



GEMINI 2008

**GIORNATE MULTIDISCIPLINARI
INTERATTIVE ITALIANE
DI PEDIATRIA**

DEDICATO AL PROF. MAURIZIO MIRAGLIA DEL GIUDICE

**15 - 17 GIUGNO 2008
CENTRO CONGRESSI SIMERI (CZ)**

IMMUNOTERAPIA SPECIFICA

Michele Miraglia del Giudice

Servizio Asma e Fisiopatologia Respiratoria Infantile

"Maurizio Miraglia del Giudice"

Dipartimento di Pediatria "F. Fede"

*Seconda **Università di Napoli***



Official Journal of the
European Academy of Allergy
and Clinical Immunology

EUROPEAN JOURNAL OF ALLERGY
AND CLINICAL IMMUNOLOGY

Allergy

Supplement 81 • Volume 61 • 2006

Sublingual Immunotherapy: Validated!

J. Bousquet

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SUPPLEMENT

*When immunotherapy is administered **subcutaneously**, it is not an ideal choice for all patients. Injections require repeated visit to a healthcare centre over periods of weeks at a time, and often at personal inconvenience. The procedure itself can be at best uncomfortable and, at worst, dangerous.*

Sublingual immunotherapy (SLIT), self-administered at home, has been widely proposed as an alternative to subcutaneous injections or continued medication.

EBM *oggi*

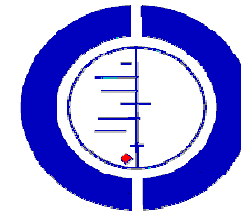
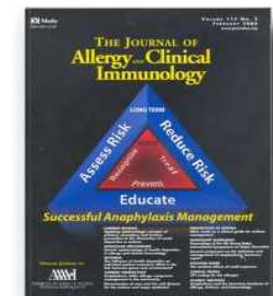


TABLE III. Experimental evidence for immunotherapy

	SCIT	SLIT
Clinical efficacy: rhinitis	Ib	Ia
Clinical efficacy: asthma	Ia	Ia
Clinical efficacy: children (rhinitis)	Ib	Ia
Prevention of new sensitizations	Ib	IIa
Long-term effect	Ib	IIa
Prevention of asthma	Ib*	Ib*



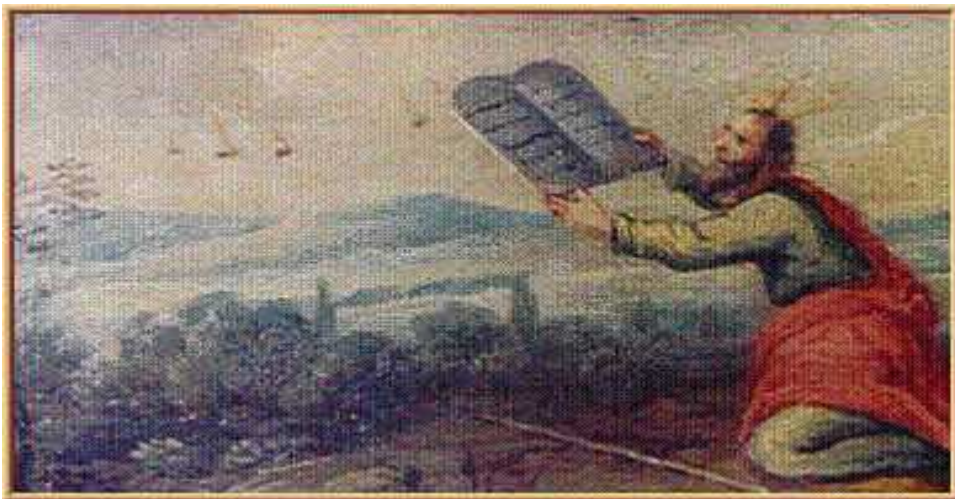
Giovanni Passalacqua, MD,a and Stephen R. Durham, MD,b in cooperation with the Global Allergy and Asthma European Network (GA2 LEN) Genoa, Italy, and London, United Kingdom in JACI 2007

EBM in Immunoterapia Specifica



LE EVIDENZE IN MEDICINA *Shekelle PG et al BMJ 99*

- 1^a → Metanalisi di trials controllati e randomizzati
- 1^b → Almeno uno studio controllato e randomizzato
- 2^a → Almeno uno studio controllato senza randomizzazione
- 2^b → Almeno uno studio sperimentale
- 3 → Risultato di studio a modello non sperimentale
(Comparativi, Caso Controllo, Correlazione)
- 4 → Pareri di esperti



RACCOMANDAZIONI

- A: BASATE SULLA CATEGORIA 1
- B: BASATE SULLA CATEGORIA 2
(o estrapolate dalla 1)
- C: BASATE SULLA CATEGORIA 3
(o estrapolate dalla 1-2)
- D: BASATE SULLA CATEGORIA 4
(o estrapolate dalla 1-2-3)

E.B.M.=Asma & SLIT 2004

Sublingual immunotherapy in asthma and rhinoconjunctivitis; systematic review of paediatric literature

S Miceli Sopo, M Macchiaiolo, G Zorzi, S Tripodi

Arch Dis Child 2004;89:620–624. doi: 10.1136/adc.2003.030411

Table 2 Methodological characteristics of included studies

Study	Randomisation process	Assessment of efficacy of randomisation†	Sample size calculation	Clear definition of end points	Drop out or lost during follow up	Compliance	Intention to treat analysis	Placebo concealment	Run in
Tari <i>et al</i> (1990)	NR	No	No	Yes	8/66 (12%)	NR	Yes	Yes	No
Hirsh <i>et al</i> (1990)	Code provided by manufacturer	Yes	Yes	Yes	None	83%	Yes	Yes	Yes
Pajno <i>et al</i> (2000)	Keyed code	Yes	No	Yes	3/24 (12.5%)	NR	Yes	Yes	Yes
Bahçeciler <i>et al</i> (2001)	NR	Yes	No	Yes	None	NR	Yes	Yes	Yes
Ippoliti <i>et al</i> (2003)	NR	Yes	No	Yes	None*	Good*	Yes*	Yes	Yes
Vourdas <i>et al</i> (1998)	NR	Yes	No	Yes	2/66 (3%)	NR	No	Yes	No
La Rosa <i>et al</i> (1999)	NR	Yes	No	Yes	8/41 (19.5%)	98%	No	Yes	No
Caffarelli <i>et al</i> (2000)	PC generated list	Yes	No	Yes	4/44 (8.4%)	“Very good”	Yes	Yes	No



Conclusions: SLIT can be currently considered to have low to moderate clinical efficacy in children of at least 4 years of age, monosensitised to HDM, and suffering from mild to moderate persistent asthma. This benefit seems to be adjunctive with respect to the environmental preventive measures against HDM.



Efficacia della SLIT
nelle allergopatie
respiratorie dei
Bambini metanalisi
2005

Rinite 2005

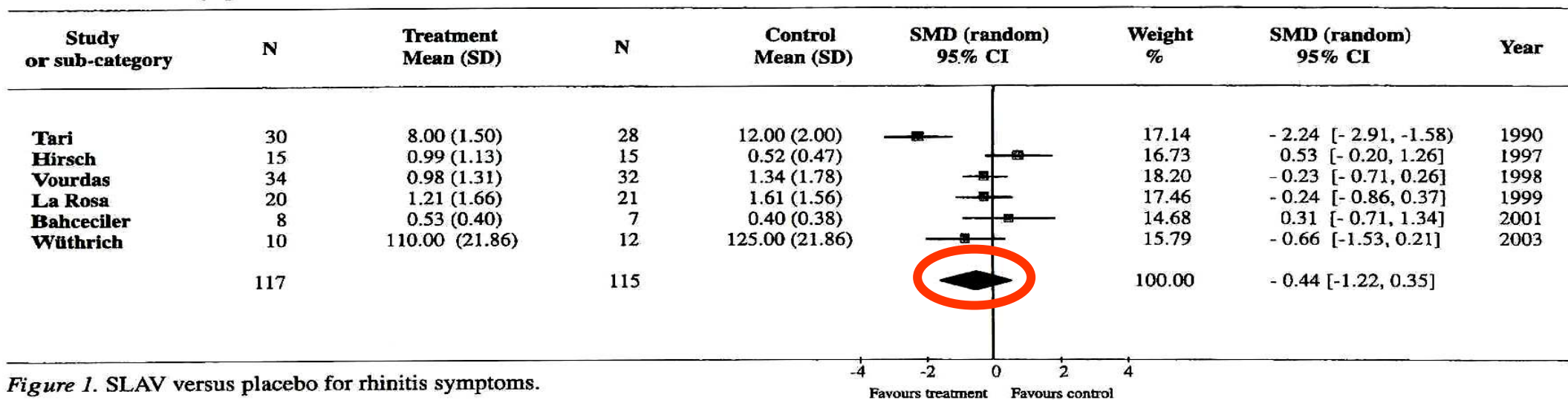


Figure 1. SLAV versus placebo for rhinitis symptoms.

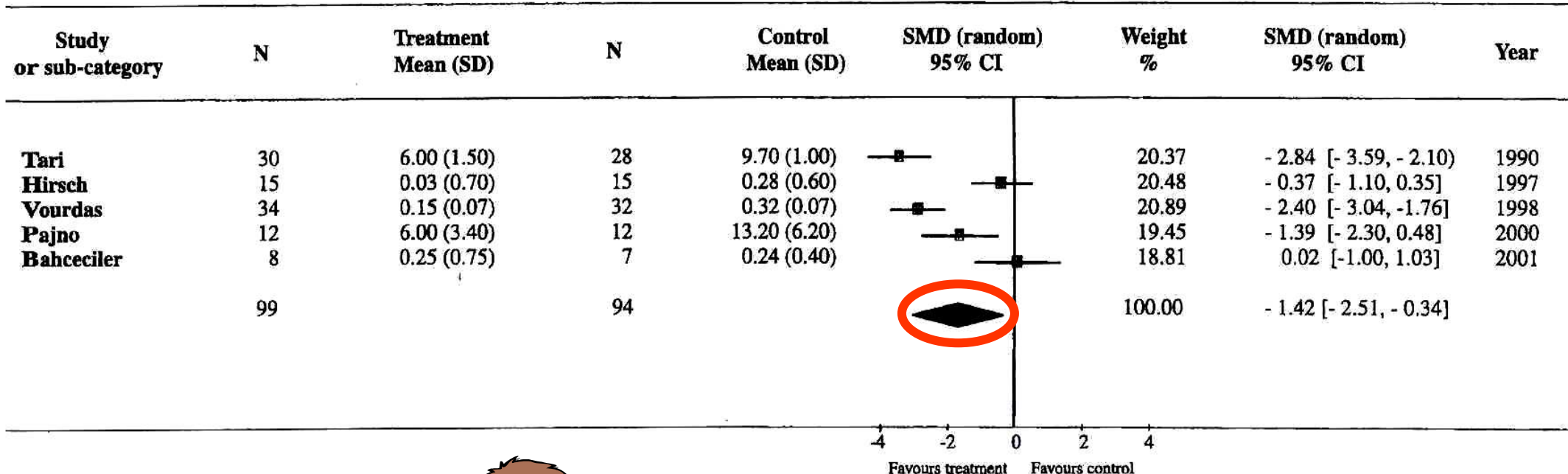




Efficacia della SLIT
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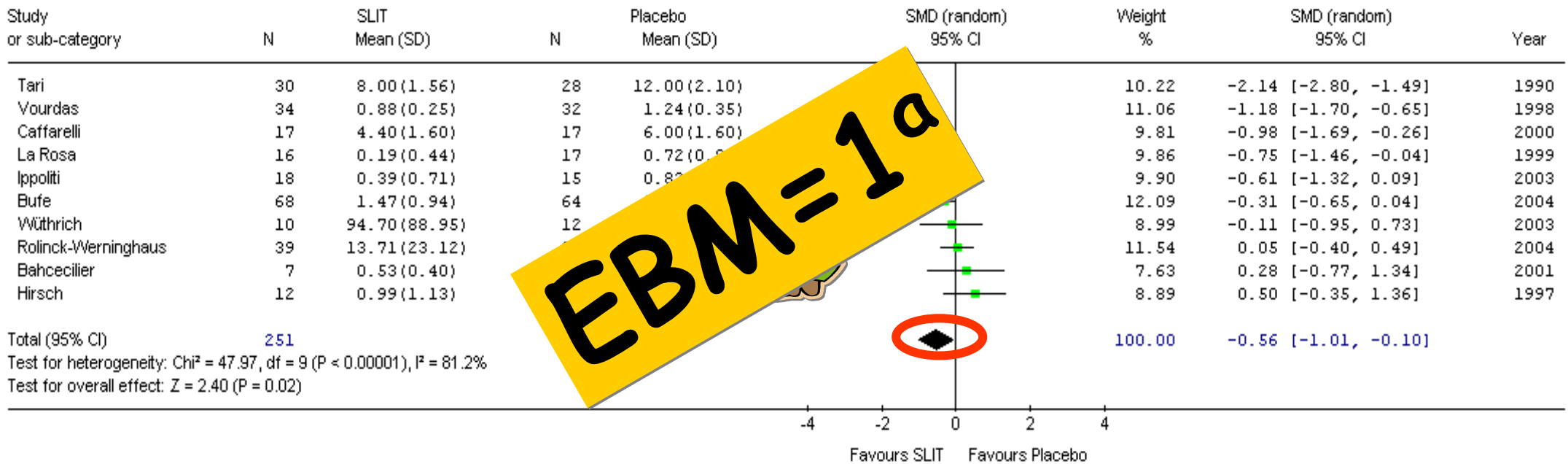
Asma 2005

ANNO 2005



E.B.M.=Rinite & SLIT 2006

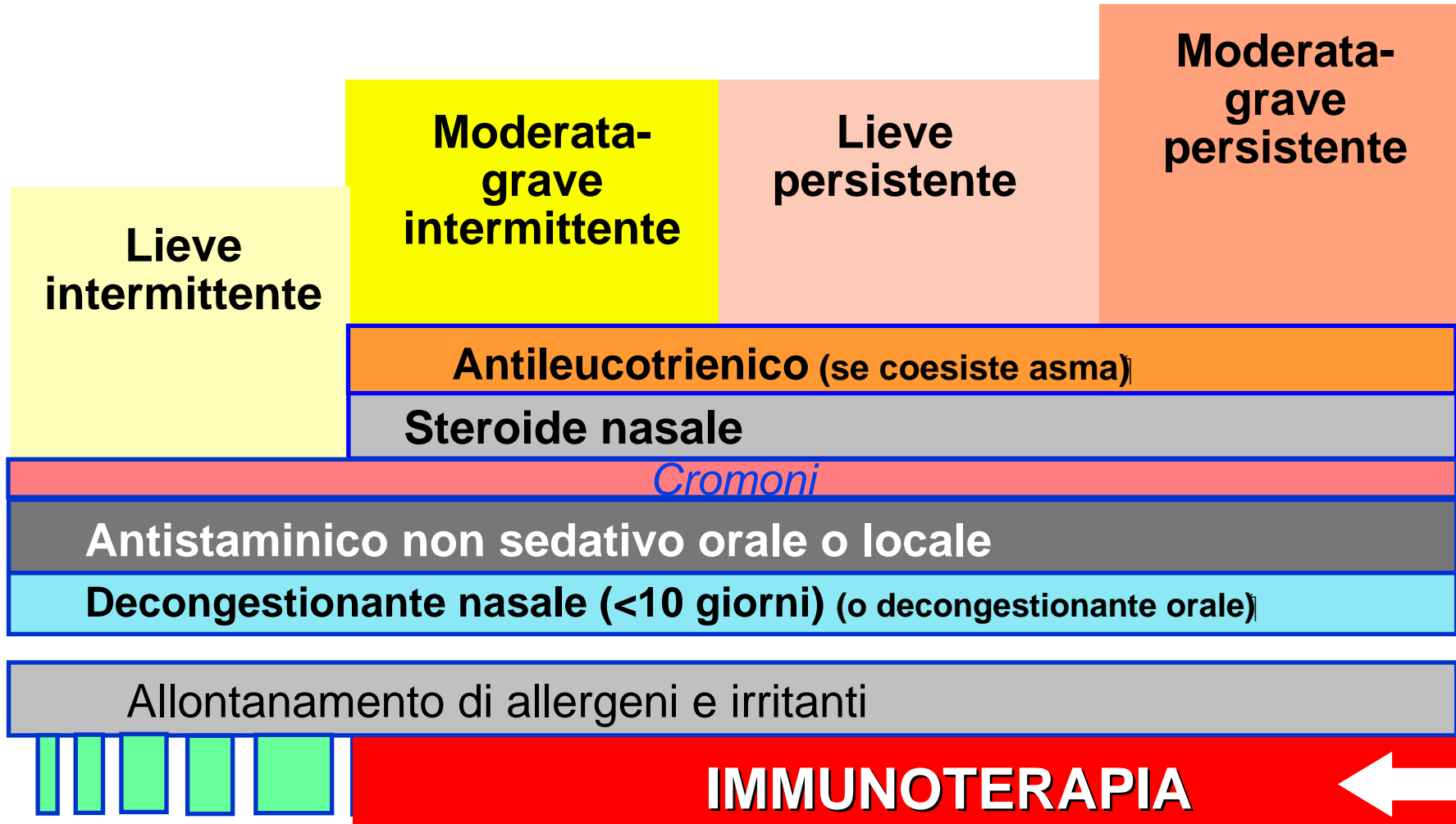
Review: Efficacy and safety of sublingual immunotherapy in the treatment of allergic rhinitis in children. Meta-analysis of randomized controlled trials.
 Comparison: 01 Nasal score rhinitis
 Outcome: 01 Nasal score rhinitis



Penagos et al. *Annals of Allergy Asthma and Immunology* 2006

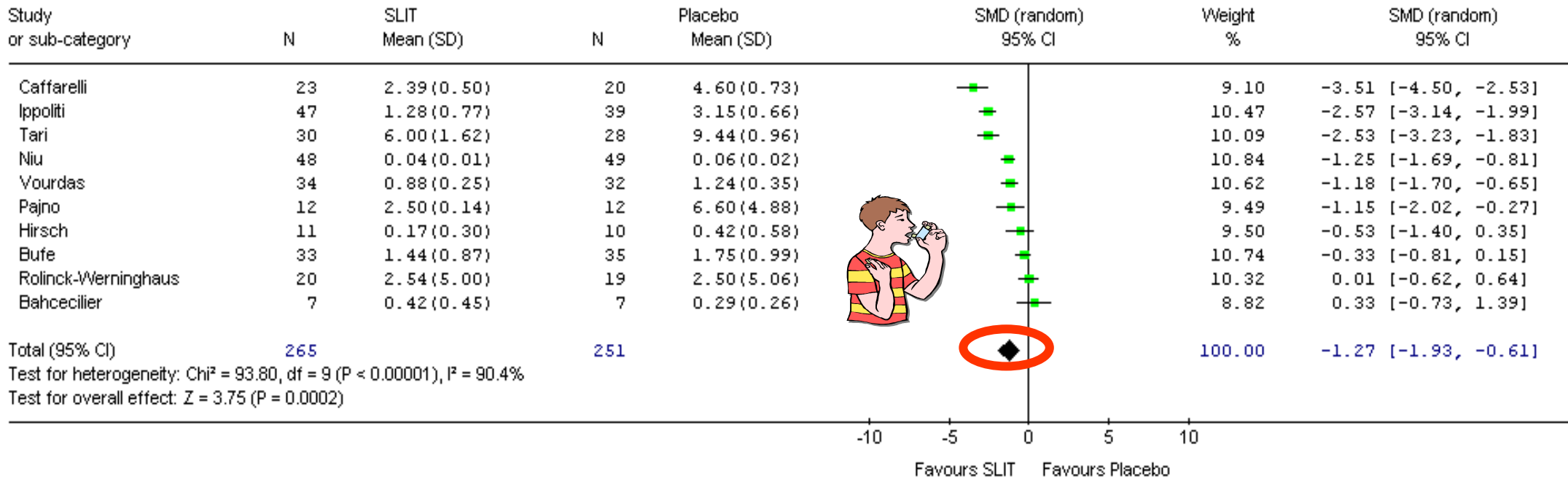
Trattamento della rinite allergica

ARIA -Allergic Rhinitis and its Impact on Asthma



E.B.M.=Asma & SLIT 2006

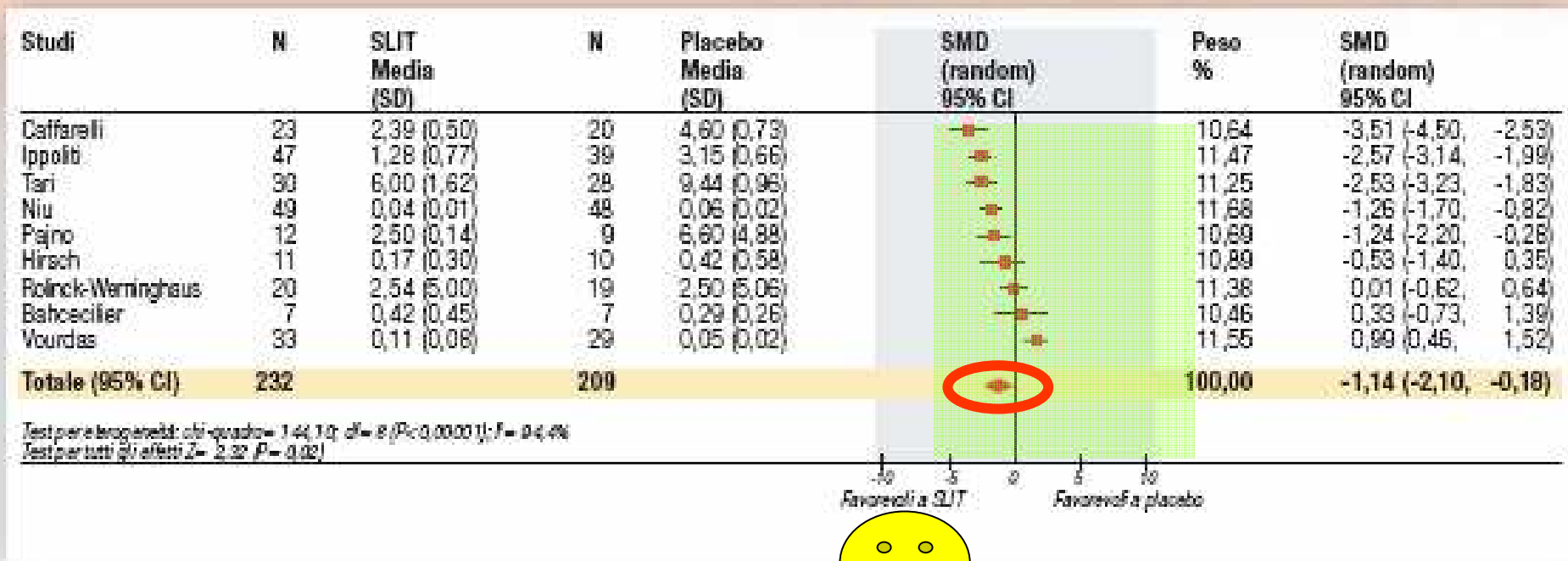
Review: Efficacy of Sublingual Immunotherapy in the treatment of asthma in children. Meta-analysis of randomized controlled trials.
 Comparison: 02 Bronchial score asthma
 Outcome: 01 Bronchial score asthma



Canonica GW et al 2006

Metaanalysis of the efficacy of sublingual immunotherapy in the treatment of allergic asthma in pediatric patients, 3 to 18 years of age. *Penagos M et al. Chest. 2008 Mar;133(3):599-609.*

PUNTEGGIO DEI SINTOMI



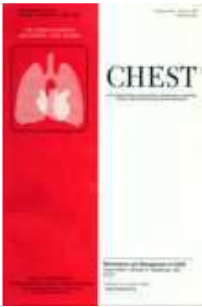
Symptom scores

9 studies



n = 441

SMD -1.14



Metaanalysis of the efficacy of sublingual immunotherapy in the treatment of allergic asthma in pediatric patients, 3 to 18 years of age. *Penagos M et al. Chest. 2008 Mar;133(3):599-609.*

UTILIZZO DI FARMACI

Studi	N	SLIT Media (SD)	N	Placebo Media (SD)	SMD (random) 95% CI	Peso %	SMD (random) 95% CI
Pajno	12	82,60 (11,73)	9	205,20 (11,73)		8,41	-8,10 (-10,95, -5,25)
Ippoliti	47	1,41 (0,73)	39	5,54 (0,73)		14,94	-4,72 (-5,56, -3,88)
Bahceciler	7	2,13 (0,83)	7	5,54 (0,83)		14,19	-0,75 (-1,85, 0,35)
Caffarelli	23	8,37 (1,51)	20	5,54 (1,51)		15,47	-0,53 (-1,14, 0,08)
Vourdas	34	1,12 (2,27)	34	5,54 (2,27)		15,71	-0,19 (-0,68, 0,29)
Niu	49	0,02 (0,31)	49	5,54 (0,31)		15,84	-0,10 (-0,50, 0,30)
Rolnick-Werninghaus	20	2,54 (3,58)	20	5,54 (3,58)		15,44	-0,08 (-0,71, 0,55)
Totale (95% CI)	192					100,00	-1,63 (-2,83, -0,44)

EBM=1^a

Test per eterogeneità chi-quadro = 130,85; df = 6; P < 0,00001; I² = 96,3%
 Test per tutti gli effetti Z = 2,69; P = 0,007

Favorevoli a SLIT Favorevoli a placebo



Medication scores

7 studies

n = 366

SMD -1.63

Indicazioni all'immunoterapia specifica (ITStra) nell'asma

- **L'ITS può essere indicata nei pazienti con asma allergica, da lieve a moderata, specialmente quando l'asma è associata a rinite, in accordo con le indicazioni già definite.**
- **Lo scopo è quello di ridurre i sintomi ed il consumo di farmaci, nonché di interferire con la storia naturale della malattia.**
- **L'immunoterapia ed il trattamento farmacologico non sono mutuamente esclusivi.**
- **L'immunoterapia non deve essere somministrata a pazienti con asma severa persistente o non adeguatamente controllata dalla terapia.**



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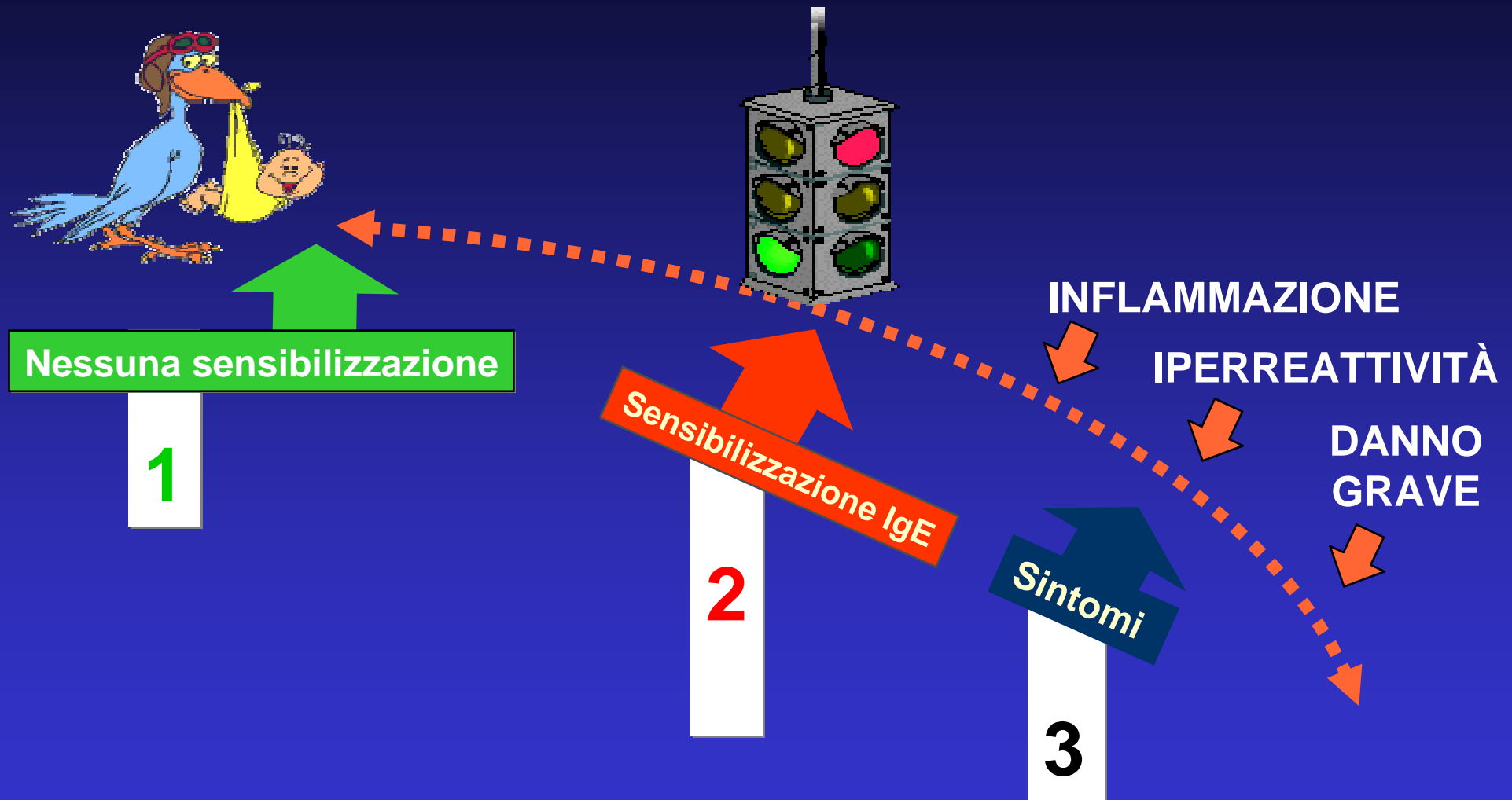
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**Immunoterapia Sublinguale:
Quando prescriverla?**

La storia naturale delle malattie allergiche

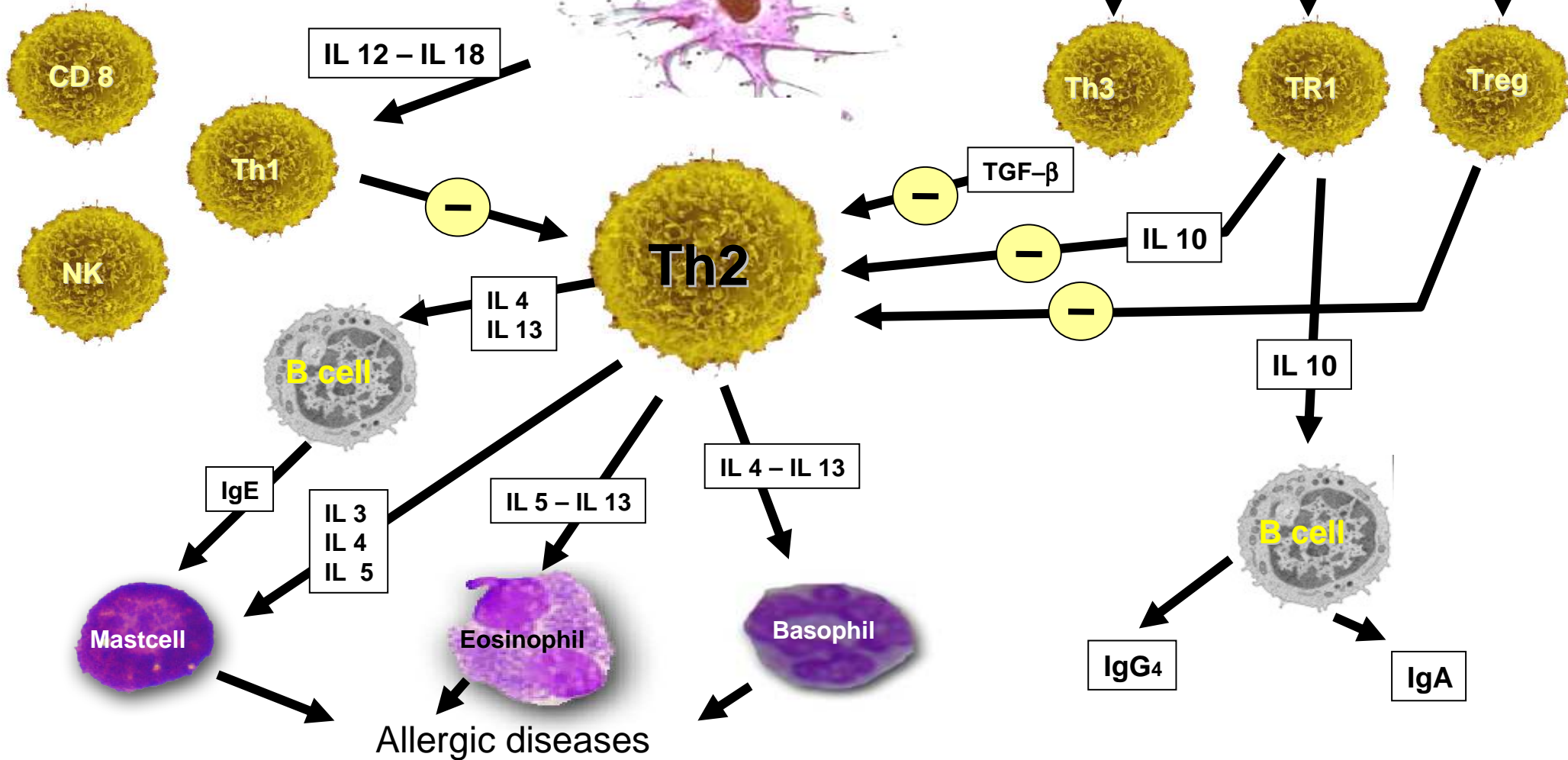


Allergen from SLIT or SCIT

IMMUNODEVIATION

IMMUNOTOLERANCE

Allergen



....SLIT and Primary prevention



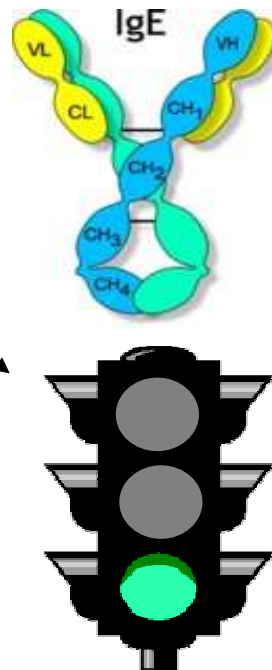
Patrick G. Holt

*Telethon Institute for Child Health
Research, Perth, Australia*

**Aetiology and pathogenesis of atopy and asthma
Immunoprophylaxis of asthma and atopy**

PG Holt

The trial will test a radical approach to prophylaxis of these diseases in “high risk” children, employing a vaccine-like approach which is conceptually similar to that used for prevention of infectious disease. This process has involved exhaustive protocol development negotiations with NIH and the US Food and Drug Administration, with final approval being granted in March 2006.. In the trial we will seek to intensify the tolerance process in children at risk of allergy, **by repeated exposure of the oral mucosa for a one year period, to a mixture of the three most important aeroallergens.....**



**Before IgE
production**



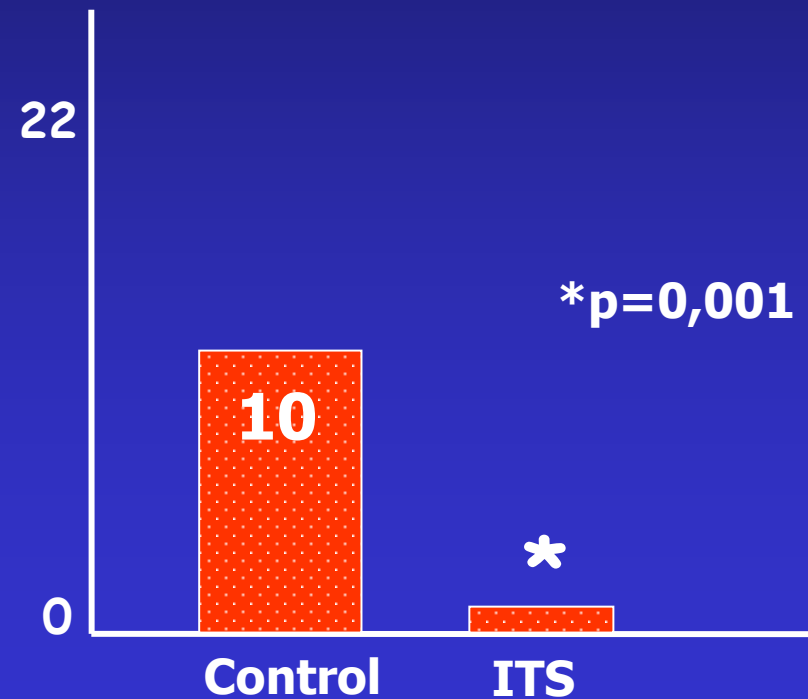
“IT with a standardized DP extract. VI. Specific IT prevents the onset of new sensitizations in children”

Des Roches A et al. (J. Bousquet)
J.A.C.I. 1997

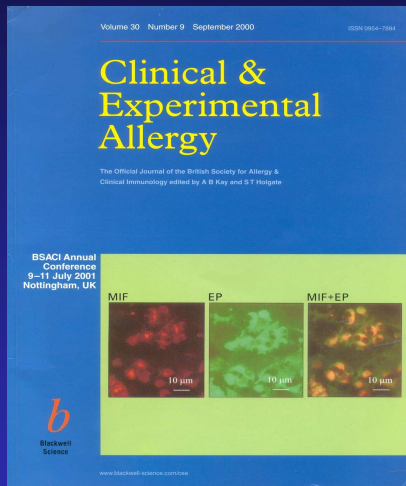


This study suggests that SIT in children monosensitized to HDM alters the natural course of allergy in preventing the development of new sensitizations.

n° of children sensitized after 3y.



ITS e ulteriori sensibilizzazioni



Prevention of new sensitizations in asthmatic children monosensitized to house dust mite by ITS. A six year follow up study

**Pajno GB et al.
CEA 2000**



ITS PER 3 ANNI

Gruppi	No ulteriori sensibilizzazioni dopo 6 anni
A: 75 pz. ITS	75%*
B: 63 pz. no ITS	33%*

*** Dato significativo**

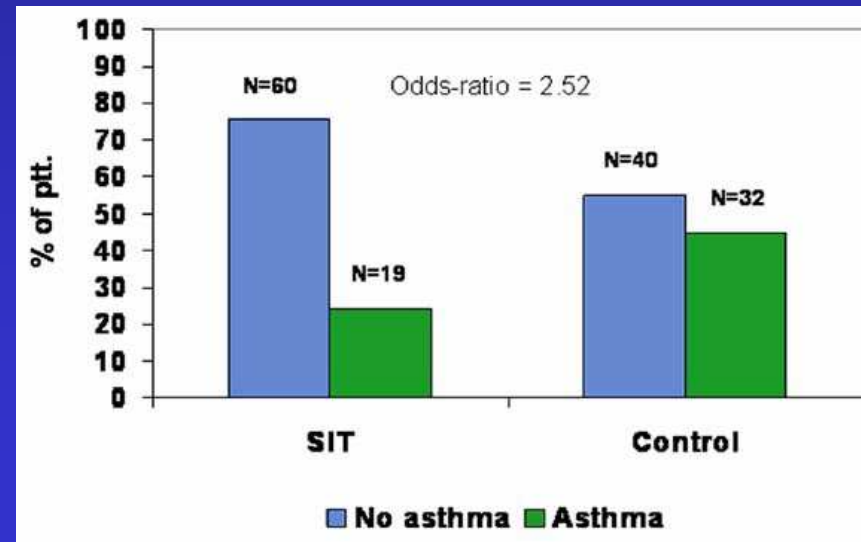
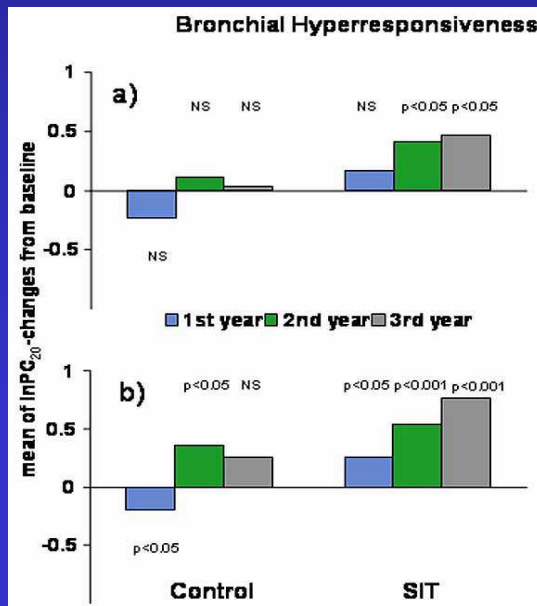
Dalla rinite all'asma...



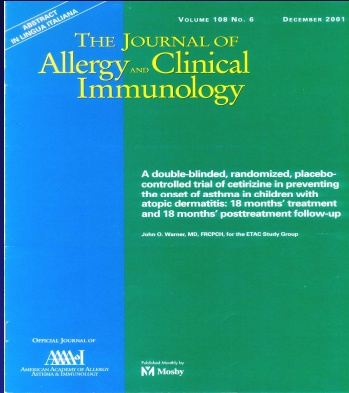
Pollen ITS reduces the development of asthma in children with seasonal rhinoconjunctivitis

Moller C, Dreborg S et al.
J Allergy Clin Immunol 2002 Feb

Studio su bambini con rinite allergica a Graminacee o Betulla per valutare l'effetto preventivo della ITS nei confronti dell'asma. Risultati dopo 3-5 anni di ITS.



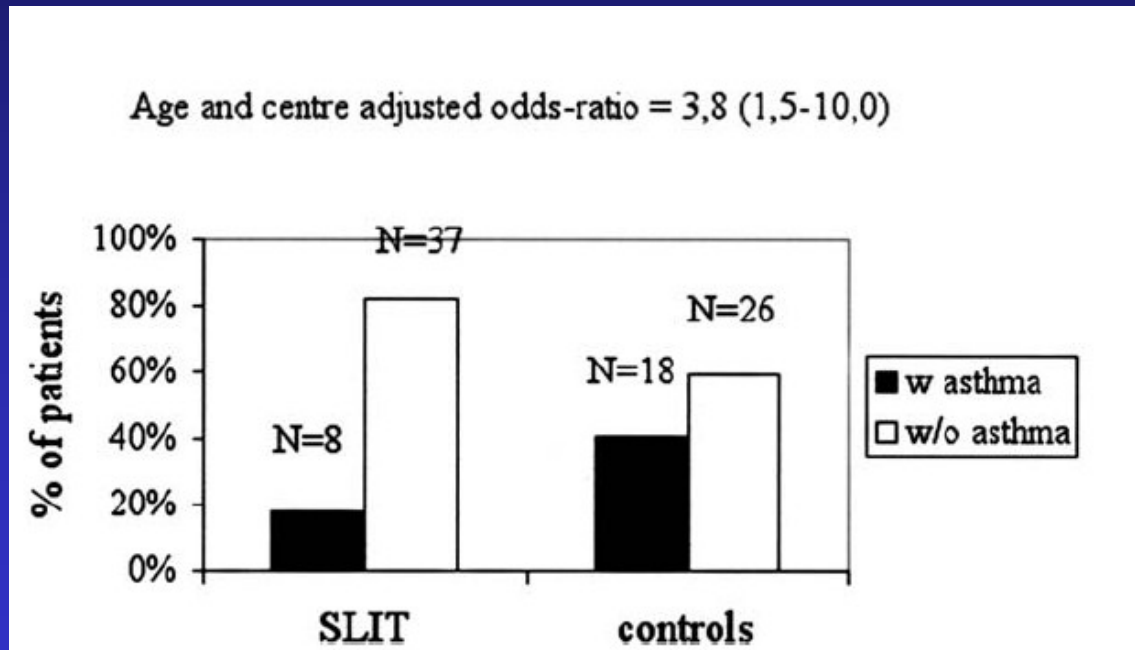
Dalla rinite all'asma...



Coseasonal SLIT reduces the development of asthma in children with allergic rhinoconjunctivitis

Novembre E et al.
J Allergy Clin Immunol 2004

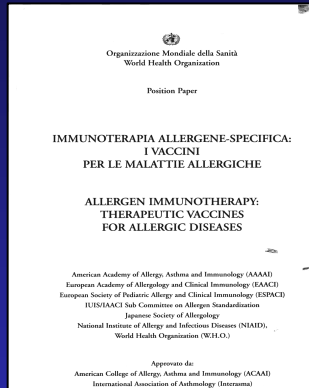
SLIT



... 3 anni di SLIT costagionale migliorano i sintomi relativi alla rinite allergica e riducono lo sviluppo di asma

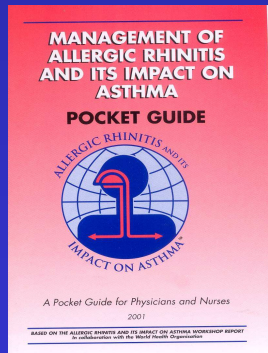


Quando iniziare ?



**DOCUMENTO
OMS 1998**

... la maggior parte degli esperti in materia consiglia di iniziare l'Immunoterapia in età pediatrica **dopo i 5 anni di età** ...
evidentemente prima si inizia e prima la marcia allergica può essere contrastata ... Necessitano ulteriori studi al di sotto dei 5 anni.

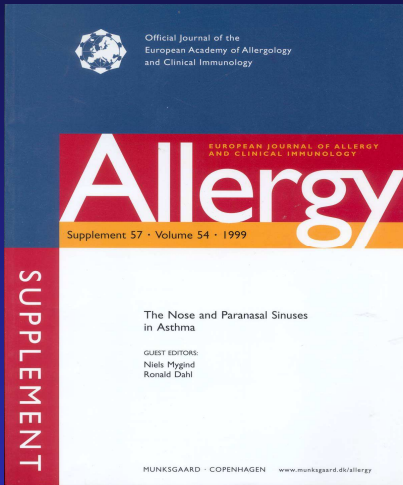


**ARIA
OMS 2001**

... si consiglia di iniziare una immunoterapia in età pediatrica dopo i **5 anni di età**, a meno che lo specialista non lo ritenga assolutamente necessario ... Necessitano ulteriori studi sotto i 5 anni di età.

... e alla fine
dell'immunoterapia specifica
la malattia riprende subito ?

Effetto Long Lasting Iniettiva



ITS with standardized Der.Pter. extract. Duration of the efficacy of ITS after cessation

**Des Roches A. e Bousquet J.
Allergy 1996**



**1- Età media 31
Durata ITS media 19 mesi**



52%

**2- Età media 27
Durata ITS media 40 mesi**



38%

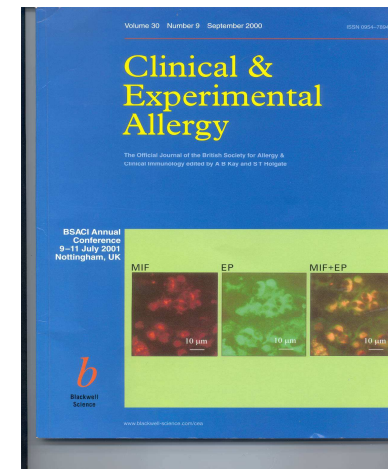
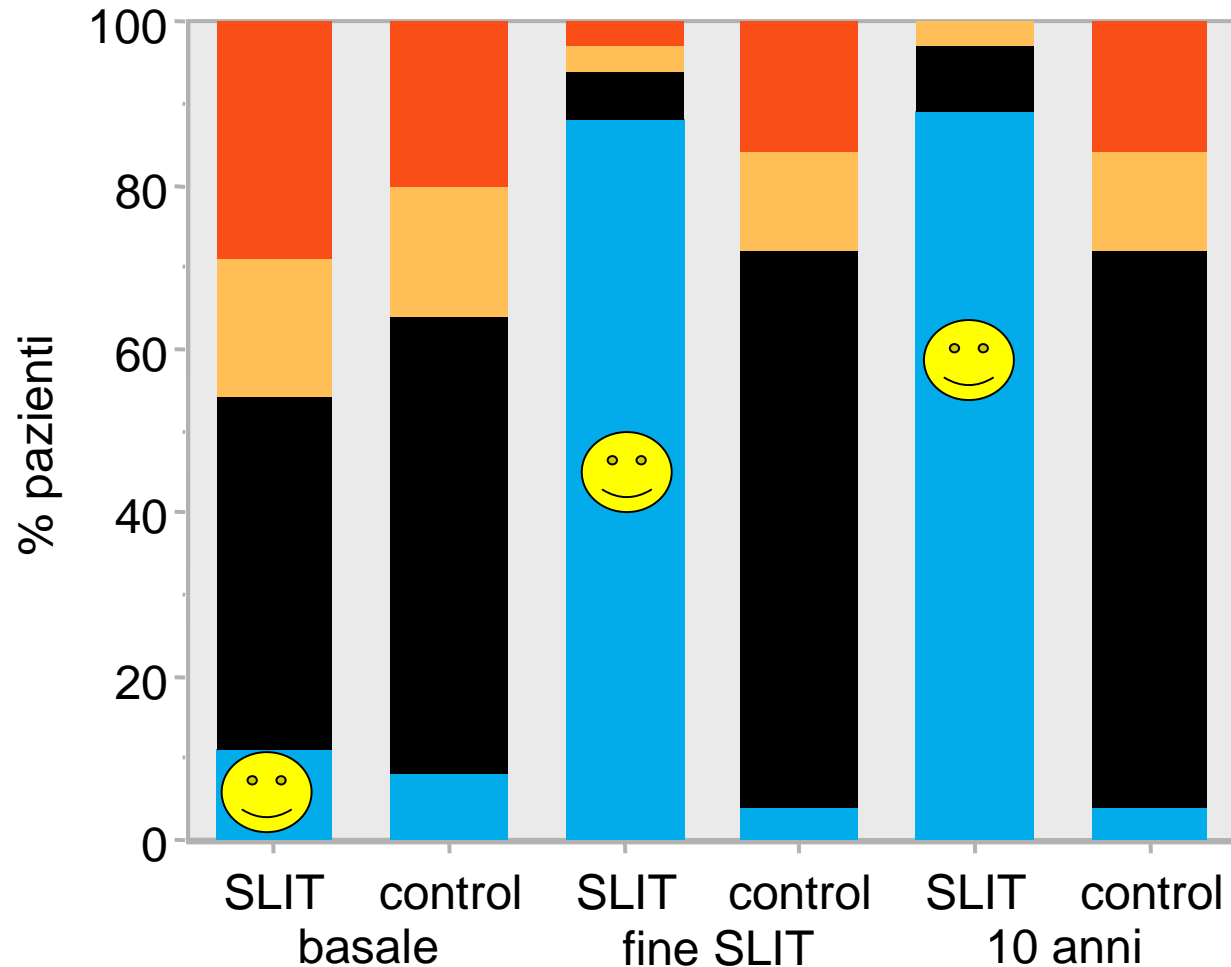
Recidive

40 Paz. asmatici in 2 gruppi con ITS per DP



Long Lasting effect of SLIT in Children with asthma due to house dust mite: a 10 year prospective study

Di Rienzo V., Canonica GW., Frati F. et al in *Clin Exp Allergy* 2003



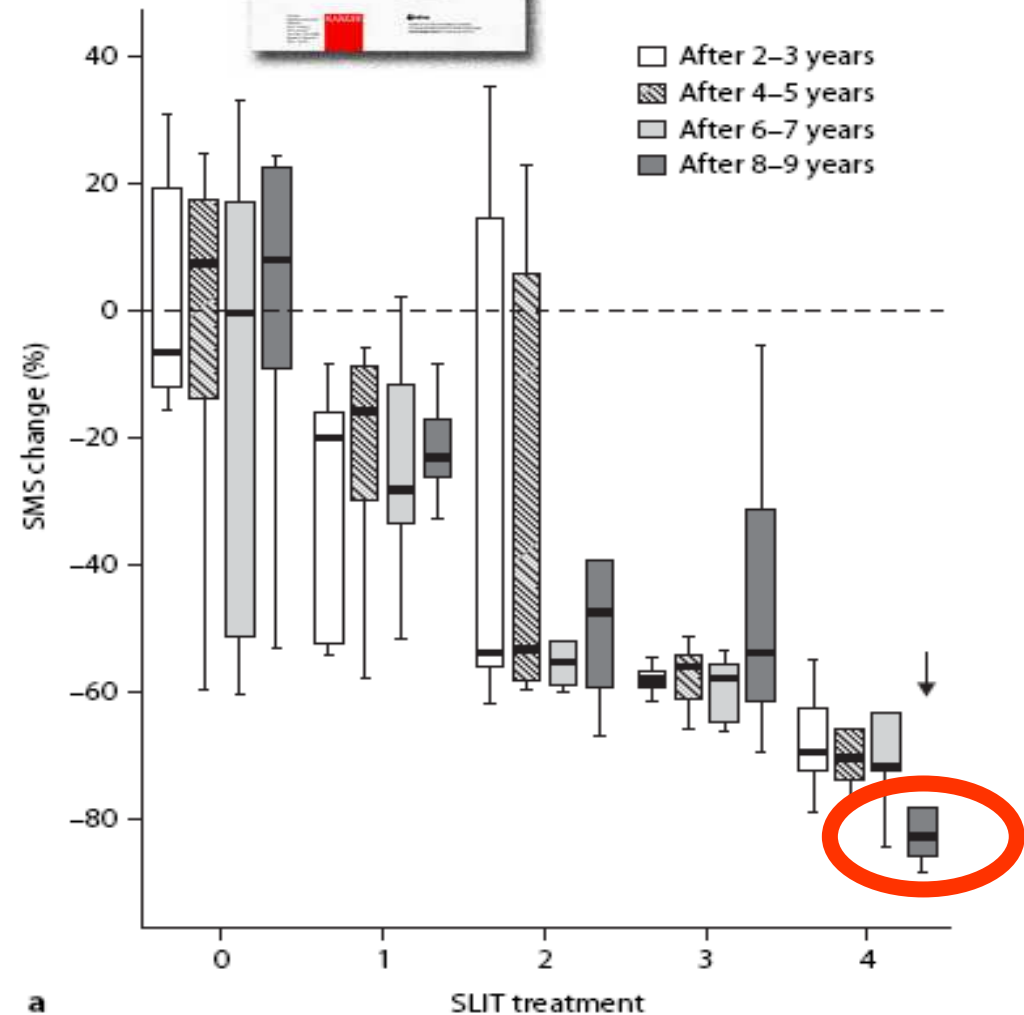
Effetto Long Lasting

Marogna et al 2007

Long-lasting effects of sublingual immunotherapy for house dust mites in allergic rhinitis with bronchial hyperreactivity: A long-term (13-year) retrospective study in real life.

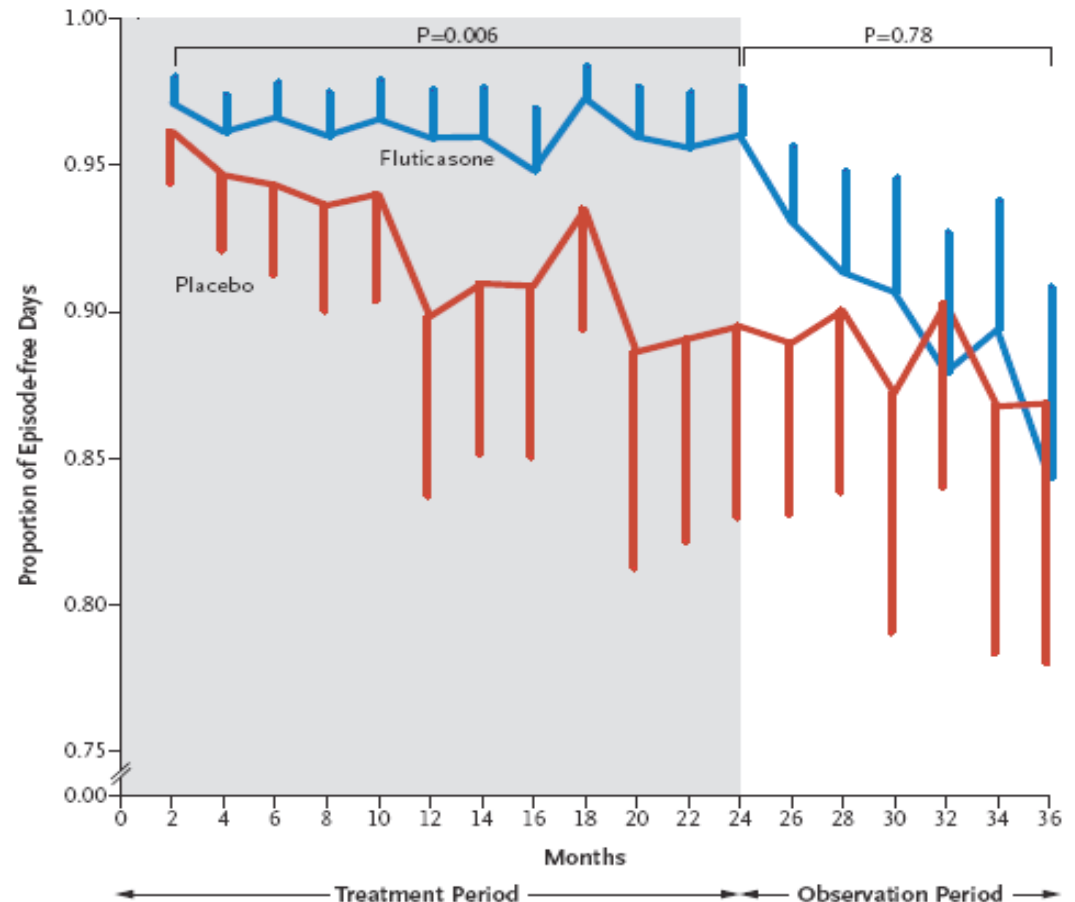
CONCLUSIONS:

SLIT shorter than 4 years yields proportionally less impressive results.



Long-Term Inhaled Corticosteroids in Preschool Children at High Risk for Asthma

Theresa W. Guilbert, M.D., Wayne J. Morgan, M.D., Robert S. Zeiger, M.D., Ph.D., David T. Mauger, Ph.D., Susan J. Boehmer, M.A., Stanley J. Szeffler, M.D., Ph.D., Leonard B. Bacharier, M.D., Robert F. Lemanske, Jr., M.D., Robert C. Strunk, M.D., David B. Allen, M.D., Gordon R. Bloomberg, M.D., Gregory Heldt, M.D., Marzena Krawiec, M.D., Gary Larsen, M.D., Andrew H. Liu, M.D., Vernon M. Chinchilli, Ph.D., Christine A. Sorkness, Pharm.D., Lynn M. Taussig, M.D., and Fernando D. Martinez, M.D.





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**Immunoterapia Sublinguale:
la sicurezza d'impiego**

Sicurezza *nei bambini*

ALLERGY Net

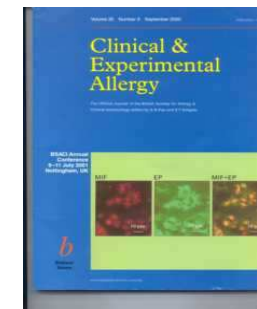
Safety of sublingual immunotherapy with a monomeric allergoid in very young children

*F. Agostinis, L. Tellarini, G. W. Canonica, P. Falagiani G. Passalacqua**



Post-marketing survey on the safety of sublingual immunotherapy in children below the age of 5 years

V. Di Rienzo, M. Minelli , A. Musarra , R. Sambugaro§, S. Pecora
W. G. Canonica and G. Passalacqua*



Safety of Sublingual immunotherapy in children aged 3-7 years

*A.Fiocchi, GB Pajno, S.La Grutta, F.Pezzuto,
C.Incorvaia,L.Sensi, F.Marcucci and F. Frati*





COCHRANE DATABASE Syst. Rev. 2003
SLIT Immunotherapy for allergic rhinitis

22 trials on 979 patients

CONCLUSION: SLIT is safe treatment



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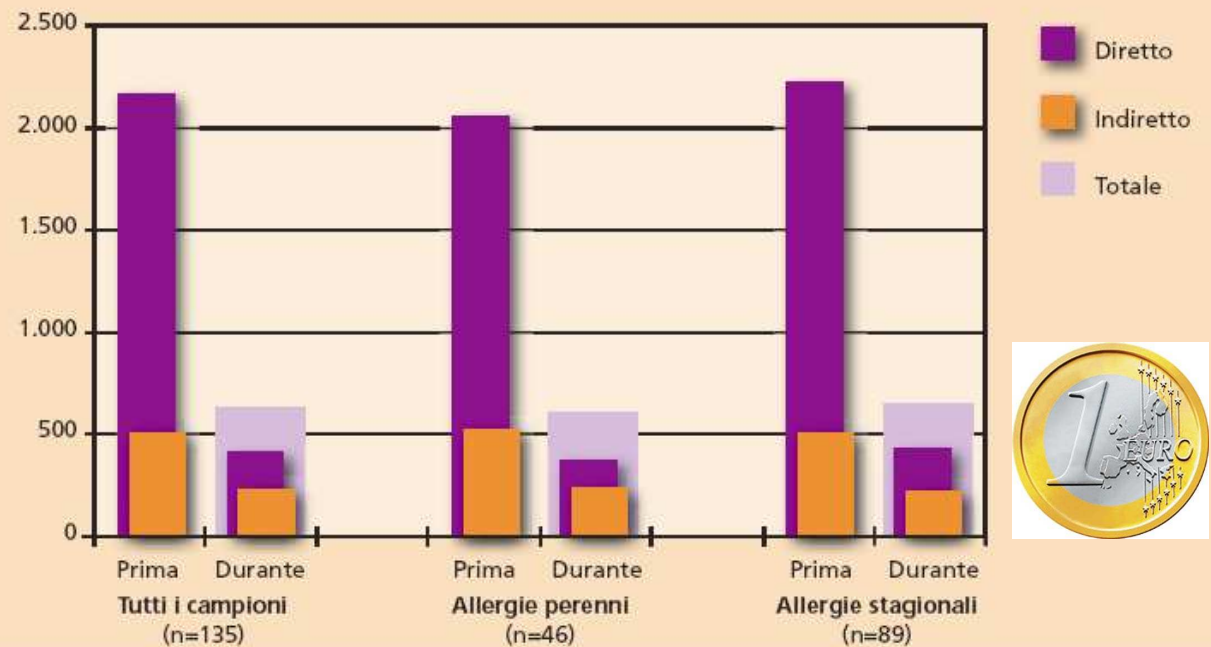


**Immunoterapia Sublinguale:
e i costi ?**

Cost Effectiveness Of Sublingual Immunotherapy In Children With Allergic Rhinitis and Asthma. Berto P. et al. *European Annals of Allergy and Clinical Immunology* 2005; 37 (8): 303-307

Il costo medio per anno per paziente è risultato marcatamente meno oneroso durante il trattamento con SLIT rispetto al pre-trattamento. La somma dei costi diretti ed indiretti è stata 3 volte più bassa (629 euro vs 2.672).

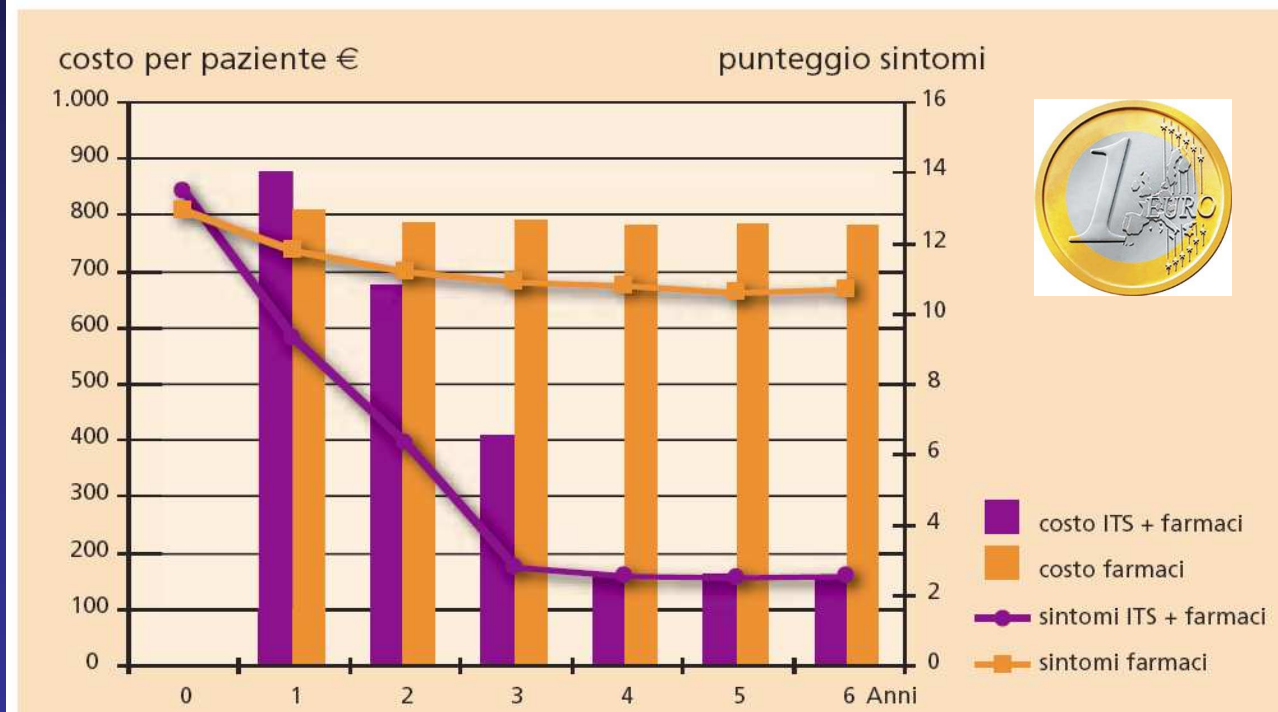
COSTO MEDIO PER ANNO PER PAZIENTE



Pharmacoeconomics of allergen immunotherapy compared with symptomatic drug treatment in patients with allergic rhinitis and asthma. *Allergy Asthma Proc* 2006;27: 159-163.

Già al **secondo anno** il costo dell'Immunoterapia associata al trattamento farmacologico è inferiore al costo della sola terapia farmacologica usuale ed a partire dal **terzo anno** diventa evidente e significativo (- 50%).
Al **sesto anno** e a **3 anni** dall'interruzione dell'immunoterapia, il risparmio raggiunge l'**80%**, mantenendo comunque un'evidente riduzione della sintomatologia rispetto alle terapie farmacologiche usuali

VALUTAZIONE DEI SINTOMI E DEI COSTI



In conclusione...

EBM

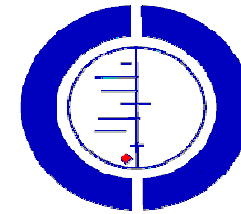
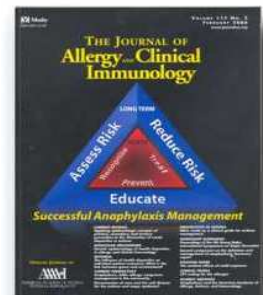


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Clinical efficacy: children (rhinitis)	Ib	Ia
Prevention of new sensitizations	Ib	IIa
Long-term effect	Ib	IIa
Prevention of asthma	Ib*	Ib*



Giovanni Passalacqua, MD,a and Stephen R. Durham, MD,b in cooperation with the Global Allergy and Asthma European Network (GA2 LEN) Genoa, Italy, and London, United Kingdom in JACI 2007



Official Journal of the
European Academy of Allergology
and Clinical Immunology



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SUPPLEMENT