Infezioni respiratorie ricorrenti: nuove evidenze e bandierine rosse per la prevenzione nella pratica quotidiana

Peroni Diego
U.O. di Pediatria
Università di Pisa

- ✓ **IRR ..**
- ✓ Le bandierine rosse
- ✓ Immunomodulanti e IRR
- ✓ IRR ma non solo ..
- ✓ Le novità ..

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Immunomodulanti oggi…
Novità ?

IN LETTERATURA NON *ESISTE*

UNA DEFINIZIONE UNIVOCA DELLE IRR

- Alte e/o basse vie respiratorie?
- Forme febbrili e non?
- Il wheezing va considerato?
- Limiti di età?
- Forme virali e/o batteriche?

Clin Rev Allergy Immunol 2002. Ballow
Pediatr Infect Dis J 2004. Griffin

Le Infezioni Respiratorie Ricorrenti

IN LETTERATURA NON ESISTE

UNA DEFINIZIONE UNIVOCA DELLE IRR

Immunology Study Group of the Italian Pediatric Society

6 o più infezioni per anno

1 o più infezioni respiratorie al mese tra Settembre e Aprile

3 o più infezioni delle vie respiratorie inferiori per

Criterio Numerico diventa il parametro Ottimale

Pediatric Allergy Immunol 2007. De Martino

Chi è il bambino con infezioni respiratorie ricorrenti?

Criteri per definire il bambino affetto da Infezioni Respiratorie Ricorrenti (IRR) in età pediatrica :

1-3 anni: 6 o più infezioni delle vie respiratorie superiori (o una o più al mese da ottobre a marzo) in un anno e/o 2 infezioni delle vie respiratorie inferiori (polmonite confermata da criteri clinici e/o radiologici) in un anno

3-6 anni: 5 o più infezioni delle vie respiratorie superiori (o una o più al mese da ottobre a marzo) in un anno e/o 2 infezioni delle vie respiratorie inferiori (polmonite confërmata da criteri clinici e/o radiologici) in un anno

- **6 anni fino a 10 anni***: 3 o più infezioni delle vie respiratorie superiori (o una o più al mese da ottobre a marzo) in un anno e/o 2 infezioni delle vie respiratorie inferiori (polmonite confermata da criteri clinici e/o radiologici) in un anno**

***** Limite di età oltre il quale la WHO definisce l'adolescente**

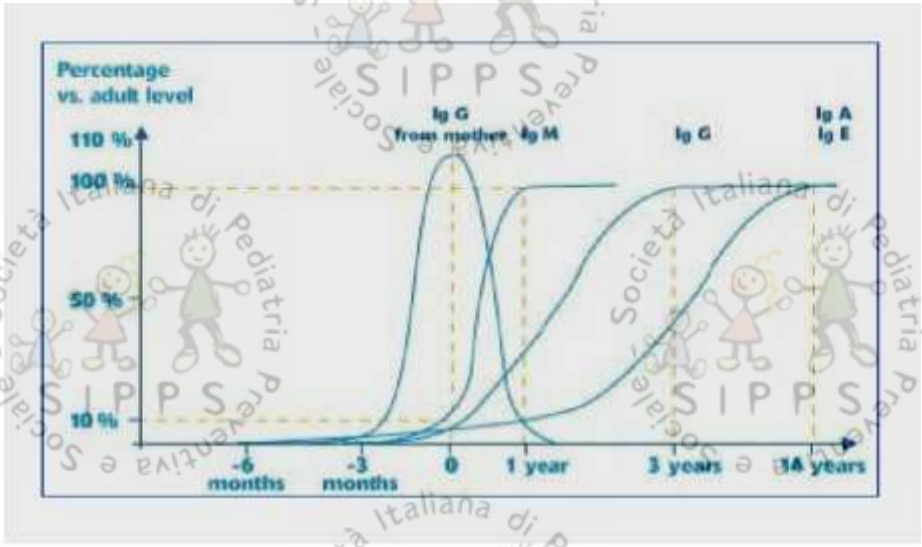
proposta dal Prof. Maurizio de Martino

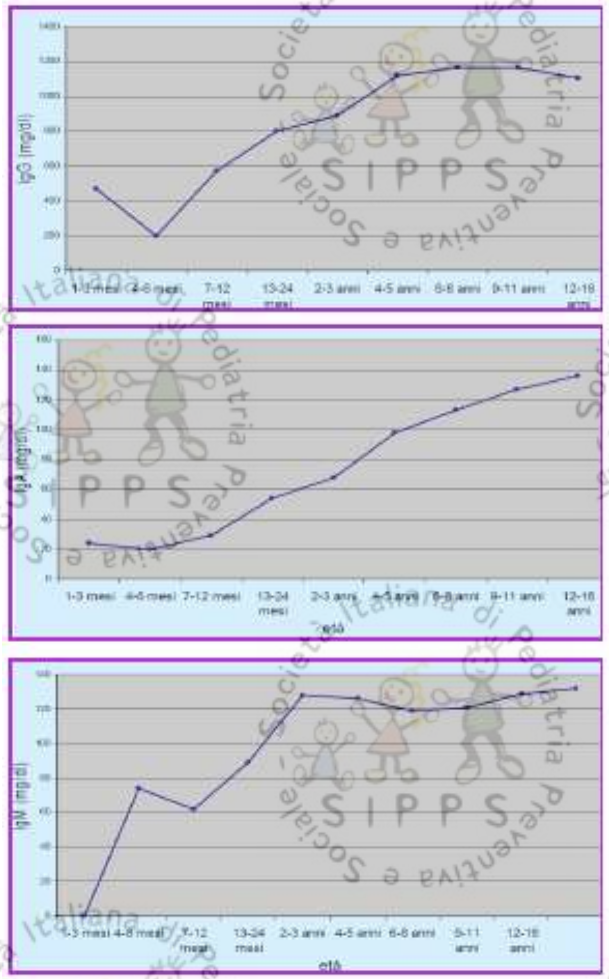
Fattori di rischio individuali

- Fattori anatomici individuali
- Immaturità immunologica
- Immunodepressione postinfettiva (convalescenza)
- Atopia

IRR : fattori di rischio individuali

Fisiologica immaturità immunologica del bambino !





IRR : fattori di rischio individuali

Presenza di Atopia

- persistente flogosi delle vie aeree
- rinosinusite ricorrente nel 25-70 % dei pazienti
- batteri colonizzatori patogeni del microbioma
- possibilità di inizio precoce di IRR
- disfunzione immunologica nel 13.2% dei casi

Fattori di rischio ambientali

- **Il fumo passivo**, (ma tutti giurano di fumare fuori al balcone)
- **La socializzazione precoce** (... sa, la nonna non ce lo tiene)
- **La presenza di fratelli** (beati i primi...)
- **Livello socioeconomico basso**

non solo i maschi si ammalano di più rispetto alle femmine (62% *vs. 38%), ma i maschi sono* più atopici delle femmine (67% *vs. 33%).*

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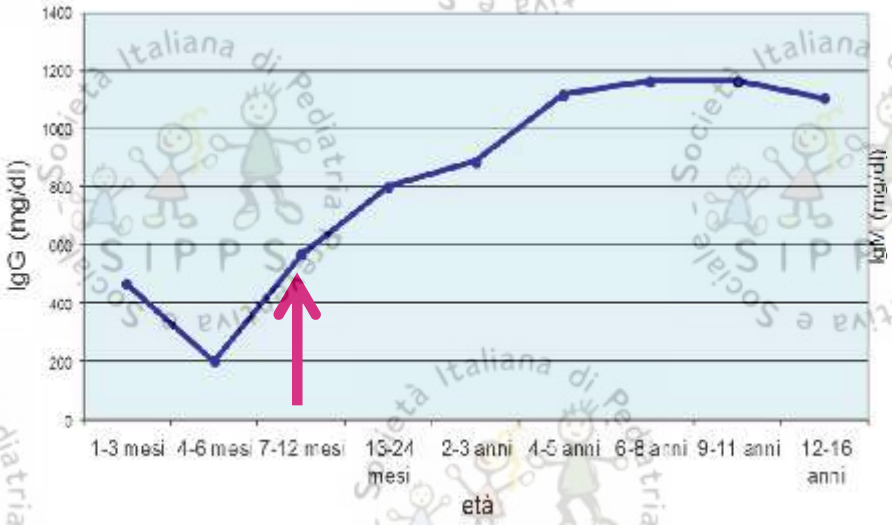
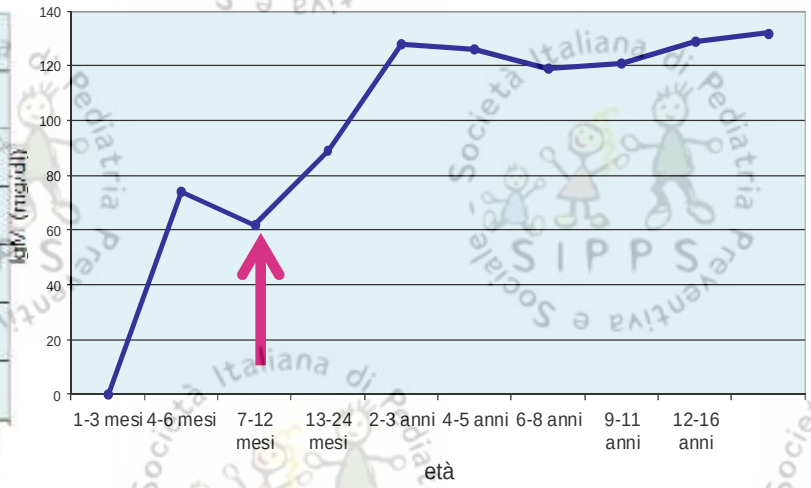
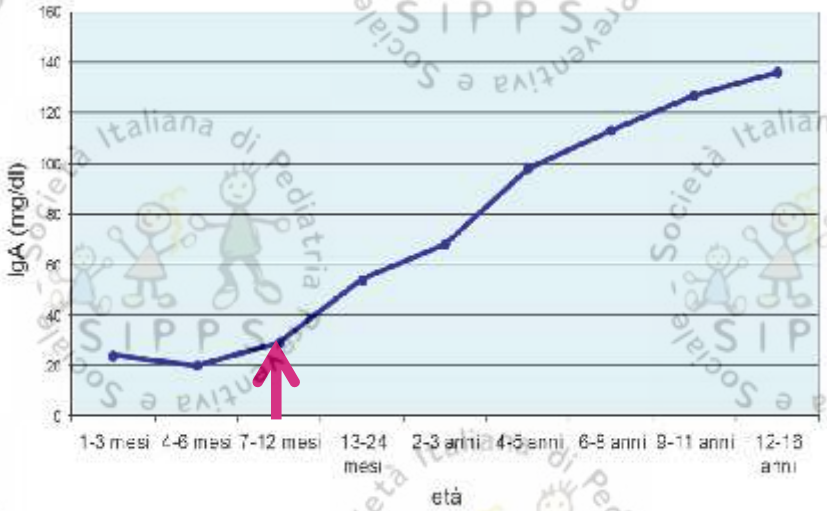
Infezioni respiratorie ricorrenti: approfondimento diagnostico

- Anamnesi – Esame obiettivo
- Esame emocromocitometrico
- Immunoglobuline sieriche

Fattori costituzionali







- Adeguata risposta a stimoli proteici
- Deficitaria risposta a stimoli polisaccaridici
- IgA secretorie: produzione dai 3 mesi e lento incremento

Infezioni respiratorie ricorrenti: approfondimento diagnostico II livello

- Anamnesi
- Esame obiettivo
- **Accertamenti immunologici:**
  - **Esame emocromocitometrico**
  - **Immunoglobuline sieriche**
  - **Sottopopolazioni linfocitarie (CD3, CD4, CD8, CD19, DR, CD16)**
  - **Ab anti-Tetano, Ab anti-epatite**
  - **Ig E totali**

Tonsilliti ricorrenti: PFAPA

PF: Periodic fever (Febbre elevata)

A: Aphthous stomatitis (Stomatite aftosa)

P: Pharingitis (Faringotonsillite)

A: Cervical Adenitis (Adenopatia laterocervicale)

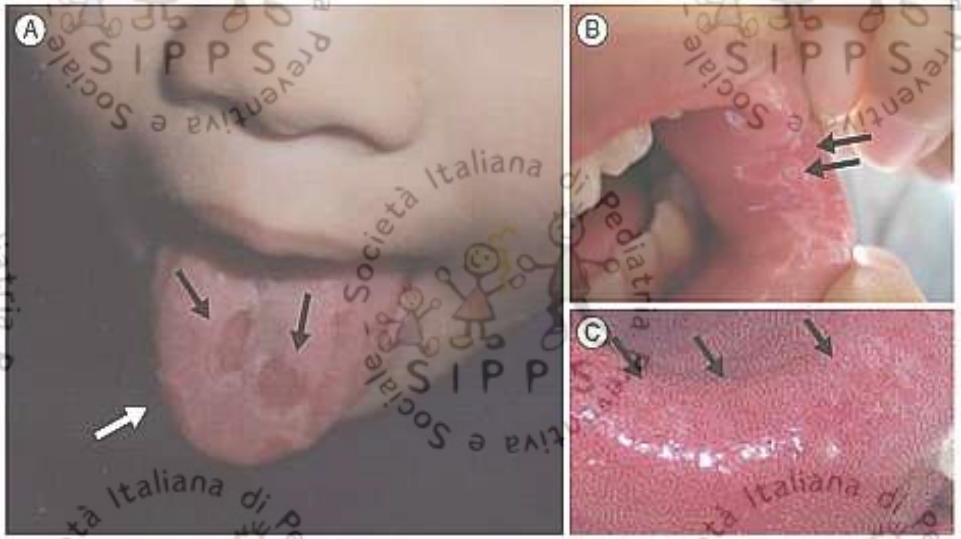


図 3　PFAPAにおける口腔内アフタ性病変

Tonsilliti ricorrenti: PFAPA

- Età di esordio < 5 anni
- Normalità intercritica
- Estrema regolarità (periodo intervallare fisso)
- Indici infiammatori elevati nella fase acuta
- Mancata risposta all'antibiotico
- SBEGA negativa
- Evoluzione: risoluzione spontanea
- Terapia:
    - monodose steroidi
    - tonsillectomia

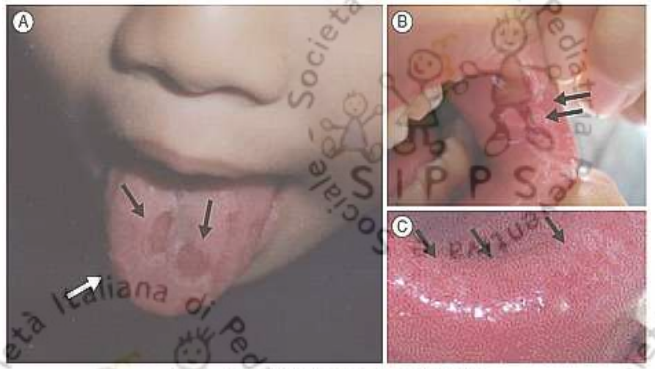


図 3 PFAPAにおける口腔内アフタ性病変

I 10 warning signs della Jeffrey Modell Foundation

1.	*Più di 4 otiti in un anno*
2.	*Più di 2 sinusiti in un anno*
3.	*Più di 2 mesi di antibiotici in un anno*
4.	*Due polmoniti in un anno*
5.	*Bambino con ritardo di crescita o sottopeso*
6.	*Ascessi ricorrenti della cute o degli organi interni*
7.	*Candidiasi orale o cutanea persistente*
8.	*Necessità di terapia antibiotica per via endovenosa per eradicare un'infezione*
9.	*Più di 2 infezioni gravi in un anno*
10.	*Familiarità per immunodeficienza primitiva*

GUIDA PRATICA

LE IMMUNODEFICIENZE NELL'AMBULATORIO DEL PEDIATRA

Sintesi InfoMedica

Società Italiana di Pediatria Preventiva e Sociale SIPPS

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Come gestire le IRR ?

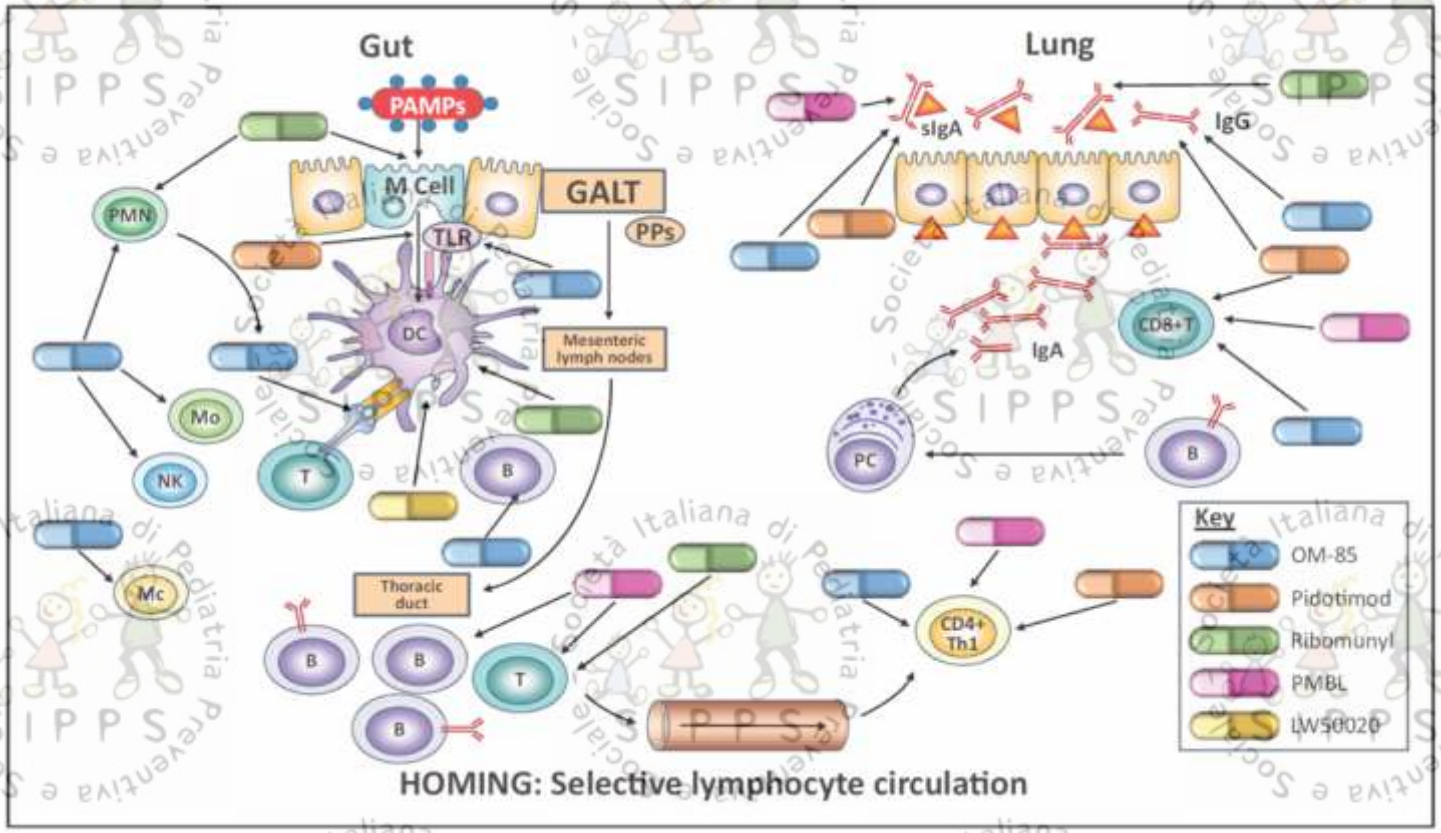
Gli Immunomodulanti

Immunostimulators are substances that **interact with the immune system and modulate its function** by stimulating a more rapid and effective immune response

Table 2 The different kinds of immune modulators
Bacterial extracts
LW 50020 (Paspat)
OM-85 BV
Immucytal/Biomunil
Plant extracts
Echinacea sp
Chemical compounds
Pidotimod CAS 121808–62-6

Nonspecific immunomodulators for recurrent respiratory tract infections, wheezing and asthma in children: a systematic review of mechanistic and clinical evidence

S Esposito, *COACI*, 2018



The gut–lung immune axis illustrating points of immunomodulator activity in RTI prophylaxis

Nonspecific immunomodulators for recurrent respiratory tract infections, wheezing and asthma in children: a systematic review of mechanistic and clinical evidence

S Esposito, *COACI*, 2018

Antigen sampling by M cells and dendritic cells resident in the Peyer's patches of the gut-associated lymphoid tissue leads **to maturation of dendritic cells** into an antigen-presenting cell phenotype.
The subsequent dendritic cell-initiated immune cascade involves **homing of cells from both innate and adaptive branches** of the immune system to the mucosal-associated lymphoid tissue of the lungs and subsequent antibody production.

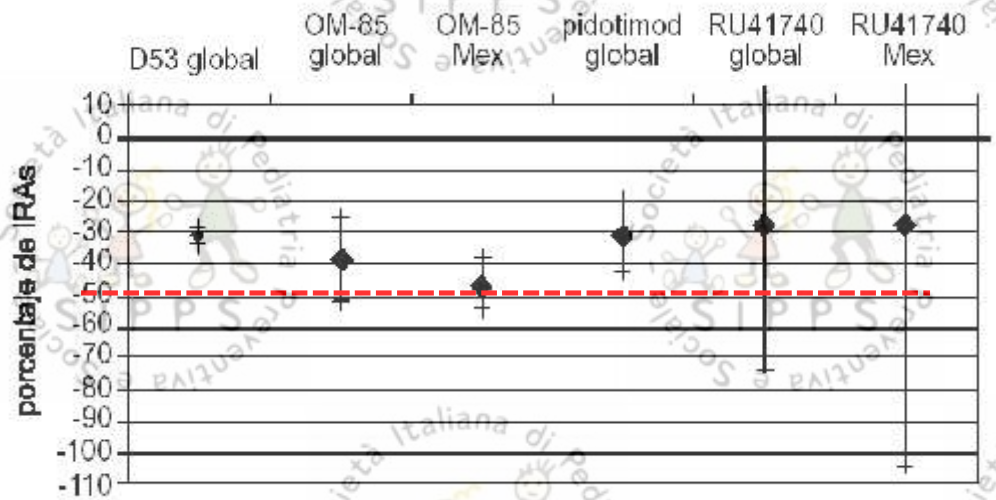
They can also act **to aid maturation** of the immune system in children, **correcting T helper cell (Th) Th1/Th2 imbalance** through **activation of T regulatory (Treg) cells**.

The correction of this Th2-oriented imbalance and other anti-inflammatory activities **may reduce atopic responses** related to wheezing and asthma.

Immunostimulants for preventing respiratory tract infection in children (Review)

Del-Rio-Navarro BE, Espinosa-Rosales FJ, Flenady V, Sienra-Monge JJL

THE COCHRANE COLLABORATION

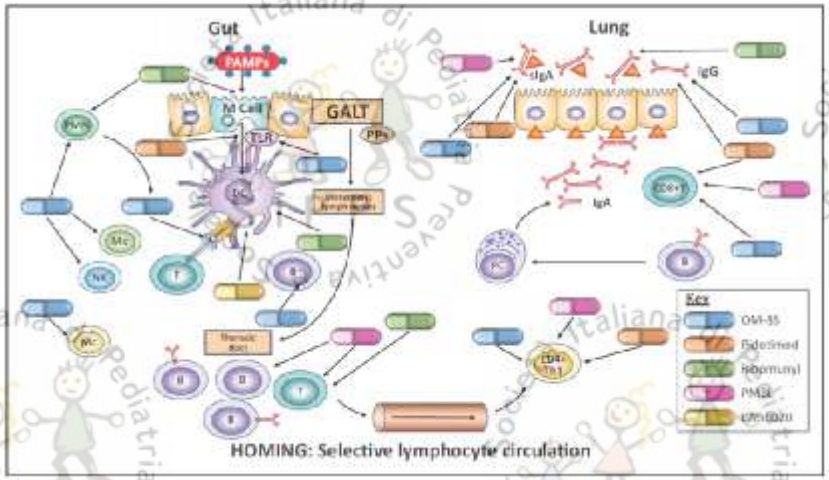


TUTTI gli immunostimolanti studiati (estratti batterici, pidotimod) riducono di circa il 40% il numero delle infezioni respiratorie, rispetto al placebo.

OM-85 is the product of alkaline lysis of **21 strains of common bacterial** respiratory tract pathogens .

The active ingredients of OM-85 are resistant to gastric transit and cause **maturation of mucosal dendritic cells** in gastrointestinal Peyer's patches, a key step in orally induced respiratory immunity.

OM-85-induced dendritic cell activation occurs in a modulated manner, resulting in a putative prealert antiinfective state in the mucosal immune system



EFFICACY OF IMMUNOMODULATORS IN CHILDREN WITH RESPIRATORY TRACT INFECTION

OM-85 reduced **the duration of infections** in children with a history of RRTI compared with placebo and versus probiotic therapy.

In a study of children with **recurrent tonsillitis**, OM-85 prophylaxis **improved outcomes** in the majority of patients and, importantly, **removed the need for surgery** in a significant proportion of those treated [Bitar MA, 2013].

In children with **subacute sinusitis**, OM-85 prophylaxis **sped recovery** and **reduced infections** [Gomez Barreto D, 1998],

whereas children with **chronic rhinosinusitis** had a **reduced symptom** burden and a **lower incidence of attacks** [Chen J, 2017].

Reductions in antibiotic and drug treatment following prophylactic therapy with OM-85 have also been demonstrated in children with a **history of RRTI**, subacute.

OM-85 therapy **reduced school absenteeism** in children

OM-85 in pediatric recurrent respiratory tract infections: A systematic review and meta-analysis. YIN J, Intern Immunopham 2018; 54,198

53 RCTs involving 4851 pediatric patients were included in this meta-analysis.

Study or Subgroup	Broncho-Vaxom Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Ahrens 1984	3.75	3.42	83	5.04	4.04	72	2.1%	-1.29 [-2.48, -0.10]
Aiping Liang 2011	3.27	1.42	36	6.78	2.13	37	2.3%	-3.51 [-4.34, -2.68]
Aiqi Zhang 2009	1.23	0.23	30	3.98	0.86	30	2.4%	-2.75 [-3.07, -2.43]
Beiling Hu 2011	1.96	1.19	44	4.05	2.3	45	2.3%	-2.19 [-2.95, -1.43]
Del-Rio-Navarro 2003	2.9	1.4	20	5.2	1.5	20	2.2%	-2.40 [-3.30, -1.50]
Fei Liu 2015	1.8	0.55	73	6.92	1.72	67	2.4%	-5.12 [-5.55, -4.69]
Gomez-Barreto 1995	1.56	1.55	26	2.22	2.37	30	2.2%	-0.66 [-1.70, 0.38]
Guie Li 2013	1.4	0.8	66	3.9	1.4	66	2.4%	-2.50 [-2.89, -2.11]
Guolin Chen 2013	1.45	0.75	75	3.85	1.35	75	2.4%	-2.40 [-2.75, -2.05]
Gutierrez-Tarango 2001	5.04	1.89	36	8	2.55	28	2.1%	-2.96 [-4.18, -1.74]
Haiying Mo 2009	1.35	0.65	50	3.82	1.36	49	2.4%	-2.47 [-2.89, -2.05]
Hongwen Zhu 2015	1.56	0.68	30	3.67	2.51	30	2.2%	-2.11 [-3.04, -1.18]
Hua Fu 2010	1.3	0.6	50	3.8	1.3	49	2.4%	-2.50 [-2.90, -2.10]
Huiqun Li 2012	2.13	1.62	35	4.67	1.48	31	2.3%	-2.54 [-3.29, -1.79]
Huiyu Zhang 2007	3.27	1.42	36	6.78	2.13	37	2.3%	-3.51 [-4.34, -2.68]
Jara-Perez 2000	1.43	0.94	99	2.99	0.81	100	2.5%	-1.56 [-1.80, -1.32]
Jiavi Liao 2014	2.15	1.53	31	5	2.23	31	2.2%	-2.85 [-3.80, -1.90]
Jingyang Li 2017	4	1.3	94	5	1.48	50	2.4%	-1.00 [-1.49, -0.51]
Jinsong Li 2008	1.75	1.09	39	6.84	1.82	38	2.3%	-5.09 [-5.76, -4.42]
Junhui Yuan 2007	2.61	1.51	15	4.19	2.06	15	2.0%	-1.58 [-2.87, -0.29]
Lanqui Lu 2013	0.59	0.03	55	4.61	0.48	54	2.5%	-4.02 [-4.15, -3.89]
Liming Yin 2016	2.19	1.69	39	3.7	1.93	39	2.3%	-1.51 [-2.22, -0.80]
Ling Su 2014	1.3	0.4	84	2.1	0.8	84	2.5%	-0.80 [-0.99, -0.61]
Maestrini 1984	2	2.05	11	5.55	5.36	9	0.9%	-3.55 [-7.26, 0.16]
Manfeng Zuo 2012	2.46	1.33	35	3.38	1.53	33	2.3%	-0.92 [-1.60, -0.24]
Mingxia Chao 2011	1.13	0.96	31	4.97	1.23	30	2.3%	-3.84 [-4.39, -3.29]
Razi 2010	5.31	1.79	40	7.75	2.88	35	2.1%	-2.44 [-3.49, -1.39]
Schaad 1986	2.89	1.77	45	2.98	1.56	49	2.3%	-0.09 [-0.77, 0.59]
Schaad 2002	2.12	1.44	120	2.48	1.63	100	2.4%	-0.36 [-0.77, 0.05]
Shaoxiong Zhuang 2015	1.99	1.32	30	3.66	1.87	30	2.3%	-1.67 [-2.49, -0.85]
Shenfeng Gu 2015	3	1	40	4	2.25	40	2.3%	-1.00 [-1.76, -0.24]
Shiyan Luo 2016	1.33	1.16	45	5.04	1.23	45	2.4%	-3.71 [-4.20, -3.22]
Tingxi Zhang 2006	0.93	0.57	15	1.13	0.72	15	2.4%	-0.20 [-0.66, 0.26]
Wei Qin 2008	2.63	1.44	45	4.28	1.87	44	2.3%	-1.65 [-2.34, -0.96]
Wei Zhang 2019	1.3	0.6	17	4.8	1.6	16	2.3%	-3.50 [-4.33, -2.67]
Xiongxiong Huang 2012	4.22	2.23	65	7.35	3.51	65	2.2%	-3.13 [-4.14, -2.12]
Ya Shen 2014	1.5	0.5	48	4.6	1.8	48	2.4%	-3.10 [-3.63, -2.57]
Ying Liao 2009	0.43	0.06	54	4.16	0.84	50	2.5%	-3.73 [-3.96, -3.50]
Yongli Wu 2008	1.51	0.63	45	3.78	2.05	45	2.3%	-2.27 [-2.90, -1.64]
Yuan Gao 2010	2.5	1.39	76	4.1	1.58	80	2.4%	-1.60 [-2.07, -1.13]
Yujing Zhang 2011	4.82	2.15	46	7.07	3.26	20	1.9%	-2.25 [-3.81, -0.69]
Yuping Zhao 2012	1.32	0.15	50	4.05	0.73	50	2.5%	-2.73 [-2.94, -2.52]
Zagar 1989	0.38	0.26	29	1.09	0.85	22	2.4%	-0.71 [-1.00, -0.42]
Zhihong Lou 2012	3	1.8	33	6.2	1.9	33	2.2%	-3.20 [-4.09, -2.31]
Total (95% CI)			2056			1936	100.0%	-2.33 [-2.75, -1.90]

Heterogeneity: Tau² = 1.89; Chi² = 1796.84, df = 43 (P < 0.00001); I² = 98%
Test for overall effect: Z = 10.75 (P < 0.00001)

Frequency of RTIs in OM-85 and control group

OM-85 in pediatric recurrent respiratory tract infections: A systematic review and meta-analysis. YIN J, Intern Immunopham 2018; 54,198

53 RCTs involving 4851 pediatric patients were included in this meta-analysis.

Study or Subgroup	Broncho-Vaxom Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Beiling Hu 2011	8	0.75	44	13	2.63	45	13.0%	-5.00 [-5.80, -4.20]
Guie Li 2013	8.4	1.5	66	11.4	4.5	66	12.2%	-3.00 [-4.14, -1.86]
Guolin Chen 2013	8.5	1.5	75	11.5	4.5	75	12.3%	-3.00 [-4.07, -1.93]
Haiying Mo 2009	7.5	2.5	50	12.5	3.5	49	12.0%	-5.00 [-6.20, -3.80]
Hua Fu 2010	7.5	2.5	50	12.5	3.5	49	12.0%	-5.00 [-6.20, -3.80]
Huiyu Zhang 2007	16.5	4.05	36	28.43	9.77	37	6.2%	-11.93 [-15.34, -8.52]
Junhui Yuan 2007	21.2	13.6	15	36.71	24.1	15	0.6%	-15.51 [-29.51, -1.51]
Manfeng Zuo 2012	26.07	9.88	35	33.47	13.39	33	3.2%	-7.40 [-13.02, -1.78]
Shengfeng Gu 2015	16	9.5	40	22	23.5	40	1.8%	-6.00 [-13.86, 1.86]
Wei Qin 2008	21.52	12.32	45	38.46	21.73	44	2.0%	-16.94 [-24.30, -9.58]
Ya Shen 2014	8.2	1.3	48	11.4	4.6	48	11.6%	-3.20 [-4.55, -1.85]
Yuan Gao 2010	9	1.2	76	15	3.38	80	13.0%	-6.00 [-6.79, -5.21]
Total (95% CI)			**580**			**581**	**100.0%**	**-5.26 [-6.41, -4.12]**

Heterogeneity: Tau² = 2.44; Chi² = 65.34, df = 11 (P < 0.00001); I² = 83%
Test for overall effect: Z = 8.05 (P < 0.00001)

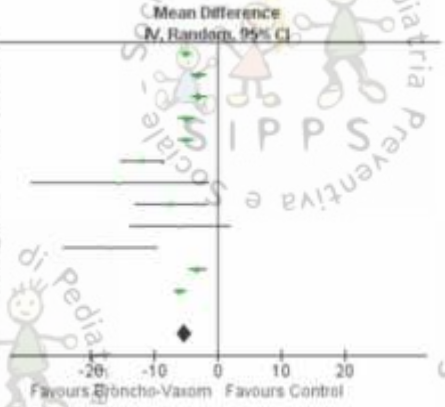


Fig. 5. The cough length in Broncho-Vaxom and control group.

Study or Subgroup	Broncho-Vaxom Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Guolin Chen 2013	6.5	2.5	75	10.5	1.5	75	13.3%	-4.00 [-4.66, -3.34]
Haiying Mo 2009	5.5	1.5	50	9.5	2.5	49	13.0%	-4.00 [-4.81, -3.19]
Hua Fu 2010	4.5	1.5	50	8.5	2.5	49	13.0%	-4.00 [-4.81, -3.19]
Huiyu Zhang 2007	5.18	2.92	36	11.24	4.33	37	10.7%	-6.06 [-7.75, -4.37]
Junhui Yuan 2007	0.21	0.47	15	1.73	2.52	15	11.8%	-1.52 [-2.82, -0.22]
Wei Qin 2008	0.18	0.42	45	1.65	0.89	44	13.8%	-1.47 [-1.76, -1.18]
Ya Shen 2014	6.3	2.1	48	10.2	1.7	48	13.1%	-3.90 [-4.66, -3.14]
Yujing Zhang 2011	4.32	1.82	46	6.57	3.41	20	11.0%	-2.25 [-3.83, -0.67]
Total (95% CI)			**365**			**337**	**100.0%**	**-3.37 [-4.52, -2.22]**

Heterogeneity: Tau² = 2.46; Chi² = 128.23, df = 7 (P < 0.00001); I² = 94%
Test for overall effect: Z = 5.75 (P < 0.00001)

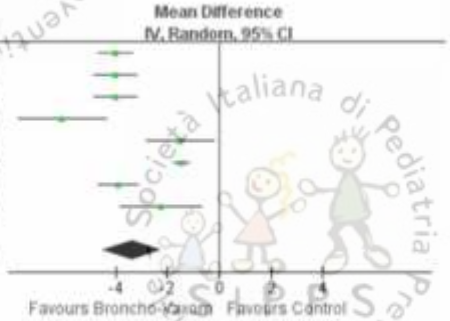


Fig. 6. Duration of wheezing in Broncho-Vaxom and control group.

Cough length and frequency of wheezing in OM-85 and control group

Impact of OM-85 Given during Two Consecutive Years to Children with a History of Recurrent Respiratory Tract Infections: A Retrospective Study. Esposito, Int. J. Environ. Res. Public Health **2019**, 16, 1065;

200 children aged three to six years

history of recurrent RTIs, defined as at least six documented episodes of acute RTI in a single year,

received OM-85 for two consecutive years (3.5 mg once a day for 10 days for 3 months of each year)

were selected and matched based on age, sex, and period of evaluation with children with recurrent RTIs who did not receive OM-85.

	First Year		Second Year	
	Treated with OM-85 (n = 200)	Untreated with OM-85 (n = 200)	Treated with OM-85 (n = 200)	Untreated with OM-85 (n = 200)
Children with respiratory infections (any)	n (%)	n (%)	n (%)	
No	128 (64.0) *	72 (36.0)	134 (67.0) *	79 (39.5)
Yes	72 (36.0)	128 (64.0)	66 (33.0)	121 (60.5)
Children with wheezing (any)				
No	167 (83.5) *	140 (70.0)	179 (89.5) *	152 (76.0)
Yes	33 (16.5)	60 (30.0)	21 (10.5)	48 (24.0)
Children treated with antibiotics (any)				
No	139 (69.5) *	90 (45.0)	146 (73.0) *	99 (49.5)
Yes	61 (30.5)	110 (55.0)	54 (27.0)	101 (50.1)
Children who required an outpatient medical visit				
No	91 (45.5) *	51 (25.5)	103 (51.5) *	62 (31.0)
Yes	109 (54.5)	149 (74.5)	97 (48.5)	138 (69.0)
Number of infections				
URTI, Mean ± SD	0.41 ± 0.39 *	0.76 ± 0.49	0.36 ± 0.25 *	0.61 ± 0.46
Wheezing, Mean ± SD	0.22 ± 0.48 *	0.36 ± 0.31	0.16 ± 0.10 *	0.31 ± 0.27
LRTI, Mean ± SD	0.16 ± 0.33	0.22 ± 0.58	0.06 ± 0.16	0.14 ± 0.19

Infezioni respiratorie ricorrenti: nuove evidenze e bandierine rosse per la prevenzione nella pratica quotidiana

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- ✓ IRR ..
- ✓ Le bandierine rosse
- ✓ Immunomodulanti e IRR
- ✓ **IRR ma non solo ..**
- ✓ Le novità ..

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EFFICACY OF IMMUNOMODULATORS IN WHEEZING AND ASTHMA

OM-85 prophylaxis reduced the **duration and incidence of wheezing/asthma exacerbations** in children with a **history or recurrent wheezing or asthma** [Lu Y, 2015, Razi C, 2010], as well as **hospitalizations related to asthma** [Chen ZG; 2009].

The reductions in exacerbations appear to be related to reduced incidence of RTIs.

Safety data and its addition to corticosteroid therapy caused no apparent issues.

EFFICACY OF IMMUNOMODULATORS IN WHEEZING AND ASTHMA

The two studies investigating **pidotimod** in asthma and the related condition obstructive syndrome **did not report data on asthma exacerbations**; however, there were reductions in the incidence of RTI in both studies [Lokshina EE, 2011].

RTI duration was also reduced in children with allergic rhinitis and asthma [Vargas Correa, 2002].

The immunostimulant OM-85 BV prevents wheezing attacks in preschool children.

Razi JACI, 2010;126:763

75 children with recurrent wheezing who were 1 to 6 years old.

Participants were randomly assigned to groups given either OM-85 or a placebo (1 cps per day for 10 days each month for 3 consecutive months) at the start of the trial.

Participants were **followed for 12 months**

TABLE II. Cumulative number of wheezing attacks per patient in the 2 groups

Period (mo)	OM-85 BV	Placebo	Mean difference (95% CI)	Cumulative % difference	*P* value*
0-3	1.60 ± 0.88 1 (1-2)	2.30 ± 1.34 2 (1-3)	−0.70 (−1.23 to −0.17)	30.4	.013
0-6	2.54 ± 1.12 3 (2-3)	3.87 ± 2.10 4 (2-5)	−1.33 (−2.12 to −0.54)	34.3	.003
0-9	3.20 ± 1.41 3 (2-4)	5.00 ± 2.50 5 (3-7)	−1.80 (−2.75 to −0.85)	36.0	.001
0-12	3.57 ± 1.61 3 (3-4)	5.75 ± 2.71 5.5 (4-8)	−2.18 (−3.22 to −1.13)	37.9	<.001

The immunostimulant OM-85 BV prevents wheezing attacks in preschool children.

Razi JACI, 2010;126:763

75 children with recurrent wheezing who were 1 to 6 years old.
Participants were randomly assigned to groups given either OM-85 or a placebo (1 cps per day for 10 days each month for 3 consecutive months) at the start of the trial.
Participants were **followed for 12 months**

TABLE III. Cumulative number of ARTIs per patient in the 2 groups

Period (mo)	OM-85 BV	Placebo	Mean difference (95% CI)	Cumulative % difference	*P* value*
0-3	2.25 ± 0.98 2 (2-3)	2.87 ± 0.93 3 (2-3)	−0.62 (−1.05 to −0.17)	21.6	.009
0-6	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
0-9	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
0-12*	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Clinical implications: OM-85 BV might be used as a complementary therapy to reduce the number and duration of ARTI-provoked wheezing attacks in preschool children with recurrent wheezing.

TABLE V. Sec[illegible]

	OM-85 BV	Placebo	Mean difference (95% CI)	*P* value
No. of hospitalizations (mean no. per patient)	0.14 ± 0.35	0.40 ± 0.81	−0.26 (−0.55 to −0.39)	.195
Duration of hospitalizations (mean days per patient)	0.80 ± 2.09	2.02 ± 4.49	−1.22 (−2.88 to −0.42)	.310
Duration of wheezing attacks (cumulative days per patient)	20.80 ± 13.15 19 (11-27)	43.22 ± 22.57 43 (26-57.5)	−22.42 (−31.09 to −13.75)	<.001
Duration of each wheezing attack (days per patient)	5.57 ± 2.10 6 (4.5-7)	7.66 ± 2.14 7.5 (6-8.5)	−2.09 (−3.06 to −1.10)	<.001
Duration of systemic steroid therapy (cumulative days per patient)	2.68 ± 4.26 0 (0-5)	4.72 ± 5.76 5 (0-5)	−2.04 (−4.39 to −0.32)	.102
No. of wheezing attacks requiring systemic steroid therapy (no. per patient)	0.57 ± 0.88 0 (0-1)	0.90 ± 1.03 1 (0-1)	−0.33 (−0.77 to −0.11)	.116

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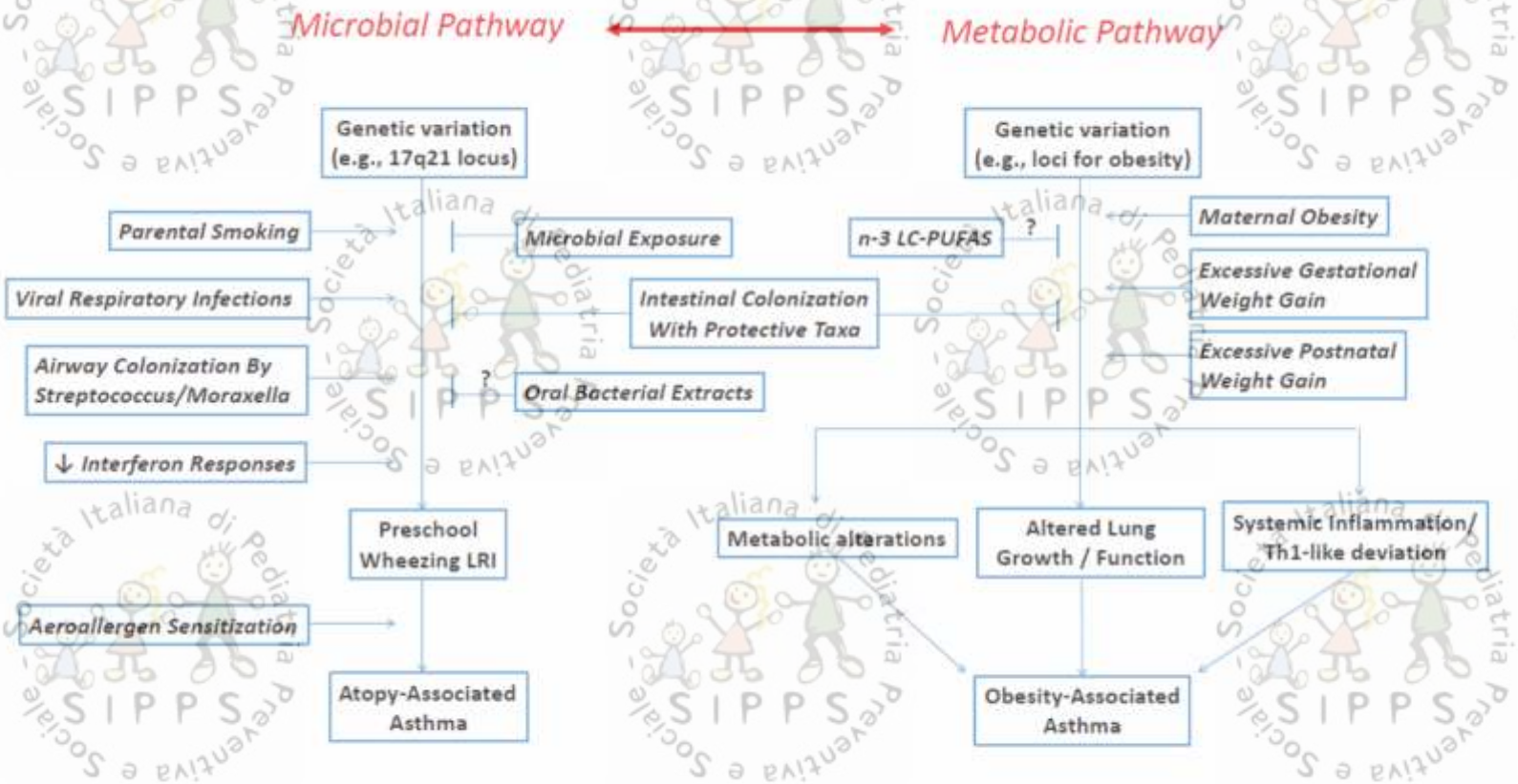
Early Origins of Asthma: Role of Microbial Dysbiosis and Metabolic Dysfunction

F. Martinez, AJRCCM 2017



Holt PG. Prevention – what is the most promising approach? Pediatr Allergy Immunol 2014;25:12-4.

And wheezing.. The next future

The **ORal Bacterial EXtracts for the prevention of wheezing lower respiratory tract illness (ORBEX)** trial represents **a step change** in **immunomodulatory research**.

This large, multicentre, **NIH-funded** RCT (NCT02148796) will enrol upwards of **1000 infants at high asthma risk** due to having atopic eczema and/or parents or siblings with asthma.

https://clinicaltrials.gov/ct2/show/NCT02148796.

And wheezing.. The next future

Participants will receive **long-term OM-85 prophylaxis (3.5 mg/day for 10 days/month for 2 years)**.

The **primary outcome will be time to first wheezing episode in the third observational year** when children are not receiving prophylaxis.

Preliminary results of the ORBEX trial are expected **by December 2022**.

https://clinicaltrials.gov/ct2/show/NCT02148796.

Ricapitolando

Che efficacia? 40% e più

Ma nel bambino complicato ..

Non solo Infezioni alte vie aeree ma anche basse vie

E la storia naturale?

Esclusione delle «bandierine..»