SIAIP
Società Italiana di Allergologia e Immunologia Pediatrica

Immunomodulanti

Le IRR: non si può fare proprio nulla per prevenirle?

F. Cardinale

UOC di Pediatria Generale e Allergo-Pneumologia

Azienda Ospedaliero - Universitaria "Policlinico – Giovanni XXIII" - Bari

[…] there is no

consensus definition of recurrent

respiratory infections (RRI)…

Fiocchi, Allergy Asthma Proc 2009;30:S21

Immunostimulants for preventing respiratory tract infection in children (Review)

Del-Rio-Navarro et al.
Cochr Database Syst Rev 2011, Issue 4. Art. No.: CD004974

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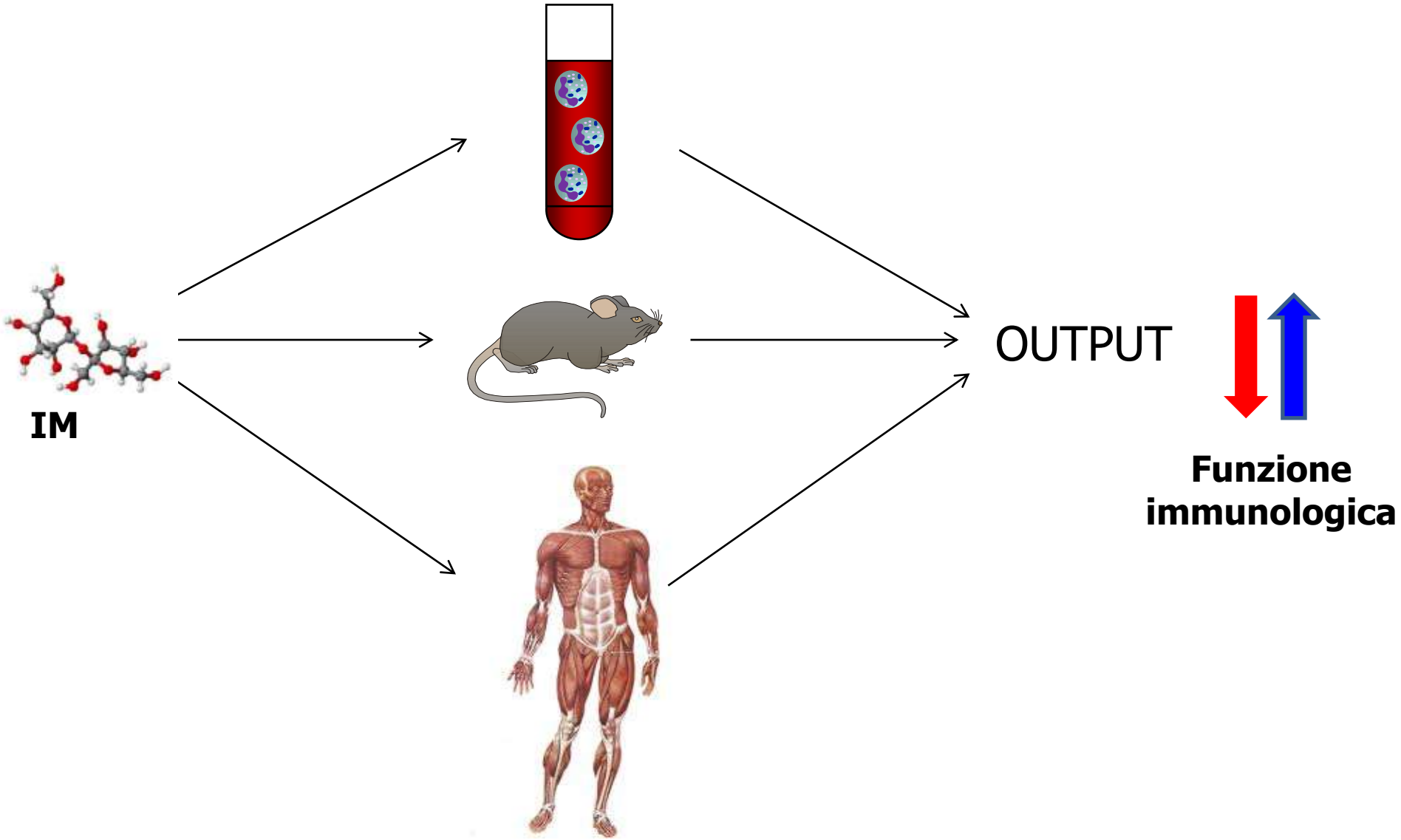
(Aggarwal 2007). Interventi[illegible]he immune system (immunostimulants) ha[illegible]fective measures to reduce ARTIs. *

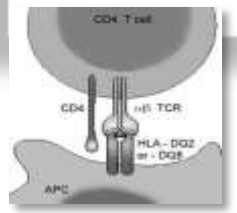
Bibliografia?

non esiste in letteratura una definizione di immunomodulanti !

Quale definizione di immunomodulanti (IM)?



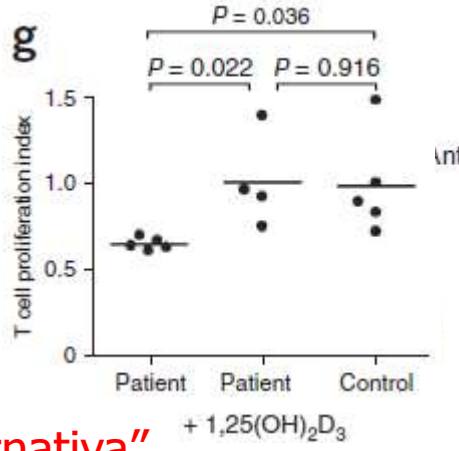
Vitamin D controls T cell antigen receptor signaling and activation of human T cells

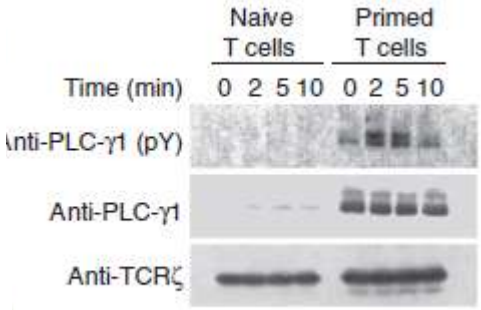


von Essen, Nat Immunol 2010;11:344-9

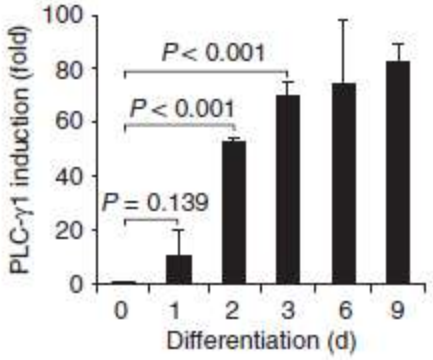
nature immunology

Nell'uomo, l'induzione della **PLC-γ1** nelle T cells, essenziale per il signalling down-stream al **TCR** attraverso la via "classica" (Lat- e PLC-γ1-dipendente) dipende dalla **vit. D** e dalla **espressione del VDR**





Le T cell "naive" esprimono il VDR dopo stimolazione attraverso la via "alternativa" (MAPK p38-dipendente) e, successivamente, in presenza di vit D, il **VDR** stimolato determina l'up-regulation della PLC-γ1 **(75 x)** permettendo il signalling a valle del TCR anche attraverso la via classica nelle T cells "primed" dall'Ag

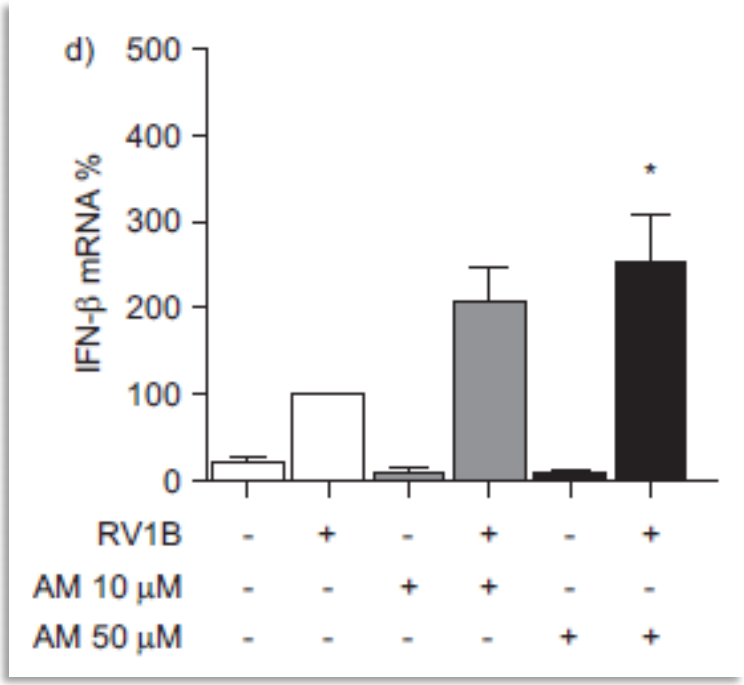


Azithromycin induces anti-viral responses in bronchial epithelial cells

Gielen, ERJ 2010;36:646

Azithromycin (but not erythromycin or telithromycin) significantly **increases** rhinovirus 1B and rhinovirus 16 induced **interferons** and interferon-stimulated gene **mRNA expression** and protein production.

Furthermore, azithromycin significantly reduces **rhinovirus replication** and release



Garlic for the common cold (Review)

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Lissimann,
Cochr Database Syst Rev 2012;3, Art. No.: CD006206

6 trials identificati come potenzialmente rilevanti

Solo uno studio ritenuto elegibile per l'analisi, di bassa qualità metodologica

Authors' conclusions

There is insufficient clinical trial evidence regarding the effects of garlic in preventing or treating the common cold. A single trial suggested that garlic may prevent occurrences of the common cold but more studies are needed to validate this finding. Claims of effectiveness appear to rely largely on poor-quality evidence.

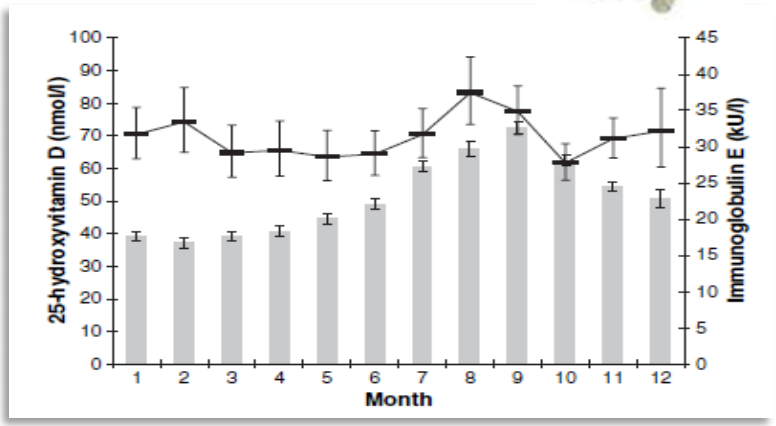
Original article

Serum 25-hydroxyvitamin D and IgE – a significant but nonlinear relationship

Hypponen, Allergy 2009: 64: 613

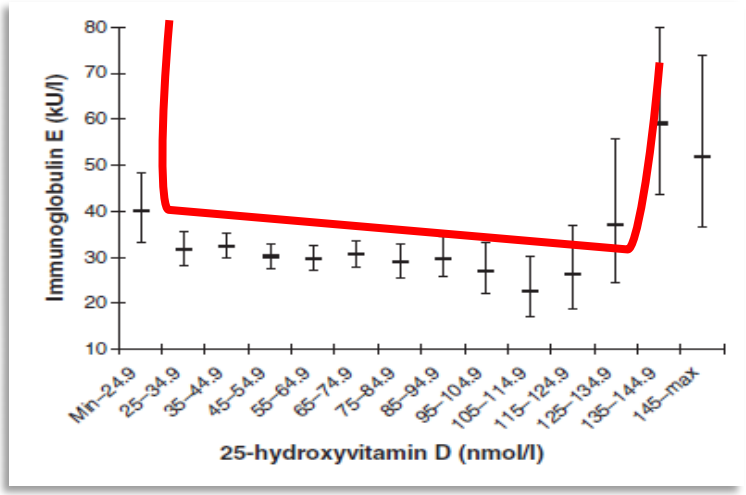
Dose-effect

9377 individui arruolati nel British Birth Coort study (n. 7288 eligibili, con dati su 25(OH)D e IgE sierici; n. 6429 con analisi genotipo CYP27B1 [-1260C>A]).



Relazione non lineare ("U-shaped") tra livelli di IgE nel siero e vit D:

Livelli di IgE ↑ **29%** per 25(OH)D **<25 nmol/L**
Livelli di IgE ↑ **56%** per 25(OH)D **>135 nmol/L**



DEFINIZIONE DI IMMUNOMODULANTE

Gruppo di Studio di Immunologia della SIAIP
F. Cardinale (coordinatore), M. Fiore, B. Martire, S. Martino, V. Moschese, A.R. Soresina
M. Bergamini, G. Simeone (revisori per l'EBM)

"Sono definite molecole o sostanze dotate di un'azione sul sistema immune, o IM, quelle che abbiano almeno 1 studio clinico (non necessariamente randomizzato) pubblicato nella letteratura internazionale"

RIAP 2013 (in press)

POTENZIALI IMMUNOMODULANTI NELLE IR

1. **Lisati ed estratti batterici**
2. **Probiotici – prebiotici**
3. **Molecole di sintesi** (pidotimod, etc)
4. **Vitamine ed oligoelementi** (vit D, vit A, ac folico, Zn, Cu, etc)
5. **Miscellanea** (resveratrolo, echinacea, curcuma, lattoferrina, oligonucleotidi CpG, omeopatia, agopuntura, aglio, etc.)

Cardinale et al, RIAP (in press)

2011

Polyvalent mechanical bacterial lysate for the prevention of recurrent respiratory infections: A meta-analysis

Mario Cazzola[a,b,*], Sreedhar Anapurapu[c], Clive P. Page[d]

Oral purified bacterial extracts in acute respiratory tract infections in childhood: a systematic quantitative review

2007

Claudia Steurer-Stey · Leonie Lagler · Daniel A. Straub · Johann Steurer · Lucas M. Bachmann

2011

S. Miceli Sopo', R. Onesimo', V. Giorgio', C. Fundarò', F. Tabacco', M. Calvani'

Efficacy of over-the-counter immunostimulants in the prevention of paediatric recurrent acute respiratory tract infections. Criticisms and pitfalls of available metanalyses

Ribosome-component immune modulation of respiratory tract infections in children

2009

Alessandro Fiocchi, M.D.,[1] Luigi Terracciano, M.D.,[1] Alberto Martelli, M.D.,[1] Luca Bernardo, M.D., Elena Calcinai, M.D.,[1] and Sergio Marcassa, M.Sc.[3]

2010

OM-85 BV, an immunostimulant in pediatric recurrent respiratory tract infections: a systematic review

Urs B Schaad
Basel, Switzerland

Immunostimoliamoci

2007

Stefano Miceli Sopo
Dipartimento di Pediatria, Policlinico "A. Gemelli", Università Cattolica del Sacro Cuore, Roma
smicelisopo@rm.unicatt.it

Immunostimulants for preventing respiratory tract infection in children (Review)

Del-Rio-Navarro et al.
Cochr Datab Syst Rev 2011, Issue 4. Art. No.: CD004974

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Cochr Database Syst Rev 2011; Issue 4. Art. No.: CD004974

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Trade name	Common name	Active ingredient
Adimod	Pidotimod	Pidotimod
Allicor	Not available	Garlic extract
Biostim	RU41740	Glycoprotein and membranes of *Klebsiella pneumoniae*
Broncho-Vaxom, Broncho-Munal, Ommunal	OM-85 or OM-85 BV	Lyophilised bacterial lysates
Chizukit	Not available	Preparation of *Echinacea purpurea*, propolis and vitamin C
Decaris	Levamisole	Levamisole
Echinacea	*Echinacea purpurea*	Extract of *Echinacea purpurea*
Immunoferon, Inmunol	AM3	Glycophosphopeptical
IRS 19	Not available	Bacterial lysates
Ismigen	Not available	Bacterial lysates
Lantigen B	Not available	Bacterial antigens
Leucotrofina, Leucogen	Thymomodulin	Thymus extract
Luivac	LW50020	Bacterial antigens
Munostin	Not available	Bacterial corpses and lysates
Not available	SL04	Bacterial extracts
Paspat	Not available	Autolysate mixture of bacterial antigens for parenteral application
Pressosine		
Pulmotabs		
Pulmonaro		
Reaferon		enetic engi-
Respivax		
Ribovac, Ribomunyl, Immucithal	D53	Proteoglycans of *K. pneumoniae* plus bacterial ribosomes
TFX	Thymus extract	Thymus extract
Umckaloabo	*Pelargonium sidoides*	Alcohol extract from the roots of *Pelargonium sidoides*

No probiotici

Hao, Cochrane Datab Syst Rev 2011;issue 9:Art. No CD006895

Types of participants

Participants younger than 18 years of age. We did not include trials that included participants who suffered from asthma, allergy and atopy, or chronic respiratory diseases.

Types of studies

Randomised controlled trials (RCTs) comparing IS, administered by any method, to placebo to prevent ARTIs. Trials referring to interferon inducers, vitamins and nutritional supplements were not included.

Immunostimulants for preventing respiratory tract infection in children (Review)

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Cochr Database Syst Rev 2011; Issue 4. Art. No.: CD004974

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35 studi RCT ritenuti elegibili (4060 participanti)

[…] When compared with placebo, the use of IS was shown to reduce ARTIs measured as the **total numbers of ARTIs** (**MD -1.24**; 95% CI -1.54 to -0.94) and the **difference in ARTI rates** (**MD -38.84%**; 95% CI -46.37% to -31.31%).

[…] Trial quality was generally poor and a high level of statistical heterogeneity was evident.

[…] The subgroup analysis of bacterial IS, D53 and OM-85 studies produced similar results, with lower heterogeneity.

[…] No difference in adverse events was evident between the placebo and IS groups.

Immunostimulants for preventing respiratory tract infection in children (Review)

Del-Rio-Navarro et al.
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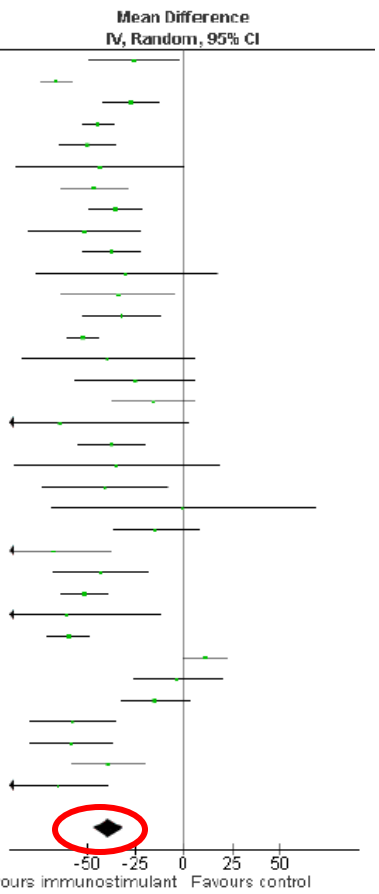
Figure 6. Forest plot of comparison: Any IS compared with placebo, outcome: 1.2 Per cent differenc ARTIs.

Study or Subgroup	Immunostimulant Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Ahrens 1984	74.4	67.86	83	100	80.16	72	2.9%	-25.60 [-49.18, -2.02]
Arroyave 1999	33.33	15.48	42	100	22.62	44	3.9%	-66.67 [-74.83, -58.51]
Careddu 1994a	72.82	96.12	329	100	97.09	342	3.6%	-27.18 [-41.80, -12.56]
Clerici 1988	55.43	13.04	20	100	13.04	20	3.9%	-44.57 [-52.65, -36.49]
Cohen 2004	50	61.11	160	100	72.22	168	3.6%	-50.00 [-64.45, -35.55]
De Loore 1979	56.62	52.17	15	100	73.91	17	1.7%	-43.38 [-87.33, 0.57]
Del-Rio-Navarro 2003	53.85	28.92	20	100	28.85	20	3.4%	-46.15 [-63.44, -28.86]
Fiocchi 1986	64.63	13.41	8	100	14.63	8	3.6%	-35.37 [-49.12, -21.62]
Garabedian 1990	48.67	58	75	100	110.67	69	2.5%	-51.33 [-80.56, -22.10]
Gutiérrez-Tarango 2001	63	24.88	26	100	31.88	28	3.5%	-37.00 [-52.20, -21.80]
Gómez-Barreto 1998	70.27	69.82	26	100	106.76	30	1.6%	-29.73 [-76.42, 16.96]
Hauguenauer 1987	66.12	42.86	45	100	87.76	42	2.5%	-33.88 [-63.23, -4.53]
Hüls 1995	68	56.4	78	100	70.8	78	3.2%	-32.00 [-52.09, -11.91]
Jara-Pérez 2000	47.83	31.44	99	100	27.09	100	3.9%	-52.17 [-60.33, -44.01]
Karam-Bechara 1995	60.92	75.86	33	100	116.48	39	1.7%	-39.08 [-83.87, 5.71]
Lacomme 1985	75.09	78.07	47	100	68.77	40	2.4%	-24.91 [-55.77, 5.95]
Litzman 1999	84.62	48.72	43	100	51.28	41	3.1%	-15.38 [-36.79, 6.03]
Maestroni 1984	36.04	36.94	11	100	96.58	9	1.0%	-63.96 [-130.73, 2.81]
Motta 1994	62.62	57.69	117	100	78.53	116	3.4%	-37.18 [-54.79, -19.57]
Paupe 1986	65.15	66.39	21	100	107.47	22	1.4%	-34.85 [-87.98, 18.28]
Pech 1987	59.04	61.7	35	100	76.06	34	2.3%	-40.96 [-73.69, -8.23]
Piquett 1986	100	104.44	17	100	108.15	20	0.9%	0.00 [-68.64, 68.64]
RB10 1994	85.61	90.91	153	100	106.06	161	3.1%	-14.39 [-36.21, 7.43]
RB17 1988	32.17	23.06	15	100	54.96	15	2.5%	-67.83 [-97.99, -37.67]
RB21 1988	56.84	63.16	45	100	52.63	42	2.9%	-43.16 [-67.53, -18.79]
RB22 1990	48.39	16.13	20	100	22.58	20	3.7%	-51.61 [-63.77, -39.45]
RB24 1990	39.13	54.35	16	100	86.96	17	1.5%	-60.87 [-110.04, -11.70]
RB25 1990	40.31	6.15	13	100	18.46	12	3.8%	-59.69 [-70.66, -48.72]
Saracho-Weber 2001	111.11	47.22	135	100	44.44	117	3.8%	11.11 [-0.22, 22.44]
Schaad 1986	96.98	59.4	45	100	52.35	49	3.0%	-3.02 [-25.74, 19.70]
Schaad 2002	85.48	59.06	98	100	65.72	85	3.3%	-14.52 [-32.61, 3.57]
Van Eygen 1976	42.11	39.47	38	100	52.63	32	3.0%	-57.89 [-80.03, -35.75]
Van Eygen 1979	41.69	48.53	53	100	61.56	53	3.1%	-58.31 [-79.41, -37.21]
Vautel 1993	60.97	38.67	32	100	39.75	32	3.3%	-39.03 [-58.24, -19.82]
Zagar 1988	34.86	23.85	29	100	59.63	22	2.7%	-65.14 [-91.53, -38.75]
Total (95% CI)			**2042**			**2018**	**100.0%**	**-38.84 [-46.37, -31.31]**

Heterogeneity: Tau² = 357.14; Chi² = 195.07, df = 34 (P < 0.00001); I² = 83%
Test for overall effect: Z = 10.11 (P < 0.00001)



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M. Bergamini

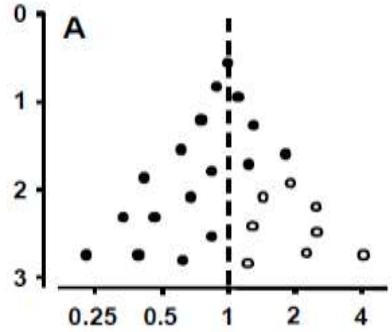
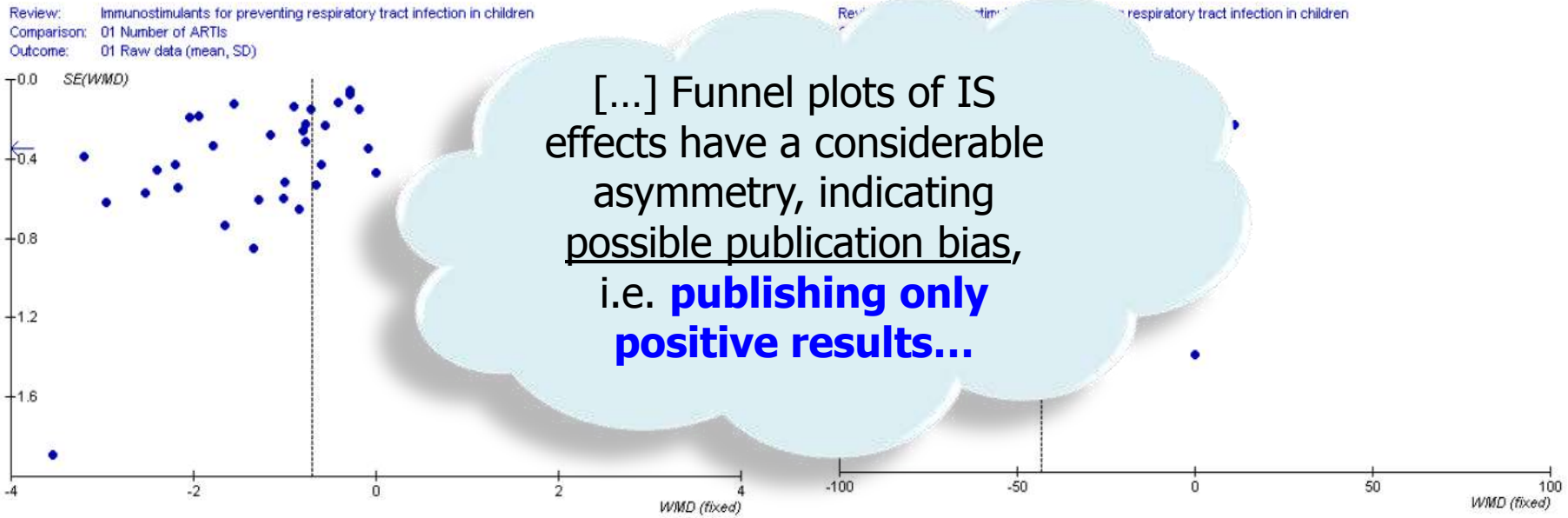


Figure 3.

Figure 4.



[…] Funnel plots of IS effects have a considerable asymmetry, indicating possible publication bias, i.e. **publishing only positive results…**

Immunostimulants for preventing respiratory tract infection in children (Review)

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SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Any immunostimulant (IS) compared with placebo for preventing respiratory tract infection in children

Patient or population: children (age <18 years) susceptible to acute respiratory tract infections (ARTIs)
Settings: outpatient
Intervention: any IS
Comparison: placebo

Outcomes	Illustrative comparative risks' (95% CI)		No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk			
	Placebo	Any IS			
Number of ARTIs	The range of ARTIs in the control group was 0.92 to 6.2	The mean Number of ARTIs in the intervention groups was 1.24 lower (0.94 to 1.54 lower)	4060 (35 studies)	⊕⊕⊕⊖ **moderate**[1]	The effect depends on the number of ARTIs in the control group
Percent difference in ARTIs		The mean Percent difference in ARTIs in the intervention groups was **39 lower** (31.31 to 46.37 lower)	4060 (35 studies)	⊕⊕⊕⊖ **moderate**[1,2]	
Incidence of gastrointestinal adverse events	**21 per 1000**	**30 per 1000** (11 to 50 per 1000)	1457 (10 studies)	⊕⊕⊖⊖ **low**[1,3]	
Incidence of skin adverse events	**3 per 1000**	**7 per 1000** (-8 to 14 per 1000)	1469 (10 studies)	⊕⊕⊖⊖ **low**[1,3]	

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3. **Molecole di sintesi** (pidotimod, etc)
4. **Vitamine ed oligoelementi** (vit D, vit A, ac folico, Zn, Cu, etc)
5. **Miscellanea** (resveratrolo, echinacea, curcuma, lattoferrina, oligonucleotidi CpG, omeopatia, agopuntura, fitoterapici, aglio, etc.)

Cardinale et al, RIAP (in press)

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Del-Rio-Navarro et al.
Cochr Database Syst Rev 2011; Issue 4. Art. No.: CD004974

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Figure 7. Forest plot of comparison: OM-85 trials, outcome: 6.2 Per cent difference in ARTIs.

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Ahrens 1984	74.4	67.86	83	100	80.18	72	11.4%	-25.60 [-49.18, -2.02]
Del-Rio-Navarro 2003	53.85	26.92	20	100	28.85	20	13.5%	-46.15 [-63.44, -28.86]
Gutiérrez-Tarango 2001	63	24.88	26	100	31.88	28	14.3%	-37.00 [-52.20, -21.80]
Gómez-Barreto 1998	70.27	69.82	26	100	106.76	30	5.7%	-29.73 [-76.42, 16.96]
Jara-Pérez 2000	47.83	31.44	99	100	27.09	100	16.4%	-52.17 [-60.33, -44.01]
Maestroni 1984	36.04	36.94	11	100	96.58	9	3.3%	-63.96 [-130.73, 2.81]
Schaad 1986	96.98	59.4	45	100	52.35	49	11.7%	-3.02 [-25.74, 19.70]
Schaad 2002	85.48	58.06	98	100	65.72	85	13.3%	-14.52 [-32.61, 3.57]
Zagar 1988	34.86	23.85	29	100	59.63	22	10.5%	-65.14 [-91.53, -38.75]
Total (95% CI)			437			415	100.0%	**-35.90 [-49.46, -22.35]**

Heterogeneity: Tau² = 275.37; Chi² = 32.26, df = 8 (P < 0.0001); I² = 75%
Test for overall effect: Z = 5.19 (P < 0.00001)

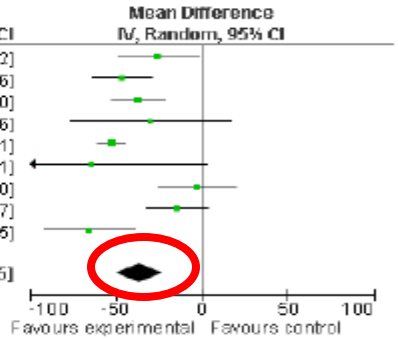

Figure 8. Forest plot of comparison: D53 trials, outcome: 7.2 Per cent difference in ARTIs.

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Garabedian 1990	48.67	58	75	100	110.67	69	7.0%	-51.33 [-80.56, -22.10]
Hauguenauer 1987	66.12	42.86	45	100	87.76	42	7.0%	-33.88 [-63.23, -4.53]
Hüls 1995	68	56.4	78	100	70.8	78	10.5%	-32.00 [-52.09, -11.91]
Lacomme 1985	75.09	78.07	47	100	68.77	40	6.5%	-24.91 [-55.77, 5.95]
RB10 1994	85.61	90.91	153	100	106.06	161	9.7%	-14.39 [-36.21, 7.43]
RB17 1988	32.17	23.06	15	100	64.96	15	6.7%	-67.83 [-97.99, -37.67]
RB21 1988	56.84	63.16	45	100	52.63	42	8.7%	-43.16 [-67.53, -18.79]
RB22 1990	48.39	16.13	20	100	22.58	20	14.6%	-51.61 [-63.77, -39.45]
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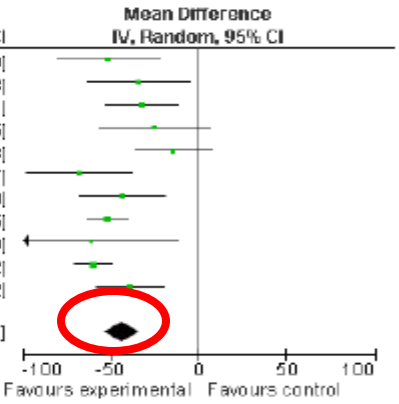
RB25 1990	40.31	6.15	13	100	18.46	12	15.2%	-59.69 [-70.66, -48.72]
Vautel 1993	60.97	39.67	32	100	39.75	32	10.9%	-39.03 [-58.24, -19.82]
Total (95% CI)			539			528	100.0%	**-43.47 [-53.22, -33.72]**

Heterogeneity: Tau² = 131.20; Chi² = 22.14, df = 10 (P = 0.01); I² = 55%
Test for overall effect: Z = 8.74 (P < 0.00001)

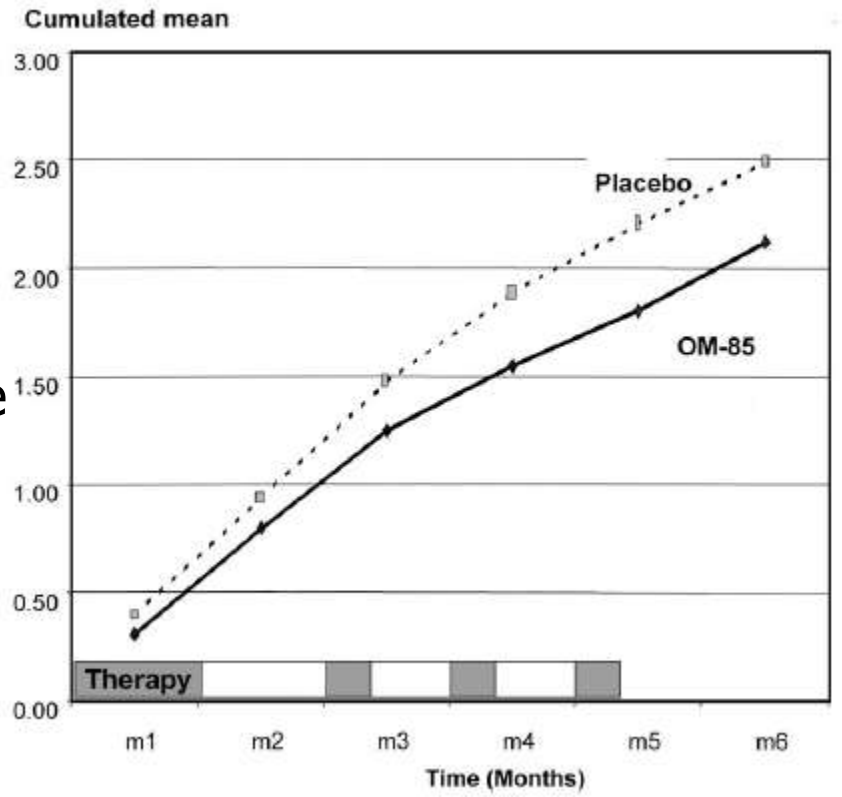


Immunostimulation With OM-85 in Children With Recurrent Infections of the Upper Respiratory Tract*

A Double-Blind, Placebo-Controlled Multicenter Study

Schaad, Chest 2002;122:2042

Double-blind, placebo-controlled, multicenter study with **OM-85** for **6 mo** (daily 1 mo; then 10 days/mo for 5 mo) in **232 patients** aged 36 to 96 months with recurrent (> 3) URTIs



Lower rate of URTIs (p <0.05) in active group (**-0.4 URTIs** in 6 mo, **-16%**);
OR for three or more URTIs **0.51** at 5 mo and **0.65** at 6 mo

The difference between OM-85 and placebo was more important in patients reporting a larger (>6/yr) number of URTIs in the previous year.

Meccanismo di azione dell'OM85: studi in vitro

Induzione maturaz. DC umane CD83+ e ↑ attività stimolatoria su T cells

Zelle-Rieser, Immunol Letter 2001;76:63

Aumento rapporto T cells CD4/CD8 e ↑ produzione IFNγ nel BAL

Emmerich, Respiration 1990;57:90

Induzione trascrizione IL-6 e IL-8 via *C-Fos/serum responsive elements*

Keul, Thorax 1996;51:150

Modulazione *gp130 signal transducer protein* e relative citochine (↑ IL-6, ↑ IL-11, TNF-α e ↓ IL-12) nell'uomo e nel ratto

Roth, Thorax 2000;55:678–684; Brough-Holub, Clin Exp imm 1995;101:302

Aumentata produzione TGF-β e NO via TLR4 e TLR2 Myd88-dependent pathways nel ratto

Alyanakion, Diabetes 2006;55:179; Brough-Holub, Clin Exp imm 1995;101:302

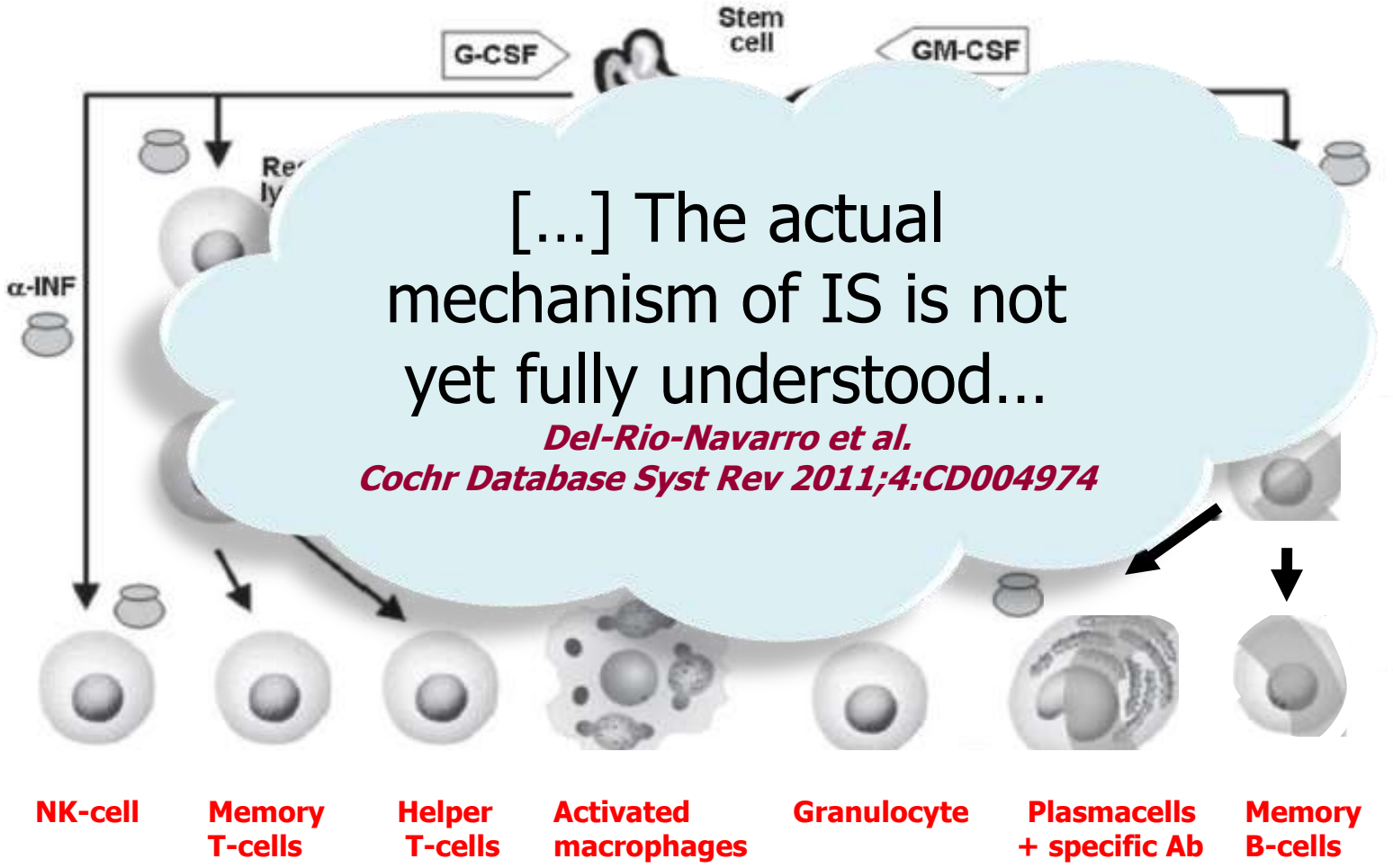
Down-regulation del TLR2 e TLR4/CD14 complex su monociti e promozione shift Th2→Th1

Nikolova, Int Immunopharmacol 2009;9:425

Aumento dei livelli di IgA secretorie e IgG A M nel siero nell'uomo

Puigdollers, Respiration 1980;40:142; Djuric, Int J Immunother 1989;V:139

Meccanismi ipotizzati di azione del D53



Pregliasco, Allergy Asthma Proc 2009;30:S5

GLI ESCLUSI

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

Razi, JACI 2010;126:763

RCT study on **75 children** (1 - 6 years old) with recurrent **infectious wheezing** assigned to receive **OM-85 BV** (1/day for 10 days each month for 3 mo) or placebo

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	3.82 ± 1.15 4 (3-5)	5.30 ± 1.84 5 (4-7)	−1.48 (−2.19 to −0.75)	27.9	<.001
0-9	4.80 ± 1.53 5 (3-6)	6.80 ± 2.34 7 (5-8)	−2.00 (−2.92 to −1.07)	29.4	<.001
0-12*	5.31 ± 1.79 6 (4-6)	7.75 ± 2.68 7 (5-10)	−2.44 (−3.50 to −1.36)	31.4	<.001

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

Follow-up at **12 months**

In the OM85 group significantly **reduced incidence of wheezing** attacks **(-37.9 %)**

OM-85 BV also **reduced** the mean **incidence of ARTIs** by **31.4%**

GLI ESCLUSI

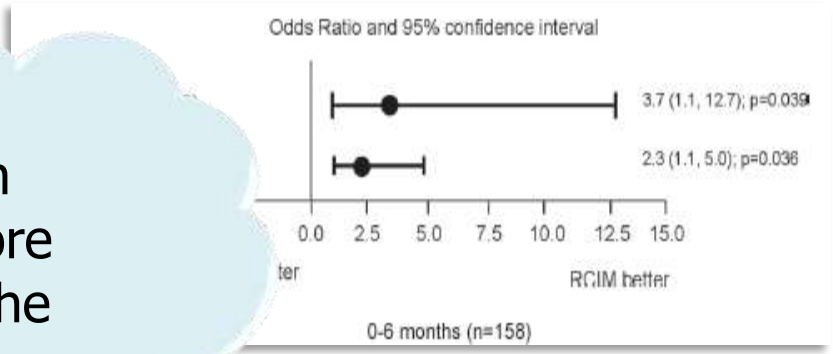
Efficacy and safety of ribosome-component immune modulator for preventing recurrent respiratory infections in socialized children

Fiocchi, Allergy Asthma Proc 2012;33:197

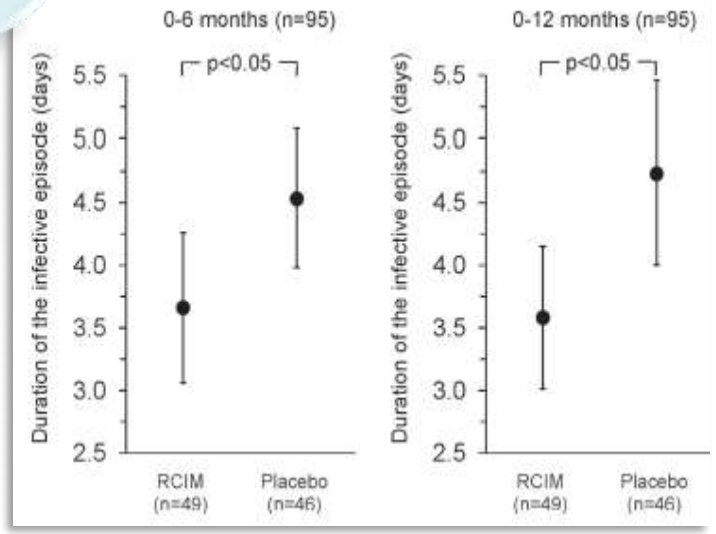
RCT multicenter study on **164 socialized children** (2-5 yrs) treated with **D53** o placebo for 6 months a additional 6 months

- Group A: ≤5 episodes A
- Group B: >5 episodes A

No difference in children with more than **5 RRIs** in the preceding year



Duration of the **infectious** significantly **shorter** with **D53**, either over 6 mo (3.7 vs 4.5 days, p=0.04) or 12 mo (3.6 vs 4.7 days: p=0.01) in **gr. A**



Proportion of pts reporting **no ARTI** significantly **higher** in the active group at 6 and 12 mo (20.4% vs 4.4%, p=0.02) in **gr. A**

POTENZIALI IMMUNOMODULANTI NELLE IRR

1. **Lisati ed estratti batterici**
2. **Probiotici – prebiotici**
3. **Molecole di sintesi** (pidotimod, etc)
4. **Vitamine ed oligoelementi** (vit D, vit A, ac folico, Zn, Cu, etc)
5. **Miscellanea** (resveratrolo, echinacea, curcuma, lattoferrina, oligonucleotidi CpG, omeopatia, agopuntura, fitoterapici, aglio, etc.)

Cardinale et al, RIAP (in press)

Probiotics for preventing acute upper respiratory tract infections (Review)

Hao et al,
Cochr Database Syst Rev 2011; Issue 9, Art. No.: CD006895

Probiotics for preventing acute upper respiratory tract infections (Review)

Hao et al,
Cochr Database Syst Rev 2011; Issue 9, Art. No.: CD006895

THE COCHRANE COLLABORATION®

How the intervention might work

1. Probiotics and the innate immune function.
   - Enhances phagocytic capacity of peripheral blood leucocytes (polymorphonuclear and monocytes).
   - Improves phagocytic activity.
   - Granulocytes show higher increases in phagocytic cell function compared with monocytes (Donnet 1999; Schiffrin 1995; Sheih 2001).

?
?

There are significant increases in the expression of receptors (CR1, CR3, FccRI and FcaR) (Pelto 1998) involved in phagocytosis (the cellular process of engulfing and ingesting solid particles, such as bacteria by the cell membrane), the phagocytic index, oxidative burst (also known as respiratory burst, is the rapid release of reactive oxygen species from some cells) (Donnet 1999), and microbicidal capacity in neutrophils (Arunachalam 2000). Natural killer (NK) cell (a type of cytotoxic cell that constitutes an important part of the innate immune system) activity is also markedly improved, and there are increases in the percentage of NK cells in the peripheral blood (Drakes 2004).

2. Probiotics and acquired immunity.
   - Significantly higher specific IgG, IgA and IgM immunoglobulins (Link 1994; Majamaa 1995).

3. Probiotics and local immunity.
   - Enhances gut barrier function and improves the local immune response (Perdigon 1995).
   - Increases the production of cytokines (for example, IL-1, IL-2, IL-6, IL-10, IL-12, IL-18, TNF-α, interferon-α) (Gill 1998; Meydani 2000).

Donnet, Journal of Dairy Science 1999

Schiffrin, Journal of Dairy Science 1995

Sheih, Journal of the American College of Nutrition 2001

Arunashalam, European Journal of Clinical Nutrition 2000

Link-Amster, *FEMS Immunol Med Microbiol. 2004*
↑ **IgA**

Majamaa, *J Pediatr Gastroenterol Nutr 1995*
↑ **IgA**

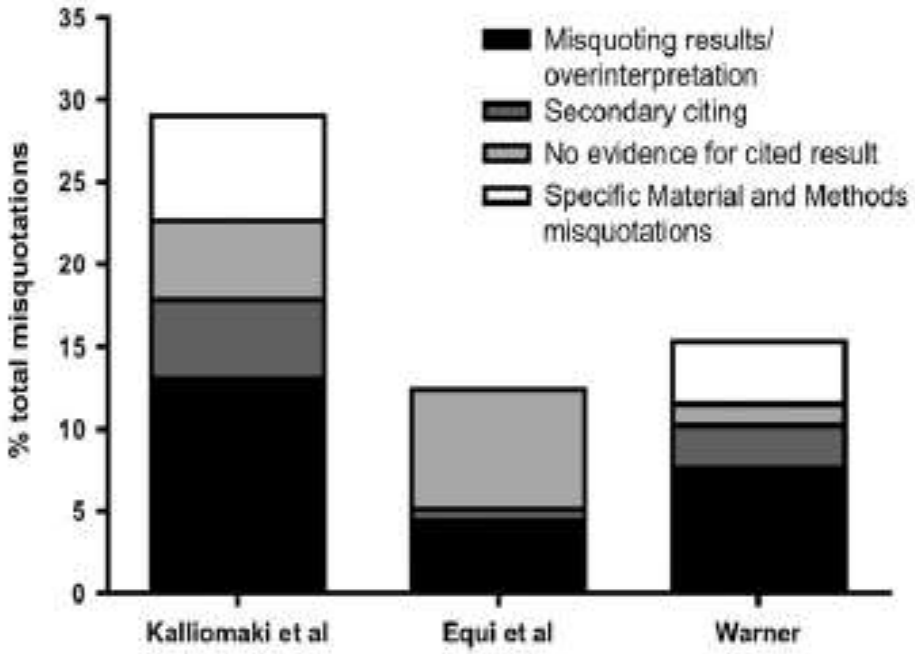
Quoting a landmark paper on the beneficial effects of probiotics

Hol & De Jongste, JACI 2009;124:1354 (letter)

"Misquoting" degli **effetti positivi** di alcuni lavori sui probiotici (*Kalliomaki, Lancet 2001;357:1076*) nel **34%** dei lavori sui **probiotici**

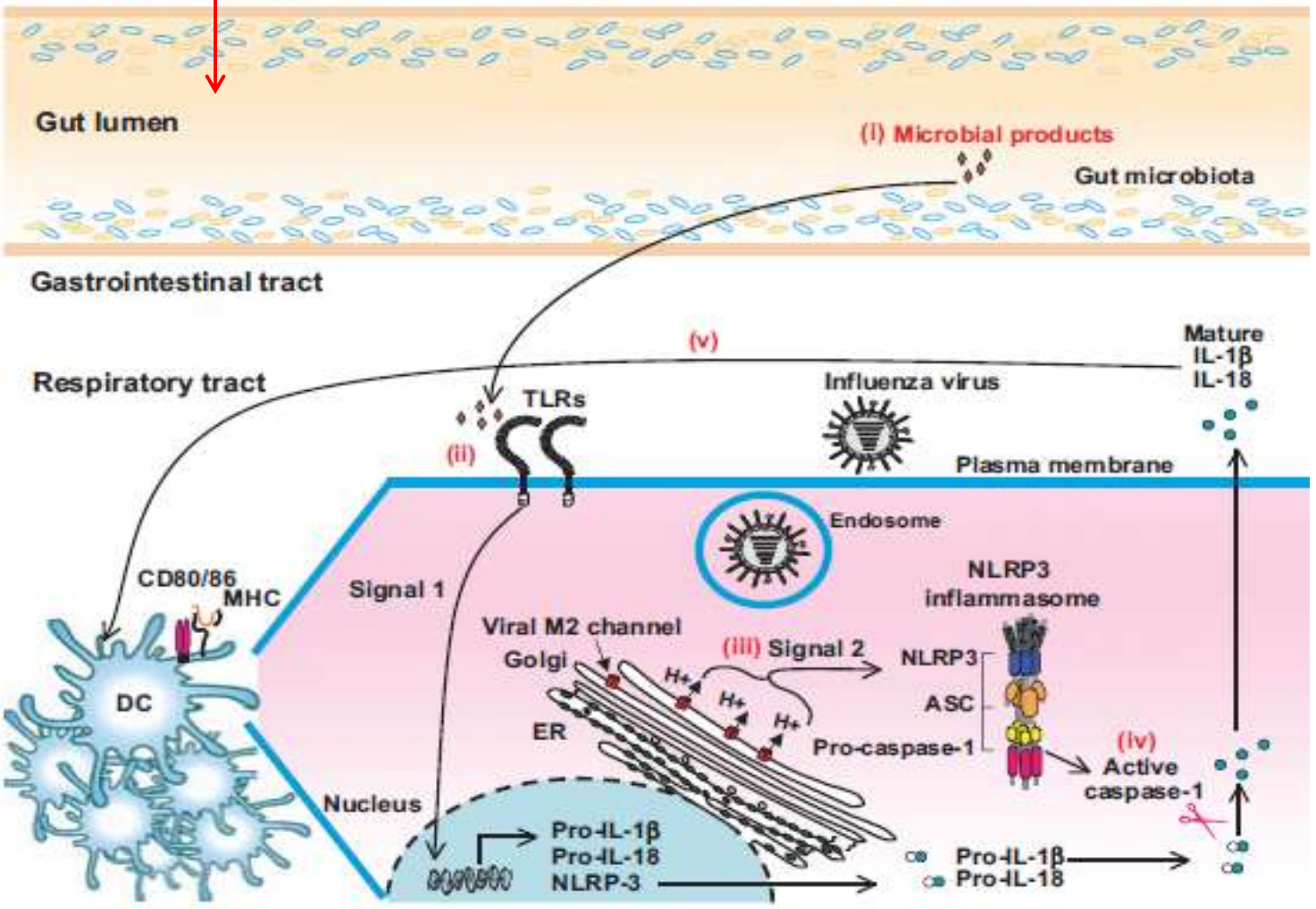
Nessuna differenza nel misquoting in rapporto all'Impact Factor della rivista

La frequenza di misquoting del lavoro sui probiotici è significativamente superiore rispetto ad altri lavori su topics differenti



Control of antiviral immunity by pattern recognition and the microbiome

Pang, Immunol Rev 2012;245:209



Probiotics for preventing acute upper respiratory tract infections (Review)

Hao et al,
Cochr Database Syst Rev 2011; Issue 9, Art. N[illegible]95

4 studi pediatrici

14 RCTs → estratti dati solo da **10 trials (3451 participanti)**

[…] probiotics were better than placebo when measuring the **number of participants** experiencing episodes of **acute URTI:**
- at least one episode: **OR 0.58** (95% CI: 0.36 to 0.92)
- at least three episodes: **OR 0.53** (95% CI 0.36 to 0.80)

rate ratio of episodes of **acute URTI:** RR 0.88 (95% CI 0.81 to 0.96)

reduced antibiotic prescription rates for **acute URTIs**: **OR 0.67** (95% CI 0.45 to 0.98)

[…] Probiotics and placebo were **similar** when measuring the mean duration of an episode of acute URTI

Probiotics for preventing acute upper respiratory tract infections (Review)

Hao et al,
Cochr Database Syst Rev 2011; Issue 9, Art. No.: CD006895

THE COCHRANE COLLABORATION®

Analysis 1.1. Comparison 1 ITT analysis: Probiotics versus placebo: primary outcome measures, Outcome 1 Number of participants who experienced URTI episodes.

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M,Random,95% CI	Weight	Odds Ratio M,Random,95% CI
1 Number of participants who experienced URTI episodes: at least 1 event					
Berggren 2010	76/159	91/159		20.7 %	0.68 [0.44, 1.06]
Hojsak 2010a	58/139	95/142		20.0 %	0.35 [0.22, 0.58]
Hojsak 2010b	8/376	20/366		14.2 %	0.38 [0.16, 0.87]
Kekkonen 2007	32/70	26/71		16.7 %	1.46 [0.74, 2.86]
Rautava 2009	7/38	20/43		11.7 %	0.26 [0.09, 0.72]
Sanz 2006	21/158	18/115		16.6 %	0.83 [0.42, 1.63]
Subtotal (95% CI)	**940**	**896**		**100.0 %**	**0.58 [0.36, 0.92]**
Total events: 202 (Experimental), 270 (Control)					
Heterogeneity: $Tau^2 = 0.23$; $Chi^2 = 16.15$, df = 5 (P = 0.01); $I^2 = 69\%$					
Test for overall effect: Z = 2.28 (P = 0.022)					
2 Number of participants who experienced URTI episodes: at least 3 events					
Berggren 2010	10/159	20/159		25.7 %	0.47 [0.21, 1.03]
Rautava 2009	4/38	10/43		10.3 %	0.39 [0.11, 1.36]
Sanz 2006	61/142	61/109		64.0 %	0.59 [0.36, 0.98]
Subtotal (95% CI)	**339**	**311**		**100.0 %**	**0.53 [0.36, 0.80]**
Total events: 75 (Experimental), 91 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.52$, df = 2 (P = 0.77); $I^2 = 0.0\%$					
Test for overall effect: Z = 3.06 (P = 0.0022)					

0.02 0.1 1 10 50

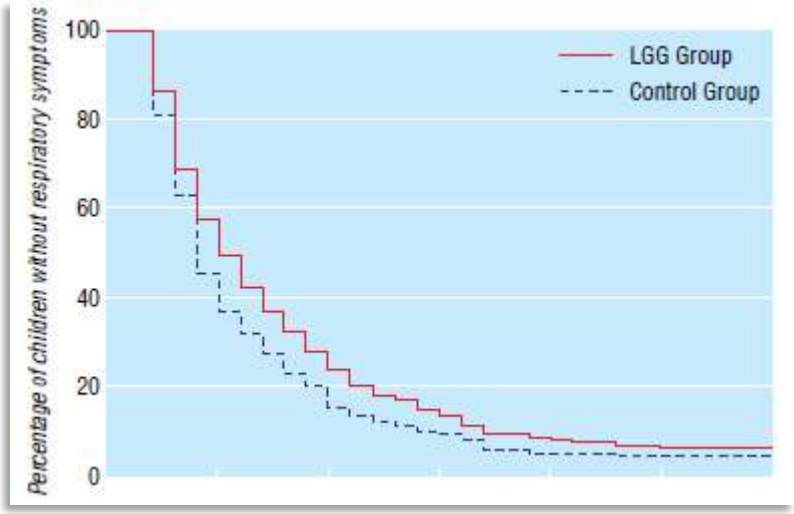
Favours experimental Favours control

GLI ESCLUSI

Effect of long term consumption of probiotic milk on infections in children attending day care centres: double blind, randomised trial

Hatakka, BMJ 2001;322:1

RCT multicenter study on **571** healthy children 1-6 years attending day cares over 7 month randomized to receive **cow's milk** enriched with **LGG** or **placebo**



↓ days of **absence from day care** because of illness (**4.9** vs **5.8** days)

Reduction of **17%** in the number of children suffering from **respiratory infections** with complications and **LRTI** and a **19%** reduction in **antibiotic treatments** for RTI

	Lactobacillus GG (n=252)	Control (n=261)	Unadjusted comparison: Absolute % reduction (95% CI)	Unadjusted comparison: P value*	Age adjusted comparison: Odds ratio (95% CI)	Age adjusted comparison: P value†
Acute otitis media	79 (31)	101 (39)	−7.3 (−15.6 to 0.01)	0.08	0.78 (0.53 to 1.14)	0.19
Sinusitis	8 (3)	10 (4)	−0.6 (−3.8 to 2.5)	0.69	0.86 (0.33 to 2.22)	0.75
Acute bronchitis	14 (6)	19 (7)	−1.7 (−6.0 to 2.5)	0.43	0.80 (0.39 to 1.64)	0.54
Pneumonia	3 (1)	4 (2)	−0.3 (−2.4 to 1.7)	1.00	0.83 (0.18 to 3.78)	0.81
All infections together	97 (39)	123 (47)	−8.6 (−17.2 to −0.1)	0.05	0.75 (0.52 to 1.09)	0.13
Antibiotic treatments for respiratory infections	111 (44)	140 (54)	−9.6 (−18.2 to −1.0)	0.03	0.72 (0.50 to 1.03)	0.08
All antibiotic treatments	119 (47)	144 (55)	−8.0 (−16.6 to 1.0)	0.07	0.78 (0.54 to 1.11)	0.17

GLI ESCLUSI

Prebiotic and Probiotic Fortified Milk in Prevention of Morbidities among Children: Community-Based, Randomized, Double-Blind, Controlled Trial

PLoS one

Sazawal, PLoS One 2010;5:e12164

RCT study in **India** on **624 children** (1–3 yrs) randomized to receive milk fortified with **Bifidobacterium Lactis + oligosaccharides** or **control milk** for 1 yr

Table 3. Effect of prebiotic oligosaccharide and probiotic *Bifidobacterium lactis HN019* fortified milk on common childhood morbidities.

	PP group (n = 312)		Co group (n = 312)		Odds Ratio (95% CI)	p value
	Actual numbers	Episodes per child year	Actual numbers	Episodes per child year		
Gastrointestinal morbidity						
Diarrhea episodes (1–4 y)	1641[a]	6.21[b]	1697[a]	6.61[b]	0.94 (0.88–1.01)	0.08
≤24 mo	603	2.3	563	2.2	0.99 (0.89–1.11)	0.91
>24 mo	1038	3.92	1134	4.41	0.90 (0.83–0.98)	0.02
Dysentery episodes	125	0.47	154	0.6	0.79 (0.62–1.00)	0.05
Respiratory morbidity						
Pneumonia episodes[c]	90	0.34	115	0.45	0.76 (0.58–1.00)	0.05
Severe ALRI episodes[d]	34	0.13	51	0.20	0.65 (0.42–1.00)	0.05
Febrile illness and others						
Days with severe illness (1–4 y)	473	1.8	550	2.14	0.84 (0.74–0.95)	0.004
≤24 mo	153	0.58	177	0.69	0.80 (0.65–0.99)	0.05
>24 mo	320	1.21	373	1.5	0.85 (0.73–0.98)	0.03
Days with ear discharge	1550	5.87	1613	6.3	0.93 (0.87–1.00)	0.06
Days with high fever	2798	10.6	2865	11.2	0.95 (0.90–1.00)	0.05
Measles	5	0.02	10	0.04	0.49 (0.17–1.42)	0.19
Doses of antibiotics consumed	7402	28.02	7625	29.7	0.94 (0.91–0.97)	<0.001

No effect of prebiotic + probiotic on diarrhea

Incidence of **pneumonia** was reduced by **24%** (95% CI: 0 to 42%; p = 0.05) and **severe acute lower respiratory** infection (ALRI) by **35%**(95% CI: 0 to 58%; p = 0.05).

GLI ESCLUSI

Probiotic Effects on Cold and Influenza-Like Symptom Incidence and Duration in Children

Leyer, Pediatrics 2009;124:e172

RCT study on **326 children** (3–5 yrs)
assigned randomly to receive placebo or
Lactobacillus acidophilus (ss), or ***L. acidophilus + Bifidobacterium animalis (ds)***
for 6 months

Single and combination probiotics reduced **fever incidence** by **53-72%**, **coughing incidence** by **41-62%** and **rhinorrhea incidence** by **28-58%**

TABLE 5 Symptom Duration According to Study Group During 6-Month Follow-up Period

	Symptom Duration		
	Placebo	*Lactobacillus acidophilus*	*L acidophilus/ Bifidobacterium lactis*
N	104	110	112
Mean ± SD, d	6.5 ± 7.3	4.5 ± 4.7	3.4 ± 3.7
Reduction vs placebo, %	NA	31.8	47.7
25th percentile, d	1	1	1
50th percentile, d	4	3	2
75th percentile, d	10	6	5

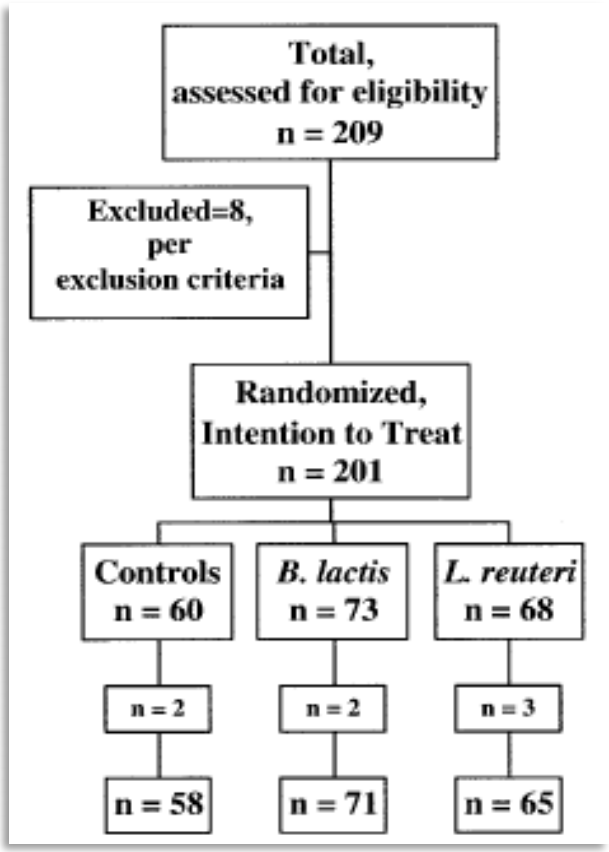
Fever, coughing, and rhinorrhea **duration** was decreased significantly, relative to placebo, by **32% (ss)** and **48% (ds)**

GLI ESCLUSI

Effect of a Probiotic Infant Formula on Infections in Child Care Centers: Comparison of Two Probiotic Agents

Weizman, Pediatrics 2005;115:5

RCT multicenter study (14 child care centers) on **201** healthy infants 4 to 10 mo old randomized to receive milk fortified **B. lactis**, **L. Reuteri** or **placebo**
Duration (including follow-up): 12 weeks



More febrile and **diarrhea** episodes in the control group

No difference in rate and duration of **respiratory illnesses**

POTENZIALI IMMUNOMODULANTI NELLE IRR

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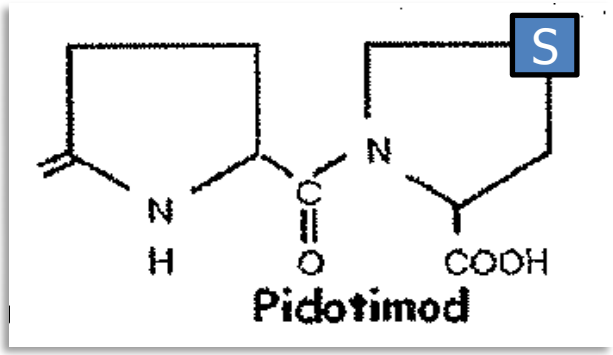
5. **Miscellanea** (resveratrolo, echinacea, curcuma, lattoferrina, oligonucleotidi CpG, omeopatia, agopuntura, fitoterapici, aglio, etc.)

Cardinale et al, RIAP (in press)

Pidotimod

Attività biologiche nell'uomo



Aumento della fagocitosi di PMN in vitro ed ex vivo

Capsoni, J Chemother 1991;3:147

Aumento del killing di macrofagi alveolari umani verso lo S. Aureo

Oddera, Drugs Exp Clin Res 1993;XIX:27

Aumento dell'attività citotossica NK di PBMC di donatori sani

Illeni, J Chemother 1991;3:157

Aumento della produzione di IFNα e IFNγ di donatori sani in risposta a vari stimoli (Poly I-C, virus Newcastle, PHA, tossoide tetanico)

Pugliese, Int J Immunother 1995;11:71

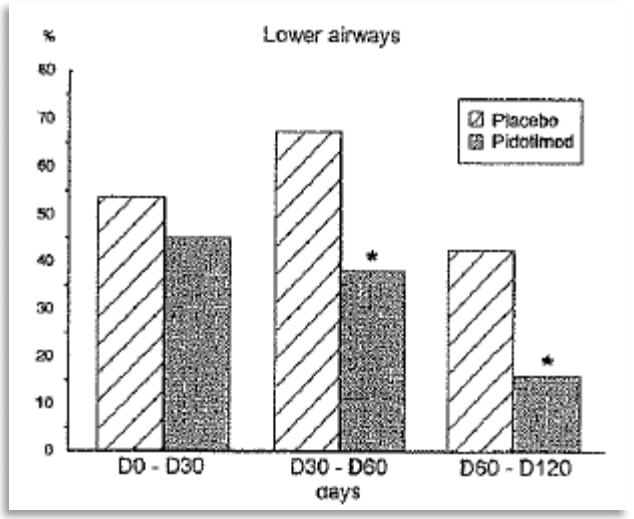
Upregolazione di geni dell'immunità innata e adattativa in bambini Down

Zuccotti, J Biol Regul Homeost Ag 2013;27:75

Immunoactivation by Pidotimod in Children with Recurrent Respiratory Infections

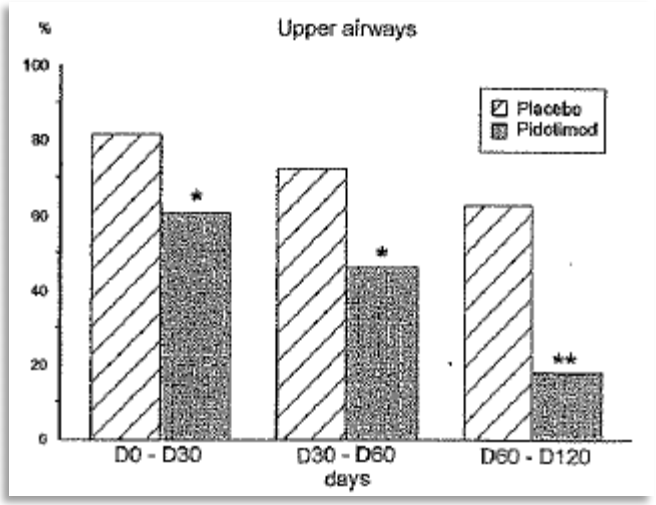
Burgio, Arzneim.-Forsch./Drug Res 1994; 44: 1525

101 bambini (2-13 anni) con storia di IRR
Randomizzati per **Pidotimod** (400 mg/die)
o placebo per 60 giorni
Follow-up altri 2 mesi



Significativa riduzione nel numero di pazienti con **infezioni respiratorie alte** (a 30, 60, 120 gg) e **basse** (a 60 e 120 gg) nel gruppo Pidotimod vs placebo

Riduzione nel numero di pazienti con **febbre** a 60 gg nel gruppo attivo

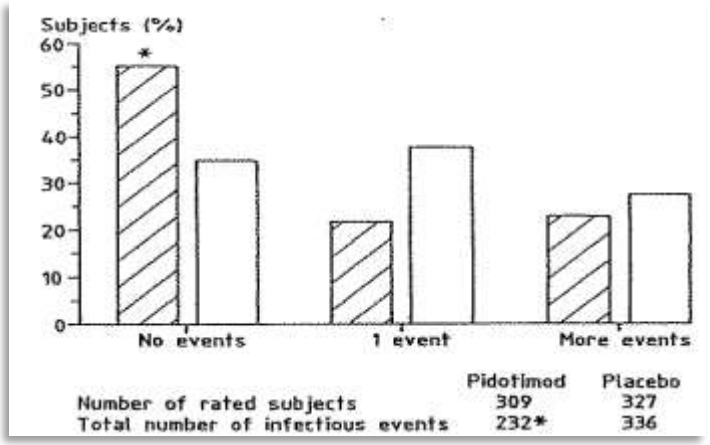


Role of Immunoactivation with Pidotimod in Children With Recurrent Respiratory Infections

Careddu, Arzneim.-Forsch./Drug Res 1994; 44: 506

748 bb (3-14 aa) con IRR arruolati in 69 centri italiani, randomizzati per **Pidotimod** (400 mg/die) vs **placebo** per 2 mesi

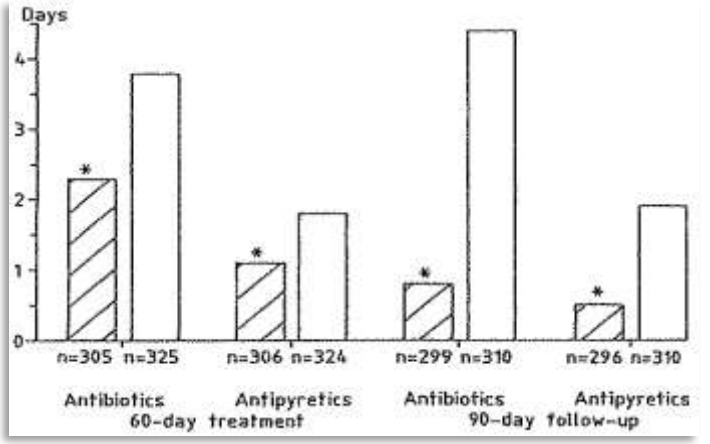
Follow-up altri 3 mesi



Durante il periodo di trattamento:

Minor **numero di IR** (M 1.8 vs 2.8) nel gruppo attivo

Minor **consumo di farmaci** e riduzione **giorni di assenza da scuola**



Effetto persistente alla sospensione (71% dei bb vs 41% liberi da IR)

POTENZIALI IMMUNOMODULANTI NELLE IRR

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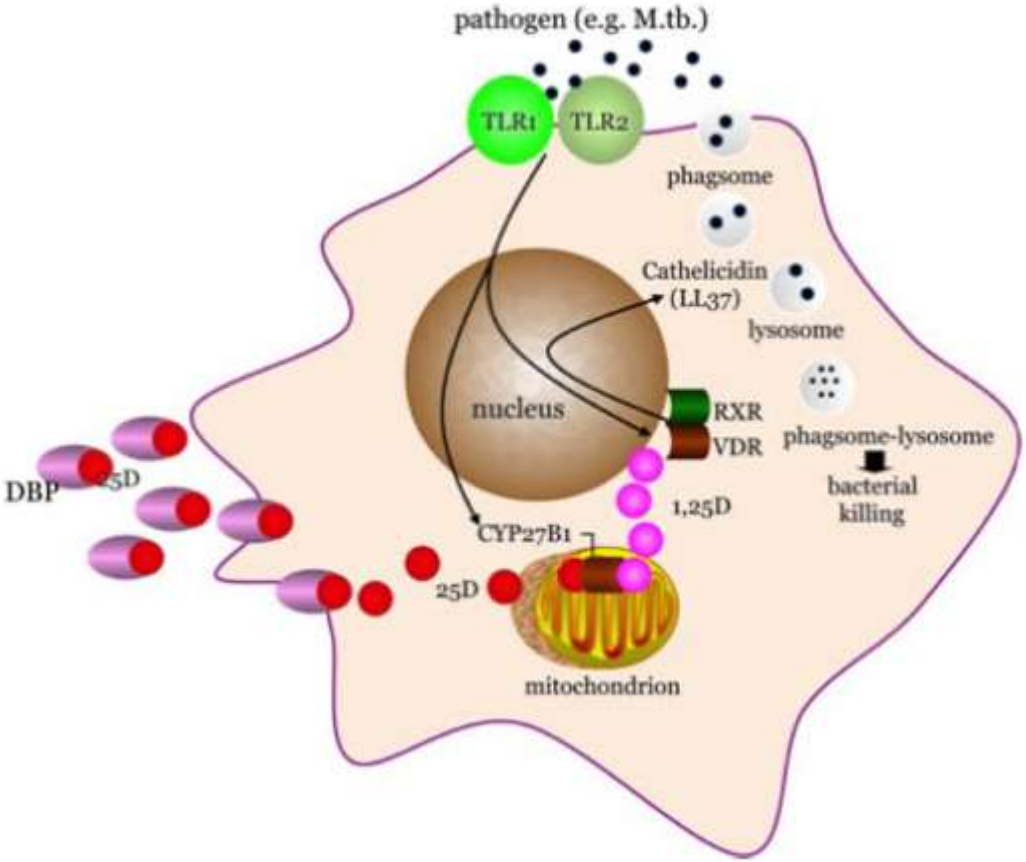
5. **Miscellanea** (resveratrolo, echinacea, curcuma, lattoferrina, oligonucleotidi CpG, omeopatia, agopuntura, fitoterapici, aglio, etc.)

Cardinale et al, RIAP (in press)

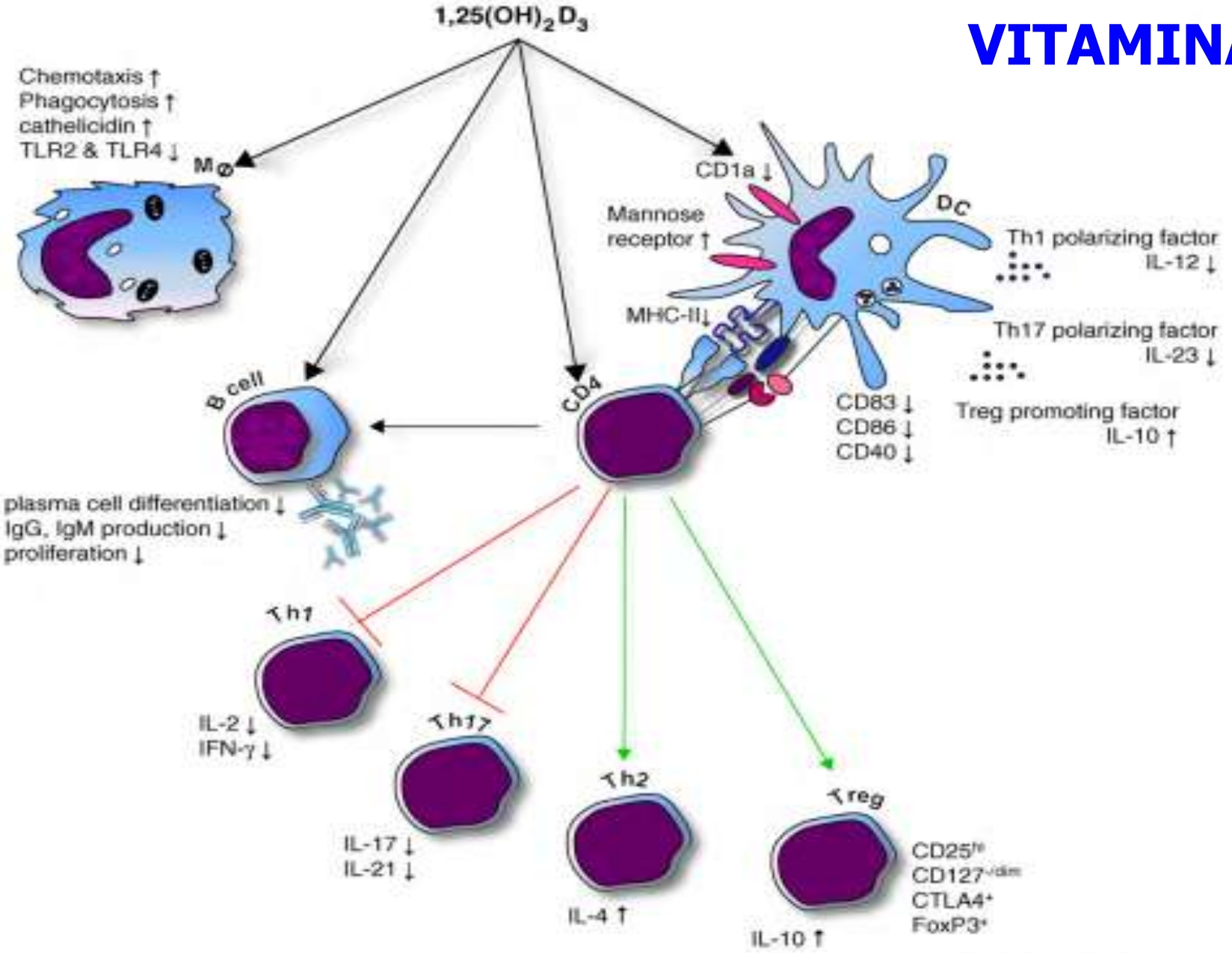
Vitamina D e catelicidine



[…] It is thought that 1,25(OH)2D maintains cellular health by acting as a sentinel… *Holick, J Clin Invest 2006;116:2062*

Wang, J Immunol 2004;173:2909
Adams, J Clin Endocrinol Metab 2010;95:471

VITAMINA D



Baeke, Curr Opin Pharmacol 2010;10:482

Randomized trial of vitamin D supplementation to prevent seasonal influenza A in schoolchildren[1–3]

Urashima, Am J Clin Nutr 2010;91:1255

Randomized, double-blind, placebo-controlled trial comparing **vit D3** supplements (1200 IU/d, 4 mo) with placebo in **167** schoolchildren.

Primary outcome: incidence of **influenza A**

TABLE 2
Influenza A as a primary outcome, subgroup

			alue	*P* value[1]
Influenza A			4	
Additional vitamin D[2]				0.04
None			6	
At least once per week[3]				
Starting age of nursery school				0.04
<3 y			0.71	
≥3 y			0.005	

no significant difference was observed for influenza B

Influenza A in 18 of 167 **(10.8%)** child. in vit D3 group vs 31 of 167 **(18.6%)** children in the placebo group [**RR= 0.58**; p=0.04]

Asthma attacks (secondary outcome) in 2 children receiving vit D3 compared with 12 children receiving placebo [**RR: 0.17**;p =0.006]

Vitamin D Supplementation for the Prevention of Acute Respiratory Tract Infection: A Randomized, Double-Blinded Trial among Young Finnish Men

Laaksi, J Infect Dis 2010;202:809

164 young adults **conscripts** randomized to receive for 6 months **Vit D 400 U** or placebo during **winter**

Higher proportion of men remaining **healthy** (**51.3%** vs **35.7%**, *P=.045*) throughout the 6-mo study period in the **vit D** group

Table 2. Study Events

Variable	All subjects (n = 164)	Vitamin D supplementation group (n = 80)	Placebo group (n = 84)	P
Days absent from duty, mean days (±SD)				
Overall	2.6 ± 3.6	2.2 ± 3.2	3.0 ± 4.0	.096
1–6 Weeks	1.1 ± 2.4	0.7 ± 2.1	1.4 ± 2.6	.060
7–14 Weeks	0.7 ± 1.8	0.7 ± 1.4	0.8 ± 2.1	.903
15–20 Weeks	0.5 ± 1.0	0.4 ± 1.0	0.5 ± 1.1	.120
21–24 Weeks	0.4 ± 1.5	0.4 ± 1.8	0.3 ± 1.1	.311
No days absent from duty[a]				
Overall	71 (43.3)	41 (51.3)	30 (35.7)	.045
1–6 Weeks	121 (73.8)	64 (80.0)	57 (67.9)	.077
7–14 Weeks	121 (76.1)	61 (77.2)	60 (75.0)	.845
15–20 Weeks	106 (75.7)	58 (82.9)	50 (69.4)	.077
21–24 Weeks	84 (80.7)	47 (79.7)	37 (82.2)	.284
Self-reported symptoms				
Cough	100 (61.0)	52 (65.0)	48 (57.1)	.303
Runny nose	122 (74.4)	59 (73.8)	63 (75.0)	.855
Sore throat	76 (46.3)	38 (47.5)	38 (45.2)	.772
Fever	57 (34.8)	25 (31.3)	32 (38.1)	.357
Common cold symptoms	89 (54.3)	45 (56.3)	44 (52.4)	.619
Hospitalization due to respiratory tract infection	9 (5.5)	3 (3.8)	6 (7.1)	.396
Length of hospital stay, mean days (±SD)	0.2 ± 1.1	0.2 ± 0.8	0.3 ± 1.3	.338

After adjustments for smoking and influenza vaccination, the adjusted hazard ratio (HR=0.71) for **absence from duty** due to respiratory tract infection was lower in the intervention group **(NNT=6.4)**

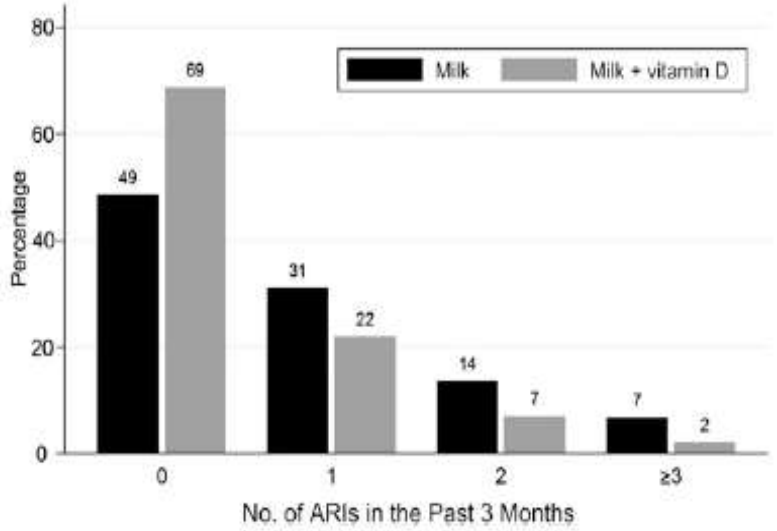
PEDIATRICS

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Randomized Trial of Vitamin D Supplementation and Risk of Acute Respiratory Infection in Mongolia

Camargo, Pediatrics 2012, Aug 20 [Epub]

RCT study on **247** Mongolian children with vitamin D deficiency in winter randomly assigned to ingestion of unfortified milk (n=104) or milk fortified with **300 IU** of vitamin D3 (n=143) from **Jan-Mar**



At baseline, the median serum 25(OH)D level was 7 ng/mL

Children receiving **vit D** reported significantly **fewer ARIs** during the study period **(M 0.80 vs 0.45**; P =.047; **RR 0.52)**

Vitamin A for preventing acute lower respiratory tract infections in children up to seven years of age (Review)

Chen,
Cochr Datab Syst Rev 2008, Issue 1. Art. No.: CD006090

THE COCHRANE COLLABORATION®

Dieci studi con 33,179 partecipanti ritenuti elegibili

[…] **Eight studies** found no significant effect of vitamin A on the incidence of acute LRTI, or prevalence of symptoms of acute LRTI.

[…] Vitamin A caused an increased incidence of acute LRTI in one study

[…] Vitamin A should not be given to all children to prevent acute LRTIs.

VITAMIN C FOR PREVENTING AND TREATING THE COMMON COLD

Douglas et al,
Cochr Datab Syst Rev 2004, Issue 4, Art. No.: CD000980

THE COCHRANE COLLABORATION®

29 studi con 11,306 partecipanti ritenuti elegibili

[…] In the general community trials, involving 10,708 participants, the pooled **RR was 0.97** with **vit C prophylaxis**

[…] **Five trials** involving a total of 598 marathon runners, skiers and soldiers on subarctic exercises yielded a **pooled RR of 0.48** (95% CI 0.35 to 0.64).

[…] The **severity of colds** was significantly **reduced** in the prophylaxis trials.

Seven trial comparisons examined the effect of **therapeutic vit C.** **No** consistent **differences** from the placebo group were seen in the **duration** or **severity** of colds.

The effect of vitamin C on upper respiratory infections in adolescent swimmers: a randomized trial

Constantini, Eur J Ped 2011;170:59

RCT study during three winter months, among **39** competitive young swimmers (mean age 13.8±1.6 years) randomized to receive **vit C (0.5 gr x 2)** or **placebo**

Table 3 The duration and severity of upper respiratory infections by treatment group

	Placebo	Vitamin C	Difference (95% CI)	Test of interaction[b] *P*
Number of URI episodes[a]	43	55		
Duration of URI episodes (days) (mean±SD)	8.9±7.8	6.9±5.4	−2.0 (−4.6, +0.7)	
Males (21+30 episodes)	10.4±7.1	5.5±5.0	−4.9 (−8.4,−1.5)	0.003
Females (22+25 episodes)	7.4±8.2	8.6±5.5	+1.2 (−2.8, +5.3)	
Severity of URI episodes (Mean±SD)	59±87	43±45	−16 (−43, +11)	
Males (21+30 episodes)	66±85	26±30	−40 (−75,−6)	0.003
Females (22+25 episodes)	52±89	64±51	+12 (−30, +54)	

No effect on the **incidence of URIs**

Significant **reduction** in the **duration** (-47%) and **severity** of infections only in **males**

POTENZIALI IMMUNOMODULANTI NELLE IRR

1. **Lisati ed estratti batterici**
2. **Probiotici – prebiotici**
3. **Molecole di sintesi** (pidotimod, etc)
4. **Vitamine ed oligoelementi** (vit D, vit A, ac folico, Zn, Cu, etc)
5. **Miscellanea** (resveratrolo, echinacea, curcuma, lattoferrina, oligonucleotidi CpG, omeopatia, agopuntura, fitoterapici, aglio, etc.):

Cardinale et al, RIAP (in press)

Efficacy and Safety of Echinacea in Treating Upper Respiratory Tract Infections in Children

A Randomized Controlled Trial

Taylor, JAMA 2003;290:2824

RCT study on healthy **children 2 to 11** years old randomized to receive **echinacea** or **placebo** for up to **3 URIs** over a 4-month period.

Study medication was begun at the onset of symptoms and continued throughout the URI, for a maximum of **10 days.**

Table 2. Comparison of Treatment Outcomes in Upper Respiratory Tract Infections (URIs) Treated With Echinacea and Placebo

Outcome	Echinacea Group (n = 337 URIs)	Placebo Group (n = 370 URIs)	*P* Value
Duration of symptoms, median (95% CI), d	9 (8-10)	9 (8-10)	.89
Severity of symptoms, median (95% CI)*	33 (29-40)	33 (30-38)	.69
Days of fever, mean (SD)	0.81 (1.50)	0.64 (1.16)	.09
Peak severity of symptoms, mean (SD)†	6.0 (2.3)	6.1 (2.4)	.68
No. of days of peak severity, mean (SD)	1.60 (.98)	1.64 (1.14)	.97
Parental assessment of severity, No. (%)‡			
Mild	153 (46.5)	170 (46.3)	.67
Moderate	128 (38.9)	157 (42.8)	
Severe	48 (14.6)	40 (10.9)	

No difference in **duration** between **URIs** treated with echinacea or placebo (*P=.89).*

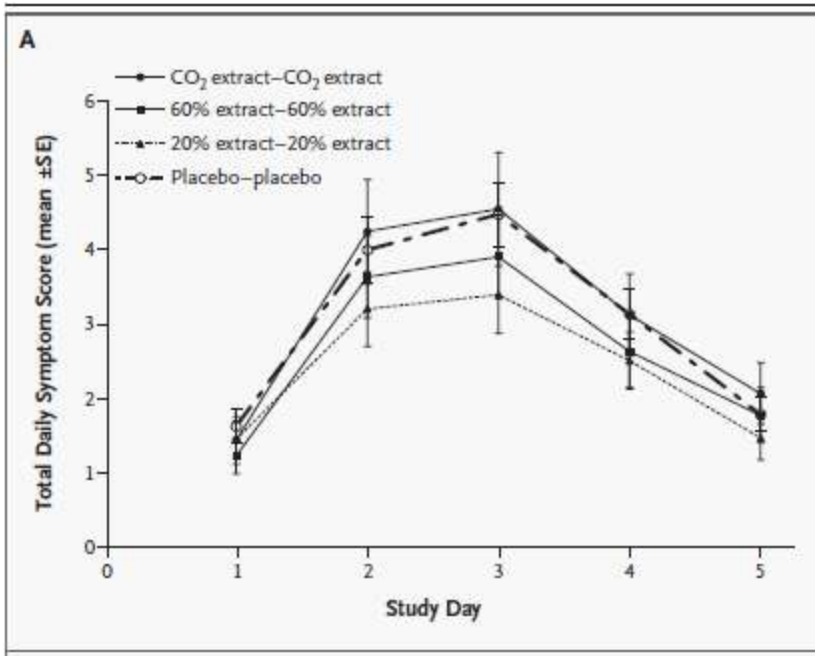
Rash occurred during 7.1% of the URIs treated with echinacea and 2.7% of those treated with placebo (*P=.008)*

The NEW ENGLAND JOURNAL of MEDICINE

An Evaluation of *Echinacea angustifolia* in Experimental Rhinovirus Infections

Turner, NEJM 2005;353;341

437 adult volunteers randomly assigned to receive either prophylaxis (beginning 7 days before the virus challenge) or treatment (beginning at the time of the challenge) with 3 preparations of **echinacea** or **placebo**

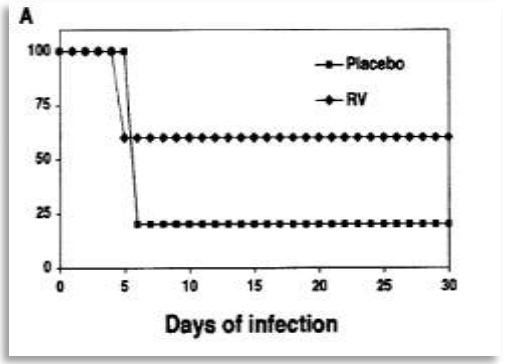


No statistically significant effects of the three **echinacea** extracts on rates of infection or severity of symptoms

Inhibition of Influenza A Virus Replication by Resveratrol

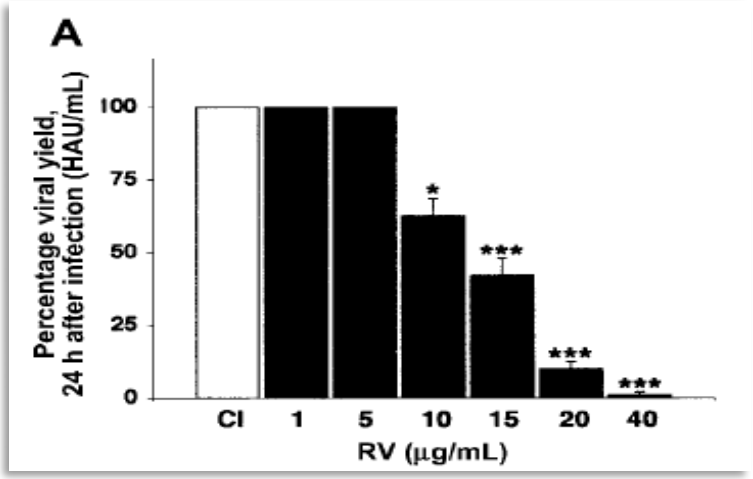
Palamara, J Infect Dis 2005:191;1719

Resveratrol (RV; 3,5,4-trihydroxy-trans-stilbene), a polyphenol that is synthesized by plants in response to physiological stimuli and environmental stress inhibits the **replication** of **influenza** virus in MDCK (*Madin-Darby canine kidney*) cells



This activity was <u>not directly related to glutathione-mediated antioxidant activity</u>

RV also significantly improved **survival** and decreased pulmonary **viral titers** in influenza **virus–infected mice**.



IMMUNE MODULATION BY LACTOFERRIN AND CURCUMIN IN CHILDREN WITH RECURRENT RESPIRATORY INFECTIONS

Zuccotti, J Biol Reg Homeost Agents 2009;23:113

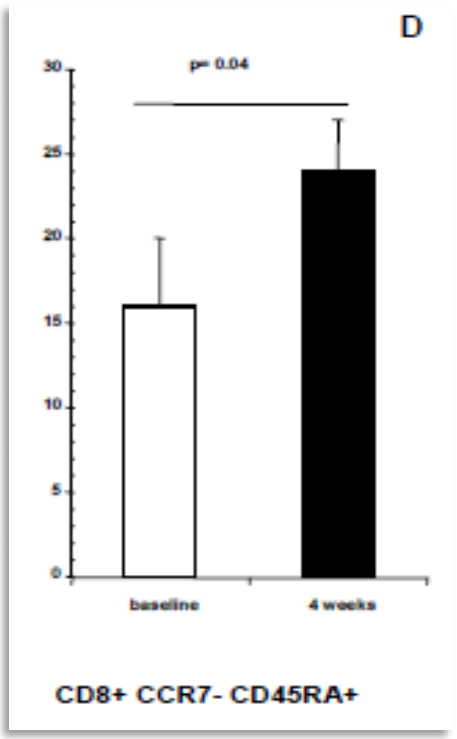
10 bb con IRR

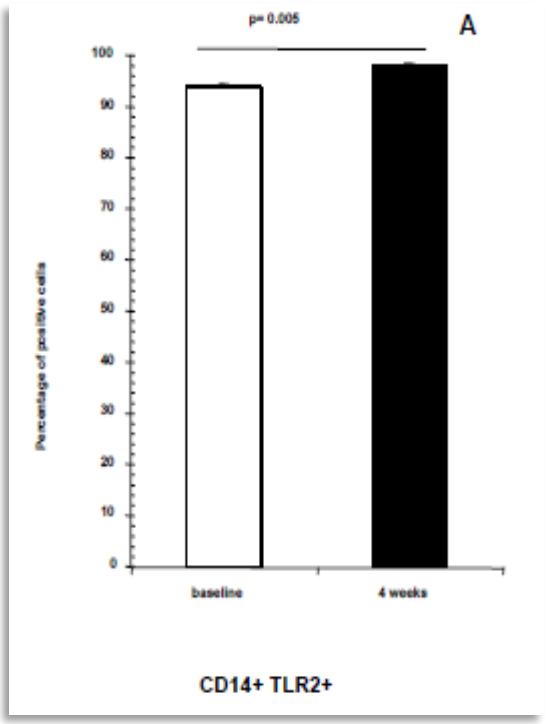
Sottoposti a trattamento con Lattoferrina + Curcuma (900 mg+100 mg) per 4 settimane

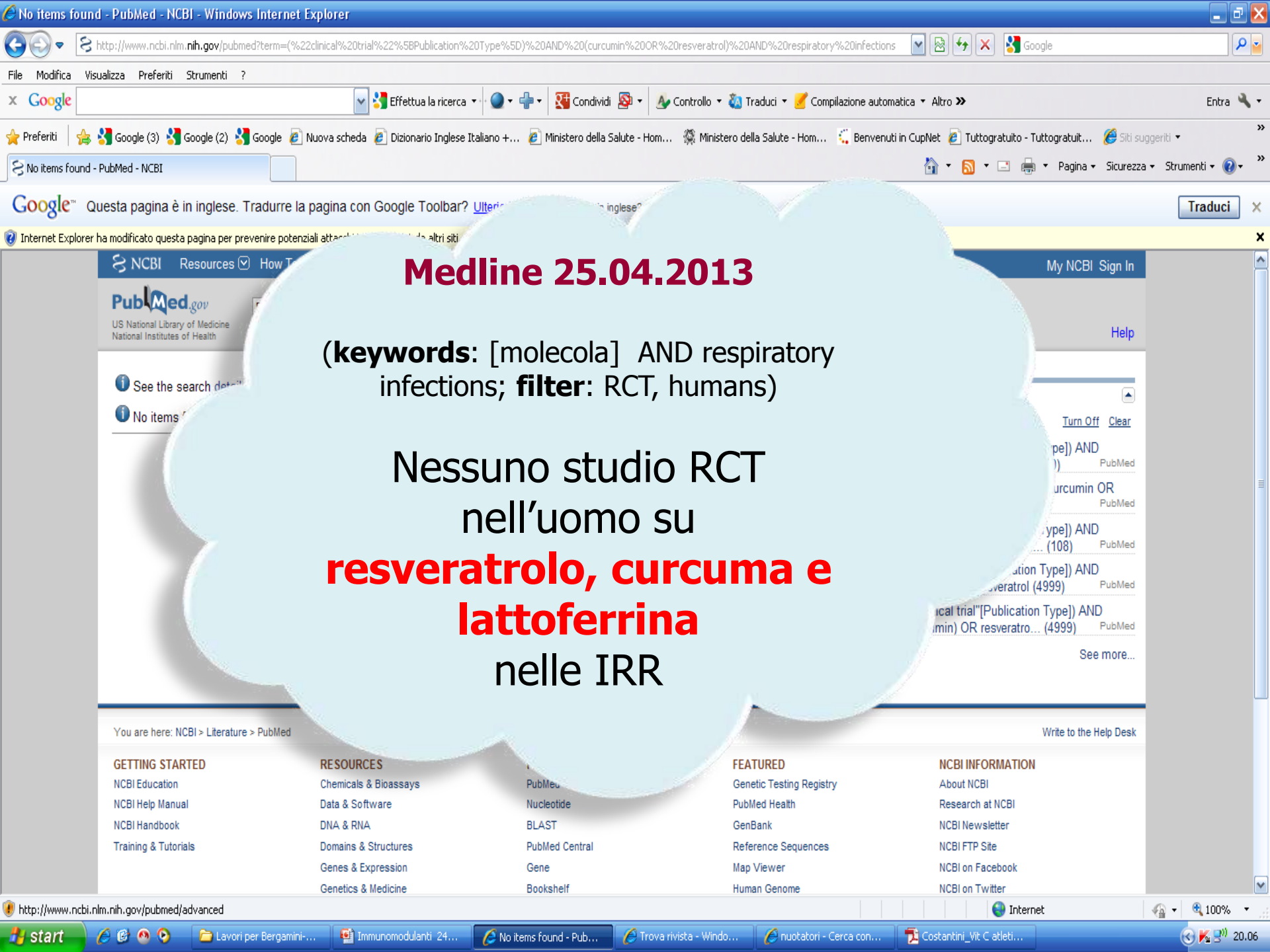
↑ **T cells CD8+ mature** effettrici e riduzione T memory

↑ monociti **CD14+TLR2+**

↓ produzione **IL-10**






No items found - PubMed - NCBI - Windows Internet Explorer
Medline 25.04.2013
(**keywords**: [molecola] AND respiratory infections; **filter**: RCT, humans)
Nessuno studio RCT nell'uomo su
resveratrolo, curcuma e lattoferrina
nelle IRR

I misteri degli immunomodulanti…

...Perché tanti lavori hanno avuto bisogno di un funding da parte delle aziende e come quantificare il peso dell'autorship delle stesse nella valutazione dei risultati?

Reference	Molecola impiegata	Presenza tra gli autori di soggetti appartenenti alla ditta sponsor	Partecipazione dell'azienda alla organizzazione dello studio
Jara-Perez, Clin Ther 2000;22:748	OM85	Si	Si (BASF Pharma)
Gutiérrez-Tarango, Chest 2001;119;1742	OM85	Si	Si (BASF Pharma)
Schaad, Chest 2002; 122:2042	OM85	Si	Si (OM Pharma)
Fiocchi, Allergy Asthma Proc 2012;33:197	D53	Si	Si (Pierre-Fabre)
Hatakka, BMJ 2001;322:1	LGG	SI	Si (Valio)
Leyer, Pediatrics 2009;124;e172	L. Acidoph. $\pm$ Bifidobact.	SI	Si (Danisco)
Sazawal, PloS One 2010;5:e12164	Bifidobacterium Lactis + prebiot	No	Si (Fronterra)

La ricerca in Italia sul Pidotimod nel 1994… e poi?

Burgio GR et al.	Immunoactivation by pidotimod in children with recurrente respiratory infections	Arzneim.-Forsch./Drug Res 1994; 44 (II): 1525-1529
Caramia G et al.	Efficacia e tollerabilità del pidotimod nella terapia delle infezioni respiratory ricorrenti in pediatria	Arzneim.-Forsch./Drug Res 1994; 44 (II):1480-1484
Careddu P	Role of immunoactivation with Politimod in Recurrent Respiratory Infections in childhood	Arzneim.-Forsch./Drug Res 1994; 44 (II): 1506-1511
Careddu P et al.	Pidotimod in the treatment of Recurrent Respiratory Infection in paediatric patients	Arzneim.-Forsch./Drug Res 1994; 44 (II): 1485-1489
Passali D et al.	Pidotimod in management of recurrent pharyngotonsillar infection in childhood	Arzneim Forsch Drug Res 1994; 44 II;N°12: 1511-1516
Clemente E et al	Therapeutic efficacy and safety of pidotimod in the treatment of Urinary Tract Infection in children	Arzneim.-Forsch./Drug Res 1994; 44 (II): 1490-1484
Pozzi E et al.	Pidotimod in the treatment in Patients affected by bacterial exacerbations of chronic bronchitis	Arzneim.-Forsch./Drug Res 1994; 44 (II): 1495-1498
Coppi G et al.	Protective effects of pidotimod against experimental bacterial infections in mice	Arzneim Forsch Drug Res 1994; 44 II;N°12: 1411-1416
Motta G et al.	Innuoactivity of pidotimod agains episodes of recurrent tonsillitis in childhood	Arzneim Forsch Drug Res 1994; 44 II;N°12: 1521-1524
Ciaccia A et al	Pidotimod activity against chronic bronchitis exacerbations	Arzneim.-Forsch./Drug Res 1994; 44 (II): 1516-1520

….Perché i lavori indipendenti sui probiotici sono proprio quelli che non hanno dimostrato effetti positivi sulle IRR ?

Effect of a Probiotic Infant Formula on Infections in Child Care Centers: Comparison of Two Probiotic Agents

Weizman, Pediatrics 2005;115:5

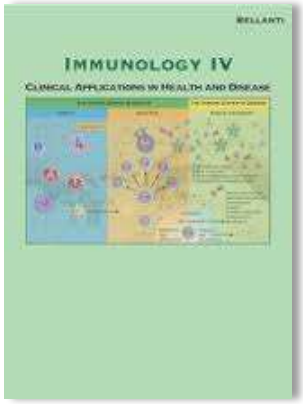
No difference in rate and duration of **respiratory illnesses** in children receiving milk fortified with **probiotics**

...perché lo stesso autore adotta due pesi e due misure?

Bacterial vaccines and the innate immune system: A journey of rediscovery for the allergist-immunologist and care providers

Bellanti, Allergy Asthma Proc 2009;30:S3

The results of studies described in this supplement suggest that this ribosomal product vaccine is effective in preventing upper and lower RRTIs in children and adults as demonstrated by a decrease in the number, duration, and severity of infectious episodes and reduction in antibacterial use and the likelihood of consequent development of bacterial resistance. The use of



Bellanti, "IMMUNOLOGY", IV ed., 2011, pag. 391-422

Sugli immunomodulanti: nulla !

"Take-home messages"

- ✓ Ancora oggi non esiste una definizione condivisa di IS
- ✓ Necessario separare gli effetti in vitro dalle dimostrazioni di efficacia in vivo
- ✓ Prodotti simili possono comportare effetti biologici diversi in rapporto alla malattia, alla sua fase di attività, al tipo di molecola, ai dosaggi impiegati e altri fattori ancora poco conosciuti
- ✓ La categoria degli IS è molto eterogenea e alcuni prodotti presentano evidenze di efficacia di grado ridotto o nullo
- ✓ Ancora oggi il livello di qualità di molti lavori (e perfino RS) è scadente
- ✓ La attendibilità dei risultati della maggior parte dei lavori è incrinata dalla sponsorship e dalla partecipazione diretta dell'azienda allo studio
- ✓Sono fortemente auspicabili studi indipendenti e di buona qualità sugli immunomodulanti