Prevenire le infezioni respiratorie ricorrenti e possibili esiti: quale ruolo hanno i lisati batterici?

Peroni Diego
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- ✓ **IRR ..**
- ✓ 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

Criterio Numerico diventa il parametro Ottimale

Pediatric Allergy Immunol 2007. De Martino

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

C'è una nuova definizione ?
De Martino M, Chiappini E e il Gruppo di lavoro IRR intersocietario

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 confermata 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

[*] I bambini con infezioni ricorrenti in un sito specifico (es. otite media ricorrente o respiro sibilante), affetti da immunodeficienze primitive o secondarie note (compreso il deficit di IgA), fibrosi cistica, dicinesia ciliare primitiva, bronchiectasie non fibrosi cistica, patologie genetiche, malformazioni note a carico dell'apparato cardio-respiratorio, patologie neuromuscolari e con altre patologie polmonari croniche preesistenti sono stati esclusi dalla presente definizione.

[**] Tale definizione non si applica a bambini al di sotto di un anno di età.

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

Costi sanitari

Se proviamo a considerare il punto di vista della famiglia che si trova a dover affrontare un numero di 10-12 episodi infettivi concentrati di solito nel periodo settembre/aprile alcune delle **nostre convinzioni sulla banalità del problema vacillano**.

COSTI DIRETTI E INDIRETTI DELLE IRR

- Durata media di ogni infezione respiratoria: 10,4 giorni
- 46,7 visite mediche/100 episodi
- 19,7 cicli di antibioticoterapia/100 episodi
- 2,2 ricoveri ogni 100 episodi
- 11,7 ore utilizzate per accudire il bambino/episodio

(Terracciano L. RIAP 2008;2:12)

Fattori di rischio individuali

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

Le Infezioni Respiratorie Ricorrenti

Condizioni cliniche associate con aumentato rischio di IRR

- **prematurità**
- **atopia**
- **anomalie congenite (apparato respiratorio)**
- **malattie cardiovascolari**
- **malattie neurologiche croniche**

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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Come gestire le IRR ?
Gli Immunomodulanti

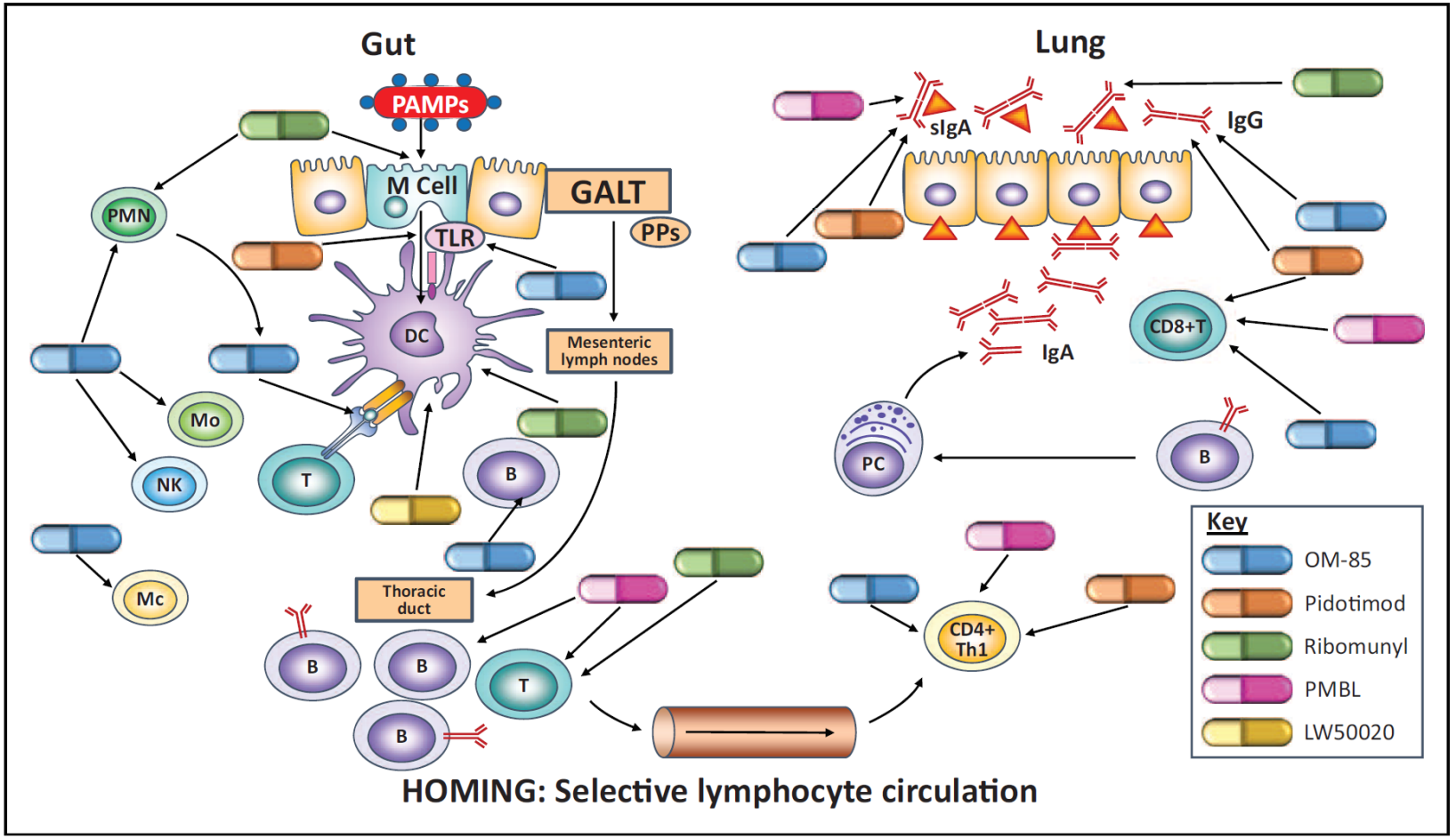
Immunostimulators are substances that **interact with the immune system and modulate its function** by stimulating a more rapid and effective immune response

Table 2 **The different kinds of immune modulators**

Bacterial extracts
LW 50020 (Paspat)
OM-85 BV (Broncho-Vaxom)
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.

Table 1. Characteristics of included immunomodulators and proposed mechanisms of action for infection prevention

Therapy	Constituents	Antigen-presenting cells	Innate immunity	Adaptive
OM-85	Alkaline lysis of 21 strains of eight species of respiratory tract pathogens: *Haemophilus influenzae, Streptococcus pneumoniae, Klebsiella pneumoniae, Klebsiella ozaenae, Staphylococcus aureus, Streptococcus pyogenes, Streptococcus viridans* and *Moraxella catarrhalis*	Maturation of mesenteric DCs [13,14,15▪] Modulated activation suggesting prealert anti-infective state [14,16▪▪] Innate and adaptive cytokine release [17] PRR yet to be determined [14,16▪▪,18,19]	Release of antimicrobial peptides [human beta-defensin-1 (hβD-1)] and C1q-R) [20,21▪] ICAM downregulated in lung epithelium [21▪] Rapid neutrophil recruitment in murine model of influenza infection [15▪] Cytokines promoting NK-cells, monocytes, phagocytosis, neutrophils (CCL2, CCL3, CXCL1, CXCL5, CXCL6 and CXCL8) [14,17] Macrophage activation (IL-1b, IL-6 and TNFα mRNA) [16▪▪,18,19] Antiviral cytokine release (INFβ) [16▪▪]	DC-induced T-cell activation [22,23] Airway $CD8^+$ T cells in murine influenza model [15▪] Pro-B-cell cytokines (IL-6, BAFF and IL-10) [14,23] Serum IgA/IgG (murine/human) [15▪,18,20] B-cell maturation from mouse splenocytes [15▪] Airway/salivary murine IgA/IgG [15▪,18,24] Immune maturation (pro-INFy and IgG2/anti-IL-4) [25] Release of antiviral cytokines INFα/INFy [14,21▪,25,26]
Pidotimod	Synthetic thymic dipeptide (3-L-pyroglutamyl-L-thiaziolidine-4 carboxylic acid)	Mucosal DC maturation and increased antigen presentation [27,28,29▪,30] Increased TLR2 and TLR4 [29▪,30] Innate and adaptive cytokine release [28,29▪]	Increased TLR2 expression in lung epithelial cells *in vitro* [31] Release of antimicrobial peptides (CAMP, LCN2, LTF and MPO) [29▪] Improved mucociliary transport [32] Cytokines promoting macrophages, monocytes, NK cells and neutrophils (CCL3, CXCL1, CXCL2, IL-18 and IL-8) [29▪,33]	Activation of cytotoxic and helper T cells ($CD3^+$, $CD4^+$ and $CD4^+/CD8^+$) [34] Immune maturation (pro-IL-12, IFNy, IL-10 and IL-18/anti-IL-4) [33–36,37▪,38] Increased mucosal sIgA [39] Release of antiviral cytokines INFy [39]
Ribomunyl	Bacterial proteoglycans and ribosomes of common respiratory tract pathogens: *K. pneumoniae* (proteoglycans and ribosomes) and *K. pneumoniae, S. pneumoniae, S. pyogenes* and *H. influenza* (ribosomes)	DC maturation [13,40,41] Innate and adaptive cytokine release [41]	Increased neutrophil adhesion molecules (+CD11c and +CD103) and phagocytosis [42,43]	DCs-induced T cells activation causing release of antiviral INFy ($CD4^+$) [13,41] Possible release of pro-TH1 cytokines (IL-12, IL-10) [13,40] Increase in $CD4^+$ and $CD8^+$ T cells [44] B cell production (humoural, tonsils, mesenteric/cervical lymph nodes) [44] Salivary sIgA [45,46] Serum IgA and IgG [44,47,48]
PMBL	Bacterial lysates of eight bacterial species: *S. aureus, S. viridans, S. pyogenes, K. pneumoniae, K. ozaenae, H. influenzae serotype B, M. catarrhalis and S. pneumoniae*	–	Putative macrophage activation (pro-IL-12) [49]	T cell activation ($CD4^+$ and $CD8^+$) [49] B cell activation [49] IgM memory B cell expansion [50] Immune maturation (+IL-2, +IL-10, IL-12 and +IFNy) [49] Release of antiviral cytokines INFy [49] Release of salivary sIgA [51]
LW50020	Bacterial lysates of seven bacterial species: *S. aureus, Streptococcus mitis, S. pyogenes, S. pneumoniae, K. pneumoniae, M. catarrhalis* and *H. influenza*	DC maturation [13]		DC-induced T cells activation [13]

Table 2. Proposed mechanisms of action for the prevention of wheezing and asthma exacerbation

Therapy	Dendritic cells/monocytes	Th1-Th2 Balance	Airway inflammation	Immunoglobulins
OM-85	Increased T-reg-related $CD103^+$ DCs in mesenteric lymph nodes [83▪▪] Reduced Th2-associated markers on induced DCs (ICOSL) [15▪] Accelerated resolution of airway DCs reaction to allergen in a mouse model of asthma [84▪]	Trafficking of IL-10 producing Tregs from gut to airway [84▪] Reduced $CD4^+$ Th2-type cells and inflammatory cytokines (IL-4, IL-5, IL-6, IL-10 and IL-13) in lungs of sensitized mice [84▪] Allograft of induced Tregs blocks Th2 and inflammatory cytokine production in sensitized mice (IL-5 and IL-13) [84▪] Induces pro-Th1/anti-Th2 cytokine induction in mouse models of allergy/asthma (Pro-IFN-γ and IL-10/anti IL-1b, IL-4, IL-5, IL-13 and TGF-b1) [18,85–87,88▪] Induced IL-10 release from human PBMCs increased under inflammatory conditions [15▪] Pro-Th1 and anti-Th2 cytokine release in children with asthma (Pro-IL-10 IFN-γ/anti-IL-4, IL-17 and IL-1b) [16▪▪,89,90▪,91]	Blocks infiltration of eosinophils, neutrophils, macrophages and lymphocytes in mouse models of asthma/allergic rhinitis [83▪▪,84▪,88▪] Allograft of induced Tregs blocks eosinophilia in sensitized mice [84▪] Reduced mucus metaplasia, hypersectretion and tissue remodelling [83▪▪,84▪,88▪]	Reduced specific-serum and nonspecific serum IgE and IgG1 in a mouse model of asthma and allergic rhinitis [16▪▪,18,84▪,85,86,88▪]
Pidotimod	Upregulates anti-inflammatory NOD-like receptor NLRP12 in monocytes [92] Inhibits proinflammatory MCP-1 [92]	Downregulates Th2-associated CD-30 in cells from normal and atopic individuals [93]	–	Reduced IgE in a mixed group of patients with RRTI some of whom were atopic [37▪]
Ribomunyl	–	Pro-Th1/anti-Th2 cytokine changes (pro-INFy/anti-IL-4, IL-5) [94,95]	–	–
PMBL	–	Anti-Th2 cytokine change (IL4) [96] Increased Treg cells [97]	–	–

DC, dendritic cell.

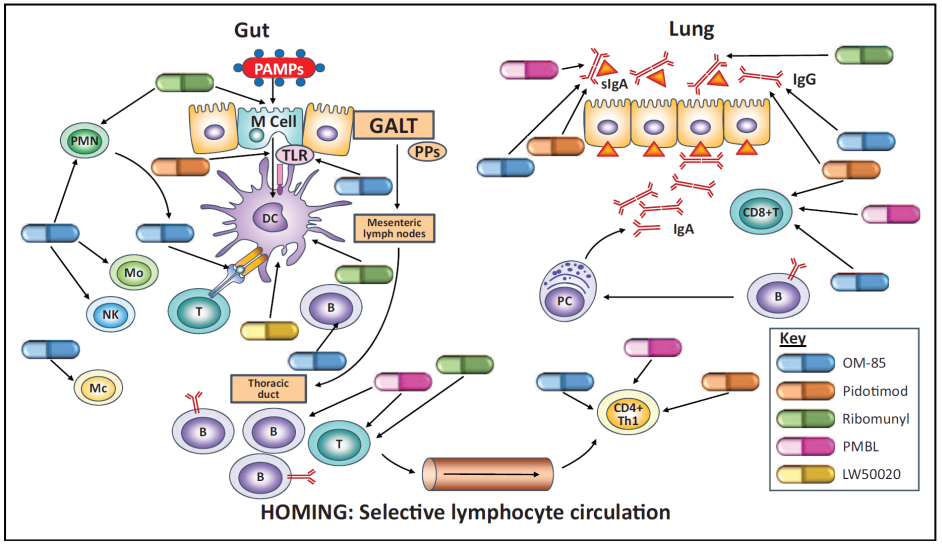
Nonspecific immunomodulators for recurrent respiratory tract infections, wheezing and asthma in children: a systematic review of mechanistic and clinical evidence

S Esposito, *COACI*, 2018

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



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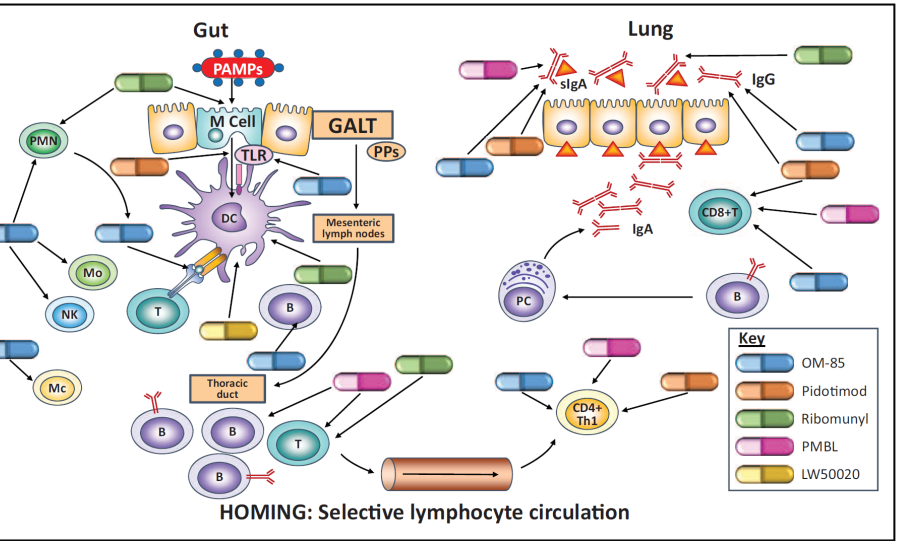


Induced dendritic cells release chemokines that act on monocytes and natural killer (NK) cells, as well as **prophagocytic chemokines** which induce polymorphonuclear neutrophil migration.

The downstream effects on OM-85 on the innate immune system include the release of antimicrobial peptides and the activation of macrophages resulting in expression of proinflammatory and antiviral cytokines.

OM-85 reduced rhinovirus infection of lung epithelial cells and cell death in vitro. Data also suggest that OM-85 causes more rapid neutrophil recruitment in response to viral infection, reducing viral load.

Broncho Vaxom (OM-85) modulates rhinovirus docking proteins on human airway epithelial cells via Erk1/2 mitogen activated protein kinase and cAMP.

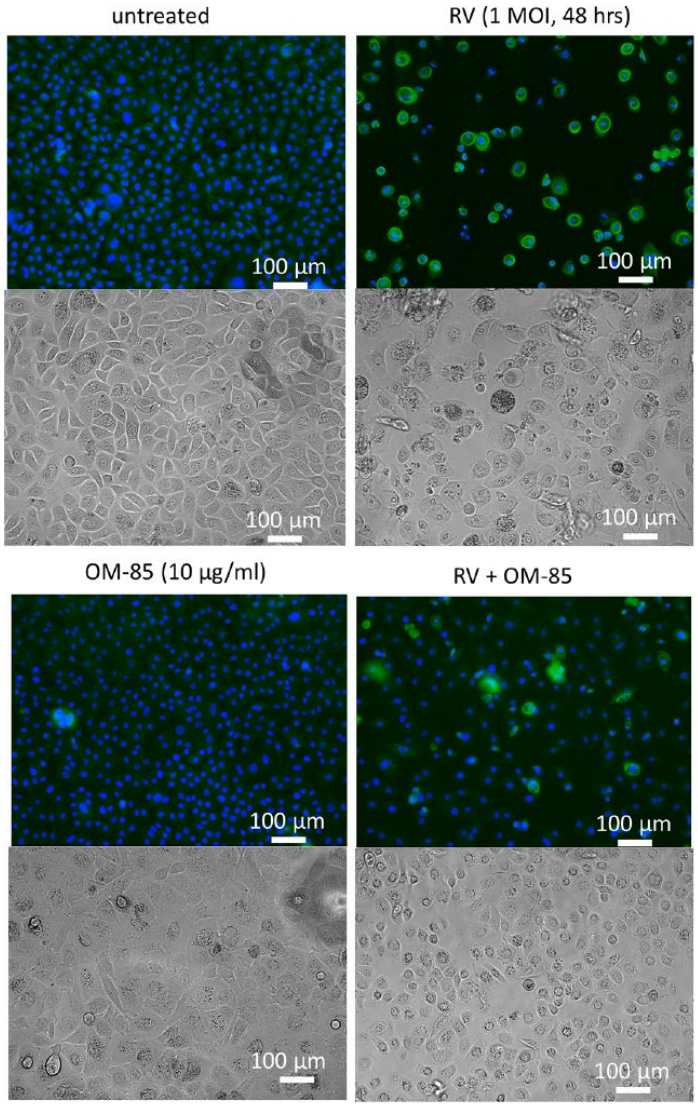
Roth M, PLoS ONE 2017; 12(11): e0188010.

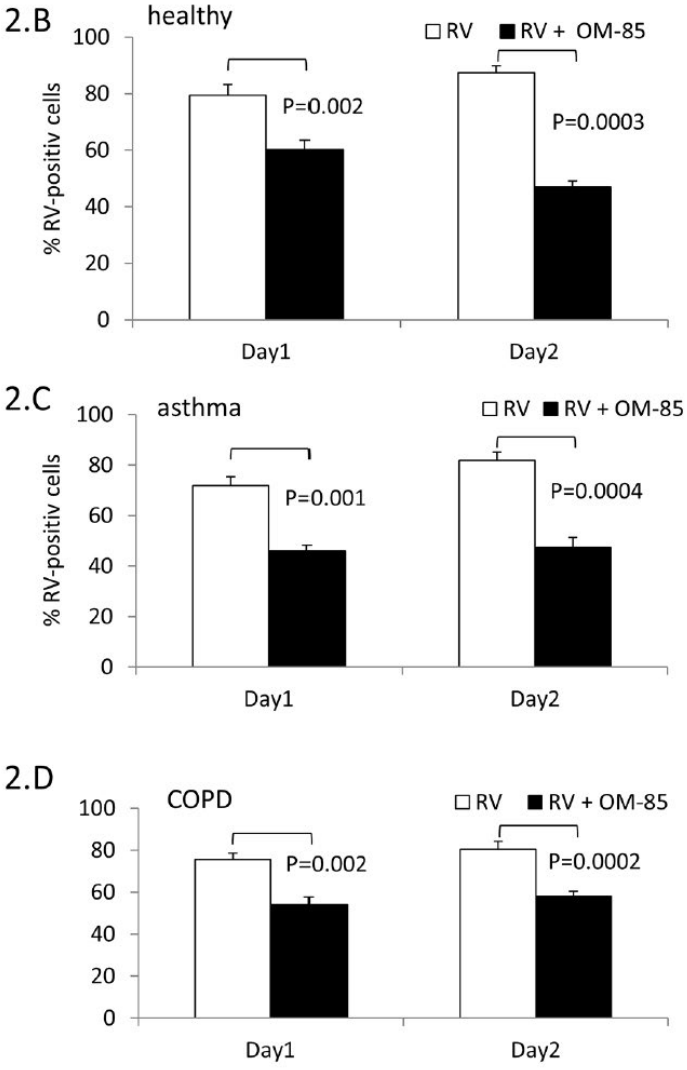
Representative IF images for RV infection (green) in primary BEC; nuclei were stained for cell counting by EVOS live cell staining kit.

Light microscopic images are depicted for the effect of OM-85 and RV infection on BEC phenotype. (B-D)

Quantitation of RV infection of BEC by IF.

BEC were pretreated for 24 or 48 hrs with OM-85 (10 µg/ml).



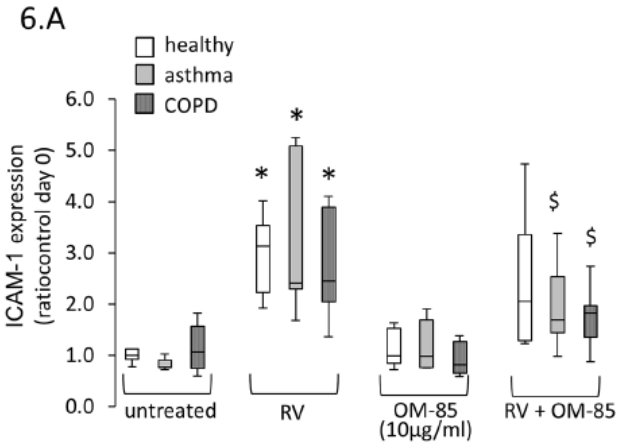


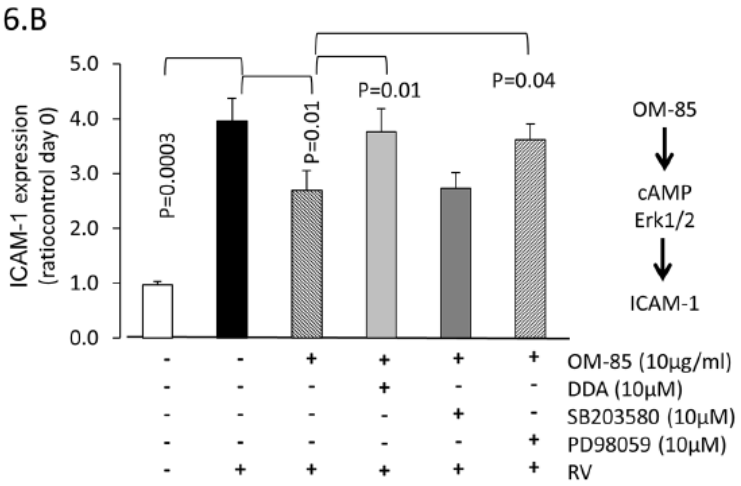
Broncho Vaxom (OM-85) modulates rhinovirus docking proteins on human airway epithelial cells via Erk1/2 mitogen activated protein kinase and cAMP.

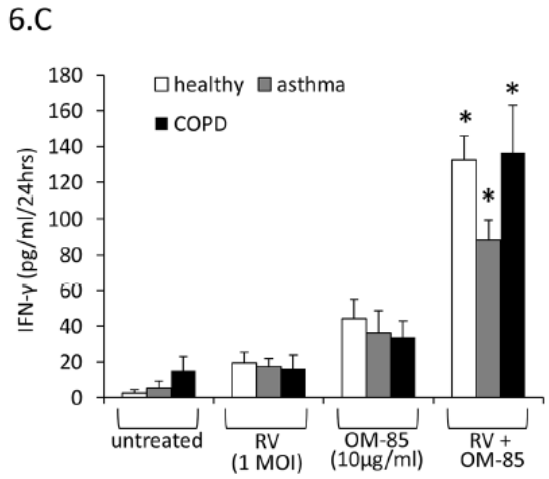
Roth M, PLoS ONE 2017; 12(11): e0188010.

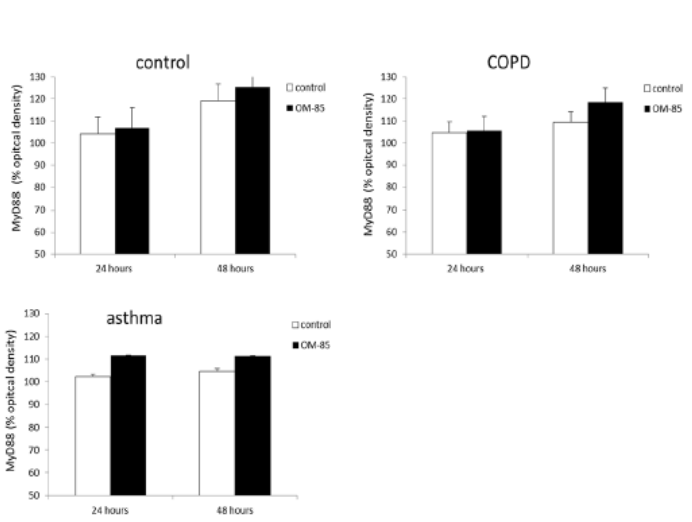
RV induced expression of ICAM-1 on BEC is prevented by OM-85 through cAMP and Erk1/2 MAPK.

Increased expression of ICAM-1 by RV and its **inhibition by OM-85 pre-incubation** (24 hrs).









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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

29 Giugno 2018
EMA/351982/2018

L' EMA avvia una revisione dei medicinali a base di lisati batterici per le patologie respiratorie

La valutazione include recenti dati sull'efficacia.

L'Agenzia Europea dei Medicinali (EMA) ha avviato una revisione dei medicinali a base di lisati batterici, che sono autorizzati in alcuni Stati Membri dell'UE per il trattamento e la prevenzione di patologie infettive del tratto respiratorio (infezioni delle vie respiratorie e dei polmoni) e per patologie respiratorie croniche (a lungo termine).

Recenti studi hanno sollevato dubbi sull'efficacia dei lisati batterici nella riduzione del numero e della gravità delle infezioni respiratorie negli adulti e nei bambini che soffrono di infezioni ripetute. Inoltre, in casi molto rari, è noto che questi medicinali causano gravi effetti avversi legati al sistema immunitario (le difese naturali del corpo).

Questa revisione è stata richiesta dall'Agenzia Italiana del Farmaco (AIFA). L' EMA revisionerà ora tutte le informazioni disponibili e raccomanderà se mantenere, variare o sospendere l'autorizzazione al commercio di questi medicinali in tutta l'UE.

I medicinali a base di lisati batterici sono utilizzati da soli o in combinazione con altri medicinali per il trattamento o la prevenzione di infezioni del tratto respiratorio superiore o inferiore o per il trattamento di patologie respiratorie croniche come la bronchite cronica (infiammazione delle vie respiratorie nei polmoni) e la malattia polmonare ostruttiva cronica (danno o blocco delle vie aeree e degli alveoli polmonari).

I lisati batterici sono costituiti da cellule batteriche che vengono disgregate con lo scopo di stimolare il sistema immunitario a riconoscere e combattere le infezioni batteriche. Questi medicinali sono assunti per via orale (come capsule, compresse, granuli / polvere per formare una miscela o gocce orali), sciolti sotto la lingua (come compresse) o inalati attraverso il naso (come un liquido).

I lisati batterici sono autorizzati con procedura nazionale. Sono disponibili in Austria, Belgio, Bulgaria, Repubblica Ceca, Germania, Grecia, Ungheria, Italia, Lettonia, Lituania, Lussemburgo, Malta, Polonia, Portogallo, Romania, Slovacchia e Slovenia con diversi nomi commerciali come Biomunil, Broncho Munal, Broncho Vaxom, Buccalin, Immubron, Immucytal, Ismigen, Lantigen B, Luivac, Ommunal, Paspat, Pir-05, Polyvaccinum, Provax, Respivax and Ribomunyl.

Maggiori informazioni sulla procedura

La revisione dei lisati batterici è stata avviata su richiesta dell' Italia, ai sensi dell' Articolo 31 della Direttiva 2001/83/EC.

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

EFFICACY OF IMMUNOMODULATORS IN CHILDREN WITH RESPIRATORY TRACT INFECTION

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Reductions in an owing 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

Gli effetti indesiderati con l'uso di OM-85 sono lievi e transitori. Questo profilo di sicurezza è stabile anche se utilizzato a lungo

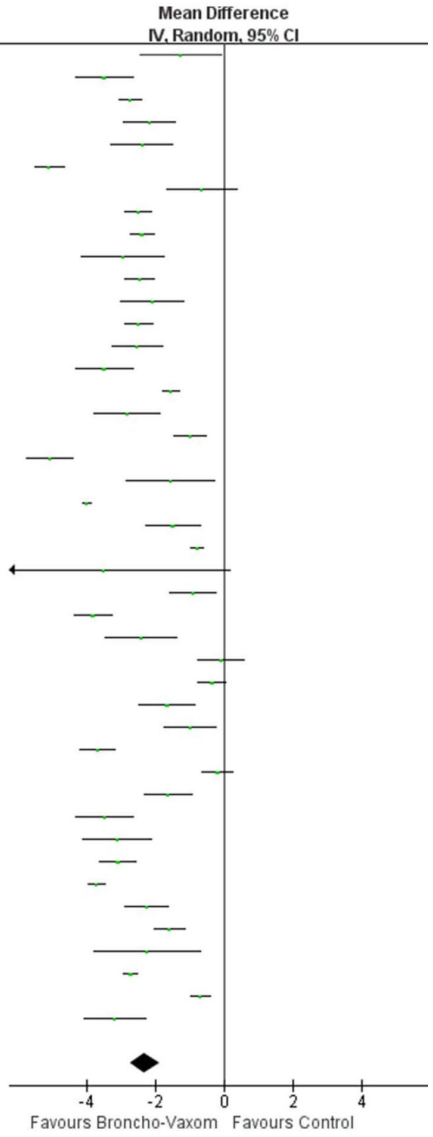
Broncho-Vaxom in pediatric recurrent respiratory tract infections: A systematic review and meta-analysis. YIN J, Intern Immunopham 2018; 54,198

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

Frequency of RTIs 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
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	1.86	1.19	44	4.05	2.3	45	2.3%	-2.19 [-2.95, -1.43]
Del-Rio-Navarro 2003	2.8	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 1998	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	1.99	26	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 Ji 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]
Jiayi 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]
Lancui 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 [-2.32, -0.70]
Ling Su 2014	1.3	0.4	84	2.1	0.8	84	2.5%	-0.80 [-0.99, -0.61]
Maestroni 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	2.4%	-3.84 [-4.39, -3.29]
Razi 2010	5.31	1.79	40	7.75	2.68	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 2000	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 2015	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 1988	0.38	0.26	29	1.09	0.65	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)



Broncho-Vaxom 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.

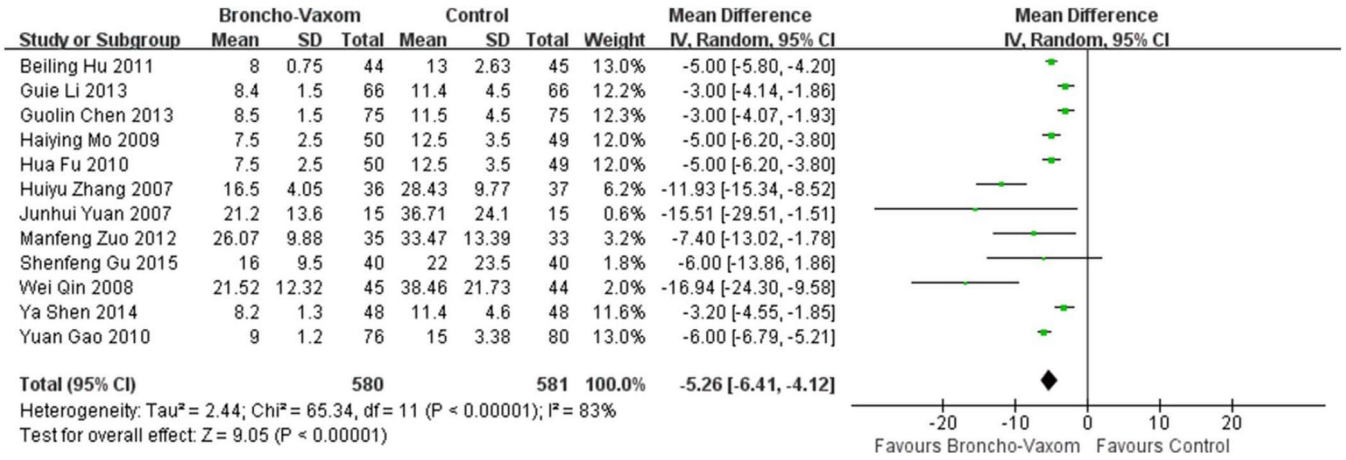


Fig. 5. The cough length in Broncho-Vaxom and control group.

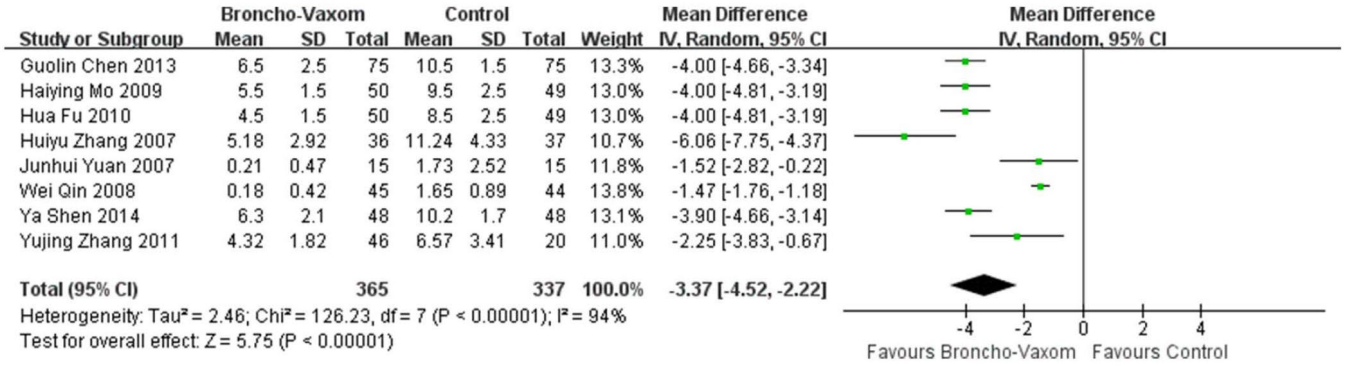
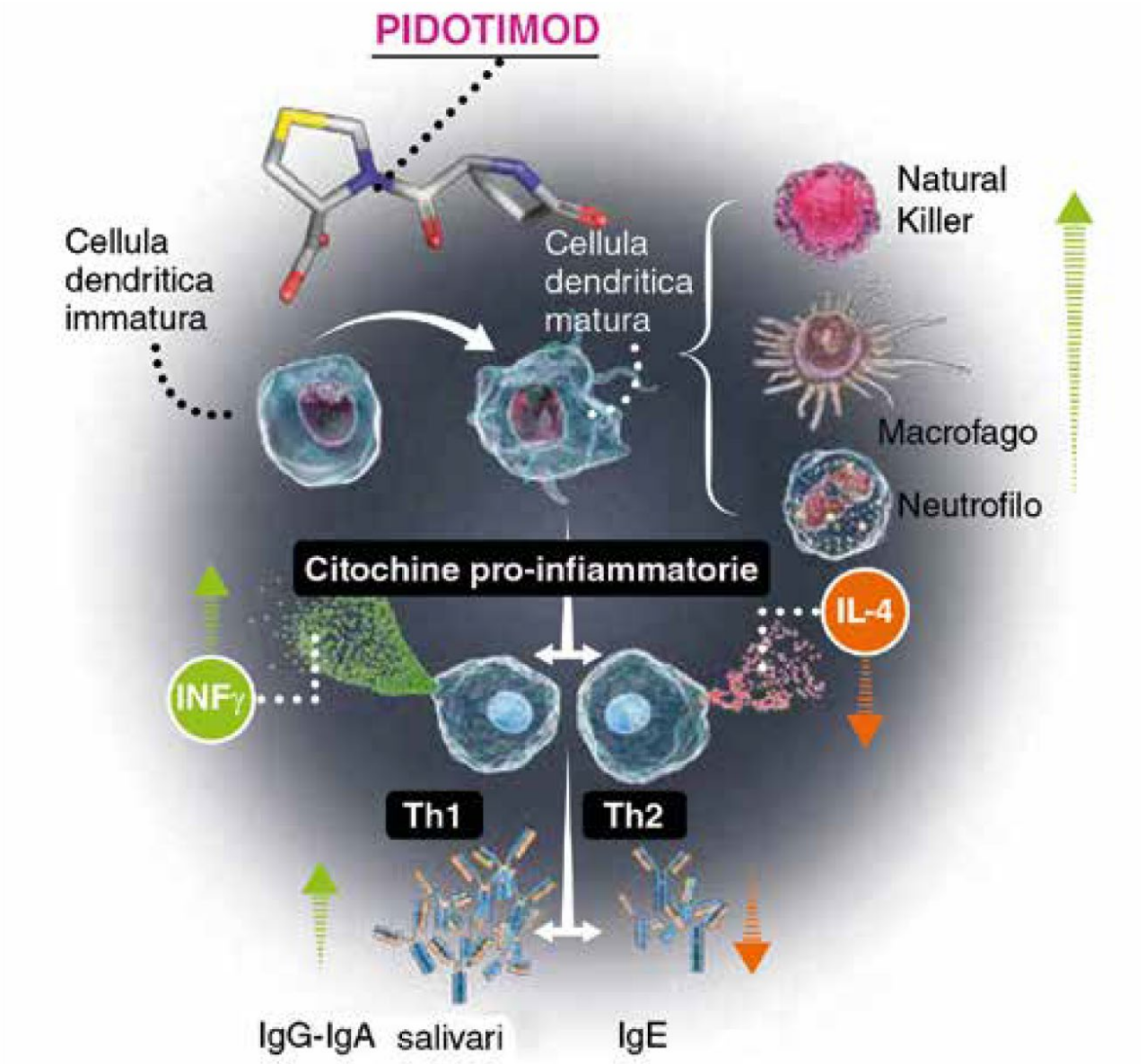


Fig. 6. Duration of wheezing in Broncho-Vaxom and control group.

Cough length and frequency of wheezing in Broncho-Vaxom and control group


PIDOTIMOD
Cellula dendritica immatura
Cellula dendritica matura
Natural Killer
Macrofago
Neutrofilo
Citochine pro-infiammatorie
IL-4
INFγ
Th1
Th2
IgG-IgA salivari
IgE

EFFICACY OF IMMUNOMODULATORS IN CHILDREN WITH RESPIRATORY TRACT INFECTION

Pidotimod prophylaxis also results in **less antibiotic use** [Namazova LS, 2014],

Less hospitalization and paediatric visits and school absenteeism [Caramia G, 2008]

Where reported, **adverse events** were infrequent, **mild and transient**.

Studies on pidotimod in particular lacked reporting of safety, control groups or information on the definition of RRTI, particularly in foreign language abstract-only publications.

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

Esposito et al. J Transl Med (2015) 13:288

20 children hospitalized for community-acquired pneumonia (CAP) were randomized at a 1:1 ratio to receive either standard antibiotics plus pidotimod (PDT) or standard antibiotics alone to evaluate the immunomodulatory activity of PDT. Blood samples

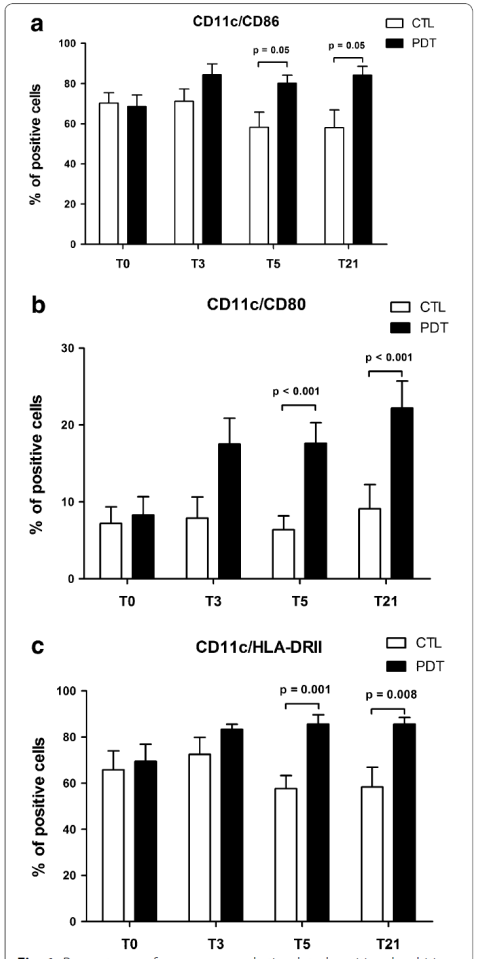


Fig. 1 Percentages of pneumococcal-stimulated positive dendritic cells ($CD11c^+$) expressing HLA-DRII (**a**), CD86 (**b**) and CD80 (**c**) molecules are shown at baseline and in response to therapy in children with community-acquired pneumonia (CAP) treated with antibiotics plus pidotimod and in controls treated with antibiotics only. For each analysis, 30,000 events were acquired and gated on CD11c expression and side scatter properties. Mean values + SD and statistically significant differences are indicated

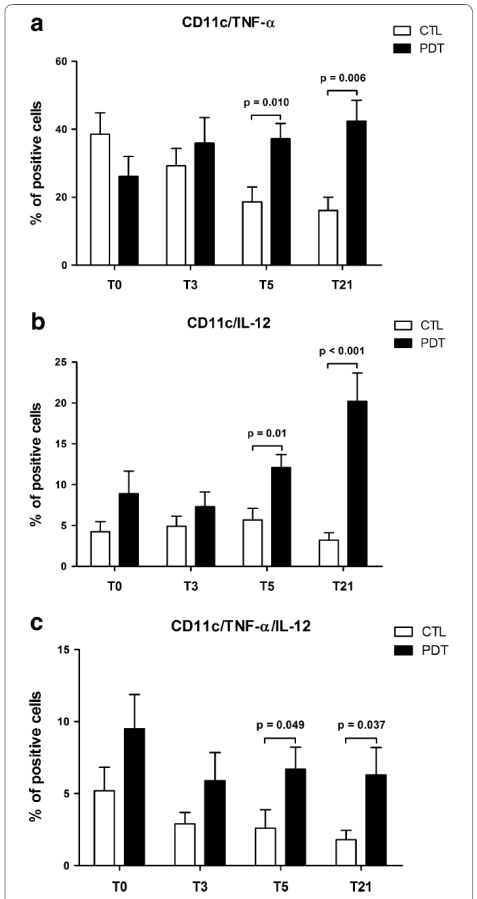
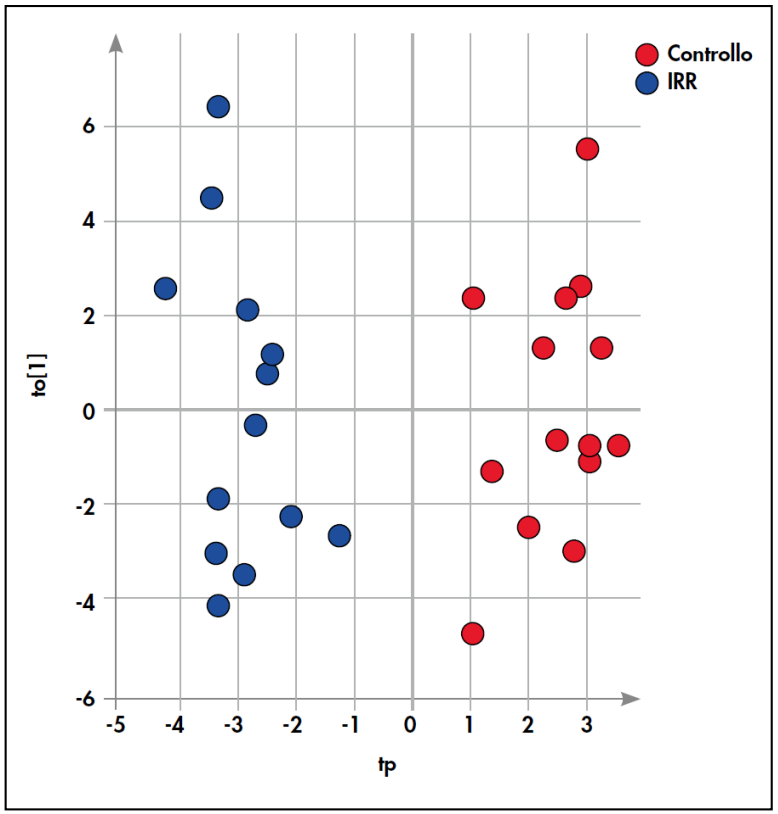


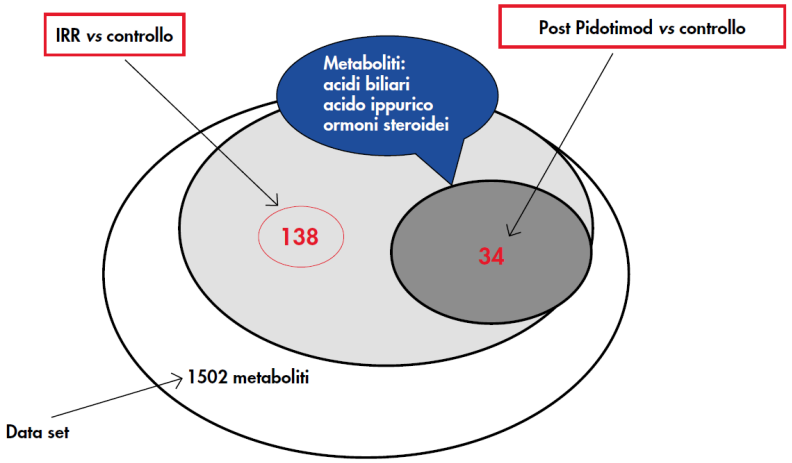
Fig. 2 Percentages of pneumococcal-stimulated dendritic cells ($CD11c^+$) secreting TNF-α (**a**) and IL-12 (**b**) are shown at baseline and in response to therapy in children with community-acquired pneumonia (CAP) treated with antibiotics plus pidotimod and in controls treated with antibiotics only. The percentage of TNF-α/IL-12 secreting $CD11c^+$ cells was higher in the therapy group than in the controls, although significant differences were observed only at T5 and T21 (**c**). For each analysis, 30,000 events were acquired and gated on CD11c expression and side scatter properties. Mean values + SD and statistically significant differences are indicated

Metabolomic profile of children with recurrent respiratory infections.

Bozzetto S Pharmacol Res 2017;115:162



L'analisi metabolomica ha evidenziato differenze sostanziali tra il profilo metabolico dei bambini con infezioni respiratorie ricorrenti (IRR) e i controlli

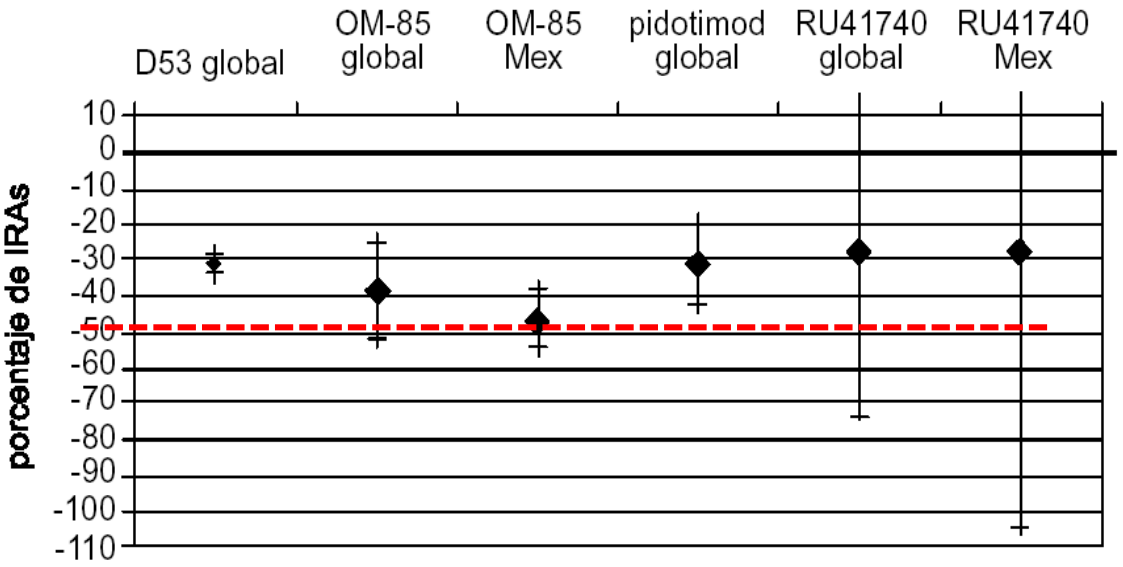


L'analisi metabolomica ha riscontrato 138 metaboliti urinari diversi tra i bambini con IRR e i controlli sani. Dopo trattamento con Pidotimod la differenza si è ridotta a 34 metaboliti.

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.

Immunostimulants for preventing respiratory tract infection in children (Review)

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

THE COCHRANE COLLABORATION®

Although a quantitative assessment of trial quality was not undertaken, observations of reporting quality were in line with data from the 2012 Cochrane review suggesting articles assessing OM-85 were of higher quality

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

Prevenire le infezioni respiratorie ricorrenti e possibili esiti: quale ruolo hanno i lisati batterici?

Peroni Diego
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- ✓ IRR ..
- ✓ Immunomodulanti e IRR
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- ✓ 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	2.30 ± 1.34	−0.70 (−1.23 to −0.17)	30.4	.013
	1 (1-2)	2 (1-3)			
0-6	2.54 ± 1.12	3.87 ± 2.10	−1.33 (−2.12 to −0.54)	34.3	.003
	3 (2-3)	4 (2-5)			
0-9	3.20 ± 1.41	5.00 ± 2.50	−1.80 (−2.75 to −0.85)	36.0	.001
	3 (2-4)	5 (3-7)			
0-12	3.57 ± 1.61	5.75 ± 2.71	−2.18 (−3.22 to −1.13)	37.9	<.001
	3 (3-4)	5.5 (4-8)			

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

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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					
0-9					
0-12*					

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

	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

Can we prevent exacerbations of asthma caused by common cold viruses? Weinberger M JACI, 2010 Oct;126(4):770

"We can put a man on the moon, so why can't we cure the common cold?" This colloquial question is certainly not trivial to those of us that care for asthma, especially asthma in the preschool-age child.
The common cold, caused by rhinovirus and other viral respiratory infections, a nuisance illness to most,
is the major cause of serious asthma exacerbations. Viral respiratory infections are the major cause of asthma exacerbations at all ages 1-3 and appear to be the major risk

Because the current controlled clinical trial was registered in ClinicalTrials.gov in 2008 as a phase IV study, is there any realistic expectation that these questions are likely to addressed? If they are not, is there any realistic likelihood that US Food and Drug Administration approval for marketing in the United States is likely to occur within the foreseeable future? These are, of course, rhetorical questions.

Prevenire le infezioni respiratorie ricorrenti e possibili esiti: quale ruolo hanno i lisati batterici?

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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.

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

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.

This is a **36 month parallel arm**, double-blind, placebo-controlled trial for the **prevention of WLRI into the third to fifth year of life** (30 to 54 mo. inclusive) in young children (6-18 months old) **at increased risk for asthma**. The trial will be divided into 2 periods. During the initial treatment period (**first and second years in the study) participants will receive OM-85 (3.5 mg) or placebo for ten days each month for two consecutive years**. This period will allow the observation of key secondary outcomes while participants are receiving therapy.

The second period (third year in the study) will be **a one year observation of the time to occurrence of the first WLRI episode** (primary outcome) while off study drug along with the secondary outcomes noted above.

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

Orbex trial

Primary Outcome Measures :

- The time to the occurrence of the first WLRI episode in the third observation year while not receiving study drug

Secondary Outcome Measures :

- The time to first WLRI during the two treatment years while receiving study drug
- The annualized rate of WLRI episodes during the two years while receiving study drug
- The annualized rate of WLRI episodes during the third observation year while not receiving study drug
- The annualized rate of severe wheezing respiratory tract illness (SWLRI) episodes during the two treatment years while receiving study drug.

- The annualized rate of severe wheezing respiratory tract illness (SWLRI) episodes during the third observation year while not receiving study drug.

- Number of participants with adverse events

- Safety and tolerability of OM-85 while receiving study drug during the two year treatment period

- Number of participants with adverse events

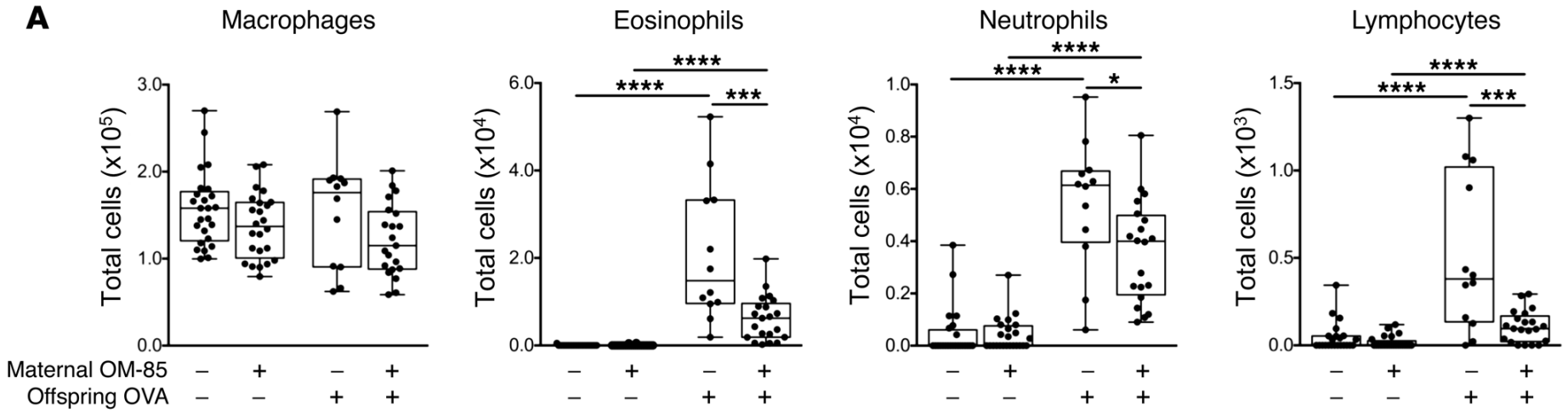
Treatment of pregnant mice with a defined, clinically approved immune modulator was shown to markedly reduce susceptibility of their offspring to development of the hallmark clinical features of allergic airway inflammatory disease

JCI The Journal of Clinical Investigation

Transplacental immune modulation with a bacterial-derived agent protects against allergic airway inflammation

Kyle T. Mincham, … , Patrick G. Holt, Deborah H. Strickland

J Clin Invest. 2018. https://doi.org/10.1172/JCI122631.



We provide evidence that the principal **target for maternal treatment effects was the fetal dendritic cell progenitor** compartment, equipping the offspring for accelerated functional maturation of the airway mucosal dendritic cell network following birth.

These data provide **proof of concept** supporting the rationale for **developing transplacental immune reprogramming approaches for primary disease prevention.**

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

29 Giugno 2018
EMA/351982/2018

L' EMA avvia una revisione dei medicinali a base di lisati batterici per le patologie respiratorie

La valutazione include recenti dati sull'efficacia.

L'Agenzia Europea dei Medicinali (EMA) ha avviato una revisione dei medicinali a base di lisati batterici, che sono autorizzati in alcuni Stati Membri dell'UE per il trattamento e la prevenzione di patologie infettive del tratto respiratorio (infezioni delle vie respiratorie e dei polmoni) e per patologie respiratorie croniche (a lungo termine).

Recenti studi hanno sollevato dubbi sull'efficacia dei lisati batterici nella riduzione del numero e della gravità delle infezioni respiratorie negli adulti e nei bambini che soffrono di infezioni ripetute. Inoltre, in casi molto rari, è noto che questi medicinali causano gravi effetti avversi legati al sistema immunitario (le difese naturali del corpo).

Questa revisione è stata richiesta dall'Agenzia Italiana del Farmaco (AIFA). L' EMA revisionerà ora tutte le informazioni disponibili e raccomanderà se mantenere, variare o sospendere l'autorizzazione al commercio di questi medicinali in tutta l'UE.