

This is a repository copy of *Allergen immunotherapy for allergic rhinoconjunctivitis: a systematic review and meta-analysis*.

White Rose Research Online URL for this paper:

<https://eprints.whiterose.ac.uk/116537/>

Version: Accepted Version

Article:

Dhami, Sangeeta, Nurmatov, Ulugbek, Arasi, Stefania et al. (38 more authors) (2017) Allergen immunotherapy for allergic rhinoconjunctivitis: a systematic review and meta-analysis. *Allergy*. ISSN 1398-9995

<https://doi.org/10.1111/all.13201>

Reuse

Items deposited in White Rose Research Online are protected by copyright, with all rights reserved unless indicated otherwise. They may be downloaded and/or printed for private study, or other acts as permitted by national copyright laws. The publisher or other rights holders may allow further reproduction and re-use of the full text version. This is indicated by the licence information on the White Rose Research Online record for the item.

Takedown

If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.

DR. SANGEETA DHAMI (Orcid ID : 0000-0002-2823-3258)

DR. MIQDAD ASARIA (Orcid ID : 0000-0002-3538-4417)

PROF. OLIVER PFAAR (Orcid ID : 0000-0003-4374-9639)

PROF. CEMAL CINGI (Orcid ID : 0000-0003-3934-5092)

Article type : Review

Original article for submission to Allergy

Allergen immunotherapy for allergic rhinoconjunctivitis: a systematic review and meta-analysis

¹Sangeeta Dhmi, ²Ulugbek Nurmatov, ³Stefania Arasi, ⁴Tahir Khan, ⁵Miqdad Asaria, ⁶Hadar Zaman, ⁷Arnav Agarwal, ⁸Gopal Netuveli, ⁹Graham Roberts, ^{10, 11}Oliver Pfaar, ¹²Antonella Muraro, ¹³Ignacio J. Ansotegui, ¹⁴Moises Calderon, ¹⁵Cemal Cingi, ¹⁴Stephen Durham, ¹⁶Ronald Gerth van Wijk, ¹⁷Susanne Halken, ¹⁸Eckard Hamelmann, ¹⁹Peter Hellings, ²⁰Lars Jacobsen, ²¹Edward Knol, ²²Desiree Larenas Linnemann, ²³Sandra Lin, ²⁴Paraskevi Maggina, ²⁵Ralph Mösges, ²⁶Hanneke Oude Elberink, ²⁷Giovanni Pajno, ²⁸Ruby Panwankar, ²⁹Elide Pastorello, ¹⁴Martin Penagos, ³⁰Constantinos Pitsios, ³¹Giuseppina Rotiroti, ³²Frans Timmermans, ³³Olympia Tsilochristou, ³⁴Eva-Maria Varga, ³⁵Carsten Schmidt-Weber, ³⁶Jamie Wilkinson, ³⁷Andrew Williams, ³⁸Margitta Worm, ³⁹Luo Zhang, ⁴⁰Aziz Sheikh

¹Evidence-Based Health Care Ltd, Edinburgh, UK; ²Cardiff University, School of Medicine, Division of Population Medicine Neuadd Meirionnydd, Heath Park, Cardiff, UK; ³Department of Pediatrics, Allergy Unit, University of Messina, Italy & Molecular Allergology and Immunomodulation-Department of Pediatric Pneumology and Immunology, Charité Medical University, Augustenburger Platz 1, Berlin, Germany; ⁴School of Pharmacy, Monash University, Malaysia; ⁵ Centre for Health Economics, University of York, UK; ⁶Bradford School of Pharmacy, UK; ⁷School of Medicine, University of Toronto, Canada; ⁸Institute for Health and Human Development, University of East London, UK; ⁹The David Hide Asthma and Allergy Research Centre, St Mary's Hospital, Newport Isle of Wight, NIHR Respiratory Biomedical Research Unit, University Hospital Southampton NHS Foundation Trust, Southampton, UK, and Faculty of Medicine, University of Southampton, Southampton, UK; ¹⁰Department of

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/all.13201

This article is protected by copyright. All rights reserved.

Otorhinolaryngology, Head and Neck Surgery, Universitätsmedizin Mannheim, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany and ¹¹ Center for Rhinology and Allergology, Wiesbaden, Germany; ¹² Food Allergy Referral Centre Veneto Region Department of Women and Child Health Padua General University Hospital, Italy; ¹³Hospital Quiron Bizkair, Bilbao, Spain; ¹⁴National Heart and Lung Institute, Imperial College, London, UK; ¹⁵Department of ENT, Eskisehir Osmangazi University Medical Faculty, Eskisehir, Turkey; ¹⁶Section of Allergology, Department of Internal Medicine, Erasmus MC Rotterdam, The Netherlands; ¹⁷Hans Christian Andersen Children's Hospital, Odense University Hospital, Odense, Denmark; ¹⁸Children's Center Bethel, EvKB, Bielefeld and Allergy Center Ruhr-University, Bochum, Germany; ¹⁹Laboratory of Experimental Immunology, University Hospitals Leuven, Belgium; ²⁰ALC, Allergy Learning and Consulting; ²¹University Medical Center, Utrecht, The Netherlands; ²²Hospital Medica Sur, Mexico City, Mexico; ²³Department of Otolaryngology-Head & Neck Surgery, John Hopkins, USA; ²⁴Allergy and Clinical Immunology Unit, 2nd Department of Pediatrics, University of Athens, P&A Kiriakou Children's Hospital, Athens, Greece; ²⁵University Medical Center Groningen, University of Groningen, Department of Allergology, Groningen Research Institute for Asthma and COPD (GRIAC), Groningen, Netherlands; ²⁶University Medical Center of Groningen, University of Groningen, Groningen, The Netherlands; ²⁷Department of Pediatrics, University of Messina, Italy; ²⁸Department of Pediatrics, Nippon Medical School, Tokyo, Japan; ²⁹University of Milano, Italy; ³⁰Department of Nutrition and Dietetics, Harokopio University, Athens, Greece; ³¹The Royal National Throat, Nose and Ear Hospital, University College London, London, UK; ³²Netherlands Anafylaxis Network, The Netherlands; ³³Charite University Hospital, Berlin, Germany; ³⁴Dept. of Paediatrics, Respiratory and Allergic Disease Division. Medical University Graz, Graz, Austria; ³⁵Pharmaceutical Group of the European Union, Brussels, Belgium; ³⁶Pharmaceutical Group of the European Union, Brussels, Belgium; ³⁷Guy's and St Thomas' NHS Foundation Trust, London, UK; ³⁸Charite-Universitätsmedizin, Berlin, Germany; ³⁹Beijing Institute of Otolaryngology, Beijing, China; ⁴⁰Asthma UK Centre for Applied Research, Usher Institute of Population Health Sciences and Informatics, The University of Edinburgh, Edinburgh, UK.

Corresponding author: Dr Sangeeta Dhami, sangeetadhami@hotmail.com

Abstract

Background

The European Academy of Allergy and Clinical Immunology (EAACI) is in the process of developing Guidelines on Allergen Immunotherapy (AIT) for Allergic Rhinoconjunctivitis. In order to inform the development of clinical recommendations, we undertook a systematic review to assess the effectiveness, cost-effectiveness and safety of AIT in the management of allergic rhinoconjunctivitis

Methods

We searched 15 international biomedical databases for published, in progress and unpublished evidence. Studies were independently screened by two reviewers against pre-defined eligibility criteria and critically appraised using established instruments. Our primary outcomes of interest were symptom, medication and combined symptom and medication scores. Secondary outcomes of interest included cost-effectiveness and safety. Data were descriptively summarized and then quantitatively synthesized using random-effects meta-analyses.

Results

We identified 5932 studies of which 160 studies satisfied our eligibility criteria. There was a substantial body of evidence demonstrating significant reductions in standardized mean differences (SMD) of symptom (SMD -0.53, 95%CI -0.63, -0.42), medication (SMD -0.37, 95%CI -0.49, -0.26) and combined symptom and medication (SMD -0.49, 95%CI -0.69, -0.30) scores whilst on treatment that were robust to pre-specified sensitivity analyses. There was in comparison a more modest body of evidence on effectiveness post-discontinuation of AIT, this suggesting a benefit in relation to symptom scores.

Conclusions

AIT is effective in improving symptom, medication and combined symptom and medication scores in patients with allergic rhinoconjunctivitis whilst on treatment, and there is some evidence suggesting that these benefits are maintained in relation to symptom scores after discontinuation of therapy.

Keywords: Allergen, allergy, allergic rhinoconjunctivitis, desensitization, allergen immunotherapy, rhinitis, subcutaneous, sublingual

BACKGROUND

Allergic rhinoconjunctivitis is a very common chronic condition that can result in considerable morbidity and impairment of quality of life.(1,2) The disease is triggered by exposure to seasonal and/or perennial allergens and, depending on the nature of the allergenic trigger(s) and patterns of exposure, symptoms may be persistent or intermittent.(3) Allergic rhinitis is typically characterized by symptoms of nasal obstruction, a watery nasal discharge, sneezing and itching, and there is often (but not invariably) involvement of the conjunctiva (allergic conjunctivitis), which manifests with itching, injection and tearing.(4) There may in addition be an impact on the ability to concentrate, on school and work performance,(5,6) and interference with daily activities and sleep; furthermore, allergic rhinitis is a risk factor for the development of asthma.(7)

Symptoms can, in many cases, be controlled with avoidance measures and pharmacological therapies such as oral, intranasal and topical (ophthalmic) H₁-antihistamines, intranasal corticosteroids and anti-leukotrienes, as mono-therapy or in combination.(8,9) Allergen immunotherapy (AIT) is an additional potential treatment option, particularly for those with more troublesome disease which remains inadequately controlled despite avoidance measures and regular pharmacotherapy.(8–10) The problem of inadequately controlled allergic rhinoconjunctivitis, despite optimal medical treatment, continues to represent a therapeutic challenge in the majority of patients.

The European Academy of Allergy and Clinical Immunology (EAACI) is in the process of developing Guidelines on AIT for Allergic Rhinoconjunctivitis and this systematic review has been undertaken in order to inform the formulation of key clinical recommendations. Specifically, we sought to assess the effectiveness, cost-effectiveness and safety of AIT in patients with allergic rhinoconjunctivitis.(11)

METHODS

As our methods have been reported in detail in our published protocol,(12) we confine ourselves to a synopsis of the methods employed.

Search strategy

A highly sensitive search strategy was developed and validated study design filters were applied to search 15 electronic bibliographic databases. The search strategy was developed on OVID MEDLINE and then adapted for the other databases (see Appendix 1, supplementary file for details). In all cases, the databases were searched from inception to October 31, 2015. Additional references were located through searching the references cited by the identified studies, and unpublished work, while research in progress was identified through discussion with experts in the field. We invited experts from a range of disciplines and regions to add to the list of included studies by identifying additional published and unpublished papers they were aware of and research in progress. There were no language restrictions employed; where possible, relevant literature was translated into English.

Inclusion criteria

We focused on studies conducted on patients of any age with allergic rhinoconjunctivitis investigating the effect of AIT. See Box 1 for full details.

Patient characteristics	Studies conducted on patients of any age with a physician-confirmed diagnosis of allergic rhinoconjunctivitis or allergic rhinitis, plus evidence of clinically relevant allergic sensitization (e.g., skin prick test or specific-IgE).
Interventions of interest	AIT for different allergens (e.g. pollen, house dust mites (HDM), animal dander, cockroach and molds), including modified allergens, administered through the subcutaneous (SCIT), sublingual (SLIT), intralymphatic (ILIT) or any other routes.
Comparator	Placebo or any active comparator.
Study designs	<i>Effectiveness:</i> Robust double-blind RCTs. Originally, we planned to include data from any RCT, irrespective of whether there was blinding. This was changed due to the volume of RCT studies. This decision was made prior to any analyses being undertaken. <i>Cost-effectiveness:</i> health economic analysis. <i>Safety:</i> double-blind RCTs and large case series (≥ 300 patients).
Study outcomes	<i>Primary outcomes:</i> effectiveness, both short-term (i.e. during treatment) and long-term (i.e. at least a year after discontinuation of AIT) as assessed by symptom and/or medication scores.

	<i>Secondary outcomes:</i> disease specific quality of life (QoL); threshold of allergen exposure to trigger symptoms on allergen challenge or in an environmental exposure chamber; health economic analysis from the perspective of the health system/payer; and safety as assessed by local and systemic reactions in accordance with the World Allergy Organization's (WAO) grading system of side-effects.(14,15)
Exclusion criteria	Reviews, discussion papers, non-research letters and editorials, animal studies and studies not employing double-blind RCT designs.

Box 1. Inclusion and exclusion criteria

Study selection

All references were uploaded into the systematic review software DistillerSR and underwent initial de-duplication. Study titles were independently checked by two reviewers (SD and UN) according to the above selection criteria and categorized as included, not included or unsure. For those papers in the unsure category, we retrieved the abstract and re-categorized as above. Any discrepancies were resolved through discussion and, if necessary, a third reviewer (AS) was consulted. Full text copies of potentially relevant studies were obtained and their eligibility for inclusion independently assessed by two reviewers (SD and UN). Studies that did not fulfil all of the inclusion criteria were excluded.

Quality assessment strategy

Quality assessments were independently carried out on each study by two reviewers (UN, SA, AA, MA or TM) using a range of instruments. RCTs were assessed for generation of allocation sequence, concealment of allocation, baseline outcome measurements, baseline characteristics, incomplete outcome data, blinding of outcome assessor, protection against contamination, selective outcome reporting and other risks of bias using the Cochrane Risk of Bias (ROB) Tool.(13) We used the Critical Appraisal Skills Programme (CASP) Economic Evaluation Checklist for health economic studies.(14) For case series, we used the quality assessment tool produced by the National Institute for Health and Clinical Excellence (NICE).(15) Any disagreements were resolved through discussion and, if necessary, a third reviewer (SD or AS) was consulted.

Data extraction, analysis and synthesis

Data were independently extracted onto a customized data extraction sheet in DistillerSR by two reviewers (UN, SA, AA, MA, SD or TM), and any discrepancies were resolved by discussion or, if agreement could not be reached, by arbitration by a third reviewer (SD or AS). A descriptive summary with detailed data tables was initially produced to summarize the literature. Where clinically and statistically appropriate, meta-analyses were undertaken using random-effects modeling.⁽¹⁶⁾ Data were extracted from primary studies, but where these were not available in a suitable format we first contacted authors for data and then if data were still not available we extracted data from previous Cochrane reviews. For outcomes for which it was not possible to produce a meta-analysis, we narratively synthesized data. Heterogeneity statistics are reported with each forest plot.

Sensitivity analyses and assessment for publication bias

Sensitivity analyses were undertaken for the primary outcomes by comparing the summary estimates obtained by excluding studies considered to be at high ROB.

Publication bias was assessed for these same primary outcomes through the creation of funnel plots, and tested by Egger's regression test and Begg's rank correlation test.^(17,18)

Subgroup analyses

A number of subgroup analyses were undertaken, which are listed in the protocol.

Registration and reporting

This review is registered with the International Prospective Register of Systematic Reviews (PROSPERO): <http://www.crd.york.ac.uk/prospero/>. The registration number is CRD42016035373. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist has been used to guide the reporting of this systematic review: <http://www.prisma-statement.org/> (Appendix 2, Supplementary file).

RESULTS

Our search strategy yielded 5,932 titles of which 161 studies (reported in 166 papers) met our overall review eligibility criteria. These eligible papers included 135 double-blind RCTs, 19 health economic analyses and seven case series (Figure 1).

Effectiveness

Description of trials

We identified 61 SCIT RCTs (reported in 63 papers) (19–81) including 6,379 patients, 71 SLIT RCTs (reported in 75 papers) (82–119,119–121,121–156) including 13,636 patients and two ILIT RCTs (157,158) including 56 patients (Tables 1a-c). The majority of studies only included adult participants. A range of allergens were assessed including weed, tree and grass pollens, moulds, cat and dog dander and house dust mites. A range of AIT protocols were utilized. The overwhelming majority of trials only reported on short-term effectiveness (Tables S2a-c). A full description of the trials is given in the online supplement.

Quality assessment

SCIT

Overall, the quality of included studies was high. Thirty-seven studies were found to be at low ROB, eight studies at high ROB, and 16 were judged at unclear ROB (Table S2d).

SLIT

The quality of studies was assessed to be low ROB in 26 studies, high ROB in 16 studies and unclear ROB in 28 studies (Table S2e). In one study, ROB could not reliably be assessed from the translation.

ILIT

Both studies had a low ROB (Table S2f).

Primary outcomes

Data on primary outcomes are summarized in Tables S2 g-i .

Symptom scores

Short-term

105 studies reported on the short-term effectiveness of AIT administered by the SCIT (n=51), SLIT (n=52) and ILIT (n=2) routes assessed by symptom scores.

We were able to pool data from 58 SCIT and SLIT studies assessing the effectiveness of AIT by symptom scores. This showed a standardized mean difference (SMD) of -0.53 (95%CI -0.63, -0.42) this suggesting a moderate effect in favor of AIT (Figure 2).

Sensitivity analysis

Sensitivity analysis was performed excluding all studies at high ROB, which demonstrated a SMD of -0.57 (95%CI -0.68,-0.46) (Figure S1, Supplementary file)

Assessment for publication bias

There was evidence of potential publication bias (Figure S2, Supplementary file) which was also suggested by the Begg (P=0.003) and Egger (P=0.003) tests.

Subgroup analyses

Subgroup analyses were undertaken to compare:

- SCIT versus SLIT: SMD -0.65 (95%CI -0.86, -0.43) for SCIT and SMD -0.48 (95%CI -0.61, -0.36) for SLIT (Figures 3a and b), these both showing evidence of benefit; data from the two ILIT trials could not be pooled, but these studies also demonstrated an improvement in short-term symptom scores.
- Children versus adults for AIT (SCIT and SLIT): SMD -0.25 (95%CI -0.46, -0.05) for children and SMD -0.56 (95%CI -0.70, -0.42) for adults (Figures 4a and b), these analyses showing evidence of benefit in both adults and children.
- Children versus adults for SLIT only: SMD -0.42 (95%CI -0.63, -0.21) for children and SMD -0.47 (95%CI -0.64, -0.29) for adults (figures S3a and b), these analyses showing benefit in both adults and children.
- Seasonal versus perennial allergens: SMD -0.37 (95%CI -0.45, -0.28) for seasonal and SMD -0.91 (95%CI -1.47, -0.36) for perennial (Figures S4a and b, Supplementary file), these demonstrating evidence of benefit from both approaches.
- Seasonal versus perennial allergens for SCIT: SMD -0.49 (95%CI -0.72, -0.27) for seasonal and SMD -1.59 (95% CI -2.44, -0.74)for perennial (results from only one study) (Figures S5a and b, Supplementary file), these demonstrating evidence of benefit from both approaches.

- Seasonal versus perennial allergens for SLIT: SMD -0.35 (95%CI -0.45, -0.26) for seasonal and SMD -0.81 (95%CI -1.41, -0.20) for perennial allergens (Figures S6a and b, Supplementary file)
- Pre-/co-seasonal versus continuous treatment in SCIT for pollen: SMD -0.51 (95%CI -0.63, -0.38) in pre/co-seasonal and SMD -0.69 (95%CI -1.09, -0.29) (Figures S7a and b, Supplementary file), these analyses demonstrating evidence of benefit from both approaches.
- Pre-/co-seasonal versus continuous treatment in SLIT for pollens : SMD -0.40 (95%CI -0.48, -0.32) in pre-/co-seasonal and SMD -0.55 (95%CI -0.98, -0.11) in continuous (Figures S8a and b, Supplementary file), these analyses demonstrating a clear benefit associated with both approaches.
- Modified allergen extracts (allergoids) versus unmodified allergen extracts in SCIT: SMD -0.60 (95%CI -0.89, -0.31) versus SMD -0.65 (95%CI -0.93, -0.36) (Figures S9a and b, Supplementary file), these analyses demonstrating evidence of benefit from both modalities
- Aqueous solutions versus tablets in SLIT: SMD -0.41 (95%CI -0.65, -0.18) in aqueous and SMD -0.56 (95% CI -0.80, -0.33) with tablets (Figures S10a and b, Supplementary file), these analyses confirming benefit with both preparations.
- Different allergens for AIT (SCIT and SLIT): HDM: SMD -0.73 (95%CI -1.37, -0.10); grass: SMD -0.45 (95%CI -0.54, -0.36); tree: SMD -0.57 (95%CI -0.92, -0.21); molds: SMD -0.56 (95%CI -2.29, 1.18); weeds: SMD -0.68 (95%CI -1.06, -0.30), these showing that AIT was clearly effective for all allergens except molds for which there was evidence suggestive of benefit but this was imprecisely estimated (Figures S11a, b, c, d and e, Supplementary file),

Long-term

In order to investigate long-term effectiveness, a number of investigators studied a discontinuation period following trials that involved randomization to AIT or placebo in which the superiority of AIT was confirmed. In this longer-term phase, patients were followed-up and outcomes were then again assessed at least one year post-discontinuation of AIT.

There were four trials that studied this outcome, one SCIT (42) and three SLIT (89,114,133), all of which were judged to be at low ROB. Meta-analysis of data was not possible. A full descriptive summary of the main findings are provided in the supplement. In summary, all four trials at low ROB found a beneficial effect on the long-term effectiveness of AIT on symptom scores.

Medication scores

Short-term

89 studies reported on the short-term effectiveness of AIT administered by the SCIT (n=46), SLIT (n=42) and ILIT (n=1) routes on medication scores.

We were able to pool data from 45 SCIT and SLIT trials. This showed an overall SMD of -0.38 (95%CI -0.49, -0.26), this suggesting a small-to-medium effect in favor of AIT in improving medication scores (Figure 5).

Sensitivity analyses

Sensitivity analysis, performed by excluding all studies at high ROB, gave an SMD of -0.35 (95%CI -0.46, -0.24) (Figure S12, Supplementary file).

Assessment of publication bias

The Funnel plot revealed evidence of potential publication bias (Figure S13, Supplementary file) which was also suggested by the Begg (P=0.004) and Egger (P=0.03) tests.

Subgroup analyses

Subgroup analyses were undertaken to compare:

- SCIT versus SLIT: SMD -0.52 (95%CI -0.75, -0.29) for SCIT and -0.31 (95%CI -0.44, -0.18) for SLIT (Figures 6a and b), these analyses demonstrating that both routes were effective.
- Children versus adults: SMD -0.21 (95%CI -0.42, 0.01) for children and SMD -0.43 (95%CI -0.56, -0.30) for adults (Figure S14a and b, Supplementary file), these showing a clear benefit in adults and the suggestion of benefit in children (but this was not confirmed)
- Children versus adults for SLIT only: SMD -0.60 (95%CI -1.12, -0.07) for children and SMD -0.45 (95%CI -0.69, -0.22) for adults showing a benefit in both. (Figure S15a and b, Supplementary file)
- Seasonal versus perennial allergens for AIT (SCIT and SLIT): SMD -0.30 (95%CI -0.43, -0.16) for seasonal and SMD -0.63 (95%CI -1.12, -0.15) for perennial allergens (Figure S16a and b, Supplementary file), these indicating that both were effective.

- Seasonal versus perennial allergens for SCIT: SMD -0.77 (95% CI -1.28, -0.25) for seasonal and SMD -0.27 (95% CI -1.01, 0.48) for perennial (results from only one study) (Figure S17a and b, Supplementary file)
- Seasonal versus perennial allergens for SLIT: SMD -0.24 (95% CI -0.38, -0.10) for seasonal, SMD -0.72 (95% CI -1.30, -0.13) (Figure S18a and b, Supplementary file), indicating that both were effective.
- Pre/co-seasonal versus continuous treatment in SCIT for pollens: SMD -0.40 (95% CI -0.56, -0.25) in pre-seasonal and SMD -1.23 (95% CI -2.34, -0.12) in continuous (Figure S19a and b, Supplementary file), these indicating that both were effective.
- Pre-/co-seasonal versus continuous treatment in SLIT for pollens: SMD -0.30 (95% CI -0.42, -0.18) in pre-/co-seasonal and SMD 0.00 (95% CI -0.32, 0.33) for continuous (Figure S20a and b, Supplementary file), these analyses suggesting that pre-/co-seasonal was effective and that continuous treatment was ineffective.
- Modified allergen extracts (allergoids) versus unmodified allergen extracts in SCIT SMD -0.94 (95% CI -1.73, -0.16) versus SMD -0.44 (95% CI: -0.64, -0.24) (Figure S21a and b, Supplementary file),
- Aqueous solutions versus tablets in SLIT: SMD -0.35 (95% CI -0.55, -0.14) for those receiving aqueous and SMD -0.42 (95% CI -0.64, -0.19) for tablets (Figure S22a and b, Supplementary file), these analyses showing that both preparations were effective.
- Different allergens for AIT (SCIT and SLIT): HDM: SMD -0.63 (95% CI -1.12, -0.15) vs Grass: SMD -0.32 (95% CI -0.46, -0.18) vs Tree: SMD -0.40 (95% CI -0.59, -0.20) vs Molds: SMD 0.34 (95% CI -0.41, 1.09) (results from only one study) vs Weeds: SMD -0.44 (95% CI -0.80, -0.09) (Figures S23a, b, c, d and e, Supplementary file), these showing evidence of benefit for all allergens except molds.

Long-term

There were three low ROB trials that assessed this outcome: one SCIT (42) and two SLIT. (114,133) These three trials are described in detail in the supplement. Overall, one trial found a benefit of AIT (SCIT) on long-term medication scores; the two other SLIT trials did not show a sustained effect.

Combined symptom and medication scores

Twenty-nine studies reported on the short-term effectiveness of AIT administered by the SCIT (n=20) and SLIT (n=9) routes on combined symptom and medication scores. Two studies (one SCIT and one SLIT) reported on long-term effectiveness in relation to this outcome.

Short-term

We were able to pool data from 15 studies. Meta-analysis found a SMD of -0.49 (95%CI -0.69, -0.30), this suggesting a small-to-moderate effect in favor of AIT (Figure 7).

Sensitivity analysis

No sensitivity analysis was possible as no studies were judged to be at high ROB.

Publication bias

The funnel plot showed evidence of potential publication bias, (Figure S24, Supplementary file) which was also suggested by the Begg (P=0.005) and Egger (P=0.03) tests.

Subgroup analyses

Subgroup analyses were undertaken to compare:

- SCIT versus SLIT: SMD -0.51 (95%CI -0.77, -0.26) for SCIT and SMD -0.47 (95%CI -0.81, -0.12) (Figures 8a and b), these analyses showing a benefit from both SCIT and SLIT.
- Children (<18) versus adults (≥ 18 years) for AIT (SCIT and SLIT): SMD -0.85 (95% CI -1.52, -0.17) (results from one study only) for children and SMD -0.44 (95%CI -0.65, -0.22) for adults (Figures S25a and b, Supplementary file), these analyses showing a benefit in both children and adults
- Pre/co-seasonal (short term treatment) versus continuous treatment in SCIT for pollen: SMD -0.41 (95%CI -0.58, -0.24) for pre-seasonal and SMD -0.86 (95%CI -1.49, -0.22) for continuous (results from one study only) (Figures S26a and b, Supplementary file), these analyses showing a clear benefit from pre/co-seasonal treatment and the suggestion (but not confirming) benefit from continuous treatment
- Modified allergen extracts (allergoids) versus unmodified allergen extracts in SCIT: SMD -0.49 (95%CI -0.79, -0.19) for allergoids and SMD -0.36 (95%CI -0.73, 0.03) (Figures S27a and b, Supplementary file), these finding a clear benefit from allergoids and suggesting (but not confirming) a benefit from unmodified preparations.
- Different allergens for AIT (SCIT and SLIT): Grass: SMD -0.41 (95%CI -0.58, -0.24) vs Tree (one study only): SMD -0.26 (95%CI -0.64, 0.13) vs Molds: SMD -0.65 (95%CI -2.06, 0.76) vs Weeds: SMD -0.69 (95%CI -1.24, -0.13) (Figures S28a, b, c and d Supplementary file), this

showing clear evidence of benefit for grass and tree pollens, and suggesting (but not confirming) evidence of benefit for molds and weeds..

Long-term

We found one SCIT trial (53) and two SLIT trials (109,133) that reported on this outcome. These are described in detail in the supplement. Overall, one of the three trials found evidence of a sustained beneficial effect on combined symptom and medication scores. The one trial at an unclear ROB (Didier 2013/2015) demonstrated a two year carry over effect of AIT in the active SLIT group that received AIT four months pre-seasonally for three consecutive seasons but not for the group which received AIT two months pre-seasonally.(109,159)

Secondary outcomes

Disease-specific quality of life

Thirty studies reported data on quality of life (QoL): these comprised of SCIT (n=17) (19,20,23,28,33,34,35,45,46,55,58,68–70,72,74,79) and SLIT (n=13) (90,99,104,106,108,110,117,129,130,132,140,145,149) trials (Tables S2j and k). The majority of trials (n=29) used one of the disease-specific, validated Rhinitis Quality of Life Questionnaire (RQLQ) instruments. However, one SLIT study (eligible because it reported on other outcomes) used a generic, non-disease specific tool, the SF-36, and this was therefore not considered further.(140) Due to inconsistencies of reporting data, it was not possible to pool results from all of the studies and no SLIT studies were suitable for inclusion in meta-analysis. Pooling data from the six SCIT studies with suitably reported data derived from the original and standardized RQLQ instruments found a SMD of -0.35 (95%CI -0.74, 0.04), this corresponding to a likely small-to-medium improvement in the AIT group when compared to placebo (Figure 9).

Allergen challenge models in AIT

A detailed description of environmental exposure chamber, nasal and conjunctival challenge studies are described in the supplement. One SCIT and three SLIT (83,120,121) chamber studies demonstrated the effectiveness of AIT. Results of nasal challenge studies for 15 SCIT (23,24,27,29,30,33,37,43,52,57–59,63,64,75) and 11 SLIT (84,86,87,92,93,122,128,136,139,146,150) (Table S2l) were conflicting making it difficult to make clear conclusions. There was no clear evidence of effectiveness in 12 SCIT (21,23,35,38,42,45,55,62-64,70,72) and four SLIT conjunctival challenges studies (120,127,138,146) (Table S2m).

Cost-effectiveness

Characteristics of studies

We identified 19 eligible studies that reported on health economic evaluations of SCIT and SLIT in both children and adults (Table S2n).(160–178) Studies were based in a range of countries. Seven of the studies reported results against disease specific outcome measures whilst the remaining 12 reported results based on quality adjusted life years (QALYs). Thirteen of the studies were based on RCT data or meta-analyses of RCT data(160–169,176–178). Full details are in the supplement.

Quality appraisal

The quality appraisal of the included studies is detailed in Table S2o.

Main findings

In general, the studies found that AIT, and where defined both SLIT and SCIT, were more effective than standard care including pharmacotherapy, but also more expensive. The studies that compared SLIT with SCIT gave very mixed results not allowing a clear conclusion to be drawn that either treatment was necessarily more effective or more costly than the other from a health system perspective. The studies comparing Grazax (SLIT) and Oralair (SLIT) suggested that Oralair is both more effective and cheaper than Grazax.(165,167)

For those studies based on RCT data conducted from a health system perspective and using QALYs as their outcome measure (n=7), we found that:

- Nasser 2008: In patients with both rhinitis and asthma in England the incremental cost-effectiveness ratio (ICER) for SLIT versus standard care was £8816 (€10851) per QALY at 2005 prices inflated using national health service (NHS) inflation indices (i.e. Personal Social Services Research Unit (PSSRU)) to £10726 (€13202) per QALY at 2014/15 prices. (177)
- Poulsen 2008: In adult patients with rhino-conjunctivitis in Denmark the ICER for SLIT versus standard care was 134105 DKK per QALY (no price year was given so we assumed study year of 2008) updating to current prices and £ at 0.1 £ per DKK gave an ICER of £15294 (€18824) per QALY at 2014/15 prices.(164)
- Keiding 2007: In adult patients with rhino-conjunctivitis in Austria, Denmark, Finland, Germany, Netherlands, Sweden the ICERs of SCIT compared to standard care in 2005 Euro per QALY

were 9716, 2586, 13683, 10300, 24519 and 22675, respectively. Updating to current prices and £ at 0.75 GBP per Euro gives ICERs of £8866, £2360, £12486, £9399, £22374 and £20691 per QALY respectively at 2014/15 prices.(162)

- Ronaldson 2014: In 5-16 year olds with rhino-conjunctivitis with or without asthma in the UK the ICER for SLIT versus standard care was £12168 (€14976) per QALY at 2008 prices. Updating to current prices gives an ICER of £13357 (€16440) per QALY at 2014/15 prices.(166)
- Westerhout 2012: In patients with rhino-conjunctivitis without asthma in Germany the ICER for SLIT (Oralair) versus standard care was 14728 euros per QALY at 2011 prices. Converting to current prices and GBP at 0.75 £ per Euro gives an ICER of £11460 per QALY.(167)
- Verheggen 2015: In patients with rhinoconjunctivitis without asthma in Germany the ICER for SLIT (Oralair) versus SCIT is 12593 euros per QALY at 2013 prices. Converting to 2014/15 prices and GBP at 0.75 GBP per Euro gives an ICER of £9627 per QALY(168)
- Reinhold 2016: In patients with rhinoconjunctivitis without asthma in Germany SCIT (Allergovit) is cheaper and more effective than SLIT (Oralair). The ICER for SCIT (Allergovit) standard care is 11000 euros per QALY at 2013 prices. Converting to 2014/15 prices and GBP at 0.75 GBP per Euro gives an ICER of £8334 per QALY.(169)

When assessing these results, it was unclear how comparable the patient populations were between the studies; a key factor that impacts the costs and quality of life observed is the proportion of patients who have asthma as well as rhinitis – these proportions were not reported in the studies. Also noteworthy was that the ICERs for AIT seemed to vary substantially between different health systems as demonstrated in Keiding et al 2007 where ICERs range from £2360 per QALY in Denmark to £22374 per QALY in the Netherlands suggesting that straightforward conclusions may not be generalizable even across seemingly similar countries.(162)

Overall interpretation

The seven key studies identified, disregarding the caveats about generalizability, suggested that SLIT and SCIT treatment would be considered cost-effective in this patient population in England at the standard NICE cost-effectiveness threshold of £20,000 (€24616) per QALY. However, the quality of the studies and the general lack of attention to characterizing uncertainty and handling missing data need to be taken into account when interpreting these results.(162,164,166–169,177)

Safety

RCTs and case-series were eligible for inclusion to consider the safety of AIT.

Randomized controlled trials

Safety data for SCIT and SLIT RCTs are summarised in Tables S2p-v. There was a great variation in reporting of adverse events and a number of grading scales including WAO and EAACI were used. As detailed in the tables some studies reported limited or unclear data on number of AEs, some studies reported no data on AEs and others reported that no AEs occurred at all through the duration of the trial period. Conversely some studies reported all treatment emergent AEs.

Total adverse events

We were able to pool data for this outcome for total number of adverse events. Safety data for 51 SCIT and SLIT RCTs were pooled to give an overall risk ratio (RR) of experiencing an adverse event (AE) of 1.64 (95%CI:1.43, 1.89).(Figure S3a)

For SCIT studies (n=19), we found an RR of 1.58 (95%CI:1.13, 2.20) of experiencing an AE and for SLIT studies (n=32) an RR of 1.68 (95%CI:1.44, 1.98).(Figures S3b and c) suggesting a comparable safety profile for both modes of AIT.

Systemic adverse events

We were able to pool data for number of systemic AEs for 39 SCIT and SLIT RCTs to give an overall RR of experiencing a systemic AE of 1.26 (95%CI:1.03, 1.55).(Figure S3d) For SCIT studies (n=15), we found a RR of 1.15 (95%CI: 0.67, 2.00) of experiencing a systemic AE and for SLIT studies (n=24) a RR of 1.31(95%CI: 1.05, 1.63).(Figures S3e and f)

We were able to pool data for the number of patients experiencing a systemic AE for SCIT and SLIT RCTs (n=18) to give a RR of 2.37 (95% CI: 1.09, 5.16). (Figure S3g)

Local adverse events

We were able to pool data for local AEs for 39 SCIT and SLIT RCTs to give an overall RR of experiencing a local AE of 1.78 (95%CI 1.51, 2.11).(Figure S3h) For SCIT studies (n=9), we found an RR of 2.21 (95%CI 1.43, 3.41) of experiencing a local AE and for SLIT studies (n=30) an RR of 1.71(95%CI 1.43, 2.05).(Figures S3i and j)

We were able to pool data for the number of patients experiencing a local AE for SCIT and SLIT RCTs (n=17) to give a RR of 1.72 (95% CI:1.32, 2.23) (Figure S3k)

Case series

Seven large case series were identified.(179–185) (Tables S2w-y) Local (LR) and systemic (SR) AEs were recorded in a range of treatment protocols, including conventional, rush, ultra-rush and cluster. In total 4045 patients were included in these case series however only 3541 were patients with allergic rhinoconjunctivitis; we therefore focused on data for these patients.

The case series were conducted in a number of countries including Spain, Colombia, US, Germany and Portugal.

The case series highlighted that where modified allergen extracts were used to deliver AIT this was safer in terms of number of AEs reported compared to unmodified extracts. (180–183)

Safety data from the rush (180) and ultra-rush (181,182) protocols were evaluated and are presented in Tables S2v and w. The studies concluded that the frequency of SRs were similar to conventional build-up schedules, but importantly rush and ultra-rush protocols were associated with improved patient adherence to treatment by reducing the number of injections required and the cost associated with treatment. Comparable benefits of cluster treatment protocol were also reported in one study. (184) Finally, one case series looked at investigating the number of AEs where patients received either conventional or cluster IT via the SLIT route. AEs were reported in 0.15% of all administered doses in which 9.3% of patients experienced a SR. The study concluded that SLIT was safe in the treatment of allergic rhinoconjunctivitis. (179)

No fatalities were reported in any of these studies.

DISCUSSION

Statement of principal findings

This review of a very substantial body of international trial evidence, many of which were judged to be at low ROB, has found clear evidence that AIT improved all three of our primary outcomes – i.e. symptom, medication, and combined symptom and medication scores over the short-term. These findings were robust to pre-specified sensitivity analyses but evidence of potential publication bias was identified for all three primary outcomes. Although the long-term studies are fewer in number, there was a modest evidence-base in support of the effectiveness of AIT in improving symptom scores after treatment discontinuation for both SCIT and SLIT. The evidence was less clear in relation to the impact on medication and combined symptom and medication scores. SCIT improved disease specific quality of life. We could draw no clear conclusions on the effectiveness of AIT on nasal and conjunctival challenges and on cost-effectiveness which may be cost-effective in an English NHS setting, but due to the poor quality of the studies this needs to be interpreted with caution. AIT increased the risk of adverse events for both SCIT and SLIT, but no fatalities occurred.

Strengths and limitations

To our knowledge, this is the most comprehensive assessment of AIT in allergic rhinoconjunctivitis ever undertaken. We employed internationally accepted techniques to systematically identify, assess and synthesize a substantial body of evidence. This involved taking advantage of and building on other recent systematic reviews focusing on distinct modes of delivering AIT.

The limitations of this review need to be considered. First, despite our extensive searches we may not have uncovered all relevant evidence on this subject. Second, we were limited by the heterogeneity in approaches used to assess outcomes, which meant we were unable to pool data from all trials or undertake all the planned subgroup analyses. Furthermore studies for which data was pooled also showed heterogeneity which may be related to the diverse populations studied, protocols followed, products used and duration of trial period. For the subgroup analyses that were undertaken, there was in some cases imprecision which impacted on our ability to draw clear conclusions. These subgroup analyses were indirect comparisons between SCIT and SLIT and the findings should therefore be cautiously interpreted. Third, because of the heterogeneity in scoring systems used, we undertook meta-analyses using random-effects modelling and pooled data using SMDs, which can be difficult to interpret. The absolute size of the SMD was used to guide assessment of the likely effect size demonstrated.⁽¹⁸⁶⁾ Finally, it needs to be borne in mind that there may have been important differences in effectiveness between specific AIT products. Investigating this issue was however beyond the scope of this review. In

terms of safety there was heterogeneity in reporting of adverse events with many differing scoring systems used due to this we were unable to report this outcome as originally planned using only the WAO grading system.

Implications for policy, practice and research

Our findings clearly show that AIT is effective in improving the three patient-reported outcomes that represented our primary outcomes, at least over the short-term, and that AIT should therefore be considered in the management of patients with allergic rhinoconjunctivitis.

Greater standardization of trial designs and reporting techniques – in particular, in relation to choice of outcomes and their reporting so as to facilitate evidence syntheses and key subgroup analyses, would greatly help to advance the research base underpinning AIT. We therefore appreciate initiatives of the EAACI in e.g. harmonizing and standardizing clinical endpoints in AIT (187) or determining threshold-level of relevant pollen seasons for assessing clinical effect sizes. (188) We also wish to highlight the need for additional studies focusing on long-term outcomes and on studies of ILIT and other novel modes of delivery. We hope that future researchers will build on the findings from this systematic review and aim to fill key evidence gaps and areas of continuing uncertainty.

The findings from this review will be used to inform the development of recommendations for EAACI's Guidelines on AIT for Allergic Rhinoconjunctivitis.

Conclusions

AIT is effective in achieving clinically important short-term improvements in symptom, medication and combined symptom and medication scores. There is a limited body of evidence on the longer-term effectiveness of AIT in improving symptom scores.

Funding: EAACI and EU grant number: 601763.

Contributorship: This review was drafted by S. Dhimi, U. Nurmatov and A. Sheikh. It was initially revised following critical review by G. Roberts and O. Pfaar, and then by all co-authors. This paper is part of the EAACI AIT guidelines project, chaired by Antonella Muraro and coordinated by Graham Roberts.

This article is protected by copyright. All rights reserved.

Acknowledgments: The EAACI Rhinoconjunctivitis AIT Taskforce would like to thank Daniela Brombin for her administrative assistance and Stefan Kuzmiak and Zakariya Sheikh for their assistance with information technology support for the activity.

Conflicts of interest:S. Dhimi: reports grants from EAACI to carry out the review, during the conduct of the study; U. Nurmatov: reports payment from Evidence-Based Health Care Ltd during the conduct of the study; S. Arasi: reports payment from Evidence-Based Health Care Ltd during the conduct of the study; T. Khan: has nothing to disclose ; M. Asaria: reports payment from Evidence-Based Health Care Ltd during the conduct of the study ; H. Zaman: has nothing to disclose.; A. Agarwal:has nothing to disclose ;G. Netuveli: has nothing to disclose.; G. Roberts: has a patent Use of sublingual immunotherapy to prevent the development of allergy in at risk infants issued and my University has received payments for activities I have undertaken giving expert advice to ALK, presenting at company symposia for ALK, Allergen Therapeutics and Meda plus as a member of an Independent Data Monitoring Committee for Merck.; O. Pfaar: reports grants and personal fees from ALK Abelló, grants and personal fees from Allergopharma, grants and personal fees from Stallergenes Greer, grants and personal fees from HAL-Allergy Holding B.V/HAL-Allergie gmbH, grants and personal fees from Bencard Allergie gmbH/Allergy Therapeutics, grants and personal fees from Lofarma, grants from Biomay, grants from Nuvo, grants from Circassia, grants and personal fees from Biotech Tools S.A., grants and personal fees from Laboratorios LETI/LETI Pharma, grants and personal fees from Novartis Pharma, personal fees from MEDA Pharma, grants and personal fees from Anergis S.A., personal fees from Sanofi Aventis, personal fees from Mobile Chamber Experts (a GA2LEN Partner), personal fees from Pohl-Boskamp, outside the submitted work; A. Muraro: reports personal fees from Novartis, personal fees from Meda Mylan , outside the submitted work; IJ. Ansotegui: reports personal fees from SANOFI, personal fees from Bayer, personal fees from Pfizer, personal fees from FAES FARMA, personal fees from MIT FARMA, personal fees from HIKMA, personal fees from Menarini, personal fees from Bial Aristegui, outside the submitted work; M. Calderon: has received honorarium in Advisory Boards for ALK and Hal-Allergy, as speaker for ALK, Merck and Stallergenes-Greer.; C. Cingi: has nothing to disclose ; S. Durham: reports grants from Regeneron, USA, grants from Biotech Tools, grants from ALK, Denmark, personal fees from Anergis, Switzerland, personal fees from Circassia, UK, personal fees from Biomay, Austria, personal fees from Merck, personal fees from Allergy Therapeutics, UK, personal fees from ALK, Horsholm, Denmark, personal fees from med Update GmbH, Germany, grants from Food Standards Agency, UK, grants from National Institute of Health Research UK, personal fees from Allergy Therapeutics, outside the submitted work; R. Gerth van Wijk: reports personal fees from ALK Abello, personal fees from Circassia, personal fees from Allergopharma, during the conduct of the study; S. Halken: reports personal fees from ALK Abelló, personal fees from Different companies e.g. MEDA, Stallergenes, Allergopharma and ALK-Abelló, outside the submitted work; E. Hamelmann: is giving lectures in industry symposia and takes part in advisory board meetings for the following companies: Boehringer Ingelheim, Novartis, ALK, HAL Allergy, Bencard, Stallergenes, Leti Pharma, Symbiopharm.; P.Hellings: has nothing to disclose.; L. Jacobsen: reports personal fees from EAMG, outside the submitted work; E.Knol: has nothing to disclose.; D. Larenas-Linnemann: No influence in the presented paper.; S. Lin: has nothing to disclose.; V. Maggina: has nothing to disclose; R. Mosges: reports personal fees from ALK, grants from ASIT biotech, personal fees from allergopharma, personal fees from Allergy Therapeutics, grants and personal fees from Bencard, grants from Leti, grants, personal fees and non-financial support from Lofarma, non-financial support from Roxall,

This article is protected by copyright. All rights reserved.

grants and personal fees from Stallergenes, grants from Optima, personal fees from Friulchem, personal fees from Hexal, personal fees from Servier, personal fees from Klosterfrau, non-financial support from Atmos, personal fees from Bayer, non-financial support from Bionorica, personal fees from FAES, personal fees from GSK, personal fees from MSD, personal fees from Johnson&Johnson, personal fees from Meda, personal fees and non-financial support from Novartis, non-financial support from Otonomy, personal fees from Stada, personal fees from UCB, non-financial support from Ferrero, grants from BitopAG, grants from Hulka, personal fees from Nuvo, grants from Ursapharm, outside the submitted work; H.Oude-Elberink: reports grants from ALK ABello, during the conduct of the study; G. Pajno: reports grants from Stallergenes, from null, during the conduct of the study; R. Panwanker: has nothing to disclose.; E. Pastorello: has nothing to disclose.; M. Penagos: reports personal fees from Stallergenes, personal fees from ALK, outside the submitted work; C. Pitsios: has nothing to disclose.; G. Rotiroti: reports personal fees from ALK Abello', outside the submitted work; F. Timmermans: has nothing to disclose.; O. Tsilochristou: Dr. Tsilochristou has nothing to disclose.; E. Varga: has nothing to disclose; C. Schmidt-Weber: reports grants from Allergopharma and Leti, honorarium from PLS-Design, Allergopharma and Leti, member of scientific advisory board Leti, holds shares in PLS-Design, and hopes to develop a patent ; J. Wilkinson: has nothing to disclose.; A. Williams: reports other from ALK Abello UK, other from Diagenics LTD UK, outside the submitted work; . Travel expenses for education meetings EAACI & BSACI; M. Worm: Allergopharma, Novartaos, Stellergens, Medic Pharma, Alk-Alelli; L. Zhang: has nothing to disclose.; A. Sheikh: reports grants from EAACI, during the conduct of the study.

Online supplement

Allergen immunotherapy for allergic rhinoconjunctivitis: a systematic review and meta-analysis

¹Sangeeta Dhami, ²Ulugbek Nurmatov, ³Stefania Arasi, ⁴Tahir Khan, ⁵Miqdad Asaria, ⁶Hader Zaman, ⁷Arnav Agarwal, ⁸Gopal Netuveli, ⁹Graham Roberts, ^{10, 11}Oliver Pfaar, ¹²Antonella Muraro, ¹³Ignacio J. Ansotegui, ¹⁴Moises Calderon, ¹⁵Cemal Cingi, ¹⁴Stephen Durham, ¹⁶Ronald Gerth van Wijk, ¹⁷Susanne Halken, ¹⁸Eckard Hamelmann, ¹⁹Peter Hellings, ²⁰Lars Jacobsen, ²¹Edward Knol, ²²Desiree Larenas Linnemann, ²³Sandra Lin, ²⁴Paraskevi Maggina, ²⁵Ralph Moesges, ²⁶Hanneke Oude-Elberink, ²⁷Giovanni Pajno, ²⁸Ruby Panwanker, ²⁹Elideanna Pastorello, ¹⁴Martin Penagos, ³⁰Constantinos Pitsios, ³¹Giuseppina Rotiroti, ³²Frans Timmermans, ³³Olympia Tsilochristou, ³⁴Eva-Maria Varga, ³⁵Carsten Schmidt-Weber ³⁶Jamie Wilkinson, ³⁷Andrew Williams, ³⁸Margitta Worm, ³⁹Luo Zhang, ⁴⁰Aziz Sheikh

¹Evidence-Based Health Care Ltd, Edinburgh, UK; ²Cardiff University, School of Medicine, Division of Population Medicine Neuadd Meirionnydd, Heath Park, Cardiff, UK; ³Department of Pediatric, Allergy Unit, University of Messina, Italy & Molecular Allergology and Immunomodulation-Department of

Pediatric Pneumology and Immunology, Charité Medical University, Augustenburger Platz 1, Berlin, Germany; ⁴School of Pharmacy, Monash University, Malaysia; ⁵Research Fellow, Centre for Health Economics, University of York, UK; ⁶Lecturer in Pharmacy Practice, Bradford School of Pharmacy, UK; ⁷Medical Department, University of Toronto, Canada; ⁸Institute for Health and Human Development, University of East London, UK; ⁹The David Hide Asthma and Allergy Research Centre, St Mary's Hospital, Newport Isle of Wight, NIHR Respiratory Biomedical Research Unit, University Hospital Southampton NHS Foundation Trust, Southampton, UK, and Faculty of Medicine, University of Southampton, Southampton, UK; ¹⁰Department of Otorhinolaryngology, Head and Neck Surgery University Hospital, Mannheim and ¹¹Center for Rhinology and Allergology, Wiesbaden, Germany; ¹²Food Allergy Referral Centre Veneto Region Department of Women and Child Health Padua General University Hospital, Italy; ¹³Hospital Quiron Bizkaia, Bilbao, Spain; ¹⁴National Heart and Lung Institute, Imperial College, London; ¹⁵Department of ENT, Eskisehir Osmangazi University Medical Faculty, Eskisehir, Turkey; ¹⁶University of Allergology, Department of Internal Medicine, Erasmus MC Rotterdam, The Netherlands; ¹⁷Hans Christian Andersen Children's Hospital, Odense University Hospital, Odense, Denmark; ¹⁸Children's Center Bethel, EvKB, Bielefeld and Allergy Center Buhr-University, Bochum, Germany; ¹⁹Laboratory of Experimental Immunology, University Hospitals Leuven, Belgium; ²⁰ALC, Allergy Learning and Consulting; ²¹University Medical Center, Utrecht, The Netherlands; ²²Hospital Medica Sur, Mexico City, Mexico; ²³Department of Otolaryngology-Head & Neck Surgery, John Hopkins, USA; ²⁴Allergy and Clinical Immunology Unit, 2nd Department of Pediatrics, University of Athens, P&A Kiriakou Children's Hospital, Athens, Greece; ²⁵University Medical Center Groningen, University of Groningen, Department of Allergology, Groningen Research Institute for Asthma and COPD (GRIAC), Groningen, Netherlands; ²⁶University Medical Center of Groningen, University of Groningen, Groningen, The Netherlands; ²⁷Department of Pediatrics, University of Messina, Italy; ²⁸Department of Pediatrics, Nippon Medical School, Tokyo, Japan; ²⁹University of Milano, Italy; ³⁰Department of Nutrition and Dietetics, Harokopio University, Athens, Greece; ³¹The Royal National Throat, Nose and Ear Hospital, University College London, London, UK; ³²Netherlands Anafylaxis Network, The Netherlands; ³³Charite University Hospital, Berlin, Germany; ³⁴Dept. of Paediatrics, Respiratory and Allergic Disease Division. Medical University Graz, Graz, Austria; ³⁵Pharmaceutical Group of the European Union, Brussels, Belgium; ³⁶Pharmaceutical Group of the European Union, Brussels, Belgium; ³⁷Guy's and St Thomas' NHS Foundation Trust, London, UK; ³⁸Charité-Universitätsmedizin, Berlin, Germany; ³⁹Beijing Institute of Otolaryngology, Beijing, China; ⁴⁰Asthma UK Centre for Applied Research, Usher Institute of Population Health Sciences and Informatics, The University of Edinburgh, Edinburgh, UK.

METHODS

The methods have been reported in detail in our published protocol (12).

Search strategy

A highly sensitive search strategy was developed and validated study design filters were applied to search electronic bibliographic databases. To retrieve randomized controlled trials (RCTs), we applied the Cochrane highly sensitive search strategy for identifying RCTs in MEDLINE.(16) We searched the following databases: Cochrane Library including, Cochrane Database of Systematic Reviews (CDSR), Database of Reviews of Effectiveness (DARE), CENTRAL (Trials), Methods Studies, Health Technology Assessments (HTA), Economic Evaluations Database (EED), MEDLINE (OVID), Embase (OVID), CINAHL (Ebscohost), ISI Web of Science (Thomson Web of Knowledge), TRIP Database (www.tripdatabase.com), Clinicaltrials.gov (NIH web), Clinical Trials Register (www.clinicaltrialsregister.eu) launched by the European Medicines Agency (EMA), Current controlled trials (www.controlled-trials.com), Australian and New Zealand Clinical Trials Registry (<http://www.anzctr.org.au>). To retrieve case series, we used the filter developed by librarians at Clinical Evidence: <http://clinicalevidence.bmj.com/x/set/static/ebm/learn/665076.html>

The search strategy was developed on OVID MEDLINE and then adapted for the other databases. In all cases, the databases were searched from inception to October 31, 2015.

Subgroup analyses

Subgroup analyses were undertaken to compare:

- Children <18 years versus adults ≥18 years; (this represented a change from our plans to compare young children versus adolescents versus adults, which was necessitated by data not being available in formats suitable to support the original planned subgroup analyses)
- SCIT versus SLIT
- AIT for seasonal versus perennial allergens
- Modified allergen extracts (allergoids) versus unmodified allergen extracts in SCIT
- Pre-seasonal (short term treatment) versus continuous treatment in SCIT

- Pre-/co-seasonal (short term treatment) versus continuous treatment in SLIT
- Aqueous solutions versus tablets in SLIT.

RESULTS

Effectiveness

Description of trials

We identified 61 SCIT RCTs (reported in 63 papers) (19–81) including 6,379 patients, 71 SLIT RCTs (reported in 75 papers) (82–119,119–121,121–156) including 13,636 patients and two ILIT RCTs (157,158) including 56 patients (Tables 1a-c). The overwhelming majority of trials only reported on short-term effectiveness (Tables 2a-c).

SCIT

The majority of trials were led by teams from the UK (n=11), followed by: France (n=7); Spain (n=7); Italy (n=6); Germany (n=5); USA (n=5); Canada (n=3); Poland (n=4); Denmark (n=2); Sweden (n=2); Germany and Austria (n=2); Austria, Denmark, France, Italy, Sweden (n=1); Austria, Spain, Germany, (n=1); Australia, Canada, UK and USA (n=1); Belgium and the Netherlands (n=1); India (n=1); Sweden and Germany (n=1), and Macedonia (n=1).

The majority of studies included adult participants (n=42). Fifteen studies included participants of any age (i.e. children and adults) and one included children aged up to 18 years of age. Three studies did not report the age of the participants.

The most common allergen administered in the included studies was: grass pollen(s) (n=28), followed by: weed pollens (n=19); tree pollens (n=16); HDM (n=6); molds (n=3); cat dander (n=2); dog dander (n=1); and storage mites (n=1).

SCIT was performed with a single allergen (i.e. allergens from the same group e.g. grasses) in 55 studies and with multiple allergens (i.e. from different groups e.g. grass and tree pollens) in the remaining six studies. In these trials, SCIT was compared with placebo (n=53), routine care (n=4) or active treatment (n=12); (there was more than one comparator arm in some studies).

SCIT was administered continuously in 27 studies, pre-seasonally in 19 studies, pre- and co-seasonally in 11 studies, pre-seasonally and continuously in different arms in one study and co-seasonally in one trial. The remaining trials (n=2) did not report on timing of administration.

The protocols used were: conventional (n=45); cluster (n=9); rush (n=8); semi-rush (n=1); and ultra-rush (n=1). Two studies uses both conventional and cluster, and a further study used both rush and conventional protocols.

The duration of treatment was heterogeneous, ranging from a single injection to four years. It was unclearly reported in one study and not reported at all in another trial.

Short-term effectiveness of SCIT was assessed by symptom scores (n=51), medication scores (n=46) and combined symptom and medication scores (n=20). Long-term effectiveness of SCIT was assessed by symptom scores (n=1) and medication scores (n=1), and combined symptom and medication scores (n=1).

See Tables 1a and 2a for further details.

SLIT

The majority of studies were carried out in: multiple European countries (n=16); Italy (n=12); Germany (n=7); France (n=6); Poland (n=4); US (n=3); Spain (n=3); the Netherlands (n=3); Austria (n=2); Canada (n=2); UK (n=2); Austria, Canada, Denmark, France and Germany (n=1); Brazil and the US (n=1); Canada and the US (n=1); China (n=1); Cyprus, Turkey and the UK (n=1); Czech Republic (n=1); Finland (n=1); Iran (n=1); Japan (n=1); South Africa (n=1); and Turkey (n=1).

The majority of studies were in adults (n=28), followed by children up to the age of 18 (n=25) and studies conducted in both adults and children (n=17), one study did not report the age of the participants.(40)

The major allergen type used in the immunotherapy was: was grass pollen(s) (n=40), followed by: HDM(s) (n=15); weed pollens (n=7); tree pollens (n=4); molds (n=3); and cat dander (n=2).

SLIT was performed with a single allergen in 67 studies and with multiple allergens in four studies. It was most commonly administered in the form of drops/solution (n=46), followed by tablets (n=22) and spray (n=1); the mode of administration was not reported in two studies. In relation to the drops/solution and tablet preparations, the SLIT was subsequently swallowed in 50 studies, expectorated in three studies and not reported in 18 studies.

This article is protected by copyright. All rights reserved.

SLIT was compared with placebo (n=67); routine care (n=1); or active treatment (n=5) (with some studies including more than one comparator).

SLIT was administered preseasonal and co-seasonally in 22 studies, pre-seasonally in seven studies and co-seasonally in five studies. The remaining studies did not report on the season of administration.

The duration of treatment varied from 28 days to four years.

Short-term effectiveness was assessed by symptom scores (n=56), medication scores (n=44); and combined symptom and medication scores (n=9). Long-term effectiveness was assessed by symptom scores (n=4), medication scores (n=2) and combined symptom and medication scores (n=2).

See Tables 1b and 2b for further details.

ILIT

The two ILIT trials were conducted in Switzerland and Sweden. They both investigated single allergen therapy, delivered through a cluster protocol to cat, and grass or birch pollen versus placebo. One used a pre-seasonal administration and the other continuous.

Both trials reported on the short-term effectiveness by symptom scores and one reported on medication scores.

See Tables 1c and 2c for further details.

Primary outcomes

Data on primary outcomes are summarized in Tables 4a-c .

Symptom scores

Long-term effectiveness

In order to investigate long-term effectiveness, a number of investigators studied a discontinuation period following trials that involved randomization to AIT or placebo in which the superiority of AIT was confirmed. In this longer-term phase, patients were followed-up and outcomes were then again assessed at least one year post-discontinuation of AIT.

This article is protected by copyright. All rights reserved.

There were four trials that studied this outcome, one SCIT and three SLIT, all of which were judged to be at low ROB. Meta-analysis of data was not possible. We therefore provide a descriptive summary of the main findings.

A trial by Durham (1999) studied discontinuation of SCIT in grass pollen allergic patients.(42) Participants had previously participated in a one year RCT in which they were randomized to SCIT or placebo, which confirmed the superiority of SCIT. (42) All patients were then given SCIT for three years (i.e. four years in total for the trial intervention arm). They were then randomized to receive either maintenance grass pollen SCIT or placebo injections for an additional three years. The authors found no significant difference in symptom scores between the two groups and concluded that the initial three/four years of AIT had induced prolonged clinical remission.

A five year double blind placebo controlled RCT by Durham (2012) had a three year SLIT tablets or placebo treatment period in grass pollen allergic patients followed by a two year blinded observation period when no active treatment was administered.(114) Two years after discontinuing treatment, the group who had received SLIT were found to have a significant improvement in symptom scores when compared to placebo ($P<0.004$).

Bergmann (2013) followed patients for one year after discontinuing one year of HDM SLIT at two different doses (300 IR or 500 IR) compared with placebo, which found that the active treatments significantly improved symptom scores.(89) One year after discontinuing AIT, the symptom improvements in the SLIT arms were maintained when compared to placebo.

Ott (2009) conducted a four year study which randomized patients to three years of seasonal grass pollen SLIT or placebo, followed by a one year discontinuation phase.(133) They found that improvements in symptom scores were maintained in the SLIT group after treatment was discontinued ($P=0.015$).

In summary, all four trials at low ROB found a beneficial effect on the long-term effectiveness of AIT on symptom scores.

These analyses were not possible.

Medication scores

Long-term effectiveness

There were three low ROB trials that assessed this outcome: one SCIT and two SLIT. These three trials are all described in more detail above when discussing long-term effects on symptom scores.

The trial by Durham (1999) in grass pollen allergic patients found that in the discontinuation RCT there was no significant difference between patients who continued SCIT when compared to those who received placebo.(42)

Another trial by Durham (2012) found that two years after discontinuing SLIT there was no difference in medication scores between those who had previously received SLIT compared to those who received placebo.(114)

Ott (2009) found that one year after completion of a trial of three years of seasonal grass pollen SLIT or placebo there was no significant improvement in medication scores ($P=0.84$). (133)

Overall, one trial found a benefit of AIT (SCIT) on long-term medication scores; the two other SLIT trials did not show a sustained effect.

Combined symptom and medication scores

Long-term effectiveness

We found one SCIT trial and two SLIT trials that reported on this outcome.

The trial by James (2011), at low ROB, studied grass allergic patients who were randomized to two years of SCIT or placebo.⁽⁵³⁾ They were randomized to receive SCIT or placebo injections during the initial trial, which found a benefit from SCIT. Those in the active arm were then randomized to a further two years of SCIT or placebo and this found low combined symptom and medication scores in both arms, similar to the scores at the end of the initial trial. The authors concluded that clinical tolerance was maintained for at least two years after discontinuation of AIT.

Ott (2009; described above), at low ROB, failed to find a significant difference in long-term combined symptom and medication scores following discontinuation of SLIT grass pollen treatment ($P=0.052$).⁽¹³³⁾

Didier (2013) conducted a four year study, at unclear ROB, in which they randomized grass pollen allergic patients to SLIT commencing either four months pre-seasonally or two months pre-seasonally (i.e. two active groups) or placebo for three consecutive seasons.⁽¹⁰⁹⁾ This showed that both active treatment arms were beneficial in improving combined symptom and medication scores. They then continued to monitor patients for an additional fourth year (during which they did not receive SLIT or placebo), which found that the average adjusted symptom score (i.e. combined rhinoconjunctivitis symptom and medication score) was significantly improved in the SLIT groups when compared to placebo (two months pre-seasonal: $P=0.0019$; four months pre-seasonal: $P=0.01$). A further post-hoc analysis of this trial, was conducted at year five – i.e. two years after discontinuing AIT – and significant improvement was demonstrated in the four months group compared to placebo ($P=0.047$), but not in the two month preseasonal group.⁽¹⁵⁹⁾

Overall, one of the three trials found evidence of a sustained beneficial effect on combined symptom and medication scores. The one trial at an unclear ROB (Didier 2013/2015) demonstrated a two year carry over effect of AIT in the active SLIT group that received AIT four months pre-seasonally for three consecutive seasons but not for the group which received AIT two months pre-seasonally.

Secondary outcomes

Allergen challenge models in AIT

The data for these outcomes were not reported in a format suitable for undertaking meta-analysis. We therefore provide a narrative description below with a focus on those trials judged to be at low risk of bias (ROB).

Environmental exposure chamber

Four studies were conducted with the use of an Allergen Exposure Challenge (AEC): one using SCIT and three SLIT. Two were for cat allergy one for grass pollen and one for birch pollen.

The SCIT study by Patel (2012) was judged to be at low ROB.(65) This exposed cat allergic patients to allergen at baseline and at 22 weeks and 52 weeks after treatment with a short course of FelD1-derived peptide antigen SCIT (CatPad) using two different dosing regimens (8x3nmol or 4x6 nmol). Each assessment was undertaken over four consecutive days with three hours exposure to allergen in the EEC. Total rhinoconjunctivitis symptom scores (TRSS) were measured at these assessments. At the assessment at 50-54 weeks, the higher dose (4x6 nmol) treated patients had a significantly improved TRSS score compared to placebo (P=0.01), but the lower dose group did not (P=0.74).

The high ROB SLIT study with natural cat extract by Alvarez Cuesta (2007) involved a natural exposure challenge (NCT) to cat allergen in a cat room before and after treatment.(83) There was a significant improvement with SLIT compared to placebo (P<0.001). The remaining two SLIT studies used the Vienna Challenge Chamber (VCC). The SLIT study by Horak 1998 for birch pollen administered AIT for 28 days followed by a three-month maintenance period VCC measurements of nasal air flow were taken at baseline and at the end of the maintenance period which demonstrated a significant improvement in the active group. (P=0.03)(120) The Horak 2009 study of 5 grass pollen SLIT showed the active group had a significantly lower average rhinoconjunctivitis symptom score than the placebo group after four months of treatment (P=0.0003)(121)

All of these studies thus demonstrate the effectiveness of AIT in an environmental exposure chamber.

Nasal challenge

Twenty-six studies performed nasal allergen challenge tests, 15 SCIT (23,24,27,29,30,33,37,43,52,57–59,63,64,75) and 11 SLIT (Table 1a).(84,86,87,92,93,122,128,136,139,146,150).

SCIT trials

Of the 15 SCIT studies, eight showed a significant improvement in the SCIT group compared to placebo (24,27,29,37,43,52,58,75) and four showed no significant difference between the active and control groups. (23,33,57,59) The remaining three studies did not report a between group comparison, but both reported an improvement in the active group with a higher threshold of reactivity to allergen and no such change in the control group.(63,64,160)

Nine SCIT studies were at low ROB; of these four showed no significant difference between SCIT and control groups (23,33,57,59) and three studies showed a significant difference between active and control groups. (29,37,43) The remaining two studies did not report a between group comparison, but both reported a higher allergen threshold of reactivity in the active group and no such improvement in the control group.(63,64)

SLIT trials

Eleven SLIT studies reported on this outcome of which three studies showed no significant difference between active and control groups (87,128,146) and five studies showed a significant reduction in nasal reactivity in the SLIT group compared to controls.(86,93,122,139,150) Of the remaining three studies, two reported no between group data (92,136) and the other had two active groups: the single allergen SLIT group had a significant difference between placebo in nasal reactivity, but this was not the case for the multiple allergen SLIT group.(84)

Of these, three SLIT studies were at low ROB with varying conclusions. The Amar (2009) study showed a significant improvement in the single allergen SLIT group, but not in the multiple allergen group compared to placebo (P=0.03 and P=0.11, respectively).(84) Aydogan (2013) showed no significant

improvement in the SLIT group compared to placebo following one year of house dust mite (HDM) SLIT ($P > 0.05$).⁽⁸⁷⁾ Finally, Hirsch (1997) demonstrated a significant improvement in PC40 nasal flow in the SLIT group compared to placebo ($P < 0.05$).⁽¹²²⁾

Nasal challenge: Overall interpretation

Due to the conflicting results from higher quality SCIT and SLIT trials it is difficult to draw any clear conclusions in relation to this outcome.

Conjunctival challenge

Conjunctival challenges were undertaken in 16 studies: SCIT ($n=12$) (21,23,35,38,42,45,55,62,63,70,72,77) and SLIT ($n=4$) (Table 1b).^(120,127,138,146)

SCIT studies

Of the 12 SCIT studies that reported on this outcome, one showed graphical information only (62) and four reported no between group results.^(38,63,72,112) These studies will therefore not be considered further. Of the remaining seven studies, five showed no significant improvement in conjunctival provocation tests (CPT) between active and control groups^(21,23,45,55,70) and two showed an improvement.^(35,77)

Concentrating on the five low ROB SCIT studies, four studies showed no significant improvement in CPT in the SCIT group compared to control (21,23,45,70) whereas one demonstrated an improvement.⁽⁷⁷⁾

SLIT studies

Four SLIT studies reported on this outcome: two were at high ROB (127,146) and two at an unclear ROB.^(120,138) Two studies demonstrated a significant improvement in CPT in the SLIT group compared to placebo (127,138) one reported no significant improvement⁽¹⁴⁶⁾ and one reported no between group comparison. (120)

Conjunctival challenge: Overall interpretation

Four SCIT studies of high quality demonstrated that AIT is not effective in improving conjunctival provocation to allergen. There were no high quality SLIT studies that reported on this outcome, which makes it difficult to draw any firm conclusions.

Cost-effectiveness

Characteristics of studies

We identified 19 eligible studies that reported on health economic evaluations of SCIT and SLIT in both children and adults (Table 2). (160–178) Two of these 19 studies focused on patients who all had both allergic rhinitis and allergic asthma (177,178) and the remaining 17 focused on patients who had allergic rhinitis, some of whom also had asthma.

Three of these studies reported results solely from a societal perspective (160,161,180) with the other 16 reporting information from a health systems perspective.

Studies were based in a range of countries: Germany (n=7), Denmark (n=4), Italy (n=4), UK (n=4), Austria (n=2), Finland (n=2), France (n=2), the Netherlands (n=2), Sweden (n=2), Canada (n=1), Czech Republic (n=1), Norway (n=1) and Spain (n=1). Three studies reported results for more than one of these countries.

Seven of the studies reported results against disease specific outcome measures whilst the remaining 12 reported results based on quality adjusted life years (QALYs).

Thirteen of the studies were based on RCT data or meta-analyses of RCT data (160–169,176–178) including two model based evaluations (165,169) with the remaining studies being based on a mixture of questionnaires, observation data and expert opinion. None of the studies based on non-random data attempted to control for selection bias. None of the RCT-based studies described the amount of missing data in the study or explained how if at all any missing data were imputed for in the analyses.

Study time horizons ranged between one year and 15 years with the longer time horizon studies, of which the last were typically based on much shorter follow-up trial data (typically one year) and assuming constant continued treatment effect even after treatment was discontinued.

Nine of the studies compared SLIT versus standard care,(161,163,169,166–171,177,178) three studies compared SCIT versus standard care,(162,169,172) two studies compared AIT (undefined) versus standard care,(173,175) seven studies compared SCIT versus SLIT (160,165,167–169,174,176) and of these two studies compared different SLIT treatments.(165,167)

References

1. Mallol J, Crane J, von Mutius E, Odhiambo J, Keil U, Stewart A. International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three: A global synthesis. 2013;41:73–85.
2. Patil VK, Kurukulaaratchy RJ, Venter C, Grundy J, Roberts G, Dean T, et al. Changing prevalence of wheeze, rhinitis and allergic sensitisation in late childhood: findings from 2 Isle of Wight birth cohorts 12 years apart. *Clinical & Experimental Allergy*. 2015 Sep 1;45(9):1430-1438. Available from, DOI: 10.1111/cea.12534.
3. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A et al. (2008) Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy*. 2008 Apr;63 Suppl 86:8-160. doi: 10.1111/j.1398-9995.2007.01620.x
4. Skoner DP. Allergic rhinitis: definition, epidemiology, pathophysiology, detection, and diagnosis. *J Allergy Clin Immunol*. 2001 Jul;108(1 Suppl):S2-8
5. Walker S, Khan-Wasti S, Fletcher M, Cullinan P, Harris J, Sheikh A. Seasonal allergic rhinitis is associated with a detrimental effect on examination performance in United Kingdom teenagers: casecontrol study. *J Allergy Clin Immunol*. 2007 Aug;120(2):381-7. Epub 2007 Jun 8.
6. Blanc PD, Trupin L, Eisner M, Earnest G, Katz PP, Israel L et al. The work impact of asthma and rhinitis: findings from a population-based survey. *J Clin Epidemiol*. 2001;54:610–618

7. Guerra S1, Sherrill DL, Martinez FD, Barbee RA. Rhinitis as an independent risk factor for adult-onset asthma. *J Allergy Clin Immunol.* 2002;109(3):419–25.

8. Zuberbier T, Bachert C, Bousquet PJ, Passalacqua G, Walter Canonica G, Merk H, et al. GA² LEN/EAACI pocket guide for allergen-specific immunotherapy for allergic rhinitis and asthma. *Allergy* 2010;65:1525–30.

9. Walker SM, Durham SR, Till SJ, Roberts G, Corrigan CJ, Leech SC, et al. Immunotherapy for allergic rhinitis. *Clin Exp Allergy.* 2011;41:1177–200.

10. Pfaar O, Bachert C, Bufe A, Buhl R, Ebner C, Eng P et al. Guideline on allergen-specific immunotherapy in IgE mediated allergic diseases – S2k Guideline of the German Society for Allergy and Clinical Immunology (DGAKI), the Society for Pediatric Allergy and Environmental Medicine (GPA), the Medical Association of German Allergologists (AeDA), the Austrian Society for Allergy and Immunology (ÖGAI), the Swiss Society for Allergy and Immunology (SGAI), the German Society of Dermatology (DDG), the German Society of Oto Rhino-Laryngology, Head and Neck Surgery (DGHNO-KHC), the German Society of Pediatrics and Adolescent Medicine (DGKJ), the Society for Pediatric Pneumology (GPP), the German Respiratory Society (DGP), the German Association of ENT Surgeons (BV-HNO), the Professional Federation of Paediatricians and Youth Doctors (BVKJ), the Federal Association of Pulmonologists (BDP) and the German Dermatologists Association (BVDD). *Allergo J Int.* 2014;23:282–319

11. Hellings PW, Fokkens WJ, Akdis C, Bachert C, Cingi C, Dietz de Loos D, et al. Uncontrolled allergic rhinitis and chronic rhinosinusitis: where do we stand today? *Allergy* 2013;68:1–7.

12. Dhami S, Nurmatov U, Roberts G, Pfaar O, Muraro A, Ansotegui, I. Allergen immunotherapy for allergic rhinoconjunctivitis: protocol for a systematic review. *Clin Transl Allergy.* 2016;DOI: 10.1186/s13601-016-0099-6.

13. Cochrane Risk of bias tool
http://handbook.cochrane.org/chapter_8/table_8_5_a_the_cochrane_collaborations_tool_for_assessing.htm.

14. CASP checklist for Economic evaluations
http://media.wix.com/ugd/dded87_3b2bd5743feb4b1aac6ebdd68771d3f.pdf Last accessed on 3rd September 2016.

15. NICE Case Series Risk of Bias tool <https://www.nice.org.uk/guidance/cg3/resources/appendix-4-quality-of-case-series-form2>.

16. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.0.2 (Chapter 11, Section 11).

17. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315(629):34.
18. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994;50(1088):101.
19. Alvarez-Cuesta E, Aragonese-Gilsanz E, Martin-Garcia C, Berges-Gimeno P, Gonzalez-Mancebo E, Cuesta-Herranz J. Immunotherapy with depigmented glutaraldehyde-polymerized extracts: changes in quality of life.[Erratum appears in *Clin Exp Allergy*. 2005 Nov;35(11):1504]. *Clin Exp Allergy*. May 2005;35(5):572–8.
20. Ariano R, Kroon A. M, Augeri G, Canonica W, Passalacqua G. Long-term treatment with allergoid immunotherapy with *Parietaria*. Clinical and immunologic effects in a randomized, controlled trial. *Allergy*. Apr 1995;54(4):313–9.
21. Arvidsson MB, Lowhagen O, Rak S. Effect of 2-year placebo-controlled immunotherapy on airway symptoms and medication in patients with birch pollen allergy. *J Allergy Clin Immunol*. 2002;109(5):777–83.
22. Balda BR, Wolf H, Baumgarten C, Klimek L, Rasp G, Kunkel G, et al. Tree-pollen allergy is efficiently treated by short-term immunotherapy (STI) with seven preseasonal injections of molecular standardized allergens. *Allergy*. Aug;53(8):740–8.
23. Bodtger U, Poulsen LK, Jacobi HH, Malling HJ. The safety and efficacy of subcutaneous birch pollen immunotherapy - a one-year, randomised, double-blind, placebo-controlled study. *Allergy*. Apr 2002;57(4):297–305.
24. Bousquet J, Hejjaoui A, Skassa-Brociek W, Guerin B, Maasch HJ, Dhivert H, et al. Double-blind, placebo-controlled immunotherapy with mixed grass-pollen allergoids. I. Rush immunotherapy with allergoids and standardized orchard grass-pollen extract. *J Allergy Clin Immunol*. Oct 1987;80(4):591–8.
25. Bousquet J, Hejjaoui A, Soussana M, et al. Double-blind, placebo-controlled immunotherapy with mixed grass-pollen allergoids IV. Comparison of the safety and efficacy of two dosages of a high-molecular-weight allergoid. *J Allergy Clin Immunol*. 1990 Feb;85(2):490-7.
26. Bousquet J, Maasch HJ, Hejjaoui SA, et al. Double-blind, placebo-controlled immunotherapy with mixed grass-pollen allergoids III. Efficacy and safety of unfractionated and high-molecular-weight preparations in rhinoconjunctivitis and asthma. *J. Allergy Clinical Immunology* October 1989;84(4)1
27. Bousquet J, Becker WM, Hejjaoui A, et al. Differences in clinical and immunologic reactivity of patients allergic to grass poflens and to multiple-pollen species II. Efficacy of a double-blind, placebo-controlled, specific immunotherapy with standardized extracts. *J. Allergy Clinical Immunology* July 1991; 88(1)

28. Bozek A, Kolodziejczyk K, Krajewska-Wojtys A, Jarzab J. Pre-seasonal, subcutaneous immunotherapy: a double-blinded, placebo-controlled study in elderly patients with an allergy to grass. *Ann Allergy Asthma Immunol.* 2016;116(2):156–61.
29. Brunet C, Bedard PM, Lavoie A, et al. Allergic rhinitis to ragweed pollen I. Reassessment of the effects of immunotherapy cellular and humoral responses. *J. Allergy Clinical Immunology* Jan 1992; 89(1)1
30. Horst M, Hejjaoui A, Horst V, Michel FB, Bousquet J. Double-blind, placebo-controlled rush immunotherapy with a standardized *Alternaria* extract. *J Allergy Clin Immunol.* Feb 1990;85(2):460–72.
31. Ceuppens JL, Bullens D, Kleinjans H, van der Werf J, Purethal Birch Efficacy Study Group. Immunotherapy with a modified birch pollen extract in allergic rhinoconjunctivitis: clinical and immunological effects.[Erratum appears in *Clin Exp Allergy.* 2012 Oct;42(10):1543]. *Clin Exp Allergy.* Dec 2009;39(12):1903–9.
32. Chakraborty P, Roy I, Chatterjee S, Chanda S, Gupta-Bharracharya S. *Phoenix sylvestris* Roxb pollen allergy: a 2-year randomized controlled trial and follow-up study of immunotherapy in patients with seasonal allergy in an agricultural area of West Bengal, India. *J Investig Allergol Clin Immunol.* 2006;16(6):377–84.
33. Charpin D, Gouitaa M, Dron-Gonzalvez M, Fardeau MF, Massabie-Bouchat YP, Hugues B, et al. Immunotherapy with an aluminum hydroxide-adsorbed *Juniperus ashei* foreign pollen extract in seasonal indigenous cypress pollen rhinoconjunctivitis. A double-blind, placebo-controlled study. *Int Arch Allergy Immunol.* 2007;143(2):83–91.
34. Colas C, Monzon S, Venturini M, Lezaun A. Double-blind, placebo-controlled study with a modified therapeutic vaccine of *Salsola kali* (Russian thistle) administered through use of a cluster schedule. *J Allergy Clin Immunol.* Apr 2006;117(4):810–6.
35. Corrigan CJ for the Study Group*, Kettner J, Doemer C, Cromwell O, Narkus A. Efficacy and safety of preseasonal-specific immunotherapy with an aluminium-adsorbed six-grass pollen allergoid. *Allergy* 2005; 60: 801–807
36. Crimi N, Li Gotti F, Mangano G, Paolino G, Mastruzzo C, Vancheri C, et al. A randomized, controlled study of specific immunotherapy in monosensitized subjects with seasonal rhinitis: effect on bronchial hyperresponsiveness, sputum inflammatory markers and development of asthma symptoms. *Ann Ital Med Int.* Apr 2004;19(2):98–108.
37. Dokic D, Schnitker J, Narkus A, Cromwell O, Frank E. Clinical effects of specific immunotherapy: a two-year double-blind, placebo-controlled study with a one year follow-up. *Makedon Akad Na Nauk Umet Oddelenie Za Biološki Meditsinski Nauki Pril. Contributions, Sci. Biol. Med. Sci.* XXVI/2 (2005) Dec;26(2):113–29.

38. Dolz I, Martinez-Cocera C, Bartolome JM, Cimarra M. A double-blind, placebo-controlled study of immunotherapy with grass-pollen extract Alutard SQ during a 3-year period with initial rush immunotherapy. *Allergy*. Jul 1996;51(7):489–500.
39. Drachenberg KJ, Wheeler AW, Stuebner P, Horak F. A well-tolerated grass pollen-specific allergy vaccine containing a novel adjuvant, monophosphoryl lipid A, reduces allergic symptoms after only four preseasonal injections. *Allergy* 2001; 56: 498–505
40. Drachenberg K, Heinzkill M, Urban E. Short-term immunotherapy with tree pollen allergoids and the adjuvant monophosphoryl lipid-A - Results from a multicentre, placebo-controlled, randomised, double-blind study..[Kurzzeit-Immuntherapie mit Baumpollen- Allergoiden und dem Adjuvans Monophosphoryl Lipid-A]. *Allergologie*. 2002 Jahrgang , Nr. 9;S. 466–474.
41. DuBuske L, Frew A, Horak F, Keith P, Corrigan C, Aberer W. Ultrashort-specific immunotherapy successfully treats seasonal allergic rhinoconjunctivitis to grass pollen. *Allergy Asthma Proc*. 2011;32(3):239–47.
42. Durham SR, Walker SM, Varga EM, Jacobson MR, O'Brien F, Noble W, et al. Long-term clinical efficacy of grass-pollen immunotherapy. *N Engl J Med*. Aug 1999;12;341(7):468–75.
43. Ewan PW, Alexander MM, Snape C, Ind PW, Agrell B, Dreborg S. Effective hyposensitization in allergic rhinitis using a potent partially purified extract of house dust mite. *Clin Allergy*. Sep 1988;18(5):501–8.
44. Fell P, Brostoff J. A single dose desensitization for summer hay fever. Results of a double blind study-1988. *Eur J Clin Pharmacol*. 1990;38(1):77–9.
45. Ferrer M, Burches E, Peláez A, Muñoz A, Hernández D, Basomba A, et al. Double-blind, placebo-controlled study of immunotherapy with *Parietaria judaica*: Clinical efficacy and tolerance. *J Invest Allergol Clin Immunol* 2005; Vol. 15(4): 283-292
46. Frew AJ, Powell RJ, Corrigan CJ, Durham SR, U. K. Immunotherapy Study Group. Efficacy and safety of specific immunotherapy with SQ allergen extract in treatment-resistant seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol*. Feb 2006;117(2):319–25.
47. Grammer LC, Zeiss CR, Suszko IM, et al. A double-blind, placebo-controlled trial of polymerized whole ragweed for immunotherapy of ragweed allergy. *Allergy Clin Immunology* June 1982;69(6)
48. Grammer LC, Shaughnessy MA, Suszko IM, Shaughnessy JJ, Patterson R. A double-blind histamine placebo-controlled trial of polymerized whole grass for immunotherapy of grass allergy. *J Allergy Clin Immunol*. Nov 1983;72(5 Pt 1):448–53.
49. Grammer LC, Shaughnessy MA, Suszko IM, , et al. Persistence of efficacy after a brief course of polymerized ragweed allergen: A controlled study. *J Allergy Clin Immunol* April 1984; 73(4)

50. Grammer LC, Shaughnessy MA, Bernhard MI, Finkle SM, Pyle HR, Silvestri L, et al. The safety and activity of polymerized ragweed: a double-blind, placebo-controlled trial in 81 patients with ragweed rhinitis. *J Allergy Clin Immunol.* Aug 1987;80(2):177–83.
51. Hoiby AS, Strand V, Robinson DS, Sager A, Rak S. Efficacy, safety, and immunological effects of a 2-year immunotherapy with Depigoid birch pollen extract: a randomized, double-blind, placebo-controlled study. *Clin Exp Allergy.* Jul 2010;40(7):1062–70.
52. Iliopoulos O, Proud D, Franklin Adkinson N, Jr., et al. Effects of immunotherapy on the early, late, and rechallenge nasal reaction to provocation with allergen: Changes in inflammatory mediators and cells. *J Allergy Clin Immunol.* April 1991; 87(4)
53. James LK, Shamji MH, Walker SM, Wilson DR, Wachholz PA, Francis JN, et al. Long-term tolerance after allergen immunotherapy is accompanied by selective persistence of blocking antibodies. *J Allergy Clin Immunol.* Feb 2011;127(2):509-516-5.
54. Juniper EF, Kline PA, Ramsdale EH, Hargreave FE. Comparison of the efficacy and side effects of aqueous steroid nasal spray (budesonide) and allergen-injection therapy (Pollinex-R) in the treatment of seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol.* Mar 1990;85(3):606–11.
55. Jutel M, Jaeger L, Suck R, Meyer H, Fiebig H, Cromwell O. Allergen-specific immunotherapy with recombinant grass pollen allergens. *J Allergy Clin Immunol.* Sep 2005;116(3):608–13.
56. Kleine-Tebbe J, Walmar M, Bitsch-Jensen K, Decot E, Pfaar O., de Rojas DH, et al. Negative clinical results from a randomised, double-blind, placebo-controlled trial evaluating the efficacy of two doses of immunologically enhanced, grass subcutaneous immunotherapy despite dose-dependent immunological response. *Clin Drug Investig.* Aug 2014;34(8):577–86.
57. Klimek L, Uhlig J, Mosges R, Rettig K, Pfaar O. A high polymerized grass pollen extract is efficacious and safe in a randomized double-blind, placebo-controlled study using a novel up-dosing cluster-protocol. *Allergy.* Dec 2014;69(12):1629–38.
58. Kuna P, Kaczmarek J, Kupczyk M. Efficacy and safety of immunotherapy for allergies to *Alternaria alternata* in children. *J Allergy Clin Immunol.* Feb 2011;127(2):502-508-6.
59. Leynadier F, Banoun L, Dollois B, Terrier P, Epstein M, Guinépain MT, et al. Immunotherapy with a calcium phosphate-adsorbed five-grass-pollen extract in seasonal rhinoconjunctivitis: a double-blind, placebo-controlled study. *Clin Exp Allergy.* 2001;31(7):988–96.
60. Metzger WJ, Dorminey HC, Richerson HB, et al. Clinical and immunologic evaluation of glutaraldehyde-modified, tyrosine-adsorbed short ragweed extract: a double-blind, placebo-controlled trial. *J Allergy Clin Immunol.* Dec 1981;68(6)
61. Mirone C, Albert F, Tosi A, Mochetti F, Mosca S, Giorgino M, et al. Efficacy and safety of subcutaneous immunotherapy with a biologically standardized extract of *Ambrosia artemisiifolia* pollen: a double-blind, placebo-controlled study. *Clin Exp Allergy.* Sep 2004;34(9):1408–14.

62. Olsen OT, Frølund L, Heinig J, Jacobsen L, Svendsen UG. A double-blind, randomized study investigating the efficacy and specificity of immunotherapy with *Artemisia vulgaris* or *Phleum pratense/betula verrucosa*. *Allergol Immunopathol (Madr)*. 1995;23(2):73–8.
63. Ortolatii C, Pastorello EA, Iticorvaia C, Ispatio M, Farioli L, Zara C, et al. A double-blind, placebo-controlled study of immunotherapy with an alginate-conjugated extract of *Parietaria Judaica* in patients with *Parietaria* hay fever. *Allergy* 1994;49:13-21
64. Pastorello EA, Pravettoni V, Incorvaia C, Mambretti M, et al. Clinical and immunological effects of immunotherapy with alum-absorbed grass allergoid in grass-pollen-induced hay fever. *Allergy* 1992; 47: 281-290.
65. Patel D, Couroux P, Hickey P, Salapatek AM, Laidler P, Larche M, et al. Fel d 1-derived peptide antigen desensitization shows a persistent treatment effect 1 year after the start of dosing: a randomized, placebo-controlled study. *J Allergy Clin Immunol*. Jan 2012;131(1):103-9-7.
66. Pauli G, Larsen TH, Rak S, Horak F, Pastorello E, Valenta R, et al. Efficacy of recombinant birch pollen vaccine for the treatment of birch-allergic rhinoconjunctivitis.[Erratum appears in *J Allergy Clin Immunol*. 2009 Jan;123(1):166 Note: Valenta, Rudolph [corrected to Valenta, Rudolf]]. *J Allergy Clin Immunol*. Nov 2008;122(5):951–60.
67. Pfaar O, Robinson D, Sager A, Emuzyte R. . Immunotherapy with depigmented-polymerized mixed tree pollen extract: a clinical trial and responder analysis. *Allergy*. 2010;65(12):1614–21.
68. Pfaar O, Urry Z, Robinson DS, Sager A, Richards D, Hawrylowicz CM, et al. A randomized placebo-controlled trial of rush preseasonal depigmented polymerized grass pollen immunotherapy. *Allergy*. Feb 2012;67(2):272–9.
69. Powell RJ, Frew AJ, Corrigan CJ, Durham SR. Effect of grass pollen immunotherapy with Alutard SQ on quality of life in seasonal allergic rhinoconjunctivitis. *Allergy*. Nov 2007;62(11):1335–8.
70. Radcliffe MJ, Lewith GT, Turner RG, Prescott P, Church MK, Holgate ST. Enzyme potentiated desensitisation in treatment of seasonal allergic rhinitis: double blind randomised controlled study. *BMJ*. 2003;327(7409):251–4.
71. Rak S, Heinrich C, Jacobsen L, Scheynius A, Venge P. A double-blinded, comparative study of the effects of short preseason specific immunotherapy and topical steroids in patients with allergic rhinoconjunctivitis and asthma. *J Allergy Clin Immunol*. Dec 2001;108(6):921–8.
72. Riechelmann H, Schmutzhard J, van der Werf JF, Distler A, Kleinjans HA. Efficacy and safety of a glutaraldehyde-modified house dust mite extract in allergic rhinitis. *Am J Rhinol Allergy*. Sep 2010;24(5):e104-9.
73. Tabar AI, Echechipia S, Garcia BE, Olaguibel JM, Lizaso MT, Gomez B, et al. Double-blind comparative study of cluster and conventional immunotherapy schedules with *Dermatophagoides pteronyssinus*. *J Allergy Clin Immunol*. Jul 2005;116(1):109–18.

74. Tabar AI, Lizaso MT, Garcia BE, Gomez B, Echechipia S, Aldunate MT, et al. Double-blind, placebo-controlled study of *Alternaria alternata* immunotherapy: Clinical efficacy and safety. *Pediatr Allergy Immunol*. Feb 2008;19(1):67–75.
75. Tari MG, Mancino M, Ghezzi E, Frank E, Cromwell O. Immunotherapy with an alum-adsorbed *Parietaria-pollen* allergoid: a 2-year, double-blind, placebo-controlled study. *Allergy*. Jan 1997;52(1):65–74.
76. Tworek D, Bochenska-Marciniak M, Kuprys-Lipinska I, Kupczyk M, Kuna P. Perennial is more effective than preseasonal subcutaneous immunotherapy in the treatment of seasonal allergic rhinoconjunctivitis. *Am J Rhinol Allergy*. Jul 2013;27(4):304–8.
77. Varney VA, Tabbah K, Mavroleon G, Frew AJ. Usefulness of specific immunotherapy in patients with severe perennial allergic rhinitis induced by house dust mite: a double-blind, randomized, placebo-controlled trial. *Clin Exp Allergy*. Aug 1991;33(8):1076–82.
78. Varney VA, Gaga M, Frew AJ, Aber VR, Kay AB, Durham SR. Usefulness of immunotherapy in patients with severe summer hay fever uncontrolled by antiallergic drugs. *BMJ*. 1991;302(6771):265–9.
79. Walker SM, Pajno GB, Lima MT, Wilson DR, Durham SR. Grass pollen immunotherapy for seasonal rhinitis and asthma: a randomized, controlled trial. *J Allergy Clin Immunol*. Jan 2001;107(1):87–93.
80. Weyer A, Donat N, L'Heritier C, Juilliard F, Pauli G, Soufflet B, et al. Grass pollen hyposensitization versus placebo therapy. I. Clinical effectiveness and methodological aspects of a pre-seasonal course of desensitization with a four-grass pollen extract. *Allergy*. Jul 1981;36(5):309–17.
81. Zenner HP, Baumgarten C, Rasp G, Fuchs T, Kunkel G, Hauswald B, et al. Short-term immunotherapy: a prospective, randomized, double-blind, placebo-controlled multicenter study of molecular standardized grass and rye allergens in patients with grass pollen-induced allergic rhinitis. *J Allergy Clin Immunol*. Jul 1997;100(1):23–9.
82. Ahmadiafshar A, Maarefvand M, Taymourzade B, Mazloomzadeh S, Torabi Z. Efficacy of sublingual swallow immunotherapy in children with rye grass pollen allergic rhinitis: a double-blind placebo-controlled study. *Iran J Allergy Asthma Immunol*. Jun 2012;11(2):175–81.
83. Alvarez-Cuesta E, Berges-Gimeno P, Gonzalez-Mancebo E, Fernandez-Caldas E, Cuesta-Herranz J, Casanovas M. Sublingual immunotherapy with a standardized cat dander extract: evaluation of efficacy in a double blind placebo controlled study.[Erratum appears in *Allergy*. 2007 Sep;62(9):1100 Note: Mancebo, E G [corrected to Gonzalez-Mancebo, E]]. *Allergy*. Jul 2007;62(7):810–7.
84. Amar SM, Harbeck RJ, Sills M, Silveira LJ, O'Brien H, Nelson HS. Response to sublingual immunotherapy with grass pollen extract: monotherapy versus combination in a multiallergen extract. *J Allergy Clin Immunol*. Jul 2009;124(1):150-156-5.
85. Andre C, Perrin-Fayolle M, Grosclaude M, Couturier P, Basset D, Cornillon J, et al. A double-blind placebo-controlled evaluation of sublingual immunotherapy with a standardized ragweed

extract in patients with seasonal rhinitis. Evidence for a dose-response relationship. *Int Arch Allergy Immunol.* Jun 2003;131(2):111–8.

86. Ariano R, Spadolini I, Panzani RC. Efficacy of sublingual specific immunotherapy in Cupressaceae allergy using an extract of *Cupressus arizonica*. A double blind study. *Allergol Immunopathol (Madr).* Nov 2001;29(6):238–44.
87. Aydogan M, Eifan AO, Keles S, Akkoc T, Nursoy MA, Bahceciler NN, et al. Sublingual immunotherapy in children with allergic rhinoconjunctivitis mono-sensitized to house-dust-mites: a double-blind-placebo-controlled randomised trial. *Respir Med.* Sep 2013;107(9):1322–9.
88. Bahçeciler NN, ik UI, Barlan IB, Ba?aran MM. Efficacy of sublingual immunotherapy in children with asthma and rhinitis: a double-blind, placebo-controlled study. *Pediatr Pulmonol.* 2001;32(1):49–55.
89. Bergmann KC, Demoly P, Worm M, Fokkens WJ, Carrillo T, Tabar AI, et al. Efficacy and safety of sublingual tablets of house dust mite allergen extracts in adults with allergic rhinitis. *J Allergy Clin Immunol.* Jun 2013;133(6):1608–14.e6.
90. Blaiss M, Maloney J, Nolte H, Gawchik S, Yao R, Skoner SP. Efficacy and safety of timothy grass allergy immunotherapy tablets in North American children and adolescents. *Pediatrics.* Oct;128(SUPPL. 3):S136.
91. Bowen T, Greenbaum J, Charbonneau Y, Hebert J, Filderman R, Sussman G, et al. Canadian trial of sublingual swallow immunotherapy for ragweed rhinoconjunctivitis. *Ann Allergy Asthma Immunol.* Nov 2004;93(5):425–30.
92. Bozek A, Ignasiak B, Filipowska B, Jarzab J. House dust mite sublingual immunotherapy: a double-blind, placebo-controlled study in elderly patients with allergic rhinitis. *Clin Exp Allergy.* Feb 2012;43(2):242–8.
93. Bozek A, Kolodziejczyk K, Warkocka-Szolysek B, Jarzab J. Grass pollen sublingual immunotherapy: a double-blind, placebo-controlled study in elderly patients with seasonal allergic rhinitis. *Am J Rhinol Allergy.* Sep 2014;28(5):423–7.
94. Bufe A, Ziegler-Kirbach E, Stoeckmann E, Heidemann P, Gehlhar K, Holland-Letz T, et al. Efficacy of sublingual swallow immunotherapy in children with severe grass pollen allergic symptoms: a double-blind placebo-controlled study. *Allergy.* May 2004;59(5):498–504.
95. Bufe A, Eberle P, Franke-Beckmann E, Funck J, Kimmig M, Klimek L, et al. Safety and efficacy in children of an SQ-standardized grass allergen tablet for sublingual immunotherapy. *J Allergy Clin Immunol.* Jan 2009;123(1)
96. Caffarelli C, Sensi LG, Marcucci F, Cavagni G. Preseasonal local allergoid immunotherapy to grass pollen in children: a double-blind, placebo-controlled, randomized trial. *Allergy.* Dec 2000;55(12):1142–7.
97. Clavel R, Bousquet J, Andre C. Clinical efficacy of sublingual-swallow immunotherapy: a double-blind, placebo-controlled trial of a standardized five-grass-pollen extract in rhinitis. *Allergy* 1998;53:493-498

98. Cortellini G, Spadolini I, Patella V, Fabbri E, Santucci A, Severino M, et al. Sublingual immunotherapy for *Alternaria*-induced allergic rhinitis: a randomized placebo-controlled trial. *Ann Allergy Asthma Immunol*. Nov 2010;105(5):382–6.
99. Cox LS, Casale TB, Nayak AS, Bernstein DI, Creticos P[S, Ambroisine L, et al. Clinical efficacy of 300IR 5-grass pollen sublingual tablet in a US study: the importance of allergen-specific serum IgE. *J Allergy Clin Immunol*. Dec 2012;130(6):1327–34.e1.
100. Creticos PS, Maloney J, Bernstein DI, Casale T, Kaur A, Fisher R, et al. Randomized controlled trial of a ragweed allergy immunotherapy tablet in North American and European adults. *J Allergy Clin Immunol*. May 2013;131(5):1342–9.e6.
101. Creticos PS, Esch RE, Couroux P, Gentile D, D'Angelo P, Whitlow B, et al. Randomized, double-blind, placebo-controlled trial of standardized ragweed sublingual-liquid immunotherapy for allergic rhinoconjunctivitis.[Erratum appears in *J Allergy Clin Immunol*. 2014 May;133(5):1502]. *J Allergy Clin Immunol*. Mar 2013;133(3):751–8.
102. Dahl R, Kapp A, Colombo G, de Monchy JG, Rak S, Emminger W, et al. Efficacy and safety of sublingual immunotherapy with grass allergen tablets for seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol*. Aug 2006;118(2):434–40.
103. Dahl R, Stender A, Rak S. Specific immunotherapy with SQ standardized grass allergen tablets in asthmatics with rhinoconjunctivitis. *Allergy*. Feb 2006;61(2):185–90.
104. de Blay F, Barnig C, Kanny G, Purohit A, Leynadier F, Tunon de Lara JM, et al. Sublingual-swallow immunotherapy with standardized 3-grass pollen extract: a double-blind, placebo-controlled study. *Ann Allergy Asthma Immunol*. Nov 2007;99(5):453–61.
105. Demoly P, Emminger W, Rehm D, Backer V, Tommerup L, Kleine-Tebbe J. Effective treatment of house dust mite-induced allergic rhinitis with 2 doses of the SQ HDM SLIT-tablet: Results from a randomized double-blind, placebo-controlled phase III trial. *J Allergy Clin Immunol* [Internet]. 2015 Aug; Available from: <http://www.ncbi.nlm.nih.gov/pubmed/26292778>
106. de Bot CMA, Moed H, Berger MY, Roder E, Hop WCJ, Groot H, et al. Sublingual immunotherapy not effective in house dust mite-allergic children in primary care. *Pediatr Allergy Immunol*. 2012;23(2):151–9.
107. Didier A, Malling HJ, M. Worm, F. Horak, S. Jäger, A. Montagut, et al. Optimal dose, efficacy, and safety of once-daily sublingual immunotherapy with a 5-grass pollen tablet for seasonal allergic rhinitis. *J Allergy Clin Immunol*. 2007;120(6):1338–45.
108. Didier A, Melac M, Montagut A, Lheritier-Barrand M, Tabar A, Worm M. Agreement of efficacy assessments for five-grass pollen sublingual tablet immunotherapy. *Allergy*. Jan 2009;64(1):166–71.
109. Didier A, Malling HJ, Worm M, Horak F, Sussman G, Melac M, et al. Post-treatment efficacy of discontinuous treatment with 300IR 5-grass pollen sublingual tablet in adults with grass pollen-induced allergic rhinoconjunctivitis. *Clin Exp Allergy*. May 2013;43(5):568–77.

110. Durham SR, Yang WH, Pedersen MR, Johansen N, Rak S. Sublingual immunotherapy with once-daily grass allergen tablets: a randomized controlled trial in seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol*. Apr 2005;117(4):802–9.
111. Durham SR, Riis B. Grass allergen tablet immunotherapy relieves individual seasonal eye and nasal symptoms, including nasal blockage. *Allergy*. Aug 2007;62(8):954–7.
112. Durham SR, Emminger W, Kapp A, Colombo G, de Monchy JG, Rak S, et al. Long-term clinical efficacy in grass pollen-induced rhinoconjunctivitis after treatment with SQ-standardized grass allergy immunotherapy tablet. *J Allergy Clin Immunol*. Jan 2009;125(1):131-8-7.
113. Durham SR, G. T. investigators. Sustained effects of grass pollen AIT. *Allergy*. Jul 2011;66 Suppl 95:50–2.
114. Durham SR, Emminger W, Kapp A, de Monchy JG, Rak S, Scadding GK, et al. SQ-standardized sublingual grass immunotherapy: confirmation of disease modification 2 years after 3 years of treatment in a randomized trial. *J Allergy Clin Immunol*. Mar 2012;129(3):717–725.e5.
115. Drachenberg KJ, Pfeiffer P, Urban E. Sublingual immunotherapy - Results from a multi-centre, randomised, double-blind, placebo-controlled study with a standardised birch and grass/rye pollen extract. [German]. *Allergologie*. 2001;24(11):525–34.
116. Feliziani V, Lattuada G, Parmiani S, Dall’Aglia PP. Safety and efficacy of sublingual rush immunotherapy with grass allergen extracts. A double blind study. *Allergy* 1992; 47:281-290
117. Frolund L, Durham SR, Calderon M, Emminger W, Andersen JS, Rask P, et al. Sustained effect of SQ-standardized grass allergy immunotherapy tablet on rhinoconjunctivitis quality of life. *Allergy*. Jun 2010; 1;65(6):753–7.
118. Guez S, Vatrinet C, Fadel R, Andre C. House-dust-mite sublingual-swallow immunotherapy (SLIT) in perennial rhinitis: a double-blind, placebo-controlled study. *Allergy* 2000; 55: 369-375
119. Halken S, Agertoft L, Seidenberg J, Bauer CP, Payot F, Martin-Munoz MF, et al. Five-grass pollen 300IR SLIT tablets: efficacy and safety in children and adolescents. *Pediatr Allergy Immunol*. Sep 2010;21(6):970–6.
120. Horak F, Stübner P, Berger UE, Marks B, Toth J, Jäger S. Immunotherapy with sublingual birch pollen extract. A short-term double-blind placebo study. *J Investig Allergol Clin Immunol*. 1998;8(3):165–71.
121. Horak F, Zieglmayer P, Zieglmayer R, Lemell P, Devillier P, Montagut A, et al. Early onset of action of a 5-grass-pollen 300-IR sublingual immunotherapy tablet evaluated in an allergen challenge chamber. *J Allergy Clin Immunol*. Sep 2009;124(3):471–477.e1.
122. Hirsch T, Sahn M, Leupold W. Double-blind placebo-controlled study of sublingual immunotherapy with house dust mite extract (D.pt.) in children. *Paediatric Allergy and Immunol*. 1997;8; 21-27

123. Hordijk GJ, Antvelink JB, Luwema RA. Sublingual immunotherapy with a standardised grass pollen extract: a double-blind, placebo-controlled study. *Allergol. Et immunopathol.*, 1998;26(5):234-240
124. Ibañez MD, Kaiser F, Knecht R, Armentia A, Schöpfer H, Tholstrup B, et al. Safety of specific sublingual immunotherapy with SQ standardized grass allergen tablets in children. *Pediatr Allergy Immunol* 2007; 18: 516–522
125. Ippoliti F, De Santis W, Volterrani A, Lenti L, Canitano N, Lucarelli S, et al. Immunomodulation during sublingual therapy in allergic children. *Pediatr Allergy Immunol* 2003; 14: 216–221
126. Kaluzinska-Parzyszek I, Majak P, Jerzynska J, Smejda K, Stelmach I. Sublingual immunotherapy is effective and safe in children. *Alerg Astma Immunol.* 2011;16(3):139–44.
127. La Rosa M, Ranno C, Andre C, Carat F, Tosca MA, Canonica GW. Double-blind placebo-controlled evaluation of sublingual-swallow immunotherapy with standardized *Parietaria judaica* extract in children with allergic rhinoconjunctivitis. *J Allergy Clin Immunol.* Aug 1999;104(2 Pt 1):425–32.
128. Marcucci F, Sensi L, Frati F, Bernardini R, Novembre E, Barbato A, et al. Effects on inflammation parameters of a double-blind, placebo controlled one-year course of SLIT in children monosensitized to mites. *Allergy.* Jul 2003;58(7):657–62.
129. Moreno-Ancillo A, Moreno C, Ojeda P, Domínguez C, Barasona MJ, García-Cubillana A, et al. Efficacy and quality of life with once-daily sublingual immunotherapy with grasses plus olive pollen extract without up dosing. *J Investig Allergol Clin Immunol.* 2007;17(6):399–405.
130. Mosbech H, Canonica GW, Backer V, de Blay F, Klimek L, Broge L, et al. SQ house dust mite sublingually administered immunotherapy tablet (ALK) improves allergic rhinitis in patients with house dust mite allergic asthma and rhinitis symptoms. *Ann Allergy Asthma Immunol.* Feb 2014;114(2):134–40.
131. Mosges R, Bruning H, Hessler HJ, Gotz G, Knaussmann HG. Sublingual immunotherapy in pollen-induced seasonal rhinitis and conjunctivitis: a randomized controlled trial. *Acta Dermatovenerol Alp Panon Adriat.* Dec 2007;16(4):143–8.
132. Okubo K, Gotoh M, Fujieda S, Okano M, Yoshida H, Morikawa H, et al. A randomized double-blind comparative study of sublingual immunotherapy for cedar pollinosis. *Allergol Int.* Sep 2008;57(3):265–75.
133. Ott H, Sieber J, Brehler R, Folster-Holst R, Kapp A, Klimek L, et al. Efficacy of grass pollen sublingual immunotherapy for three consecutive seasons and after cessation of treatment: the ECRIT study.[Erratum for *Allergy.* 2009 Jan;64(1):179-86; PMID: 19076534]. *Allergy.* Sep 2009;64(9):1394–401.

134. Nelson HS, Oppenheimer J, Vatsia GA, Buchmeier A. A double-blind, placebo-controlled evaluation of sublingual immunotherapy with standardized cat extract. *J Allergy Clin Immunol.* Aug 1993;92(2)
135. Pajno GB, Vita D, Parmiani S, Caminiti L, La Grutta S, Barberio G. Impact of sublingual immunotherapy on seasonal asthma and skin reactivity in children allergic to *Parietaria* pollen treated with inhaled fluticasone propionate. *Clin Exp Allergy.* Dec 2003;33(12):1641–7.
136. Palma-Carlos AG, Santos AS, Branco-Ferreira M, Pregal AL, Palma-Carlos ML, Bruno ME, et al. Clinical efficacy and safety of preseasonal sublingual immunotherapy with grass pollen carbamylated allergoid in rhinitic patients. A double-blind, placebo-controlled study. *Allergol Immunopathol (Madr).* Sep 2006;34(5):194–8.
137. Panzner P, Petrás M, Sýkora T, Lesná I. Double-blind, placebo-controlled evaluation of grass pollen specific immunotherapy with oral drops administered sublingually or supralingually. *Respir Med.* 2008;102(9):1296–304.
138. Passalacqua G, Albano M, Fregonese L, Riccio A, Pronzato C, Mela GS, et al. Randomised controlled trial of local allergoid immunotherapy on allergic inflammation in mite-induced rhinoconjunctivitis. *Lancet.* Feb 1998;28;351(9103):629–32.
139. Passalacqua G, Albano M, Riccio A, Fregonese L, Puccinelli P, Parmiani S, et al. Clinical and immunologic effects of a rush sublingual immunotherapy to *Parietaria* species: A double-blind, placebo-controlled trial. *J Allergy Clin Immunol.* Nov 1999;104(5):964–8.
140. Passalacqua G, Pasquali M, Ariano R, Lombardi C, Giardini A, Baiardini I, et al. Randomized double-blind controlled study with sublingual carbamylated allergoid immunotherapy in mild rhinitis due to mites. *Allergy.* 2006;61(7):849–54.
141. Pfaar O, Klimek L. Efficacy and safety of specific immunotherapy with a high-dose sublingual grass pollen preparation: a double-blind, placebo-controlled trial. *Ann Allergy Asthma Immunol.* 2008;100:256–263.
142. Pradalier A, Basset D, Claudel A, Couturier P, Wessel F, Galvain S, et al. Sublingual-swallow immunotherapy (SLIT) with a standardized five-grass-pollen extract (drops and sublingual tablets) versus placebo in seasonal rhinitis. *Allergy.* Aug 1999;54(8):819–28.
143. Purello-D'Ambrosio F, Gangemi S, Isola S, La Motta N, Puccinelli P, Parmiani S, et al. Sublingual immunotherapy: a double-blind, placebo-controlled trial with *Parietaria judaica* extract standardized in mass units in patients with rhinoconjunctivitis, asthma, or both. *Allergy.* Sep 1999;54(9):968–73.
144. Queiros MG, Silva DA, Siman IL, Ynoue LH, Araujo NS, Pereira FL, et al. Modulation of mucosal/systemic antibody response after sublingual immunotherapy in mite-allergic children. *Pediatr Allergy Immunol.* Dec 2013;24(8):752–61.

145. Rak S, Yang WH, Pedersen MR, Durham SR. Once-daily sublingual allergen-specific immunotherapy improves quality of life in patients with grass pollen-induced allergic rhinoconjunctivitis: a double-blind, randomised study. *Qual Life Res.* Mar 2006;16(2):191–201.
146. Rolinck-Werninghaus C, Wolf H, Liebke C, Baars JC, Lange J, Kopp MV. A prospective, randomized, double-blind, placebo-controlled multi-centre study on the efficacy and safety of sublingual immunotherapy (SLIT) in children with seasonal allergic rhino-conjunctivitis to grass pollen. *Allergy* 2004; 59: 1285–1293
147. Sabbah A, Hassoun S, Le Sellin J, Andre C, Sicard H. A double-blind, placebo-controlled trial by the sublingual route of immunotherapy with a standardized grass pollen extract. *Allergy.* May 1994;49(5):309–13.
148. Stelmach I, Kaluzinska-Parzyszek I, Jerzynska J, Stelmach P, Stelmach W, Majak P. Comparative effect of pre-coseasonal and continuous grass sublingual immunotherapy in children. *Allergy.* Mar 2012;67(3):312–20.
149. Roder E, Berger MY, Groot H, Wijk RG. Immunotherapy in children and adolescents with allergic rhinoconjunctivitis: a systematic review (Structured abstract). *Pediatr Allergy Immunol.* 2008;19(3):197–207.
150. Tari MG, Mancino M, Monti G. Efficacy of sublingual immunotherapy in patients with rhinitis and asthma due to house dust mite. A double-blind study. *Allergol Immunopathol (Madr).* Sep 1990;18(5):277–84.
151. Valovirta E, Jacobsen L, Ljørring C, Koivikko A, Savolainen J. Clinical efficacy and safety of sublingual immunotherapy with tree pollen extract in children. *Allergy.* 2006;61(10):1177–83.
152. Van Niekerk CH, De Wet JJ. Efficacy of grass-maize pollen oral immunotherapy in patients with seasonal hay-fever: a double-blind study. *Clin Allergy.* Nov 1987;17(6):507–13.
153. Vourdas D, Syrigou E, Potamianou P, Carat F, Batard T, Andre C, et al. Double-blind, placebo-controlled evaluation of sublingual immunotherapy with standardized olive pollen extract in pediatric patients with allergic rhinoconjunctivitis and mild asthma due to olive pollen sensitization. *Allergy.* Jul 1998;53(7):662–72.
154. Wang DH, Chen L, Cheng L, Li KN, Yuan H, Lu JH, et al. Fast onset of action of sublingual immunotherapy in house dust mite-induced allergic rhinitis: a multicenter, randomized, double-blind, placebo-controlled trial. *Laryngoscope.* Jun 2013;123(6):1334–40.
155. Wahn U, Klimek L, Ploszczuk A, Adelt T, Sandner B, Trebas-Pietras E, et al. High-dose sublingual immunotherapy with single-dose aqueous grass pollen extract in children is effective and safe: a double-blind, placebo-controlled study. *J Allergy Clin Immunol.* Oct 2012;130(4):886–93.e5.
156. Wahn U, Tabar A, Kuna P, Halken S, Montagut A, de Beaumont O, et al. Efficacy and safety of 5-grass-pollen sublingual immunotherapy tablets in pediatric allergic rhinoconjunctivitis. *J Allergy Clin Immunol.* Jan 2009;123(1):160–166.e3.

157. Hylander T, Larsson O, Petersson-Westin U, Eriksson M, Kumlien Georén S, Winqvist O. Intralymphatic immunotherapy of pollen-induced rhinoconjunctivitis: a double-blind placebo-controlled trial. *Respir Res.* 2016;DOI: 10.1186/s12931-016-0324-9.
158. Senti G, Cramer R, Kuster D, Johansen P, Martinez-Gomez J, Graf N. Intralymphatic immunotherapy for cat allergy induces tolerance after only 3 injections. *J Allergy Clin Immunol.* 2012;129(5):1290–6.
159. Didier A, Malling HJ, Worm M, Horak F, Sussman GL. Prolonged efficacy of the 300IR 5-grass pollen tablet up to 2 years after treatment cessation, as measured by a recommended daily combined score. *Clin Transl Allergy.* 2015 May;5:12.
160. Meadows A, Kaambwa B, Novielli N, Huissoon A, Fry-Smith A, Meads C, et al. A systematic review and economic evaluation of subcutaneous and sublingual allergen immunotherapy in adults and children with seasonal allergic rhinitis. *Health Technol Assess.* Jul 2013;17(27):vi, xi–xiv, 1-322.
161. Canonica GW, Poulsen PB, Vestenbaek U. Cost-effectiveness of GRAZAX for prevention of grass pollen induced rhinoconjunctivitis in Southern Europe. *Respir Med.* Sep 2007;101(9):1885–94.
162. Keiding H, Jorgensen KP. A cost-effectiveness analysis of immunotherapy with SQ allergen extract for patients with seasonal allergic rhinoconjunctivitis in selected European countries. *Curr Med Res Opin.* May 2007;23(5):1113–20.
163. Bachert C, Vestenbaek U, Christensen J, Griffiths UK, Poulsen PB. Cost-effectiveness of grass allergen tablet (GRAZAX) for the prevention of seasonal grass pollen induced rhinoconjunctivitis - a Northern European perspective. *Clin Exp Allergy.* May 2007;37(5):772–9.
164. Poulsen PB, Pedersen KM, Christensen J, Vestenbaek U. [Economic evaluation of a tablet-based vaccination against hay fever in Denmark]. *Ugeskr Laeger.* Jan 2008; 14;170(3):138–42.
165. Dranitsaris G, Ellis AK. Sublingual or subcutaneous immunotherapy for seasonal allergic rhinitis: an indirect analysis of efficacy, safety and cost. *J Eval Clin Pract.* Jun 2014;20(3):225–38.
166. Ronaldson S, Taylor M, Bech PG, Shenton R, Bufe A. Economic evaluation of SQ-standardized grass allergy immunotherapy tablet (Grazax) in children. *Clin Outcomes Res.* Apr 2014;6(1):187–96.
167. Westerhout KY, Verheggen BG, Schreder CH, Augustin M. Cost effectiveness analysis of immunotherapy in patients with grass pollen allergic rhinoconjunctivitis in Germany. *J Med Econ.* 2012;15(5):906–917 12p.
168. Verheggen B, Westerhout K, Schreder C, Augustin M. Health economic comparison of SLIT allergen and SCIT allergoid immunotherapy in patients with seasonal grass-allergic rhinoconjunctivitis in Germany. *Clin Transl Allergy.* 2015;5(1).

169. Reinhold T, Brüggjenjürgen B. Cost-effectiveness of grass pollen SCIT compared with SLIT and symptomatic treatment. *Allergo J Int*. 2016
170. Ruggeri M, Oradei M, Frati F, Puccinelli P, Romao C, Dell'Albani I, et al. Economic evaluation of 5-grass pollen tablets versus placebo in the treatment of allergic rhinitis in adults. *Clin Drug Investig*. 2013;33(5):343–9.
171. Berto P, Passalacqua G, Crimi N, Frati F, Ortolani C, Senna G, et al. Economic evaluation of sublingual immunotherapy vs symptomatic treatment in adults with pollen-induced respiratory allergy: the Sublingual Immunotherapy Pollen Allergy Italy (SPAI) study. *Ann Allergy Asthma Immunol*. Nov 2006;97(5):615–21.
172. Bruggenjurgen B, Reinhold T, Brehler R, Laake E, Wiese G, Machate U, et al. Cost-effectiveness of specific subcutaneous immunotherapy in patients with allergic rhinitis and allergic asthma. *Ann Allergy Asthma Immunol*. Sep 2008;101(3):316–24.
173. Schadlich PK, Brecht JG. Economic evaluation of specific immunotherapy versus symptomatic treatment of allergic rhinitis in Germany. *Pharmacoeconomics*. Jan 2000;17(1):37–52.
174. Omnes LF, Bousquet J, Scheinmann P, Neukirch F, Jasso-Mosqueda G, Chicoye SA, et al. Pharmacoeconomic assessment of specific immunotherapy versus current symptomatic treatment for allergic rhinitis and asthma in France. *Eur Ann Allergy Clin Immunol*. May 2007;39(5):148–56.
175. Peterson K, Gyrd-Hansen D, Dahl R. Health-economic analyses of subcutaneous specific immunotherapy for grass pollen and mite allergy. *Allergol Immunopathol (Madr)*. 2005;33(6):296–302.
176. Pokladnikova J, Krcmova I, Vlcek J. Economic evaluation of sublingual vs subcutaneous allergen immunotherapy. *Ann Allergy Asthma Immunol*. 2008;100(5):482–9.
177. Nasser S, U. Vestenbaek, A. Beriot-Mathiot, P. B. Poulsen. Cost-effectiveness of specific immunotherapy with Grazax in allergic rhinitis co-existing with asthma. *Allergy*. Dec 2008;63(12):1624–9.
178. Ariano R, Berto P, Incorvaia C, Di Cara G, Boccardo R, La Grutta S. Economic evaluation of sublingual immunotherapy vs symptomatic treatment in allergic asthma. *Ann Allergy Asthma Immunol*. 2009;103(3):254–9.
179. Almagro E, Asensio, O, Bartolome J, Bosque M, De La Hoz B, Dolz i. [Multicenter drug surveillance of sublingual immunotherapy in allergic patients]. *Allergol Immunopathol (Madr)*. 1994;23(4):153–9.

180. Brehler R, Klimek L, Pfaar O, Hauswald B, Worm M, Bieber T. Safety of a rush immunotherapy build-up schedule with depigmented polymerized allergen extracts. *Allergy Asthma Proc Vol 31 Ocean Publ Inc.* 2010;31.
181. Cardona R, Lopez E, Beltrán J, Sánchez J. Safety of immunotherapy in patients with rhinitis, asthma or atopic dermatitis using an ultra-rush buildup. A retrospective study. *Allergol Immunopathol (Madr).* 2014;42(2):90–5.
182. Casanovas M, Martin R, Jiménez, C, Caballero R, Fernández-Caldas E. Safety of an ultra-rush immunotherapy build-up schedule with therapeutic vaccines containing depigmented and polymerized allergen extracts. *Int Arch Allergy Immunol.* 2006;139(2):153–8.
183. Casanovas M, Martin R, Jiménez C, Caballero R, Fernández-Caldas E. Safety of immunotherapy with therapeutic vaccines containing depigmented and polymerized allergen extracts. *Clin Exp Allergy.* 2007;37(3):434–40.
184. Pfaar O, Mösges R, Hörmann K, Klimek L. Safety aspects of Cluster immunotherapy with semi-depot allergen extracts in seasonal allergic rhinoconjunctivitis. *Eur Arch Otorhinolaryngol.* 2010;267(2):245–50.
185. Yi H, Liu Y, Ye J, Yu. Clinical observation of the adverse effects of standardized dust mite allergen preparation in the treatment of allergic rhinitis. *J Clin Otorhinolaryngol Head Neck Surg.* 2014;28(23):1870–2, 1876.
186. Cohen J. *Statistical Power Analysis for the Behavioral Sciences.* Vol. 2nd ed. Hillsdale, NJ: Erlbaum; 1988.
187. Pfaar O, Demoly P, Gerth van Wijk R, Bonini S, Bousquet J, Canonica G, et al. Recommendations for the standardization of clinical outcomes used in allergen immunotherapy trials for allergic rhinoconjunctivitis: an EAACI Position Paper. *Allergy.* 2014 Jul;69(7):854–67.
188. Pfaar O, Basti K, Berger U, Buters J, Calderon M, Clot B, et al. Defining pollen exposure times for clinical trials of allergen immunotherapy for pollen-induced rhinoconjunctivitis - an EAACI position paper. *Allergy* 2016 Nov 22. doi: 10.1111/all.13092

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/all.13201

This article is protected by copyright. All rights reserved.

AIT for allergic rhinoconjunctivitis: a systematic review and meta-analysis
 Tables and figures to accompany main paper

Table 1a: Characteristics of SCIT studies (n=61 studies, reported in 63 papers)

Study (First author, y, country)	Allergen(s) type							Allergen no.	Comparator	AIT Protocol										Short-term effectiveness			Long-term effectiveness			Safety	Quality of life					
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mold(s)	Insect dust/mite	Cat	Dog			Other(s)	Single	Multiple	Placebo	Home care	Active	Pre-seasonal	Co-seasonal	Continuous	Conventional	Cluster	Semi-rush	RUSH	Ultra-rush	Rx duration	Product type/ Name (manufacturer)			Symptom score	Medication score	Combined score	Symptom score	Medication score
Alvarez-Cuesta, 2005, Spain	X	X							X	X						X	X					1 y	Glutaraldehyde-polymerized extracts / NR (Laboratorios LETI, S.L.)	X	X					X	X	
Ariano, 1999, Italy			X					X	X						X	X						1 y	Glutaraldehyde modified allergoid extract of <i>Parietaria judaica</i> (50%) & <i>Parietaria officinalis</i> (50%)/ Purethal®			X					X	
Arvidsson, 2002, Sweden		X						X	X							X	X					2 y	Birch depot extract adsorbed onto aluminum hydroxide / Alutard SQ®	X	X						X	
Balda, 1998,		X						X	X				X			X						7	Purified and standardized extracts composed of equal parts of <i>Corylus avellana</i> , <i>Abnus glutinosa</i> , and	X	X						X	

Study (First author, y, country)	Allergen(s) type							Allergen no.	Comparator	AIT Protocol											Short-term effectiveness			Long-term effectiveness			Safety	Quality of life					
	Grass pollen(s)	Tree pollen(s)	Weeds(s)	Molds(s)	House dust mite	Cat	Dog			Other(s)	Single	Multiple	Placebo	Routine care	Active	Pre-seasonal	Co-seasonal	Conventional	Cluster	Semi-rush	Ultra-rush	Rx duration	Product type/ Name (manufacturer)	Symptom score	Medication score	Combined score			Symptom score	Medication score	Combined score		
																																Conjunctivitis	Rhinitis
Germany																				W	<i>Betula verrucosa</i> / ALK7 Frühblüthermischung®												
Bodtger, 2002, Denmark		X							X	X				X	X		X			1 y	<i>Betula verrucosa</i> extract / Soluprick SQ® (ALK-Abello)	X	X									X	
Bousquet, 1987, France	X								X	X				X	X			X		10 m	Six-mixed grass-pollen allergoid and standardized orchard grass-pollen extract / Alyostal ST® (Stallergenes)	X	X									X	
Bousquet, 1989, France	X								X					X	X			X		8 m	SCIT with a high-molecular-weight formalinized allergoid (HMW-GOIG) vs SCIT with unfractionated allergoid (GOIG) vs SCIT with standardized extract vs placebo / NR	X	X									X	
Bousquet, 1990, France	X								X	X				X	X			X		NR	High-molecular weight mixed grass pollen allergoids / NR	X	X									X	
Bousquet, 1991, France	X	X	X							X	X			X				X		1 y	Standardized extracts from orchard grass (<i>Dactylis glomerata</i>), olive (<i>Olea europaea</i>), plane tree (<i>Platanus occidentalis</i>), mugwort (<i>Artemisia vulgaris</i>), and <i>Parietaria officinalis</i> pollens / NR (manufactured by Stallergenes)			X								X	

Study (First author, y, country)	Allergen(s) type							Allergen no.	Comparator	AIT Protocol										Short-term effectiveness			Long-term effectiveness			Safety	Quality of life				
	Grass pollen(s)	Tree pollen(s)	Weeds(s)	Molds(s)	House dust mite	Cat	Dog			Other(s)	Single	Multiple	Placebo	Home care	Active	Pre-seasonal	Co-seasonal	Conventional	Cluster	Semi-rush	Ultra-rush	Rx duration	Product type/ Name (manufacturer)	Symptom score	Medication score			Combined score	Symptom score	Medication score	Combined score
Bozek, 2016, Poland	X								X	X				X		X					3 y	Pollen mixture extract solution of grass pollens (<i>Agrostis stolonifera</i> , <i>A odoratum</i> , <i>Arrhenatherum elatius</i> , <i>D glomerata</i> , <i>Festuca rubra</i> , <i>Holcus lanatus</i> , <i>Lolium perenne</i> , <i>P pratense</i> , <i>P pratensis</i> , <i>Secale cereal</i> , and <i>Loe edasi</i>) / Purethal grasses (HAL Allergy BV)	X	X	X				X	X	
Brunet, 1992, Canada			X						X	X			X		X						3 m	Alum-precipitated aqueous ragweed extracts / NR	X	X					X		
Ceuppens, 2009, Belgium & the Netherlands		X							X	X					X	X					18 m	Glutaraldehyde-modified birch pollen extract adsorbed onto aluminium hydroxide /PURETHAL® Birch			X					X	
Chakraborty, 2006, India		X							X	X					X	X					2 y	<i>Phoenix sylvestris</i> Roxb or sugar palm allergoid extract / NR			X					X	
Charpin, 2007, France		X							X	X					X	X					15 m	Standardized, aluminum hydroxide-adsorbed <i>Juniperus ashei</i> extract/ Alustal® (Stallergenes)	X	X						X	X
Colas, 2006,			X						X	X					X	X					1 y	Depigmented and glutaraldehyde polymerized extract of <i>Salsola kali</i> absorbed onto aluminium	X	X						X	X

Study (First author, y, country)	Allergen(s) type							Allergen no.	Comparator	AIT Protocol										Short-term effectiveness			Long-term effectiveness			Safety	Quality of life						
	Grass pollen(s)	Tree pollen(s)	Weeds(s)	Molds(s)	House dust mite	Cat	Dog			Other(s)	Single	Multiple	Placebo	Routine care	Active	Pre-seasonal	Co-seasonal	Continuous	Conventional	Cluster	Semi-rush	Rush	Ultra-rush	Rx duration	Product type/ Name (manufacturer)			Symptom score	Medication score	Combined score	Symptom score	Medication score	Combined score
Spain																							hydroxide/ NR (supplied by Laboratorios LETI, SL.)										
Corrigan, 2005, UK	X							X	X				X									2 y	Aluminium-adsorbed six-grass pollen allergoid / Allergovit®	X	X						X	X	
Crimi, 2004, Italy			X					X	X						X			X				3 y	Intact <i>Parietaria judaica</i> extract adsorbed onto aluminum hydroxide / Alutard SQ®	X	X						X		
Dokic, 2005, Macedonia					X			X	X						X							3 y	Aluminium hydroxide adsorbed <i>D.pt.</i> allergoid / NR (Allergopharma)	X	X						X		
Dolz, 1996, Spain	X							X	X					X						X		3 y	Grass-pollen allergen extract (<i>Pheum, Dactylis, Lolium</i>) adsorbed onto aluminum hydroxide / Alutard SQ® (ALK-Abelló)	X	X						X		
Drachenberg, 2001, Germany and Austria	X							X	X				X									4-7 w	Tyrosine-adsorbed glutaraldehyde-modified grass pollen extract containing monophosphoryl lipid A as adjuvant / Pollinex Quattro®	X	X	X					X		
Drachenberg, 2002,		X						X	X				X									4-7	L-tyrosine-adsorbed birch, alder, hazel pollen allergoids treated with glutaraldehyde plus			X					X		

Study (First author, y, country)	Allergen(s) type							Allergen no.	Comparator	AIT Protocol										Short-term effectiveness			Long-term effectiveness			Safety	Quality of life													
	Grass pollen(s)	Tree pollen(s)	Weeds(s)	Molds(s)	House dust mite	Cat	Dog			Other(s)	Single	Multiple	Placebo	Routine care	Active	Pre-seasonal	Co-seasonal	Continuous	Conventional	Cluster	Semi-rush	Ultra-rush	Rx duration	Product type/ Name (manufacturer)	Symptom score			Medication score	Combined score	Symptom score	Medication score	Combined score								
Germany																					4 w	monophosphoryl lipid-A (MPL) / Pollinex Quattro ®																		
DuBuske, 2011, USA, Canada, UK, Austria	X								X	X			X			X					4-8 w	Modified Allergen Tyosine Adsorbate (MATA) consisting of a mixture of modified pollen allergens from 13 grass species adsorbed onto tyosine/ Pollinex Quattro, Pollinex Complete; Allergy Therapeutics, U.K.			X												X			
Durham, 1999, UK Primary study Varney, 1991	X							X	X	X					X	X					3 y	Standardized, aluminum hydroxide-adsorbed, depot grass pollen vaccine / Alutard SQ® (ALK Abelló)					X	X									X			
Ewan, 1988, UK					X			X	X										X		3 m	Partially purified extract of <i>D. pteronyssinus</i> / Pharmed®	X															X		
Fell, 1988, UK	X							X	X				X								X	1 injectio	Enzyme (glucuronidase) potentiated grass pollen allergens / (Pharmacia)	X	X															

Study (First author, y, country)	Allergen(s) type							Allergen no.	Comparator	AIT Protocol										Short-term effectiveness			Long-term effectiveness			Safety	Quality of life						
	Grass pollen(s)	Tree pollen(s)	Weeds(s)	Molds(s)	House dust mite	Cat	Dog			Other(s)	Single	Multiple	Placebo	Routine care	Active	Pre-seasonal	Co-seasonal	Continuous	Conventional	Cluster	Semi-rush	Rush	Ultra-rush	Rx duration	Product type/ Name (manufacturer)			Symptom score	Medication score	Combined score	Symptom score	Medication score	Combined score
Ferrer, 2005, Spain			X						X	X						X	X					20 m	Biologically standardized extract of <i>Parietaria judaica</i> adsorbed onto aluminium hydroxide gel / Pangramin ®Depot, ALK-ABELLÓ	X	X	X						X	X
Frew, 2006, UK	X							X	X		X		X	X	X							1 y	Standardized depot preparations of grass pollen extract / Alutard SQ grass pollen® (ALK-Abello)	X	X							X	X
Grammer, 1982, USA			X					X	X	X			X			X						15 w	Polymerized ragweed extract (PRW)/NR	X								X	
Grammer, 1983, USA	X							X	X				X			X						4 m	Six grass pollen allergoid prepared by polymerization with glutaraldehyde / NR	X	X							X	
Grammer, 1984, USA			X					X	X	X			X			X						>30 m (UR)	Polymerized ragweed extract / NR			X				X		X	
Grammer,	X							X	X				X			X						4	Polymerized ragweed extract / NR				X					X	

Study (First author, y, country)	Allergen(s) type							Allergen no.	Comparator	AIT Protocol										Short-term effectiveness			Long-term effectiveness			Safety	Quality of life						
	Grass pollen(s)	Tree pollen(s)	Weeds(s)	Molds(s)	Inhouse dust/mite	Cat	Dog			Other(s)	Single	Multiple	Placebo	Home care	Active	Pre-seasonal	Co-seasonal	Continuous	Conventional	Cluster	Semi-rush	Rush	Ultra-rush	Rx duration	Product type/ Name (manufacturer)			Symptom score	Medication score	Combined score	Symptom score	Medication score	Combined score
1987, USA																							m										
Höiby, 2010, Sweden & Germany		X						X	X						X	X							18 m	Depigmented polymerized birch pollen (Betula alba) extract adsorbed onto aluminium hydroxide/ Depigoid ®(Laboratorios LETI S)			X					X	
Horst, 1989, France				X				X	X						X								1 year	lyophilized and standardized Alt extract Stallergnes Laboratories			X					X	
Iliopoulos, 1991, USA		X						X	X				X	X	X								~8 m	Short ragweed extract / NR (Greer Laboratories, Lenoir, N.C.)			X					X	
James, 2011, UK	X							X	X					X	X								2/4 y	<i>Phleum pratense</i> extract adsorbed with aluminum hydroxide / Alutard SQ ®				X		X			
Juniper, 1990, Canada		X						X		X			X	X	X								6 w	Modified ragweed tyosine adsorbate / Pollinex® (Bencard Allergy Service)	X	X						X	
Jutel, 2005, Poland	X							X	X				X	X	X								8-9 m	Five recombinant grass pollen allergens / NR (Allergopharma)			X					X	X

Study (First author, y, country)	Allergen(s) type							Allergen no.	Comparator	AIT Protocol										Short-term effectiveness			Long-term effectiveness			Safety	Quality of life							
	Grass pollen(s)	Tree pollen(s)	Weeds(s)	Molds(s)	House dust mite	Cat	Dog			Other(s)	Single	Multiple	Placebo	Home care	Active	Pre-seasonal	Co-seasonal	Continuous	Conventional	Cluster	Semi-rush	Ultra-rush	Rx duration	Product type/ Name (manufacturer)	Symptom score			Medication score	Combined score	Symptom score	Medication score	Combined score		
Kleine-Tebbe, 2014, Spain, Germany & Austria	X								X	X		X				X	X					1 y	Aluminium hydroxide adsorbed Phleum pratense extract / AVANZ® Phleum pratense (ALK)	X	X								X	
Klimek, 2014, Germany	X		X						X	X			X	X				X				1 y	Glutaraldehyde-modified high polymerized allergen extract containing 6 grasses (60%) and rye pollen adsorbed onto aluminum hydroxide / CLUSTOID® (ROXALL Medizin)	X	X	X							X	
Kuna, 2011, Poland				X					X	X							X	X				3 y	<i>Alternaria alternata</i> extract in a depot formulation with aluminum hydroxide / Novo-Helisen Depot® <i>A alternata</i> 100% (Allergopharma)	X	X	X							X	X
Leynadier, 2001, France	X								X	X							X	X				1 y	Standardized five-grass-pollen (equal parts of: orchard, meadow, rye, sweet vernal and timothy) depot extract adsorbed onto calcium phosphate / Phostal® (Stallergenes)	X	X	X							X	
Metzger, 1981, England			X						X	X			X									5 w	Glutaraldehyde-modified, tyosine-adsorbed short ragweed extract / NR (Beecham Laboratories)	X									X	

Study (First author, y, country)	Allergen(s) type							Allergen no.	Comparator	AIT Protocol										Short-term effectiveness			Long-term effectiveness			Safety	Quality of life						
	Grass pollen(s)	Tree pollen(s)	Weeds(s)	Molds(s)	House dust mite	Cat	Dog			Other(s)	Single	Multiple	Placebo	Home care	Active	Pre-seasonal	Co-seasonal	Continuous	Conventional	Cluster	Semi-rush	Ultra-rush	Rx duration	Product type/ Name (manufacturer)	Symptom score			Medication score	Combined score	Symptom score	Medication score	Combined score	
Mirone, 2004, Italy			X						X	X						X	X					1y	<i>Ambrosia artemisiifolia</i> absorbed onto aluminium (D hydroxide and suspended in phenolated (0.4% w/v) saline solution / NR (ALK-Abello')	X	X							X	
Olsen, 1995, Denmark	X	X	X						X			X			X	X						2y	Aluminium hydroxide adsorbed extracts of standardized extracts of <i>Betula</i> , <i>Phleum</i> and <i>Artemisia</i> / Alutard® SQ (ALK)	X								X	
Ortolani, 1994, Italy			X					X	X						X	X						1y	Partially purified alginate-conjugated extract of <i>Parietaria judaica</i> / Conjuvac Parietaria ® (Dome Hollister-Stier)			X						X	
Pastorello, 1992, Italy	X							X	X			X	X	X	X	X						5-12m	Formalinized depot 6 grass allergoid absorbed onto aluminum hydroxide / NR (Allergopharma)			X						X	
Patel, 2012, Canada						X		X	X		X						X					3m	Feld 1–derived peptide antigen (Cat-PAD) / NR (Bachem and Patheon)	X*						X*		X	

Study (First author, y, country)	Allergen(s) type							Allergen no.	Comparator	AIT Protocol										Short-term effectiveness			Long-term effectiveness			Safety	Quality of life								
	Grass pollen(s)	Tree pollen(s)	Weeds(s)	Molds(s)	House dust mite	Cat	Dog			Other(s)	Single	Multiple	Placebo	Home care	Active	Pre-seasonal	Co-seasonal	Continuous	Conventional	Cluster	Semi-rush	Ultra-rush	Rx duration	Product type/ Name (manufacturer)	Symptom score			Medication score	Combined score	Symptom score	Medication score	Combined score			
Pauli, 2008, Austria, Denmark, France, Italy & Sweden		X							X	X		X				X	X					2 y	Aluminum hydroxide-adsorbed vaccines of birch pollen extract, <i>rBet v 1</i> , and <i>nBet v 1</i> / NR (Stallergenes SA)	X	X								X		
Pfaar, 2010, Lithuania, Poland & Germany		X						X	X						X	X						19 m	Standardized depigmented and glutaraldehyde-polymerized tree pollen extract (33% <i>Corylus avellana</i> , 33% <i>Alnus glutinosa</i> , 34% <i>Betula alba</i>) adsorbed onto aluminium hydroxide / Depigoid(Laboratorios LETI SL, Tres Cantos, Spain),	X		X							X		
Pfaar, 2011, Germany	X							X	X				X						X			2 y	Depigmented and glutaraldehyde-polymerized grass pollen mix adsorbed onto aluminum hydroxide / Depiquick® (Laboratorios LETI)	X	X	X							X	X	
Powell, 2007, UK Primary study Frew, 2006	X							X	X		X				X	X						14 m	Standardized depot preparations of grass pollen extract / Alutard® SQ grass pollen (ALK-Abello)											X	

Study (First author, y, country)	Allergen(s) type								Allergen no.	Comparator	AIT Protocol										Short-term effectiveness			Long-term effectiveness			Safety	Quality of life								
	Grass pollen(s)	Tree pollen(s)	Weeds(s)	Molds(s)	House dust mite	Cat	Dog	Other(s)			Single	Multiple	Placebo	Home care	Active	Pre-seasonal	Co-seasonal	Continuous	Conventional	Cluster	Semi-rush	Ultra-rush	Rx duration	Product type/ Name (manufacturer)	Symptom score	Medication score			Combined score	Symptom score	Medication score	Combined score				
Radcliffe, 2003, UK	X	X	X	X	X	X	X	X		X	X			X								2-3 m	Enzyme potentiated mixed inhaled allergen extract (pollen mixes for trees, grasses, and weeds; allergenic fungal spores; cat and dog danders; dust and storage mites) / NR	X									X	X		
Rak, 2001, Sweden		X							X			X		X				X				1 y	Birch pollen extract adsorbed onto aluminum / Alutard® (ALK-Abelló)	X	X											
Riechelmann, 2010, Germany & Austria					X				X	X					X	X						1 y	Single-strength glutaraldehyde-modified aluminum hydroxide-adsorbed extract / HDM PURETHAL Mites® (HAL-Allergy)	X	X								X	X		
Tabar, 2005, Spain					X				X			X				X	X					1 y	Biologically standardized HDM depot extract adsorbed on aluminum hydroxide / Pangramin Depot UM D pteronysinus® (ALK-Abello)	X	X								X			
Tabar, 2008, Spain				X					X	X						X	X					18 m	Metabolic extract of <i>Alternaria alternata</i> / Allergovac® depot	X	X								X	X		
Tari, 1997, Italy			X						X	X						X	X					2 y	Alum-adsorbed <i>Parietaria judaica</i> pollen allergoid/ Allergovit® (Allergopharma)	X	X								X			

Study (First author, y, country)	Allergen(s) type							Allergen no.	Comparator	AIT Protocol										Short-term effectiveness			Long-term effectiveness			Safety	Quality of life					
	Grass pollen(s)	Tree pollen(s)	Weeds(s)	Molds(s)	House dust mite	Cat	Dog			Other(s)	Single	Multiple	Placebo	Routine care	Active	Pre-seasonal	Co-seasonal	Continuous	Conventional	Cluster	Semi-rush	Ultra-rush	Rx duration	Product type/ Name (manufacturer)	Symptom score			Medication score	Combined score	Symptom score	Medication score	Combined score
Tworek, 2013, Poland	X		X						X			X	X		X	X					3 y	Allergoid preparation consisting of 80% grass pollen and 20% rye pollen extracts / Allergovit® (Allergopharma)	X	X	X				X			
Varney, 1991, UK		X						X		X			X	X		X					8 m	Partially purified and standardised extract of <i>Phleum pratense</i> adsorbed onto aluminium / Alutard SQ® (ALK-Abelló)	X	X					X			
Varney, 2003, UK					X			X						X	X						1 y	Intact HDM extract vaccine adsorbed onto aluminum hydroxide/ Alutard SQ® (ALK-Abelló)	X	X					X			
Walker, 2001, UK	X							X		X				X		X					2 y	Alutard SQ (ALK Abelló, Horshølm, Denmark), a standardized extract of <i>Phleum pratense</i> (timothy grass pollen),7 aluminum adsorbed for slow release	X	X					X	X		
Weyer, 1981, France	X							X		X			X		X						8 m	Crude 4 grass pollen extract / NR	X	X	X				X			

Study (First author, y, country)	Allergen(s) type							Allergen no.	Comparator	AIT Protocol										Short-term effectiveness			Long-term effectiveness			Safety	Quality of life			
	Grass pollen(s)	Tree pollen(s)	Weeds(s)	Molds(s)	House dust mite	Cat	Dog			Other(s)	Single	Multiple	Placebo	Home care	Active	Pre-seasonal	Co-seasonal	Conventional	Cluster	Semi-rush	Ultra-rush	Rx duration	Product type/ Name (manufacturer)	Symptom score	Medication score			Combined score	Symptom score	Medication score
Zenner, 1997, Germany	X		X					X	X						X	X				4 m	Partially purified and standardized extracts of 6 grasses (50%, <i>Dactylis glomerata</i> , <i>Lolium perenne</i> , <i>Arena elatior</i> , <i>Pbleum pratense</i> , <i>Poa pratensis</i> , and <i>Fetuca pratensis</i>) and rye, (50%, <i>Secale cereale</i>) adsorbed onto aluminum hydroxide / NR (manufactured by ALK A/S)	X	X						X	

AIT, allergen specific immunotherapy; *m*, month; *NBS*, not better specified; *NR*, not reported; *Rx*, treatment; *SCIT*, subcutaneous immunotherapy; *SLIT*, sublingual immunotherapy; *UR*, unclear reporting *w*, week; *y*, y.

*environmental exposure chamber

Table 1b: Characteristics of SLIT studies (n=71 studies, reported in 75 papers)

Study (First author, y, country)	Allergen(s) type											Com parat or	AIT Protocol											Short term effective ness			Long term effecti veness			Quality of life
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mold(s)	House dust mite	Cat	Dog	Other(s)	Mite	Placebo	Routine care		Active	Pre-seasonal	Continuous	Conventional	Sublingual	Rush	Ultra-rush	Rx duration	Product type/ Name (manufacturer)	Symptom score	Medication score	Combined score	Symptom score	Medication score	Combined score	Safar		
																													Safar	
Ahmadiashar, 2012, Iran	X								X	X			X	X					X	6 m	10, 100, and 300 IR rye grass spray (Staloral 638)	X	X							X
Alvarez-Cuesta, 2007, Spain						X			X	X										12 m	Aqueous solution of cat dander extract with NaCl 0.9%, phenol 0.4% and glycerol 50% (protocol supplied by Laboratorios LETI, S.L.)	X								X
Amar, 2009, US	X								X	X		X		X						10 m	Monotherapy group: timothy extract Multiple allergen group: same amount of timothy plus 1 mL each of an additional 9 unstandardized extracts 1:20 wt/vol in 50% glycerin: maple, ash, juniper, American elm, cottonwood, Kochia, ragweed, sagebrush, and Russian thistle (ALK-Abello).	X	X							X
André, 2003, France			X						X	X			X							6.5 m	standardized ragweed extract (Stallergènes SA, Antony, France)	X	X							X
Ariano, 2001, Italy & France		X							X	X				X						12 m	Aqueous solution of an allergic fraction of <i>Cupressus arizonica</i> partially purified through dialysis in a physiological solution with 15% glycerin.	X	X							X
Aydogan, 2013, Turkey, UK & Cyprus.					X				X	X										12 m	1:1 mixture of <i>D. pteronyssinus</i> and <i>D. farinae</i> (STALORAL, Stallergenes SA, Antony, France)	X	X							
Bahçeciler, 2007, Turkey					X				X	X										6 m	<i>D. pteronyssinus</i> and <i>D. farinae</i> 50/50 extract.	X								
Bergmann, 2013, Germany, France, the Netherlands & Spain					X				X	X										2 y	Oral tablets of 1:1 mixture of <i>D pteronyssinus</i> and <i>D farinae</i> (28 mg and 120 mg respectively for the 500 IR tablet, 16 mg and 68 mg respectively for the 300 IR tablet)	X				X			X	
Blaiss, 2010, US & Canada	X								X	X										18 m	f 2,800 bioequivalent allergen units of grass AIT treatment (oral lyophilisate, <i>Pbleum pratense</i> , 75,000 standardized quality tablet, containing approximately 15 mg of Phl p 5; Schering-Plough Corp, a division of Merck & Co, Kenilworth, NJ)	X	X	X					X	X
Bowen, 2004,			X						X	X		X								4	Ragweed allergen extract	X	X							X

De Bot, 2011, The Netherlands				X			X	X										2 years	aqueous extract of house dust mites (<i>D. pter.</i>) in a glycerinated isotonic phosphate-buffered solution (Oralgen Mijten) / placebo treatment consisting of the glycerol-containing solvent	X	X						X	X
Demoly, 2015, Europe				X			X	X										1 y	1:1 mixture of two species of house dust mite allergens (<i>D. pteronyssinus</i> and <i>D. farinae</i>) (1:1:1:1 ratio of the major allergens <i>Der p 1</i> , <i>Der f 1</i> , <i>Der p 2</i> , and <i>Der f 2</i>)	X	X					X	X	
Didier, 2007, Europe	X						X	X		X	X							6 m	Mixture of 5 grass pollens (orchard, meadow, perennial rye, sweet vernal, and timothy grasses)	X							X	X
Didler, 2009, France, Germany & Spain	X						X	X		X	X							6 m	Lyophilized vaccines of five grass pollens (orchard or cocksfoot (<i>Dactylis glomerata</i>), meadow (<i>Poa pratensis</i>), perennial rye (<i>Lolium perenne</i>), sweet vernal (<i>Anthoxanthum odoratum</i>) and timothy (<i>Phleum pratense</i>))	X						X		
Didier, 2013, Denmark, Austria, France, Canada & Germany	X						X	X		X	X							4 y	300IR tablets containing mixture of 5 grasses [cocksfoot (<i>Dactylis glomerata</i>), meadow (<i>Poa pratensis</i>), rye (<i>Lolium perenne</i>), sweet vernal (<i>Anthoxanthum odoratum</i>) and timothy (<i>Phleum pratense</i>)	X						X	X	
Durham, 2005, Canada, Denmark & Sweden	X						X	X		X	X							2 y	Fast-dissolving grass allergen tablet (ALK-Abello A/S) containing timothy grass extract (<i>Phleum pratense</i>)	X	X						X	X
Durham, 2007, UK Primary study: Dahl, 2006	X						X	X										16 w	Grass allergen tablet (Grazax)									
Durham, 2009, UK Results after 1 y follow-up of Dahl, 2006 study	X						X	X		X	X							3 y	Grass allergen tablet with <i>Phleum pratense</i> 75,000 SQ-T/2,800 BAU (ALK-Abello', Hørsholm, Denmark) (Grazax)									
Durham, 2011, UK Results of 2 y follow-up of Dahl 2006 trial	X						X	X										X 2 y	SQ-standardized grass allergy tablet (<i>Phleum pratense</i> 75 000 SQ-T/2,800 BAU, ALK, Denmark) (Grazax)								X	
Durham., 2012, UK, Austria, Germany, the Netherlands, Sweden & Denmark Results of 2 y follow-up of Dahl 2006 trial	X						X	X		X	X							3 y	SQ-standardized grass allergy tablet (Grazax)					X			X	
Drachenberg, 2002, Germany	X	X					X	X			X								Grass, rye or birch pollens	X	X	X						
Feliziani, 1995, Italy	X						X	X		X	X								Grass pollen extracts (5 x 1 drop of 0.04 BU/ml, up until 5 x 1 drop of 100 BU/ml)	X	X						X	
Frolund, 2010, Austria, Denmark & UK	X						X	X		X	X							4 y	SQ-standardized grass allergy immunotherapy tablet (AIT), Grazax (<i>Phleum pratense</i> 75,000 SQ-T/2800 BAU; ALK, Denmark).									X
Guez, 2000,				X			X	X										24	<i>D. pteronyssinus</i> and <i>D. farinae</i>	X	X						X	

Table 1c. Characteristics of ILIT studies (n = 2)

Study (First author, year, country)	Allergen(s) type										Allergen number	Route AIT	Comparator	AIT Protocol										Short term effectiveness	Long term effectiveness				Quality of life	
	Grass pollen	Birch pollen	Wheat	Alfalfa	Timothy	Orchard grass	Red top	Lucerne	Citrus	Mulberry				Other	ILIT	Process	Route	Active	Pre-treatment	Concomitant	Concomitant	Cluster	Subcutaneous		Other	Product type/ Name (manufacturer)	Symptom score	Quality of life score		Completed score
Hylan et al, 2016, Spain	X	X									X		X		X			X				2 aluminium hydroxide adsorbed, depot m birch- or grass-pollen o vaccine / Alutard (ALK s Abéllo)	X	X					X	
Senti et al, 2012, Switzerland					X						X	X				X	X					2 recombinant major cat dander allergen m Fel d 1 fused to a o modular antigen s transporter (MAT) vaccine (MAT–Fel d 1)/ NR (extract purchased from Stallergenes)	X	*					X	X

* assessment after 300 days of discontinuation of ILIT

AIT, allergen specific immunotherapy; mo, month; NR, not reported; Rx, treatment; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy, ; ILIT, intralymphatic immunotherapy.

Identification
Screening
Eligibility
Included

Figure 1: PRISMA Diagram

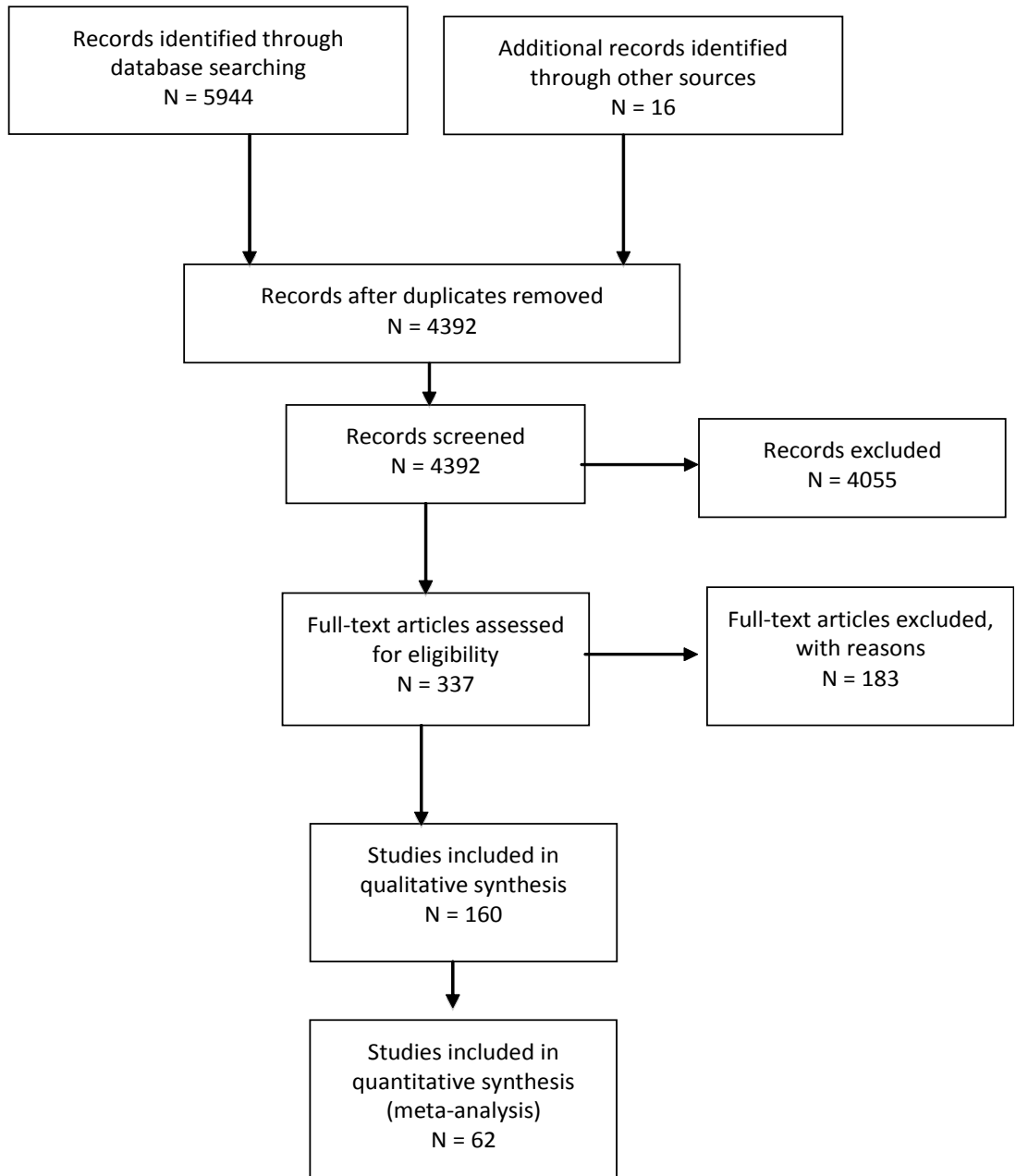
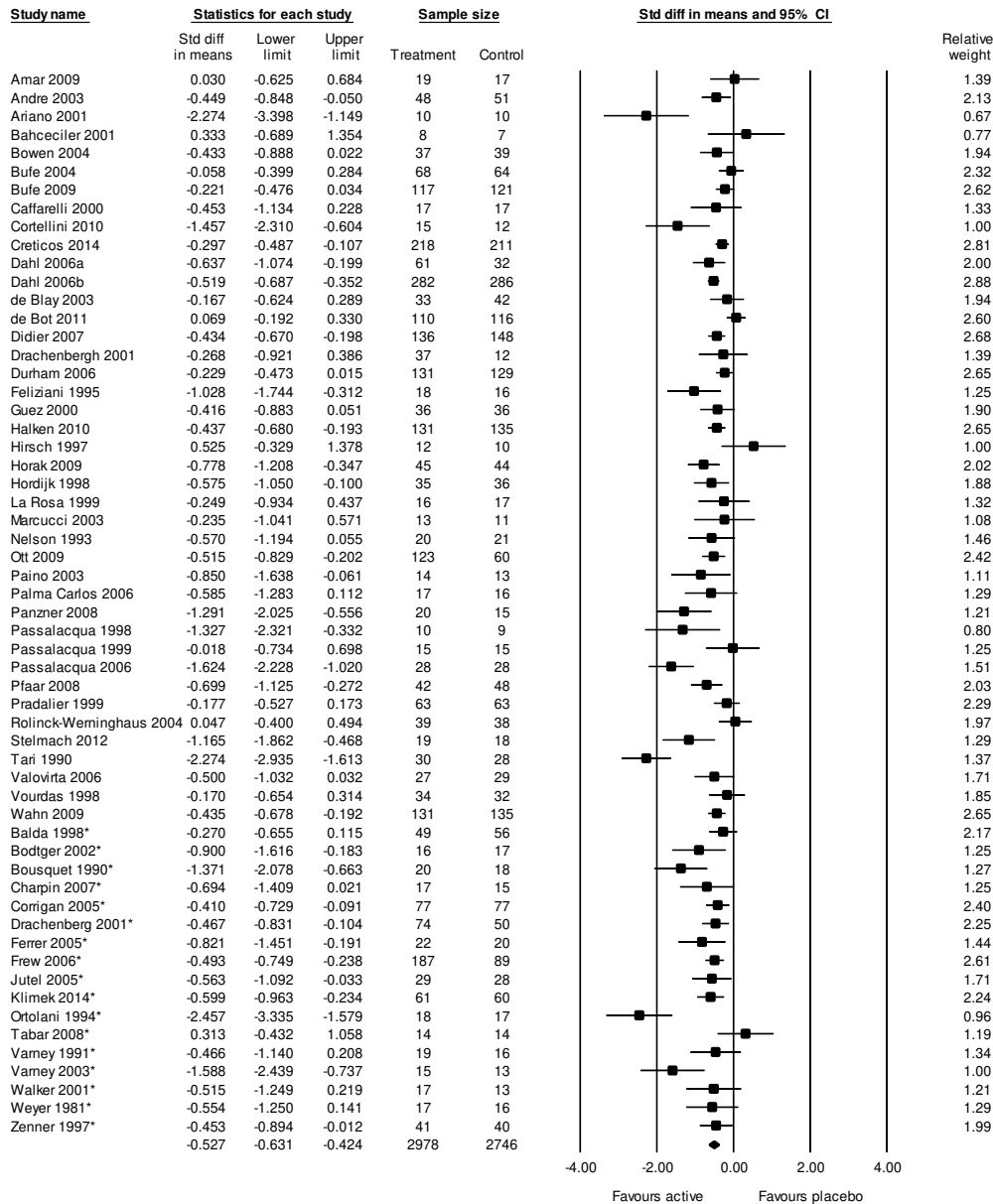


Figure 2: Meta-analysis of double-blind RCTs comparing symptom scores between AIT (SCIT or SLIT) and placebo groups (random-effects model)



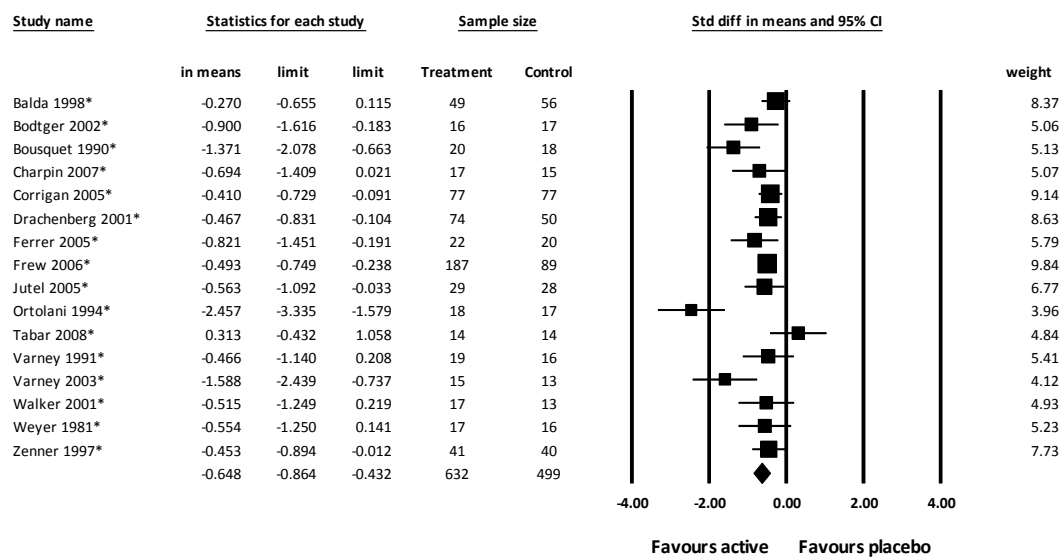
Heterogeneity: $\tau^2 = 0.090$; $\chi^2 = 173.586$, $df = 57$ ($P < 0.0001$); $I^2 = 67\%$;

Test for overall effect: $Z = -9.992$ ($P < 0.0001$)

*denotes SCIT studies

Figure 3: Meta-analysis of double-blind RCTs comparing symptom scores between (a) SCIT and placebo groups and (b) SLIT and placebo group (random-effects models)

a)



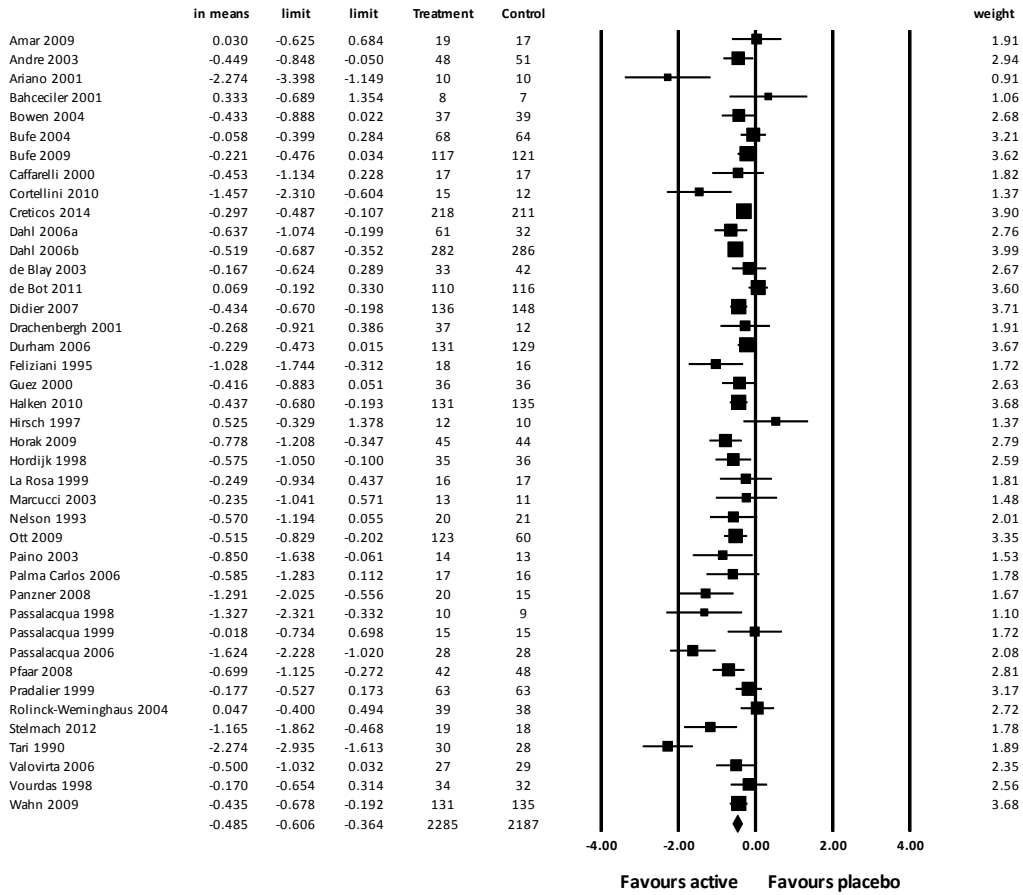
Heterogeneity: $\tau^2 = 0.106$; $\chi^2 = 39.357$, $df = 15$ ($P < 0.001$); $I^2 = 62\%$;

Test for overall effect: $Z = -5.875$ ($P < 0.0001$)

*denotes SCIT studies

b)

Study n



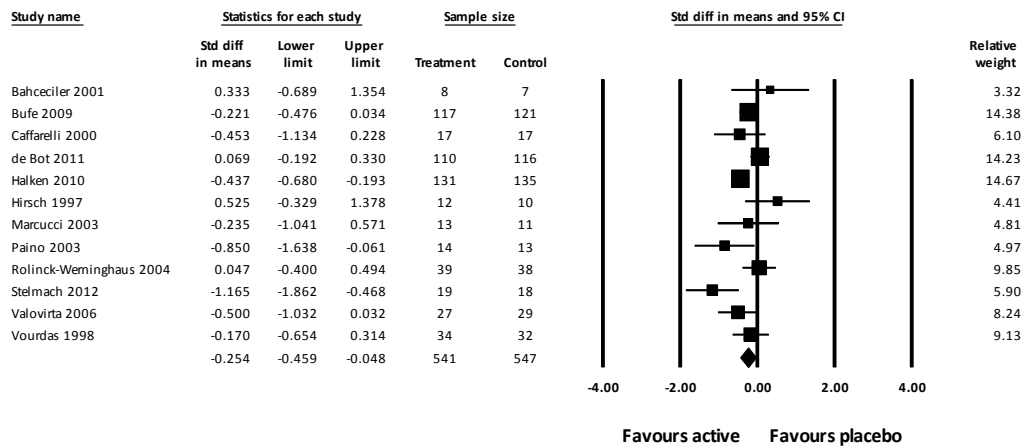
Heterogeneity: $\tau^2 = 0.088$; $\chi^2 = 129.171$, $df = 40$ ($P < 0.0001$); $I^2 = 69\%$;

Test for overall effect: $Z = -7.855$ ($P < 0.0001$)

*denotes SCIT studies

Figure 4: Meta-analysis of double-blind RCTs comparing symptom scores between AIT (SCIT or SLIT) and placebo group in (a) those <18 years old and (b) those ≥ 18 years old (random-effects models)

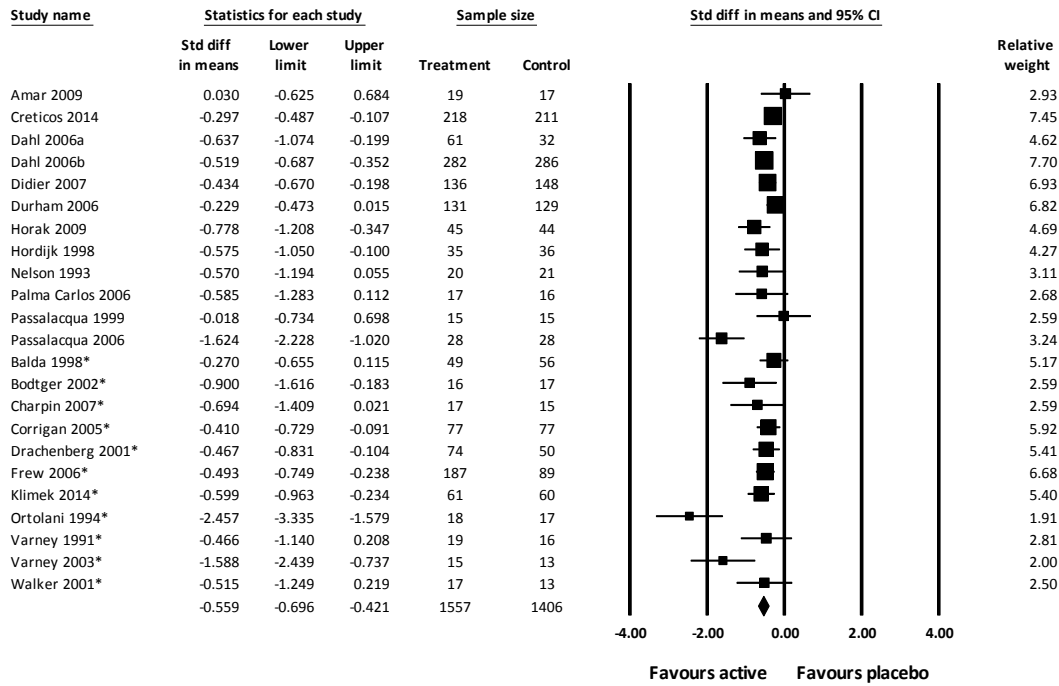
a)



Heterogeneity: $\tau^2 = 0.059$; $\chi^2 = 24.209$, $df = 11$ ($P < 0.012$); $I^2 = 54\%$;

Test for overall effect: $Z = -2.423$ ($P < 0.015$)

b)

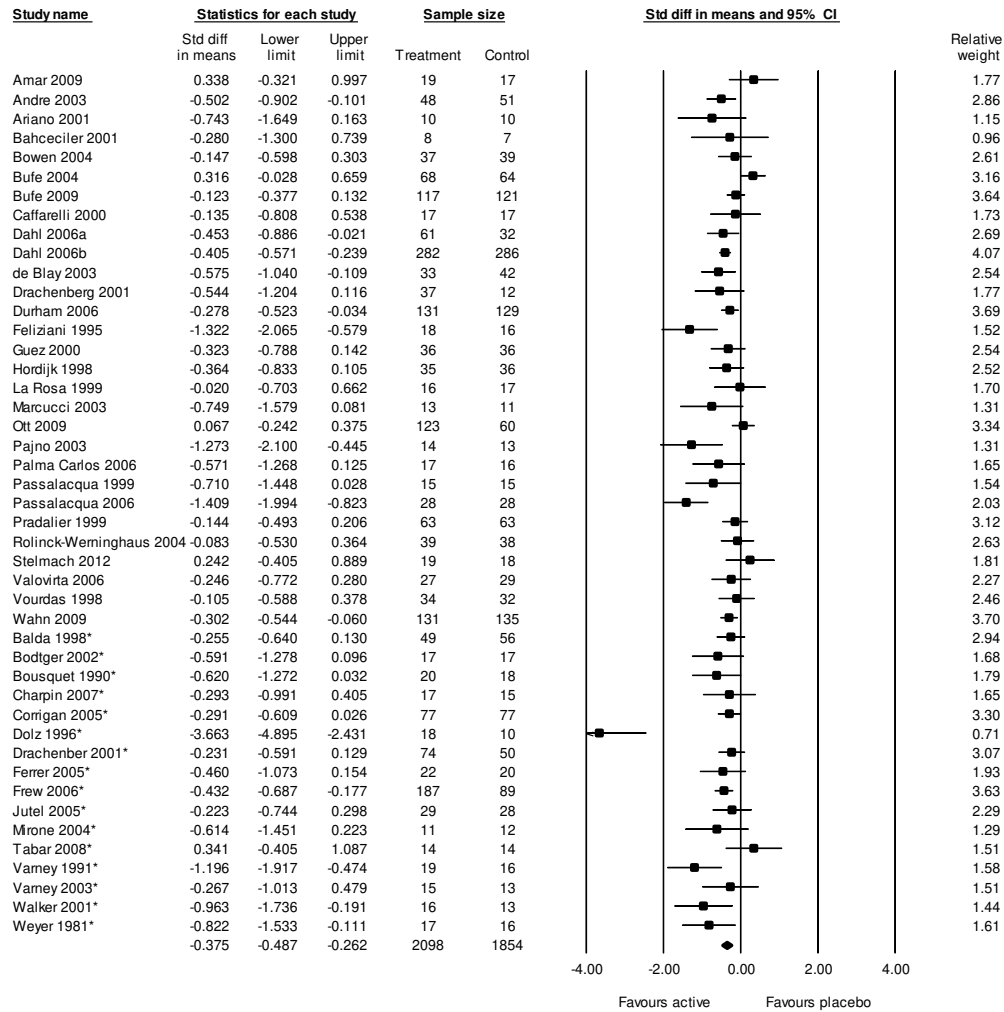


Heterogeneity: $\tau^2 = 0.057$; $\chi^2 = 57.748$ df = 22 ($P < 0.0001$); $I^2 = 62\%$;

Test for overall effect: $Z = -7.969$ ($P < 0.0001$)

*denotes SCIT studies

Figure 5: Meta-analysis of double-blind RCTs studies comparing medication scores between AIT (SCIT or SLIT) and placebo groups (random-effects model)



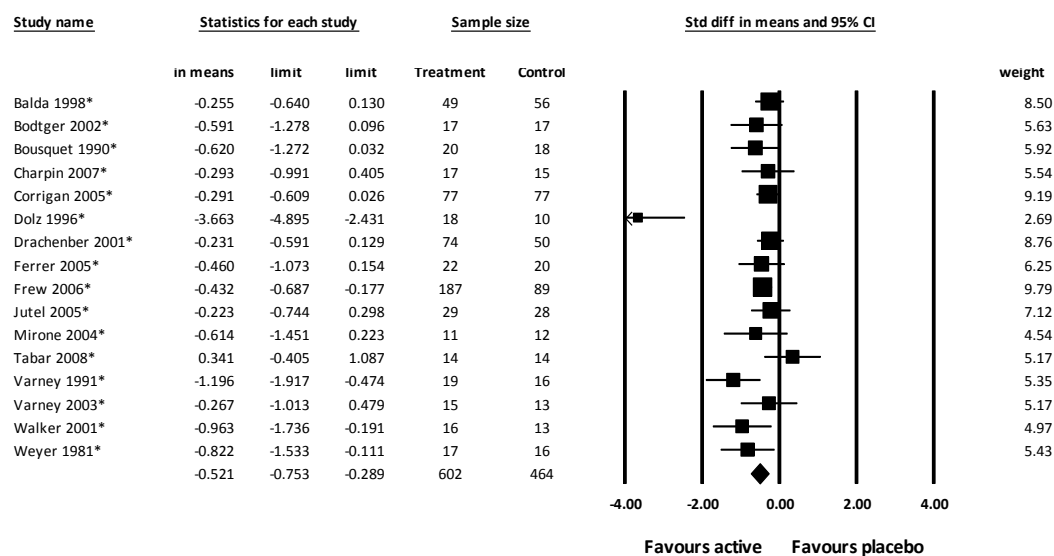
Heterogeneity: $\tau^2 = 0.074$; $\chi^2 = 110.337$, $df = 44$ ($P < 0.0001$); $I^2 = 60\%$;

Test for overall effect: $Z = -6.502$ ($P < 0.0001$)

*denotes SCIT studies

Figure 6: Meta-analysis of double-blind RCTs comparing medication scores between (a) SCIT and placebo groups and (b) SLIT and placebo groups (random-effects models)

a)

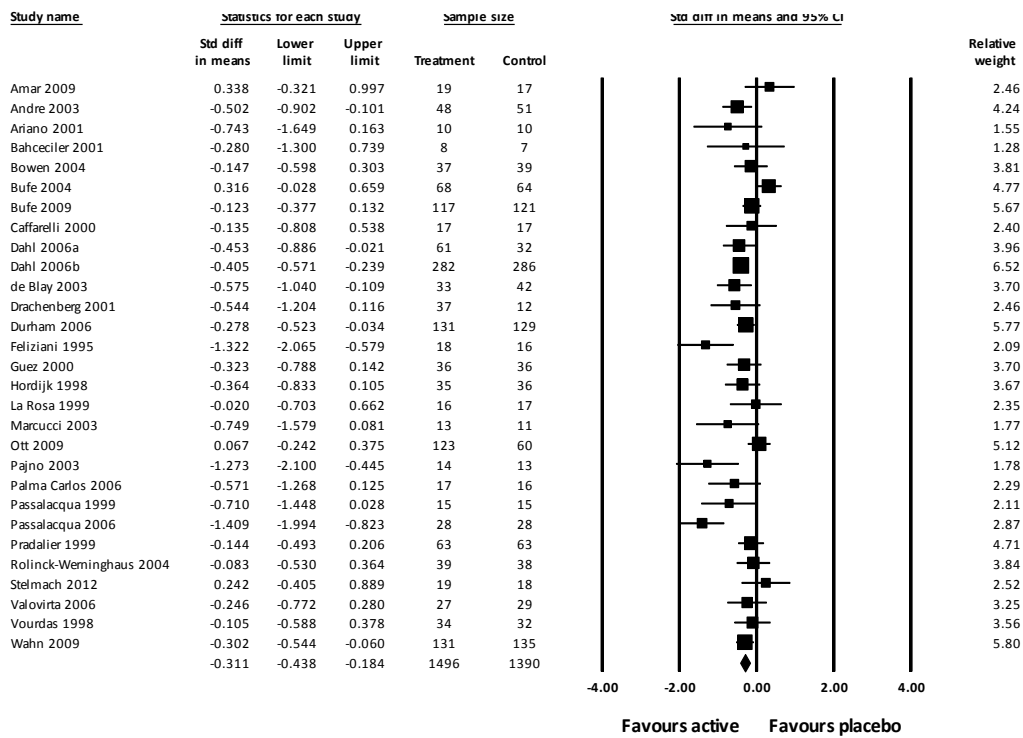


Heterogeneity: $\tau^2 = 0.126$; $\chi^2 = 42.241$, $df = 15$ ($P < 0.0001$); $I^2 = 64\%$;

Test for overall effect: $Z = -4.399$ ($P < 0.0001$)

*denotes SCIT studies

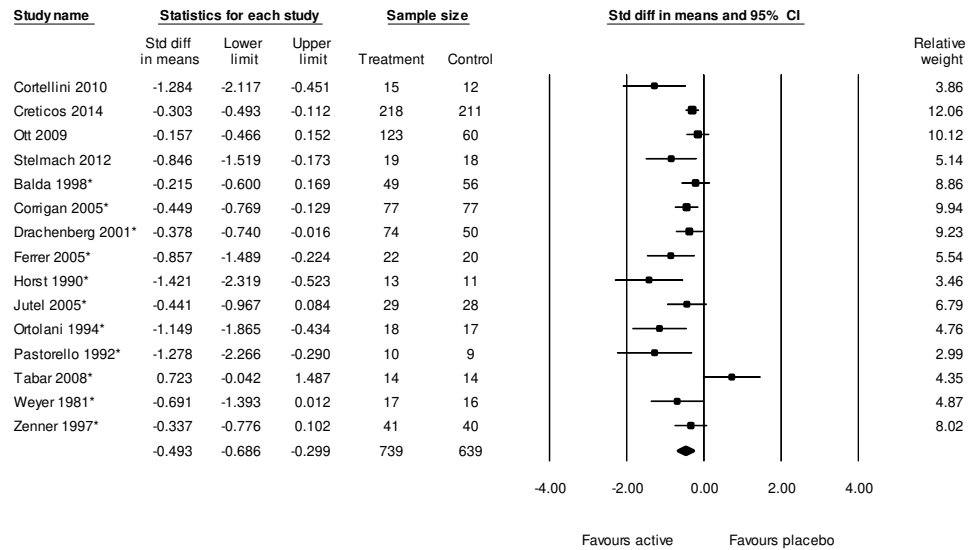
b)



Heterogeneity: $\tau^2 = 0.057$; $\chi^2 = 64.535$, $df = 28$ ($P < 0.0001$); $I^2 = 57\%$;

Test for overall effect: $Z = -4.805$ ($P < 0.0001$)

Figure 7: Meta-analysis of double-blind RCTs studies comparing combined symptom and medication scores between AIT (SCIT or SLIT) and placebo groups (random-effects model)



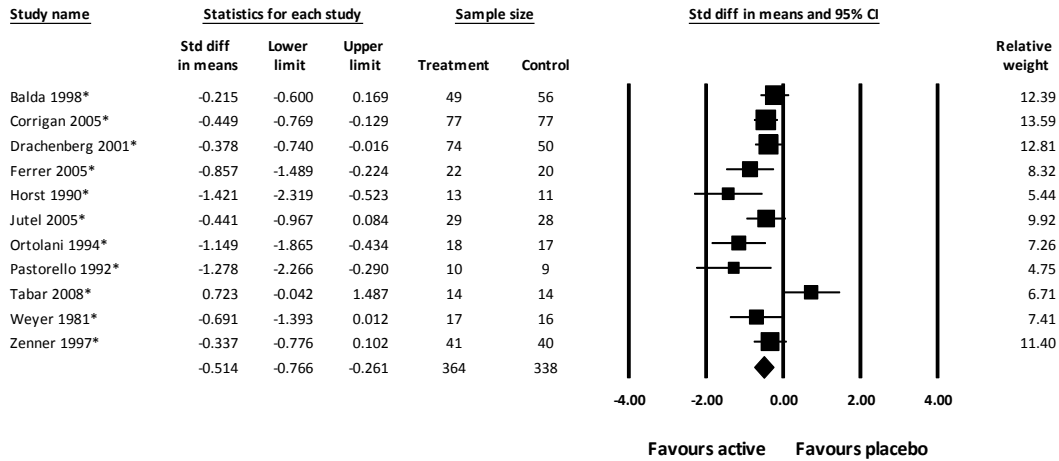
Heterogeneity: $\tau^2 = 0.071$; $\chi^2 = 33.631$, $df = 14$ ($P < 0.002$); $I^2 = 58\%$;

Test for overall effect: $Z = -4.997$ ($P < 0.001$)

*denotes SCIT studies

Figure 8: Meta-analysis of double-blind RCTs comparing combined symptom and medication scores between (a) SCIT and placebo groups and (b) SLIT and placebo groups (random-effects models)

a)

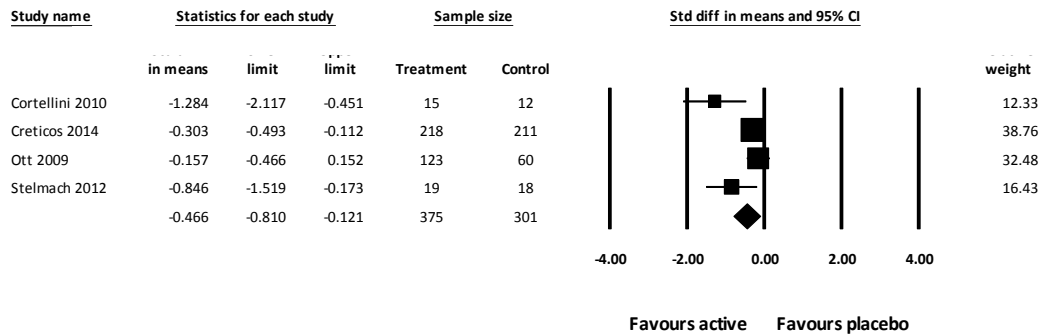


Heterogeneity: $\tau^2 = 0.096$; $\chi^2 = 23.777$, $df = 10$ ($P < 0.008$); $I^2 = 58\%$;

Test for overall effect: $Z = -3.984$ ($P < 0.0001$)

*denotes SCIT studies

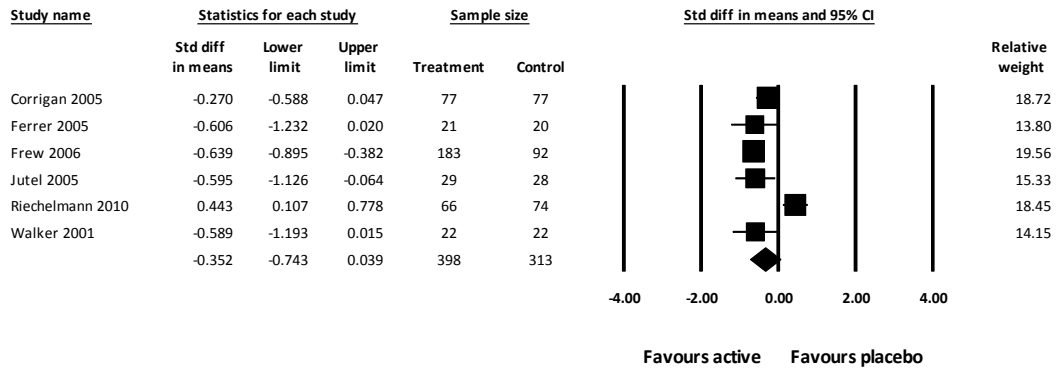
b)



Heterogeneity: $\tau^2 = 0.070$; $\chi^2 = 8.584$, $df = 3$ ($P < 0.035$); $I^2 = 65\%$;

Test for overall effect: $Z = -2.648$ ($P < 0.008$)

Figure 9: Meta-analysis of double-blind RCTs comparing quality of life scores between SCIT and placebo groups (random-effects models)



Heterogeneity: $\tau^2 = 0.186$; $\chi^2 = 28.432$, $df = 5$ ($P < 0.0001$); $I^2 = 82\%$;

Test for overall effect: $Z = -1.764$ ($P < 0.078$)