Joint Congress of
APAAACI and
APAPARI
2016
Kuala Lumpur, Malaysia

Joint Congress of Asia Pacific Association of Allergy, Asthma and Clinical Immunology (APAAACI) and Asia Pacific Association of Pediatric Allergy, Respirology & Immunology (APAPARI) 2016

17th -20th October 2016 • Shangri-La Hotel Kuala Lumpur

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alergia e inmunología

CLÍNICA SUBIZA

One airway, one disease: Immunotherapy with SLIT

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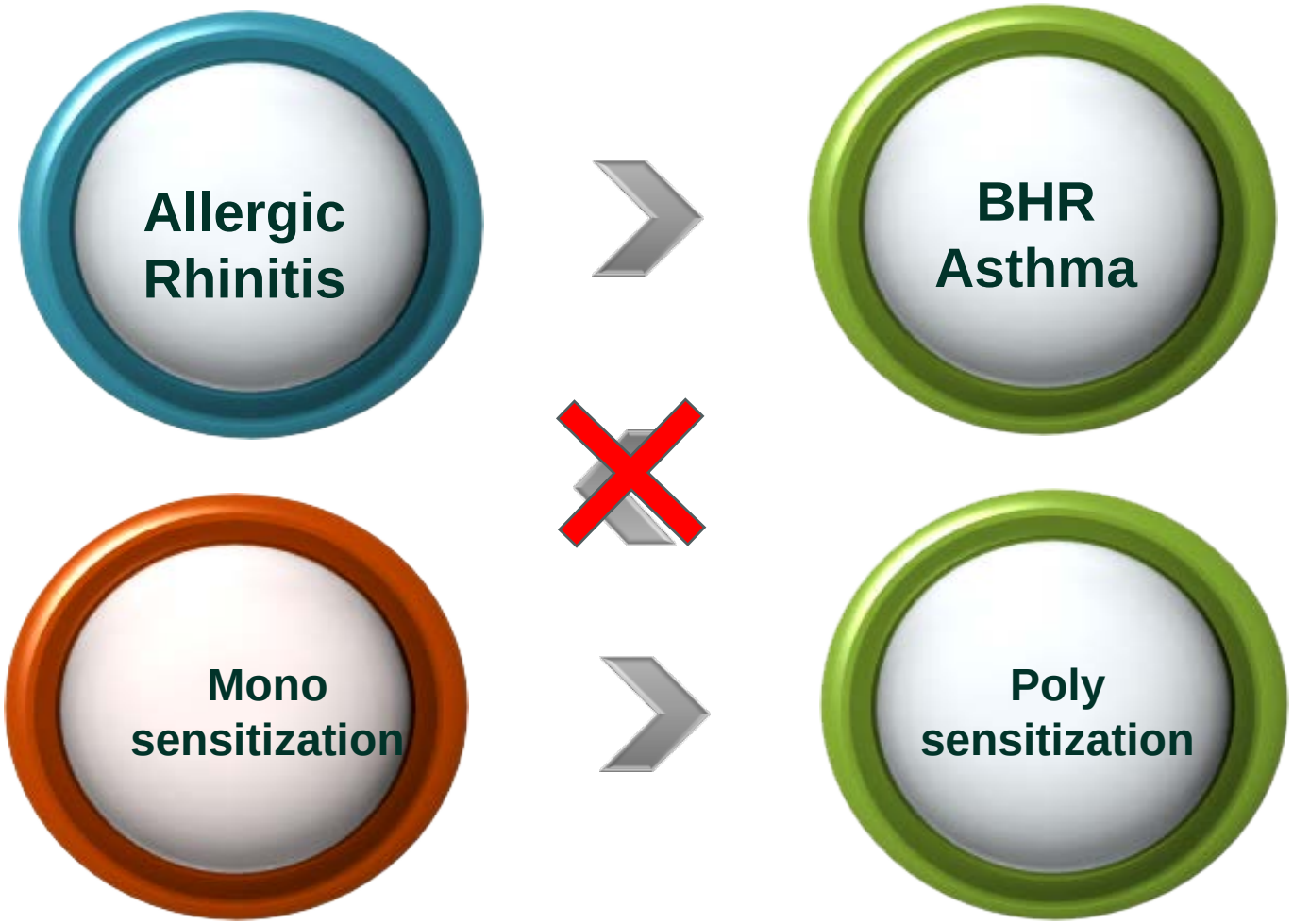
Subiza Asthma and Allergy Centre
Madrid, Spain

Introduction

Respiratory allergy: upper and lower airways "one airway disease"



Allergen Immunotherapy

"One airway one disease" concept

- Over 80% of asthmatics have rhinitis

Bousquet J et al. J Allergy Clin Immunol 2001;108:S147–S334
Levnaert B et al J Allergy Clin Immunol 1999;104:301–304
Brydon MJ Asthma J 1996:29–32

- 10-40% of patients with rhinitis develop asthma

Leynaert B et al. J Allergy Clin Immunol 2004; 113:86-93
Guerra S et al. J Allergy Clin Immunol 2002; 109:419-25
Shaaban R et al. Lancet 2008; 372:1049-57

"One airway disease" and Allergen Immunotherapy

- Allergic rhinitis (AR) subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (**SLIT**) : primary indication for Allergen Immunotherapy (AIT)

- **USA**
  - SCIT is approved for AR and pediatric asthma
  - **SLIT** is used off-label for asthma
- **Europe**
  - SCIT and **SLIT** are approved for AR and asthma

SUBLINGUAL IMMUNOTHERAPY

- Sublingual immunotherapy (**SLIT**)
  - Small doses to increase tolerance to the allergen

- **SLIT** has demonstrated its efficacy and safety in the past 10 years

- **<u>The efficacy of SLIT is dose dependent</u>**

SUBLINGUAL IMMUNOTHERAPY

Vials

Pump
Doseuse

Disposable single dose

Soluble tablets

Spray bottle

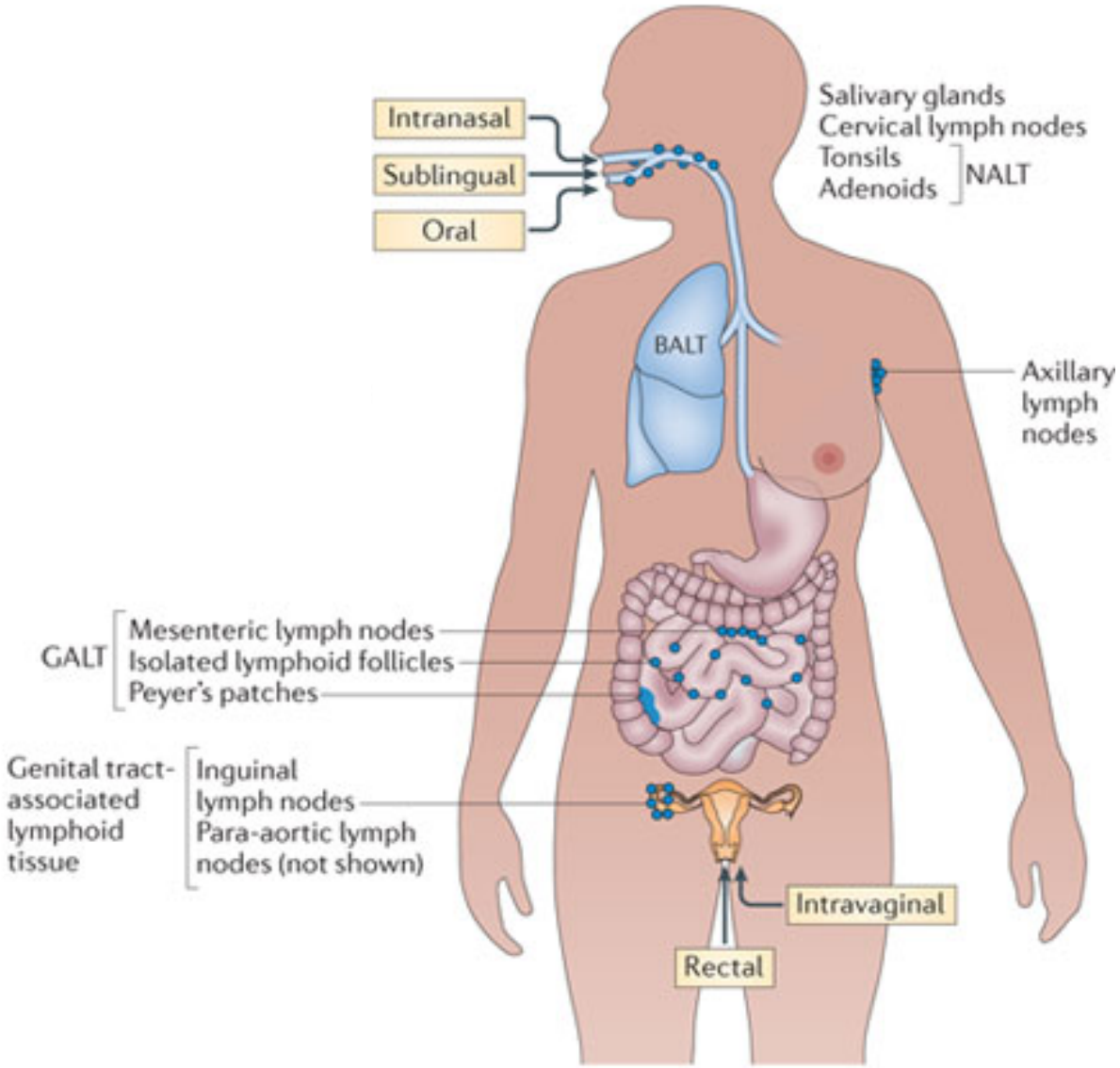
Regulatory

- Spain and other European countries
  - Produced under GMPs
  - Individual preparations for individual patients

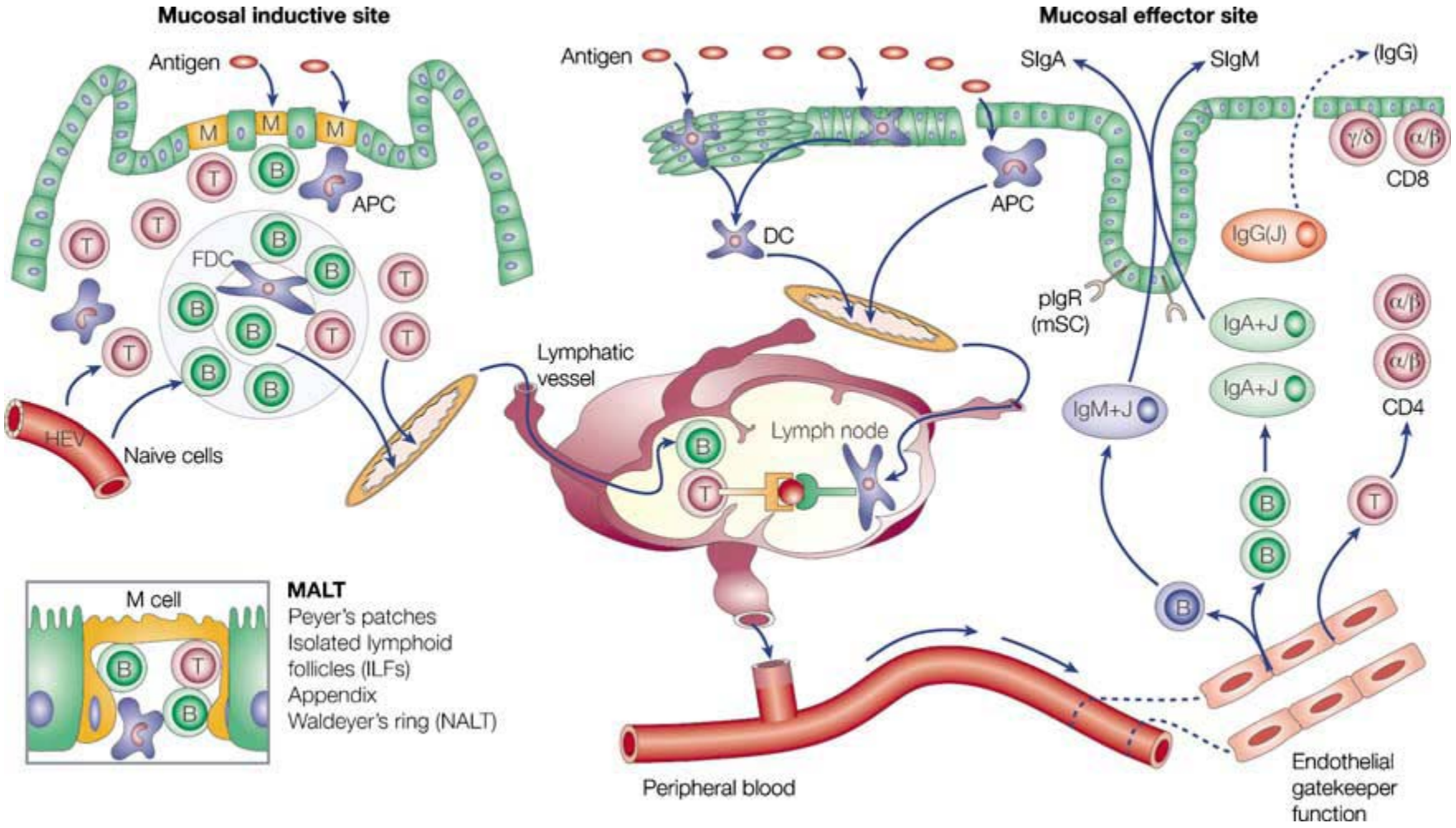
- Registration in European countries: Germany, Italy and Austria

- Registration include quality data and evaluation of the Health Authorities

Immunological mechanisms



Nature Reviews | Immunology


Mucosal inductive site
Antigen
M
M
M
T
B
APC
T
FDC
B
T
HEV
Naive cells
Lymphatic vessel
Lymph node
M cell
MALT
Peyer's patches
Isolated lymphoid follicles (ILFs)
Appendix
Waldeyer's ring (NALT)
Mucosal effector site
Antigen
SIgA
SIgM
(IgG)
γ/δ
α/β
CD8
APC
DC
IgG(J)
pIgR (mSC)
IgA+J
IgA+J
IgM+J
α/β
α/β
CD4
Peripheral blood
Endothelial gatekeeper function

The mucosal immunity system fulfills the following basic tasks:

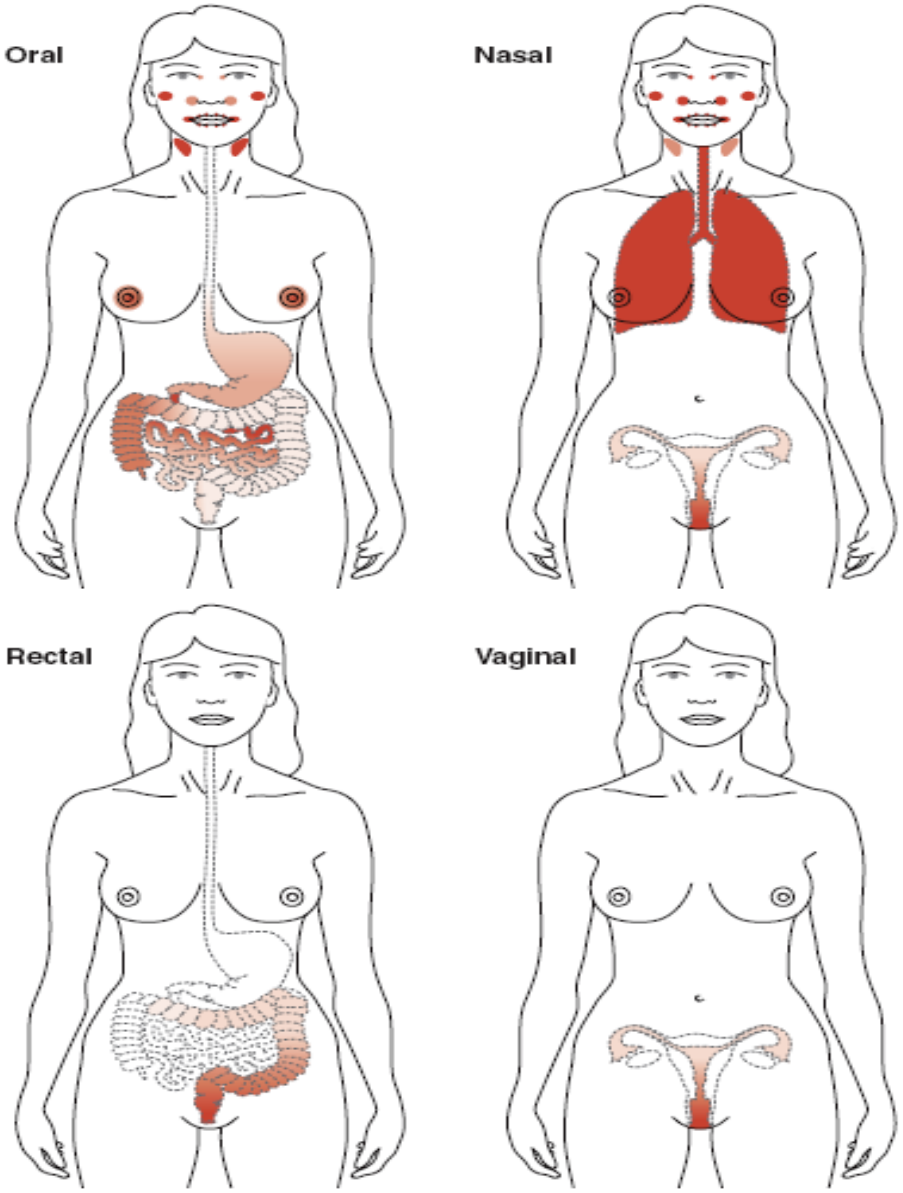
1. Protection from harmful microbial pathogens

2. Barrier against penetration of infectious and immunogenic components

3. Low reactivity to harmless Ag present on mucosa

4. Maintenance of mucosal homeostasis

Tiaskalová-Hogenová, H. *et al*. 2002.

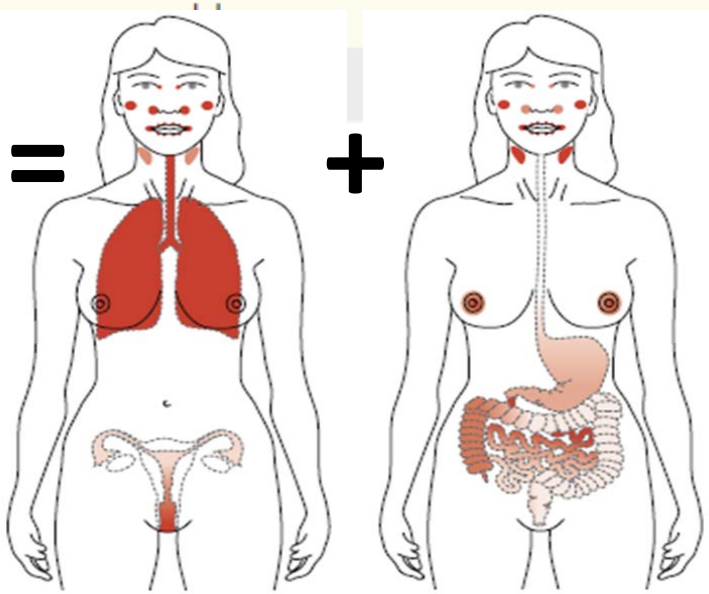


Holmgren, J. *et al*. 2005.

Table 1. Comparative anatomic dissemination of the mucosal SIgA antibody response after different routes of immunization

	Sublingual	Nasal	Oral
Upper respiratory	+++	+++	-
Lower respiratory	+++	+ to +++	-
Stomach	+/+++	-	+/+++
Small intestine	+++	-	+++
Colon	?	-	±
Rectum	?	-	±
Genital tract	+++		
Blood	++		

Sublingual



Çuruburu *et al. Vaccine, 2007*

Czerkinsky *et al. Human Vaccines, 2011*

- Sublingual mucosa
  - Dense network of dendritic-like cells (DC) in lamina propia and epithelium
  - Tolerance induction producing IgG4 and regulatory T cells

- **Sublingual inmunotherapy**
  - **Ovoalbumin and cholera toxin: vigorous systemic and mucosal antibody responses**
  - **Comparable to intranasal IT**
  - **Superior to oral IT**

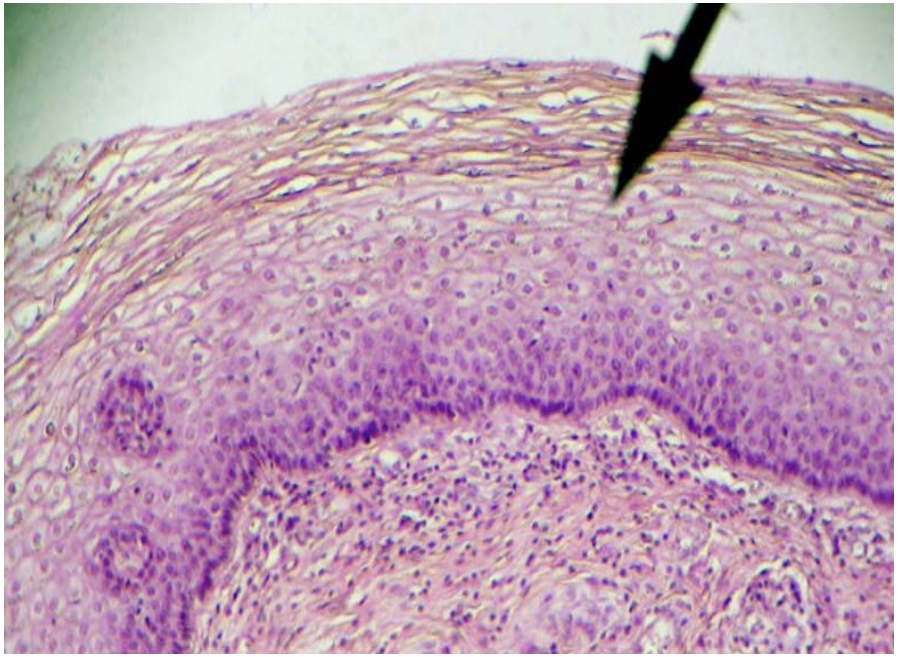
Çuburu ,N. *et al*. 2007

Inmunological Response

- Modulation of the antibodies response to specific allergens
- Activation and recruitment reduction of pro-inflamatories cells
- Changes in specific allergen T cells response pattern

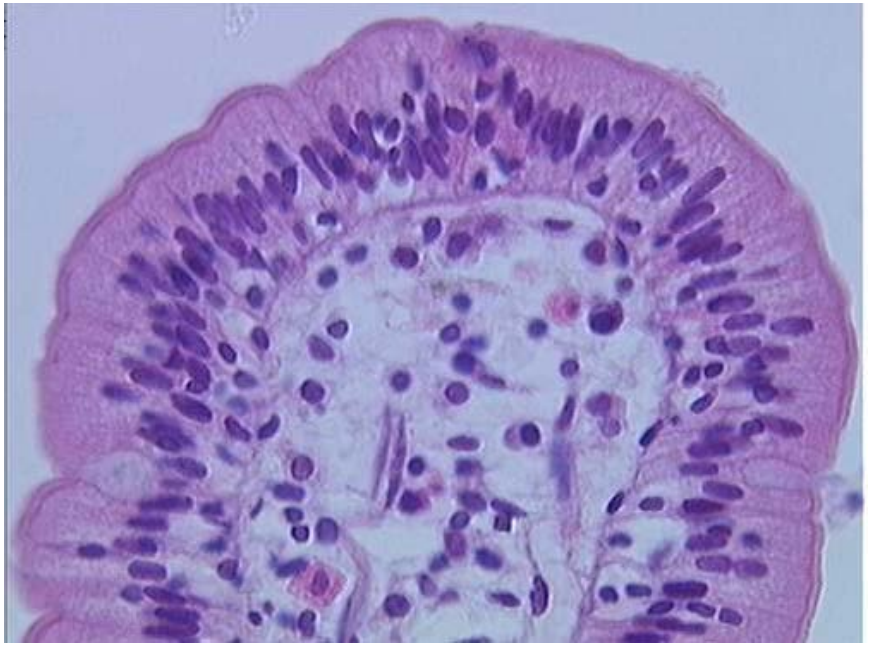
Mucosal Epithelia

Oral

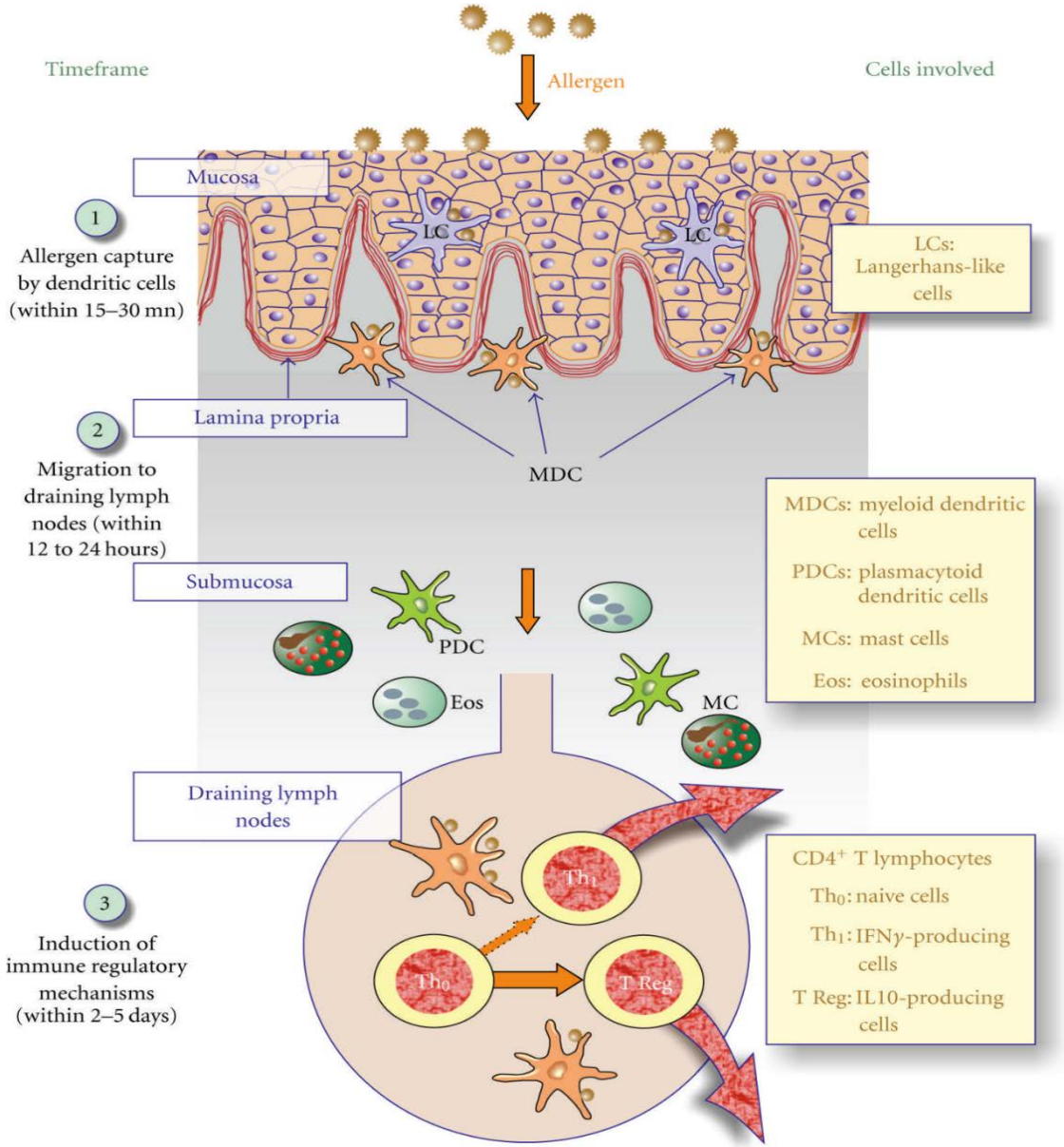


Stratified Squamous

Intestinal

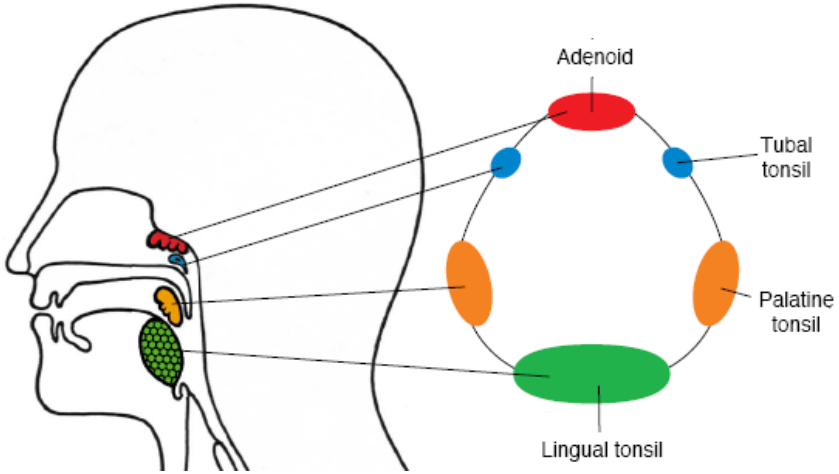


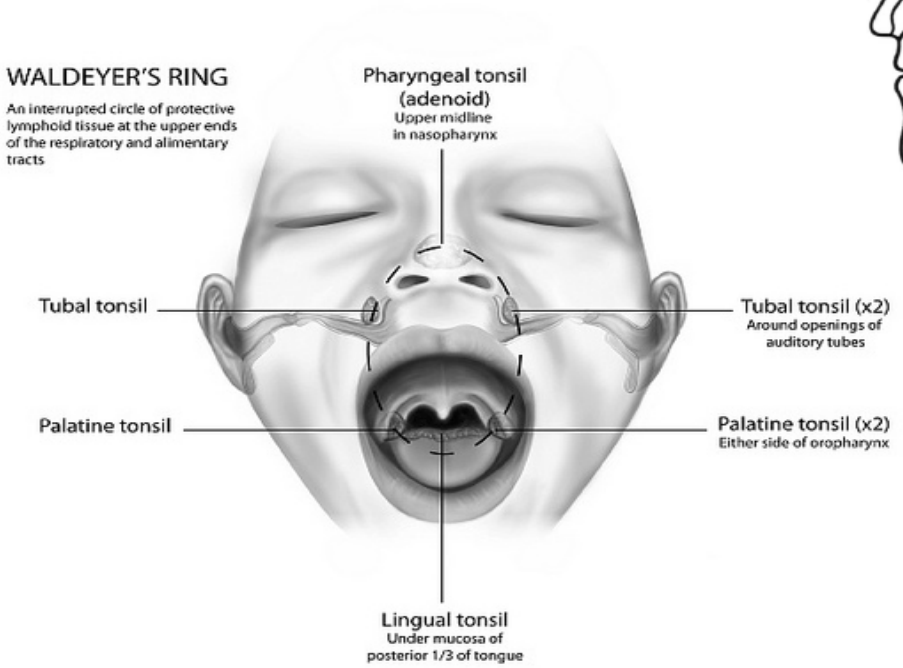
Simple Columnar



Moingeon, P. *et al*. 2012.

Waldeyer's Ring

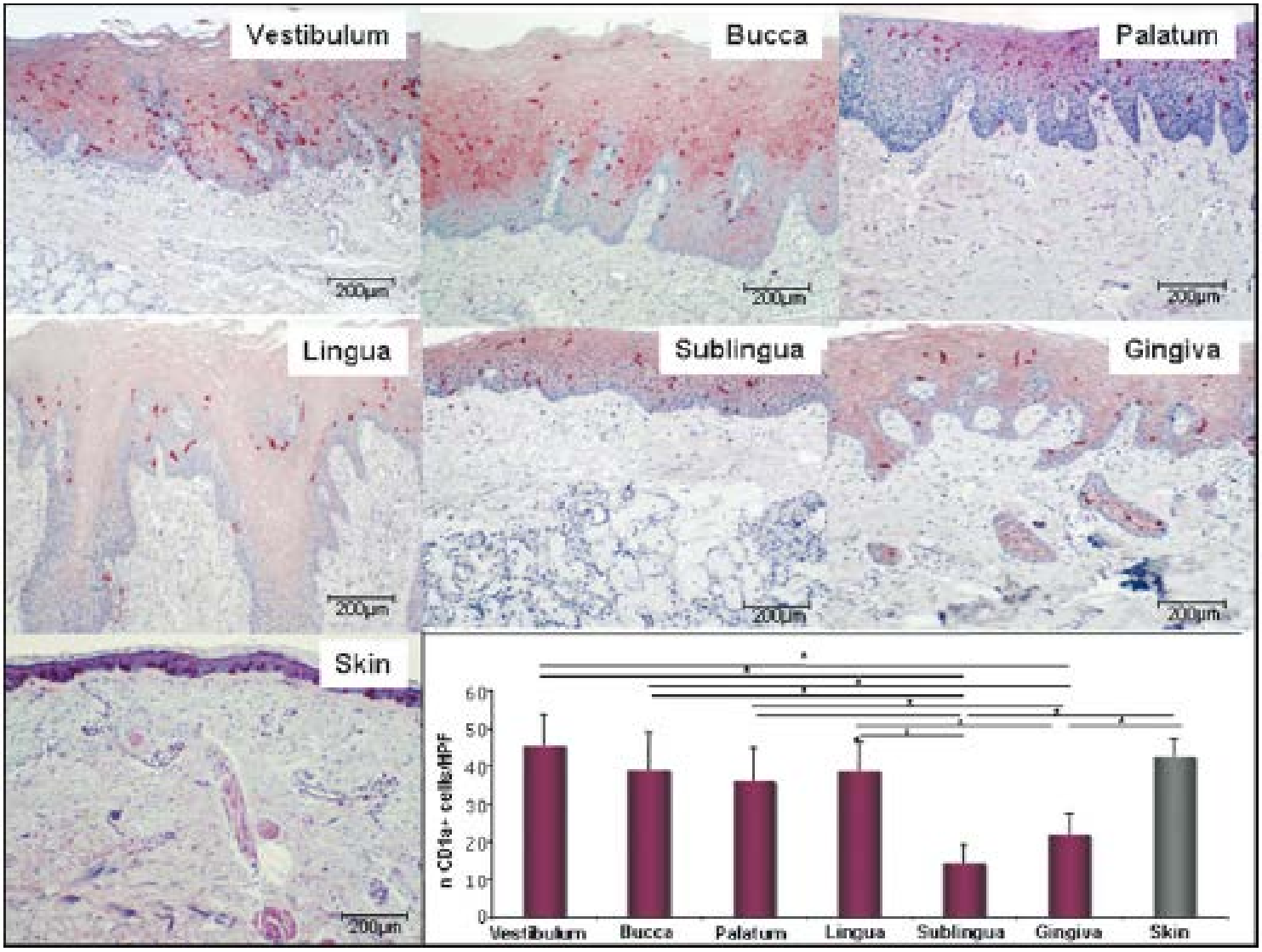




Otolaryngology: Waldeyer's Ring
Toronto Notes 2010 OT40
Photoshop CS4

Use of SPRAY vs DROPS

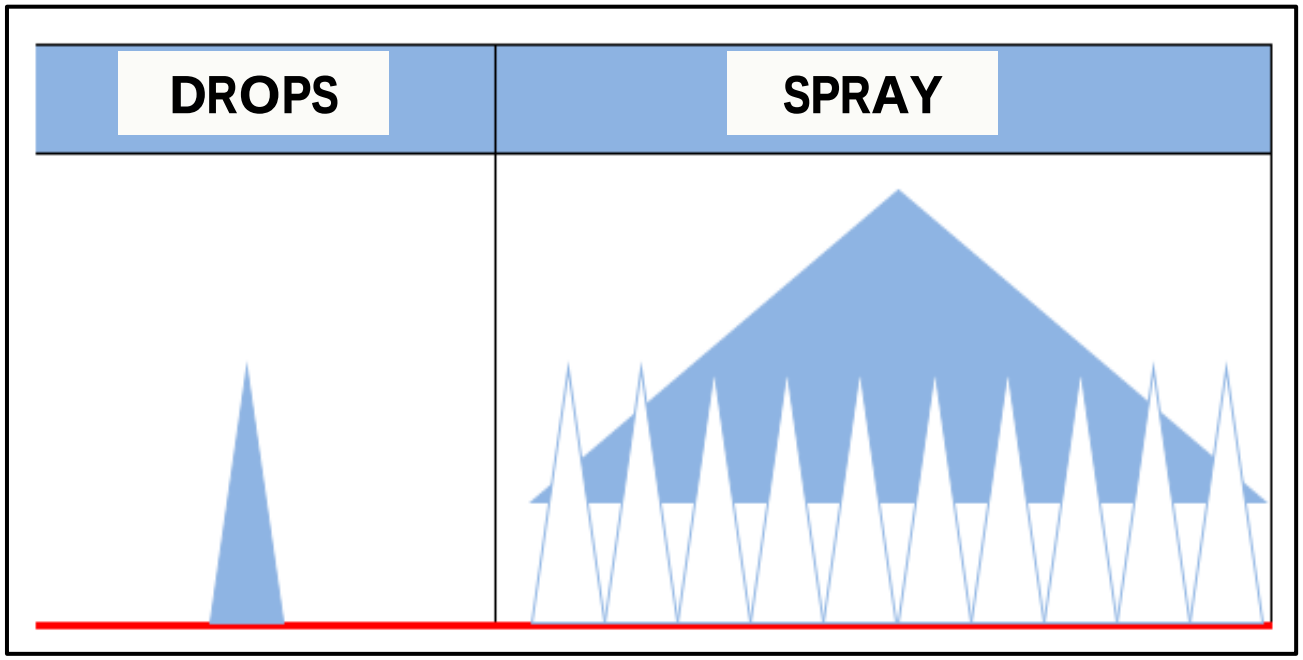
ORAL MUCOSA: High density of ANTIGEN PRESENTING CELLS



Allam *et al. Allergy, 2008*

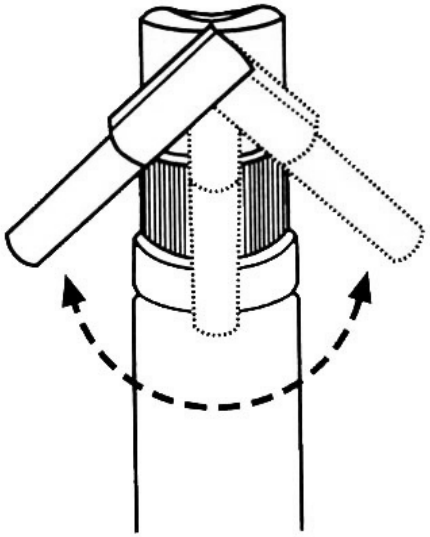
Why Spray?

- ✓ Larger area of oral mucosa
- ✓ Greater uptake by Antigen Presenting Cells



Why Spray?

- ✓ High concentration of vaccine without the dilution of saliva
- ✓ Better control : administered dose and treatment compliance
- ✓ Ideal for young children



Importance of excipients in SLIT Products

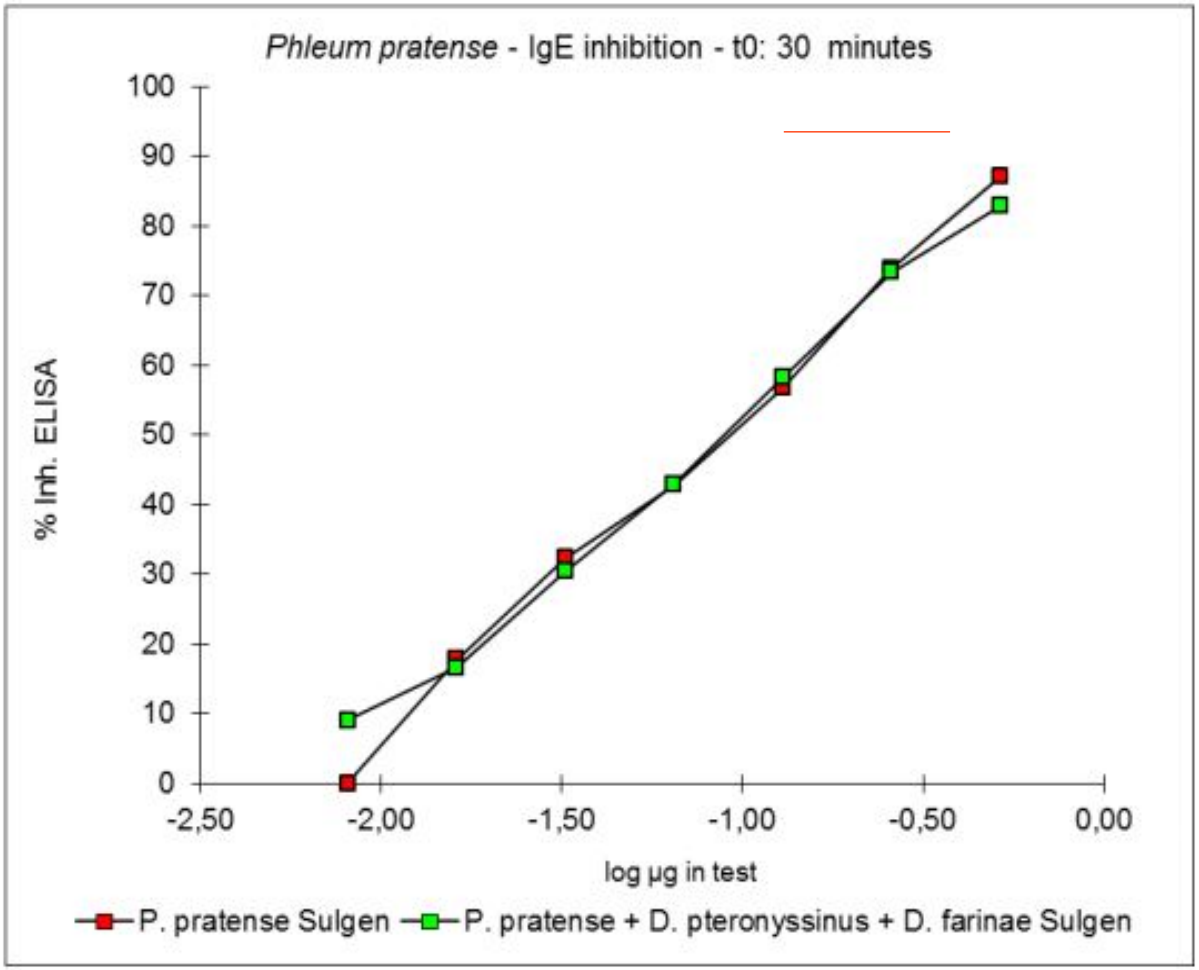
Advantages of SLIT Glycerinated Products

GLYCEROL

- Preserving properties[1] (antimicrobial and antiviral effect)
- Inhibition of proteolytic activity[2] and protein aggregation[3] has been proven
- Glycerol viscosity prolongs the contact of Ag with surfaces[4]
- Increasing capture of allergens by antigen presenting cells

[1]Scadding G. et al Clin Transl Allergy 2011
[2]Nelson H. Allergens and allergen immunotherapy 1999
[3]Vagenende V. et al Biochemistry 2009
[4]Pennington AK. et al Int J Pharm 1998

GLYCEROL:
Stability of mixtures
Phleum pratense + Dermatophagoides spp.



Internal data INMUNOTEK, S.L.

GLYCEROL:
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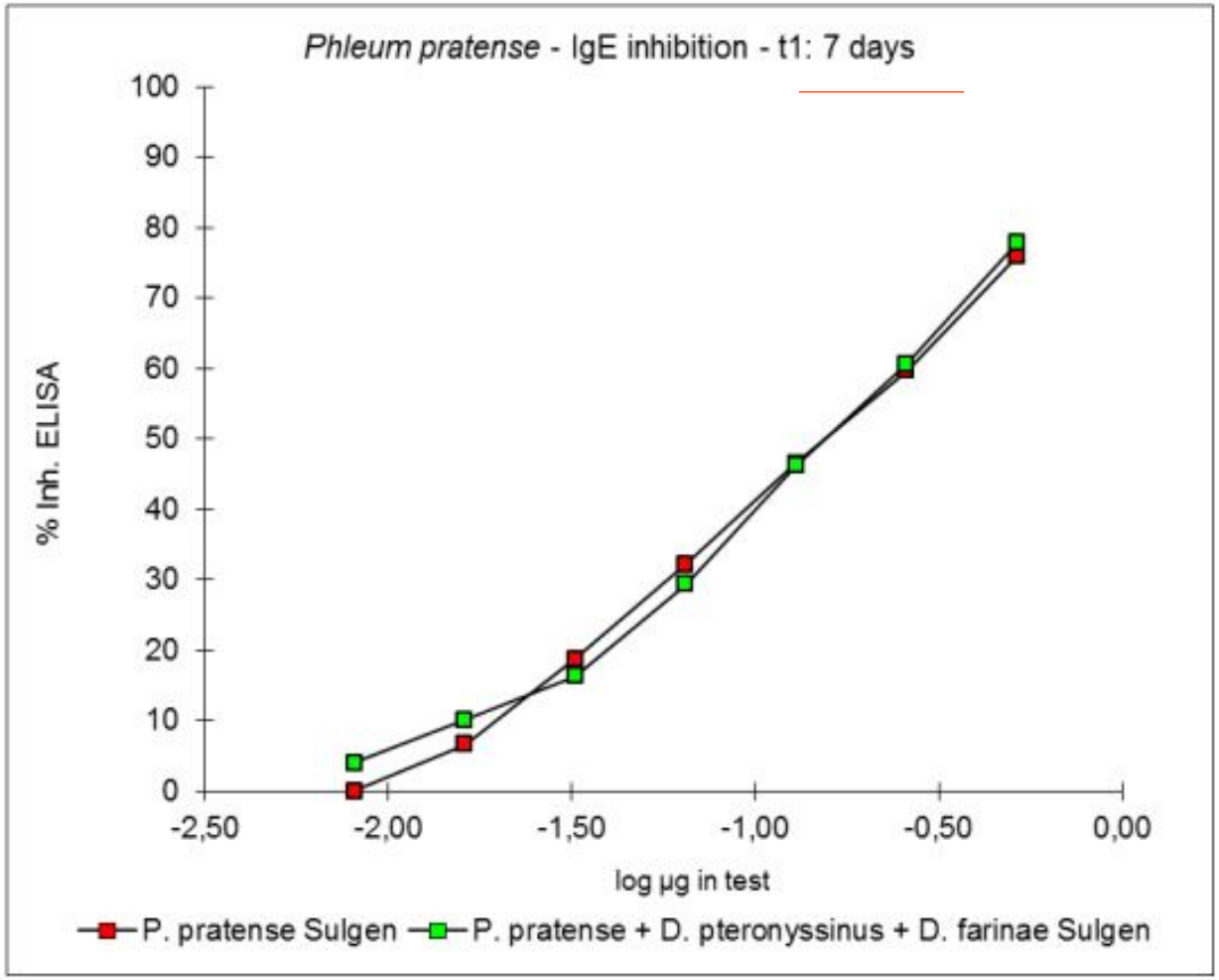

Internal data INMUNOTEK, S.L.

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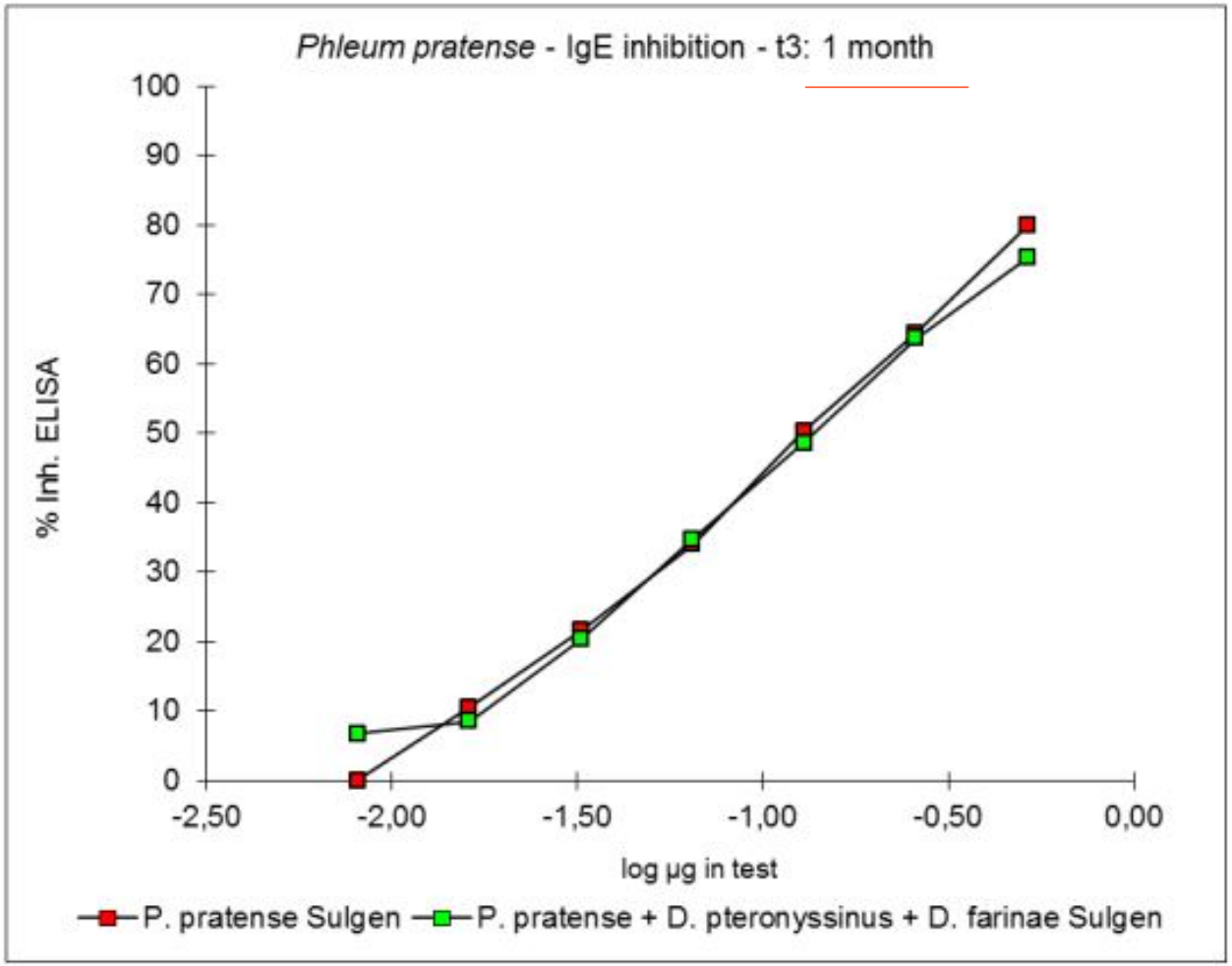


Internal data INMUNOTEK, S.L.

Advantages of tasty SLIT Products

- Tasty Excipients in SLIT preparations as fruit flavours increase patient adherence
- Artificial flavours adequate for allergic patients
- Importance for SLIT that is home administered
- Specially relevant for children

Advantages of SLIT products without build-up period

SLIT PRODUCTS WITHOUT BUILD-UP PERIOD

- Since the first day the patient is on the maximum dose
- Excellent safety profile and maximum efficacy
- Better patient compliance than with longer build up periods

Safety of ultra-rush perlingual immunotherapy in allergic rhinitis.

G.Traina, E. Allievi, A. Busani, D. Origgi, G. Piacentini, L. Serradori, A. Martelli.
Department of Paediatrics, S. Corona Hospital – Garbagnate Milanese. Italy.

(*Allergy 2012;67, s 96:411*).

Material and Methods

- **54 children** (27 males, 27 females, aged between 5 and 18 years)
- Allergic rhinoconjunctivitis
- 51 polysensitized
- 6 months SLIT
- **2 sprays since 1st day.**

Allergens	Children with SLIT
Grass	29
Dust mites	22
Cynodon dactylon	14
Alternaria	2
Ambrosia	2
Birch	1
Cat dander	1

Safety of ultra-rush perlingual immunotherapy in allergic rhinitis.

G.Traina, E. Allievi, A. Busani, D. Origgi, G. Piacentini, L. Serradori, A. Martelli.
Department of Paediatrics, S. Corona Hospital – Garbagnate Milanese. Italy.

(*Allergy 2012;67, s 96:411*).

Results

- Excellent patient compliance: All children completed treatment
  - 13,889 doses administered
- Excellent safety profile:
  - Only two children reported transient oral itching (<5 minutes)
  - Daily maintenance dose of (sprays/day) neither local nor systemic reactions
  - No anaphylaxis

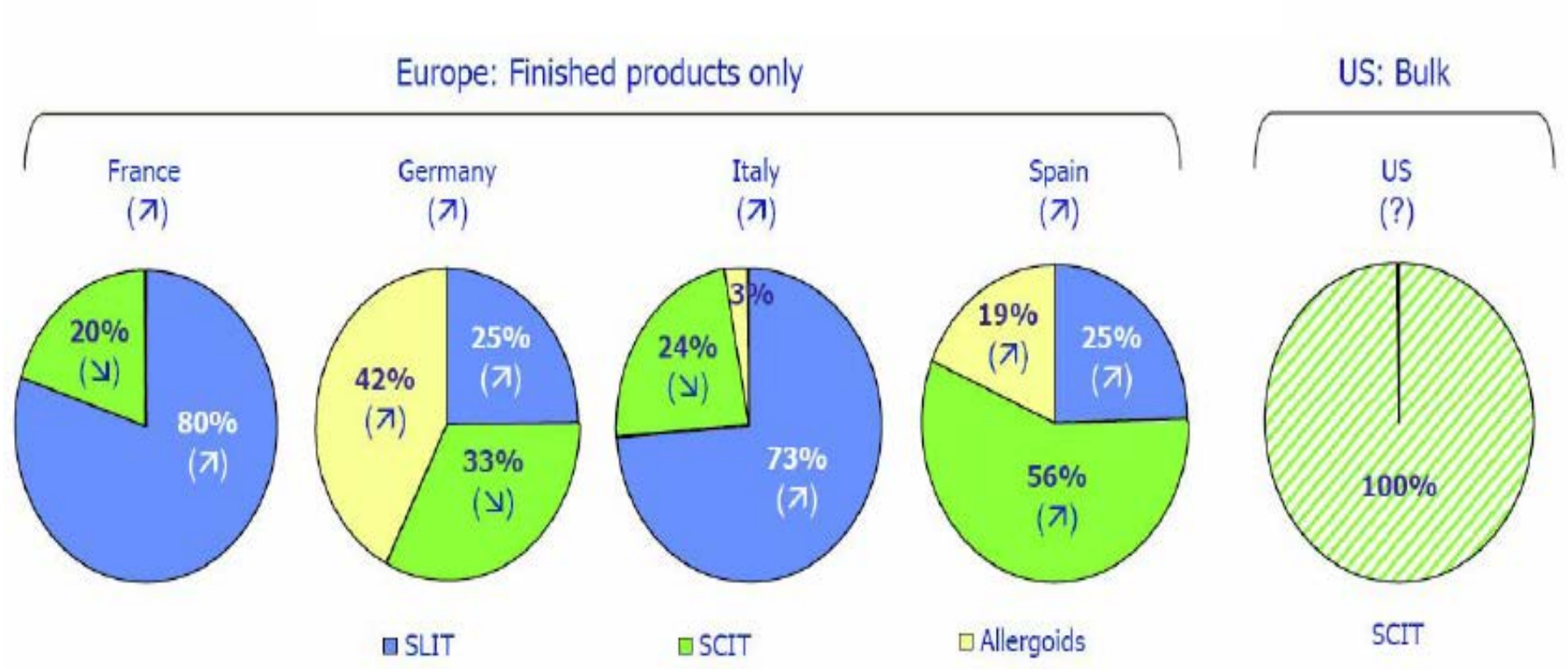
Use of SLIT vs SCIT

Specific Allergen Immunotherapy

1911	1960	1970	1986	1998	2000	2005	2006	2007	2008
SCIT	First RCT SCIT	SLIT	First RCT SLIT	WHO	ARIA	First Meta SLIT	Large RCT SCIT	First Meta SCIT	Large RCT SLIT

- 1st SCIT RCT in children: Dreborg S et al.1986
- 1st SLIT RCT in children: Tari MG et al. 1990

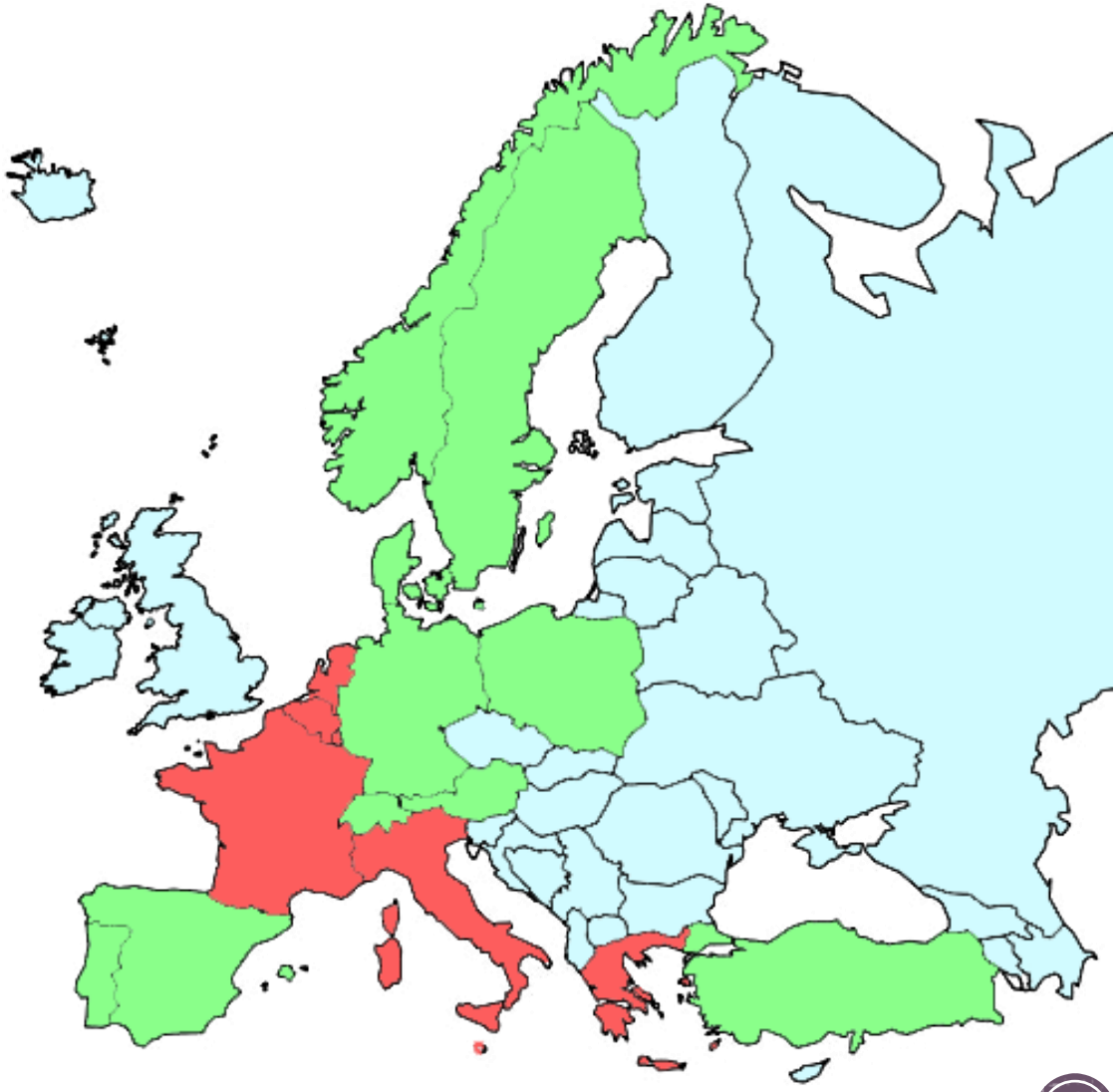
- SLIT is used widely (50% in some European countries). Full regulatory and government backing
- U.S. allergy leaders are writing in support of SLIT



SIT – PREFERRED OPTION IN EUROPE

SCIT > 50%

SLIT > 50%



Source: FASIT 2008

SUBLINGUAL IMMUNOTHERAPY

1998

- The World Health Organization indicated its use in its 1998 position paper.

2007 -2008

- **ARIA** (Allergy Rhinitis and its Impact on Asthma) guidelines indicating SLIT as a viable treatment approach

- Allergen-specific immunotherapy was traditionally administered by the subcutaneous route but local routes are now available.
- Specific immunotherapy needs a precise diagnosis of IgE-mediated allergy.
- Subcutaneous immunotherapy is effective in adults and children for pollen and mite allergy, but it is burdened by the risks of side effects. These reactions may be life-threatening.
- Sublingual immunotherapy is recommended for the treatment of pollen allergy in adults.
- Sublingual immunotherapy may be used for the treatment of patients with mite allergy.
- Intranasal immunotherapy may be used for the treatment of patients with pollen allergy.
- Allergen-specific immunotherapy may alter the natural course of allergic diseases.
- Subcutaneous immunotherapy appears to be effective several years after its cessation.
- Immunotherapy appears to reduce the development of new sensitizations.
- Administered to patients with rhinitis, immunotherapy appears to reduce the development of asthma (secondary prevention of asthma).

Aria 2008 update

Table 23. Indications for sublingual immunotherapy

High-dose sublingual swallow-specific immunotherapy may be indicated in the following cases:
Carefully selected patients with rhinitis, conjunctivitis and/or asthma caused by pollen and mite allergy
Patients insufficiently controlled by conventional pharmacotherapy
Patients who have presented with systemic reactions during injection-specific immunotherapy
Patients showing poor compliance with or refusing injections

Aria 2008 update

Level of evidence

Ia: Meta-analysis of randomized-controlled trials (RCT)

Ib: At least one RCT

IIa: At least one controlled study without randomization

IIb: At least one other type of study

III: Nonexperimental descriptive studies

IV: Expert committee reports or opinions or clinical experience of respected authorities

Strength of recommendation

A: Category I evidence

B: Category II evidence or extrapolated recommendation from category I evidence

C: Category III evidence or extrapolated recommendation from category I or II evidence

D: Category IV evidence or extrapolated recommendation from category I, II or III evidence

Level of evidence produced according to Shekelle et al. Aria 2008 update.

Table 27. Level of evidence of different interventions in allergic rhinitis: The level of evidence was produced according to Shekelle et al. (12), adapted from Refs (24–28).

	Seasonal rhinitis		Perennial rhinitis (mostly applies for studies ≤ 4 weeks)*		Persistent rhinitis†
Intervention	Adults	Children	Adults	Children	
H_1-antihistamine					
Oral	A	A	A	A	A
Intranasal	A	A	A	A	No data
Intraocular	A	A	B	B	No data
Glucocorticosteroid					
Intranasal	A	A	A	A	No data
Oral	A	B	B	B	No data
IM	A	B	B	B	No data
Cromones					
Intranasal	A	A	A	B	No data
Intraocular	A	A	B	B	No data
NAAGA (topical)	B	C	C	C	No data
Antileukotriene	A	A over 6 years			No data
Decongestant					
Intranasal	C	C	C	C	No data
Oral	A				No data
Oral + H_1-antihistamine	A	B	B	B	No data
Anticholinergic			A	A	No data
Homeopathy	D	D	D	D	No data
Acupuncture	D	D	D	D	No data
Phytotherapy	B	D	D	D	No data
Other CAM	D	D	D	D	No data
Specific immunotherapy: rhinoconjunctivitis					
Subcutaneous	A	A	A	A	No data
Sublingual‡	A	A	A	A	No data
Intranasal‡	A				No data
Specific immunotherapy: asthma					
Subcutaneous	A	A	A	A	
Sublingual‡	A	A	A	A	
Anti-IgE	A	A over 12 years	A	A over 12 years	No data
Allergen avoidance					
House dust mites	D	D	D	D	No data
Other indoor allergens	D	D	D	D	No data
Total avoidance of occupational agent			A (for asthma)		No data
Partial avoidance of latex			B		No data

* Very few studies longer than 4 weeks.
† Applies to treatments only carried out in studies with persistent rhinitis.
‡ Applies to high-dose treatment.

Aria 2008 update

Clinical data

SLIT vs SCIT for Asthma (Meta-analysis and systematic reviews)

Table 1 Meta-analysis and systematic reviews on AIT for asthma

AIT	Study	Patients	Population	Allergen/s	Symptom scores SMD (95% CI)	Medication scores SMD (95% CI)
SLIT	Olaguíbel et al. (2005) (14)	193	Pediatric	Multiple	−1.42 (−2.51, −0.34)*	Not reported
	Calamita et al. (2006) (15)	1706	Pediatric and adult	Multiple	−0.38 (−0.79, 0.03)	−0.91 (−1.94, 0.12)
	Penagos et al. (2008) (16)	441	Pediatric	Multiple	−1.14 (−2.10, −0.18)*	−1.63 (−2.83, −0.44)*
	Compalati et al. (2009) (17)	476	Pediatric and adult	HDM	−0.95 (−1.74, −0.15)*	−1.48 (−2.70, −0.26)*
	Normansell et al. (2014) (18)	5077	Pediatric and adult	Multiple	Not reported†	Not reported†
	Liao et al. (2015) (19)	454	Pediatric	HDM	−1.20 (−2.07, −0.33)*	−0.52 (−1.75, 0.71)
SCIT	Abramson et al. (2010) (20)	3459	Pediatric and adult	Multiple	−0.59 (−0.83, −0.35)*	−0.53 (−0.80, −0.27)*

AIT, allergen immunotherapy; HDM, house dust mite; SCIT, subcutaneous allergen immunotherapy; SLIT, sublingual immunotherapy.
*Statistically significant ($P < 0.05$).
†Authors felt unable to perform meta-analysis due to high variability of reporting and use of nonvalidated scores.

Allergy 2016 Jul 20. doi: 10.1111/all.12989.

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Sublingual immunotherapy for asthma

Authors' conclusions:

Lack of data for important outcomes such as exacerbations and quality of life and use of different unvalidated symptom and medication scores have limited our ability to draw a clinically useful conclusion. Further research using validated scales and important outcomes for patients and decision makers is needed so that SLIT can be properly assessed as clinical treatment for asthma. Very few serious adverse events have been reported, but most studies have included patients with intermittent or mild asthma, so we cannot comment on the safety of SLIT for those with moderate or severe asthma. SLIT is associated with increased risk of all adverse events.

Read the full abstract...

Normansell R, Kew KM, Bridgman A. Sublingual immunotherapy for asthma. Cochrane Database Syst Rev 2015;8: CD011293.

Abramson MJ, Puy RM, Weiner JM. Injection allergen immunotherapy for asthma. Cochrane Database Syst Rev 2010;8: CD001186.c

SLIT vs SCIT Asthma prevention and New sensitizations

Table 2 Immunotherapy for the secondary prevention of asthma onset and new sensitizations

Outcome	AIT	Study	Population	Allergen	Result	Evidence*
Asthma onset	SCIT	Grembiale et al. (2000) (59)	Adults	HDM	Positive	Ib
		Möller et al. (2002) (60)	Children	Birch/grass	Positive	
		Jacobsen et al. (2007) (61)	Children	Birch/grass	Positive	
	SLIT	La Rosa et al. (1999) (67)	Children	Parietaria	Negative	IIb
		Madonini et al. (2003) (68)	Adults and children	Multiple	Positive	
		Novembre et al. (2004) (65)	Children	Grass	Positive	
		Milani et al. (2008) (69)	Adults and children	Multiple	Positive	
		Marogna et al. (2008) (66)	Children	Multiple	Positive	
New sensitizations	SCIT	Des Roches et al. (1997) (70)	Children	HDM	Positive	III
		Pajno et al. (2001) (71)	Children	HDM	Positive	
		Purello-D'Ambrosio et al. (2001) (73)	Adults (>14 years)	Multiple	Positive	
		Eng et al. (2002) (74)	Children	Grass	Positive	
		Inal et al. (2007) (72)	Children	HDM	Positive	
		Eng et al. (2006) (75)	Children	Grass	Positive	
	SLIT	Marogna et al. (2004) (76)	Adults	Multiple	Positive	IIB
		Marogna et al. (2008) (66)	Children	Multiple	Positive	
		Marogna et al. (2010) (77)	Adults	HDM	Positive	
		Szépfalusi et al. (2014) (78)	Children	HDM	Negative	

AIT, allergen immunotherapy; HDM, house dust mite; SCIT, subcutaneous allergen immunotherapy; SLIT, sublingual immunotherapy.
*Evidence according to Shekelle et al. (79).

Allergy 2016 Jul 20. doi: 10.1111/all.12989.

SLIT for Allergic Rhinitis

ARIA

- More modern research on **SLIT** compared to SCIT
- Higher quality (WHO guidelines)

- Several publications : efficacy and safety of **SLIT** on AR

- **Cochrane Review**
  - 2011- **SLIT** : safe and effective

Cochrane

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Informed decisions.
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Sublingual immunotherapy for allergic rhinitis (including hay fever)

Allergy

REVIEW ARTICLE

Systematic reviews of sublingual immunotherapy (SLIT)

S. Radulovic[1], D. Wilson[2], M. Calderon[3] & S. Durham[3]

[1]Paediatric Allergy, King's College, London; [2]Selly Oak Hospital, University Hospitals Birmingham NHS Trust, Birmingham, UK; [3]Royal Brompton Hospital, Upper Respiratory Medicine, London, UK

To cite this article: Radulovic S, Wilson D, Calderon M, Durham S. Systematic reviews of sublingual immunotherapy (SLIT). *Allergy* 2011; **66**: 740–752.

Authors' conclusions:

This updated review reinforces the conclusion of the original 2003 Cochrane Review that sublingual immunotherapy is effective for allergic rhinitis and has been proven to be a safe route of administration.

Read the full abstract...

Background

- Allergic disease can impair QoL
- Interest in alternative routes of delivery
- Injection IT: associated with systemic reactions

Objectives

- Evaluate the efficacy of **SLIT** compared with placebo:
  - Reductions in symptoms and/or medication
  - Altering immunological markers in blood and allergen sensitivity in target organs (nose, eye, skin).
  - Safety

Selection criteria

- Studies: DBPC
- Participants
  - Any age: children and adults
  - All patients: History of AR with or without conjunctivitis and with or without asthma
  - Sensitivity proven : positive SPT and/or specific IgE
- Exclusion
  - The existence of other clinical sensitivities
  - Trials dealing with asthma alone

Main results

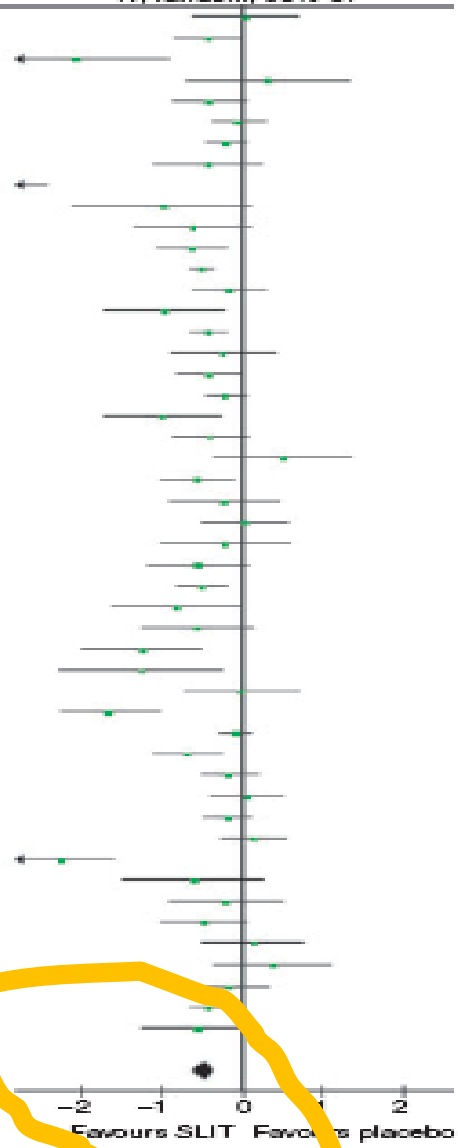
- **Pollen**: 39 (Grasses: 23, Parietaria: 5, Ragweed: 2 Trees: 9 Grass+Birch: 1) **Mites**: 8 **Cat**: 1

- Patients: 4,598 (Active: 2,333 Placebo: 2,256)
- Age: Adults: 34 Children: 15

- Treatment lasted for:
  - < 6 months: 17 6-12 months: 16 > 12 months: 16
- Major allergen:
  - < 5 µg: 8 5-20 µg: 12 > 20 µg: 12

Study or subgroup	SLIT Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. mean difference IV, random, 95% CI
Amar 2009	3.93	4.9	19	3.71	2.7	17	1.9%	0.03 [−0.62, 0.68]
Andre 2003	2.27	1.42	48	3.09	2.14	51	2.4%	−0.45 [−0.84, −0.05]
Ariano 2001	1.8	1.75	10	5.58	1.57	10	1.1%	−2.06 [−3.19, −0.93]
Bahceciler 2001	0.53	0.4	8	0.4	0.38	7	1.2%	0.31 [−0.71, 1.34]
Bowen 2004	3.95	2.45	37	5.03	2.54	39	2.3%	−0.43 [−0.89, 0.03]
Bufe 2004	1.54	0.77	68	1.59	0.96	64	2.5%	−0.06 [−0.40, 0.28]
Bufe 2009	2.67	2.38	117	3.17	2.14	121	2.7%	−0.22 [−0.48, 0.03]
Caffarelli 2000	4.2	3.7	17	5.9	3.8	17	1.9%	−0.44 [−1.12, 0.24]
Cao 2007	0.65	0.88	85	2.64	0.46	91	2.4%	−2.85 [−3.27, −2.43]
Casanovas 1994	5.46	3.56	9	10.98	7.1	8	1.1%	−1.00 [−2.11, 0.12]
D'Ambrosio 1999	509	514.2	14	897.06	678.2	16	1.7%	−0.62 [−1.36, 0.12]
Dahl 2006a	2.1	1.7	61	3.3	2.2	32	2.3%	−0.63 [−1.07, −0.19]
Dahl 2006b	2.4	1.6	282	3.4	2.2	286	2.8%	−0.52 [−0.69, −0.35]
de Blay 2003	20.55	15.89	33	23.49	18.76	42	2.3%	−0.17 [−0.62, 0.29]
Di Rienzo 2006	0.4	0.3	19	0.8	0.5	14	1.7%	−0.98 [−1.72, −0.23]
Didier 2007	3.58	2.976	136	4.93	3.229	148	2.7%	−0.43 [−0.67, −0.20]
Drachenberg 2001	29.5	24.2	37	36.4	30.4	12	1.9%	−0.26 [−0.92, 0.39]
Dubakiene 2003	0.48	0.3	47	0.84	0.43	53	2.4%	−0.42 [−0.82, −0.03]
Durham 2006	2.48	2.1	131	2.96	2.09	129	2.7%	−0.23 [−0.47, 0.02]
Feliziani 1995	109.7	92.46	19	215.8	114.2	18	1.7%	−1.00 [−1.72, −0.28]
Guez 2000	2.3	1.9	36	3.2	2.4	36	2.3%	−0.41 [−0.88, 0.06]
Hirsch 1997	0.99	1.13	12	0.52	0.47	10	1.5%	0.50 [−0.35, 1.36]
Hordijk 1998	3.21	3.05	35	5.13	3.6	36	2.2%	−0.57 [−1.04, −0.09]
La Rosa 1999	1.21	1.66	16	1.61	1.56	17	1.9%	−0.24 [−0.93, 0.44]
Lima 2002	2,494	2,326	28	2,465	1,537	28	2.1%	0.01 [−0.51, 0.54]
Marcucci 2005	412.92	332.55	13	517.27	548.18	11	1.6%	−0.23 [−1.03, 0.58]
Nelson 1993	12.15	8.69	20	18.67	13.56	21	1.9%	−0.56 [−1.19, 0.07]
Ott 2009	−1.02	4.54	123	1.32	4.54	60	2.6%	−0.51 [−0.83, −0.20]
Pajno 2003	4	5.19	14	10	8.65	13	1.6%	−0.82 [−1.62, −0.03]
Palma Carlos 2006	31.15	32.81	17	55.96	50.49	18	1.9%	−0.57 [−1.27, 0.13]
Panzner 2009	111.95	114.91	20	321.6	211.22	15	1.7%	−1.26 [−2.00, −0.52]
Passalacqua 1998	59.6	27.9	10	109.1	45.7	9	1.3%	−1.27 [−2.29, −0.26]
Passalacqua 1999	199	113	15	191	108	15	1.7%	−0.02 [−0.73, 0.70]
Passalacqua 2006	1.92	0.23	28	2.18	0.2	28	2.0%	−1.65 [−2.26, −1.04]
Peter 2009	0.732	0.483	176	0.78	0.544	189	2.7%	−0.09 [−0.30, 0.11]
Ptaar 2008	146.2	123	42	236.2	133.6	48	2.3%	−0.69 [−1.12, −0.27]
Pradalier 1999	2.33	1.6	63	2.65	2	63	2.5%	−0.18 [−0.53, 0.17]
Rolinck-Werninghaus 2004	13.71	23.12	39	12.66	21.65	38	2.3%	0.05 [−0.40, 0.49]
Röder 2007	2.45	1.49	91	2.74	1.66	77	2.6%	−0.18 [−0.49, 0.12]
Smith 2004	2.58	2.48	45	2.32	1.67	51	2.4%	0.12 [−0.28, 0.52]
Tari 1990	8	1.5	30	12	2	28	1.9%	−2.24 [−2.91, −1.58]
Tonnel 2004	2.74	2.14	10	4.11	2.19	12	1.5%	−0.61 [−1.47, 0.25]
Troise 1995	97	76	15	102	58	16	1.9%	−0.22 [−0.92, 0.49]
Valovirta 2006	1.5	1.4	27	2.2	1.4	29	2.1%	−0.49 [−1.03, 0.04]
Vervloet 2006	2.68	1.64	19	2.44	2.06	19	1.9%	0.13 [−0.51, 0.76]
Voltolini 2001	190	154	15	93	79	15	1.7%	0.97 [−0.35, 1.10]
Vourdas 1998	1.07	1.63	34	1.38	2.01	32	2.2%	−0.17 [−0.65, 0.3
Wahn 2009	3.25	2.96	131	4.51	2.991	135	2.7%	−0.43 [−0.69, −0.1
Wessner 2001	0.32	0.26	14	0.51	0.39	19	1.9%	−0.56 [−1.27, 0.1
Total (95% CI)			2333			2256	100.0%	−0.49 [−0.64, −0.3

Heterogeneity: $\tau^2 = 0.20$; $\chi^2 = 256.76$, df = 48 ($P < 0.00001$); $I^2 = 81\%$
Test for overall effect: $Z = 6.35$ ($P < 0.00001$)



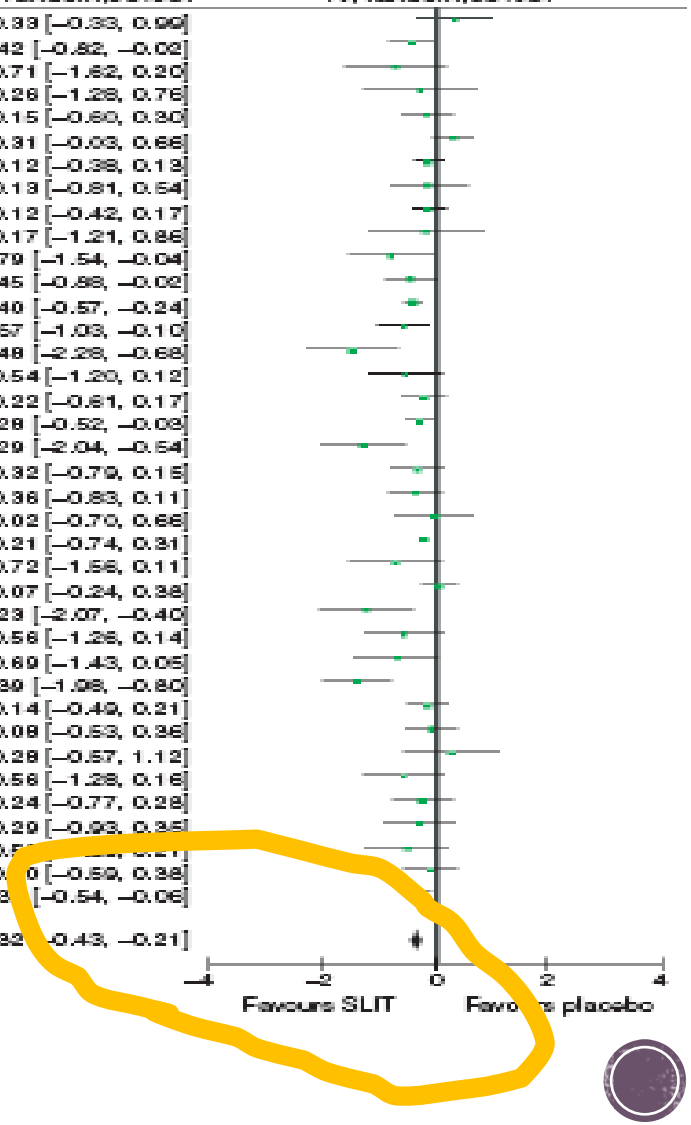
Main results

Medication scores

- Only 38 studies reported data)
- **SMD -0.32** 95% confidence interval (-0.43 - -0.21. *P* < 0.00001)
- Important degree of heterogeneity

Study or subgroup	SLIT Mean	SLIT SD	SLIT Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. mean difference IV, random,95%CI
Amar 2009	0.44	1.2	19	0.14	0.24	17	1.9%	0.33 [−0.33, 0.99]
Andre 2008	2.41	3.09	48	4	4.24	51	3.5%	−0.42 [−0.82, −0.02]
Ariano 2001	2.5	2.1	10	5.3	4.9	10	1.2%	−0.71 [−1.62, 0.20]
Bahceciler 2001	1.25	1.04	8	1.57	1.25	7	1.0%	−0.28 [−1.28, 0.76]
Bowen 2004	1.05	1.6	37	1.26	1.24	39	3.1%	−0.15 [−0.60, 0.30]
Bufe 2004	0.24	0.19	68	0.18	0.19	64	3.9%	0.31 [−0.03, 0.66]
Bufe 2009	2.13	3.48	117	2.53	3.03	121	4.8%	−0.12 [−0.38, 0.13]
Caffarelli 2000	8.1	6.4	17	9	6.9	17	1.9%	−0.13 [−0.81, 0.54]
Cao 2007	0.01	0.1	85	0.18	1.92	91	4.4%	−0.12 [−0.42, 0.17]
Casanovas 1994	1.89	2.46	9	2.13	2.22	6	0.9%	−0.17 [−1.21, 0.86]
D'Ambrosio 1999	48.1	46.6	14	124.37	121	16	1.6%	−0.79 [−1.54, −0.04]
Dahl 2006a	2.4	3.9	61	4.2	4.1	32	3.2%	−0.45 [−0.88, −0.02]
Dahl 2006b	1.5	1.9	282	2.4	2.5	286	5.8%	−0.40 [−0.57, −0.24]
de Blay 2003	3.48	5.37	33	7.57	8.23	42	3.0%	−0.57 [−1.03, −0.10]
Di Rienzo 2006	3.2	0.7	16	4.9	1.5	14	1.4%	−1.48 [−2.28, −0.68]
Drachenberg 2001	12.5	18.7	37	23.8	26.4	12	1.9%	−0.54 [−1.20, 0.12]
Dubakiene 2008	0.13	0.17	47	0.17	0.19	53	3.5%	−0.22 [−0.61, 0.17]
Durham 2006	1.4	2.13	131	2.03	2.39	129	4.9%	−0.28 [−0.52, −0.03]
Faliziani 1995	24.06	25.72	18	75.9	50.3	16	1.6%	−1.29 [−2.04, −0.54]
Guez 2000	4.1	5.5	36	6.1	6.8	36	3.0%	−0.32 [−0.79, 0.15]
Hordijk 1998	0.16	0.37	35	0.31	0.45	36	2.9%	−0.36 [−0.83, 0.11]
La Rosa 1999	2.28	3.89	16	2.36	3.95	17	1.8%	−0.02 [−0.70, 0.66]
Lima 2002	2,334	2,616	28	2,837	2,052	28	2.6%	−0.21 [−0.74, 0.31]
Marcucci 2005	21.92	30.45	13	87.45	83.77	11	1.3%	−0.72 [−1.56, 0.11]
Ott 2009	−0.28	11.55	123	−0.92	2.47	60	4.3%	0.07 [−0.24, 0.38]
Pajno 2003	10.27	7.26	14	28.27	16.5	13	1.3%	−1.23 [−2.07, −0.40]
Palma Carlos 2006	15.38	32.08	17	44.57	85.05	16	1.8%	−0.56 [−1.26, 0.14]
Passalacqua 1999	42	49.5	15	83	65	15	1.6%	−0.69 [−1.43, 0.05]
Passalacqua 2006	110	44	28	166	35	28	2.2%	−1.39 [−1.98, −0.80]
Pradalier 1999	1.77	2.3	63	2.13	2.7	63	3.9%	−0.14 [−0.49, 0.21]
Rolinck-Werninghaus 2004	2.54	3.58	39	2.85	3.87	38	3.1%	−0.09 [−0.53, 0.36]
Tonnel 2004	18.16	22.37	10	12.6	16.14	12	1.3%	0.28 [−0.57, 1.12]
Troise 1995	17	21	15	33	33	16	1.7%	−0.56 [−1.28, 0.16]
Valovirta 2008	2.9	3.4	27	3.9	4.6	29	2.6%	−0.24 [−0.77, 0.28]
Vervloet 2006	3.39	3.94	19	4.71	5	19	2.0%	−0.29 [−0.93, 0.35]
Vottolini 2001	22	30	15	39	34	15	1.7%	−0.[illegible]
Vourdas 1998	1.39	3.41	34	1.77	3.85	32	2.8%	−0.[illegible]0 [−0.59, 0.38]
Wahn 2009	0.6	0.611	131	0.79	0.647	125	4.9%	−0.3[illegible] [−0.54, −0.06]
Total (95% CI)			1737			1642	100.0%	−0.32 [illegible]0.43, −0.21]

Heterogeneity: $\tau^2 = 0.05$; $\chi^2 = 79.32$, df = 37 ($P = 0.0008$); $I^2 = 50\%$
Test for overall effect: $Z = 5.77$ ($P < 0.00001$)



Main results: specific serum antibodies

	Number of studies	n (active)	n (placebo)	SMD (95% CI)	*P*
sIgE	14	675	659	0.27 (-0.01; 0.55)	0.05
sIgG	3	286	304	0.95 (0.78; 1.12)	<0.00001
sIgG4	13	588	599	0.46 (0.29; 0.63)	<0.00001

Main results: safety

		Active		Placebo		
Local reactions	Studies	Patients	Total events (per patient)	Patients	Total events (per patient)	*P*
Labial oedema	11	604	55 (0.09)	536	7 (0.01)	<0.0001
Buccal pruritus	21	1126	1798 (1.6)	1075	492 (0.46)	<0.0001
Buccolingual oedema	8	648	143 (0.22)	606	2 (0.003)	<0.0001
Throat irritation	10	770	243 (0.30)	747	29 (0.04)	<0.0001
Oral (nonspecified)	3	68	143 (2.10)	71	24 (0.34)	<0.0001
Local (nonspecified)	3	119	7 (0.06)	116	3 (0.03)	0.3356

Main results: safety

Systemic reactions	Studies	Active		Placebo		
		Patients	Total events (per patient)	Patients	Total events (per patient)	*P*
Urticaria	8	204	7 (0.03)	199	9 (0.04)	0.6202
Pruritus/rash	10	363	13 (0.04)	222	9 (0.04)	0.8247
Conjunctivitis	8	262	774 (2.95)	238	786 (3.30)	0.2810
Rhinitis	16	965	1403 (1.45)	912	1034 (1.13)	<0.0001
Rhinoconjunctivitis	6	184	60 (0.33)	176	58 (0.33)	>0.9999
Asthma/wheeze	15	488	51 (0.10)	450	42 (0.09)	0.6637
Cough	8	337	313 (0.93)	304	211 (0.69)	0.0151
Gastrointestinal	20	630	88 (0.14)	561	10 (0.02)	<0.0001
Headache	6	535	70 (0.20)	548	68 (0.12)	0.7868
Anaphylaxis	6	291	0	288	0	-
Systemic nonspecified	5	330	4 (0.01)	36	0	>0.9999

Ann Allergy Asthma Immunol. 2008;100:475–481.

Sublingual-oral administration of standardized allergenic extracts: phase 1 safety and dosing results

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trained on the emergency use and administration of epinephrine, and those who refused were excluded. The correspondent asks practical and relevant questions regarding dose adjustments, the use of epinephrine, and the level of supervision required during SLIT. It is our opinion that epinephrine should be available anywhere immunotherapy is given, including at home. Dose adjustments were based on individual patients' tolerance, and this seemed to be a safe approach. Finally, it is our opinion that SLIT, like subcutaneous immunotherapy, should be supervised by physicians who are experienced in the administration of allergen immunotherapy.

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ROBERT K. BUSH, MD†
DAVID PEDEN, MD‡
RICHARD F. LOCKEY, MD§
*Research and Development

Reviewerers' conclusions

- **SLIT**
  - Viable alternative to allergen injection immunotherapy

- **SLIT**
  - Safer after compared to SCIT

- Inclusion of other evaluations are needed to define the place of **SLIT** in the treatment of RC

MAIN CONCLUSIONS

- Evidence support the efficacy of immunotherapy in allergic rhinitis and asthma
- Similar rates of efficacy and compliancy are associated with SLIT and SCIT
- The safety profile of SLIT is improved compared to SCIT
- Further trials SLIT *vs* SCIT are warranted

MAIN CONCLUSIONS

SLIT products need to be chosen taking into account:

1) Simplicity of administration schedule
2) Patient compliance
3) Safety
4) Efficacy

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CLÍNICA SUBIZA

Thank you!