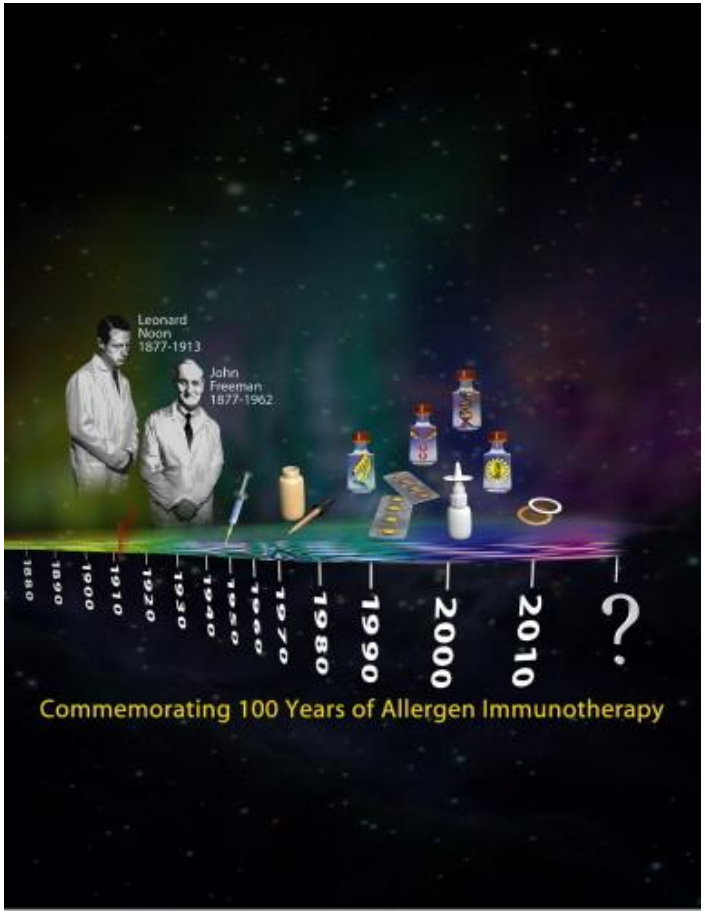
Sublingual Immunotherapy (SLIT) in Primary Care - The potential.



Dermot Ryan, FRCGP, Woodbrook Medical Centre, Loughborough, United Kingdom

Allergy and Respiratory Research Group, Centre for Population Health Sciences: GP Section, University of Edinburgh, Edinburgh, Scotland;

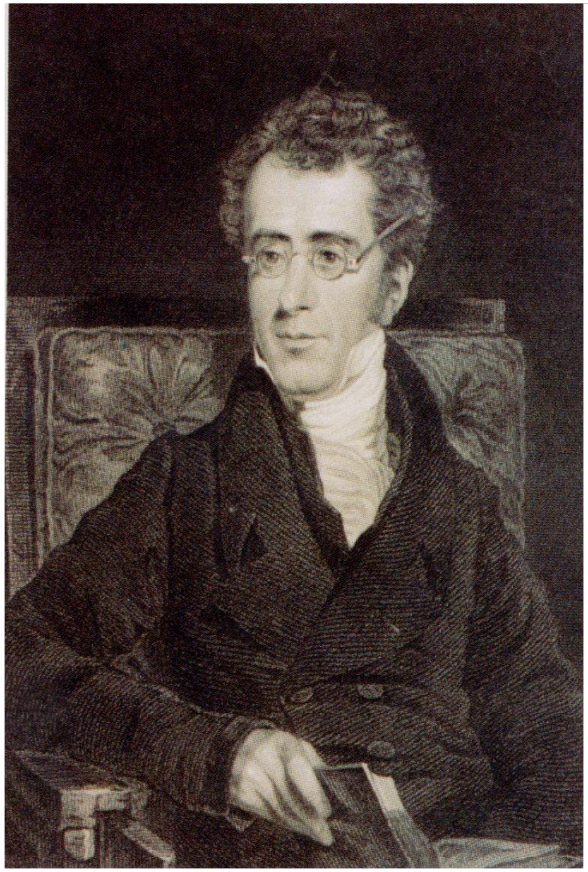
What is allergen immunotherapy?

Administration of an allergen in order to achieve immunologic tolerance

Current use for : Allergic rhinitis
Asthma
Venom anaphylaxis

First description of hay fever

John Bostock, Med Chir Trans, 1819; 10: 161



"About the beginning or middle of June in every year …. A sensation of heat and fullness is experienced in the eyes …. To this succeeds irritation of the nose producing sneezing … To the sneezeings are added a further sensation of tightness of the chest, and a difficulty of breathing"

EXPERIMENTAL RESEARCHES

ON THE

CAUSES AND NATURE

OF

CATARRHUS AESTIVUS

(HAY-FEVER OR HAY-ASTHMA)

BY

CHARLES H. BLACKLEY, M.R.C.S. ENG.

'When a small portion of pollen, just enough to tinge the tip of the finger yellow, was applied to the mucous membrane of the nares, some of the symptoms of hay fever were invariably developed, the severity and continuance of which were dependent on the quality and on the number of times it was used.'

LONDON:
BAILLIÈRE, TINDALL & COX,
KING WILLIAM STREET, STRAND.
PARIS: BAILLIÈRE | MADRID: BAILLIÈRE.
1873.

History of immunotherapy

THE LANCET

PROPHYLACTIC INOCULATION AGAINST HAY FEVER

L. Noon B.C. CANTAB., F.R.C.S. ENG., (From the Laboratory of the Department for Therapeutic Inoculation, St. Mary's Hospital.)

Volume 177, Issue 4580, 10 June 1911, Pages 1572-1573

THE LANCET

FURTHER OBSERVATIONS ON THE TREATMENT OF HAY FEVER BY HYPODERMIC INOCULATIONS OF POLLEN VACCINE..

The Lancet, Volume 178, Issue 4594, Pages 814-817

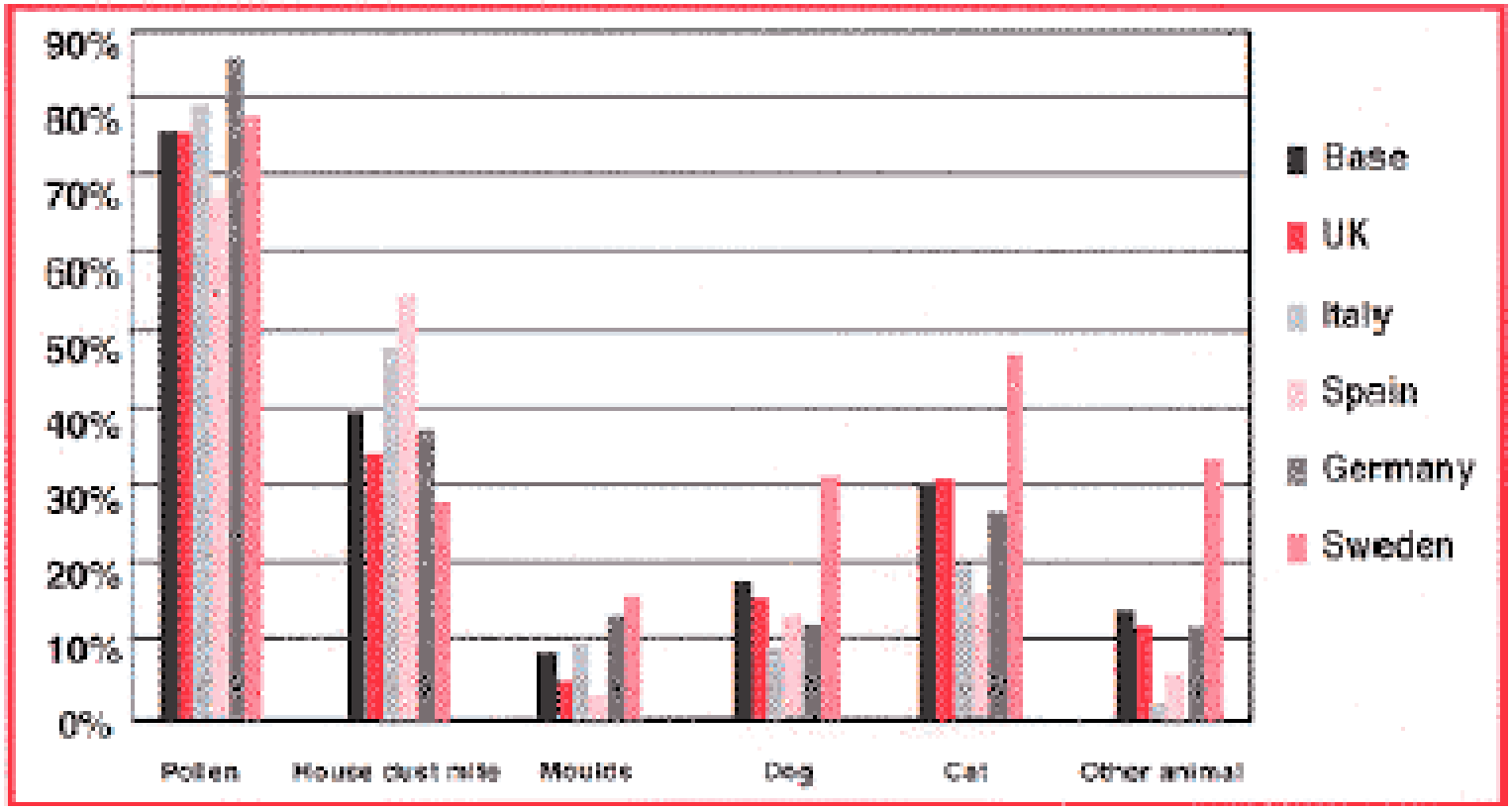
J. Freeman

……**described conjunctival provocation of patients with allergic rhino- conjunctivitis and successful treatment using subcutaneous inoculation of extract**

EFA 2001

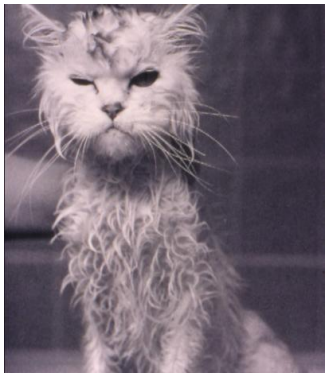
Allergens

The most frequent allergens reported were pollen, house dust mite, moulds, dog, cat and other animals (Fig. 2).



Allergens of Proven Efficacy in Double Blind Placebo Controlled Studies

Pollens
Cat
House dust mite
Hymenoptera



WHO position paper: allergen immunotherapy

- High dose, standardised vaccines (5-20mcg major allergen per monthly maintenance injection)
- Mixtures of allergens in polysensitised patients are of no proven value
- Administer in specialist clinics by trained persons with immediate access to adrenaline etc
- Observation period after injections 30min
- Risks of immunotherapy are increased in asthma
- Optimum duration of immunotherapy: 3-5 years

Bousquet J, Lockey RF, Malling HJ et al.
Allergy 1998;53:suppl 44:1-42

CSM UPDATE: Desensitising vaccines

BMJ 1986;293:948

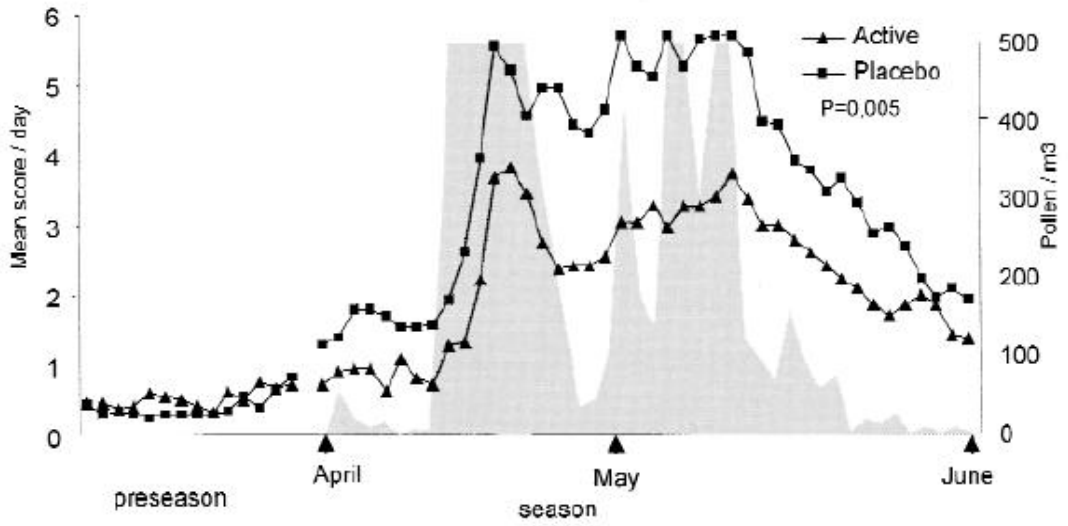
- 26 fatalities 1957-1986
- 16/17 in patients with asthma

- Immunotherapy only to be carried out in clinics offering full range of life support.

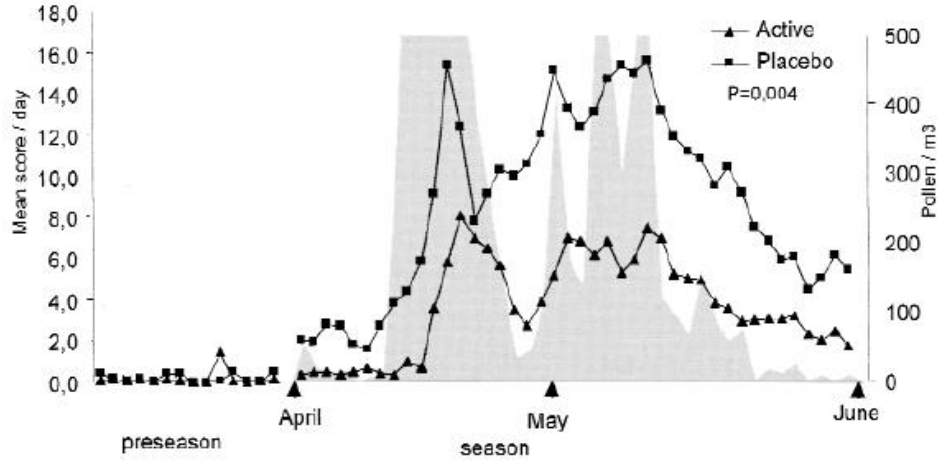
Birch pollen immunotherapy for hayfever

(2 years, n=46) year 2, 1998

Symptoms

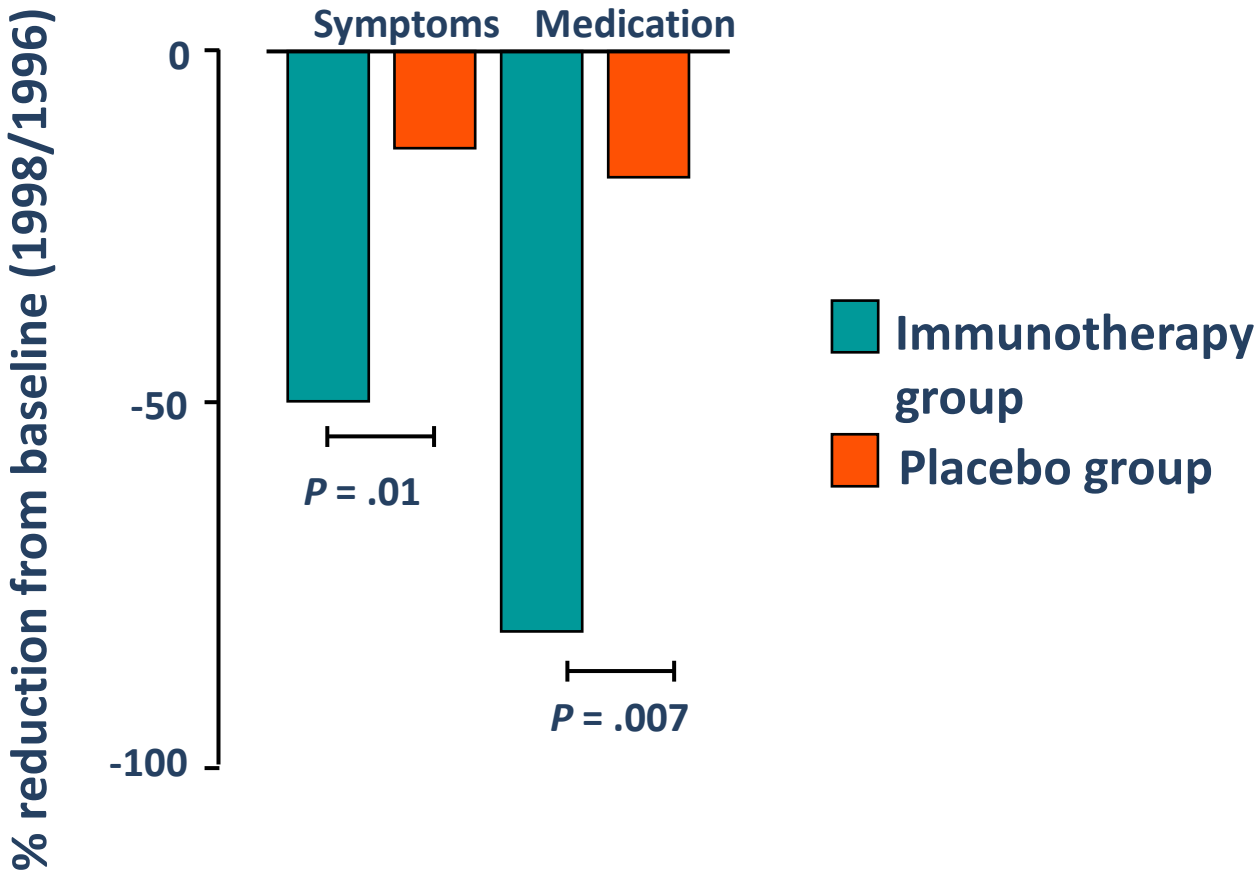


Medication



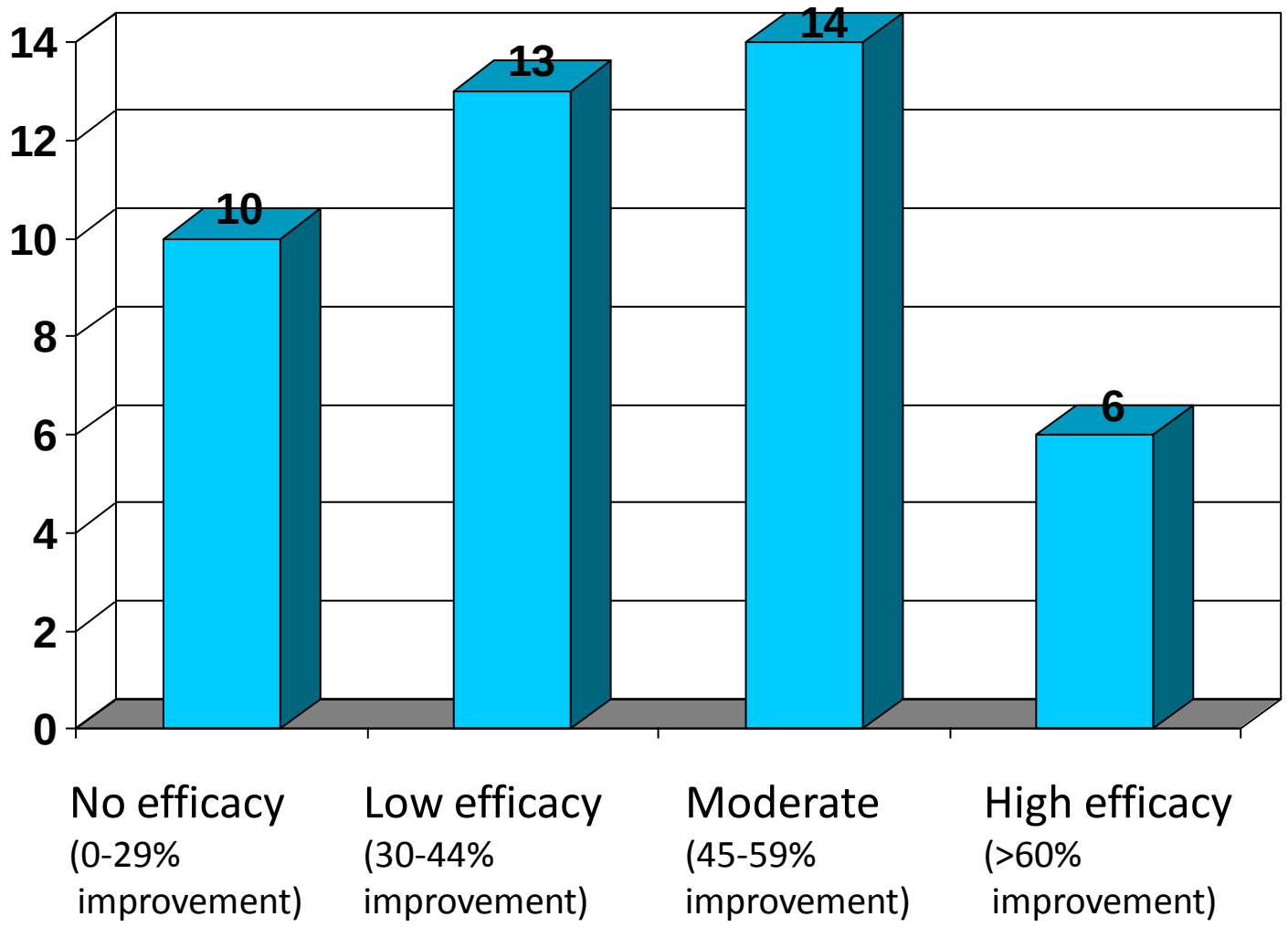
Arvidsson, M. et al. J Allergy Clin Immunol 2002; 109:777-83

Grass pollen immunotherapy for seasonal rhinitis/asthma



Walker SM et al., J Allergy Clin immunol 2001;**107**:87-93

Immunotherapy for rhinitis (43 studies)



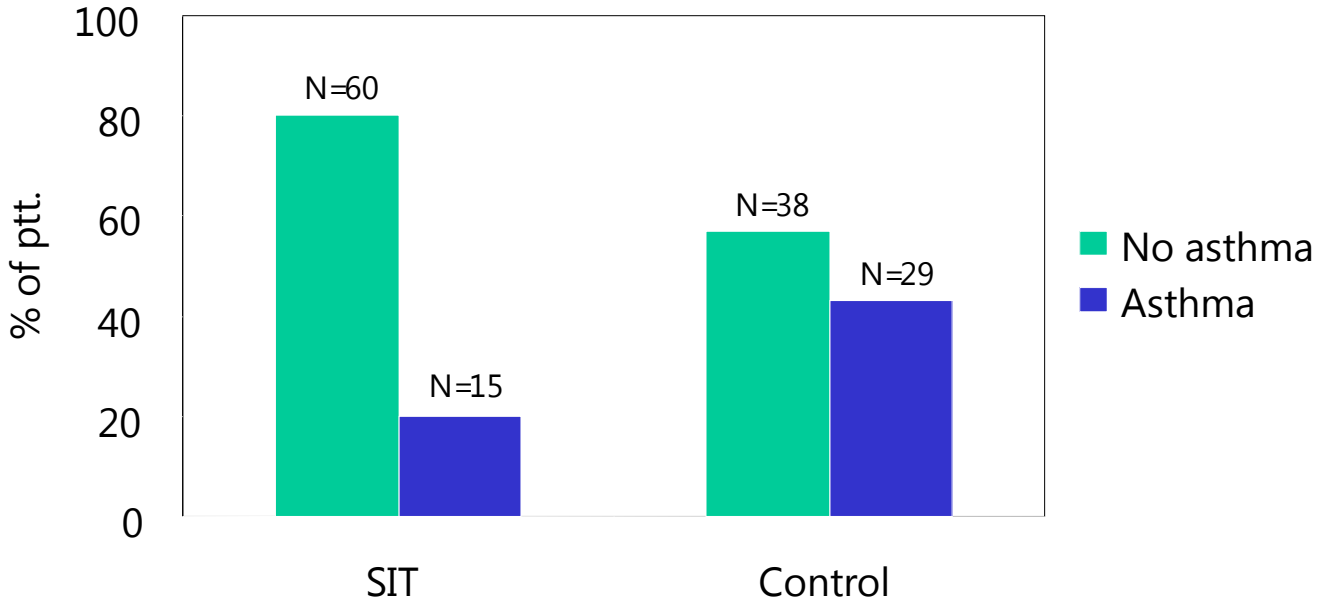
Malling HJ. Allergy 1998;53:461-472

Preventative allergy treatment study

Development of asthma at 5 years

N = 142 patients without asthma in season one

Odds-ratio = 2.68 (1.3 – 5.7)



Moller C et al, J Allergy Clin Immunol 2002;109:251-6 (follow up results)

IT: Prevention of New Sensitizations

New sensitizations after 3 years:
55% SIT group vs 100% control group.

Des Roches et al, JACI 1997

New sensitizations after 3 years:
25% SIT group vs 67% control group.

Pajno et al, Clin Exp Allergy 2001

New sensitizations after 4 years
23% SIT group vs 68% control group.
Purello D'Ambrosio et al, Clin Exp Allergy 2001

Immunotherapy in asthma: systematic review (88 randomised controlled trials 1954-2005)

Odds ratios (<1 favours immunotherapy)

Significant improvement in asthma scores -0.59

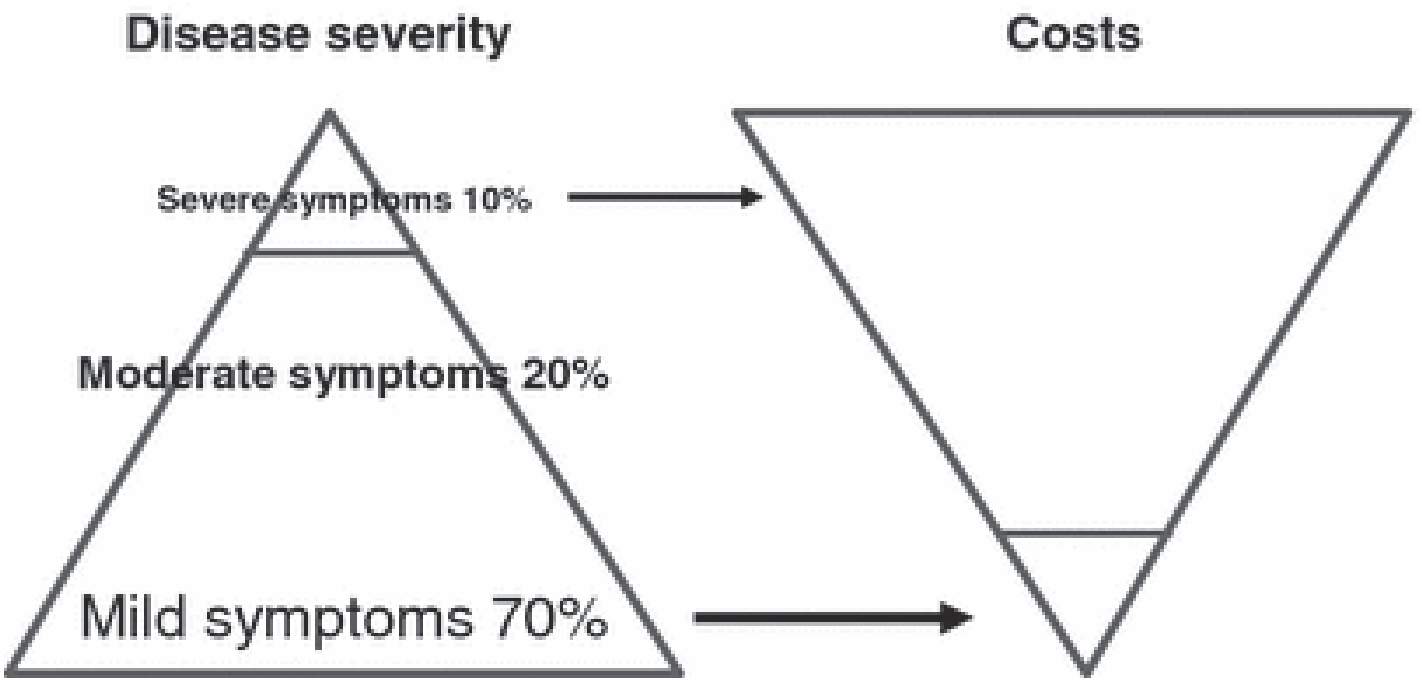
NNT to prevent exacerbation 3

NNT to avoid increased medication 4

Significantly reduce specific bronchial hypereactivity

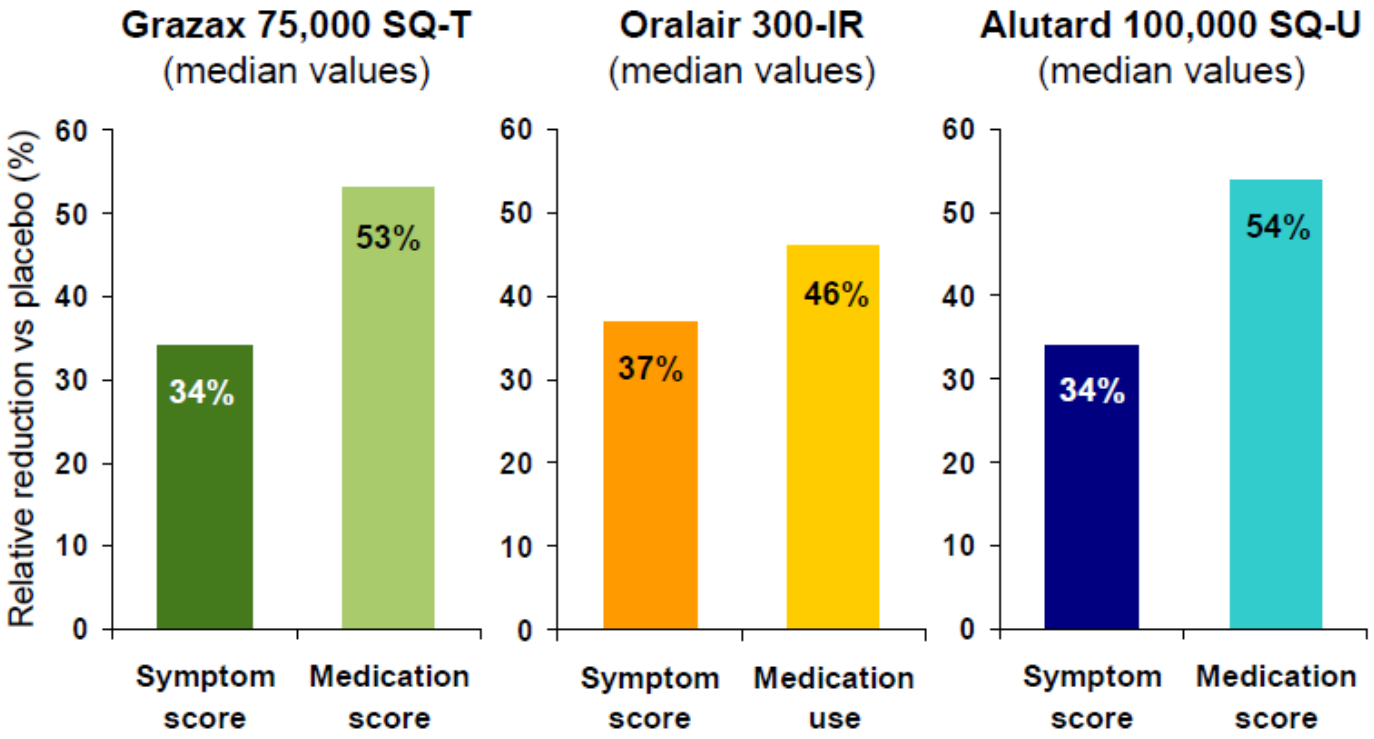
Abramson MJ, Puy RM, Weiner JM. Injection allergen immunotherapy for asthma. Cochrane Database of Systematic Reviews 2010, Issue 8

Finnish Allergy Programme 2008–2018 – time to act and change the course



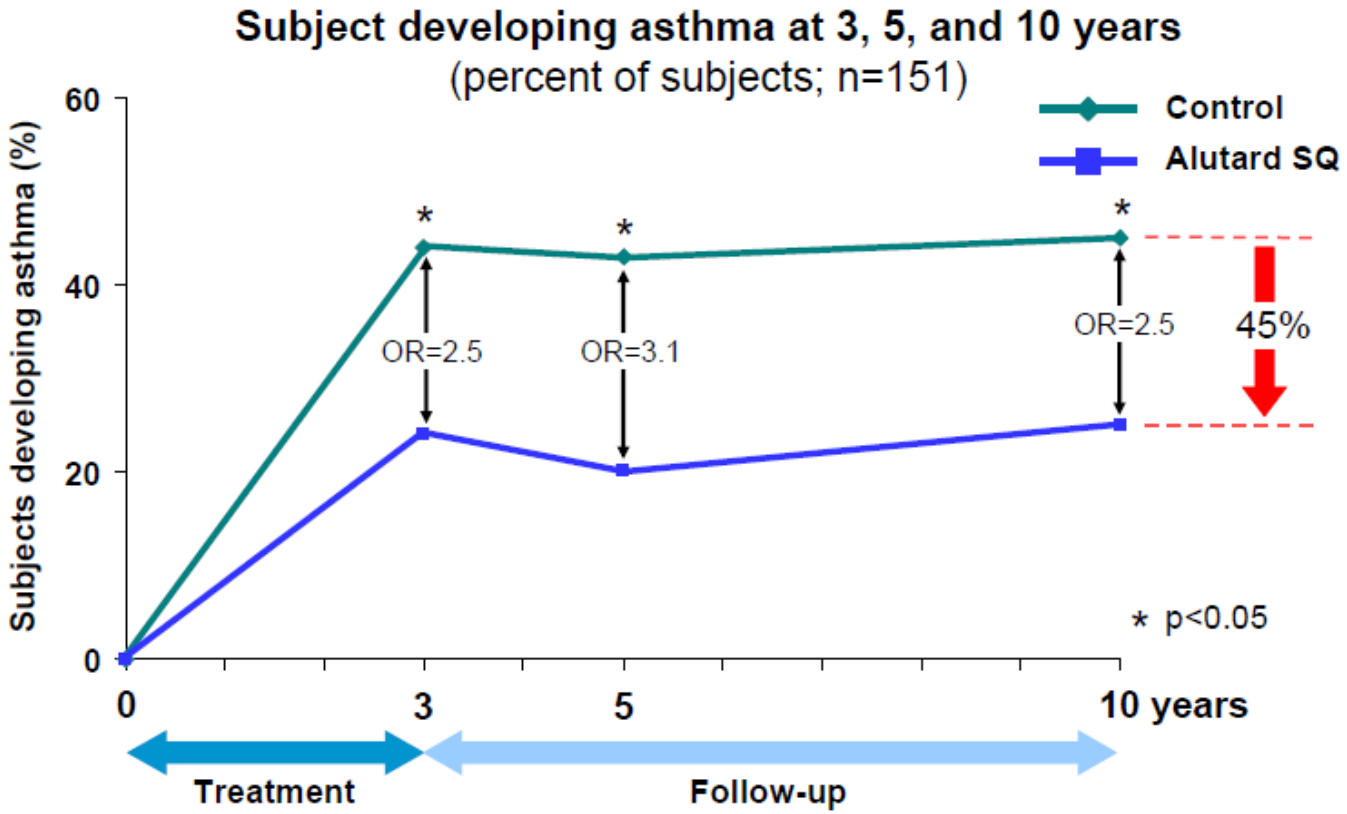
Allergy
Volume 63, Issue 6, pages 634-645, 25 APR 2008 DOI: 10.1111/j.1398-9995.2008.01712.x
http://onlinelibrary.wiley.com/doi/10.1111/j.1398-9995.2008.01712.x/full#f1

Efficacy 1st treatment season: adults
Comparable to sub-cutaneous immunotherapy



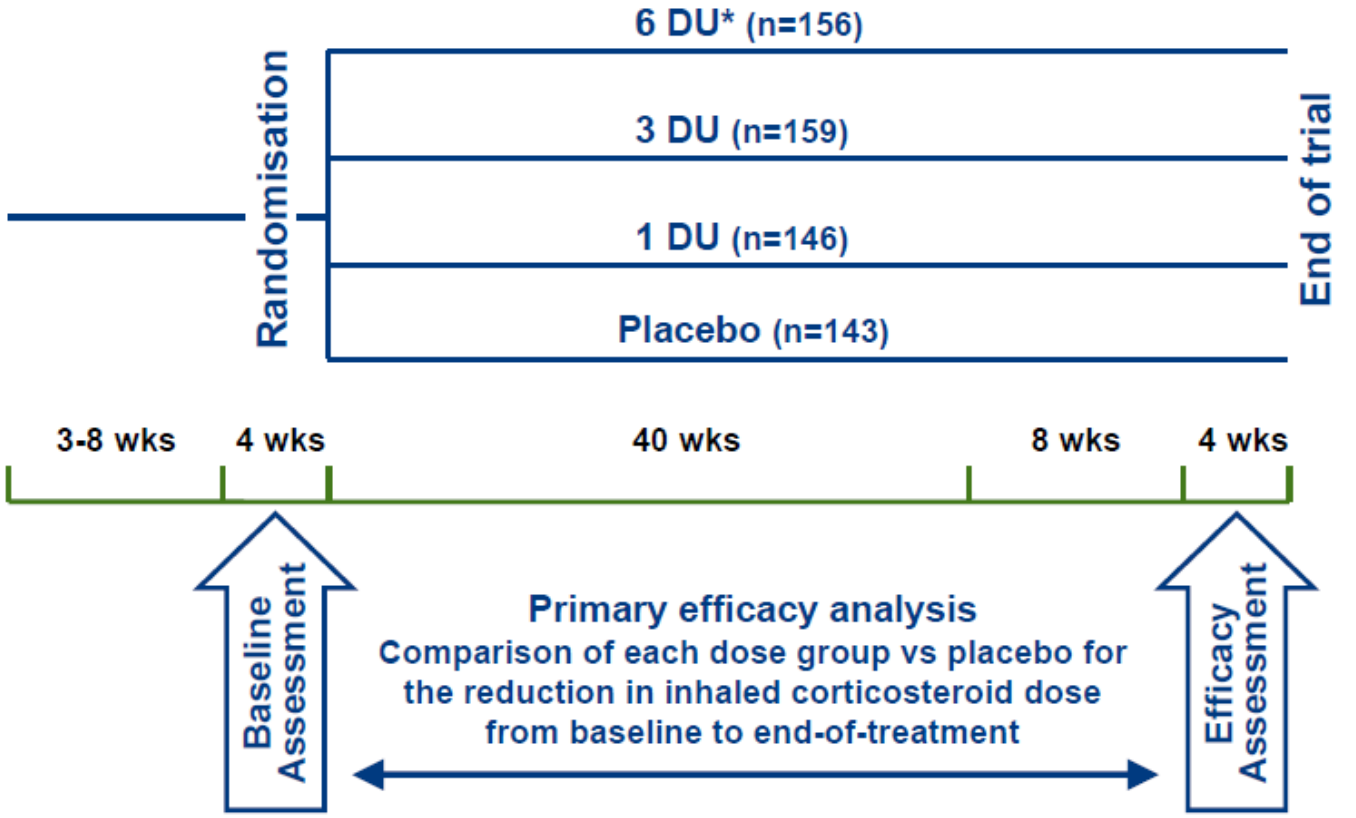
Dahl et al. JACI 2006;118:434-40; Didier et al. JACI 2007;120:1338-45; Frew et al. JACI 2006117:319-25

SCIT preventive effect
Reduced risk of developing asthma



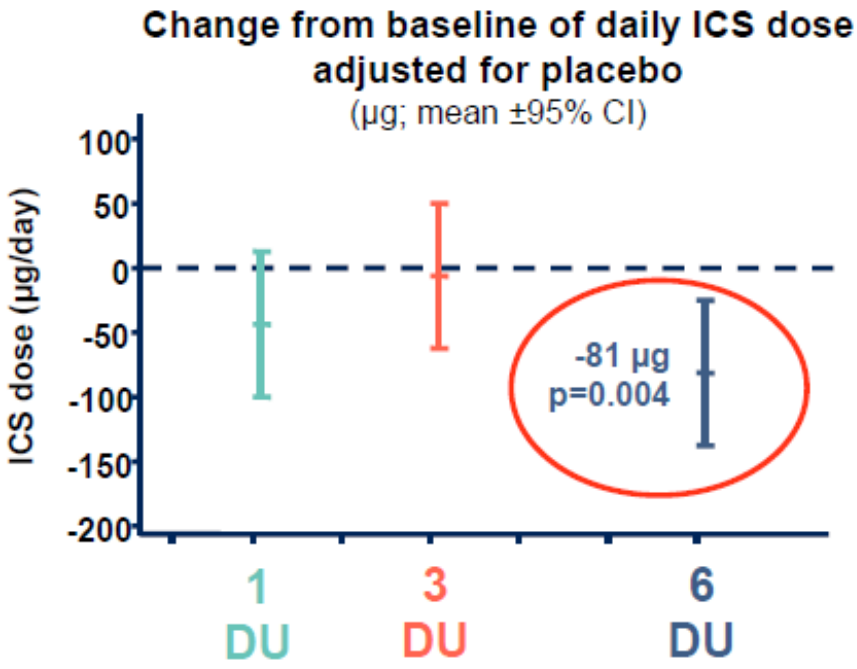
1. Möller et al. JACI 2002;109:251-6 2. Jacobsen et al. Allergy 2007:62:943-8

ALK house dust mite AIT
Clinical proof of concept in asthma: MT-02 trial



* DU = Development Unit (allergen content not disclosed, contains *Der p* and *Der f* major allergen)

ALK house dust mite AIT
Median ICS dose reduced by 50% in 6 DU group



	N	Change from baseline: Median	Change from baseline: %	Diff vs placebo
Placebo	143	-100 µg	**–25%**	–
6 DU	156	-200 µg	**–50%**	–100 µg

Confirmatory phase III trial programme being planned

Mosbech et al. Allergy 2009;64 (Suppl. 90):184; Data on file, ALK-Abello

Post Hoc analysis: presented EACCI 2011: de Blay,Riis,Canonica

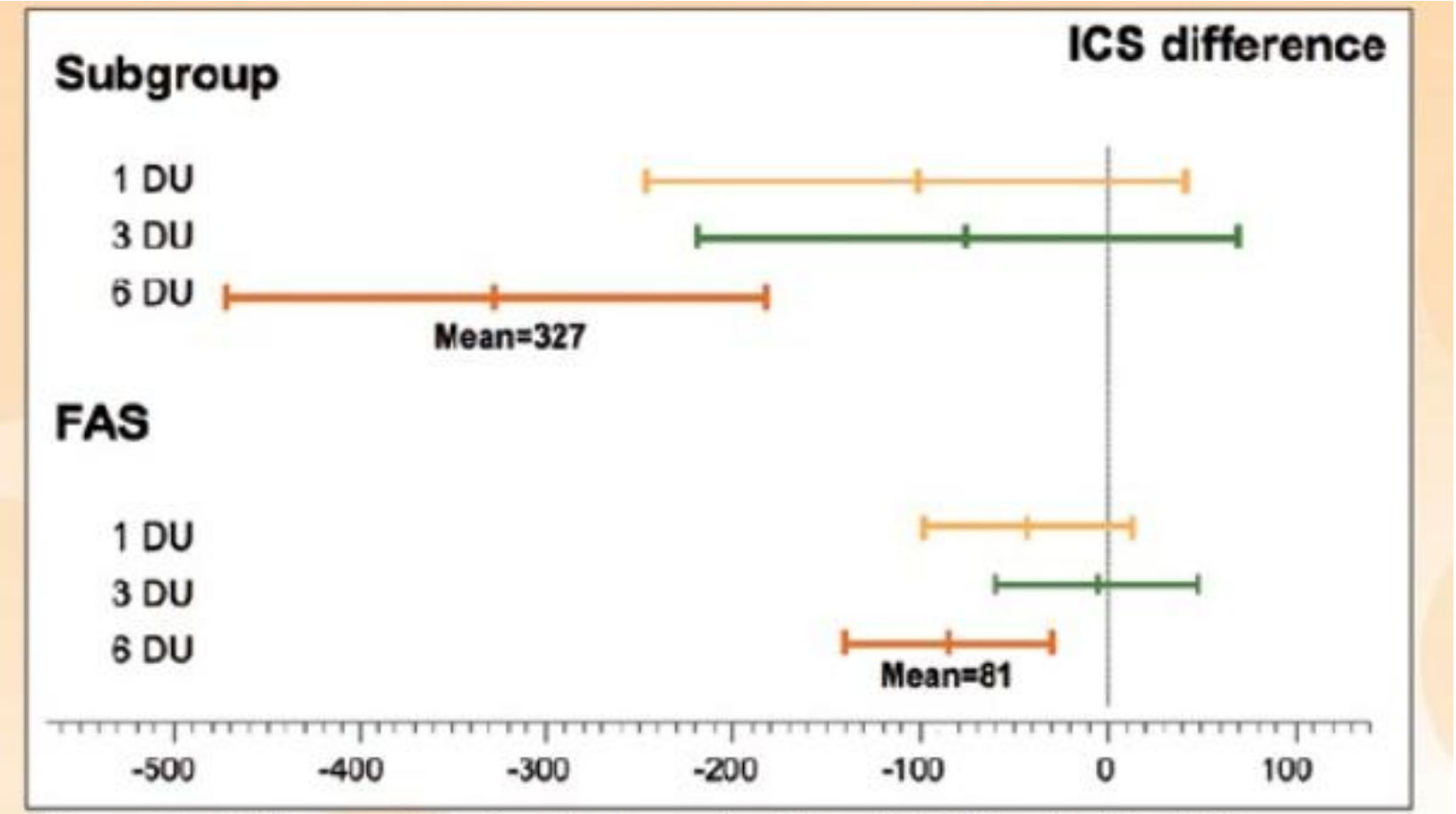


Figure 1: Difference to placebo in reduction of ICS (µg) with 95% confidence intervals; FAS: full analysis set (N=604); Subgroup: daily ICS use of 400-800 µg and ACQ score of 1-1.5 (N=108)

Sub group: ACQ 1-1.5, Max dose bud 800 mcg

Post Hoc analysis: presented EACCI: de Blay,Riis,Canonica

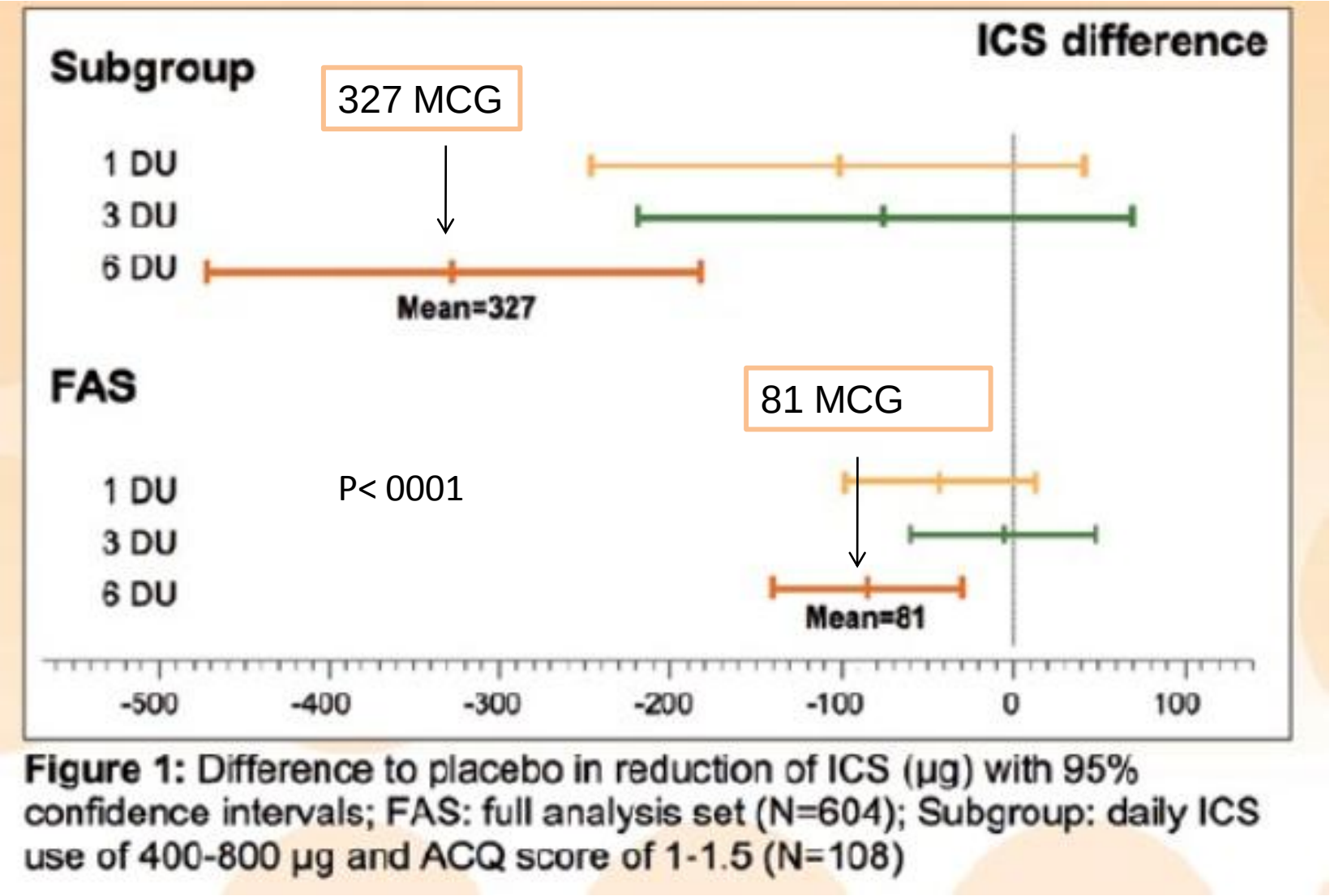


Figure 1: Difference to placebo in reduction of ICS (µg) with 95% confidence intervals; FAS: full analysis set (N=604); Subgroup: daily ICS use of 400-800 µg and ACQ score of 1-1.5 (N=108)

Sub group: ACG 1-1.5, dose bud 400-800 mcg

Post Hoc analysis: presented EACCI: de Blay,Riis,Canonica

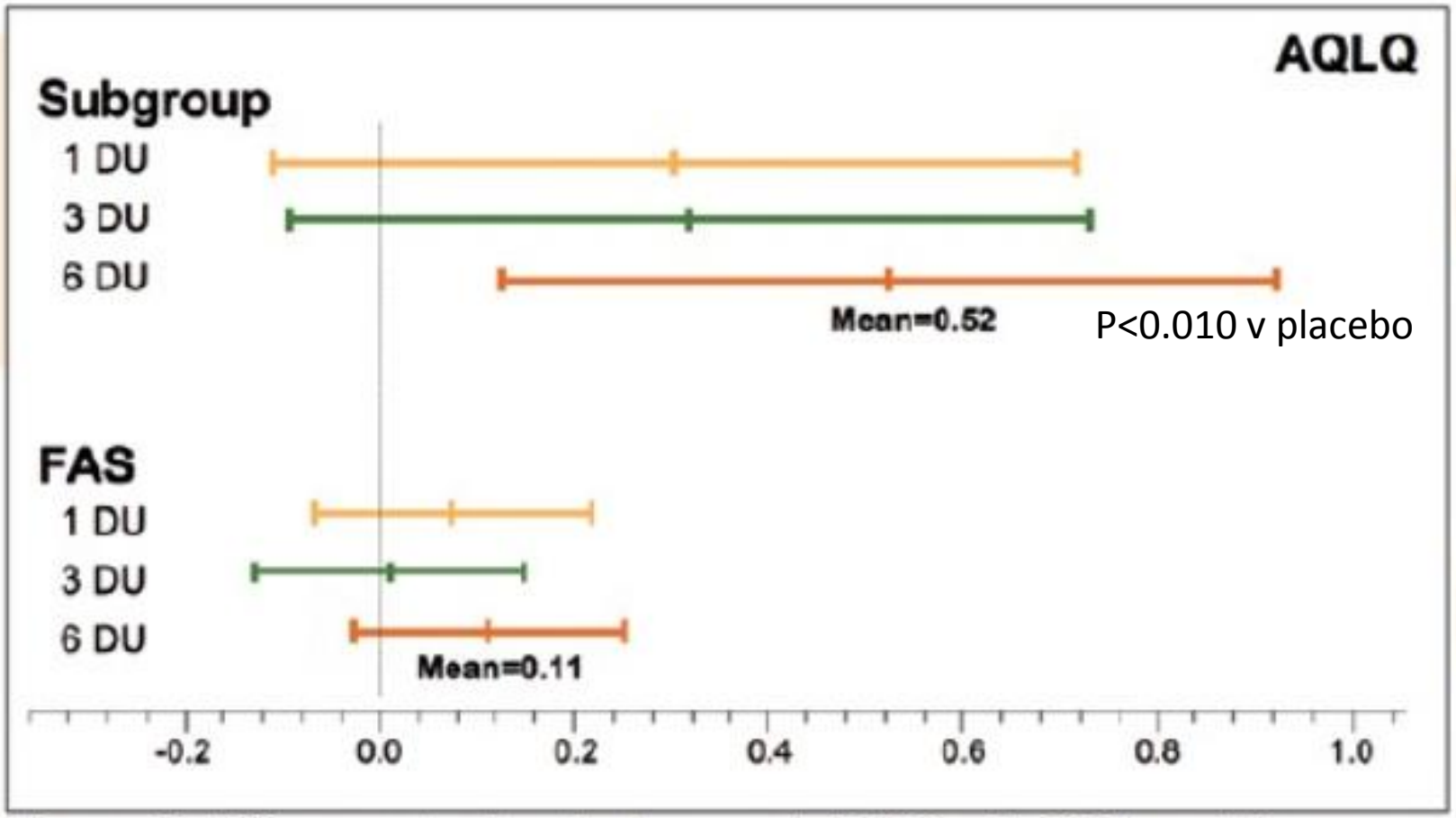


Figure 2: Difference to placebo in overall AQLQ with 95% confidence intervals; FAS: full analysis set (N=604); Subgroup: daily ICS use of 400-800 µg and ACQ score of 1-1.5 (N=108)

Long term evidence for sublingual immunotherapy

Immunotherapy:

how do subcutaneous and sublingual compare on evidence

	Subcutaneous	**Sublingual**
Efficacy	Proven[1-6]	**Proven[7-9]**
Long-term efficacy	Proven[1-4]	**Anticipated[7]**

1. Durham SR *et al. NEJM* 1999
2. Jacobsen L *et al. Allergy* 1997
3. Hedlin G *et al. JACI* 1995
4. Mosbech H *et al. Allergy* 1988
5. Frew AJ *et al. JACI* 2006
6. Möller C *et al. JACI* 2002
7. Di Rienzo V *et al. Clin Exp Allergy* 2003
8. Novembre E *et al. JACI* 2004
9. Dahl *et al. Allergy* 2006

Long term efficacy of immunotherapy

3 years treatment with subcutaneous immunotherapy has been shown to be effective to give at least 6 years benefit after treatment[1]

3 years continuous treatment with Grazax is under evaluation (clinical study GT-08)

Study is in its 3rd year

The World Health Organisation position paper states that many clinicians advise 3-5 years of therapy for patients who have had a good therapeutic response[2]

1. Jacobsen L *et al. Allergy* 1997
2. Bousquet *et al,* WHO Position Paper, *JACI* 1998

Could Primary care assist in delivering tolerance induction to allergens?

Se puede atención primaria ayudar a entregar la inducción de tolerancia a los alergenos?

Hypoallergenic foods
Alimentos hipoalergénicos

Aggressive cleaning
Limpieza agresiva

Pet removal
eliminación de animales domésticos

Could Primary care assist in delivering tolerance induction to allergens?

Hypoallergenic foods
Alimentos hipoalergén

Avoidance is of little benefit

Aggressive cleaning
Limpieza agresiva

Pet removal
eliminación de animales domésticos

Evitación se demuestra un beneficio limitado

Efficacy of sublingual immunotherapy in asthma: systematic review of randomized-clinical trials using the Cochrane Collaboration method

Z. Calamita H. Saconato, A. B. Pelá Á. N. Atallah

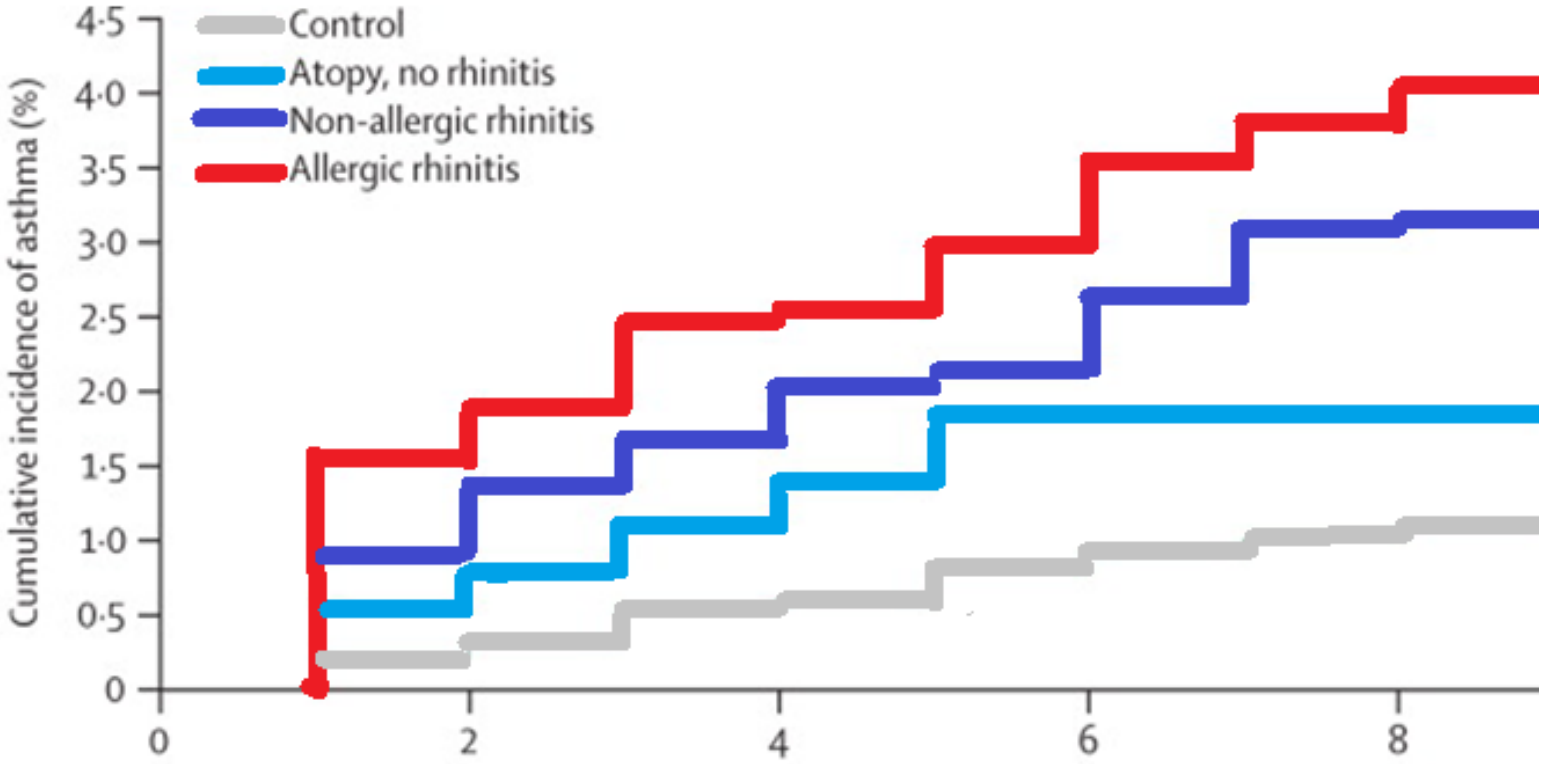
25 Studies

NNT to prevent worsening 3.7

Standardised mean difference -0.38

Allergy Symptoms SMD -1.18

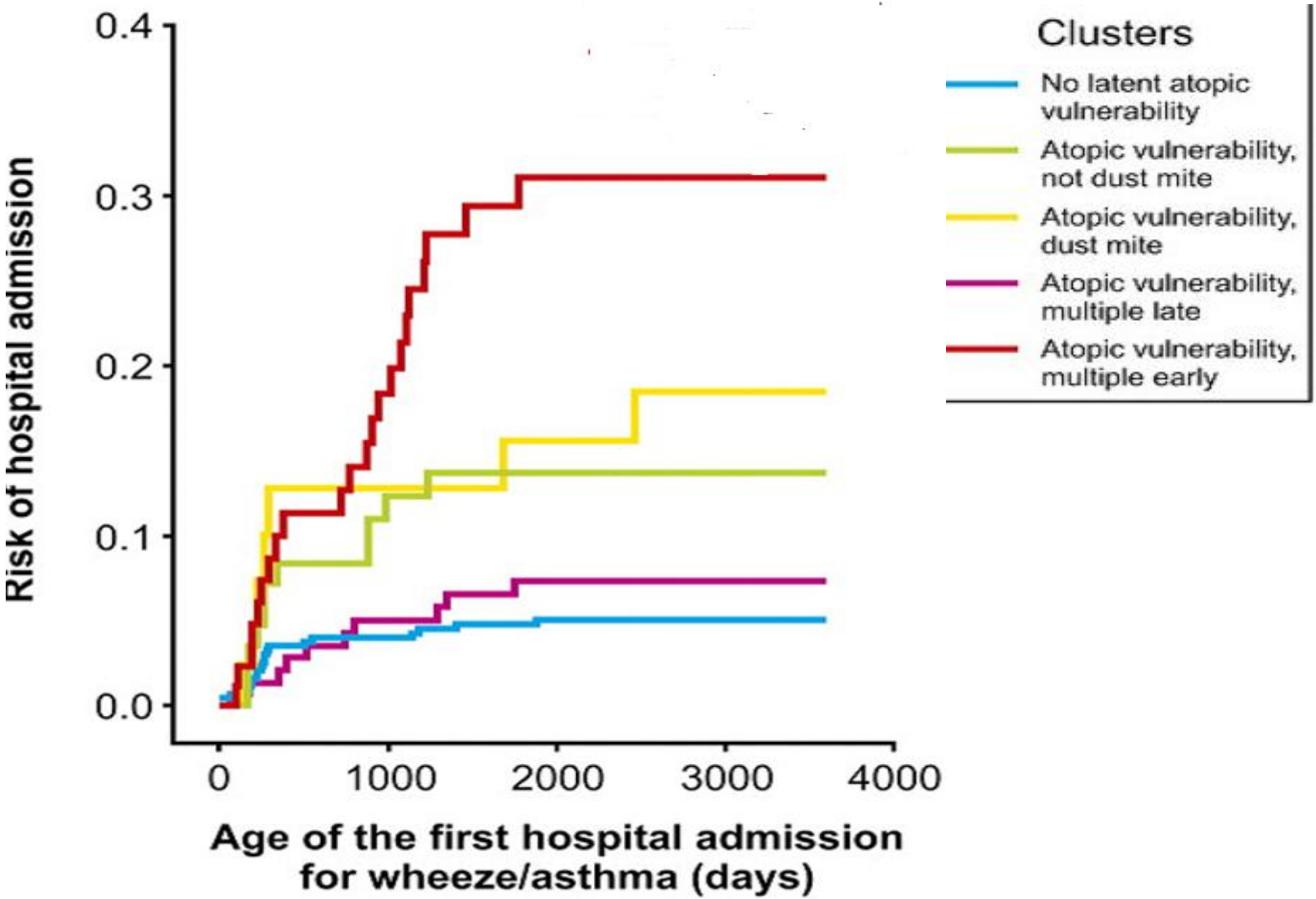
Resp function SMD 1.48



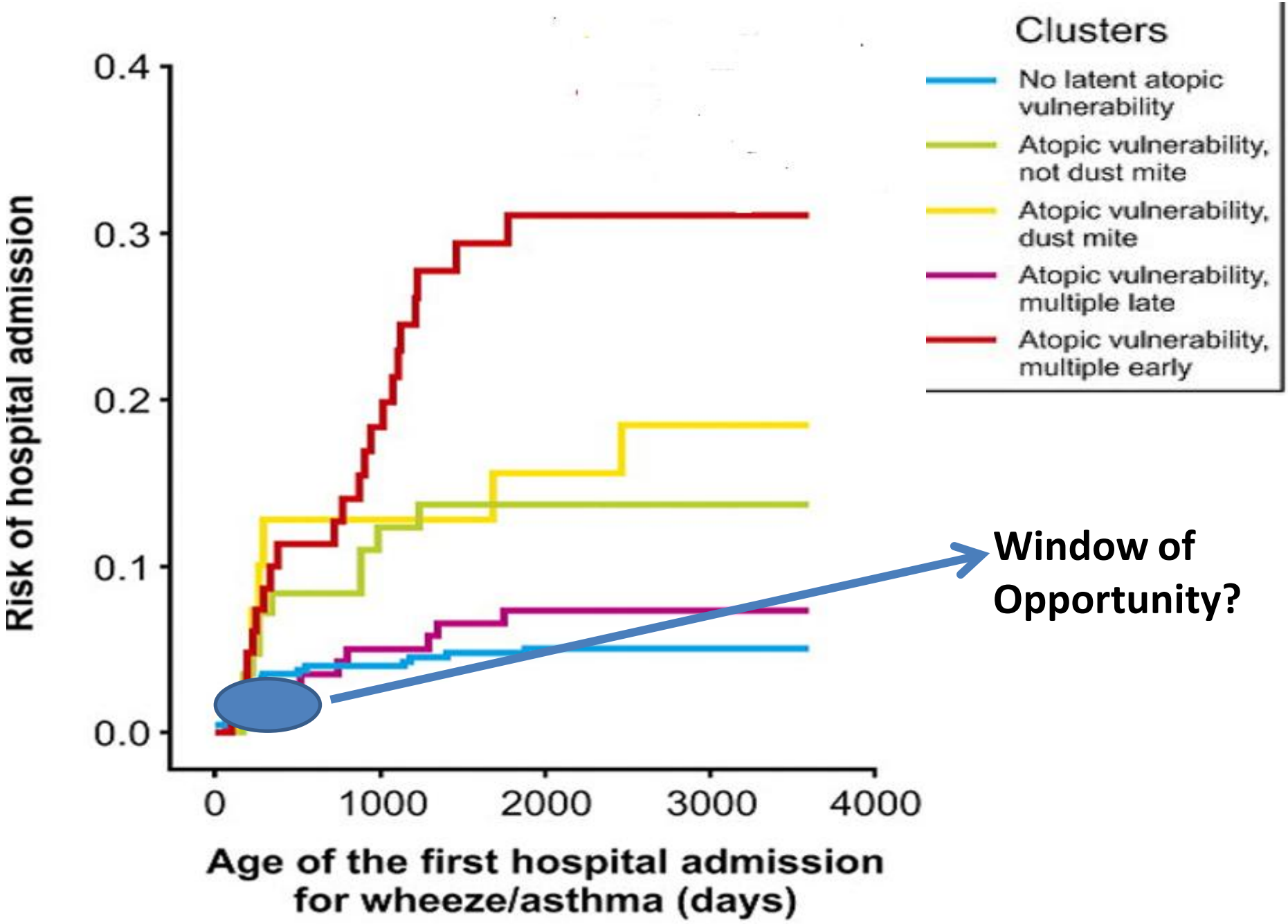
Probability of developing asthma, % (95% CI)

Control	0	0·2 (0·1–0·5)	0·5 (0·3–0·9)	0·8 (0·5–1·2)	1·0 (0·7–1·5)
Atopy, no rhinitis	0	0·6 (0·2–1·5)	1·1 (0·6–2·3)	1·9 (1·1–3·2)	1·9 (1·1–3·2)
Non-allergic rhinitis	0	0·9 (0·5–1·5)	1·7 (1·1–2·5)	2·2 (1·5–3·1)	3·1 (2·3–4·1)
Allergic rhinitis	0	1·6 (1·0–2·4)	2·5 (1·7–3·5)	3·0 (2·2–4·1)	3·8 (2·9–5·1)

1. ***Rhinitis and onset of asthma: a longitudinal population-based study 2008 Lancet 372 1049-57 Shaaban R, Zureik M,Soussan D, et al***



Simpson et al AJCCRM doi: 10.1164/rccm.200907-1101OC


Clusters
No latent atopic vulnerability
Atopic vulnerability, not dust mite
Atopic vulnerability, dust mite
Atopic vulnerability, multiple late
Atopic vulnerability, multiple early
Risk of hospital admission
0.0
0.1
0.2
0.3
0.4
0
1000
2000
3000
4000
Age of the first hospital admission for wheeze/asthma (days)
Window of Opportunity?

Summary

-Allergic disease is on the increase
-Early multiple sensitisation is a factor in the genesis of asthma
-HDM is an important component of this

Hypothesis:
Identifiying those with multiple sensitisations
Administering SLIT for HDM/Grass/Pollen could reduce further
Allergic sensitisation and reduce the development of asthma

Unkowns:
Whom?
How Long?
What dose?