Allergen Immunotherapy Update

(and preliminary considerations in the 4th Update of AIT PP)

David I Bernstein MD

Professor Emeritus of Medicine
Division of Immunology, Allergy and Rheumatology
Eastern Allergy Conference 2025

UNIVERSITY OF Cincinnati

Allergen Immunotherapy Update

Objectives

1. Discuss new data regarding SLIT since the third update of the AIT Practice Parameter.

2. Review relative efficacy and safety of SLIT and SCIT, and effective measures to reduce risk.

3. Identify new developments and unmet needs

AIT Practice Parameter 4th Update

What's can we say about SLIT?

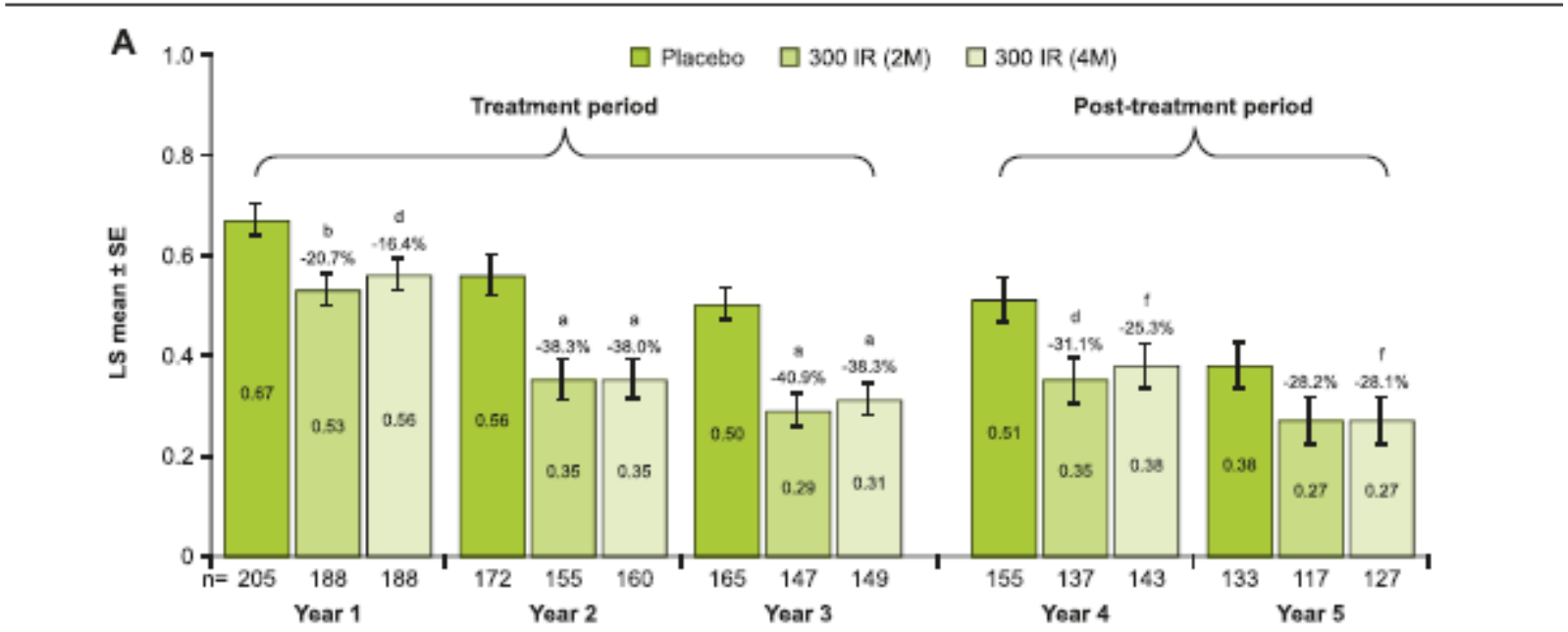
- *Sustained efficacy for SLIT tablets after 3 years of treatment.*
  - *Either year round or pre/co-seasonal treatment*
- *Evidence supporting efficacy for HDM SLIT for house dust mite asthma and atopic dermatitis (not FDA approved)*
- *SLIT tablet monotherapy is effective in poly-allergic patients*
- *Relative efficacy of SLIT versus SCIT?*
- *Insufficient evidence to evaluate SLIT drops*
- *Strong evidence supporting safety of SLIT*

How is sustained efficacy best achieved with SLIT grass tablets?

Preliminary statement: *Three years of pre- and co-seasonal therapy in as effective as 3 years of continuous therapy* ***(Evidence: moderate-high)***

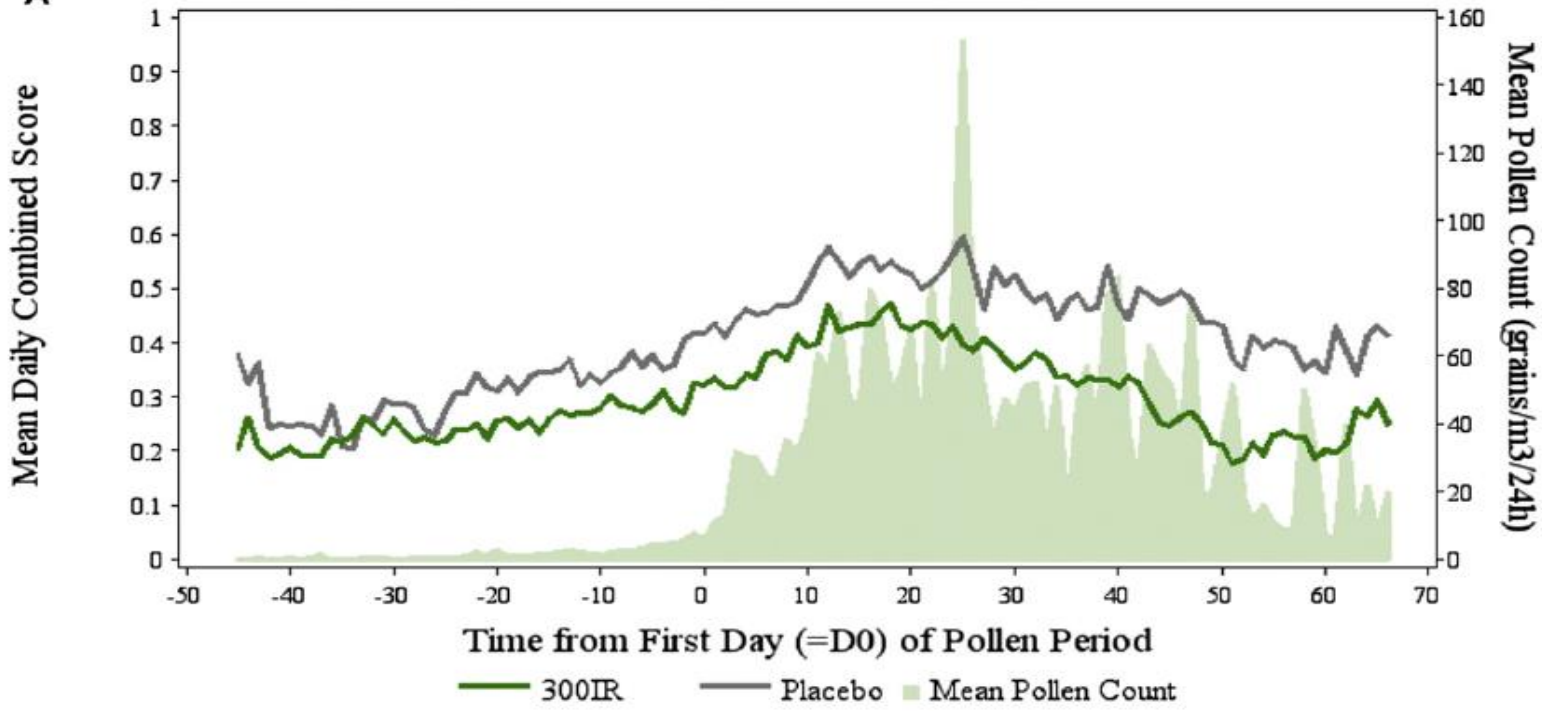
Pre- and co-seasonal administration of FDA approved 5-grass pollen SLIT for 3 years.

Daily combined Symptom score



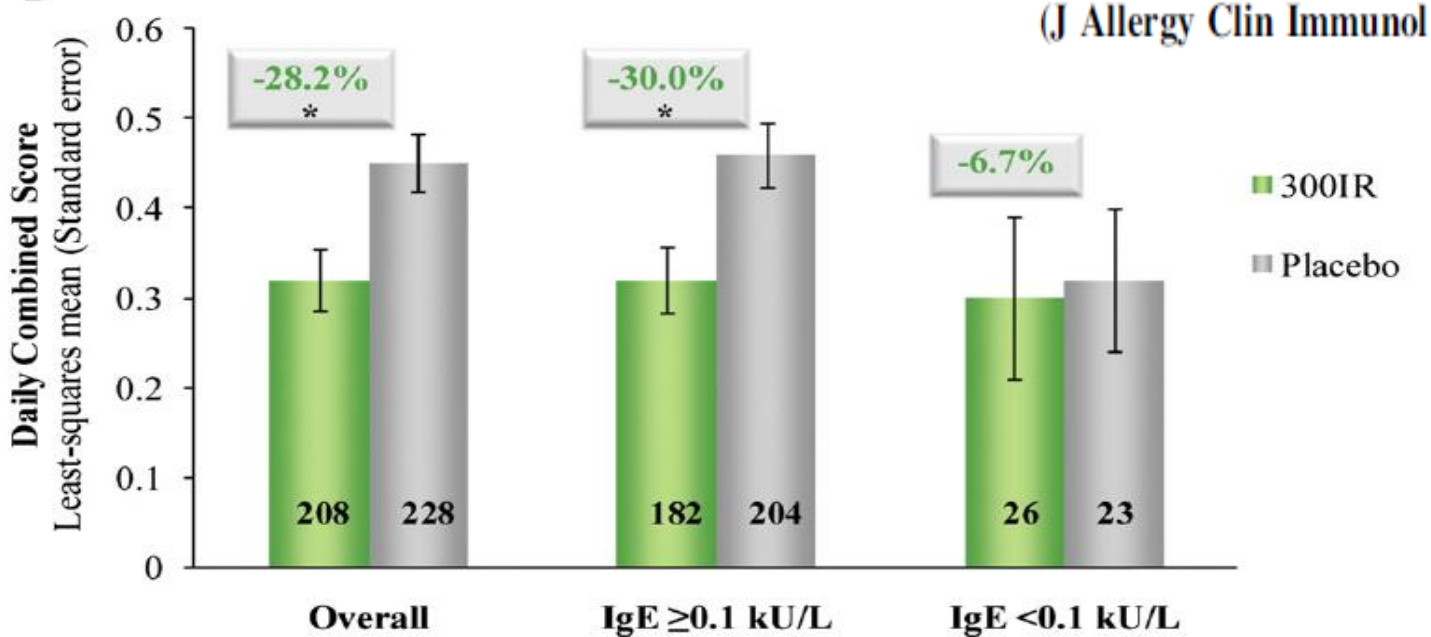
Didier et al. Clinical and Translational Allergy (2015) 5:12
DOI 10.1186/s13601-015-0057-8

A



B

(J Allergy Clin Immunol 2012;130:1327-34.)



Confirmation of persistent effect of SLIT for 2 years after initial 3 years of perennial treatment in a randomized trial

Durham SR et al. JACI 2012 Mar;129: 717-723

Combined Symptoms/med scores

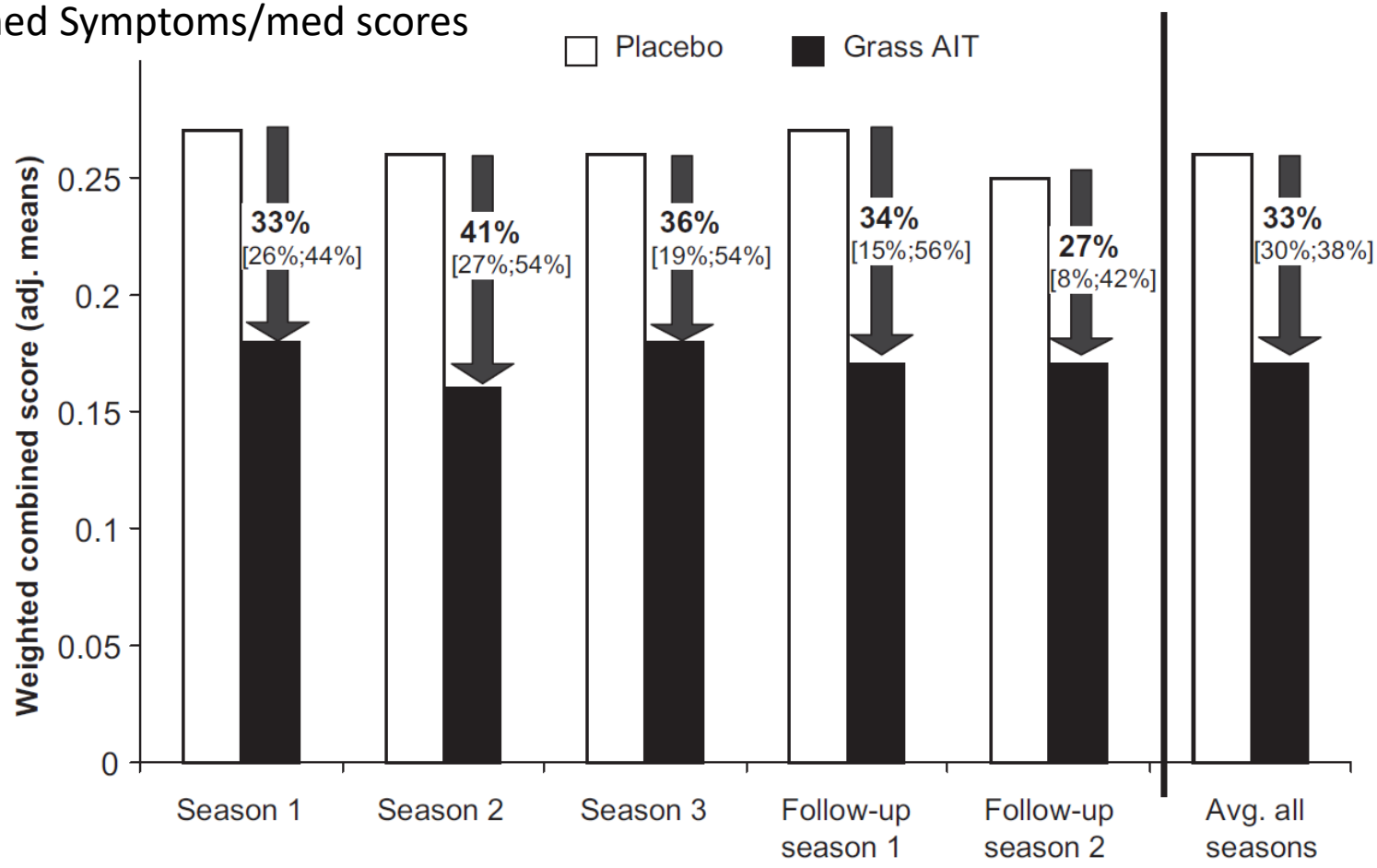
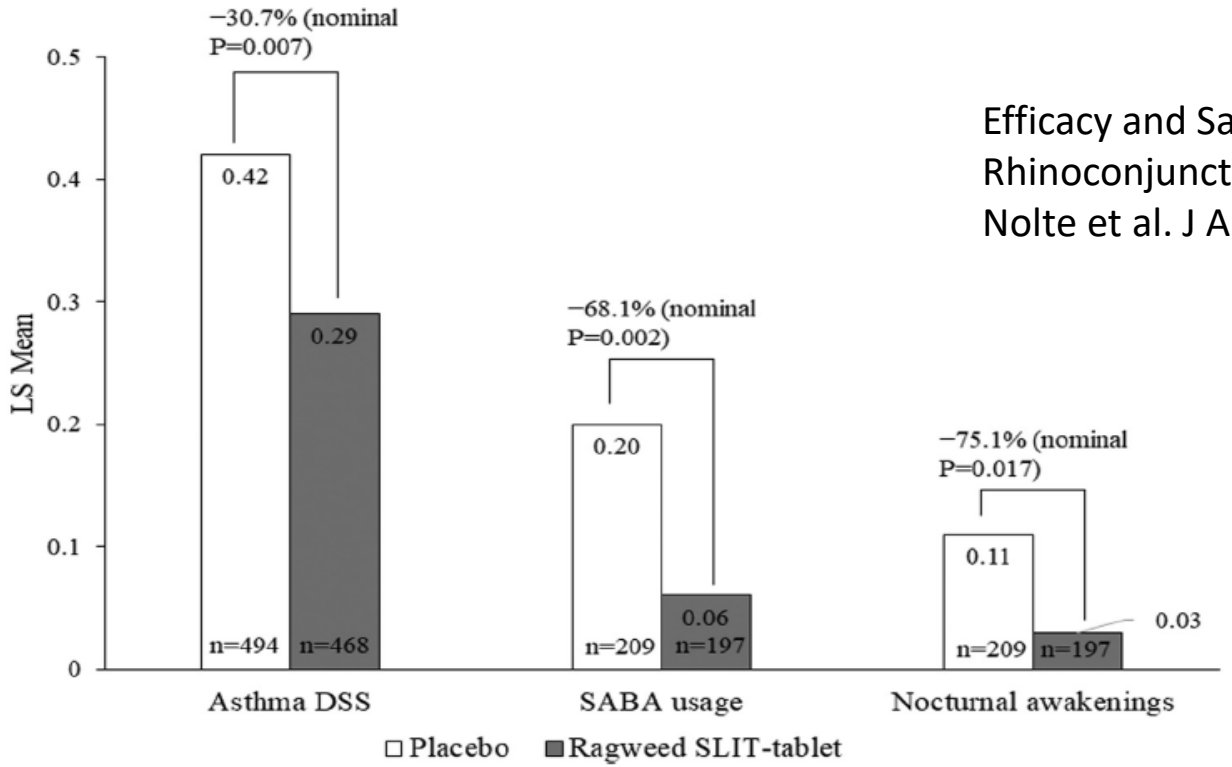


FIG 1. Weighted rhinoconjunctivitis combined symptom and medication score for the 5 grass pollen seasons of the trial and averaged over all seasons with relative differences between groups and 95% CI. All relative differences were statistically significant. *Adj.*, Adjusted; *avg.*, averaged.

What is short term efficacy of ragweed SLIT in mild-moderate asthma?

Preliminary Statements: (Evidence: low)

- ***Seasonal rhinitis studies have shown statistically significant improvements in exploratory asthma outcomes in patients on ragweed SLIT-T, but the clinical relevance of these findings is unclear***
- ***Uncontrolled or severe asthma are considered absolute contraindications to Ragweed SLIT, given safety concerns for all forms of immunotherapy in such patients***



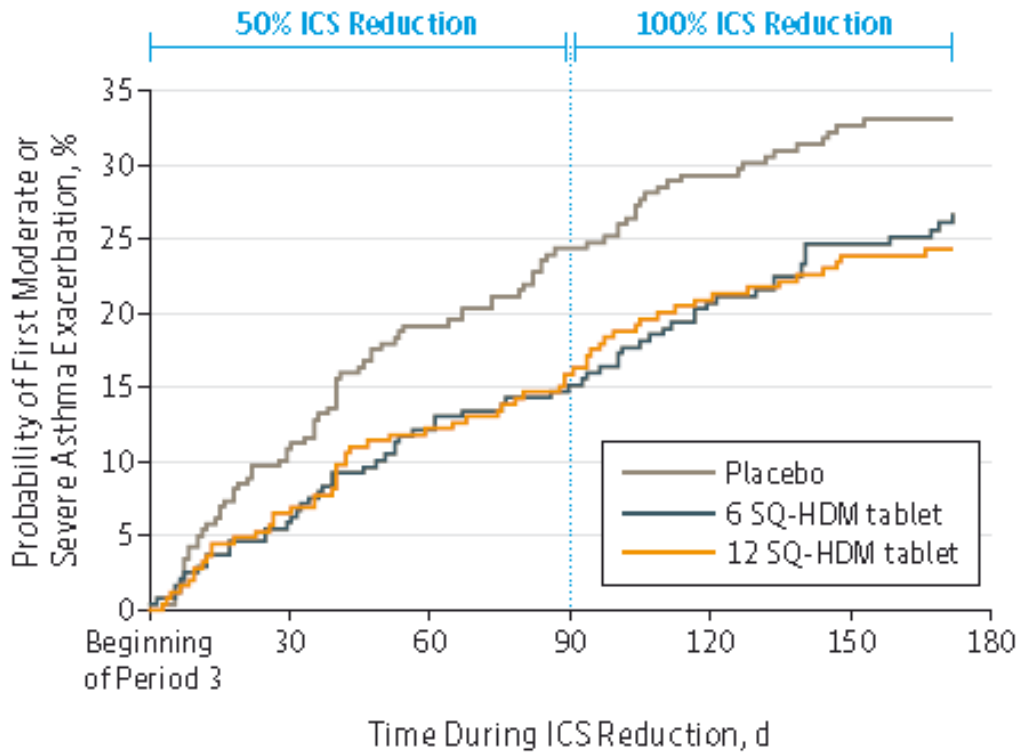
Efficacy and Safety of Ragweed SLIT-Tablet in Children with Allergic Rhinoconjunctivitis in a Randomized, Placebo-Controlled Trial. Nolte et al. J Allergy Clin Immunol Pract 2020;8:2322-31)

Efficacy of a House Dust Mite (HDM) Sublingual Allergen Immunotherapy Tablet in Adults with Allergic Asthma (N= 834)

Virchow et al. JAMA 2016

- Adults asthma patients uncontrolled on an ICS and short-acting β2-agonist salbutamol.
- 1:1:1 randomization to once-daily treatment with
- placebo (n = 277) or
- HDM SLIT doses 6 SQ-HDM [n = 275] or 12 SQ-HDM [n = 282])
- Primary outcome → Time to first asthma exacerbation during 6 month tapering of inhaled corticosteroid by 50% followed by complete withdrawal

Figure 2. Probability of Having the First Moderate or Severe Asthma Exacerbation in the Full Analysis Set

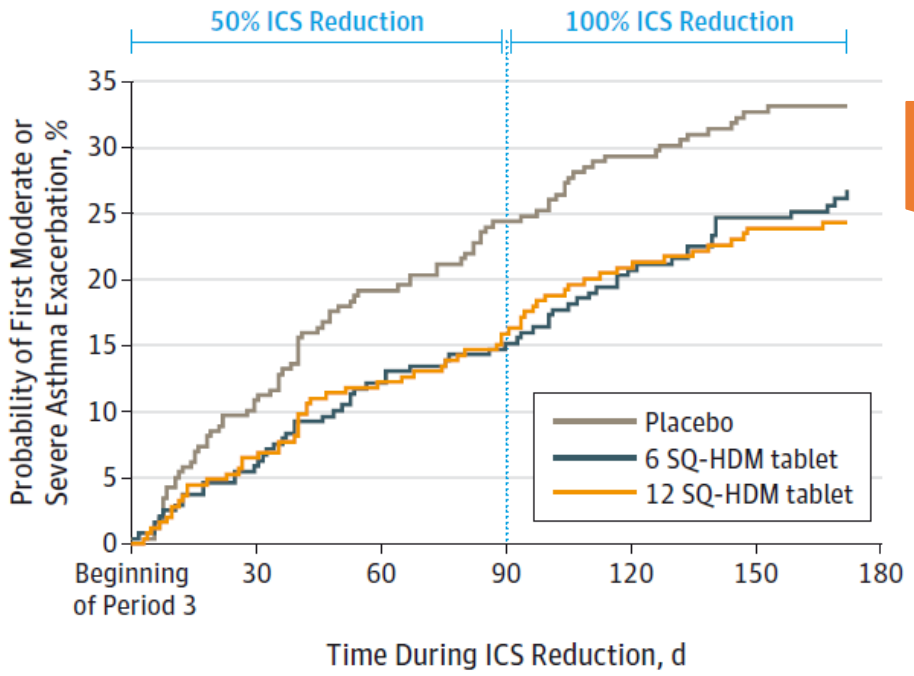


No. at risk							
Placebo	257	228	200	188	171	163	109
6 SQ-HDM tablet	237	224	207	201	187	171	122
12 SQ-HDM tablet	248	228	214	207	189	180	121

European HDM asthma study : Primary & key secondary endpoints

34% risk reduction of moderate-severe asthma exacerbations

Primary endpoint



-34%
(p=0.017)[1-2]

36% risk reduction for **nocturnal awakening or increase in daily symptoms** (p=0.031)[1,2]

42% risk reduction of **deterioration in lung function** (p=0.022)[1,2]

51% risk reduction of **severe asthma exacerbation** (p=0.076)[1,2]

48% risk reduction of **increased SABA use** (p=0.029)[1,2]

Virchow et al. *JAMA.* 2016;315(16):1715-1725

Should HDM SLIT be recommended in patients with asthma?

Preliminary statement: *(Evidence: High)*

Specialist should consider HDM SLIT tablets for mild to moderate persistent asthma patients to improve asthma symptoms and lower inhaled steroid dose

- **HDM SLIT tablets for mild/moderate persistent asthma improve asthma symptoms and reduce ICS doses.**
- **Effect on exacerbation reduction and airway inflammation was either mixed or limited.**

House Dust Mite SLIT?

Preliminary – PP Work Group: ***Atopic Dermatitis?***

The specialist should consider HDM SLIT for HDM allergic atopic dermatitis to reduce symptoms in patients who are not controlled with topical and oral medications

(Evidence: moderate-high)

Preliminary – PP Work Group: ***Duration of Rx for sustained efficacy?***

The specialist may counsel the patient that if they have achieved meaningful clinical improvement following a minimum of three years of HDM SCIT that they are likely to have continued clinical improvement an additional 1-3 years

(Evidence: Low)

When considering SLIT, should sublingual drops be considered as effective as FDA approved sublingual tablets?

Unable to evaluate efficacy SLIT drops with products marketed in the USA due to lack of clinical evidence.

Preliminary Statement:

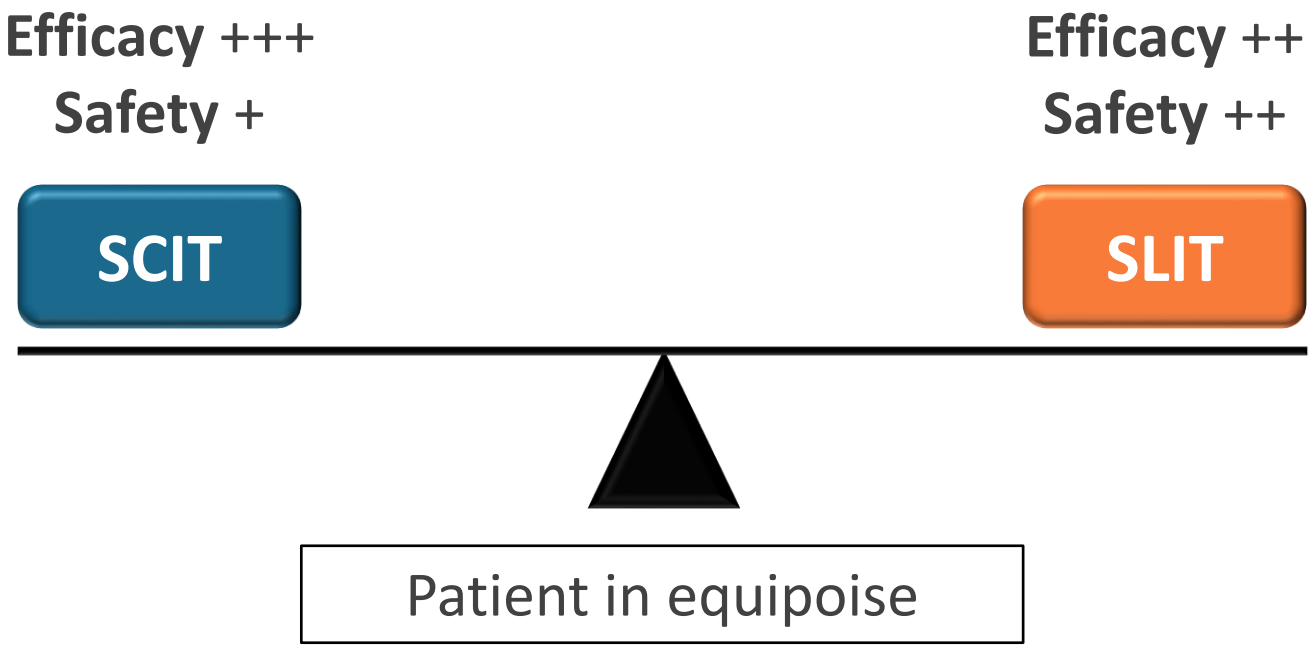
Given the limited evidence for the efficacy of SLIT drops, allergy specialists should favor use of SCIT with FDA approved SLIT tablets with demonstrated efficacy in randomized controlled trials for approved indications.

Is SCIT more effective than SLIT tablets?

Preliminary statement:

Allergists should recognize there is limited evidence directly comparing SLIT tablets and SCIT for the treating allergic rhinitis and asthma with mixed results, favoring SCIT over SLIT tablets in some studies and noninferiority of SLIT in others.

SCIT vs SLIT: A Balance of Efficacy and Safety



Durham SR et al. *J Allergy Clin Immunol*. 2016;137(2):339-349.e10.

Caveat

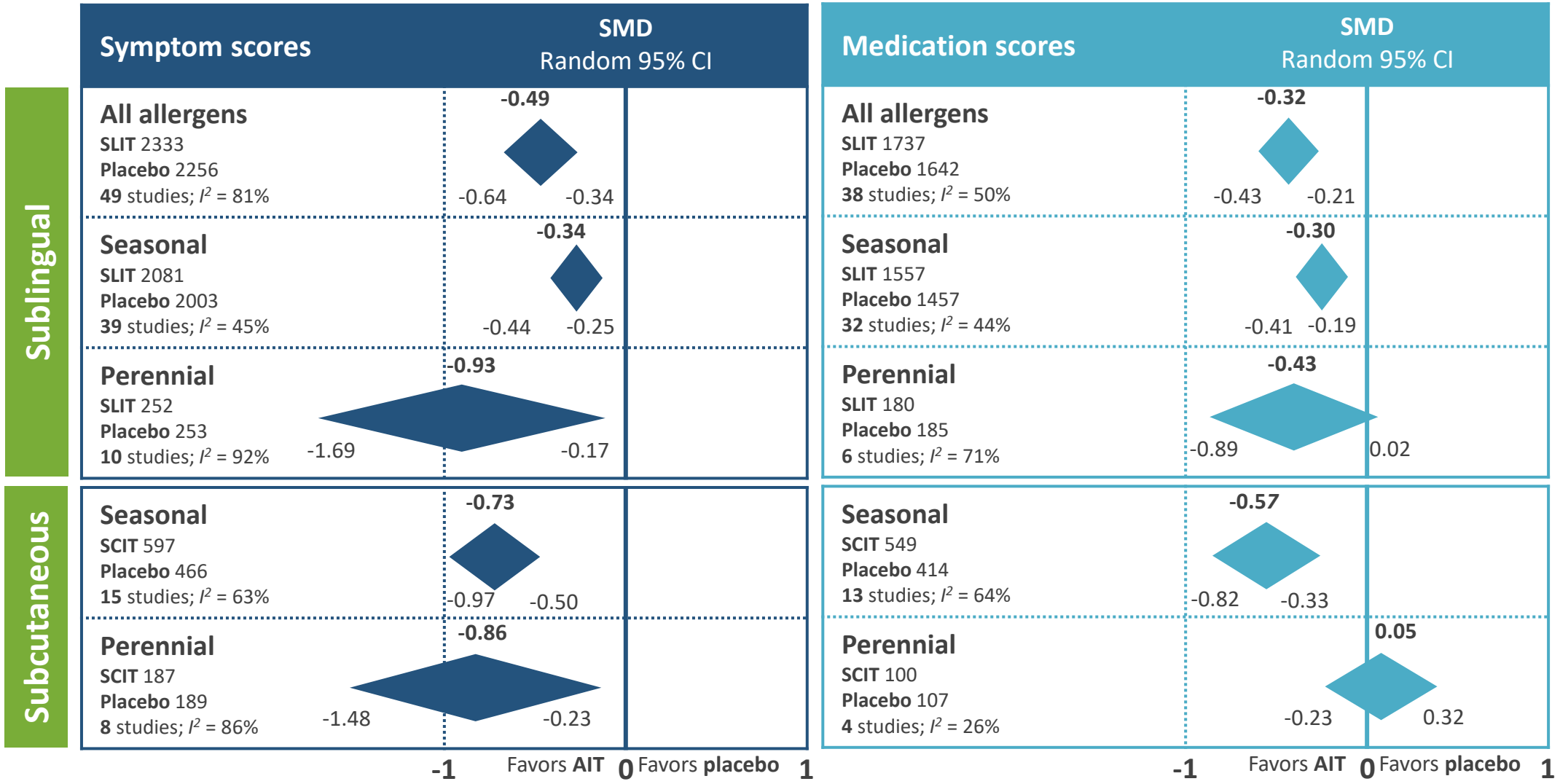
Low level of evidence for SCIT injections from multiple-allergen mixed vials

Nelson H et al. Review of 13 SCIT studies in with ≥ 2 allergens.

- Suboptimal study design
- Little data on single vs. multiple allergens
- Population sizes : 24 – 208 subjects.
- **Caveat: SCIT with multiple allergens can be effective but more and better data in needed.**

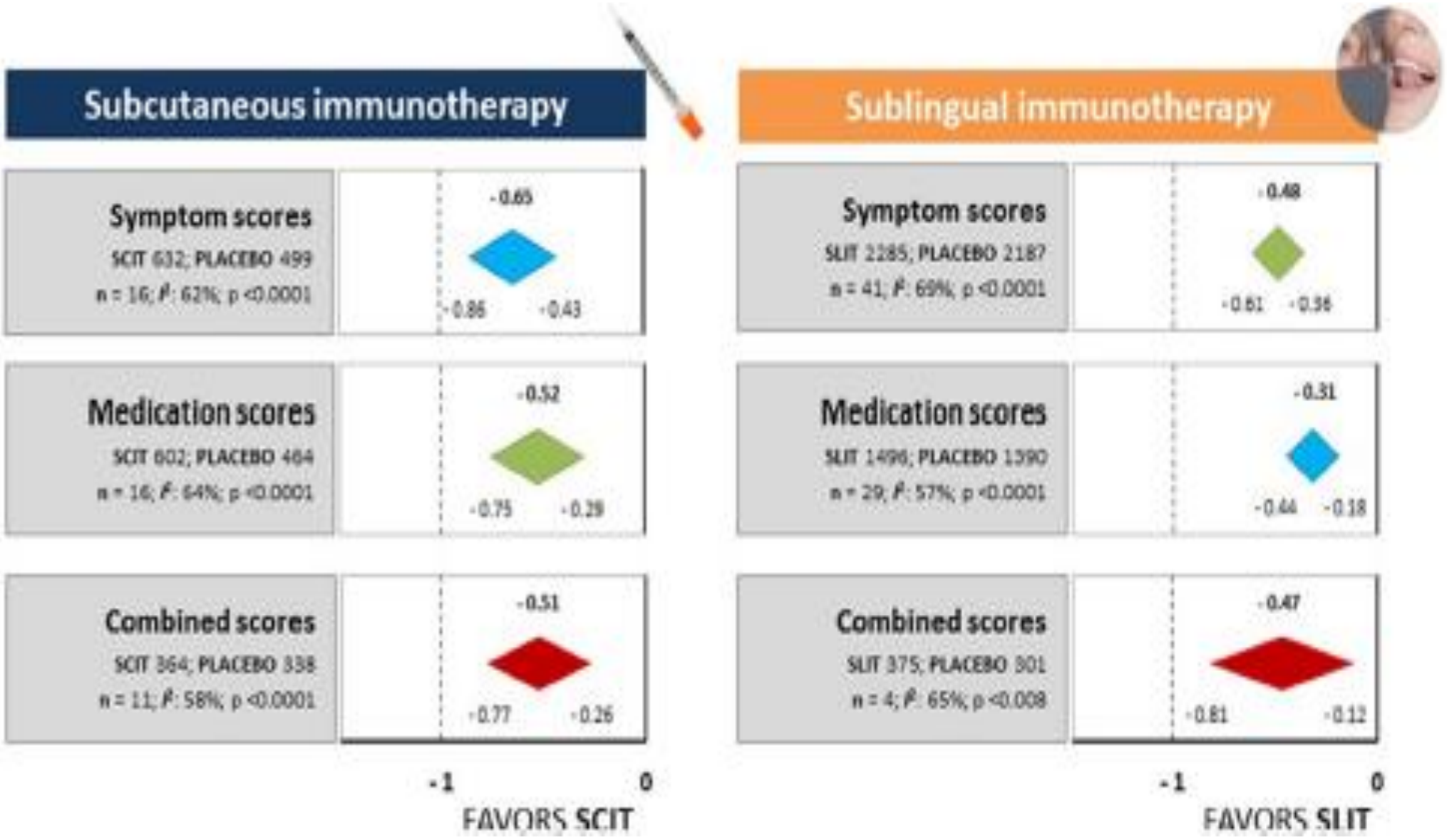
(JACI 2009; 123: 763)

Efficacy: Cochrane Meta-Analyses of SCIT and SLIT for Allergic Rhinitis



Durham SR et al. *J Allergy Clin Immunol*. 2016;137(2):339-349.e10.

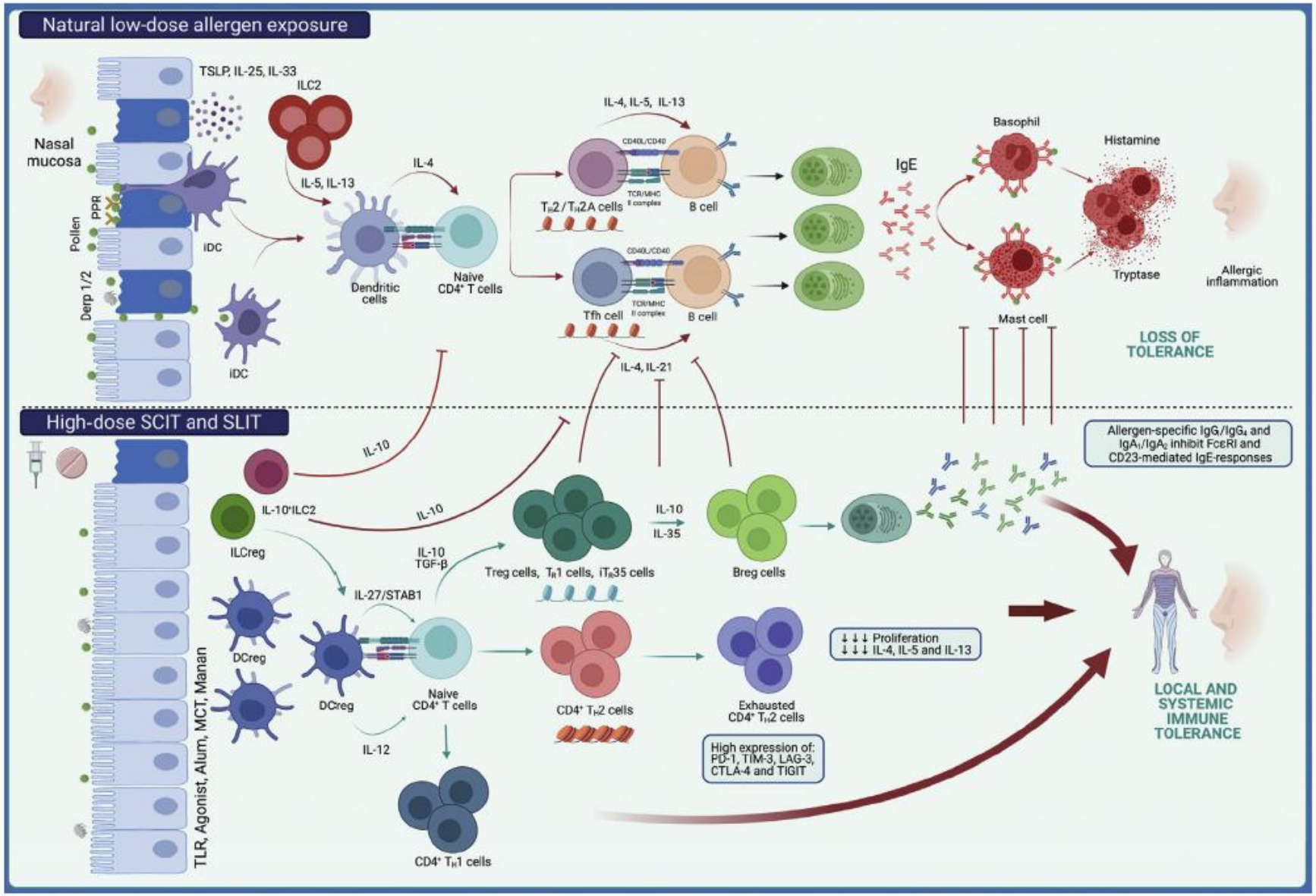
Relative efficacy of SCIT and SLIT compared with Placebo



Creticos P. et al. JACI In Practice. 2024;12: 1415-27.

Diverse immune mechanisms

Shamji M et al. JACI 2022



North American Allergen Immunotherapy Safety Study (NAAISS)

(2008-present)

Project AIMS:

1. Estimate annual incidence of fatal reactions from SCIT and skin testing in North America
2. Define relative incidence of systemic allergic reactions of varying severity for SCIT and SLIT (Sublingual Allergen Immunotherapy; initiated 2013)
3. Identify clinical practice patterns that may impact risk of fatal and non-fatal reactions
4. Identify local skin or systemic infections following SCIT requiring antibiotics (initiated 2014)

Bernstein *AAACI* 2010

AAAAI/ACAAI Surveillance Study Participation– 2008-2023

Population: AAAAI and ACAAI members prescribing SCIT

Year	Responses	Practitioners	# of patients	Response rate*	Injection visits
1 (2008-2009)	806	1922		49%	8.3 million
2 (2009-2010)	630	1453		37%	5.6 million
3 (2010-2011)	513	1072		27%	5.1 million
4 (2011-2012)	402	1073		27%	4.3 million
5 (2012-2013)	617	1754		51%	5.6 million
6 (2013-2014)	565	1349	1,383,029	39%	8.2 million
7 (2014-2015)	494	1046	1,360,828	30%	9.5 million
8 (2015-2016)	363	1017	535,585	30%	7.8 million
9 (2016-2017)	351	945	351,445	25%	7.2 million
10 (2017-2018)	250	658	247,701	19%	2.9 million
11 (2018-2019)	120	501	107,055	13%	2.1 million
12 (2019-2020)	255	828	302,976	21%	7.3 million
13 (2020-2021)	176	582	266,610	23%**	2.3 million
14 (2021-2022)	151	541	165,994	21%**	3.4 million
15 (2022-2023)	88	471	184,314	19%**	4.5 million

*Number of practitioners responding/ Number who received survey

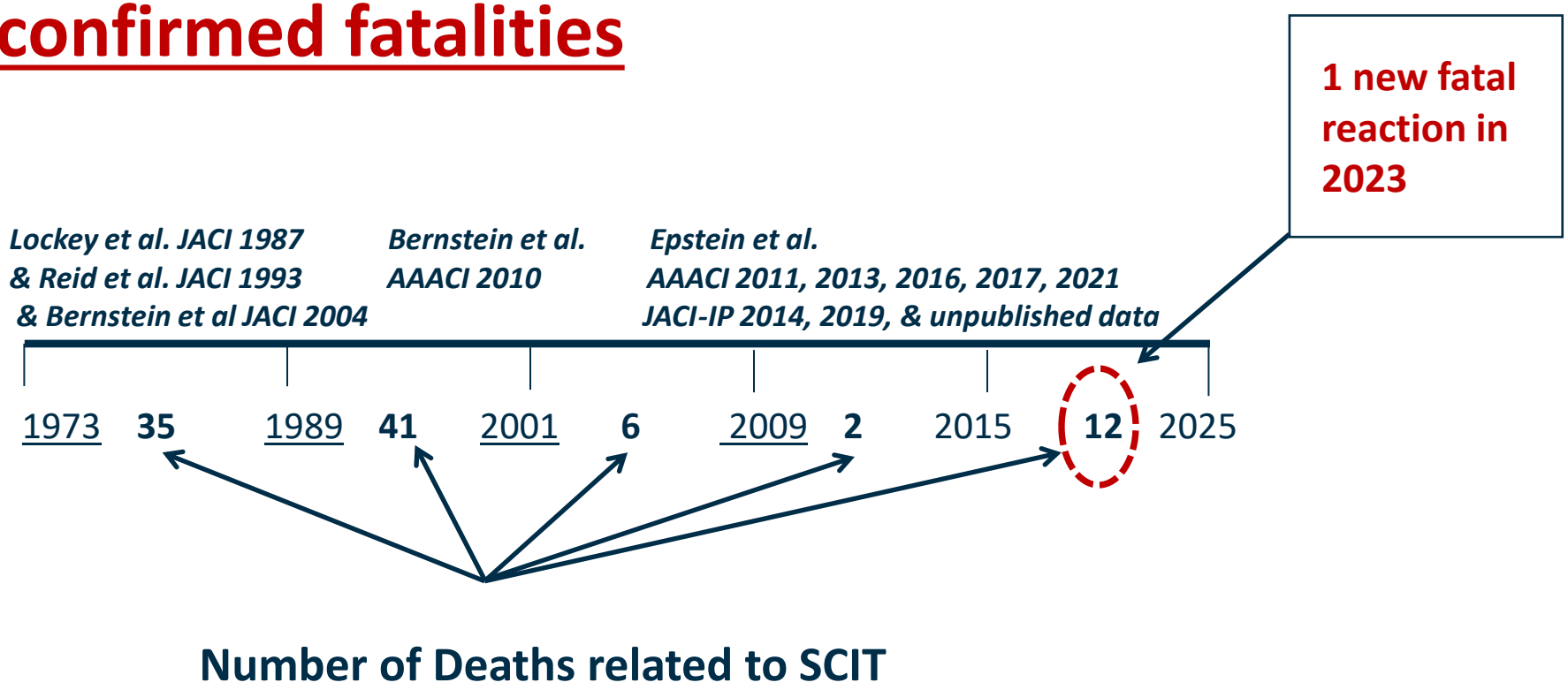
**Adjusted for number of current practitioners with contact information

Total=84.1 million injection visits

Bernstein *AAACI* 2010; Epstein *AAACI* 2011, 2013, 2016, 2017, 2021; Epstein *JACI-IP* 2014, 2019, and unpublished data

AAAAI 50+ Year History of Fatal Reactions to Subcutaneous Immunotherapy Injections (SCIT) in the US

96 confirmed fatalities



Number of Deaths related to SCIT

New Fatal Reaction (indirectly reported)

A 22-year-old female died after a SCIT injection in autumn of 2023. The fatal reaction occurred after a maintenance injection. The reaction began within two minutes and reportedly the patient developed flushing and then collapsed. No other clinical details were reported. She expired after 5 days on life support.

Unpublished report

WAO Severity Grading of SRs after SCIT injections (2010)

- **Grade I → Symptom(s)/ signs of 1 organ system present**: generalized urticaria with/without angioedema ***or*** nausea ***or*** upper respiratory symptoms (e.g., itching of the palate and throat, sneezing) *or* conjunctival symptoms.

- **Grade 2 → Asthma RESPONDING to an inhaled bronchodilator and/*or*** GI symptoms including abdominal cramps, vomiting, or diarrhea, *or* uterine cramps.

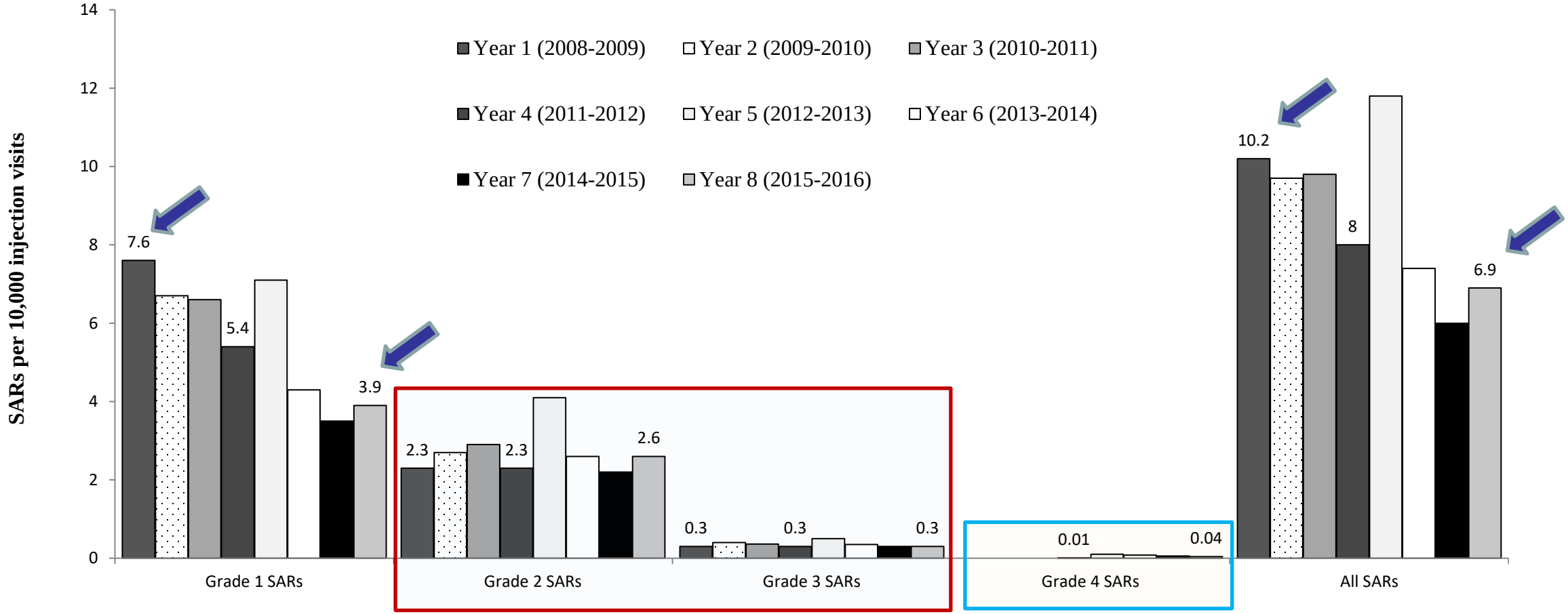
- **Grade 3 → Severe asthma NOT RESPONDING to a bronchodilator** *or* **laryngeal, uvular, or tongue edema,** with or without stridor

- **Grade 4 → Respiratory failure or hypotension with/without loss of consciousness**

Modified from Cox *JACI* 2010

Systemic Allergic Reactions per # of injection visits (2008-16)

1 event in 1,000 visits (0.1%) and in 0.7% of SCIT patients



Epstein et al. JACI – IP 2019

Systemic allergic reactions with SLIT
(Years 1-10; 2008-2018)

- Systemic allergic reactions occurred in 76-85% of practices
- Grade 4 SRs (i.e., near fatal anaphylaxis)
  - 1 in 160,000 injection visits (2011-2018)
    - 0.005% of patients (2014-2016)
    - 0.01% of patients for 2017-2018

Bernstein *AAACI* 2010, Epstein *AAACI* 2011, 2013, 2016, 2017; Epstein *JACI IP* 2014, 2019

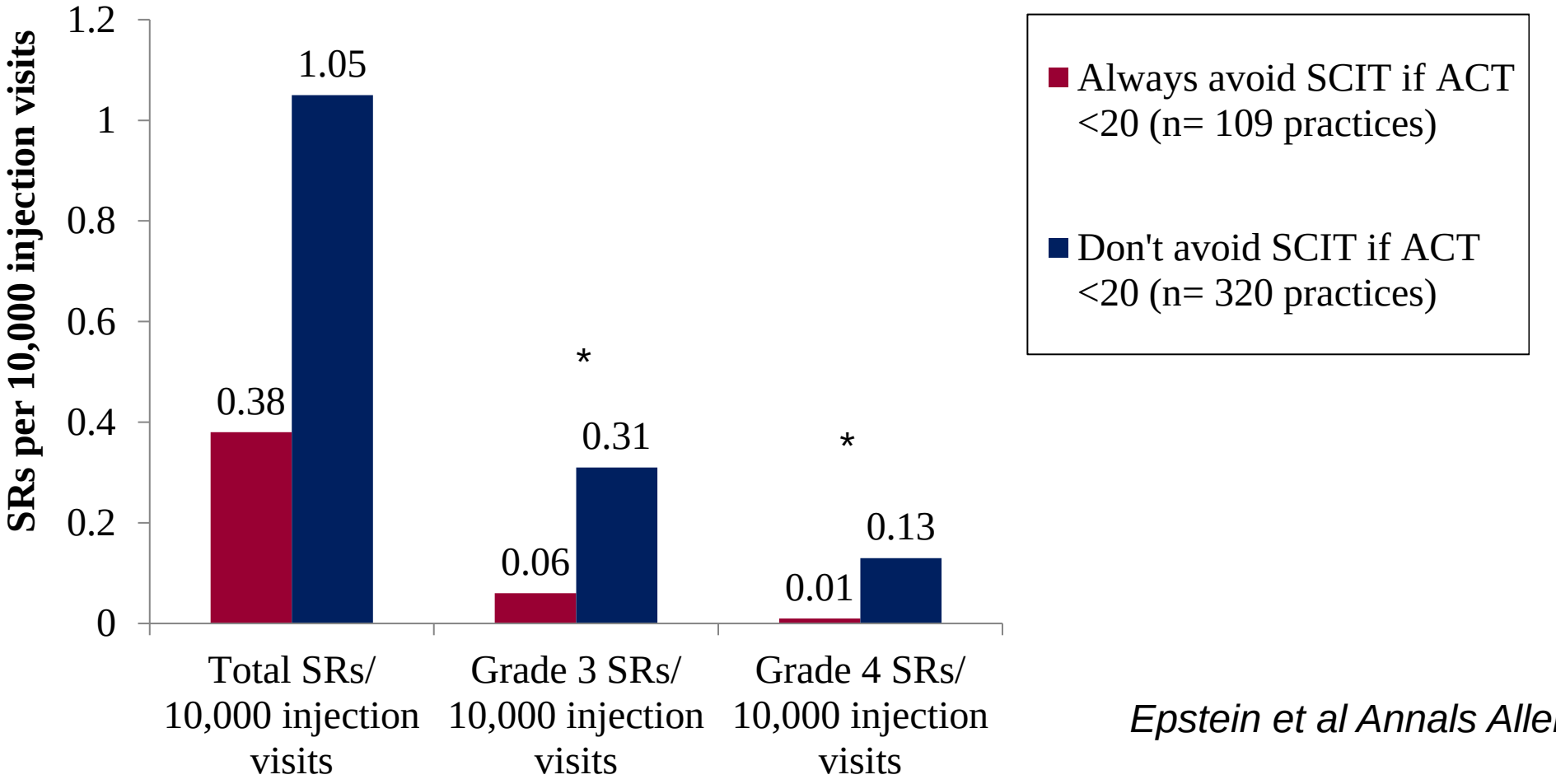
Severe Asthma and SCIT:
(2016-2018 survey data)

- Severe Asthma using EPR/ATS 2014 definition
  - Persistent asthmatic symptoms despite treatment with optimal doses of inhaled corticosteroids, in whom response to treatment of comorbidities is incomplete
- Higher total SRs in practices with a higher percentage of Severe Asthmatics on SCIT ($p<0.0001$) *(N=599,146 patients on SCIT)*
- 50% of Grade 3 or 4 SRs (WAO) occurred in severe asthmatics for 2017-2018 *(N=247,701 patients on SCIT)*

Epstein et al. AAAAI 2019 abstract

Do you avoid starting SCIT in Asthmatics with ACT scores < 20 ?

AAAAI/ACAAI Annual Survey Year 5 (2012-2013):

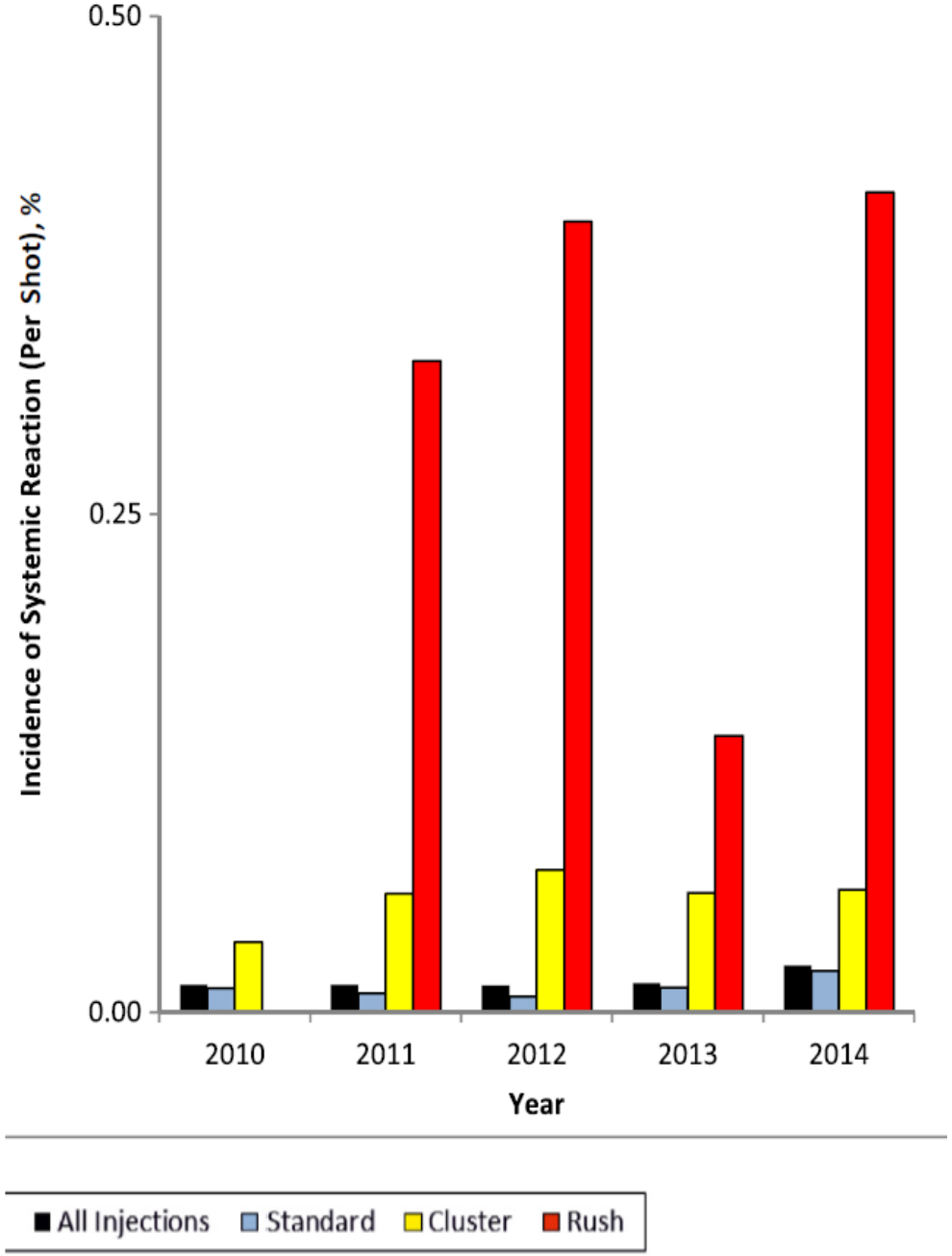


Epstein et al Annals Allergy 2016

*p<0.05; Practices that never started SCIT in patients with ACT scores <20 (uncontrolled Asthma) had significantly fewer Grade 3 (OR 0.7 [95% CI 0.5-1.0] and Grade 4 SRs (OR 0.3 [0.1-0.8]).

Cluster buildup is associated with Systemic Reactions

- 31% (140/453 respondents) use cluster build-up strategies (Year 5)
- Increased risk of Grade 1, 2 and 3 SRs reported in practices uses cluster *(Annals 2013, JACI –IP 2014, Epstein et al.)*
- Sub-study: a lower target dose at end of cluster prior to transitioning to maintenance doses was associated with lower risk of severe SRs (p=0.07) *(JACI –IP 2014, Epstein et al.)*



A.W. Winslow et al. / Ann Allergy Asthma Immunol 117 (2016) 542–545

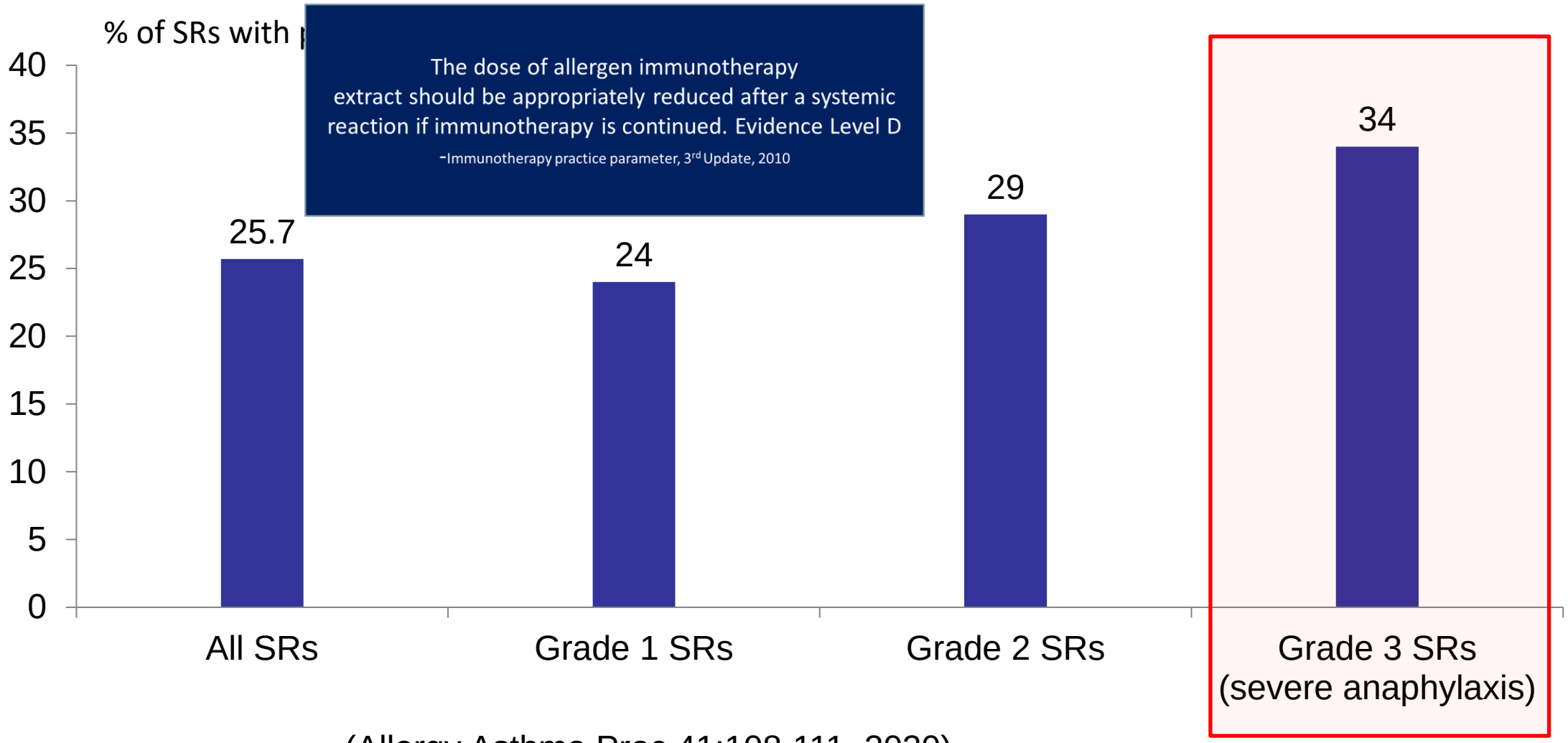
Comparison of **systemic reaction** in rush, cluster, & standard build aeroallergen immunotherapy

Annual incidence per shot during 5-year period (2010 – 2014

Rush IT protocols was used for stinging Hymenoptera Venom IT; fewer SRs seen with VIT vs other allergens.

Year 2 (2009-2010): Percent of Reactions Preceded by a Prior Systemic Reaction?

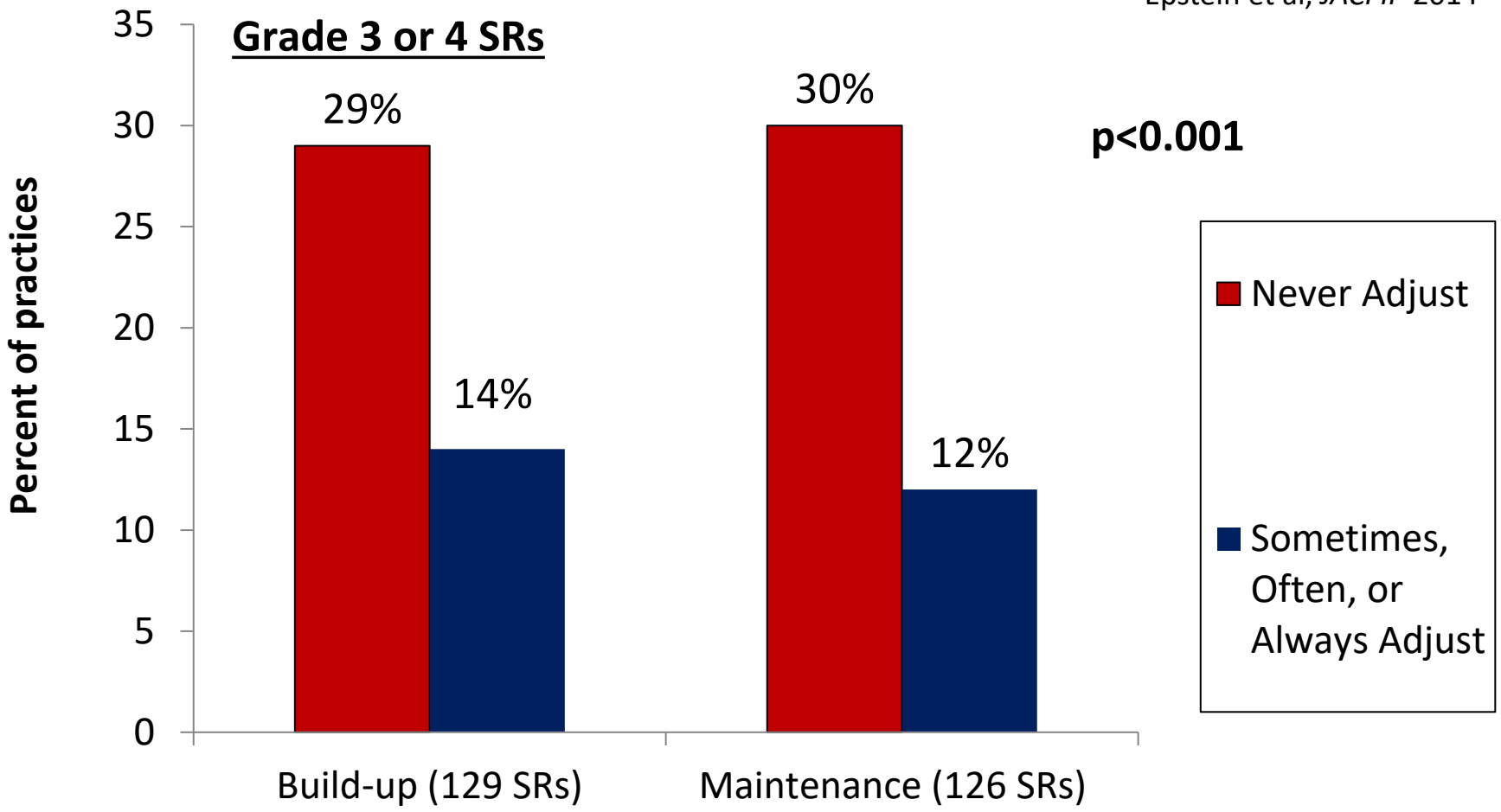
(0.6% of all patients reported in the survey had SRs)



(Allergy Asthma Proc 41:108-111, 2020)

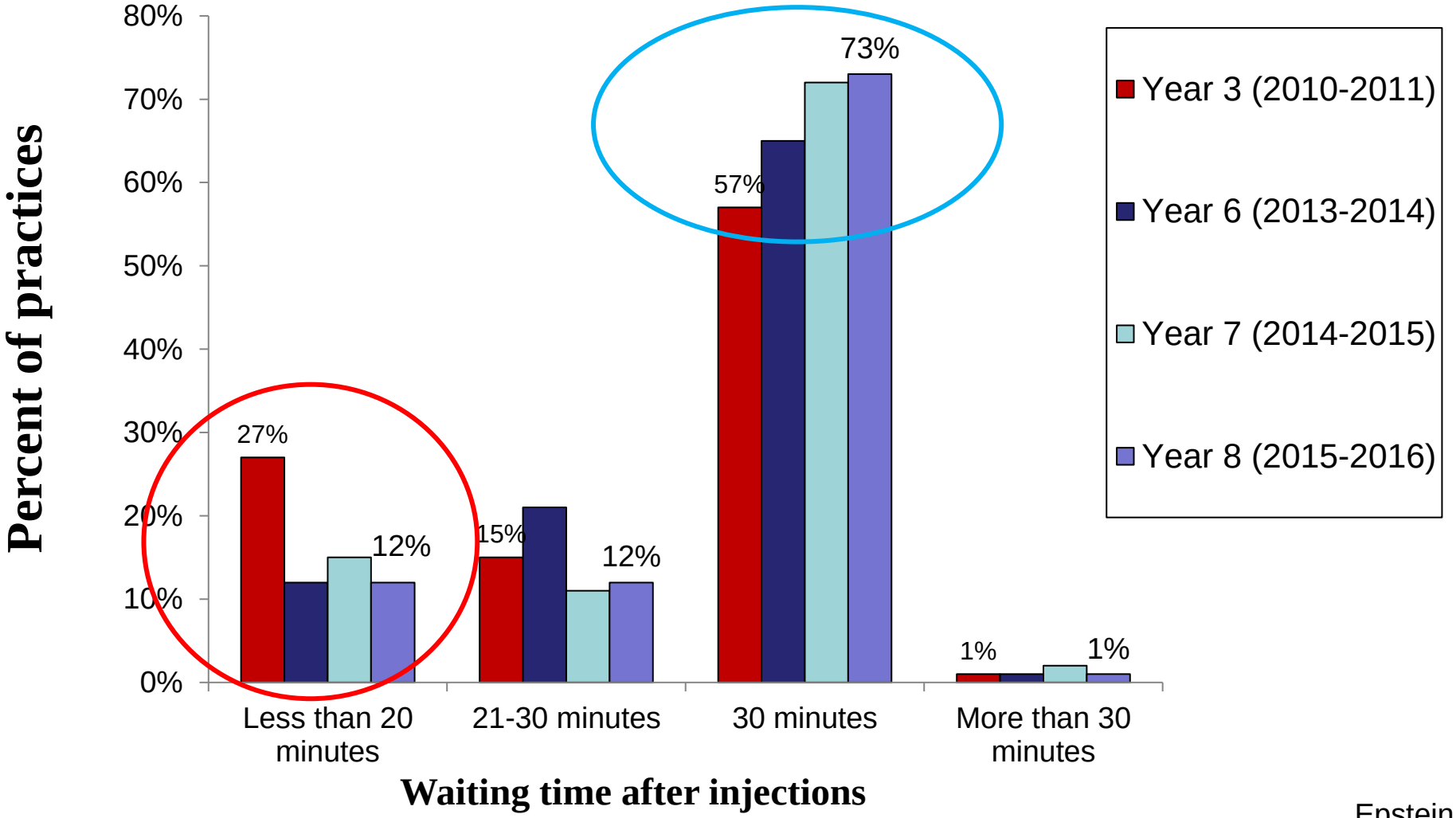
Does adjusting doses during peak pollen seasons impact SR rates in build-up or maintenance vials (Year 4, n=235)?

Epstein et al, *JACI IP* 2014



Practices never reducing doses during peak pollen seasons in build-up or maintenance vials were significantly more likely to report Grade 3 or 4 SRs

Waiting time trends (2010; 2013-2016)

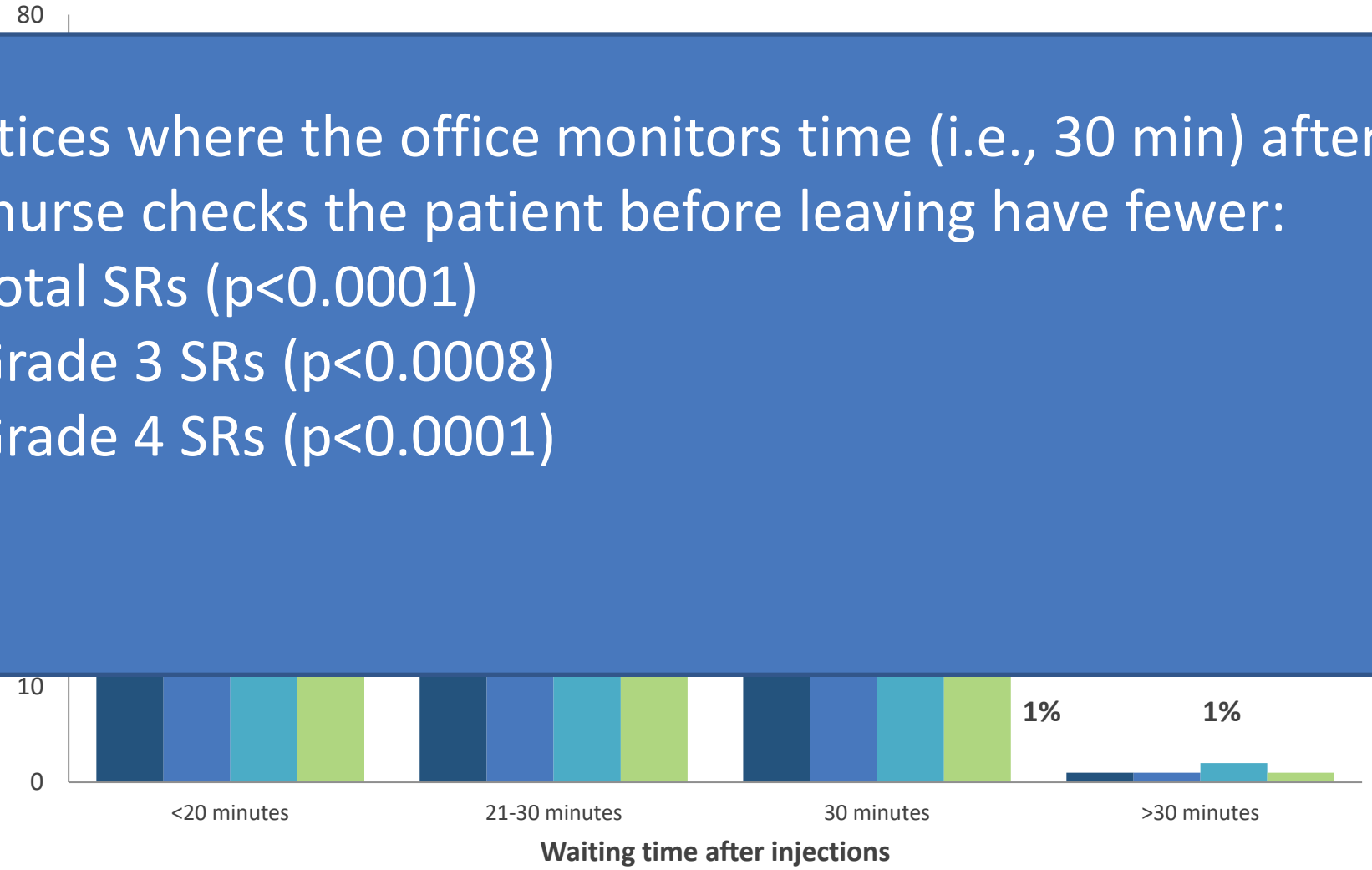


Epstein, *JACI IP* 2019

Waiting Time Trends (2010; 2013-2016)

Practices where the office monitors time (i.e., 30 min) after injections and the nurse checks the patient before leaving have fewer:

- Total SRs (p<0.0001)
- Grade 3 SRs (p<0.0008)
- Grade 4 SRs (p<0.0001)



Epstein TG et al. *J Allergy Clin Immunol Pract*. 2019; Epstein TG et al. *Annal of Allergy Asthma and Immunology* 2021

Modifiable Risk Factors

1. Severe, uncontrolled asthma
2. Injections administered in suboptimal settings
   - *< 30 minute observation with no direct monitoring of patients*
   - *Home based SCIT (isolated reports of Fatal SRs)*
   - *Delay in diagnosis & treatment of anaphylaxis (delay in epinephrine)*
   - *Dosing errors*
3. Accelerated build-up (modifiable by dose adjustments?)
4. History of prior systemic allergic reactions
5. Peak pollen seasons (conflicting data) ??

Risk of infection after SCIT injections (2014-2024)

- A single local infection associated with a SCIT injection has now been reported and verified. This is the first such event documented and confirmed in the history of this annual survey.
  - Physician reported post-injection cellulitis on two occasions after consecutive injections from the same vial requiring treatment with oral antibiotics. Bacterial contamination of the vial was suspected despite having been diluted in phenol and saline. Since preparing a new vial, cellulitis has not recurred.
  - This was in North America but not in the United States. FDA is watching.
- 1 local infection in 55.2 million injection visits and ~ 5 million patients

Unpublished report to AAAAI IT and Diagnostics Committee (2025)

SLIT Safety

Preliminary – Parameter Work Group:

The risk of a systemic or near fatal reaction to SLIT is very low.

Quality of evidence: High

Preliminary – Parameter Work Group:

Administering pre-medications prior to each dose of SLIT to decrease the risk of local reactions is not routinely recommended.

Quality of evidence: Low

Anaphylaxis with SLIT is rare, No fatal SRs

Case Report	Scenario	Reaction
Blazowski et al, *Allergy* 2008	**Missed HDM doses for 3 weeks then self-administered 6X dose**	Hypotension, Asthma, ICU
Eifan et al, *Allergy* 2007	New start multi-allergen SLIT	Severe lip swelling, fever, chest pain, GI symptoms
Dunsky et al, *Allergy* 2006	New start multi-allergen SLIT	Generalized pruritus, severe hand/foot swelling, dizziness, wheezing
de Groot et al, *Allergy* 2009	**2 cases with Grass tablet, both patients had previous SRs to SCIT, 1 patient with mild asthma**	Case #1: Angioedema (tongue, eyes), urticaria Case #2: hypotension, wheezing
Cochard et al, *JACI* 2009	Two cases with multiallergen liquid SLIT Case #1: **previous large local reactions to SCIT**, Case #2: **asthma exacerbations with SCIT**	Case #1: Repeated asthma attacks Case #2: Heavy nasal congestion, asthma

Is SLIT safe in treating patients with asthma?

Preliminary - Parameter Work Group:

SLIT should be held in patients with an active asthma exacerbation.

Preliminary – Parameter Work Group:

House dust mite SLIT is tolerated in patients with uncontrolled IgE dependent asthma due to HDM with no apparent risk of worsening asthma.

Safety of SLIT tablets in clinical trials

- No severe SRs identified in a large DBPC trials evaluating the efficacy and safety of HDM SLIT tablets in patients with HDM triggered asthma not controlled on inhaled corticosteroids[1].

- HDM SLIT tablets did not increase asthma-related events in patients with mild-moderate asthma in allergic rhinitis clinical trials [2,3].

1- Virchow et al. 2016; 2- Bernstein et al. 2018; 3 – Maloney et al. 2016

Limitations/Unmet Needs

- Inadequate Evidence - multiple allergen dosing with SCIT
- Inadequate data – multiple allergen SLIT
- Inadequate Evidence - sublingual drops with USA products
- Suboptimal adherence needed for sustained response (SLIT)
- Training patients on self-management of systemic allergic reactions including self-administration of epinephrine.
- Real world outcome studies in the US to demonstrate long term clinical and cost effectiveness.

New Directions

1. Combining biologics and AIT for disease modifying properties
2. Alum absorbed extracts, allergoids to improve safety ?
3. Intralymphatic immunotherapy – more data needed
4. Microneedle immunotherapy *(Gill H. JACI 2024)*
   - feasible in pre-clinical animal models
   - device technology is well developed
   - no human trials yet
   - potential for allergy vaccines, combining allergen and adjuvants