Infezioni respiratorie ricorrenti… Asma e BPCO Ruolo della prevenzione

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Pediatria ad Alta Intensità di Cura
Università degli Studi di Milano
Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico

Sofia ha 3 anni e mezzo
Milano, 16 settembre 2016
I visita la mamma racconta:

- 6 - 8 episodi di otite (ultimo a giugno)
- raffreddore persistente in inverno 2016
- tre episodi di bronchite asmatica in inverno
- rinosinusite a marzo 2016
- frequenta la scuola materna a tempo pieno da un anno
- ha un fratello di 6 anni
- usa il ciuccio anche di giorno
- cresce bene; mai ricoveri
- atopica con sensibilizzazione ad acari

Infezioni respiratorie ricorrenti (IRR) : due definizioni

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

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

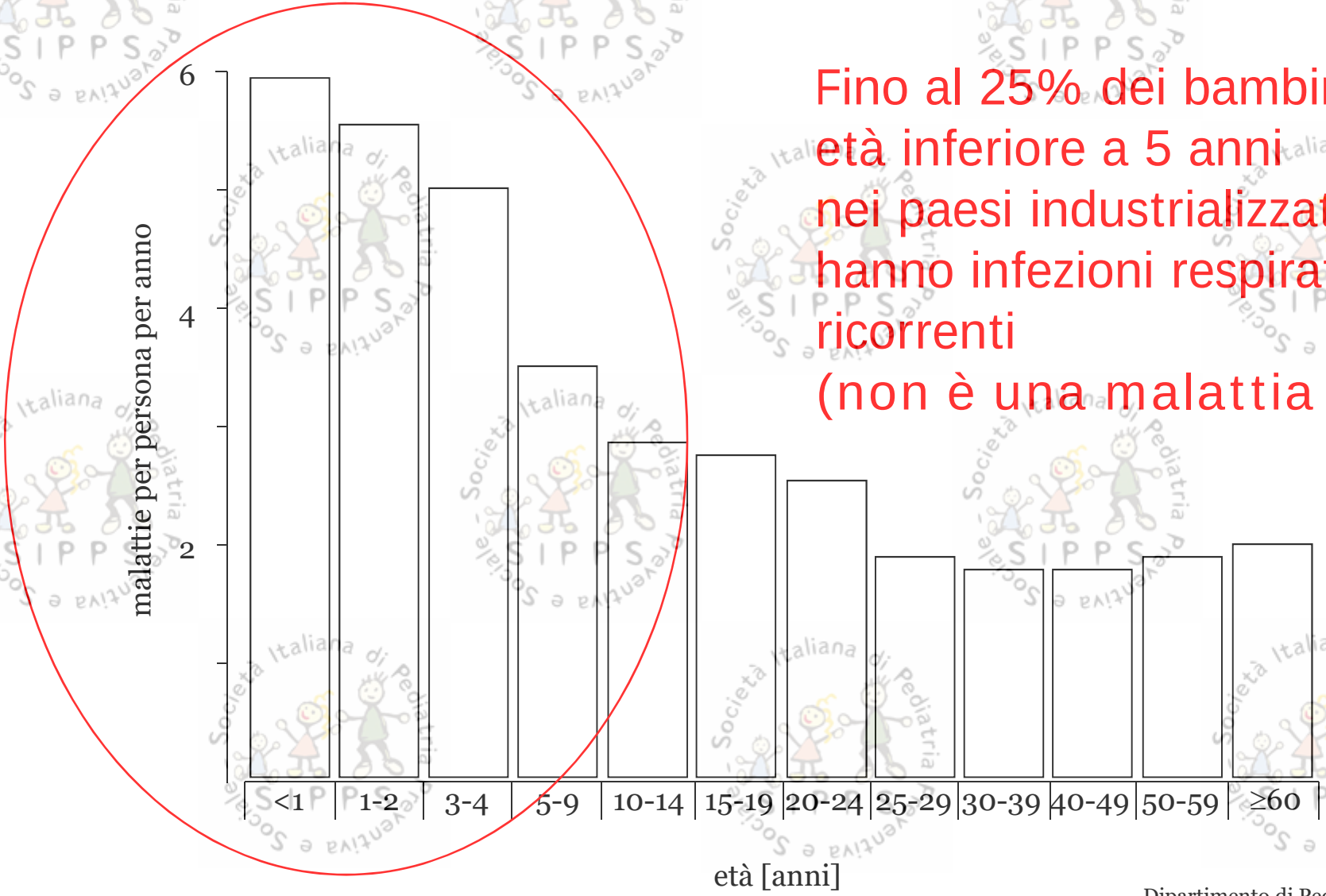
Età < 3 anni	→	**ñ 8 IVAS /anno**
Età ≥ 3 anni	→	**ñ 6 IVAS/anno**
Tutte le età	→	**ñ 2 IVAI/anno**

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

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

incidenza annuale media di infezioni respiratorie per classe di età

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



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

EZIOLOGIA DELLE INFEZIONI RESPIRATORIE RICORRENTI

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

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

L'impatto negativo delle infezioni respiratorie ricorrenti

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

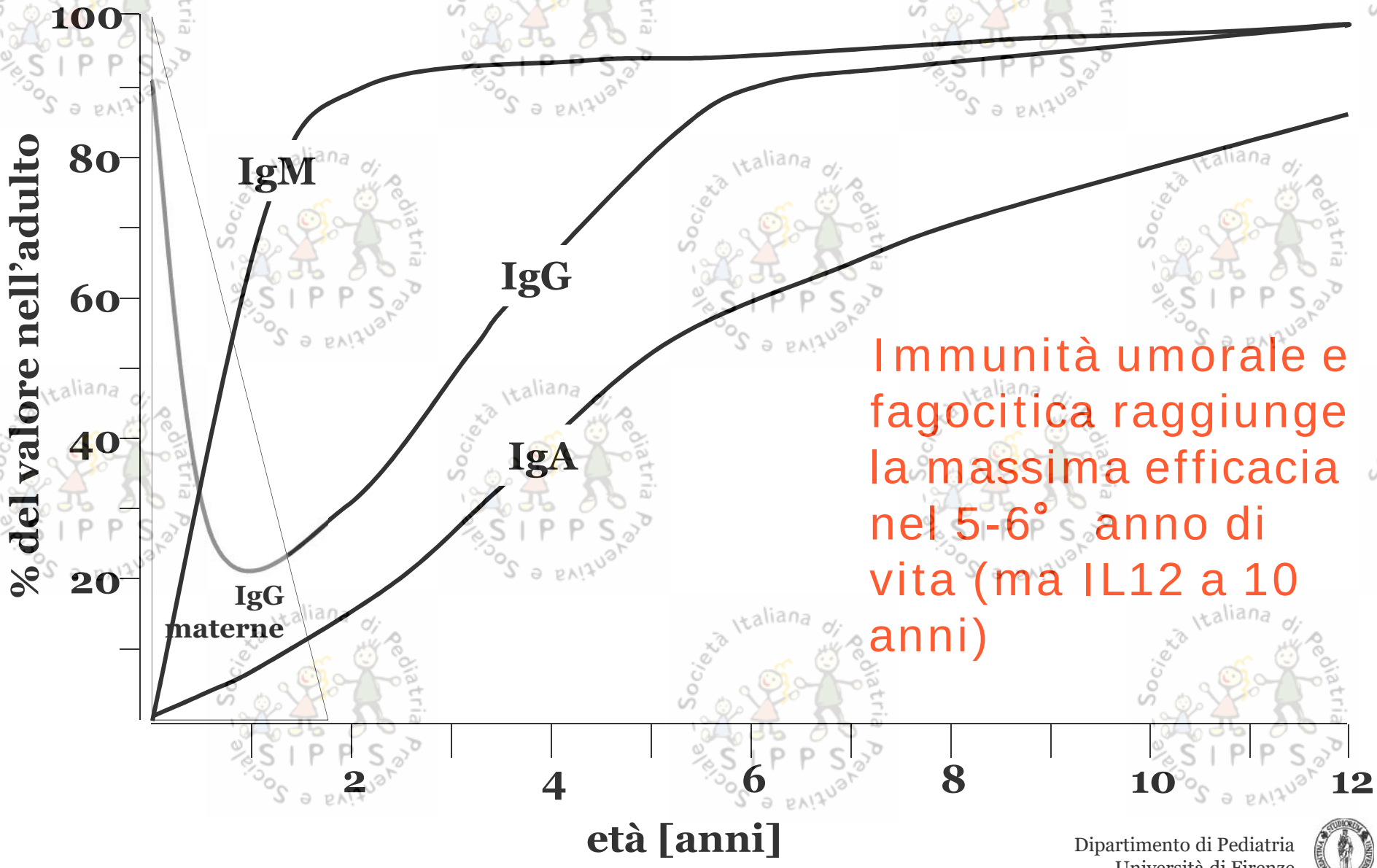
THE FIRST CAUSE OF RECURRENT RESPIRATORY INFECTIONS IN CHILDREN IS…

CHILDHOOD ITSELF

(J.G. Wheeler 1996)

classi immunoglobuliniche per età

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

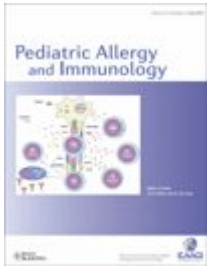


Immunità umorale e fagocitica raggiunge la massima efficacia nel 5-6° anno di vita (ma IL12 a 10 anni)

Dipartimento di Pediatria
Università di Firenze

The child with recurrent respiratory infections: normal or not?

De Martino, Pediatr Allergy Immunol 2007;18: 3



Recurrent respiratory infections children have no significant alteration of immunity ...

THE FIRST CAUSE OF RECURRENT RESPIRATORY INFECTIONS IN CHILDREN IS…

CHILDHOOD ITSELF

(J.G. Wheeler 1996)

WAIT : let age do its job

THE FIRST CAUSE OF RECURRENT RESPIRATORY INFECTIONS IN CHILDREN IS…

CHILDHOOD ITSELF

(J.G. Wheeler 1996)

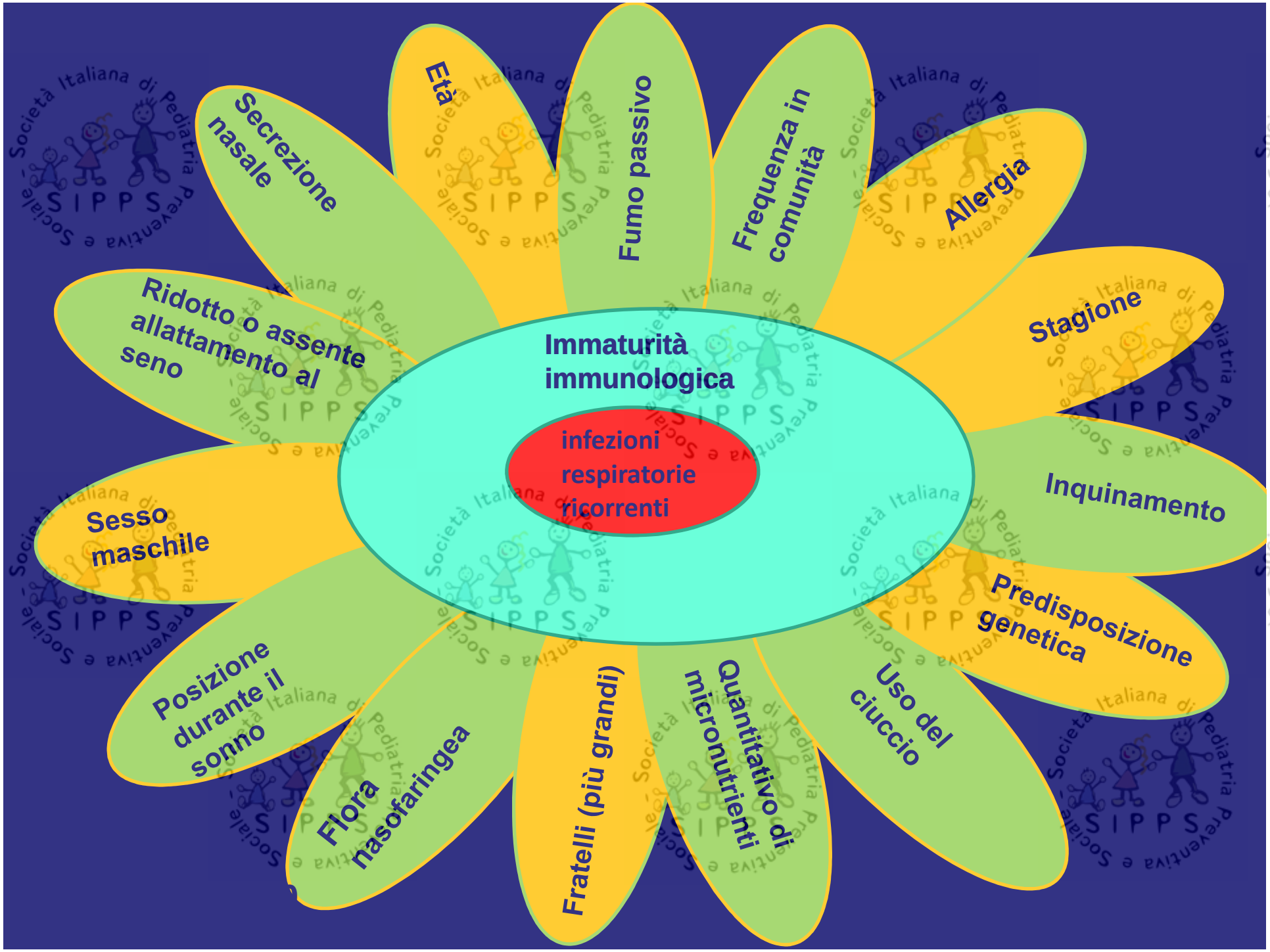
REDUCTION OF RISK FACTORS

Risk factors for recurrent respiratory infections

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

JESENAK M et al 2012

Società Italiana di Pediatria Preventiva e Sociale SIPPS

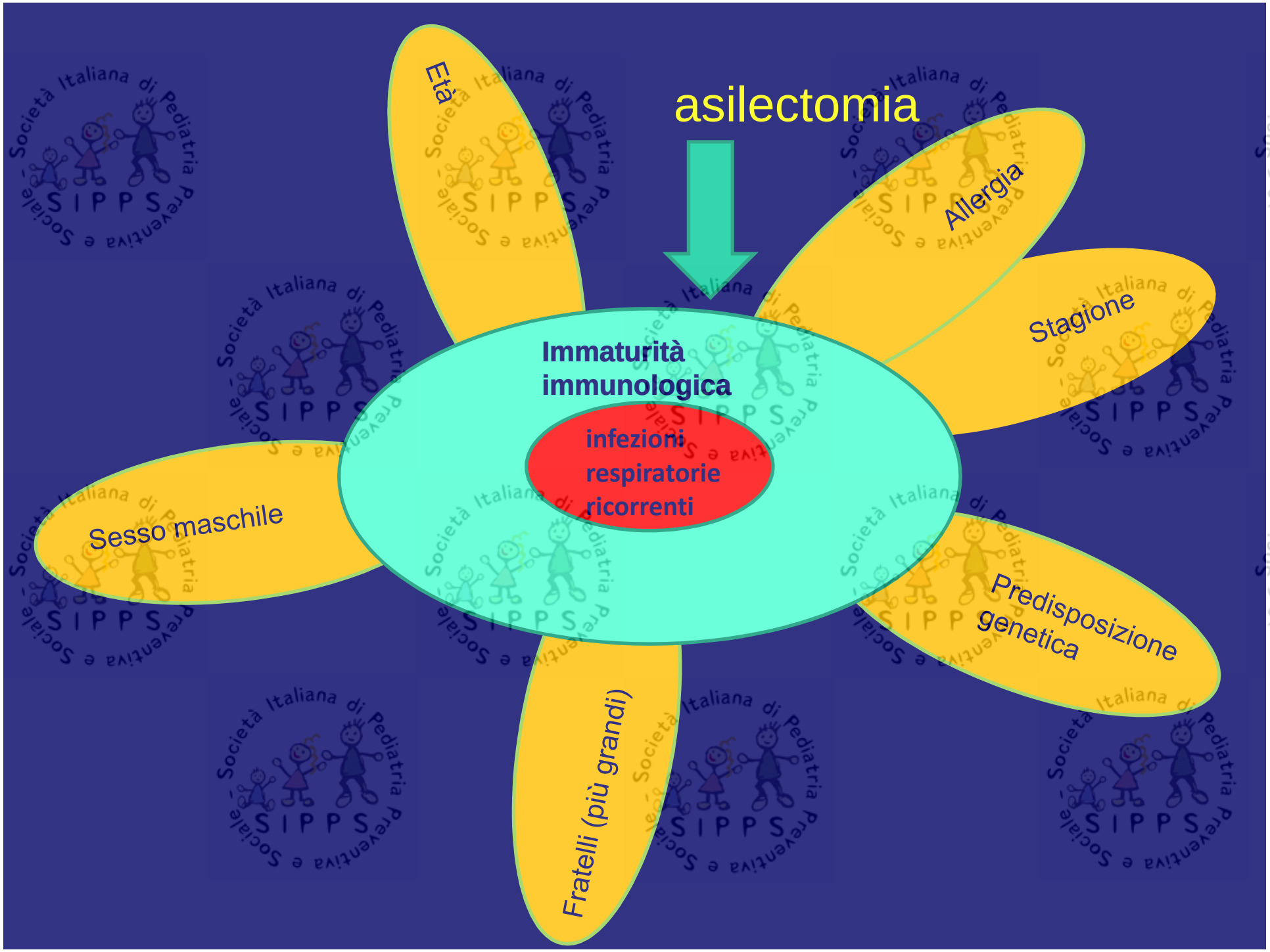

Età
Fumo passivo
Frequenza in comunità
Allergia
Stagione
Inquinamento
Predisposizione genetica
Uso del ciuccio
Quantitativo di micronutrienti
Fratelli (più grandi)
Flora nasofaringea
Posizione durante il sonno
Sesso maschile
Ridotto o assente allattamento al seno
Secrezione nasale
Immaturità immunologica
infezioni respiratorie ricorrenti

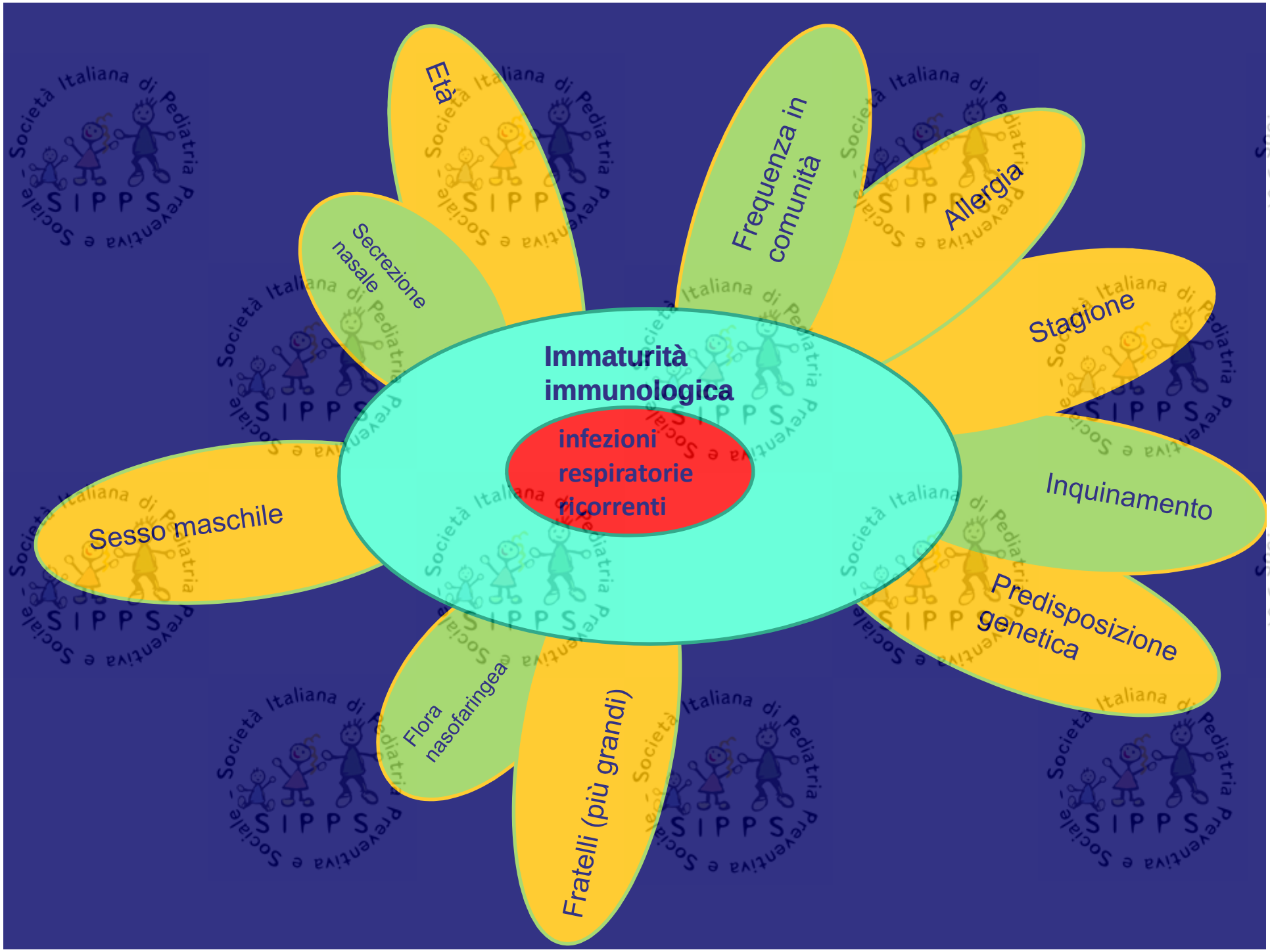
Allergic children have more numerous and severe respiratory infections than non-allergic children

Ciprandi G et al, Pediatr Allergy Immunol 2006: 17: 389–391

Table 1. Weighted mean ± s.d. of number and duration of respiratory infections (RI) in children with recurrent RI

Total number and forms of RI	Non-allergic children (n = 71)	Allergic children (n = 46)
Total RI number (p = 0.0001)	0.94 ± 1.37	1.26 ± 0.73
Mild RI number (p < 0.00001)	0.53 ± 0.64	1.02 ± 0.7
Total RI duration (days) (p = 0.009)	4.85 ± 5.24	8.92 ± 9.64
Mild RI duration (days) (p = 0.0007)	2.99 ± 3.91	7.82 ± 9.87


asilectomia
Età
Allergia
Stagione
Immaturità immunologica
infezioni respiratorie ricorrenti
Sesso maschile
Predisposizione genetica
Fratelli (più grandi)


Immaturità immunologica
infezioni respiratorie ricorrenti
Età
Frequenza in comunità
Allergia
Stagione
Inquinamento
Predisposizione genetica
Fratelli (più grandi)
Flora nasofaringea
Sesso maschile
Secrezione nasale

Short- and Long-term Risk of Infections as a Function of Group Child Care Attendance

Arch Pediatr Adolesc Med. 2010;164(12):1132-1137

Sylvana M. Côté, PhD; Amélie Petitclerc, PhD; Marie-France Raynault, MD; Qian Xu, MSc; Bruno Falissard, PhD; Michel Boivin, PhD; Richard E. Tremblay, PhD

Variable	Early Preschool (Aged 1½-2½ y)		Late Preschool (Aged 3½-4½ y)	
	IRR (95% CI)	*P* Value	IRR (95% CI)	*P* Value
Respiratory Tract Infections				
GCC enrollment age and size[a]				
Started S-GCC or L-GCC late	1.21 (0.93-1.58)	.16	1.20 (0.93-1.54)	.16
S-GCC early, never in L-GCC	1.15 (0.91-1.44)	.24	1.13 (0.92-1.40)	.25
S-GCC early, L-GCC late	1.28 (0.98-1.69)	.07	1.47 (1.15-1.88)	.002
L-GCC early	1.61 (1.27-2.03)	<.001	1.02 (0.80-1.30)	.90

SGCC small group child care LGCC large group child care

Low Serum 25-Hydroxyvitamin D Level and Risk of Upper Respiratory Tract Infection in Children and Adolescents

Michelle Science,[1,2] Jonathon L. Maguire,[3,4,5,6] Margaret L. Russell,[7] Marek Smieja,[2,8] Stephen D. Walter,[2] and Mark Loeb[2,8,9]

Table 3. Serum 25-Hydroxyvitamin D Level as a Predictor of Recurrent Respiratory Virus Infections, Adjusted for Age and Sex

Variable	Adjusted HR (95% CI)	*P* Value
Age		
Per 1-y change	0.93 (.88–.98)	.011
Per 5-y change	0.69 (.52–.92)	.011
Male sex	0.80 (.59–1.07)	.135
Serum 25(OH)D level, nmol/L[a]		
Per 1-unit change in log	0.57 (.39–.83)	.003
levels (dichotomized)		
<50 nmol/L vs ≥50 nmol/L	1.49 (1.11–2.02)	.008
<75 nmol/L vs ≥75 nmol/L	1.50 (1.11–2.03)	.009

< 20 ng/ml = < 50 nmol/L - < 30 ng/ml = < 75 nmol/L

Clinical Infectious Diseases 2013;57(3):392–7

Supplemento al numero 3 - ANNO X - 2015 - ISSN 1970-8165

PEDIATRIA PREVENTIVA & SOCIALE

ORGANO UFFICIALE DELLA SOCIETÀ ITALIANA DI PEDIATRIA PREVENTIVA E SOCIALE

Consensus

Vitamina D in età pediatrica

Conclusioni

Sebbene esistano evidenze piuttosto robuste che correlano il deficit di vitamina D con le infezioni respiratorie a tutte le latitudini e in tutti i contesti sociali, ad oggi gli studi di intervento sono estremamente pochi, in particolare in pazienti non gravemente carenti e non appartenenti a popolazioni disagiate sotto il profilo socio-conomico. Non va neppure dimenticato che in alcuni studi tanto i bassi livelli quanto gli alti livelli di vitamina D sono stati correlati con un aumentato rischio di infezioni (Ali 2015, Nielsen 2010). Pertanto, non è raccomandabile ad oggi l'utilizzo routinario della vitamina D, tanto nella prevenzione quanto nella terapia delle infezioni respiratorie, a dosaggi diversi da quelli utilizzati nella profilassi secondo le vigenti raccomandazioni oppure in assenza di livelli ematici che attestino una condizione di insufficienza o di franco deficit vitaminico.

Deficit grave
< 10 ng/ml

Deficit
< 20 ng/ml

Insufficienza
20-29 ng/ml

Sufficienza
≥ 30 ng/ml

THE FIRST CAUSE OF RECURRENT RESPIRATORY INFECTIONS IN CHILDREN IS…

CHILDHOOD ITSELF

(J.G. Wheeler 1996)

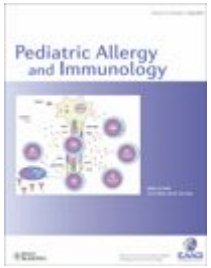
WAIT : let age do its job

REDUCTION OF RISK FACTORS

USE OF IMMUNOSTIMULANTS/ IMMUNOMODULANTS

The child with recurrent respiratory infections: normal or not?

De Martino, Pediatr Allergy Immunol 2007;18: 3



Fattori di rischio

Aumentata suscettibilità

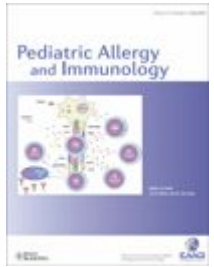
Infezioni virali

"RRI children have no significant alteration of immunity ...

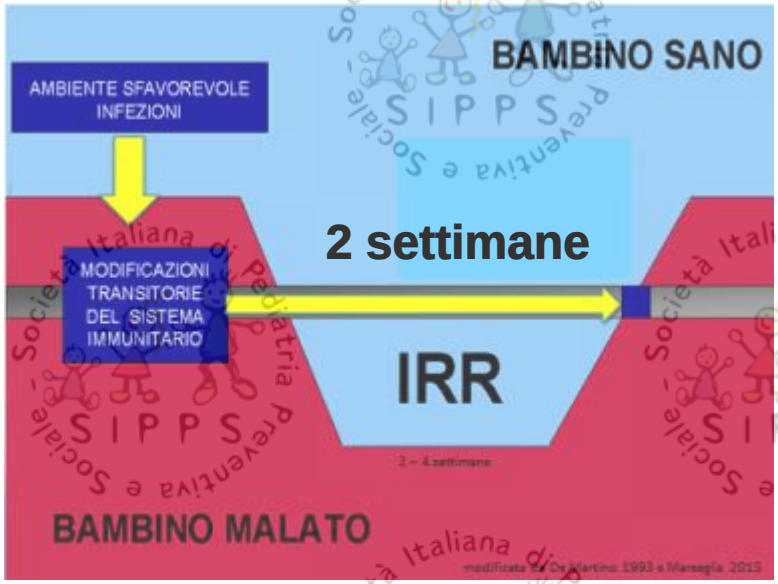
ma ...

la risposta immunitaria raggiunge la massima efficacia nel 5-6° anno di vita

The child with recurrent respiratory infections: normal or not?



De Martino, Pediatr Allergy Immunol 2007:18: 3



Fattori di rischio

↓

Aumentata suscettibilità

OMA
CAP

Immunodeficit transitorio secondario

Infezioni virali

Coexistence of (Partial) Immune Defects and Risk of Recurrent Respiratory Infections

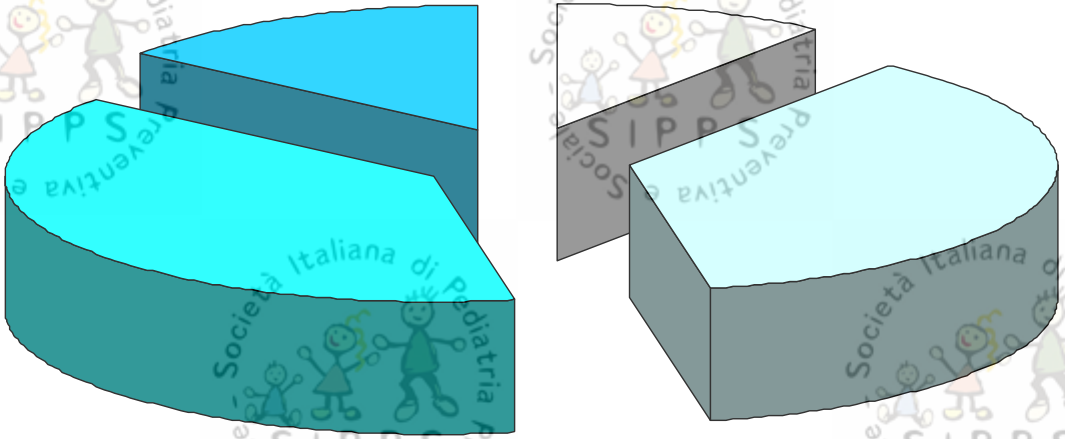
Xavier Bossuyt,[1*] Leen Moens,[1] Erna Van Hoeyveld,[1] Axel Jeurissen,[1] Guy Bogaert,[2] Kate Sauer,[3] Marijke Proesmans,[3] Marc Raes,[3] and Kris De Boeck[3]

nessun difetto [n: 6 = 10.9 %]

1 difetto [n: 20 = 36.3 %]

3 difetti [n: 8 = 14.7 %]

2 difetti [n: 21 = 38.1 %]



*** deficit parziale di:**

- **IgA**
- **sottoclassi di IgG**
- **C_4**
- **C_2**
- **lectina legante il mannosio**
- **linfociti B**
- **linfociti T $CD4^+$**
- **cellule NK**
- **risposta ad antigeni polisaccaridici**

Clinical Chemistry 53:1 124–130 (2007)

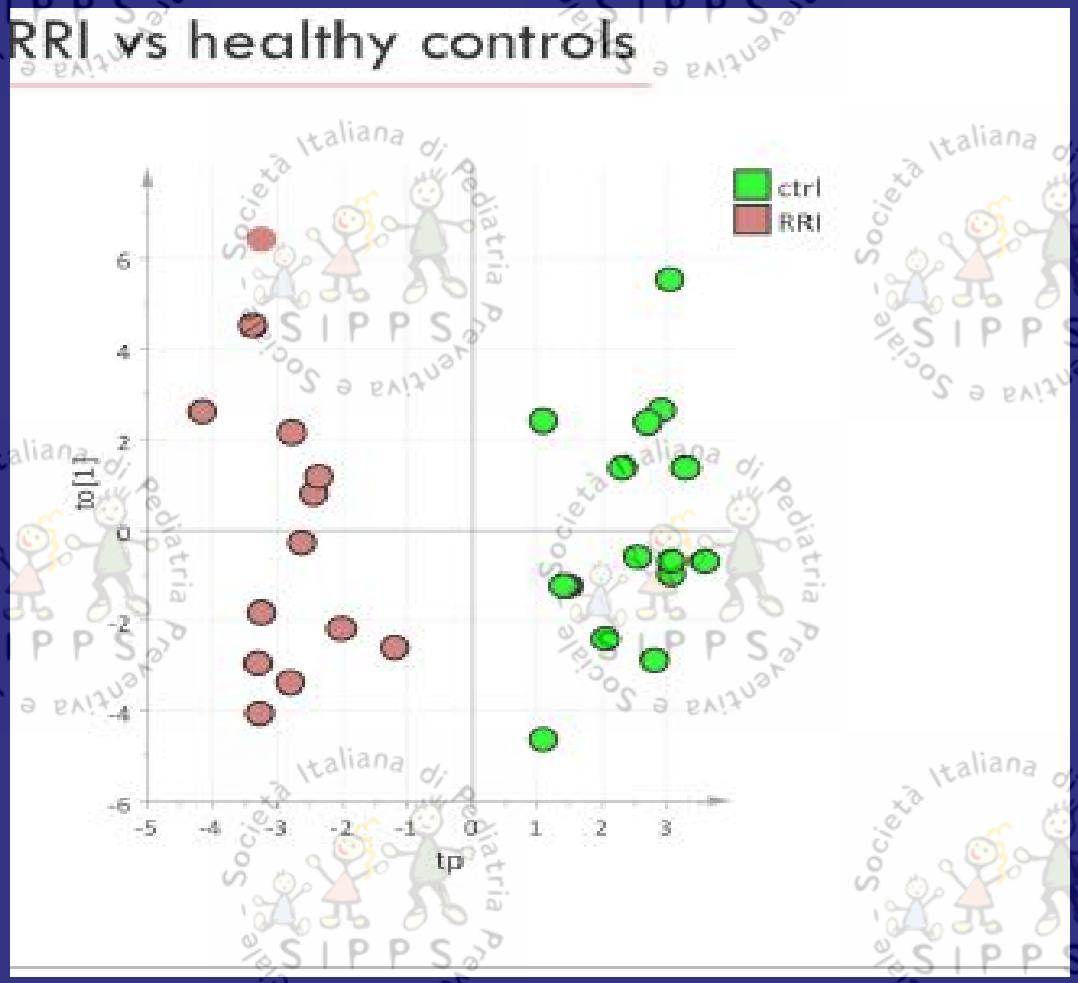
Alterations in immune system observed in children with recurrent respiratory tract infections

- defects of Fcγ receptor IIIa (CD16) on natural killer cells,
- defect of interleukin receptor-associate kinase 4 (IRAK4),
- reduction in IL-12 production,
- polymorphisms in genes *CCR2*, *CCR5* and mannose-binding lectin gene,
- mutations in TLR-4 encoding sequences,
- defective removal of the apoptotic neutrophils by alveolar macrophages,
- pathologic phagocytosis and production of reactive oxygen intermediates from polymorphonuclear cells,
- decrease neutrophil chemotaxis,
- mild decrease in the number of $CD4^+$, $CD8^+$, $CD19^+$ and NK-cells,
- alterations in the cytokine production by lymphocytes (↑ IL-4, ↑ IL-10, ↓ IFN-γ, ↓ IL-2),
- decreases IgM, IgA, IgG subclasses, mannose-binding lectin, L-ficolin,
- defects in the production post-infectious specific antibodies.

JESENAK M et al. Chapter 8 – Infectious Diseases - 2012
open access DOI: 10.5772/19422

PROFILO METABOLOMICO DI BAMBINI CON INFEZIONI RESPIRATORIE RICORRENTI

Gruppo Prof Baraldi – SIMRI ottobre 2015



Analisi metabolomica di un campione di urine, per identificare la presenza di profili di metaboliti caratteristici di bambini con IRR

3D PLS-DA Score plot che dimostra la separazione tra bambini con IRR (in marrone) e controlli sani (in verde)

Razionale dei farmaci immunostimolanti

Maturazione della cellula dendritica

↓

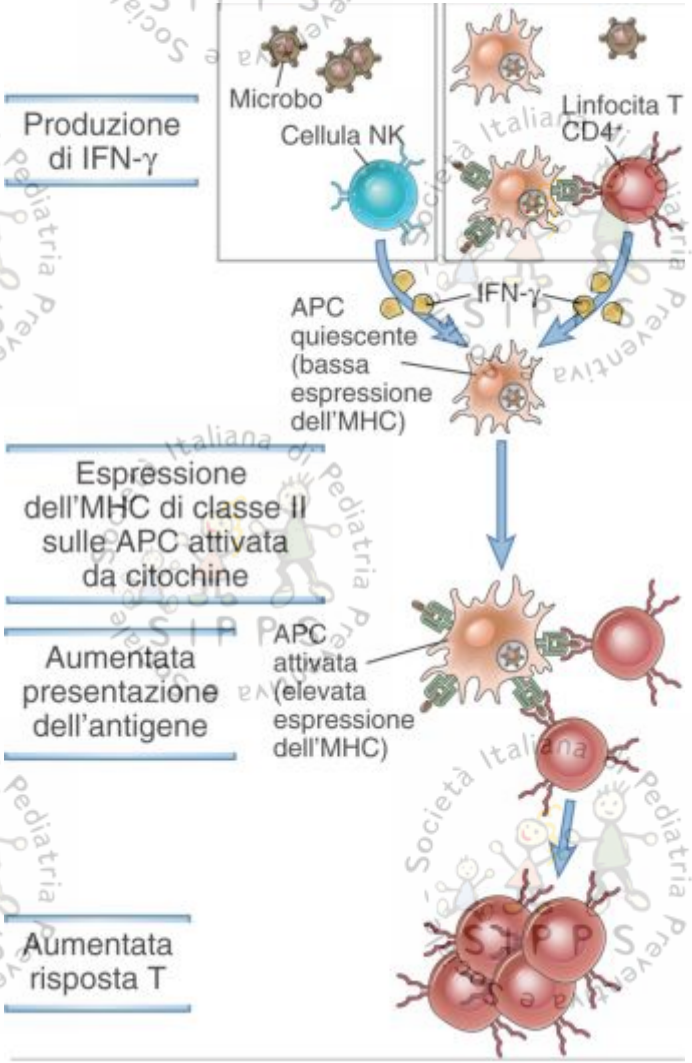
Aumentata espressione sulla sua superficie dei TLR e delle molecole HLA di classe II

↓

Produzione di IL1, IL6 e IL12

↓

Differenziazione dei linfociti T → Th1



grazie a R. Di Marco, 2013

Il passato …

Immunostimulants for preventing respiratory tract infection in children (Review)

Cochrane Library 2011, issue 6

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

Main results

Thirty-five placebo-controlled trials (4060 participants) provided data in a form suitable for inclusion in the meta-analyses. 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.

Authors' conclusions

This review shows that IS reduce the incidence of ARTIs by 40% on average in susceptible children. Studies in healthy children are not available. Although the safety profile in the studies was good, some IS may be unsafe. ARTI-susceptible children may benefit from IS treatment. Further high-quality trials are needed and we encourage national health authorities to conduct large, multicentre, double-blind, placebo-controlled RCTs on the role of IS in preventing ARTIs in children.

Immunostimulants for preventing respiratory tract infection in children (Review)

THE COCHRANE COLLABORATION®

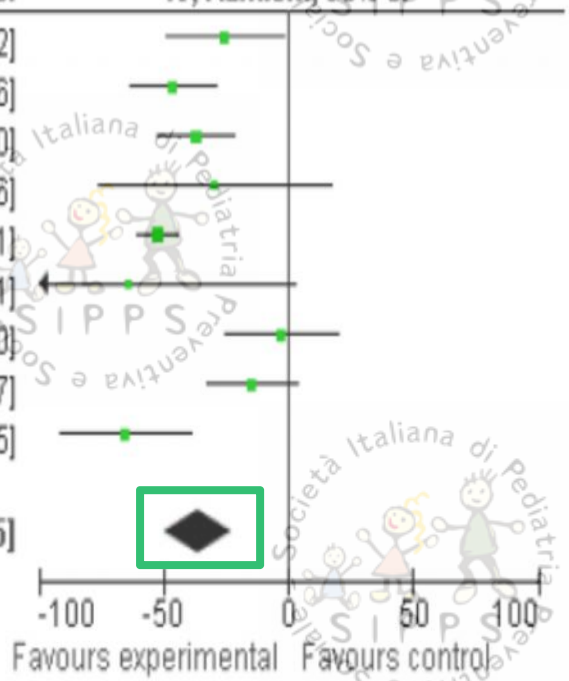
OM-85 lisato batterico

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

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Ahrens 1984	74.4	67.86	83	100	80.16	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]
Gutierrez-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)



Immunostimulants for preventing respiratory tract infection in children (Review)

THE COCHRANE COLLABORATION®

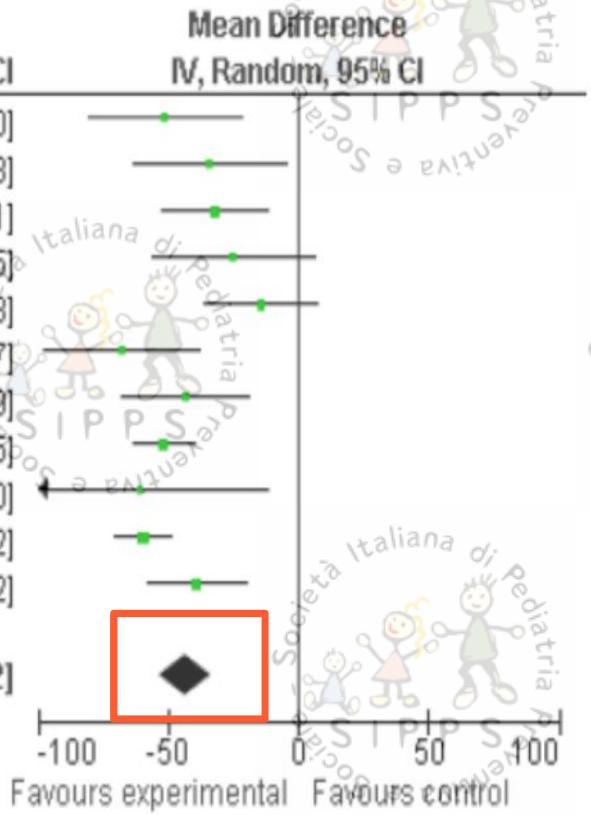
Lisato di frazioni ribosomiali

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

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control 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	54.96	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]
RB24 1990	39.13	54.35	16	100	86.96	17	3.3%	-60.87 [-110.04, -11.70]
RB25 1990	40.31	6.15	13	100	18.46	12	15.2%	-59.69 [-70.66, -48.72]
Vautel 1993	60.97	38.67	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)



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

THE PAST

ITALIAN JOURNAL OF PEDIATRICS

COMMENTARY Open Access

Pidotimod: the past and the present

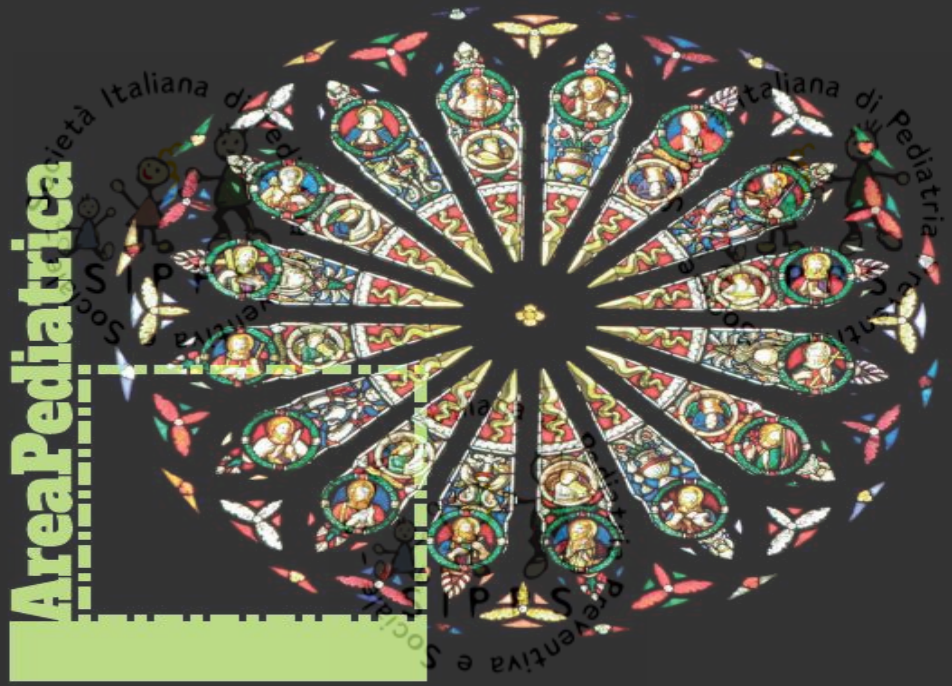
Gian Vincenzo Zuccotti* and Chiara Mameli

DIPEPTIDE SINTETICO

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

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

Il presente …



AreaPediatrica

Società Italiana di Pediatria

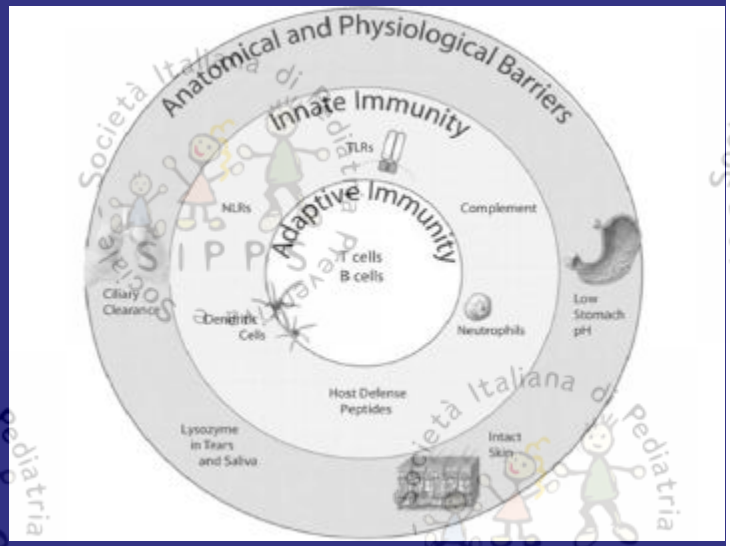
Rivista ufficiale
di Formazione continua
della Società Italiana di Pediatria
| Vol. 17 | supp. n. 1 al n. 1 |
gennaio–marzo 2016

Il Pensiero Scientifico Editore

Opinioni a confronto in Pediatria: gli immunomodulatori

Atti del meeting interspecialistico pediatrico organizzato dalla Società Italiana di Allergologia e Immunologia Pediatrica (SIAIP)

Diverse strategie da integrare nella nostra pratica quotidiana



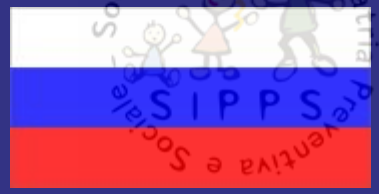
- PREVENZIONE DELLE IRR
- IMMUNOSTIMOLAZIONE e IMMUNOMODULAZIONE IN FASE ACUTA CON PROLUNGAMENTO DELL'EFFETTO IN FASE CONVALESCENZIALE E RIDUZIONE RECIDIVE

Int J Immunopathol Pharmacol. 2014 Jul-Sep;27(3):413-9.

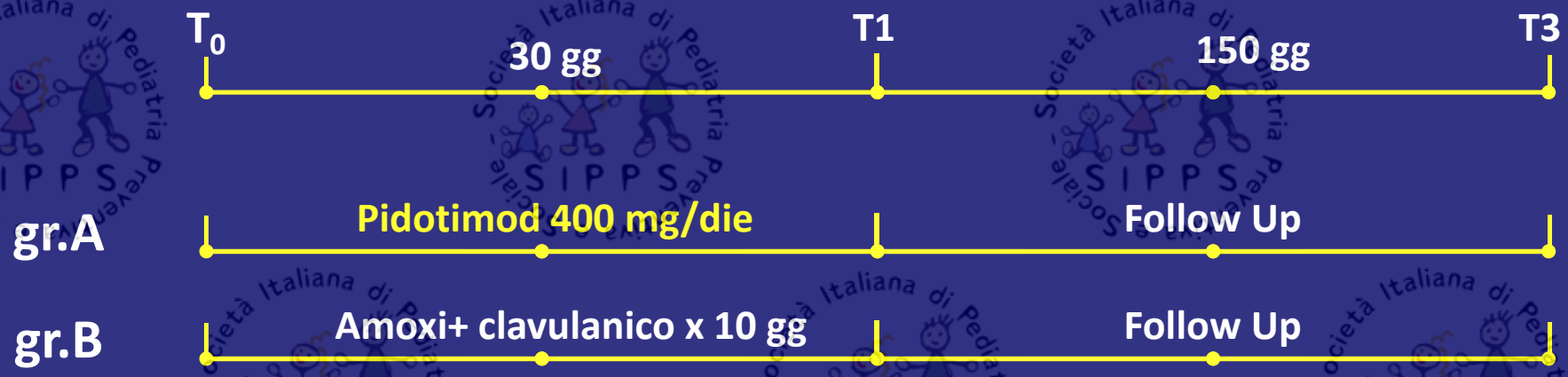
Efficacy and safety of pidotimod in the prevention of recurrent respiratory infections in children: a multicentre study.

Namazova-Baranova LS[1], Alekseeva AA[1], Kharit SM[2], Kozhevnikova TN[3], Taranushenko TE[4], Tuzankina IA[5], Scarci F[6].

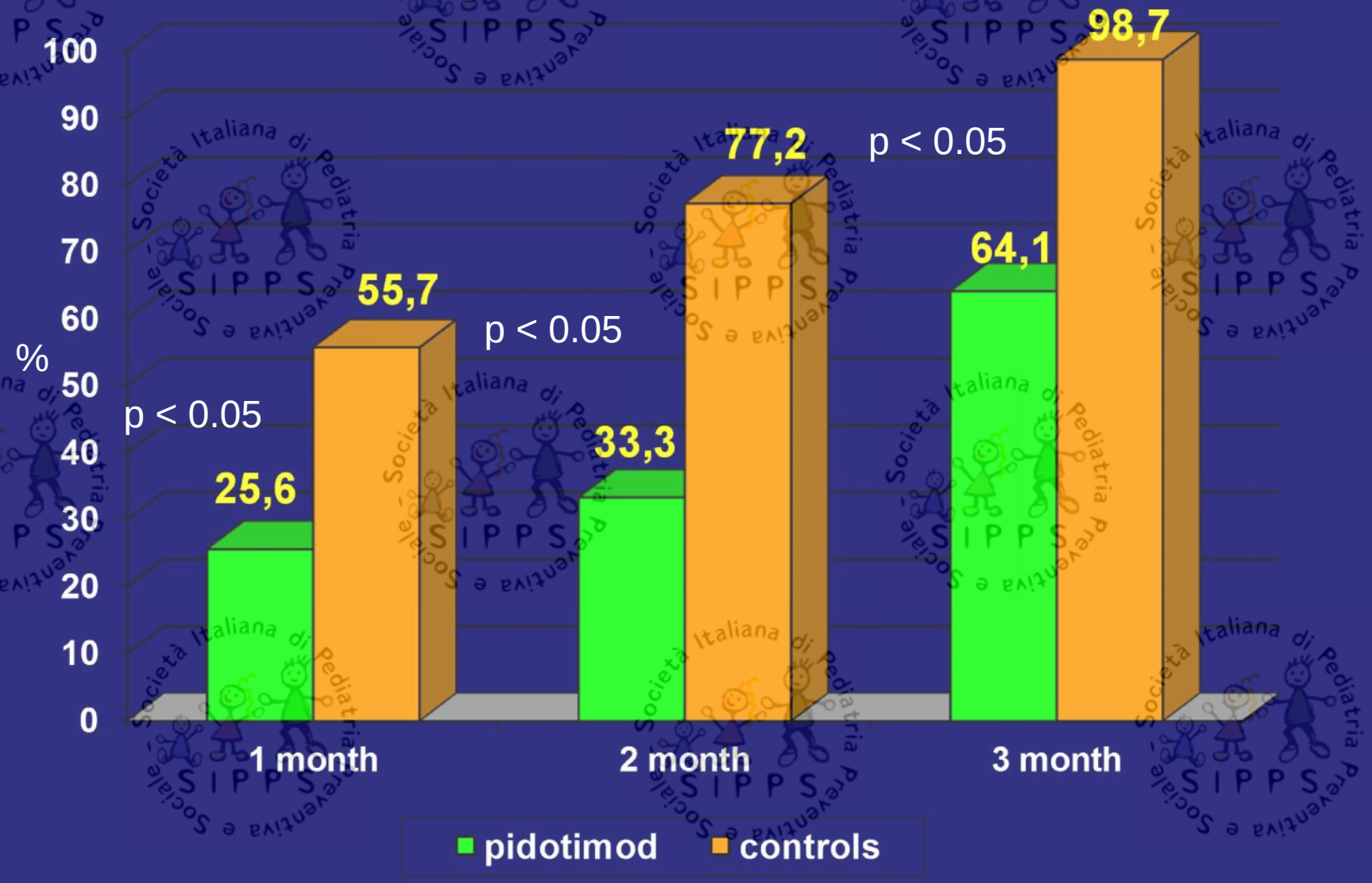
- **Studio prospettico randomizzato a gruppi paralleli**
  trattati (78, 400 mg/die) vs controlli (79) (età range 3- 6 anni) (storia di IRR= > 6 episodi/12 mesi, 50% allergici)



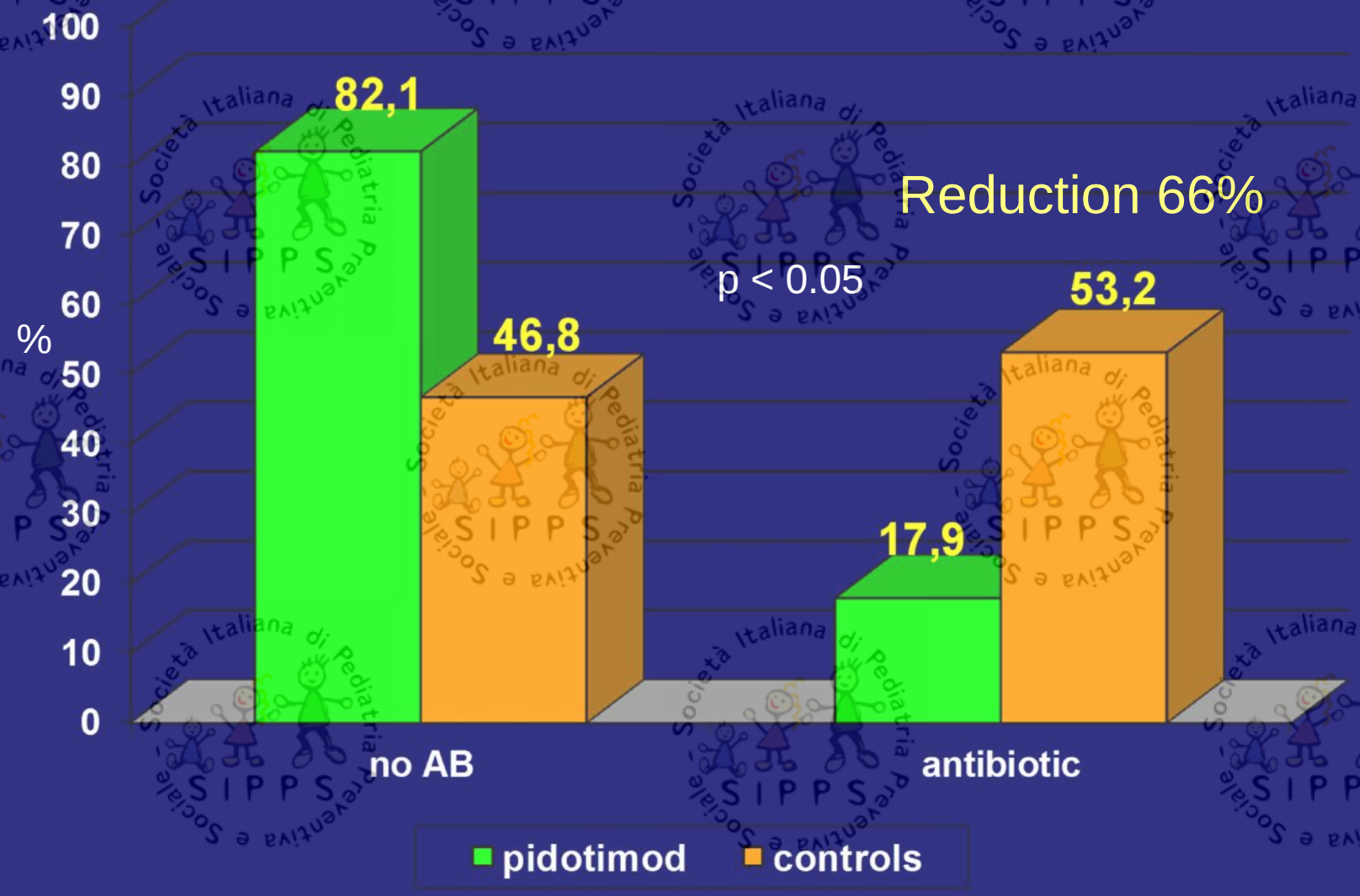
- **Schema di trattamento:**



Proportion of children with respiratory infections during the first follow-up period



Administration of antibiotic therapy during the 6 month follow-up period



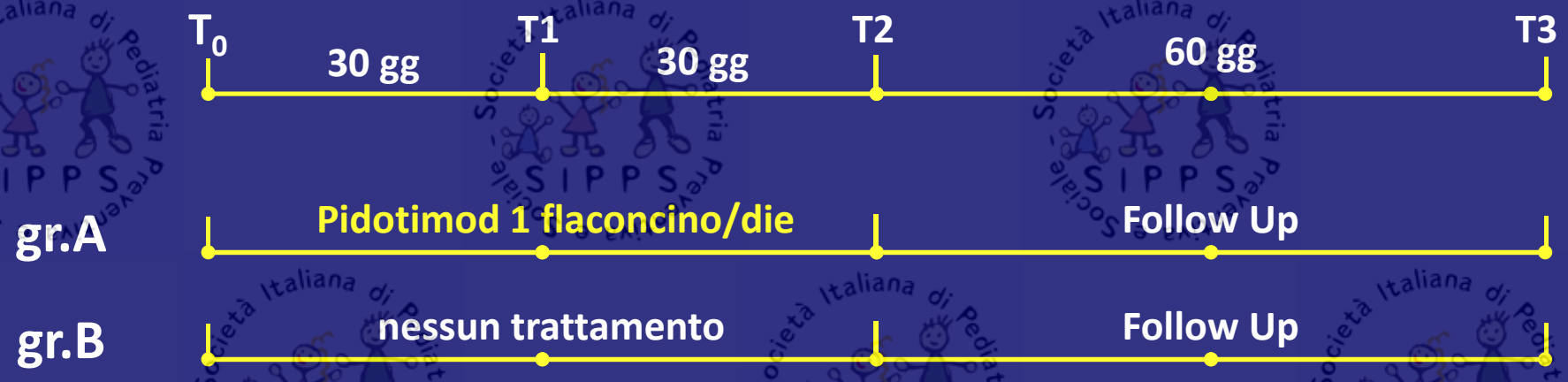
Minerva Pediatr. 2014 Oct;66(5):363-7.

Pidotimod may prevent recurrent respiratory infections in children.

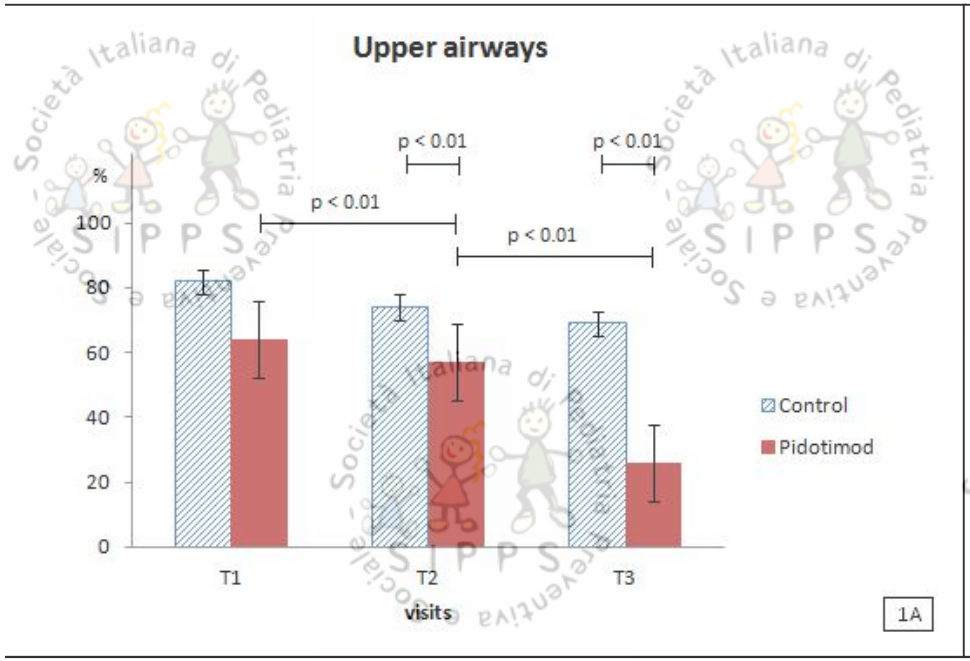
Licari A[1], De Amici M, Nigrisoli S, Marseglia A, Caimmi S, Artusio L, Marseglia GL.

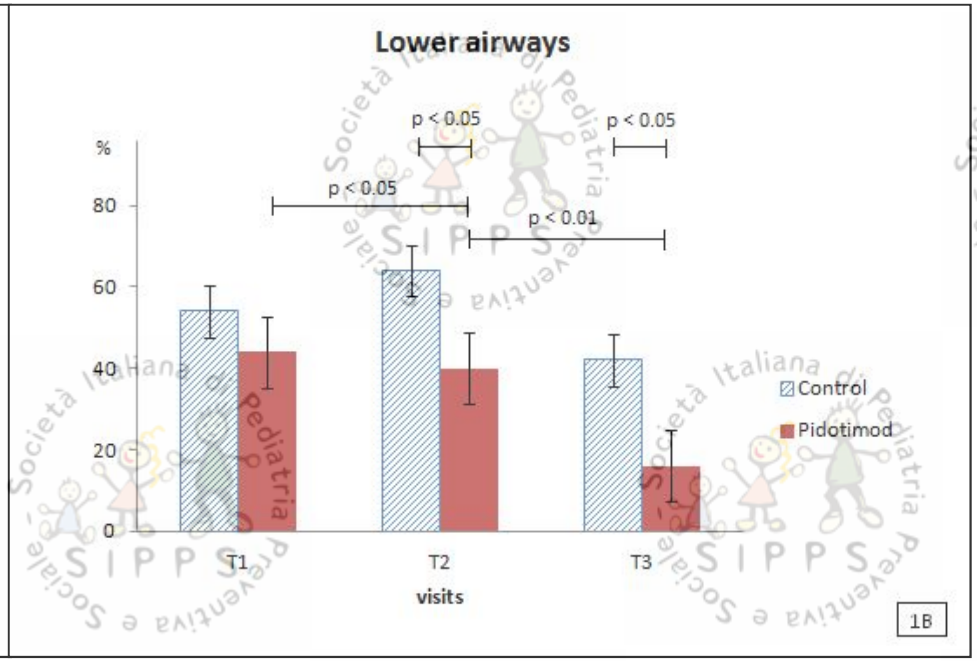
- **Studio prospettico randomizzato a gruppi paralleli**
  gruppo Trattati (45 bambini , 400 mg/die) vs gruppo non Trattati (44 bambini) (età 4.9 anni, range 3- 10 anni)

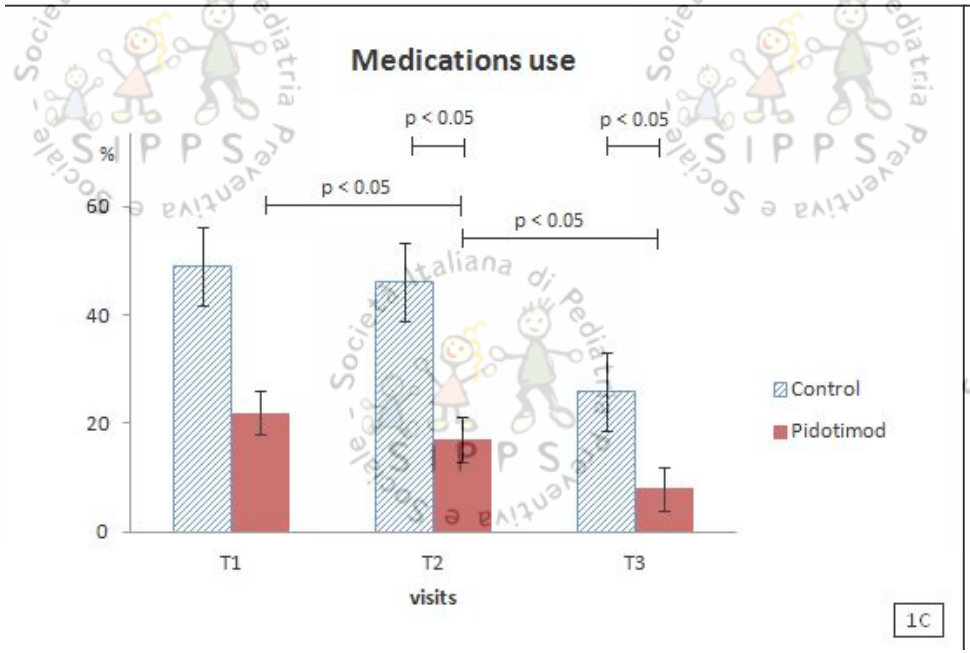
- **Schema di trattamento:**

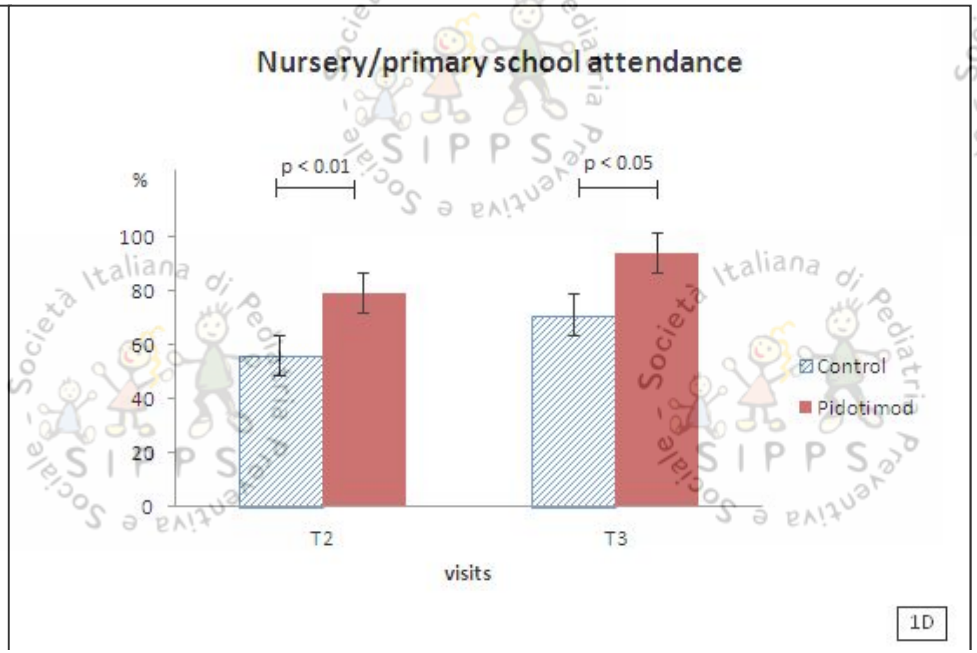


- **Periodo di studio: novembre – febbraio**


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


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


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


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

Pharmacological Research
Available online 27 April 2015
In Press, Uncorrected Proof — Note to users

Pidotimod for the prevention of acute respiratory infections in healthy children entering into daycare: A double blind randomized placebo-controlled study

Chiara Mameli[a], Angela Pasinato[b], Marina Picca[c], Giorgio Bedogni[d], Stefania Pisanelli[e], Gian Vincenzo Zuccotti[a], for the AX-Working group[1]

Protocollo sperimentale N° : 1/2013
Codice EudraCT N° : 2013-002273-22

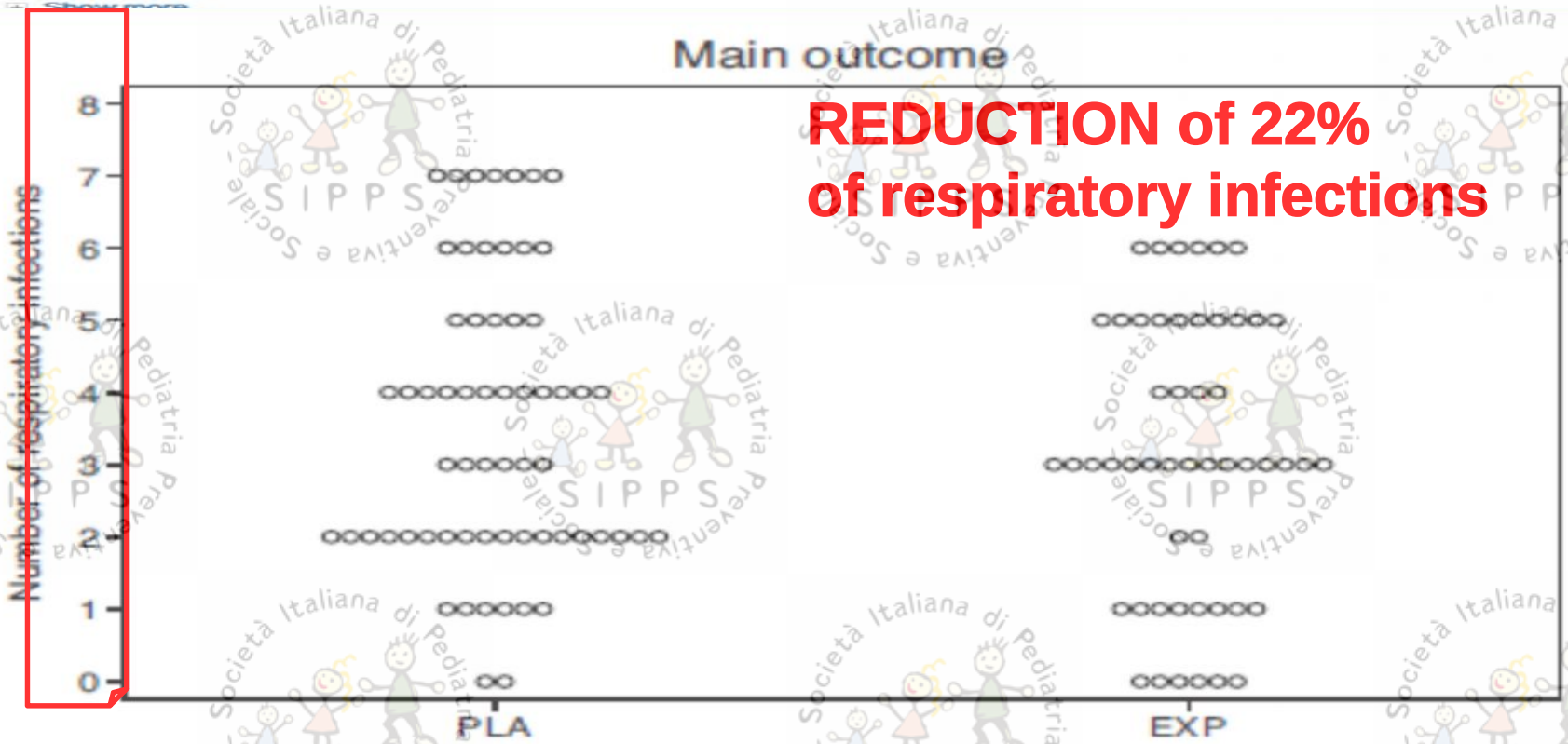
Coordinatore GV Zuccotti
con pediatri di famiglia di SICCUP LOMBARDIA e CESPER Veneto

Valutare **l'efficacia di Pidotimod (400 mg x 2/die x 10 giorni al mese per 6 mesi da ottobre ad aprile) nella prevenzione delle infezioni respiratorie** in **bambini sani di 3 anni senza fattori di rischio e che non avevano mai frequentato la comunità infantile** in termini di riduzione di numero di infezioni respiratorie durante il periodo dello studio in confronto al gruppo trattato con placebo.

Pharmacological Research
Available online 27 April 2015
In Press, Uncorrected Proof — Note to users

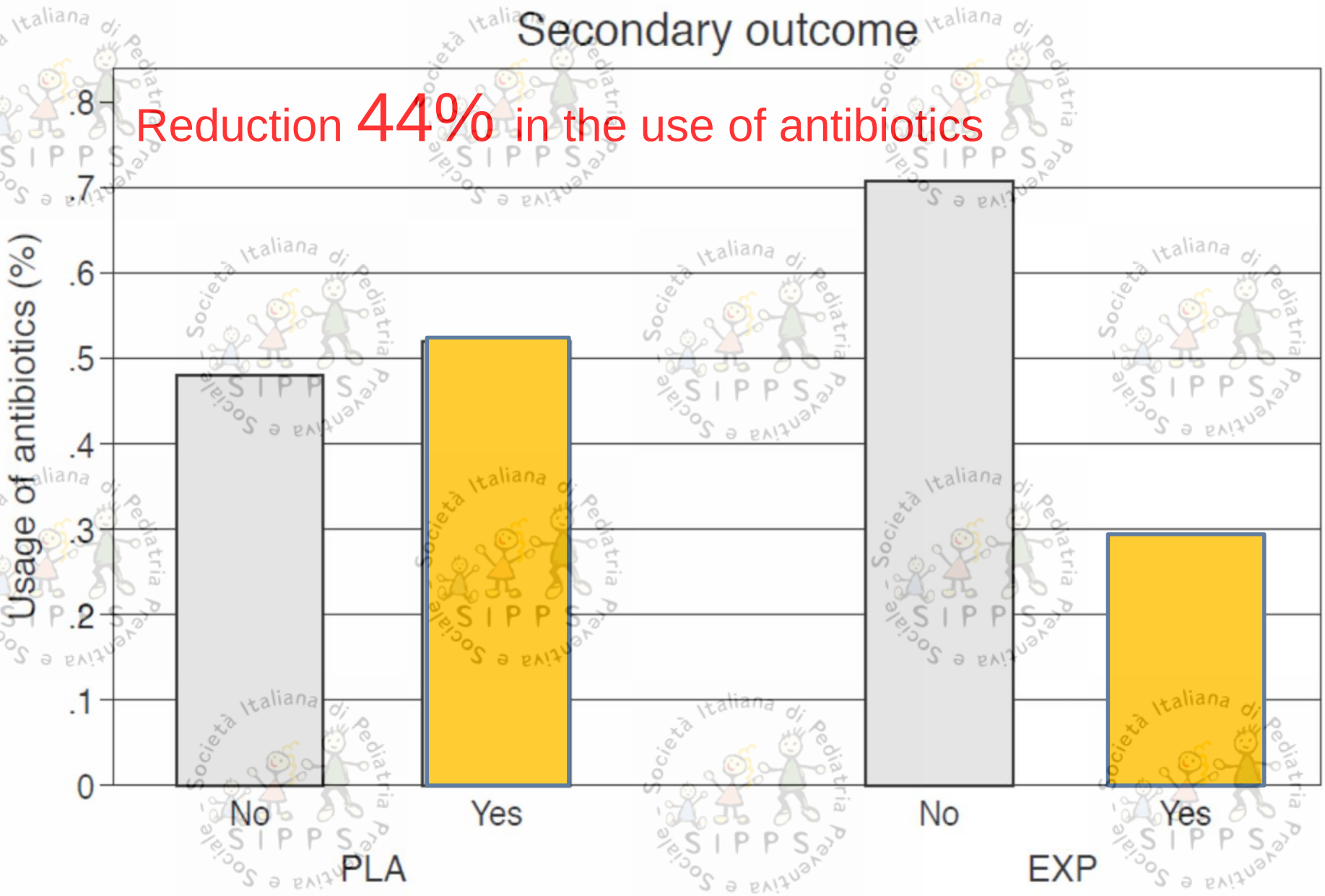
Pidotimod for the prevention of acute respiratory infections in healthy children entering into daycare: A double blind randomized placebo-controlled study

Chiara Mameli, Angela Pasinato, Marina Picca, Giorgio Bedogni, Stefania Pisanelli, Gian Vincenzo Zuccotti, for the AX-Working group



REDUCTION of 22% of respiratory infections

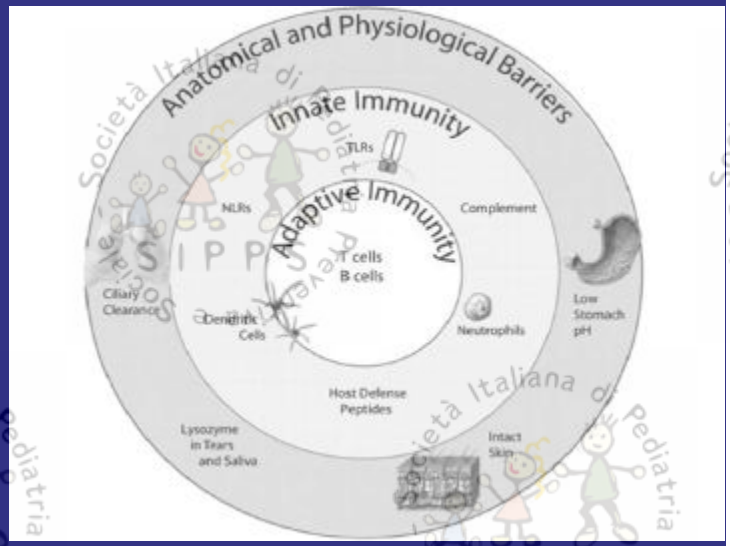
Fig. 2. Number of respiratory infections in Pidotimod and placebo-treated group. EXP: Pidotimod; PLA: placebo.


Secondary outcome
Reduction 44% in the use of antibiotics
Usage of antibiotics (%)
0
.1
.2
.3
.4
.5
.6
.7
.8
No
Yes
No
Yes
PLA
EXP

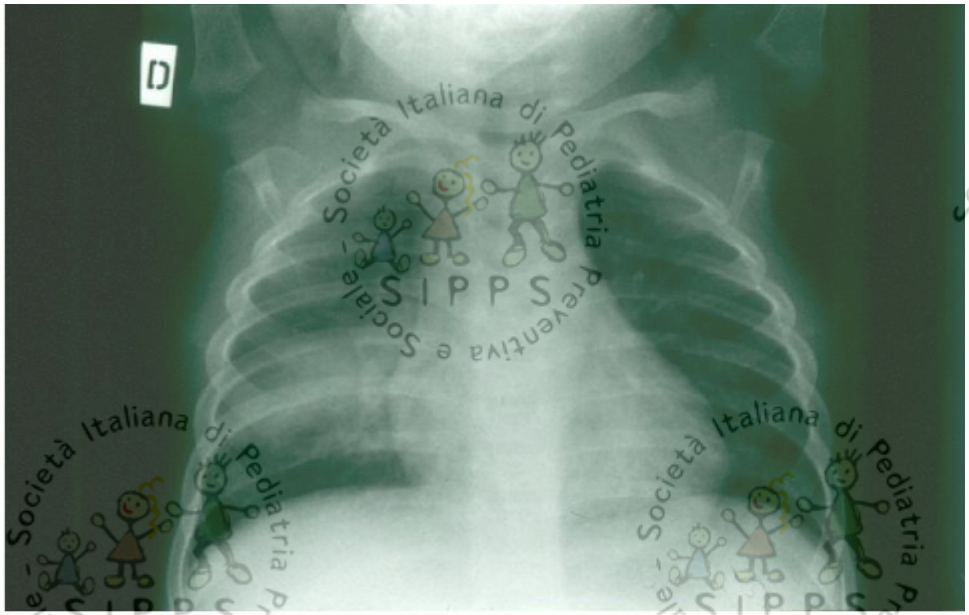
Due schemi di prevenzione delle IRR con pidotimod

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

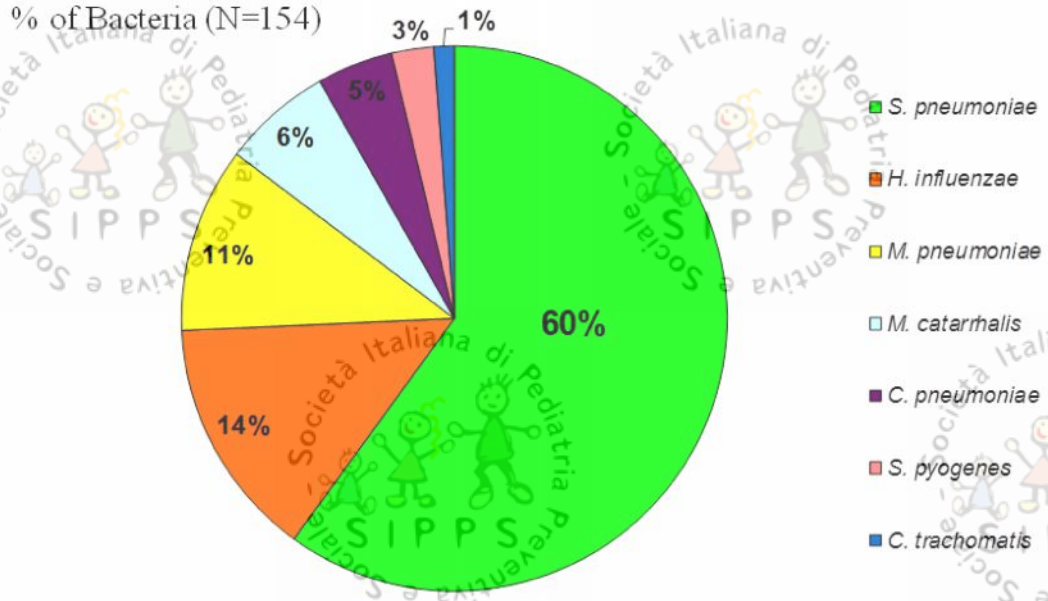
Diverse strategie da integrare nella nostra pratica quotidiana



- PREVENZIONE DELLE IRR
- IMMUNOSTIMOLAZIONE e IMMUNOMODULAZIONE IN FASE ACUTA CON PROLUNGAMENTO DELL'EFFETTO IN FASE CONVALESCENZIALE E RIDUZIONE RECIDIVE



Bacterial Etiology of Childhood Community-acquired Pneumonia



37 children were ,1 year of age, 71 between 1 and 2 years, 84 between 2 and 5 years and 62 were >5 years of age.

Taina Juven, et al. **Clinical profile of serologically diagnosed pneumococcal pneumonia**. Pediatr Infect Dis J, 2001;20:1028–33

Changes of immune function in children with refractory *Mycoplasma pneumoniae* pneumonia and effects of pidotimod

YAN Yong-dong
(Children's Hospital Affiliated to Soochow University, Suzhou 215003, Jiangsu, China)

Objective: To investigate the changes of immune function in children with refractory Mycoplasma pneumoniae pneumonia (MPP) and therapeutic effects of pidotimod. **Methods:** Peripheral immunoglobins and lymphocyte subsets of 66 patients with refractory MPP and 40 with common MPP were assayed using immune transmission turbidity method and flow cytometry technique, using 18 healthy children as control. The 66 patients with refractory MPP were assigned to two groups. The MPP treatment group was exposed to oral administration of azithromycin and pidotimod and the MPP control group to oral administration of only azithromycin; the two groups accepted the same doses and course of treatment.

Pidotimod 400 mg x 2 volte al giorno x 1 mese e successivamente 400 mg/die per 1 mese
In associazione a terapia con azitromicina

(J Clin Pediatr Vol.26 No.7 Jul.2008;

Changes of immune function in children with refractory *Mycoplasma pneumoniae* pneumonia and effects of pidotimod

YAN Yong-dong

(J Clin Pediatr Vol.26 No.7 Jul.2008;

(Children's Hospital Affiliated to Soochow University, Suzhou 215003, Jiangsu, China)

Indicator	MPP treatment group (n=40)				MPP control group (n=26)			
	Before treatment	After treatment	t value	P	Before treatment	After treatment	t value	P
IgG (g/L)	11.07±0.52	10.46±0.66	0.96	>0.05	10.26±0.57	10.97±0.56	0.46	>0.05
IgA (g/L)	1.15±0.13	1.17±0.14	0.45	>0.05	1.16±0.14	1.14±0.13	0.58	>0.05
IgM (g/L)	2.02±0.14	1.96±0.16	0.84	>0.05	1.98±0.12	1.97±0.13	0.55	>0.05
$CD3^+$ (%)	56.88±6.25	67.21±7.14	2.22	<0.05	58.12±5.24	59.26±6.34	0.86	>0.05
$CD4^+$ (%)	31.02±3.12	37.26±4.29	2.13	<0.05	30.46±3.41	30.23±3.01	0.27	>0.05
$CD8^+$ (%)	28.56±3.62	28.26±3.54	0.24	>0.05	28.39±3.22	27.92±3.44	0.92	>0.05
$CD4^+/CD8^+$	1.04±0.35	1.58±0.27	2.35	<0.05	1.03±0.36	1.08±0.23	0.44	>0.05
$CD19^+$ (%)	19.31±2.28	18.12±2.11	1.25	>0.05	19.42±2.37	18.26±2.42	1.26	>0.05
$CD16^+$ $CD56^+$ (%)	5.61±1.86	11.26±2.36	2.44	<0.05	5.74±1.68	5.16±2.08	0.75	>0.05

Changes of immune function in children with refractory *Mycoplasma pneumoniae* pneumonia and effects of pidotimod

YAN Yong-dong
(Children's Hospital Affiliated to Soochow University, Suzhou 215003, Jiangsu, China)

Comparison of the two refractory MPP groups

Group	*n*	Number of recurrences
MPP treatment group	40	0.43 ± 0.06
MPP control group	26	2.16 ± 0.84
T value		2.87
P		<0.01

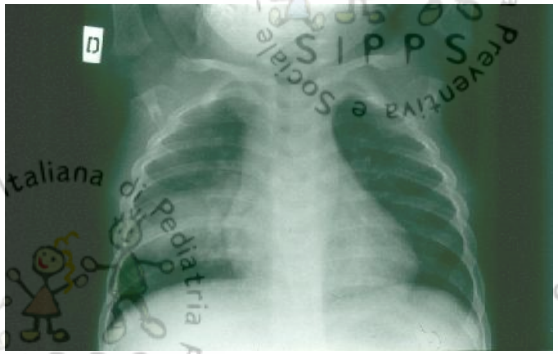
(J Clin Pediatr Vol.26 No.7 Jul.2008;

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

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

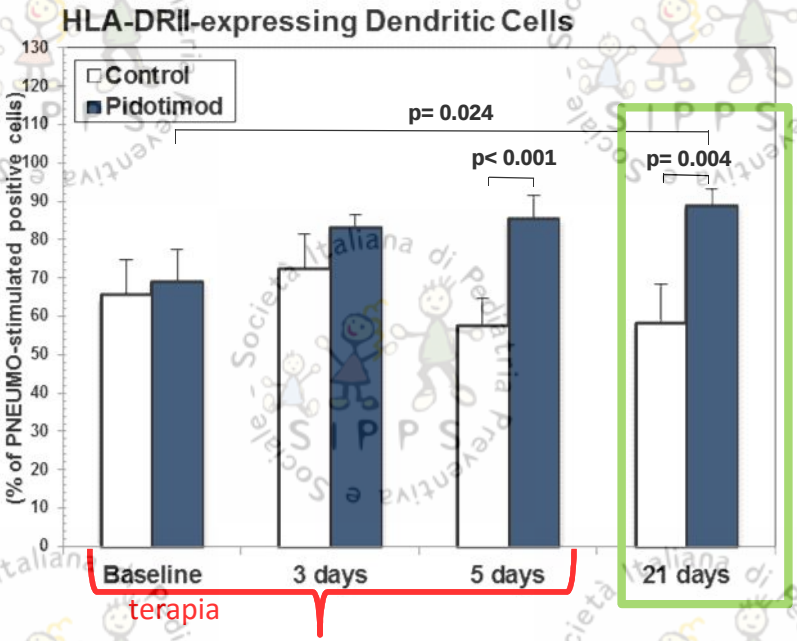
Esposito *et al. J Transl Med* (2015) 13:288

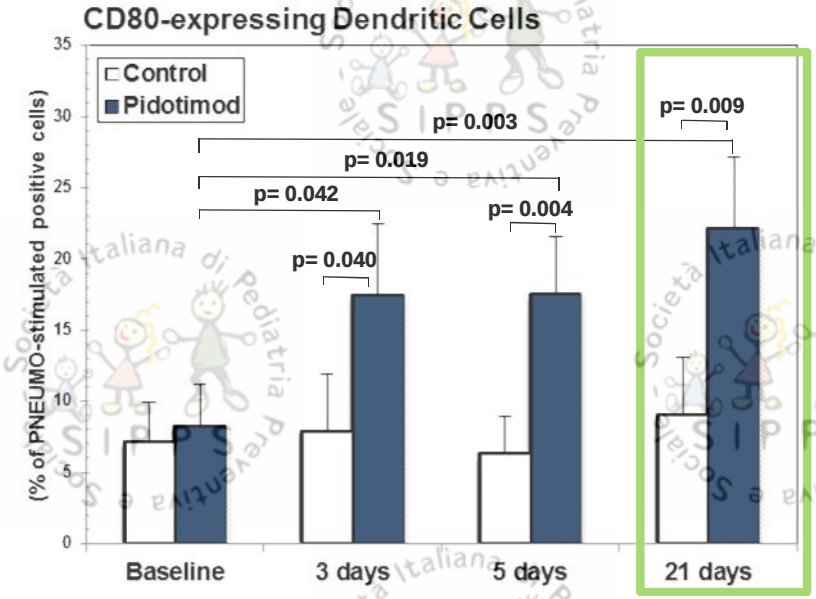
- Studio randomizzato in doppio cieco
- inverno 2013-2014
- 20 pazienti (età > 3 anni)
- ricoverati per CAP medio-grave e confermata
- da Rx torace e randomizzati a
  - Terapia antibiotica + PIDOTIMOD
  - Terapia antibiotica

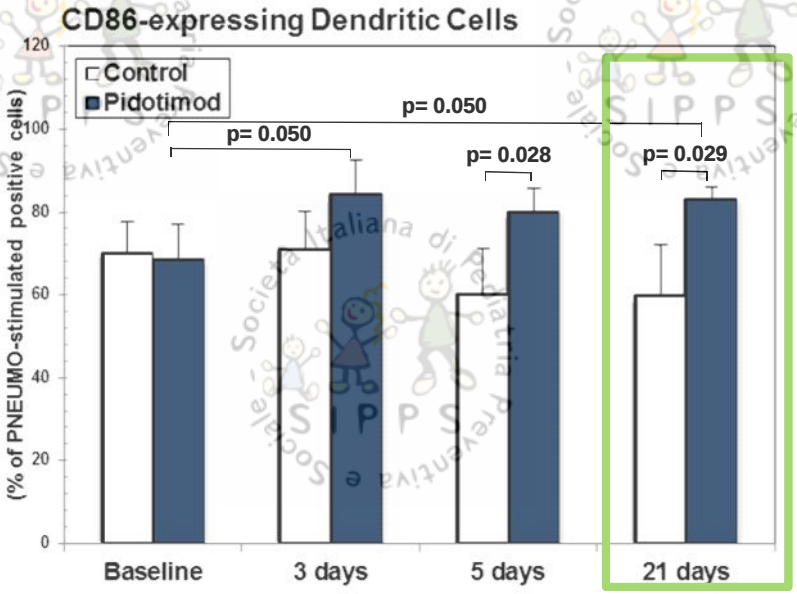


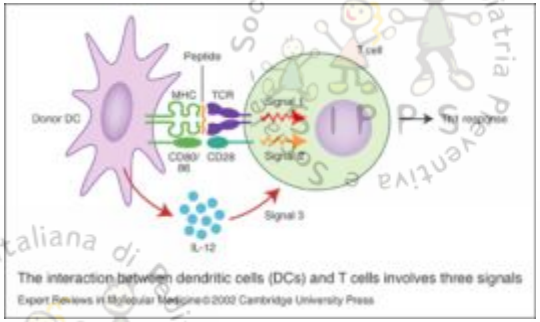
- <u>Terapia antibiotica</u>: Amoxicillina + Acido clavulanico 80 mg/kg/die per os in 3 somministrazioni/die in associazione a claritromicina 15 mg/kg/die in 2 somministrazioni /die per os per 10 - 14 giorni
- **<u>PIDOTIMOD</u>: 400 mg x 2 volte/die per os per 10 giorni**
- Valutazioni immunologiche al basale e a T3, T5 e T21 giorni

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



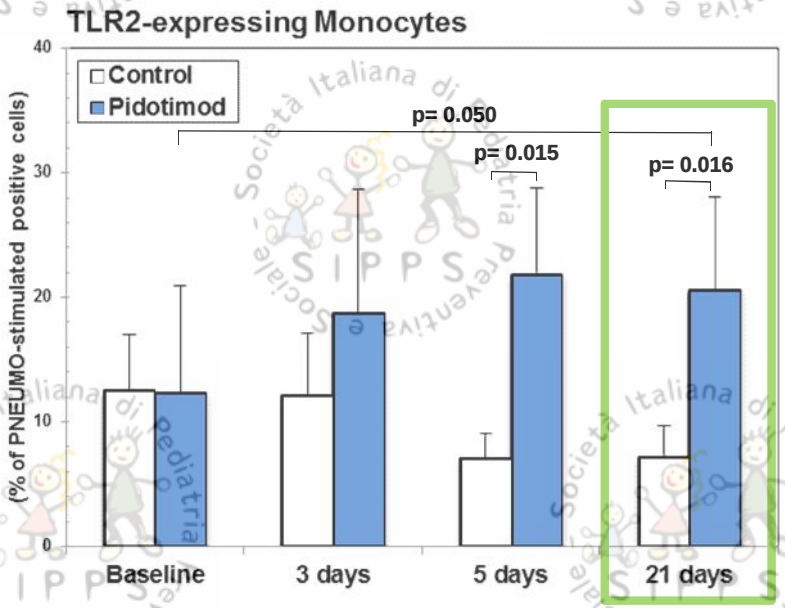


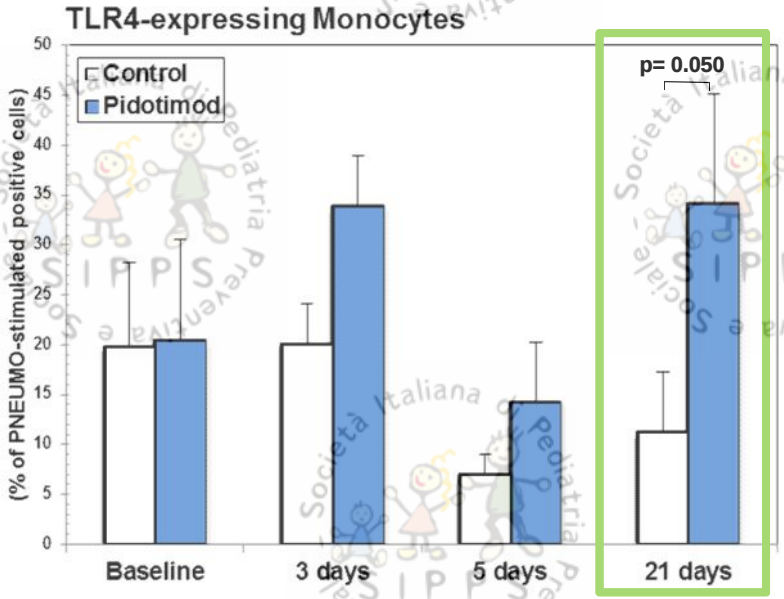


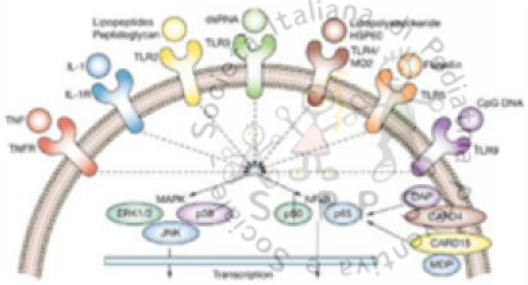


Stimolazione con pool di peptidi di pneumococco (antigeni specifici per CAP)

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







TLR : «allerta» per riconoscimento patogeni

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

JOURNAL OF TRANSLATIONAL MEDICINE

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

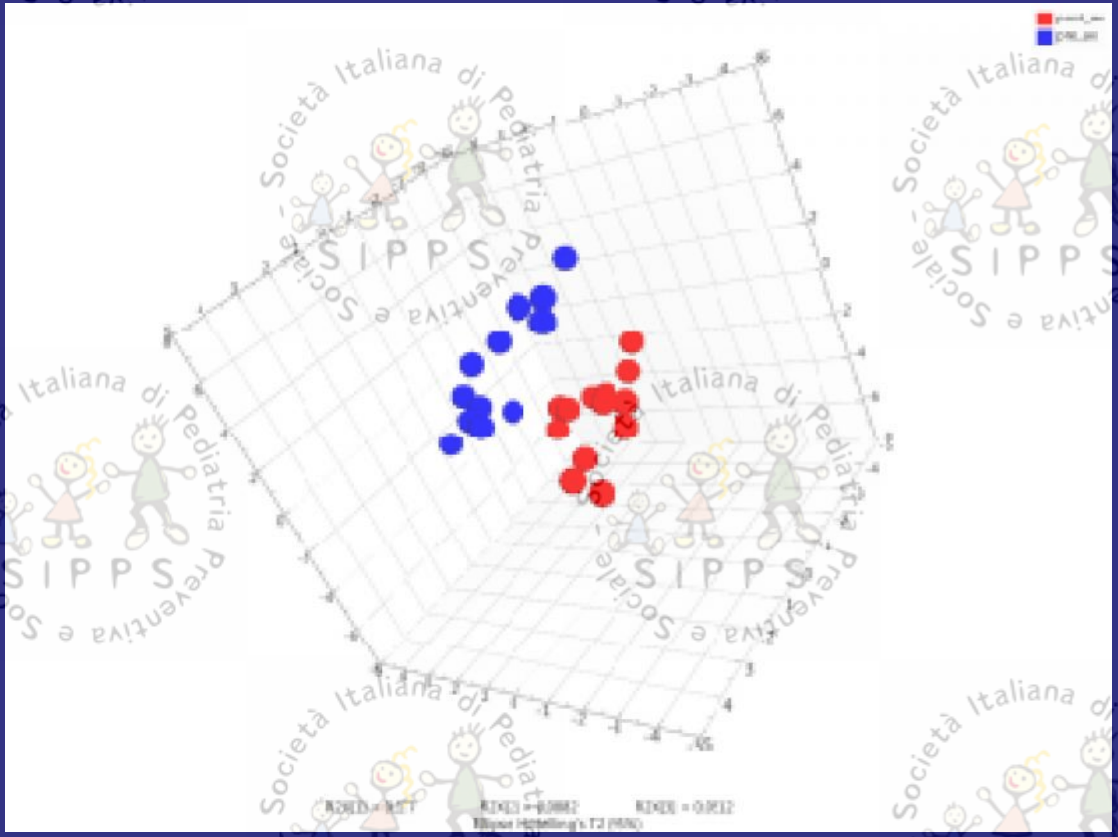
Conclusions

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

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

PROFILO METABOLOMICO DI BAMBINI CON INFEZIONI RESPIRATORIE RICORRENTI

Gruppo Prof Baraldi – SIMRI ottobre 2015



Analisi metabolomica di un campione di urine, per identificare la presenza di profili di metaboliti caratteristici di bambini con IRR pre e post terapia di 3 mesi con Pidotimod. **Dopo la terapia, i bambini con IRR non risultavano più significativamente differenti rispetto ai controlli sani.**

3D PLS-DA Score plot che dimostra la separazione tra il gruppo di bambini pre Pidotimod (in blu) e il gruppo post (in rosso).

THE FIRST CAUSE OF RECURRENT RESPIRATORY INFECTIONS IN CHILDREN IS…

CHILDHOOD ITSELF

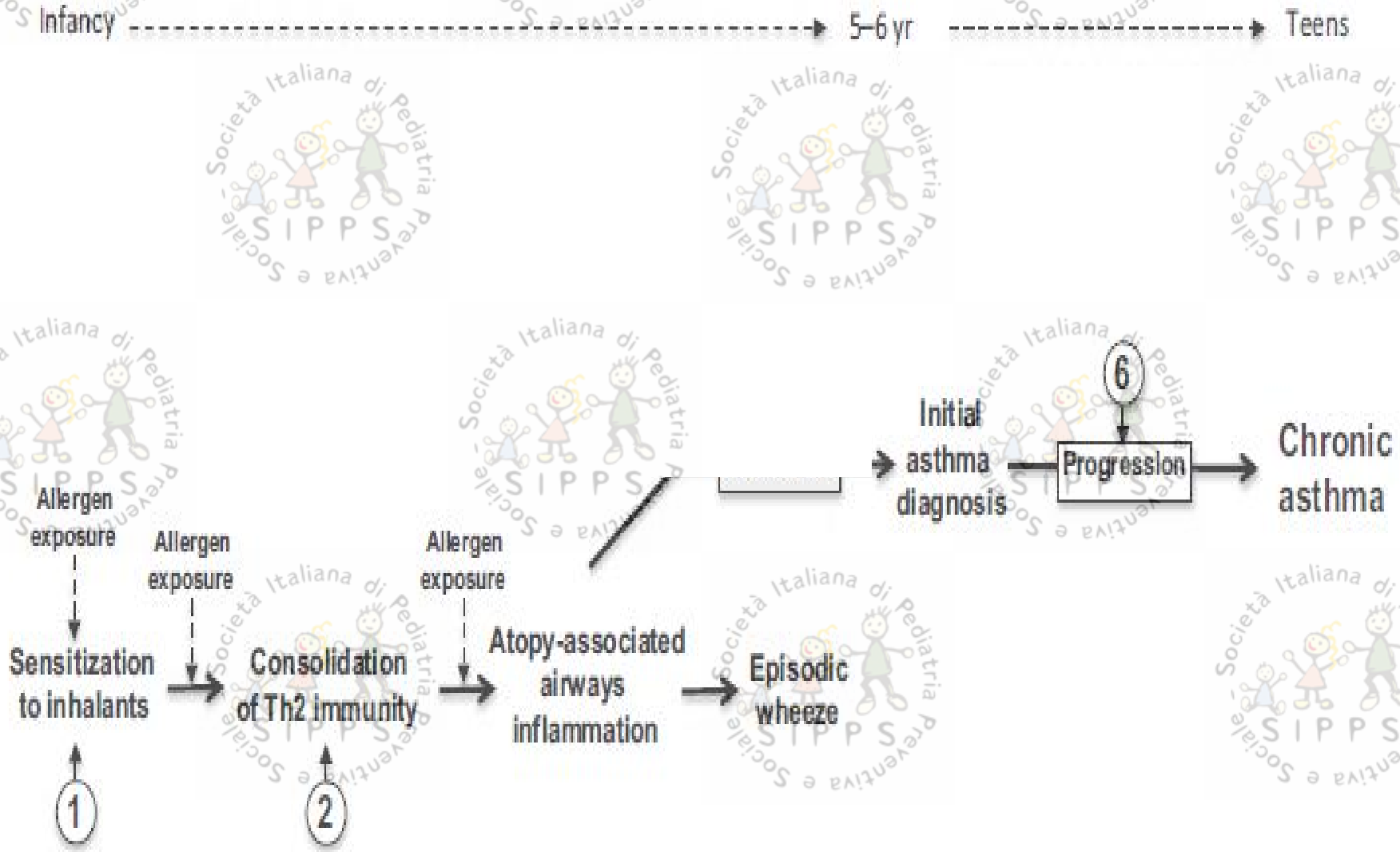
(J.G. Wheeler 1996)

Ma guardiamo avanti…

Prevention – what is the most promising approach?

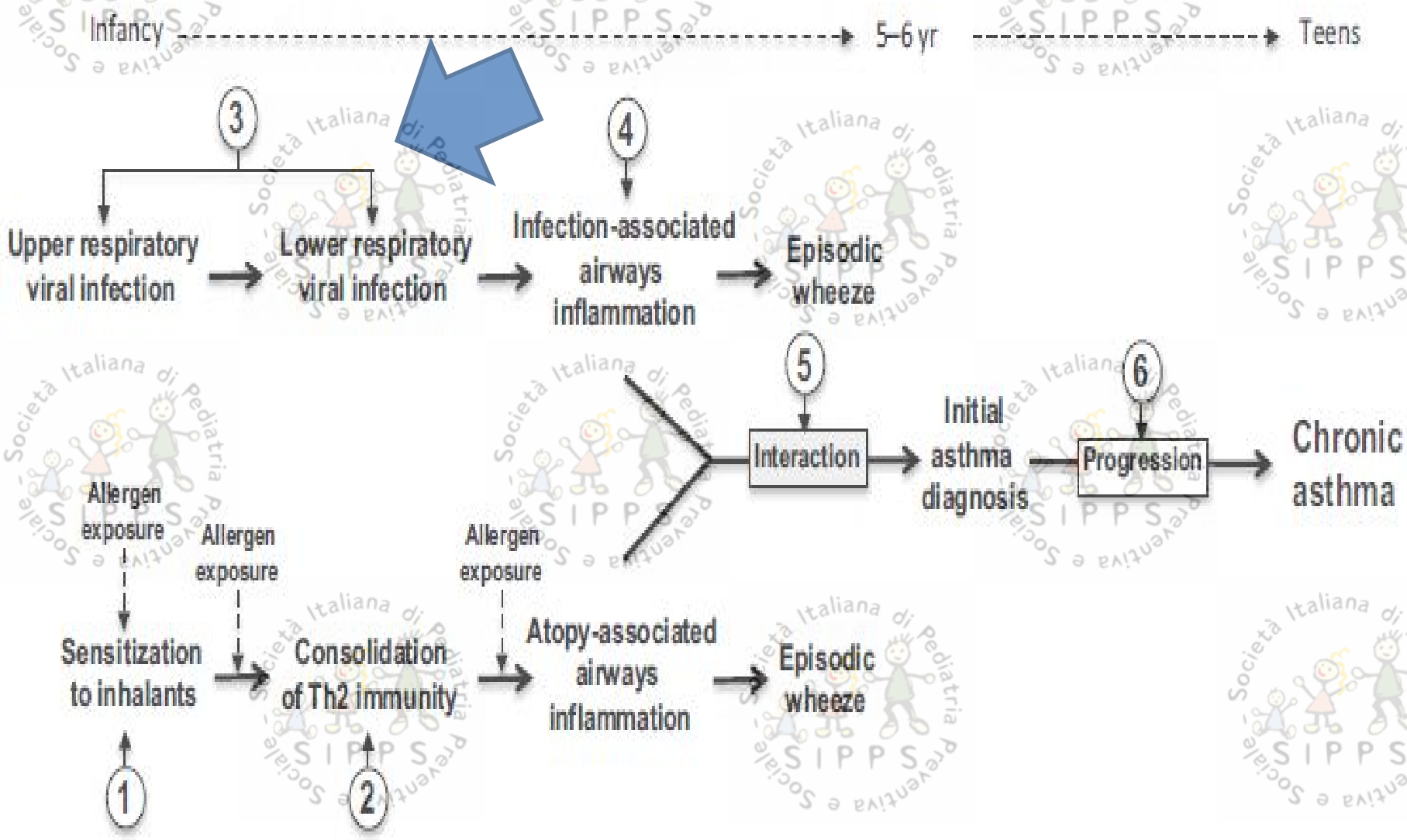
HOLT PG. PAI 2014

CASUAL PATHWAYS LEADING TO ASTHMA IN CHILDHOOD



Il possibile futuro : dalla prevenzione delle IRR alla prevenzione dell'asma

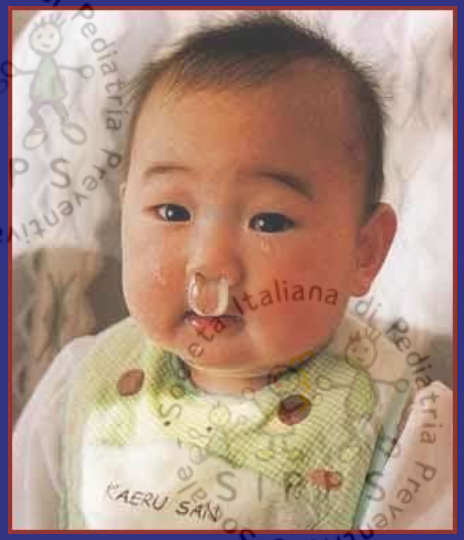
Holt PG PAI 2014



J. L. Paradise's law since 1985

DO NOT FORGET THE NOSE!

IF THE NOSE
IS SNOTTY,
THE EAR WILL
NOT CLEAR



IF THE NOSE IS SNOTTY,
(U)RTI WILL RECURR

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

CHILDHOOD ITSELF

(J.G. Wheeler 1996)

From

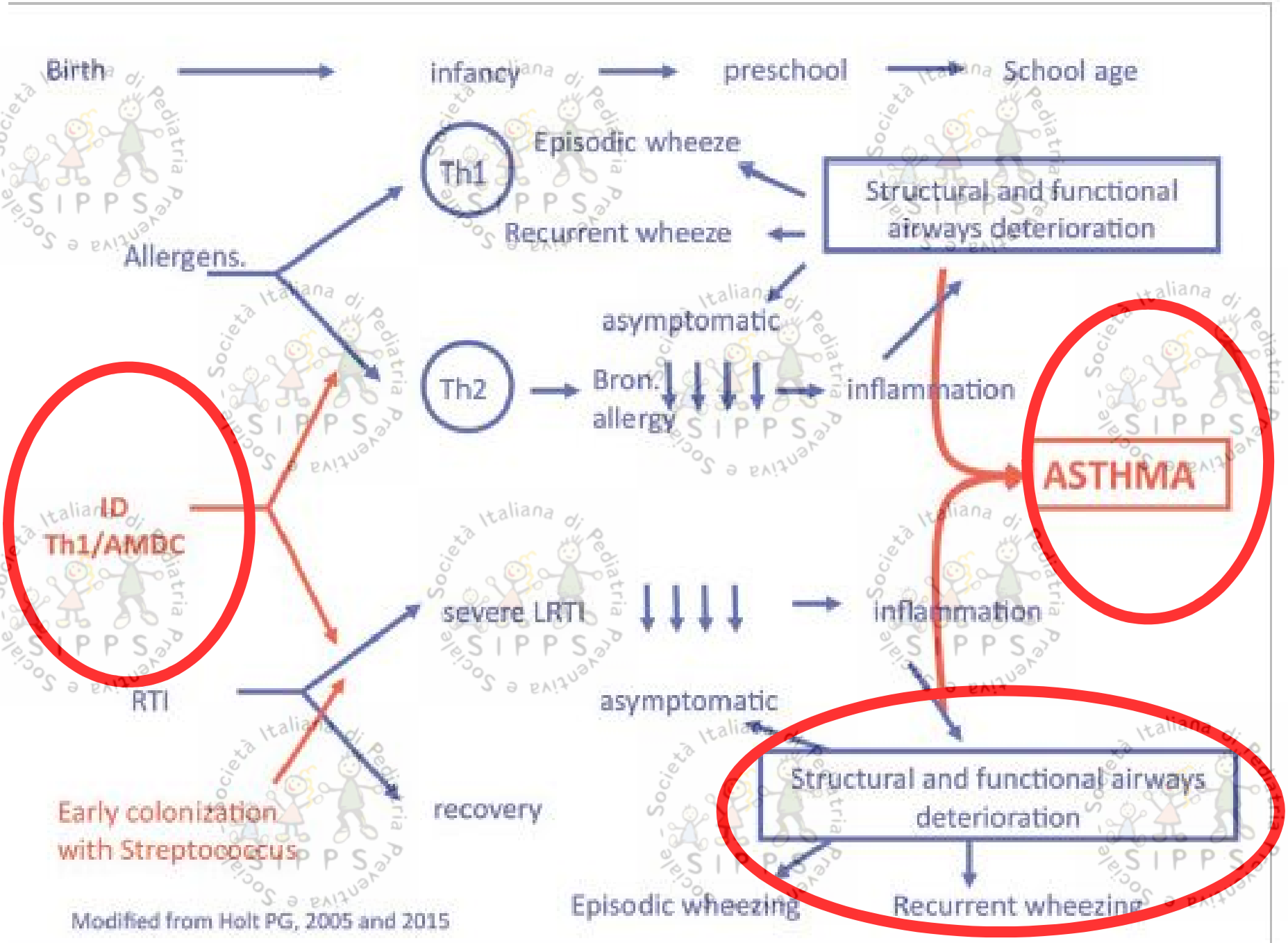
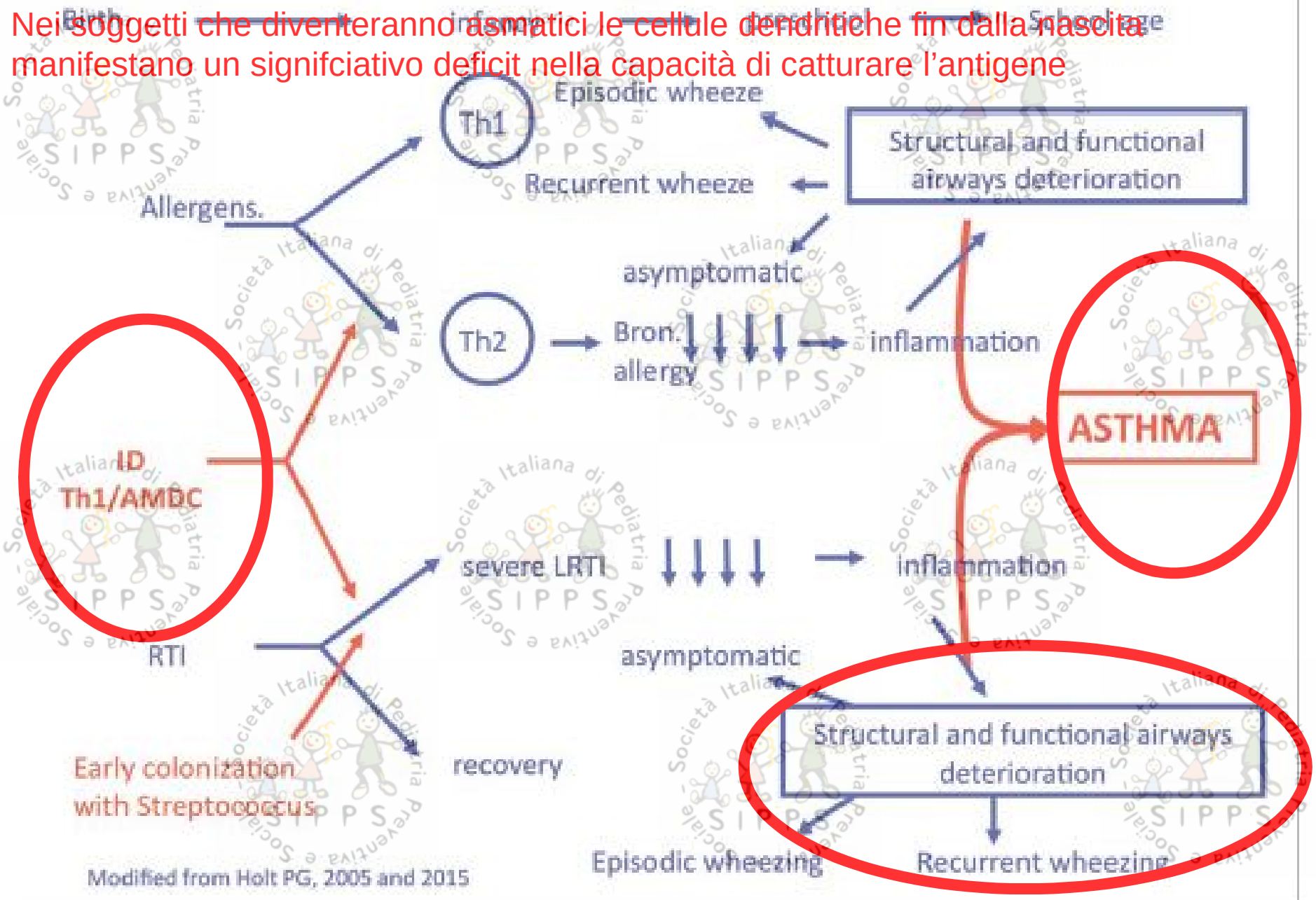
WAIT AND SEE

DO THE BEST YOU CAN

BASED ON

PEDIATRIC , WEIGHED AND SHARED EVIDENCE MEDICINE

grazie per l’attenzione


Birth
infancy
preschool
School age
Th1
Episodic wheeze
Recurrent wheeze
Structural and functional airways deterioration
Allergens.
asymptomatic
Th2
Bron. allergy
inflammation
ASTHMA
ID
Th1/AMDC
severe LRTI
inflammation
RTI
asymptomatic
Structural and functional airways deterioration
Early colonization with Streptococcus
recovery
Episodic wheezing
Recurrent wheezing
Modified from Holt PG, 2005 and 2015

Nei soggetti che diventeranno asmatici le cellule dendritiche fin dalla nascita manifestano un signifciativo deficit nella capacità di catturare l'antigene