti interventi chirurgici;*
 - j) *patologie associate a un aumentato rischio di aspirazione delle secrezioni respiratorie (ad es. malattie neuromuscolari);*
 - k) *epatopatie croniche.*
- **Soggetti di età pari o superiore a 65 anni.**
- Bambini e adolescenti in trattamento a lungo termine con acido acetilsalicilico, a rischio di Sindrome di Reye in caso di infezione influenzale.
- Individui di qualunque età ricoverati presso strutture per lungodegenti.
- Familiari e contatti (adulti e bambini) di soggetti ad alto rischio di complicanze (indipendentemente dal fatto che il soggetto a rischio sia stato o meno vaccinato).

INFLUENZA AND ASTHMA: EFFICACY OF THE VACCINATION

(Kramarz P et al., J Pediatr 2000)

	Influenza season		
	1993-1994*	1994-1995*	1995-1996†
No. of cases‡	577	969	2,075
No. of asthma exacerbations	710	1,146	2,564
Follow-up time (child-months)	3,904	6,520	14,067
Adjusted incidence rate ratio (95% CI)§	0.78 (0.55-1.10)	0.59 (0.43-0.81)	0.65 (0.52-0.80)
P value	.15	.001	.0001

*Three HMOs.

†Four HMOs.

‡Children with asthma who had at least one asthma exacerbation during the influenza season.

§Incidence rate ratio (95% CI) of asthma exacerbation occurring after influenza vaccination compared with the period before vaccination in the same individual; estimated by conditional Poisson regression models stratified by individual child and adjusted for 2-week periods of calendar time from October 1 through April 30 of each season.

Type of vaccine	Route of administration	Age	No. of subjects	Population	End results	Adverse reactions (AE)
SV bivalent	According to insert	6–16 yr	79	Children with chronic asthma	Transient decrease in peak expiratory flow rate at 48 hr. Good serologic response	No acute ill AE at 24 hr
SV monovalent	NS	7–25 yr	31	Children and adults with CF	A direct dose response observed	Similar to placebo group
SV trivalent	IM	2–25 yr	76	Infants, children & adults with asthma or CF	Among the unprimed individuals, after 1 dose of vaccine, the geometric mean responses to both strains of influenza A were 100, whereas the same responses to the B component were 32.	No febrile reactions within 24 hr, 6 to 7 recipients from each vaccine group had local arm tenderness
SU trivalent	IM	7 mo–12 yr	95	Infants & children with asthma	No child had asthma worsening	Limited motion of limb for 8–12 hr after vaccination
SV trivalent	IM	3–8 mo	113	Infants with BPD or CHD	Seroconversion (i.e., a 4-fold increase in titer) required 2 doses of vaccine	More frequent solicited AE in young infants
CRIV	IN	11.2 yr	71	Children with asthma, 19; severe SPR pts., 52	CRIV demonstrated significant protective effects against natural exposure to the A H1N1 virus	Well tolerated and safe when given to patients with bronchial asthma and severe psychomotor retardation
CRIV	IN	10.5 yr	68	Children with asthma, 20; severe SPR pts., 48	The vaccines were mostly seropositive & asthmatic attacks were not observed	Severe adverse reactions were not observed, but more febrile in PSR pts.
SU trivalent	IM	2–14 yr	137	Children with asthma	Total vaccine efficacy, 42.1%; 61.7% in children with over 7 yr of age, but 16.1% in young children	No differences in the severity or frequency of asthmatic attack between both groups
SV trivalent	IM	6 mo–18 yr	109	Control, 59; children with asthma, 50	Influenza vaccination can be given to asthmatic children regardless of asthma Sxs	AEs were not different in the two groups
SV trivalent	IM	8–21 mo	6	Infants with BPD	Large postvaccination increases of GMT for all HA and NA components	No fever or pain at the vaccine site
SV trivalent	IM	3–64 yr	2,032	Children & adults with asthma	The frequency of exacerbations of asthma was similar in the two weeks after the influenza vaccination	Body aches were more frequent after the vaccine injection
CAIV-T	IN	9–17 yr	48	Children & adolescents with moderate to severe asthma	Not result in important reductions in pulmonary function, and not worsen clinical features & symptom scores	No serious adverse events in either group
SV trivalent	IM	6–17 yr	696	Children with asthma: 349 placebo, 347 study group	Influenza-related asthma exacerbations was 3 days shorter in the vaccine group (not statistically significant)	Local and systemic AE significantly more often in the vaccine group
SV trivalent	IM	3–64 yr	272	Children & adults with asthma	Chronic ICS did not affect the humoral immune response to influenza A antigens. But, high dose ICS therapy may affect to immune response to the B antigen	NA
CAIV-T	IN	6–17 yr	2,229	Children with asthma: CAIV-T, 1114; SV-trivalent, 1115	CAIV-T had a significantly greater relative efficacy of 35% compared with TIV in this high-risk population	The nasal Sx was higher for CAIV-T (66.2%) recipients.
SV trivalent	IM					Approximately 70% of TIV recipients reported injection site reactions
SV trivalent	IM	5–9 yr	163	Children with asthma: 31 placebo, 132 study group	The inactivated influenza vaccine was immunogenic, no significant impact on pulmonary function tests among vaccine recipients	Safe in terms of local and systemic side effects compared to placebo
SV trivalent	IM	6–35 mo	130	Healthy infants, 68; recurrent wheezing infants, 62	Seroconversion and seroprotection rates showed no difference overall between healthy children and children with recurrent wheezing	Solicited local and systemic AE showed no differences between healthy children and children with recurrent wheezing

Studies carried out in children with asthma to evaluate immunogenicity and safety of TIV or LAIV

Most of them demonstrate immunogenicity and safety quite similar to those of reported in healthy subjects

From Kang JH. Korean J Pediatr 2014

CARDIORESPIRATORY PARAMETERS AND ADVERSE EVENTS IN THE 4 H AFTER INFLUENZA VACCINATION

(Esposito S et al., Vaccine 2008)

Parameter	Children with persistent asthma and egg allergy			Children with persistent asthma but without egg allergy (n = 44)
	Mild (n = 14)	Moderate (n = 19)	Severe (n = 11)	
Cardiorespiratory parameters				
Median SatO ₂ (range), %	99 (97–100)	99 (96–100)	99 (98–100)	99 (96–100)
Median heart rate (range) per min	82 (60–105)	78 (68–111)	76 (68–125)	80 (69–103)
Median breath rate (range) per min	24 (22–27)	23 (20–27)	23 (18–28)	24 (18–30)
Median blood pressure (range), mmHg				
Systolic	90 (86–105)	90 (84–120)	95 (88–109)	90 (85–110)
Diastolic	65 (63–70)	60 (50–70)	65 (54–85)	65 (55–70)
Adverse events				
No. (%)	1 (7.1)	0 (0.0)	1 (9.1)	1 (2.25)
Erythema, No. (%)	0 (0.0)	0 (0.0)	1 (9.1)	0 (0.0)
Bronchospasm, No. (%)	1 (7.1)	0 (0.0)	0 (0.0)	1 (2.25)
Drug use for adverse events				
Aerosol with salbutamol, No. (%)	1 (7.1)	0 (0.0)	0 (0.0)	1 (2.25)
Oral prednisone, No. (%)	1 (7.1)	0 (0.0)	0 (0.0)	1 (2.25)

No significant between-group difference

IMMUNOMODULATION

Immunostimulation:

- ↑ Immune response
- ↓ Infections

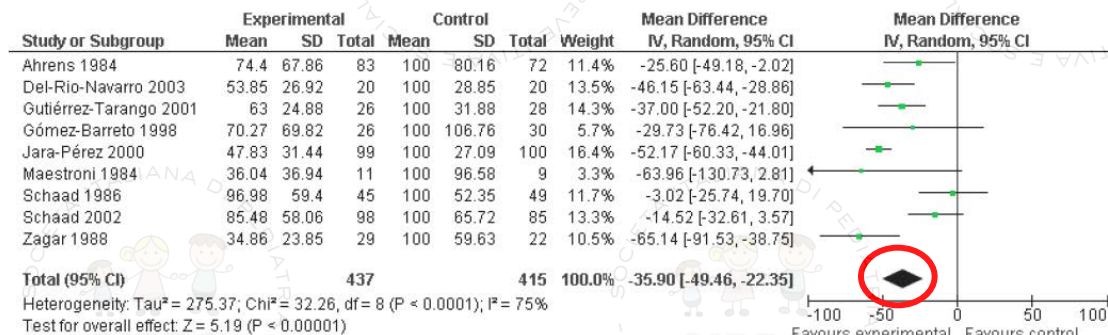
Immunoregulation:

- ↑ Tolerance response
- ↓ Inflammation

Dual
Response

WHAT IS THE REDUCTION OF ARTIS IN CHILDREN TREATED WITH OM-85 PROPHYLAXIS?

852 patients: 437 OM-85 and 415 placebo
3 of the listed studies classified as grade 'A' quality*



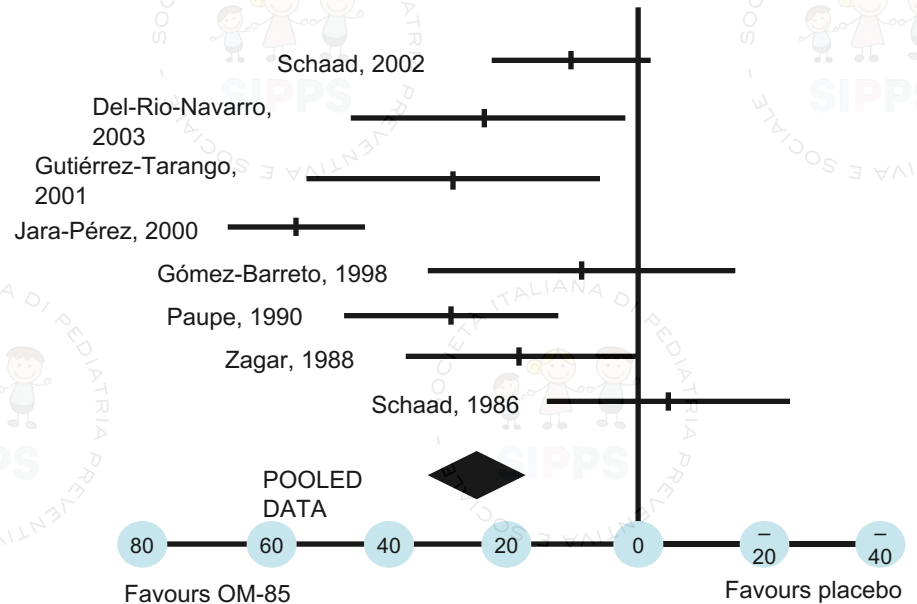
**OM-85 SIGNIFICANTLY REDUCED TOTAL NUMBER ARTIS BY 35.9%
(95% CI -49.5, 22.4)**

*Randomization, blinding, follow-up data. Further research is very unlikely to change confidence in the estimate of effect

SCHAAD META-ANALYSIS SHOWED SIGNIFICANTLY FEWER PATIENTS WITH RECURRENT RTIS IN OM-85 GROUP

Overall, **26.2%** fewer patients experienced recurrent RTI in OM-85 group vs placebo (32% vs 58.2%, respectively; $p < 0.001$)

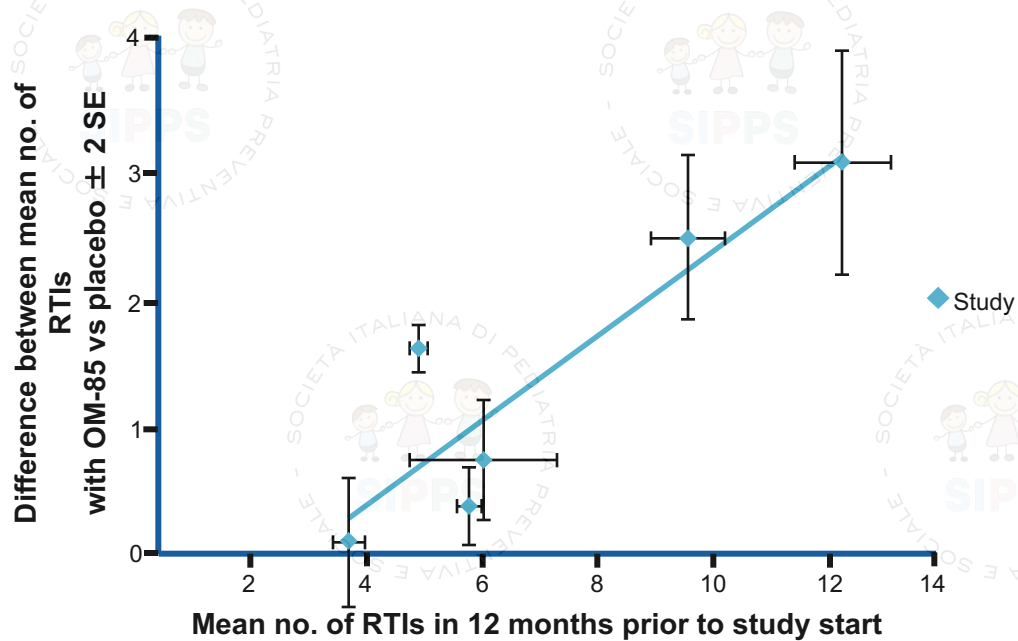
Overall mean number of ARTIs reduced by **35.5%** with OM-85



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

Used with permission: Schaad UB. *World J Pediatr* 2010;6:5-12.

THE GREATER THE RISK OF RECURRENT RTIS, THE GREATER THE BENEFIT WITH OM-85



Beneficial effect is proportional to the number of RTIs in the previous 12 months and is larger in younger children

SE, standard error

Used with permission: Schaad UB. *World J Pediatr* 2010;6:5-12.

Product	Main data	Main limitations	Consensus statement and suggestions for future research
Pidotimod	Positive influence on innate and adaptive immunity <i>in vitro</i> , efficacy in prevention of RTIs in RTI-prone children, duration and severity of respiratory symptoms, antibiotic use, good safety profile.	Licensed for children ≥ 3 yrs, to be given 2 hrs before or after meals, available only in few countries, few studies available with sufficient details on randomization method and using blind approach, heterogeneity in dosages and schedule of administration.	Pidotimod could play a role in prevention of respiratory recurrences in RTI-prone children ≥ 3 yrs old, although further randomized, double-blind studies are needed to confirm population that could have advantages and to define the dosages and schedule of administration.
OM-85	Positive influence on innate and adaptive immunity <i>in vitro</i> , downregulation of inflammatory state, efficacy in prevention of RTIs in RTI-prone children, duration and severity of respiratory symptoms, antibiotic use, days of absence from day-care of children and working days lost by parents, efficacy in children with recurrent wheezing and asthma, excellent safety profile.	Absence of biomarkers able to predict the best responder profile and a precise-host tailored medicine.	OM-85 should be recommended for prevention of respiratory recurrences in RTI-prone children ≥ 6 months old, although further studies on detection of biomarkers able to support the identification of best responder profile and a precise-host tailored medicine are needed.



microorganisms



Review

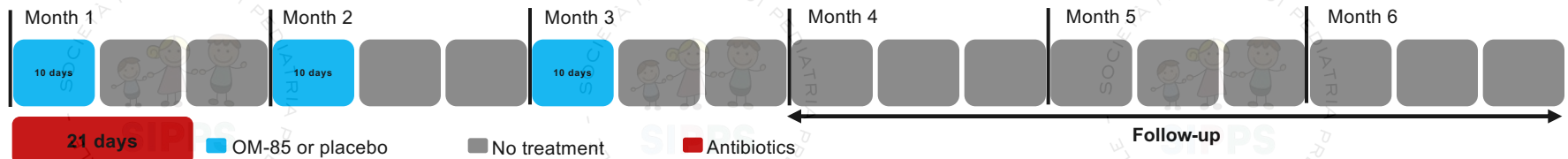
Prevention of new respiratory episodes in children with recurrent respiratory infections: an expert Consensus statement

Susanna Esposito¹, Marcus Herbert Jones², Wojciech Feleszko³, José A. Ortega Martell⁴, Oana Faloup Pecorariou⁵, Natalia Geppé⁶, Federico Martinon Torres⁷, Kun-Ling Shen⁸, Michael Roth⁹, Nicola Principi¹⁰ for the World Association of Infectious Diseases and Immunological Disorders (WAidid)

New!

OM-85 IN TREATMENT OF SUBACUTE SINUSITIS: STUDY DETAILS

- **Design:** Double blind, randomized, placebo controlled
- **Population:** Children (n=56), aged 6 months to 9 years, with subacute* sinusitis
- **Duration:** 6 months (3 months' treatment + 3 months' follow-up)
- **Study medication:** OM-85 3.5 mg/day (n=26) or placebo (n=30), + 21 days of antibiotic therapy† in month 1



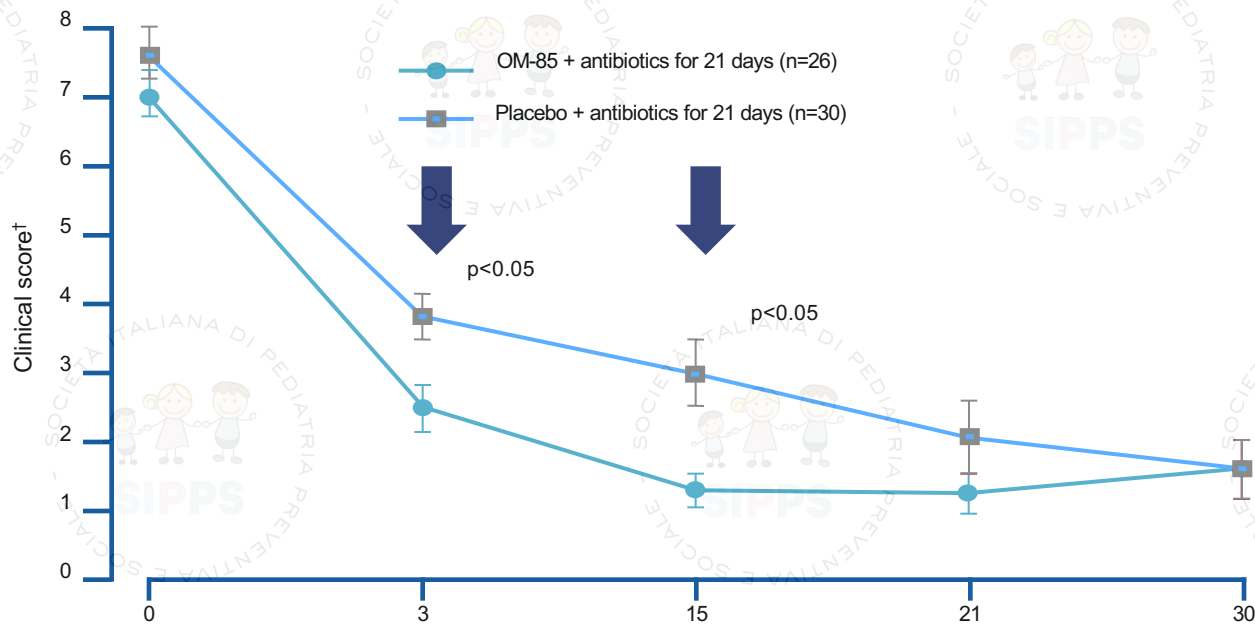
- **Primary endpoint:** Clinical symptom score (treatment) and RTI
- **Other endpoints:** Time to cure in acute phase, days of illness

Gomez Barreto *et al. Allergol et Immunopathol* 1998

*Subacute: condition must have an evolved over a period of ≥ 30 to < 90 days

†Amoxicillin/clavulanate

CLINICAL IMPROVEMENT IN SINUSITIS SYMPTOMS VISIBLE AFTER 2 WEEKS



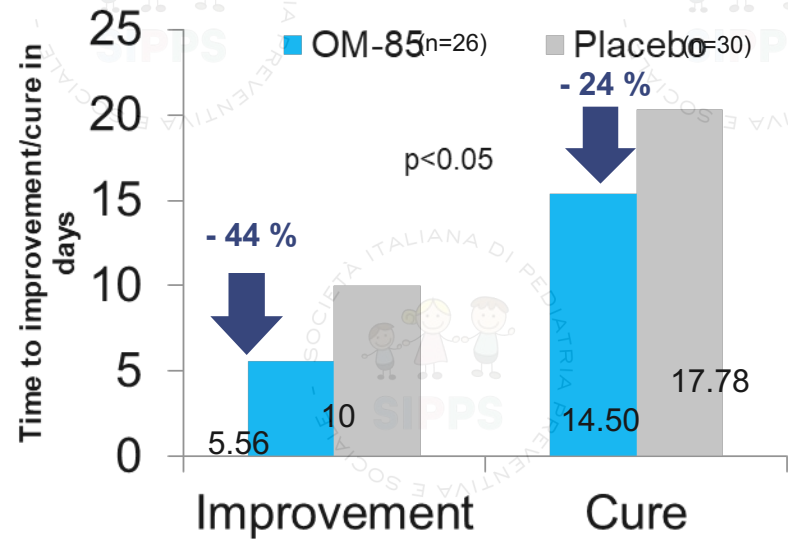
†Defined based on presenting signs/symptoms, including nasal/postnasal discharge, nasal congestion, cough, malodorous breath, facial tenderness, erythematous nasal mucosa, fever and headache. A score of <8 was mild, ≥8 severe (range 0–15) p<0.05

LESS RTIS AND LESS DAYS OF ILLNESS AND WITH OM-85

Patients treated with OM-85 had significantly fewer infections and fewer days of illness than placebo-treated patients

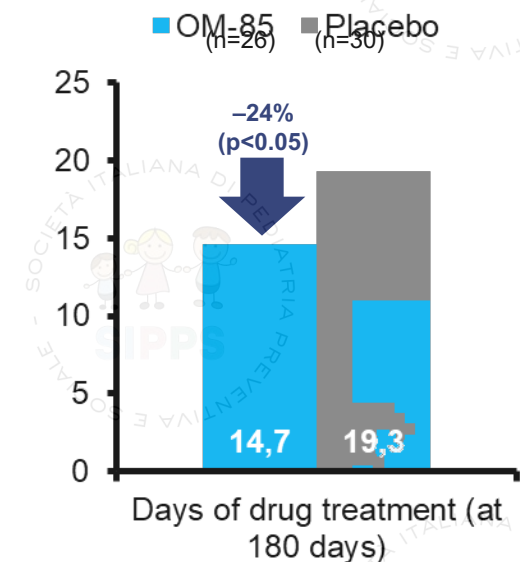
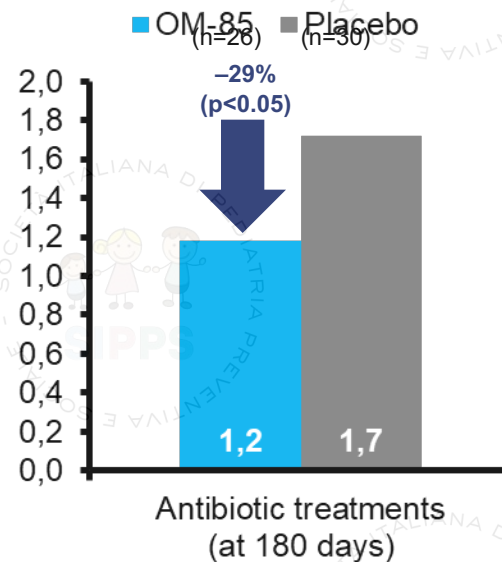
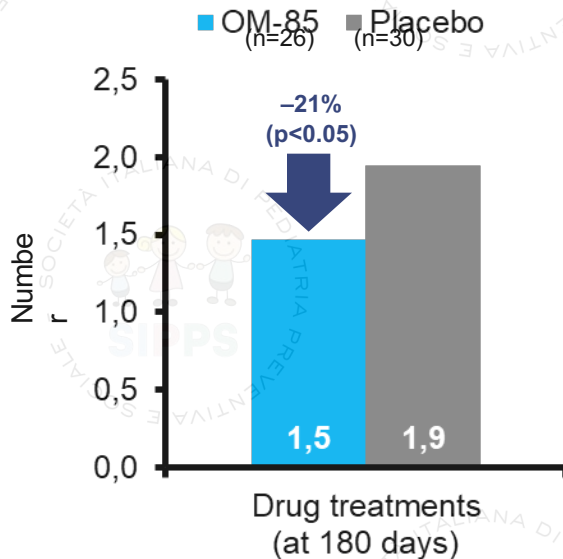
	90 days	180 days	
Infections, n			
OM-85	1.056 ± 0.249*	1.556 ± 0.305*	-33%
Placebo	1.600 ± 0.303	2.222 ± 0.432	
Days of illness			
OM-85	9.39 ± 2.34*	14.50 ± 3.19*	-24%
Placebo	13.25 ± 2.79*	17.78 ± 3.61*	

*p<0.05



OM-85 SIGNIFICANTLY REDUCED USE AND DURATION OF CONCOMITANT MEDICATION

Patients receiving OM-85 required significantly fewer concomitant medications versus placebo, including antibiotics ($p < 0.05$)



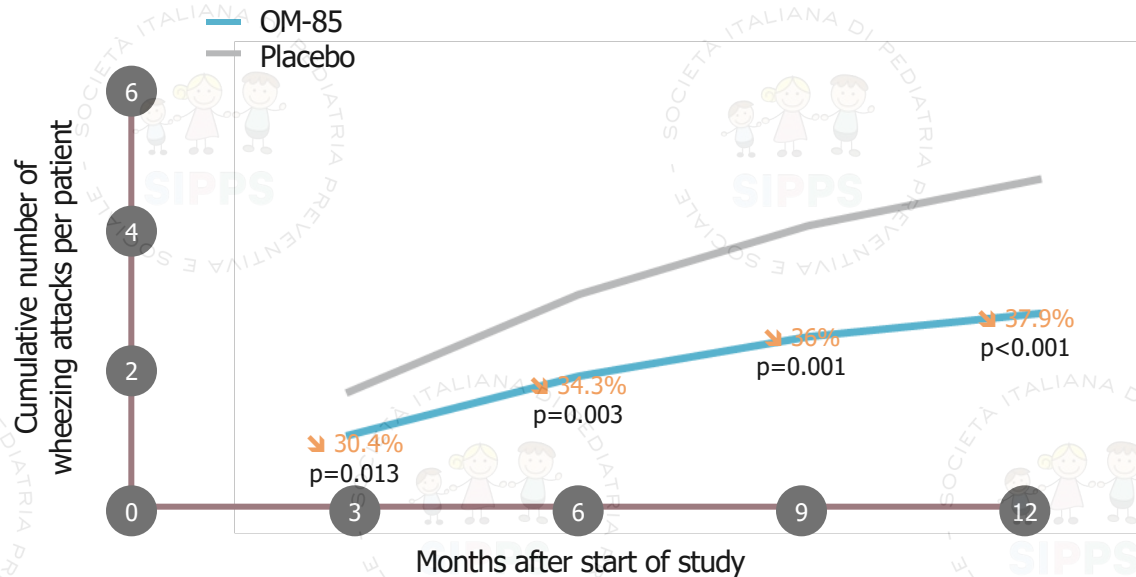
Gomez Barreto et al. *Allergol et Immunopathol* 1998

STUDY DESIGN

- Randomized, double-blind, placebo-controlled, parallel-group study
- 75 children (aged 1–6 years) with recurrent wheezing (≥ 3 in 6 months)
- **Duration of study:** 1 year
- **Primary endpoint:** number of wheezing attacks
- **Other endpoints:** acute RTI incidence, acute nasopharyngitis incidence, wheezing attacks duration, hospitalization rate, safety
- **Dosage regimen:** OM-85 (3.5mg) or placebo, 1 capsule/day

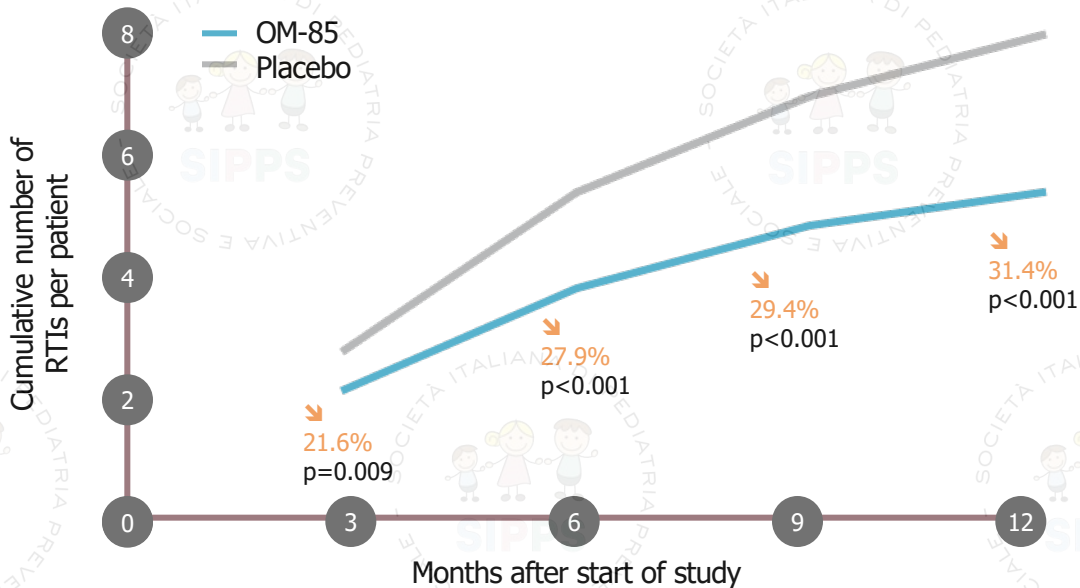


OM-85 PREVENTED WHEEZING ATTACKS IN PRE-SCHOOL CHILDREN



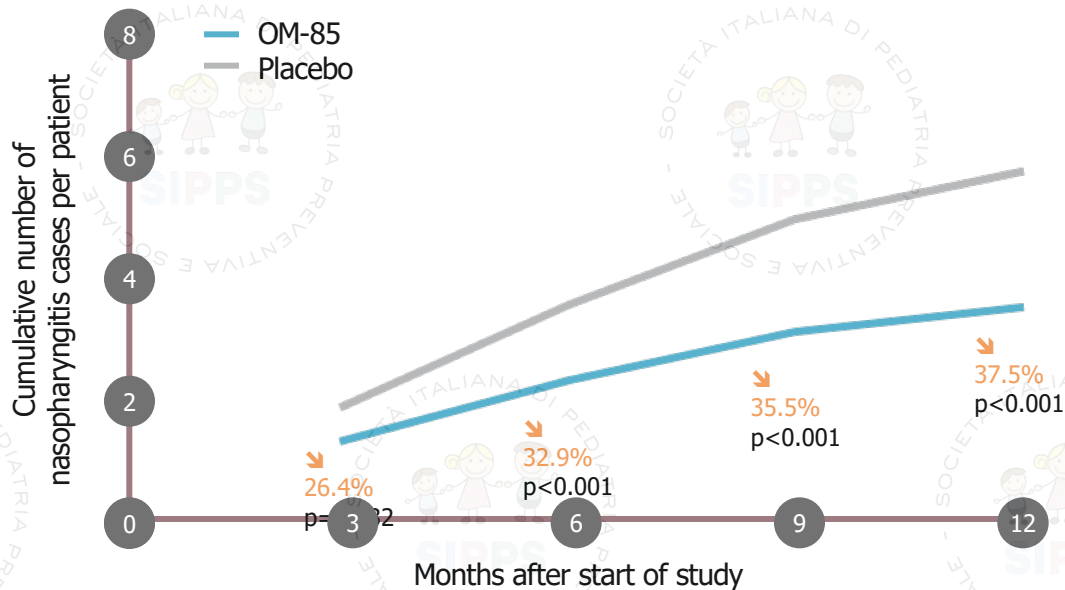
The cumulative difference in wheezing attacks between the 2 groups was **2.18** wheezing attacks per patient in 12 months; there was a **37.9%** reduction in the group given OM-85 compared with the group given placebo ($P < 0.001$)

OM-85 REDUCED THE NUMBER OF RTIS



The main difference in RTIs between the 2 groups was **2.5** per patient in 12 months (7.8 vs 5.3); there was a **31.4%** cumulative reduction in the group given OM-85 compared with the group given placebo (p < 0.001)

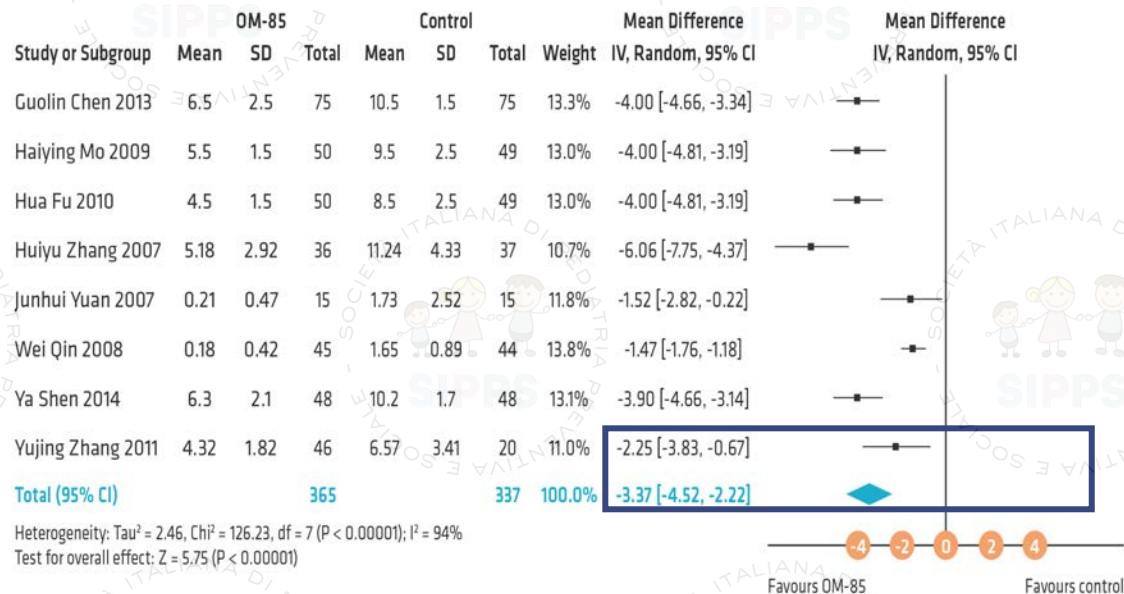
OM-85 REDUCED THE NUMBER OF NASOPHARYNGITIS



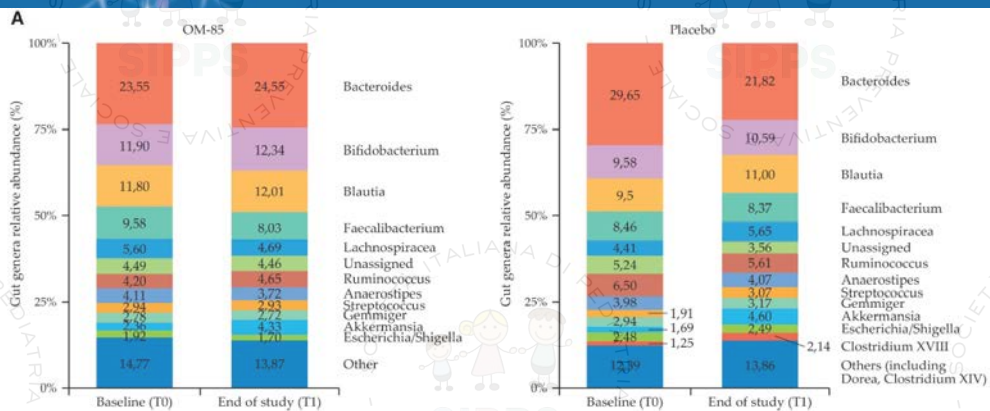
The main difference in nasopharyngitis between the 2 groups was **2.11** per patient in 12 months (5.62 vs to 3.51); there was a cumulative **37.5%** reduction in the group given OM-85 compared with the group given placebo (p < 0.001)

OM-85 SHOWED TO DECREASE THE DURATION OF WHEEZING

- Immunomodulation with OM-85 protect from RTI with a mean difference of 2.33 RTI/patient vs control

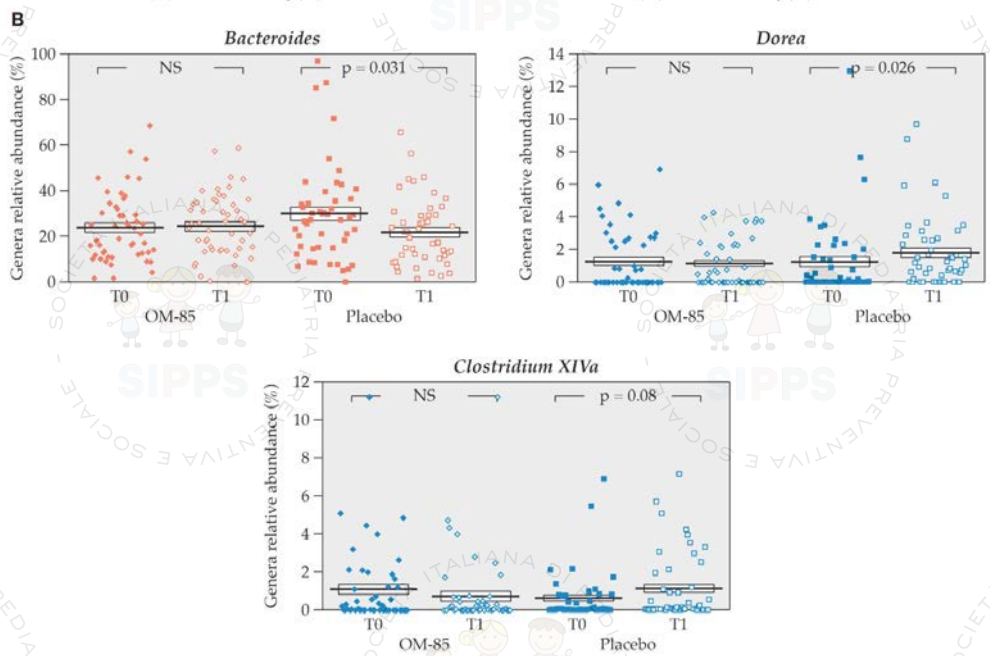


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Microbiota profiles in pre-school children with respiratory infections: Modifications induced by the oral bacterial lysate OM-85

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• Esposito S et al. Front Cell Infect Microbiol 2022

Expert consensus on the role of OM-85 in the management of recurrent respiratory infections: A Delphi study

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ABSTRACT

Recurrent infections of upper and lower respiratory tract have an important clinical and economic impact, which can be reduced through appropriate preventive measures, including the use of immunomodulating agents, such as OM-85, which proved to be effective and safe in both adults and children. Although OM-85 can be useful for the prevention of respiratory tract infections, it is still underused in clinical practice. In order to evaluate the level of awareness of the disease burden of recurrent respiratory infections in adults and children and to assess the level of agreement on the prophylactic and therapeutic approach to the disease, including the use of immunomodulants, a Delphi study was performed. A board of six experts in the field of respiratory infections was appointed to elaborate a series of statements covering four main topics (disease, prevention, OM-85, and future strategies), which were thereafter voted by a panel of 30 experts. Results showed that prevention is unanimously recognized as the most important intervention to reduce disease burden, and the use of immunomodulation to improve the effectiveness of vaccination is gaining increasing favor among clinicians. In this respect, OM-85 is recognized as the most studied immunomodulating agent currently available, whose efficacy and safety make it a valuable tool to optimize the management of recurrent respiratory infections in both adults and children. In particular, the combined use of OM-85 and influenza vaccine was recognized as an effective and safe approach to improve the current prevention strategies in order to reduce the burden of recurrent respiratory infections.

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4^a EDIZIONE

Pediatria

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