EAACI
EUROPEAN ACADEMY OF ALLERGY AND CLINICAL IMMUNOLOGY

Allergen Immunotherapy Guidelines

Part 1: Systematic reviews

Translating knowledge into clinical practice

European Academy of Allergy and Clinical Immunology

EAACI GUIDELINES

Allergen Immunotherapy Guidelines Part 1: Systematic reviews

Editors

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The European Academy of Allergy and Clinical Immunology (EAACI) is a non-profit organisation active in the field of allergic and immunologic diseases such as asthma, rhinitis, eczema, occupational allergy, food and drug allergy and anaphylaxis. EAACI was founded in 1956 in Florence and has become the largest medical association in Europe in the field of allergy and clinical immunology. It includes over 10,000 members from 122 countries, as well as over 60 national and international member societies.

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For all EAACI Members
and to our patients

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Foreword

EAACI has a long history and strong ethos in implementing the latest research findings to deliver better healthcare for patients with allergies. Over the last decades this mission has become even more important with allergic diseases now affecting the lives of millions of people around the world. This represents a major burden for patients as well as their clinicians, governments, legislators and regulators. The current challenge is to deliver appropriate treatments that are able to prevent lifetime disabilities, shifting from "treating a disease " to "promote health" in a sustainable context.

Allergen immunotherapy (AIT) has been used for a century. Several terms including "desensitization", "hyposensitization" and "vaccines" have been used, and often misused, to indicate administration of incremental doses of allergenic substances to reduce the clinical manifestations of allergy. However AIT has also been the subject of considerable controversy in terms of its efficacy. The dispute has impacted on the dissemination of knowledge about AIT, the availability of the products in many countries and the relevant policies for their reimbursement. Some of these issues result from an inadequate translation of the scientific data into daily practice, with clinical judgment being established on expert opinion instead of the objective evaluation of valid scientific studies.

These Guidelines for clinical practice aim to define the current literature and they have synthesized the scientific evidence in a well structured, systematic and reproducible process. This has been combined with the expertise of clinicians, the preferences of patients and the needs of policy makers. The purpose has been to develop clinically valid, operational recommendations which serve as a strong basis to help the allergist to advocate for AIT, practitioners to refer patients onto appropriate management, the patient to request the best standard of care for their disease and quality of life and the regulators to evaluate the sustainability for the health-care system. Of note, these recommendations cannot, and will not, stand forever but will need to be revised as soon as new research developments are available.

These guidelines follow the previous guidelines on Food Allergy and Anaphylaxis. Together, they have defined a crucial change resulting in a framework of a rigorous methodological approach for future guidelines. The ambition for EAACI is to drive the perception of clinicians and stakeholders from relying on old "pre-cooked recipes" to focusing on critical thinking and applicability of the recommendations.

Almost all the EAACI groups have worked on these AIT Guidelines. It is thanks to the tireless efforts of the many task forces Chairs, to the Sections and to the Interest Groups that we have been able to develop comprehensive Guidelines. We also need to thank the commitment of the EAACI members who contributed through the public comment, the Board of Officers and the Executive Committee and almost 100 experts from all over the world who have worked with enthusiasm and who have been instrumental to maintain the pace over the last 2 years. I feel privileged for their vision and continuous support.

This is, indeed, the start of the journey. Implementing the Guidelines both nationally and internationally will measure the success of this project. We are sure that EAACI members have the strength and dedication to accomplish this achievement.

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Abbreviations

AAI	Adrenaline auto-injector
AE	Adverse event
AHR	Airways hyperactivity
AIT	Allergen immunotherapy
AR	Allergic rhinitis / allergic rhinoconjunctivitis
BHR	Bronchial hyperactivity
BSACI	British Society for Allergy & Clinical Immunology
CASP	Critical appraisal skills programme
CBA	Controlled before-after
CCT	Controlled clinical trials
CDSR	Cochrane database of systematic reviews
CI	Confidence Interval
CMA	Cow's milk allergy
DARE	Database of reviews of effectiveness
DBPCFC	Double-blind, placebo-controlled food challenge
DR-QoL	Disease-related quality of life
EAACI	European Academy of Allergy and Clinical Immunology
EED	Economic evaluation database
EPIT	Epicutaneous immunotherapy
EPOC	Cochrane effective practice & organisation of care
HDM	House dust mite
HEA	Hen's egg allergy
HTA	Health Technology Assessments
ICER	Incremental cost-effectiveness ratio
ICS	Inhaled corticosteroid
IgE	Immunoglobulin E
ILIT	Intralymphatic immunolotherapy
IgG4	Immunoglobulin G4
IT	Immunotherapy
ITS	Interrupted time series
LEAP	Learning early about peanut allergy study
LR	Local reaction
NNT	Number needed to treat
Nc	Number in control group
NHS	UK National Health Service
Ni	Number in intervention group
NICE	National Institute for Health & Clinical Excellence
NR	Not reported
NRS	Non-randomised studies
OAS	Oral allergy syndrome
OFC	Oral food challenge
OIT	Oral immunotherapy
OR	Odds ratio
PAT	Preventive allergy treatment study
PEF	Peak Expiratory Flow
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PROSPERO	International prospective register of systematic review
PSSRU	Personal Social Services Resource Unit
QALY	Quality-adjusted life years
QOL	Quality of life
RCT	Randomised controlled crial
ROB	Risk of bias
RQLQ	Rhinoconjunctivitis quality of life questionnaire
RR	Risk ratios
Rx	Treatment
SBPCFC	Single-blind, placebo-controlled food challenge
SCIT	Subcutaneous Immunotherapy
SIT	Specific immunotherapy
SLIT	Sublingual Immunotherapy
sIgE	Specific Immunoglobulin- E
SMD	Standardised Mean Difference
SPT	Skin Prick Test
SR	Systematic reaction
UK	United Kingdom
USA	United States of America
VIT	Venom immunotherapy
VQLQ	Vespid allergy quality of life questionnaire
WAO	World Allergy Organisation
WBE	Whole body extract

Preface

A third of the population in Europe now suffers from at least one allergic disease. Allergic rhinitis, asthma, food allergy and other allergies represent major burdens to individuals, families and to health services. We now have a good understanding of these diseases and how to manage them. Most patients have good disease control and quality of life with avoidance strategies and simple pharmacotherapy. Unfortunately, a minority still have persistent symptoms or remain at risk of life-threatening allergic reactions; they need additional therapy.

Allergen immunotherapy (AIT) is an approach where administration of allergen can be used to ameliorate a specific IgE associated response thereby controlling allergic disease symptoms. The therapy has been used for over a century and there have been considerable advances in the approach over the last decade. Typically the subcutaneous, sublingual or oral routes are used. AIT has the capacity to control allergic symptoms that are not responsive to avoidance strategies or pharmacotherapy; it may also change the natural history of allergic disease.

These AIT Guidelines have been prepared by the European Academy of Allergy and Clinical Immunology's (EAACI) AIT Guidelines Taskforces in a Presidential project chaired by Antonella Muraro and coordinated by Graham Roberts. They aim to provide evidence-based recommendations for the use of AIT for patients with allergic disease. As such, their primary audience are clinical allergists, although the guidelines will be of relevance to other healthcare professionals (e.g. primary care workers, other specialist doctors, nurses and pharmacists working across a range of clinical settings) dealing with allergic disease. We have tried to anticipate the patient journey across the health system and potential pathways to envisage the potential service delivery in different contexts and countries.

The Guidelines have been generated using the Appraisal of Guidelines for Research & Evaluation (AGREE II) approach which is a structured approach to developing guidelines. In following this approach, the Taskforces have ensured that there has been appropriate representation of the full range of stakeholders, a careful search for and critical appraisal of the relevant literature, a systematic approach to the formulation and presentation of recommendations and steps to ensure that the risk of bias is minimized at each step of the process. The process started in April 2015 beginning with detailed face-to-face discussions agreeing the process and the key clinical areas to address, followed by face-to-face meetings and regular web-conferences in which professional and lay representatives participated.

This two part book represents a compilation of the underpinning systematic reviews, the guideline documents plus position papers focusing on regulatory aspects and primary care. All the documents have been published in Allergy, Pediatric Allergy and Immunology or Clinical and Translational Allergy; they are reproduced with permission of the publishers. Part 1 of the book focuses on the systematic reviews with chapters covering the prevention of allergy (Chapter 1), insect venom allergy (Chapter 2), IgE-mediated food allergy (Chapter 3), allergic asthma (Chapter 4) and allergic rhinoconjunctivitis (Chapter 5). Meanwhile, Part 2 of the book includes the guideline documents plus the regulatory and primary care position papers. A considerable amount of supplementary materials are available for each of the chapters. These can be downloaded from the EAACI website.

This massive project has only been possible with the active engagement of numerous friends and colleagues. We would like to thank the Taskforce Chairs who have successfully steered each of the chapters to completion: Susanne Halken (Prevention) with support from Moises Calderon, Gunter Sturm and Eva-Maria Varga (Venom), Giovanni Pajno and Montserrat Fernandez Rivas (Food allergy), Ioana Agache, Susanne Lau and Marek Jutel (Allergic Asthma), Oliver Pfaar and Graham Roberts (Allergic Rhinoconjunctivitis), Stefan Vieths and Andreas Bonertz (Regulatory paper) and Dermot Ryan, Liz Angier, Ronald van Ree and Roy Gerth van Wijk (Primary care and health economics papers). Also, we would like to thank Frans Timmermans of the EAACI Patient's organizations committee for coordinating

the input of the patient representatives into the guideline process. The Taskforces have been supported by a team of methodologists led by Aziz Sheikh; we are especially indebted to the help of Sangeeta Dhami and Stefania Arasi. We would like to thank EAACI for funding this project and the headquarters for supporting it. We are very grateful to all the Taskforce members who have dedicated time to be actively involved in this project, reviewing evidence and then generating recommendations. Also, a huge thanks to our external experts and EAACI members who have taken time to review the draft guidelines and provide feedback; this has helped us ensure that the final versions are accurate and relevant for healthcare professionals and patients.

These Guidelines have been an exciting and important journey. Unlike pharmacotherapy, AIT has the potential to really modify our patients' journeys delivering them long term therapeutic benefit. Now that we have evidence-based recommendations, we need to all work to disseminate and implement them for the benefit of all our patients. This will rely on the involvement of healthcare professionals from across health systems. We hope that this EAACI book will serve as a key educational resource for this process.

Graham Roberts and Antonella Muraro

Editors

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ALLERGEN IMMUNOTHERAPY FOR THE PREVENTION OF ALLERGY

A SYSTEMATIC REVIEW AND META-ANALYSIS

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***Background**: There is a need to establish the effectiveness, cost-effectiveness and safety of allergen immunotherapy (AIT) for the prevention of allergic disease.*

***Methods**: Two reviewers independently screened nine international biomedical databases. Studies were quantitatively synthesized using random-effects meta-analyses.*

***Results**: A total of 32 studies satisfied the inclusion criteria. Overall, meta-analysis found no conclusive evidence that AIT reduced the risk of developing a first allergic disease over the short-term (RR=0.30; 95% CI 0.04 to 2.09) and no randomized controlled evidence was found in relation to its longer-term effects for this outcome. There was however a reduction in the short-term risk of those with allergic rhinitis developing asthma (RR=0.40; 95% CI 0.30 to 0.54), with this finding being robust to a pre-specified sensitivity analysis. We found inconclusive evidence that this benefit was maintained over the longer-term (RR=0.62; 95% CI 0.31 to 1.23). There was evidence that the risk of new sensitization was reduced over the short-term, but this was not confirmed in the sensitivity analysis (RR=0.72; 95% CI 0.24 to 2.18). There was no clear evidence of any longer-term reduction in the risk of sensitization (RR=0.47; 95% CI 0.08 to 2.77). AIT appeared to have an acceptable side-effect profile.*

***Conclusions**: AIT did not result in a statistically significant reduction in the risk of developing a first allergic disease. There was however evidence of a reduced short-term risk of developing asthma in those with allergic rhinitis, but it is unclear whether this benefit was maintained over the longer-term. We are unable to comment on the cost-effectiveness of AIT.*

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BACKGROUND

Over recent decades, allergen immunotherapy (AIT) has been investigated and used for the treatment of allergic rhinitis (AR)/rhinoconjunctivitis, asthma and venom allergy. AR and asthma often co-exist and up to 50% of patients with AR have bronchial hyperreactivity (BHR) (1). Children with AR have over three times greater risk of developing asthma later on in life when compared to those without AR (2), especially those with BHR (3). Studies assessing the long-term effectiveness of AIT–especially in those with AR–suggest that AIT might reduce the risk of developing asthma (4, 5). AIT may also result in a reduced risk for development of new allergic sensitization(s) suggesting a possible mechanism through which this protection is conferred (6, 7, 8). As a consequence, interest has broadened from a sole focus on the therapeutic effects of AIT treatment to one that also includes investigation of the potential preventive effects of AIT.

Several populations might benefit from the preventive effects of AIT. Firstly, in healthy individuals, with or without IgE-sensitization, AIT might prevent the development of allergic diseases. Secondly, in individuals with allergic manifestations at any stage, AIT may prevent the development of other allergic conditions such as the development of asthma in those with AR. Finally, AIT may prevent the development of addiitonal sensitization in patients who are already sensitized, as well as the spreading of allergic sensitization at the molecular level.

The European Academy of Allergy and Clinical Immunology (EAACI) is in the process of developing Guidelines for AIT. This systematic review is one of five inter-linked evidence syntheses conducted in order to provide a state-of-the-art synopsis of the current evidence base in relation to evaluating AIT for the treatment of AR, food allergy, venom allergy, allergic asthma and its role in allergy prevention. The focus of this review is on assessing the preventive capacity of AIT. The information derived from this systematic review will help to inform key clinical recommendations and the identification of future research needs. The potential effect of early introduction of different food allergens into the diet of infants will not be addressed in this review, since it will be covered by the planned update of the prevention part of the EAACI Food Allergy and Anaphylaxis Guidelines.

AIMS

We sought to assess the effectiveness, cost-effectiveness and safety of AIT for the prevention of allergic disease and allergic sensitization.

METHODS

Details of the methodology used for this review, including search terms and filters; databases searched; inclusion and exclusion criteria; data extraction and quality appraisal have been previously reported (9). We therefore confine ourselves here to a synopsis of the methods employed.

Inclusion criteria

Patient characteristics

We were interested in studies on subjects of any age with or without allergic sensitization(s) and subjects with or without allergic disease.

Interventions and comparators

We were interested in AIT administered through any route (e.g. subcutaneous (SCIT), sublingual (SLIT)) compared with no intervention, placebo or any active comparator using different allergens (e.g. pollens, house dust mites (HDM)), including modified allergens.

Outcomes

Primary outcomes

The primary outcomes of interest were the development of first allergic disease or of a new allergic disease, in those with a previous allergic condition, assessed over the short-term (i.e. <2 years of completion of AIT) and longer-term (i.e. ≥2 years post-completion of AIT) using well defined diagnostic criteria.

Secondary outcomes

Secondary outcomes were: the development of: new allergic sensitization(s) (or allergic immunresponse(s)); spreading of allergic sensitization(s) from one allergen to other non-related allergen(s); spreading of allergic sensitization(s) at molecular level, from one allergenic molecule to other molecules; development of new oral allergy syndrome (OAS); health economic analyses 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 (10, 11).

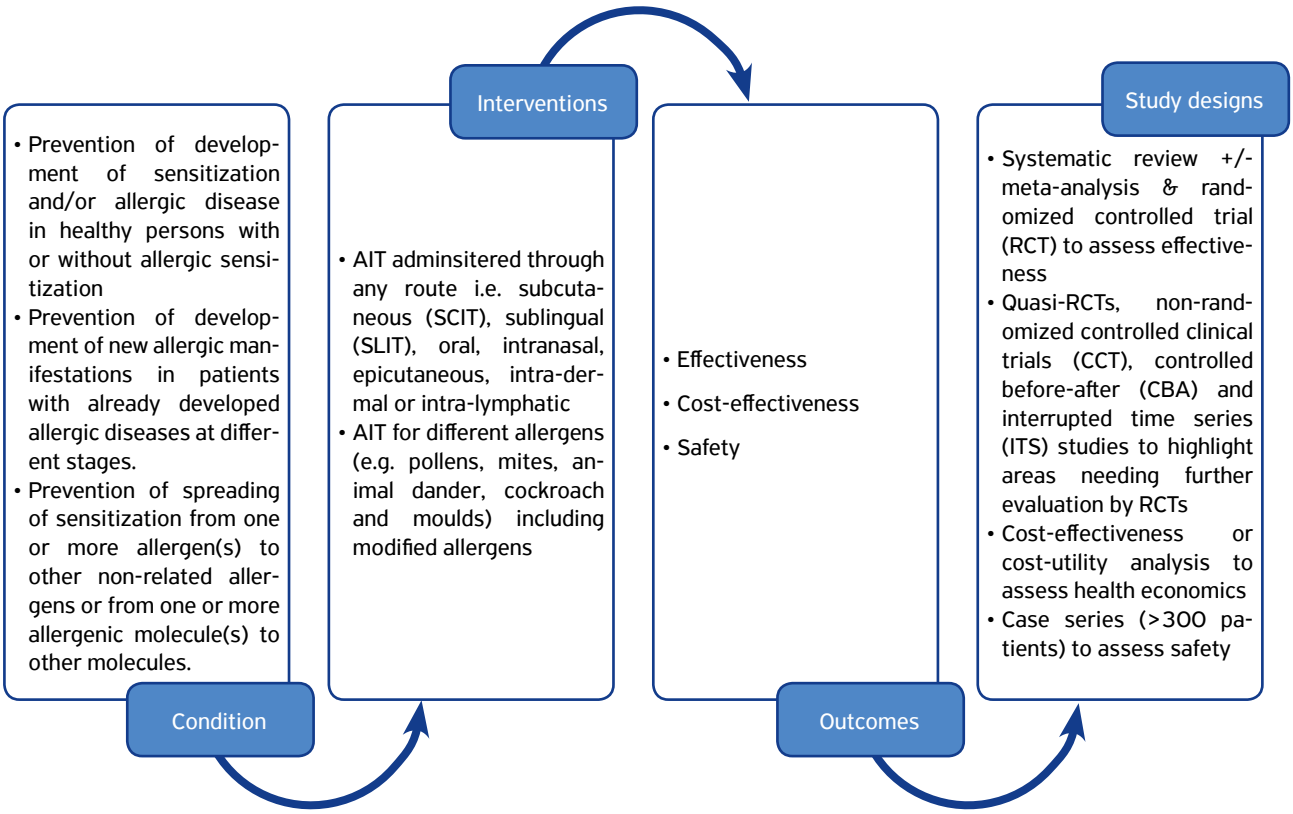

Figure 1 Conceptualization of systematic review of allergen immunotherapy for the prevention of allergic disease

Study design

We were interested in systematic reviews, randomized controlled trials (RCTs), quasi-experimental studies, health economic analyses, and large case series with a minimum of 300 patients.

Search strategy

Our search strategy (Appendix 1.1) was conceptualized to incorporate the four elements shown in Figure 1. Additional unpublished work and research in progress was identified through discussion with experts in the field (Appendix 1.2). No language restrictions were employed.

Quality assessment

Quality assessment was conducted using established tools as detailed in the protocol (9). Assessments were independently carried out on each study by two reviewers. Any discrepancies were resolved by discussion or, if agreement could not be reached, by arbitration by a third reviewer.

Data analysis and synthesis

Data were independently extracted onto a customized data extraction sheet in DistillerSR by two reviewers, and any discrepancies were resolved by discussion or, if agreement could not be reached, by arbitration by a third reviewer.

A descriptive summary with data tables was produced to summarize the literature. Where possible and appropriate, meta-analysis was undertaken using random-effects meta-analyses using Stata (version 14).

Sensitivity and subgroup analyses, and assessment for publication bias

Sensitivity analyses were undertaken by comparing the summary estimates obtained by excluding studies judged to be at high risk of bias with those judged to be at low or moderate risk of bias.

Subgroup analyses were undertaken to compare:

- Children versus adults
- Route of administration
- Allergens used for AIT.

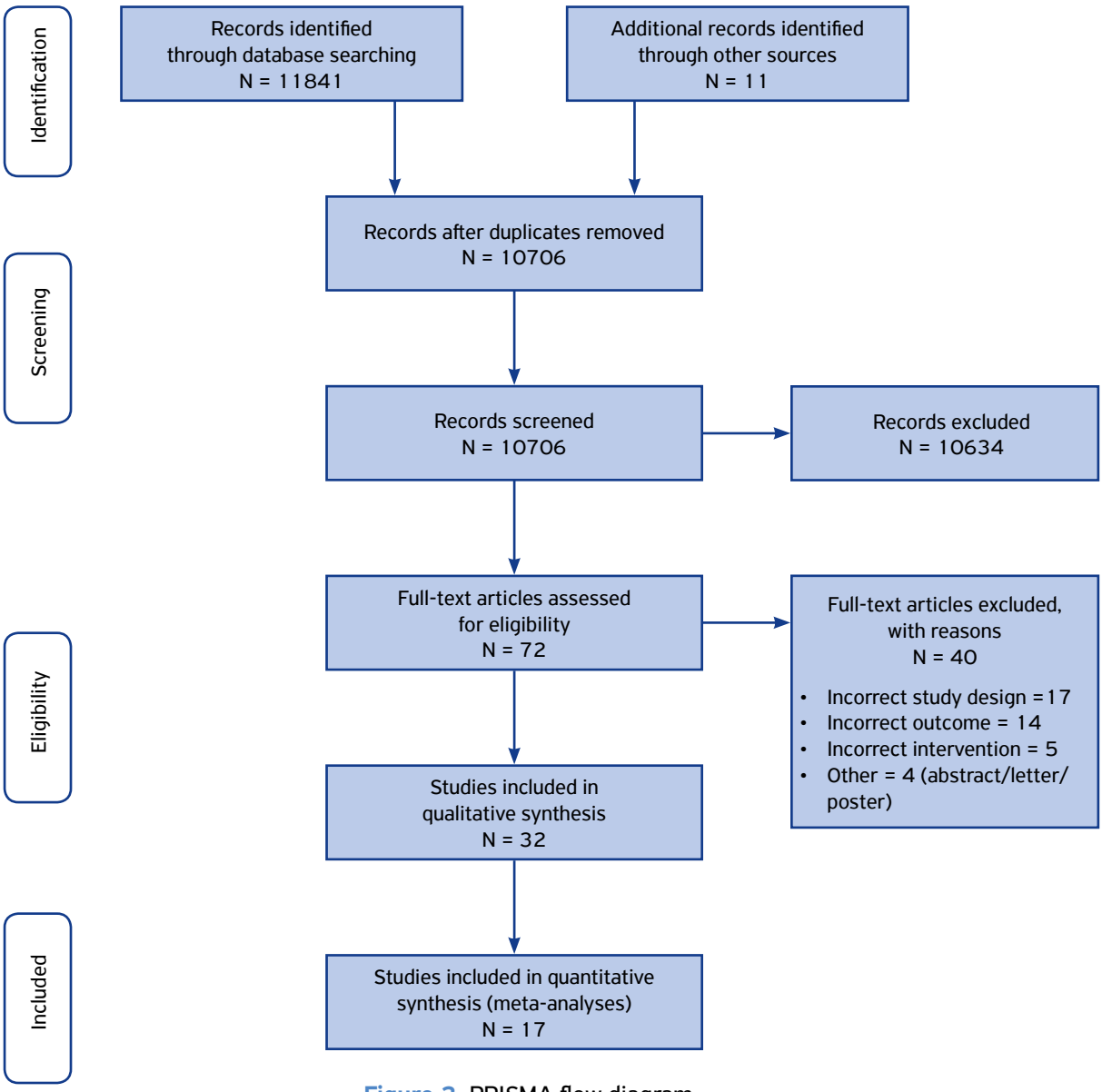

Figure 2 PRISMA flow diagram

We were unable to assess publication bias through the creation of funnel plots due to the small number of studies, but were able to use Eggar's test (12).

Registration and reporting of this systematic review

This systematic review is registered with PROSPERO with registration number: CRD42016035380. It is reported in accordance with the PRISMA guidelines (Appendix 1.3).

RESULTS

Overview of studies

We identified a total of 10,706 potentially eligible studies after removal of duplicates. Of these, 32 studies reported in 34 publications and one entry into an online trial repository fulfilled the inclusion criteria (Figure 2) (3, 6-8, 13-43).

In terms of study design, 17 RCTs and 15 controlled-before-after (CBA) studies were identified. The key characteristics and main findings of the RCTs can be found in Table 1 and for the CBAs in Table 2. Nineteen

Table 1 Characteristics and main findings from RCTs

Author/ year/ country	Number of studies (N) / subjects included(n) / age	Participants: Disease status	Specified primary outcome, and secondary outcomes of interest	Comparators (intervention/controls)/ route of administration	Type of allergy and allergens used for AIT	Quality	Main outcome/key findings	Comment
PRIMARY OUTCOME: DEVELOPMENT OF NEW ALLERGIC DISEASE IN PREVIOUSLY HEALTHY SUBJECTS OR DEVELOPMENT OF A SECOND ALLERGIC DISEASE IN SUBJECTS ALREADY SUFFERING FROM ANOTHER ALLERGIC DISEASE								
Crimi, 2004, Italy	n=30 15 randomized to receive injections of Parietaria pollen vaccine, 15 received placebo injections Age range: 20-54 yrs.	Non-asthmatic subjects with seasonal rhinitis and monosensitized to *Parietaria judaica*.	Effect on development of asthma and bronchial hyperresponsiveness.	SCIT vs. placebo Rapid updosing cluster regimen for 7 weeks, followed by monthly injections for 34 months.	Allergic rhinitis. Parietaria pollen.	Medium	A total of 9/29 patients developed asthma symptoms at the end of the study: of these 7 (47%) were in the placebo group, 2(14%) in the SCIT group (P=0.056). No changes seen in bronchial hyper-responsiveness to methacholine or sputum eosinophilia.	Authors conclude that Parietaria SCIT appears to prevent natural progression of allergic rhinitis to asthma suggesting that SCIT should be considered earlier in the management of AR, however the results were not statistically significant.
Grembiale, 2000, Italy	n=44 22 randomized to receive increasing doses of house dust mite allergen extract subcutaneously, 22 received placebo. Age range: 10-38 yrs.	Subjects with a documented history of atopic rhinitis, no reported symptoms compatible with asthma.	Effect on development of asthma and bronchial hyperresponsiveness.	SCIT vs. placebo Increasing doses of allergen extract followed by monthly maintenance treatment.	Allergic rhinitis. House dust mite.	High	None of the SCIT group developed asthma at the end of the 2-yrs treatment period compared to 9% in the placebo group (p=0.49). At end of study, methacholine $PD_{20}FEV_1$ was within normal range of 50% of treated subjects ($p<0.0001$) and it was significantly higher in intervention group compared to placebo group ($p<0.0001$). No changes in methacholine $PD_{20}FEV_1$ in placebo group throughout the study.	All subjects had normal lung function test at inclusion and were well matched on methacholine responsiveness at the beginning of the study. All subjects underwent Methacholine challenge after 1 yr and 2 yrs of treatment. Positive correlation between methacholine $PD_{20}FEV_1$ before SCIT and magnitude of improvement in bronchial reactivity suggest that early intervention is likely to be of greater benefit.

Table 1 Continued

Author/ year/ country	Number of studies (N) / subjects included(n) / age	Participants: Disease status	Specified primary outcome, and secondary outcomes of interest	Comparators (intervention/controls)/ route of administration	Type of allergy and allergens used for AIT	Quality	Main outcome/key findings	Comment
Holt, 2013, USA and Australia	n=50 25 randomized to receive mixture of soluble allergens given daily for 12 months, 25 randomized to placebo. Age range: 18-3 months, subsequently reduced to 12 months.	Children with positive atopic family history; a personal history of atopic dermatitis, and sensitization to one or more food allergen.	Effect on development of asthma and sensitizations, safety.	SLIT (drops) vs. placebo. 12 months course of SLIT. Outcome assessment at 48 months.	Atopic dermatitis. House dust mite, cat, timothy grass.	Medium	No difference in asthma prevalence between the two groups (4/25 in SLIT group; 4/25 in placebo group) at 48 months. No significant differences in rates of sensitization.	Since there was no differences in antibody titers between active and placebo group at the 6-month sampling point, recruitment was terminated and the study status changed to pilot study.
Jacobsen, 2007, multi-sited study (Europe) Niggemann, 2006 Möller, 2002	n=205 at baseline, 103 randomized to 3 yrs of subcutaneous SIT, 102 served as open control group. Age range at baseline: 6-14 yrs. Total follow up at 10 yrs: n=147 (79 from intervention group, 68 controls). Follow-up at 5 years (2 years after end of treatment): 183. Follow-up at 3 years (end of treatment): 191.	Children with history of birch and/or grass pollen induced seasonal AR.	Effect on development of asthma and bronchial hyperresponsiveness.	SCIT vs. no intervention 3-year course of SCIT after a 0-season. Up-dosing performed with depot extracts with weekly injections over 15-20 weeks or as rush immonutherapy with aqueous extracts. Maintenance injections every 6 weeks for 3 yrs.	Allergic rhinitis. Grass, birch.	Low	Longitudinal treatment effect shows OR for no-asthma 4.6 (95% CI; 1.5-13.7) in favour of SCIT group after 10 years. At 5 yrs. follow-up, SCIT-group had significantly less asthma compared to controls (OR 2.68, 95% CI; 1.3-5.7). Result after 3 years i.e. at end of treatment show significantly fewer asthma symptoms among actively treated children compared to controls (OR 2.52, P<0.05). No significant differences between SCIT and control group in bronchial responsiveness to methacholine in change from baseline of PC20 after 10 years.	Treatment effect was adjusted for bronchial hyperresponsiveness and asthma status at baseline, and includes observations at 3, 5 and 10 yrs follow-up. Authors conclude that findings from the 10 yrs. follow up demonstrated the long-lasting benefit of SCIT in relation to prevention of asthma.

Table 1 Continued

Author/ year/ country	Number of studies (N) / subjects included(n) / age	Participants: Disease status	Specified primary outcome, and secondary outcomes of interest	Comparators (intervention/controls)/ route of administration	Type of allergy and allergens used for AIT	Quality	Main outcome/key findings	Comment
Marogna, 2008, Italy	n=216 144 randomized to SLIT, 72 received drugs only. Age range: 5-17 yrs.	Children with allergic rhinitis with/without intermittent asthma.	Effect on development of asthma, new sensitizations and bronchial hyperreactivity. Safety.	SLIT vs. pharmacotherapy. Build-up phase for approx. 50 days followed by SLIT 3 times a week in the maintenance phase. SLIT administered as drops. 98 for mites, 41 for grasses, 4 for birch, and 1 for Parietaria.	AR, asthma. Mite, grass, birch, Parietaria.	Low	Higher occurence of intermittent and persistent asthma in control group (30/66, 45.4%) compared to the SLIT group (17/130, 13.1%). Lower occurence of new sensitizations in SLIT group (4/130) than among controls (23/66) (OR 0.06; 95% CI, 0.02-0.17). Increased rate of polysensitizations in control group compared to SLIT group (OR SLIT vs. control at yr. 3: 0.33; 95% CI, 0.17-0.61). One patient reported systemic itching	Patients were followed up for 3 yrs. Adherence to SLIT was 80% or higher in 73.8% of patients. No difference in dropout frequency between groups. Reduced onset of new sensitizations and intermittent or mild persistent asthma, and decreased bronchial hyperreactivity in children 3 years after treatment.
Möller, 1986, Sweden	n=30 14 randomized to active capsules (birch pollen preparation), 16 to placebo. Age range: 8-16 yrs.	Children with rhinoconjunctivitis.	Effect on development of asthma and safety (part of aim of studying immune responses during OIT).	Oral (capsules) vs. placebo. Treatment with capsules continued for 10 months.	Rhinoconjunctivitis due to birch pollinosis. Birch.	Medium	No development of asthma in oral IT arm compared with 5 patients in the placebo arm.	Similar side effects noted (nausea, abdominal colic, diarrhea) in both groups. No systemic reactions seen.
Novembre, 2004, Italy	n=113 54 randomized to SLIT group, 59 randomized to standard symptomatic therapy. Age range: 5-14 yrs.	Children with hay fever limited to grass pollen.	Effect on development of asthma.	SLIT (drops) vs. pharmacotherapy. A 3-year coseasonal protocol was used consisting of build-up and maintenance phases with an extract of mixed grass pollens. SLIT was administered for 4 months a year.	Hay fever due to grass pollen. Mixed grass pollens.	Medium	After first year of treatment, 6 of the SLIT patients had asthma compared to 6 in the control group. After the second year, 7 SLIT patients and 16 controls had asthma (p=.058). After the third year, 8 SLIT patients and 18 controls had asthma (P=.0412). Relative risk of development of asthma after 3 years was 3.8 (95 CI; 1.5-10.0) in control group compared to intervention group.	At entry into the study, no subject reported seasonal asthma with more than 3 episodes per season.

Table 1 Continued

Author/ year/ country	Number of studies (N) / subjects included(n) / age	Participants: Disease status	Specified primary outcome, and secondary outcomes of interest	Comparators (intervention/controls)/ route of administration	Type of allergy and allergens used for AIT	Quality	Main outcome/key findings	Comment
Song, 2014, China	n=102 51 randomized to SCIT, 51 to pharmacotherapy/symptomatic treatment only. Age: >5 yrs.	Patients with AR allergic to house dust mites.	Effect on onset of asthma and development of new sensitizations.	SCIT vs. pharmacotherapy. SCIT for 3 yrs. with initial updosing followed by maintenance once every 6 weeks for 3 yrs.	AR, asthma. House dust mite.	Low	In the SCIT group no patients developed asthma and few new sensitizations occurred (2/43, [4.7%]). In the control group, 9/41 (22%) developed asthma and 17/41 (41.5%) new sensitizations. Differences were statistically significant (p<0.01).	Follow-up 2 yrs. after discontinuation of SCIT. Authors conclude that early application of SCIT can prevent the development of asthma.
Valovirta, multinational (11 European countries)	n=812 after seven months of screening Age range: 5-12 yrs.	Patients with grass pollen-induced AR, without asthma, and no overlapping symptomatic allergies.	Time to onset of asthma	SLIT vs. placebo once daily for 3 years, followed by a blinded observational period of 2 years. SQ-standardized grass allergy immunotherapy tablet	Grass.	High	In SLIT group of 398 patients 34 developed asthma and in the control group of 414, 39 developed asthma defined by strict diagnostic criteria including beta-2-reversibilitest, no difference demonstrated between groups P=0.67. At the end of the five year trial period the number of subjects with asthma symptoms or asthma medication usage in the SLIT group was less than in the placebo group (OR 0.66; P 0.036; 95%CI [0.45;0.97]).	Not yet published but data available at EudraCT
Yamanaka, 2015, Japan	n=29 (27 due to withdrawal during the course of the study). 13 were randomized to SLIT group, 14 to placebo group. Age range: 18-52 yrs.	Asymptomatic subjects sensitized to Japanese cedar pollen.	Effect on development of cedar pollinosis.	SLIT vs. placebo. SLIT group received graded extracts of standardized Japanese cedar pollen followed by maintenance therapy.	Sensitized to pollen. Japanese cedar pollen.	Low	No significant difference in development of symptoms of pollionosis between groups after first year of treatment (4 in SLIT/1 in placebo group). In the second year, 7 of the placebo group and none of the SLIT group developed symptoms. Ratio of development of pollinosis in the SLIT group was significantly lower than in the placebo group in the second year of the trial (p=.0098, Fisher's exact test).	Significant increase in IL-10 producing T cells and B cells in SLIT group, Significant decrease in IL-10 producing monocytes in placebo group.

Table 1 Continued

Author/ year/ country	Number of studies (N) / subjects included(n) / age	Participants: Disease status	Specified primary outcome, and secondary outcomes of interest	Comparators (intervention/controls)/ route of administration	Type of allergy and allergens used for AIT	Quality	Main outcome/key findings	Comment
Zolkipli, 2015, United Kingdom	n=111 57 assigned to house dust mite oral IT, 54 assigned to placebo. Age range: less than 1 yr.	Infants at high risk of atopy (2 or more first-degree family members with allergic diseases (asthma, AR, eczema, or food allergy) but negative skin prick test responses to common allergens at randomization.	Effect on development of eczema, wheeze, and food allergy; development of sensitizations and, and adverse events/ safety.	Oral AIT (drops) vs. placebo. House dust mite extract and placebo solution were administered orally twice daily for 12 months.	High risk. House dust mite.	High	No effect on house dust mite sensitization, eczema, wheeze, and food allergy. Significant reduction (P=.03) in sensitization to any common allergen (16%; 95% CI 1.7-30.4%) in the active group (5[9.4%]) compared to the placebo group (13[25.5%]) after 12 months of treatment. Treatment was well tolerated with no differences in numbers or nature of adverse events between groups.	Children were assessed every 3 months. Differences in morbidity and pet ownership across groups did not influence direction or size of estimated differences in outcomes.
SECONDARY OUTCOME: DEVELOPMENT OF NEW ALLERGIC SENSITIZATION(S) (OR ALLERGIC IMMUNRESPONSE(S)) AFTER END OF INTERVENTION								
Dominicus, 2012, Germany	n=154 77 patients were randomized to receive SCIT with grass pollen, 77 were assigned to placebo group. Follow-up included 26 patients from ex-SCIT group and 13 control patients. Age range:18-60 years.	Adult patients allergic to grass pollen with rhinoconjunctivitis with or without asthma.	Effect on development of new sensitizations.	SCIT vs. placebo. Patients received weekly pre-seasonal subcutaneous immunotherapy with either grass pollen extract or placebo for 2 yrs. Both groups received active treatment in the third treatment yr.	Grass pollen allergy. Grass pollen.	Low	Number of patients who did not develop new sensitizations during the 3 year's follow-up after cessation of SCIT was higher in Ex-SCIT group (20 patients, 77%) compared to control group (3 patients, 23%).	This prospective follow-up study ended 3 yrs after cessation of SCIT. Authors conclude that SCIT has long-term effects in reducing onset of new sensitizations.
García, 2010, Spain	n=56 37 patients were randomized to the SLIT group, 17 were in the placebo group. Age range: 18-65 yrs.	Peach-allergic patients.	Effect on development of new sensitizations.	SLIT vs. placebo. Treatment with standardized peach extract or placebo continued for 6 months.	Peach allergy. Peach.	High	A total of 3 patients in the SLIT group developed clinically irrelevant sensitizations. No new sensitizations in the placebo group.	New sensitizations were to single allergens and rated as of scarce magnitude and no clinical relevance.

Table 1 Continued

Author/ year/ country	Number of studies (N) / subjects included(n) / age	Participants: Disease status	Specified primary outcome, and secondary outcomes of interest	Comparators (intervention/controls)/ route of administration	Type of allergy and allergens used for AIT	Quality	Main outcome/key findings	Comment
Limb, 2006, USA	n=82 41 were randomized to immunotherapy, 41 to placebo. Subjects were enrolled in childhood (age at inclusion 5-12 yrs) and followed up in adulthood (age at follow-up 17-31yrs).	Children with moderate-to-severe asthma.	Effect on development of new sensitizations	SCIT vs. placebo. SCIT was given with a mixture of up to seven aeroallergen extracts and maintenance injections continued every 2 weeks for 24 months, and every 3 weeks until debriefing.	Asthma. Broad-spectrum aero-allergens.	Medium	Similar acquisition of new skin test sensitivities from time of randomization into original childhood trial to debriefing (15 vs. 20%; p=0.28) and to adult follow-up (30 vs. 31%; p=0.75) among both SCIT and placebo group. 23/41 (56%) in the SCIT group vs. 31/41 (76%) in the placebo group acquired one or more new sensitivity between randomization and debriefing (p=0.19). From debriefing to adult follow-up, 38/40 (95%) in the SCIT group vs. 33/39 (85%) in the placebo group acquired at least one more new sensitivity.	The 82 evaluated patients did not differ from the remaining 39 patients from the original trial with regard to age, ethnicity, gender, number of positive skin tests or treatment-designated allergens at randomization, or total serum IgE (all p-values >0.1). Long-term evaluation of broad-spectrum IT (mean follow -up 10.8 yrs). Types of new ensitivities were similar between treatment and placebo groups.
Marogna, 2004, Italy	n=511 319 patients were randomized to SLIT, 192 patients to control group. Mean age SLIT group = 22.8 yrs Mean age control group = 21.5 yrs.	Patients with allergic rhinitis with/without intermittent asthma.	Effect on development of new sensitizations, safety/ adverse events.	SLIT vs. pharmacotherapy. Patients were evaluated in an observation period of 1 yr, followed by SLIT prescribed for relevant allergens in a build-up and maintenance phase for approximately 3 yrs.	AR, asthma. Mites, grass, birch, parietaria, mugworth.	Low	Significantly lower incidence of new sensitizations in SLIT group (16/271 [5.9%]) compared to pharmacotherapy group (64/170 [38%]) at the end of the 3-yrs. treatment period (p < 0.0001). Four of 271 patients (1.5%) reported one episode of generalized itching within 30 min. of taking the dose, all appeared in maintenance phase and self-resolved without therapy in <2 hours. Five dropouts in SLIT group due to adverse events (oral itching, asthma, abdominal pain).	Adherence to SLIT measured by volume of remaining extract. During the 3yrs of study,70 patients dropped out: 48 (15%) in SLIT group, 22 (12%) in control group. No significant overall difference between the two groups.

Table 1 Continued

Author/ year/ country	Number of studies (N) / subjects included(n) / age	Participants: Disease status	Specified primary outcome, and secondary outcomes of interest	Comparators (intervention/controls)/ route of administration	Type of allergy and allergens used for AIT	Quality	Main outcome/key findings	Comment
Pifferi, 2002, Italy	n=29 15 patients were randomized to SCIT group, 14 to control group. Age range: 6-14 yrs.	Children with asthma and monosensitizedto house dust mite.	Effect on development of new sensitizations, bronchial hyperreactivity and safety.	SCIT vs. Pharmacotherapy (?) After a 1-yr. run-in period, SCIT were administered through gradually increasing doses until maximum tolerated dose. SCIT continued for 3 yrs.	Asthma, AR. House dust mite.	Medium	SCIT group showed significant decrease in non-specific bronchial hyperreactivity. The ratio of incidence of "non-improvement" in bronchial reactivity in the SCIT group compared to controls was 0.3; 95%CI 0.11-0.87). No new sensitivity occured in SCIT group whilst 5/10 in the control group developed new sensitizations (P=0.01). No major local or systemic side-effects reported during the study.	All SCIT patients reached the suggested dose for maintenance phase. Four dropouts in control group. Treatment and control groups were matched for age, asthma severity, respiratory function and bronchial hyperreactivity.
Szépfalusi, 2015, Austria	n=31 15 randomized to SLIT group with either grass pollen or house dust mite extract according to the individual sensitization profile), 16 randomized to placebo group. Age range: 2-5 yrs.	Healthy persons with allergic sensitizations but no clinical disease.	Effect on development of new sensitizations. Safety.	SLIT vs. placebo. After dose-up phase, therapy continued for 2 yrs.	Sensitization to pollen and/or mites. House dust mite, grass.	High	Preventive application of SLIT in young children was safe (no relevant side effects in 21.170 single applications). No difference in rate of new sensitizations in SLIT group compared to placebo group after 12 and 24 months of treatment. Verum-treated patients had a significant up-regulation of allergen-specific IgG (p<0.05) and IL10-dependent inhibition was observed in vitro in treatment group but not in placebo group.	Children were mono/ oligoclonally sensitized, clinically asymptomatic. Rate of new Sensitizations increased significantly over time in both groups.

Table 2 Characteristics and main findings from CBAs

Author/ year/ country	Number of studies (N) / subjects included(n) / age	Participants: Disease status	Specified primary outcome, and secondary outcomes of interest	Comparators (intervention / controls) / route of administration	Type of allergy and allergens used for AIT	Quality	Main outcome / key findings	Comment
PRIMARY OUTCOME: DEVELOPMENT OF NEW ALLERGIC DISEASE IN PREVIOUSLY HEALTHY SUBJECTS OR DEVELOPMENT OF A SECOND ALLERGIC DISEASE IN SUBJECTS ALREADY SUFFERING FROM ANOTHER ALLERGIC DISEASE								
Schmitt, 2015, Germany	n=118,754 stratified into one group exposed to AIT in 2006 (n=2,431) or an unexposed group (n=116,323) All ages included.	Patients with AR but without comorbid asthma. AR at least two ICD-10 codes for AR.	Effect on onset of asthma.	AIT stratified as SCIT, SLIT drops, SLIT tablets, and combinations.	Asthma. All types of allergens used for AIT included.	Low	Risk of incident asthma was significantly lower in patients exposed to AIT (RR, 0.60;95% CI, 0.42-0.84) compared to patients not exposed to AIT in 2006. Sensitivity analyses found significant preventive effects of SCIT (RR, 0.57; 95% CI, 0.38-0.84) and AIT including native allergens (RR, 0.22; 95% CI, 0.02-0.68) but no statistical significance for SLIT drops, or combinations of SCIT and SLIT. AIT for 3 yrs. tended to have stronger preventive effects than AIT for a shorter duration (RR, 0.62; 95% CI, 0.39-0.98 vs. 0.57; 95% CI, 0.34-0.94). No effect modification by age and sex was observed.	Consecutive cohort of patients based on routine health care data from German National Health Insurance beneficiaries. Exposed and unexposed groups were observed for incident asthma from 2007-12. Authors conclude that AIT effectively prevents asthma in patients with AR in a real-world setting.

Table 2 Continued

Author/ year/ country	Number of studies (N) / subjects included(n) / age	Participants: Disease status	Specified primary outcome, and secondary outcomes of interest	Comparators (intervention / controls) / route of administration	Type of allergy and allergens used for AIT	Quality	Main outcome / key findings	Comment
SECONDARY OUTCOME: DEVELOPMENT OF NEW ALLERGIC SENSITIZATION(S) (OR ALLERGIC IMMUNRESPONSE(S)) AFTER END OF INTERVENTION								
Asero, 2004, Italy	n=691 284 patients received SCIT as part of routine outpatient care, 407 not undertaking SCIT served as controls. Age range: >12 years	Patients monosensitized to airborne allergens (grass, pellitory, ragweed, birch or house dust mite) first seen between Jan 1st 1989-Dec 31st 1998 and reevaluated no less than 2 years after the first visit/after the end of SCIT.	Effect on development of new sensitizations	SCIT/pharmacotherapy. SCIT was administered following a perennial schedule. Patients enrolled in SCIT treatment according to own choice. Weekly doses given during build-up phase followed by maintenance doses.	Sensitization to pollen. Grass, pellitory, birch, ragweed, house dust mite.	Low	Significantly higher prevalence of new sensitizations to ragweed and/or birch pollen in subjects receiving SCIT (132/284; 46%) than among controls (95/407; 23%) (p<0.001). Denovo sensitizations to other airborne allergens (besides ragweed and birch pollen) were rare and did not show any difference between SCIT and control groups.	No preventive effect against denovo sensitizations to birch and ragweed pollen in adult monosensitized patients.
Des Roches, 1997, France	n=44 22 patients received SCIT, 22 age-matched patients served as controls. Age range: 2-6 yrs.	Children with asthma and monosensitizedto house dust mite.	Effect on development of new sensitizations	SCIT vs. pharmacotherapy. Rush immunotherapy and maintenance injections using a standardized Dermatophagoides pteronyssinus extract. Follow-up on an annual basis for 3 yrs.	Asthmatic children sensitized to house dust mites. *Dermatophagoides pteronyssinus*.	Low	Ten of 22 children in SCIT group (45%) did not develop new sensitizations compared to none of the 22 children in the control group. Occurence of new sensitizations was thus significantly less in SCIT group compared to controls (p<0.001).	The findings suggest that SCIT in asthmatic children monosensitized to house dust mites alters the natural course of allergy by preventing the development of new sensitizations.

Table 2 Continued

Author/ year/ country	Number of studies (N) / subjects included(n) / age	Participants: Disease status	Specified primary outcome, and secondary outcomes of interest	Comparators (intervention / controls) / route of administration	Type of allergy and allergens used for AIT	Quality	Main outcome / key findings	Comment
Di Rienzo, 2003, Italy	n=60 35 accepted treatment with SLIT, 25 received only medication. Age range: 3-17, mean age 8.5 yrs.	Children with AR and/or mild to moderate asthma due to house dust mites.	Effect on development of new sensitizations.	SLIT vs. pharmacotherapy. SLIT was administered continuously for 4-5 yrs. according to guidelines.	AR with/without asthma. 28 children were monosensitized to mites alone, the remaining patients had concomitant sensitizations. House dust mite.	Low	No significant difference in onset of new sensitizations in the two groups. Only 3/35 patients in SLIT group and 2/25 patients in control group developed new sensitizations during the 10 yrs. period.	Patients were evaluated at baseline, end of SLIT and 4-5 yrs. after SLIT discontinuation.
Eng, 2006, Switzerland	n=28 included in the original study and self-assigned to receive either SCIT (n=14) or standardized pharmacotherapy (n=14) for 3 yrs. At 6 yrs. follow-up after discontinuation of SCIT, 13 SCIT patients and 10 controls were included. At 12 yrs. of follow-up, 12 SCIT patients and 10 controls were included. Age range at inclusion: 5-16 yrs.	Children with a history of severe grass pollen AR for at least 2 yrs. with/without asthma but with immunoglobulin (Ig)E-mediated sensitivity to seasonal allergens only (grass pollen with/without tree pollen).	Effect on development of new sensitizations.	SCIT vs. pharmacotherapy. Grass pollen SCIT was administered preseasonally for 3 years.	AR, asthma. Grass.	Low	Six yrs. after discontinuation of SCIT, a significantly lower number of SCIT patients had developed new sensitizations (8/13) compared to controls (10/10) ($p<0.02$). There was a significantly lower occurence of new sensitizations in SCIT group compared to controls at 12-yrs follow-up (58% vs. 100%; $p<0.05$).	The two study groups were matched for gender, age, prevalence of seasonal asthma, and wheal size at study enrollment. This prospective follow-up study finds a reduction in onset of new sensitizations 6 yrs after discontinuation of SCIT. The reduction is sustained at 12 yrs. of follow-up.

Table 2 Continued

Author/ year/ country	Number of studies (N) / subjects included(n) / age	Participants: Disease status	Specified primary outcome, and secondary outcomes of interest	Comparators (intervention / controls) / route of administration	Type of allergy and allergens used for AIT	Quality	Main outcome / key findings	Comment
Gulen, 2007, Turkey	n=129 patients. 70 patients accepted SCIT, 59 were treated with medication only. Age range: 6-10 yrs.	Children with asthma monosensitized to house dust mite.	Effect on development of new sensitizations.	SCIT vs. pharmacotherapy. SCIT was administered for four yrs.	Asthma. House dust mite.	Low	At the end of the 6-yrs. study period, a total of 41 (33%) of patients had developed new sensitizations. Significantly higher prevalence of new sensitizations in SCIT group (31/68; 45.5%) compared to controls (10/55; 18.1%) (OR 3.77, 95% CI, 1.52-9.5, p=0.001).	The study found no association between family history of atopy and development of new allergic sensitizations.
Harmanci, 2010, Turkey	n=122 patients. 62 patients accepted SCIT, remaining 60 patients were treated with medication only. Age range: 8-18 yrs.	Children with intermittent asthma with/ without AR, monosensitized to house dust mite.	Effect on development of new sensitizations.	SCIT vs. pharmacotherapy. SCIT was administered for four yrs.	Asthmawith/ without AR. House dust mite.	Low	No significant difference in development of new sensitizations after the 4-yrs. study period. A total of 36/53 (67.9%) patients in SCIT group had no new sensitizations compared to 38/52 (73.0%) in control group (P=0.141).	Authors conclude that SCIT may not prevent onset of new sensitizations in asthmatic children who are monosensitized to house dust mites.
Inal, 2007, Turkey	n=147 45 patients underwent SCIT with absorbed extracts, 40 patients underwent SCIT with aqueous extracts, 62 patients were controls receiving only pharmacologic treatment. Age range: 6-16 yrs.	Children with rhinitis and/ or asthma monosensitized to house dust mite.	Effect on development of new sensitizations.	SCIT vs. pharmacotherapy. SCIT treatment continued for 5 yrs. Follow-up at end of treatment. SCIT group was subdivided into absorbed extracts and aqueous extracts because the latter was used more commonly than absorbed extracts at the beginning of the study.	AR/asthma. House dust mite.	Low	At 5 year follow-up, a total of 64/85 (75.3%) in the SCIT group showed no new sensitizations compared to 29/62 children (46.7%) in the control group (P=.002).	SCIT was recommended to all patients. Those who rejected SCIT were included as controls. Children developing new sensitizations had higher atopy scores compared to those who did not develop new sensitizations. The same pattern was observed in the SCIT group but this was not statistically significant.

Table 2 Continued

Author/ year/ country	Number of studies (N) / subjects included(n) / age	Participants: Disease status	Specified primary outcome, and secondary outcomes of interest	Comparators (intervention / controls) / route of administration	Type of allergy and allergens used for AIT	Quality	Main outcome / key findings	Comment
Marogna, 2010, Italy	n=78 57 in SLIT group subdivided into different length of SLIT (3 yrs: 19; 4 yrs: 21; 5 yrs:17) 21 patients in control group. Adult patients (mean age of 22.2 +/- 5.2 yrs. at inclusion).	Patients with allergic rhinitis with/without asthma lasting for at least 2 yrs and monosensitized to house dust mites.	Effect on development of new sensitizations and bronchial hyperreactivity. Safety.	SLIT for 3, 4 or 5 yrs. vs. pharmacotherapy. Build-up phase for approx. 50 days followed by SLIT 3 times a week in the maintenance phase.	AR, asthma, sensitized to house dust mites. House dust mite.	Low	New sensitizations occurred in all control subjects over 15 yrs. Among the SLIT group, 3/14 (21.4%) in the SLIT3 group, 2/16 (12.5%) in the SLIT4 group, and 2/17 (11.7%) in the SLIT5 group developed new sensitizations. Difference in occurence of new Sensitizations across SLIT and control group became significant at year 6 (P=.03). 5 patients had transient oral itching during build-up phase, 2 patients reported 1 episode of generalized itching on maintenance. All adverse events occurred 30 min. after dosing and spontaneously disappeared.	The study-design was prospective, open, controlled, 4-parallel-group, partially randomized. If patients refused SLIT,they were assigned to the control group. Assignment to groups was made yearly. Length of follow -up was 15 yrs. All dropouts were due to protocol deviations. Adherence to SLIT greater than 80% measured by volume of extract in returned vials.
Ohashi[a], 2009, Japan	n=159 80 in mite immunotherapy group, 27 in house dust mite IT group, 52 in pharmacotherapy group. Age: >20 yrs.	Patients monosensitized to house dust mites.	Effect on development of new sensitizations	IT (unknown route) for 4 yrs using a) *D. farinae* extracts (mite immunotherapy group) or b) house dust mite mixtures vs. pharmacotherapy.	Monosensitized to mites. House dust mite.	Unclear	Four years after enrollment, the incidence of new sensitizations to pollen was 28.0% in the pharmacotherapy group, 6.3% in the mite IT group, and 22.2% in the house dust mite IT group. Significantly lower incidence of new sensitizations in mite IT group compared to control group (p=0.0008), but no significant differences between HD IT group and controls (p=0.5999).	Patients were divided into groups according to their own choice.

Table 2 Continued

Author/ year/ country	Number of studies (N) / subjects included(n) / age	Participants: Disease status	Specified primary outcome, and secondary outcomes of interest	Comparators (intervention / controls) / route of administration	Type of allergy and allergens used for AIT	Quality	Main outcome / key findings	Comment
Ohashi[b], 2009, Japan	n=176, 194 in pollen immunotherapy group, 72 in pharmacotherapy group. Age: adult.	Patients monosensitized to Japanese cedar pollen.	Effect on development of new sensitizations	IT (unknown route) for 4 yrs. vs. pharmacotherapy	Monosensitized to Japanese cedar pollen. Japanese cedar pollen.	Unclear	After four years of follow-up, there were no significant differences in new sensitizations (to other types of pollen) between groups.	Patients were divided into groups according to their own choice. Authors conclude that new sensitizations in allergic patients can be inhibited by mite immunotherapy but not by immunotherapy using other kinds of allergen extracts.
Pajno, 2001, Italy	n=134 enrolled 75 patients in SCIT group, 63 children in control group according to own choice. Age range: 5-8 yrs.	Children with intermittent asthma with/ without rhinitis monosensitized to house dust mite.	Effect on development of new sensitizations.	SCIT vs. pharmcotherapy. SCIT with mite mix was administered during the first three years in the intervention group. After induction phase, maintenance dose was administered once a month for 3 years.	AR, asthma. House dust mite.	Low	At the end of the 6-year study period, 52/69 (75.4%) patients in the SCIT group showed no new sensitizations compared to 18/54 (33.3%) in the control group ($p<0.0002$). Authors conclude that SCIT may prevent onset of new sensitizations in children with respiratory symptoms monosensitized to house dust mite.	Allocation to treatment vs. control arm dependent upon parent's willingness to accept SCIT. All patients had intermittent asthma at enrolment. All patient's parents were instructed to decrease exposure to mites (e.g. by frequent vacuuming, washing sheets at least once a week, removal of plants/ soft toys from bedroom). Both groups were followed for a total of 6 yrs.

Table 2 Continued

Author/ year/ country	Number of studies (N) / subjects included(n) / age	Participants: Disease status	Specified primary outcome, and secondary outcomes of interest	Comparators (intervention / controls) / route of administration	Type of allergy and allergens used for AIT	Quality	Main outcome / key findings	Comment
Purello-D'Ambrosio, 2001, Italy	n=8396 Group A included 7182 patients given SCIT for 4 yrs. Followed by drugs for at least 3 yrs. Group B included 1214 patients treated only with drugs for at least 7 yrs. Age range: >13 yrs old.	Patients with allergic rhinitis and/or asthma monosensitized to respiratory allergens.	Effect on development of new sensitizations	SCIT vs. pharmacotherapy. Patients in group A underwent SCIT with relevant allergens for 4 yrs. with an induction phase followed by maintenance injections at 4-week intervals.	Asthma, AR, monosensitization. Parietaria, grass, olea, Compositae (mix), Corylaceae-Betulaceae (mix), mites.	Low	Significantly lower risk of new sensitizations in SCIT group (1706/7182, [23.75%]) compared to controls (826/1214, [68.03%]) after 4 yrs. of treatment. Three yrs. later, 1936/7182 (26.95%) among SCIT group and 932/1214 (76.77%) in control group had developed new sensitizations. Both comparisons were highly significant ($p<0.0001$). Asthmatic patients, treated with SIT or not, were more prone to develop polysensitization compared to patients with rhinitis only.	Effect of SCIT observed retrospectively SCIT was proposed to all patients. Those who accepted were allocated into group A. Both groups were divided into subgroups according to presence of asthmatic symptoms at enrolment. All patients were followed-up as outpatients in the period 1980-99. Authors conclude that specific immunotherapy reduced new sensitizations in monosensitized subjects suffering from respiratory allergic diseases.
Reha, 2007, Turkey	n=107 56 patients in the SCIT group, 51 patients in the control group. Age range: 7-12 yrs.	Children with intermittent asthma sensitized to house dust mite or pollen species.	Effect on development of new sensitizations.	SCIT vs. pharmacotherapy.	Asthma, AR, monosensitization to grass pollen species or house dust mites. House dust mite, grass.	Low	At 5 years follow-up, 35/43 (81.39%) of patients in house dust mite IT group and 10/13 (76.92%) patients in grass pollen IT group showed no new sensitizations. In the control group, 20/51 (53.84%) had developed new sensitizations. Difference between SIT groups and control group was statistically significant ($p=0.033$).	SCIT and control group were matched for age, asthma and/or AR severity, and respiratory function. Authors conclude that SCIT appears to prevent development of new sensitizations.

Table 2 Continued

Author/ year/ country	Number of studies (N) / subjects included(n) / age	Participants: Disease status	Specified primary outcome, and secondary outcomes of interest	Comparators (intervention / controls) / route of administration	Type of allergy and allergens used for AIT	Quality	Main outcome / key findings	Comment
Tella, 2003, Spain	n=100 66 were treated with SCIT, 34 received medication only. Age range: 6-69 yrs.	Patients with AR and/or asthma monosensitized.	Effect on development of new sensitizations.	SCIT vs. pharmacotherapy. Duration of treatment was at least 3 yrs.	AR, asthma, monosensitization to grass pollen, *Parietaria judaica* pollen or *Dermatophagoides spp.* Grass pollen, *Parietaria judaica, Dermatophagoides pteronyssinus, Dermatophagoides farinae.*	Low	No statistically significant differences in risk of developing new sensitizations between SCIT group and controls (RR=0.97, 95% CI, 0.72-1.3). A total of 24/66 (36.4%) patients in the SCIT group had new sensitizations compared to 13/34 (38.2%) among controls.	Comparisons were made between baseline and after 3-5 yrs. of SCIT.

Table 3 Quality assessment of RCTs

Author, year	Design	Adequate sequence generation	Allocation concealment	Blinding patients/ personnel	Blinding of outcome assessors	Incomplete outcome data addressed	Free of selecting reporting	Free of other bias*	Overall quality assessment
Crimi, 2004	RCT	Yes	Yes	Yes	Yes	No	Yes	No	Medium
Dominicus, 2012	RCT	Unclear	Yes	Yes	No	Unclear	No	No	Low
Garcia, 2010	RCT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Grembiale, 2000	RCT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Holt, 2013	RCT	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Medium
Jacobsen, 2007	RCT	Yes	Yes	No	No	No	Yes	No	Low
Limb, 2006	RCT	Yes	Yes	Yes	Yes	No	Yes	No	Medium
Marogna, 2004	RCT	Yes	No	No	No	Yes	Yes	No	Low
Marogna, 2008	RCT	Unclear	No	No	No	Yes	Yes	No	Low
Möller, 1986	RCT	Unclear	Yes	Yes	Yes	No	Yes	No	Medium
Novembre, 2004	RCT	Yes	No	No	No	Yes	Yes	No	Medium
Pifferi, 2002	RCT	Unclear	Unclear	Unclear	Yes	No	Yes	Yes	Medium
Song, 2014	RCT	Yes	No	Unclear	Unclear	No	Yes	Yes	Low
Szepfalusi, 2014	RCT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Valovirta, 2016	RCT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Yamanaka, 2014	RCT	No	Unclear	Unclear	Unclear	Yes	Yes	Yes	Low
Zolkipli, 2015	RCT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High

studies included children; eight studies enrolled adults only; and five studies included both child and adult subjects. The numbers of subjects included in these studies varied from 28 to 691 for the majority (N=30) of studies. However, two CBAs reported on substantially larger populations: 8,396 subjects (7), and 118,754 subjects (16), respectively.

The allergens in the AIT studied were HDM, peach, pollen from grass, birch, ragweed, Japanese cedar or *Parietaria Judaica, Cladosporium herbarum, Penicillium notatum, Aspergillus fumigatus, Alternaria alternata, Mucor racemosus, Quercus alba, Cynodon dactylon, Ambrosia elatior, Plantago lanceolata, Phleum pratense/Dactylis glomerata/Lolium perenne* (PDL) grass mix, *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*, either as single allergens or as multiple allergens. Peach was the only food allergen included in the identified AIT studies. The routes of administration were SCIT, oral and SLIT in the form of tablets and drops.

The overall quality of the identified RCTs varied with five RCTs judged to be at low risk of bias (8, 14, 19, 31, 42) six at medium risk (13, 18, 23, 24, 35, 40) and six at high risk of bias (3, 17, 22, 25, 28, 37). All CBAs were judged to be at high risk of bias (Tables 3 and 4).

Our main findings are presented according to primary and secondary outcomes of the review.

Table 4 Quality assessment of CBAs

Author, year	Design	Adequate sequence generation	Allocation concealment	Blinding patients/ personnel	Blinding of outcome assessors	Incomplete outcome data addressed	Free of selecting reporting	Free of other bias*	Overall quality assessment
Asero, 2004	CBA	No	No	No	No	Yes	Yes	No	Low
Des Roches 1997	CBA	No	No	No	No	Yes	Yes	No	Low
Di Rienzo, 2003	CBA	No	No	No	No	Yes	Yes	No	Low
Eng 2006	CBA	No	No	No	No	Yes	Yes	No	Low
Gulen, 2007	CBA	No	No	No	No	Yes	Yes	No	Low
Harmanci, 2010	CBA	No	No	No	No	Yes	Yes	No	Low
Inal, 2007	CBA	No	No	No	No	Yes	Yes	No	Low
Marogna, 2010	CBA	No	No	No	No	Yes	Yes	No	Low
Ohashi, 2009	CBA	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low
Ohashi, 2009	CBA	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low
Pajno, 2001	CBA	No	No	No	No	Yes	Yes	No	Low
Purello D'Ambrosia, 2001	CBA	No	No	No	No	Yes	Yes	No	Low
Reha, 2007	CBA	Unclear	Unclear	Unclear	Unclear	Yes	Yes	No	Low
Schmitt, 2015	CBA	No	No	No	No	Yes	Yes	No	Low
Tella, 2003	CBA	No	No	No	No	Yes	Yes	No	Low

Primary outcomes: development of new allergic disease

We identified 12 studies reported in a total of 14 publications and an entry into an online trial repository on the effectiveness of AIT for the prevention of development of new allergic disease in previously healthy subjects or in subjects already suffering from one or more allergic disease (3, 8, 13, 15-25). All except the study by Schmitt (16) were RCTs. The Preventive Allergy Treatment (PAT) study reported two updates from the same trial (i.e. three reports in total) (3, 20, 21).

Two RCTs investigated the preventive effects of AIT in relation to development of the first allergic disease in healthy asymptomatic individuals. They focused on the effect of SLIT on cedar pollinosis (25), or oral AIT on eczema, wheeze and food allergy (8), respectively.

The majority of studies (N=8) focused on the preventive effect of AIT in relation to the development of asthma in patients with established AR (3, 14, 15, 17-24). SCIT was used in four of these RCTs (3, 17-21) whilst SLIT through drops or tablets were used in four RCTs (14, 15, 22-24). In the CBA study using routine healthcare data, patients were stratified according to mode of administration (i.e. SCIT, SLIT drops, SLIT tablets, and combinations of SCIT and SLIT) (16).

Short-term preventive effects of AIT

The short-term preventive effect of AIT was investigated in two RCTs judged to be at low risk of bias (8, 19), three RCTs at medium risk of bias (18,

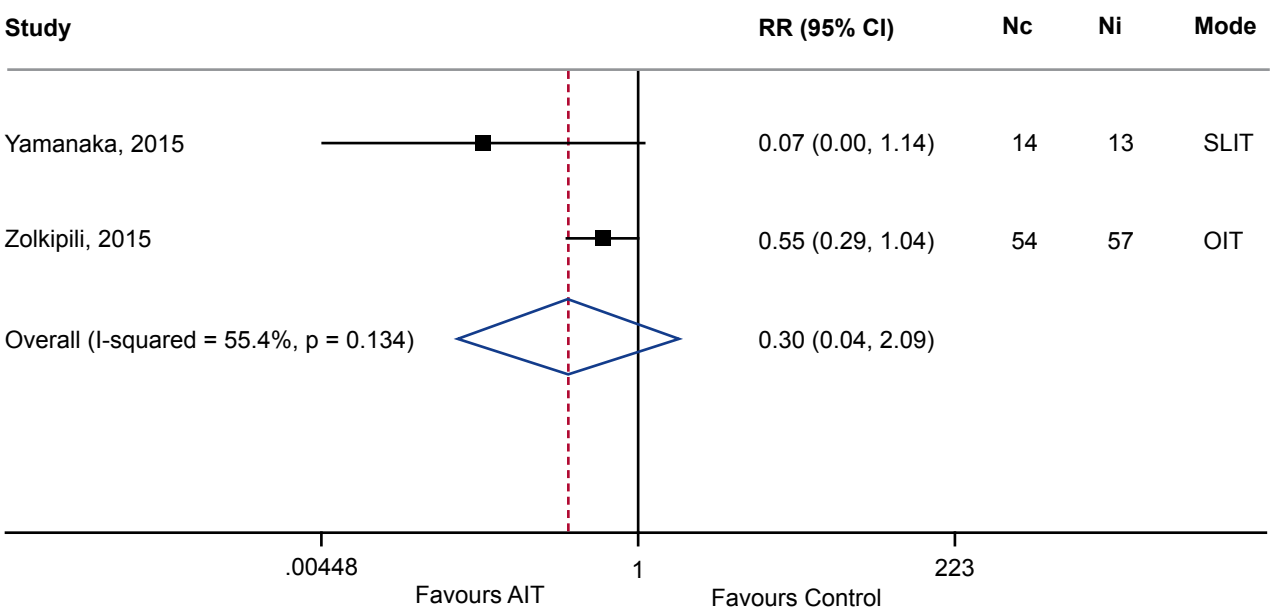

Figure 3 Random-effects meta-analysis of effectiveness of AIT in preventing short-term risk of developing first new allergic disease. Nc = number in control group; Ni = number in intervention group; mode = route of administration of AIT.

23, 24), two RCTs at high risk of bias (22, 25), and one CBA at high risk of bias (16).

In terms of mode of administration, SCIT was used in two RCTs (18, 19), oral (drops or capsules) in two RCTs (8, 23) and SLIT (tablets and drops) in the remaining three RCTs (22, 24, 25). In the CBA, SCIT, SLIT drops and SLIT tablets were administered (16).

RCTs on short-term preventive effects

Prevention of the onset of first allergic disease

The potential effects of oral AIT for the primary prevention of atopic eczema, wheeze, food allergy and sensitizations were investigated in a recent RCT at low risk of bias by Zolkipli (8). Infants at high risk of atopy based on family history of allergic diseases were randomized to receive either oral HDM AIT (drops) or placebo twice daily for a year. Upon completion of the trial, no significant difference was seen between the active or placebo groups in the risk of developing eczema (P=0.20), wheeze (P=0.40) or food allergy (P=0.26) in these children (8).

A second RCT by Yamanaka, at high risk of bias, looked at primary prevention in asymptomatic adults sensitised to Japanese cedar pollen. They were randomized to SLIT or placebo and in the second year none of the active group had developed pollinosis compared to seven in the placebo group (P=0.0098) (25).

Meta-analysis of data from these two trials showed no overall reduction in the risk of developing a first allergic disease: RR=0.30 (95% CI 0.04 to 2.09) (Figure 3). Sensitivity analysis excluding Yamanaka did not alter this conclusion.

Prevention of onset of asthma in those with established AR

An RCT at low risk of bias by Grembiale, investigating the preventive effects of SCIT administered for a two-year period to subjects with AR, found no significant differences in asthma prevalence at the end of the trial among the AIT group compared to controls (P=0.49) (19).

The RCT at medium risk of bias by Crimi investigated the effect of SCIT for three years on the development of asthma and BHR among 30 non-asthmatic adults with seasonal AR who were mono-sensitized to *Parietaria judaica* (18). No significant differences in preventive effect were identified across intervention and control group. At the end of the trial, 47% of patients in the placebo group (7/15) had developed asthma compared to 14% (2/14) in the SCIT group (P=0.056) (18).

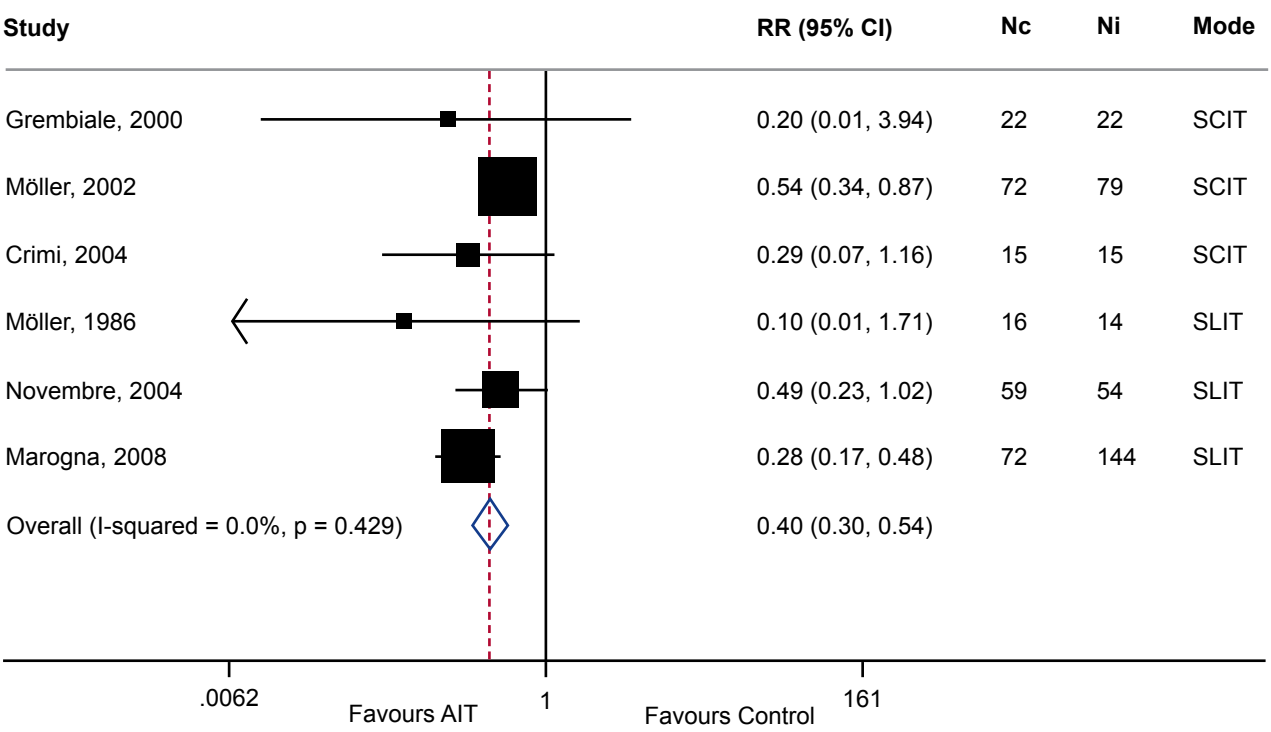

Figure 4 Random-effects meta-analysis of effectiveness of AIT in short-term prevention of asthma in those with allergic rhinitis. Nc = number in control group; Ni = number in intervention group; mode = route of administration of AIT.

The RCT by Moller, at medium risk of bias, randomized 30 children with AR to birch pollen to AIT capsules or placebo (23). They found no cases of asthma at the end of the 10-month treatment period in the AIT group and five cases out of 16 in the control group (P-value not given).

The large RCT by Novembre, at medium risk of bias, randomized 113 children, aged 5-14 with hay fever to grass pollen to SLIT drops co-seasonally for three years or conventional pharmacotherapy (24). At the end of the three year trial, the relative risk of developing asthma was 3.8 (95% CI 1.5 to 10.0; P=0.041) in control subjects compared to the SLIT group (24).

In the RCT by Marogna, at high risk of bias, 216 children with AR and intermittent asthma were randomized to SLIT or conventional pharmacotherapy for a period of three years. They found a lower occurrence of asthma in the SLIT group (30/66, 45.4%) compared with the control group (OR=0.04; 95% CI 0.01 to 0.17) (22).

Random effects meta-analysis of these five RCTs plus the short-term effects of the first publication from the PAT trial (20) demonstrated a significant reduction in the risk of developing asthma: RR=0.40 (95% CI 0.30 to 0.54) (Figure 4). There was no evidence of publication bias (P=0.27). This result remained significant after excluding the trials by Marogna and Moller (2002), which were both judged to be at high risk of bias: RR=0.38 (95% CI 0.20 to 0.72). Subgroup analyses showed that AIT was beneficial in those:

- aged <18 (RR=0.40; 95% CI 0.26 to 0.61), but not in those aged ≥18 years (RR=0.28; 95% CI 0.07 to 1.15)
- receiving SLIT (RR=0.33; 95% CI 0.21 to 0.50) and those receiving SCIT (RR=0.49; 95% CI 0.32 to 0.77)
- receiving pollen AIT (RR=0.48; 95% CI 0.33 to 0.71), but not those receiving HDM AIT (RR=0.20; 95% CI 0.01 to 3.94).

CBAs on short-term preventive effects

Prevention of the onset of first allergic disease

We found no relevant studies.

Prevention of onset of asthma in those with established AR

Only one CBA investigated the preventive effects of AIT (16). The study by Schmitt looked at 118,754 patients with AR, but with no comorbid asthma,

between 2007-12. Patients were stratified according to exposure to AIT in 2006 and followed to assess incident asthma. The authors reported a preventive effect of AIT on the progression from AR to asthma in patients exposed to AIT through any mode of administration (RR=0.60; 95% CI 0.42 to 0.84; P=0.003) compared to unexposed patients. When subdivided according to route of administration, there was a significant preventive effect of SCIT (RR=0.57; 95% CI 0.38 to 0.84; P=0.005) whereas effects of SLIT drops and combinations of SCIT and SLIT did not reach statistical significance (16).

Long-term preventive effects of AIT

There were four RCTs, one judged to be at low risk (15), one to be medium risk (13) and two assessed to be of high risk of bias (3, 17) investigating the longer-term preventive effects of AIT.

RCTs on long-term preventive effects

Prevention of onset of first allergic disease

We found no relevant studies.

Prevention of onset of asthma in those with established atopic dermatitis or AR

An RCT at medium risk of bias explored the effect of 12 months of daily SLIT on prevention of asthma and new sensitizations in children with atopic dermatitis and sensitization to one or more food allergens (13). As no differences in antibody levels between the SLIT and the placebo group could be identified six months into the trial, recruitment was terminated and the trial reduced to pilot study status. After 48 months of follow-up, there were no differences in asthma prevalence between the two groups (13).

A large yet unpublished trial at low risk of bias explored the effect of SLIT tablets on the prevention of asthma in 812 children with grass pollen allergic rhinoconjuctivitis. Based on data available in EudraCT, the trial, undertaken in mono-sensitized children carried out over a five year period with three years of treatment and two years of follow-up study, failed to demonstrate the preventive effect of AIT on the development of asthma (OR=0.9; (95% CI 0.57 to 1.43) (14, 15).

A third RCT by Jacobsen, at high risk of bias, explored the preventive effects of SCIT in relation to onset of asthma over a 10-year follow-up period (3, 20, 21). This trial enrolled 205 children with seasonal AR at baseline who were randomized to a three-year course of SCIT or no intervention. At 10-years follow-up, the adjusted treatment effect showed a significantly higher OR of not having asthma of 4.6 (95% CI 1.5 to 13.7) among subjects treated with SCIT compared to controls.

The RCT by Song, at high risk of bias, looked at patients with AR, allergic to HDM, two years after discontinuation of three years of SCIT compared to standard pharmacotherapy. They found that no (0/51) patients in the SCIT group developed asthma compared to 9/51 in the control group (P-value not given) (17).

Meta-analysis showed no overall evidence of reduction in the long term risk of developing asthma: RR=0.62; (95% CI 0.31 to 1.23) (Figure 5).

Secondary outcomes

We were planning to assess a range of six different secondary outcomes according to the protocol (9). However, we did not find studies related to spreading of allergic sensitization(s) at the molecular level, nor did we identify studies exploring development of new OAS after the end of the intervention or health economic analyses of AIT used for prevention.

In the sections below, findings related to development of new allergic sensitization(s) and safety will be described.

Development of new allergic sensitization

We found 23 studies investigating the effect of AIT on the development of new allergic sensitizations (6-8, 17, 22, 26-43) including one trial reported in two publications (29, 30). Nine studies were RCTs (8, 17, 22, 28, 31, 35, 36, 40, 42) and three of these (8, 31, 42) were assessed to be at low risk of bias. The remaining studies were all CBAs assessed to be at a high risk of bias. Of these, 12 (six RCTs and six CBAs) provided data on short-term effects and 11 (three RCTs and eight CBAs) provided data on long-term effects.

Short-term preventive effects

RCTs

There were six RCTs investigating this outcome. Three low risk of bias RCTs investigated the short-term effects of AIT on the risk of developing new sensitizations (8, 31, 42). The remaining three RCTs were moderate (40) or high risk of bias (22, 36).

The Zolkipli HDM oral AIT trial among infants at high risk of developing allergic disease found a significant reduction in sensitization to any common allergen in the active group compared to the placebo group (P=0.03) at the end of the trial, but no difference

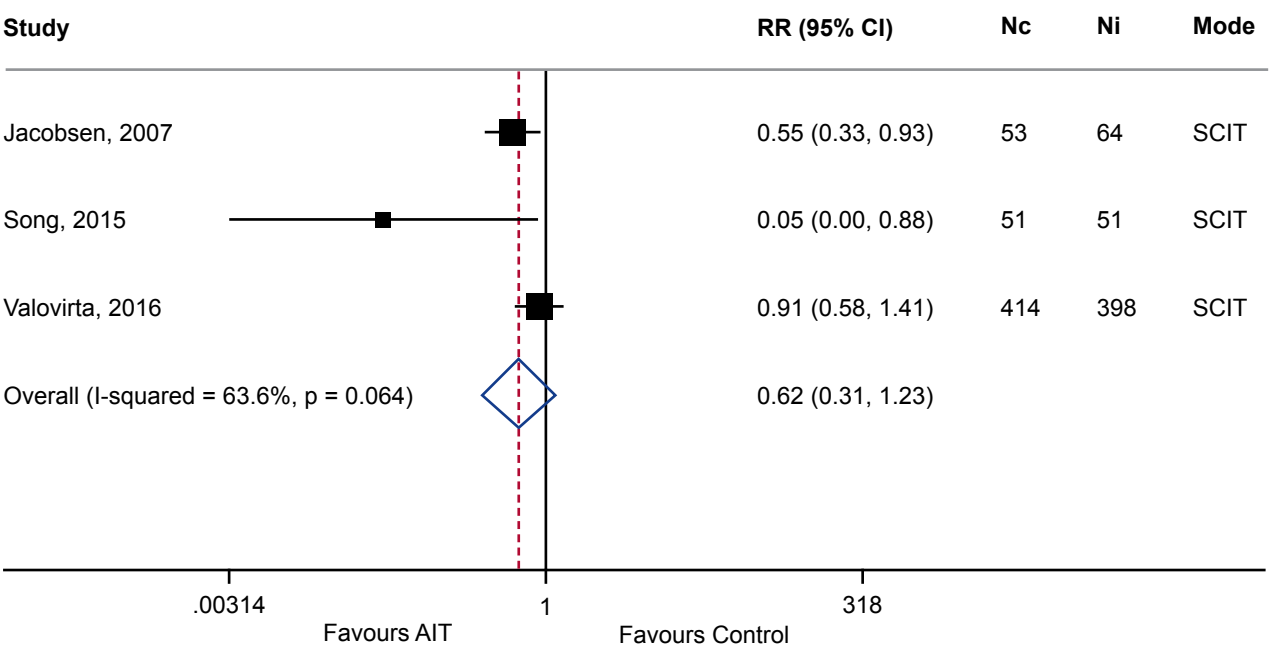

Figure 5 Random-effects meta-analysis of effectiveness of AIT in long-term prevention of asthma in those with allergic rhinitis. Nc = number in control group; vNi = number in intervention group; vmode = route of administration of AIT.

in HDM sensitization between the AIT (5.7%) and control groups (7.8%): risk difference: 2.2%; 95% CI -7.5 to 11.8; P=0.61 (8).

Garcia studied adult patients allergic to peach, and found no relevant new sensitizations in the placebo group (n=17) and three new sensitizations to single allergens among the 37 patients in the SLIT group after six months of treatment; the AIT was therefore judged to be ineffective (31).

The RCT by Szépfalusi looked at the preventive effect of SLIT with grass pollen or HDM extract in mono-sensitized children aged 2-5 years; they found no difference in the rate of new sensitizations to HDM between groups after 12 and 24 months of SLIT (42).

Three additional RCTs investigating the short-term effects of AIT, of medium to high risk of bias, found significantly lower incidence of new sensitizations among children and adults with AR. The first, Marogna, found that in the group treated with SLIT for three years, 4/130 developed new sensitizations compared to the controls in whom 23/66 developed new sensitisations (OR=0.06; 95% CI 0.02 to 0.17). They further concluded that the SLIT group was less likely to be polysensitized compared to the SLIT group at year 3: OR=0.33 (95% CI 0.17 to 0.61) (22). A second RCT conducted by Marogna found a significantly lower incidence of new sensitizations among the SLIT group compared to controls (36). At the end of the three-year treatment period, 16/271 (5.9%) in the SLIT group had developed new sensitizations compared to 64/170 (38%) among controls (P<0.001). The third RCT by Pifferi looked at children with asthma monosensitized to HDM treated with SCIT for three years compared to controls (40). At the end of treatment, they found no new sensitizations in the SCIT group (0/15) compared to 5/14 in the control group (P=0.01).

Meta-analysis showed an overall reduction in the risk of allergic sensitization: RR=0.33 (95% CI 0.12 to 0.93) (Figure 6). The Eggar test showed no evidence of publication bias (P=0.60). Sensitivity analyses excluding the two studies by Marogna, at high risk of bias, however failed to confirm this risk reduction: RR=0.72; 95% CI 0.24 to 2.18.

Subgroup analyses lacked precision, but suggested that AIT was:

- likely to be beneficial in those aged <18 (RR=0.32; 95% CI 0.08 to 1.28), but not in those aged ≥18 years (RR=3.32; 95% CI 0.18 to 60.85)

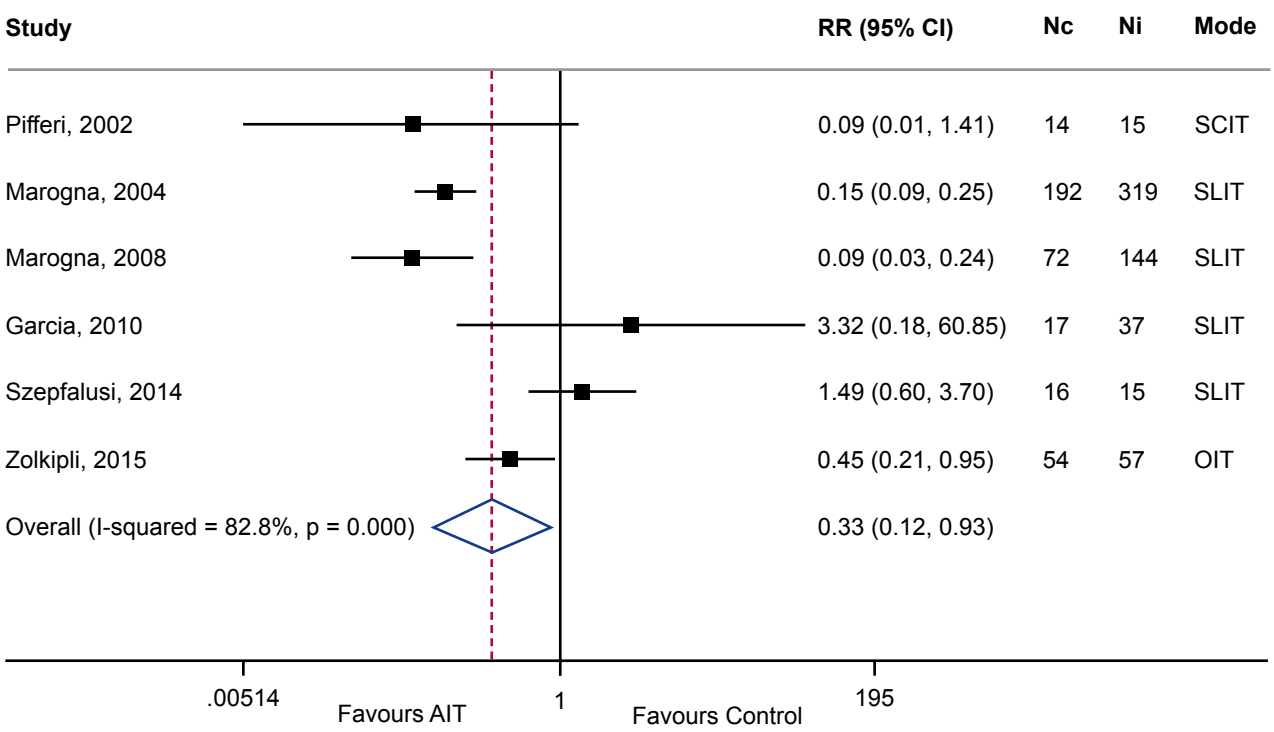

Figure 6 Random-effects meta-analysis of effectiveness of AIT in short-term prevention of allergic sensitization. Nc = number in control group; Ni = number in intervention group; mode = route of administration of AIT.

- more likely to be beneficial in those receiving ≥3 years therapy (RR=0.13; 95% CI 0.08 to 0.21) than in those receiving <3 years therapy (RR=0.74; 95% CI 0.13 to 4.21)
- more likely to be beneficial in those receiving SCIT (RR=0.09; 95% CI 0.01 to 1.41) than SLIT (RR=0.38; 95% CI 0.13 to 1.13)
- likely to be beneficial in those receiving HDM (RR=0.33; 95% CI 0.09 to 1.20), but not in those receiving peach (RR=3.32; 95% CI 0.18 to 60.85).

CBAs

The inconsistent evidence found in RCTs was also reflected in the included CBAs with four studies finding a lower occurrence of new sensitizations among AIT exposed subjects compared to unexposed subjects (6, 34, 38, 41), one study reporting higher occurrence in the AIT group compared to controls (26), and three studies reporting no differences between groups (Table 2) (33, 38, 43).

Long term preventive effects of AIT on the development of new allergic sensitization

RCTs

Three RCTs investigated the preventive long term (i.e. post-intervention) effects of AIT on onset of new sensitizations (17, 28, 35).

The Limb RCT, at medium risk of bias, explored the effect of SCIT for 24 months with a mixture of up to seven aero-allergens among children with moderate-to-severe asthma recruited between 5-12 years of age and followed into adulthood (35). The mean follow-up time of the 82 subjects was 10.8 years. There was a similar development of new sensitivities among both the SCIT and placebo groups (P=0.13), and the types of new sensitivities were also found to be similar across groups (35).

The high risk of bias RCT conducted by Dominicus followed adult patients with allergic rhinoconjuncitivitis three years after cessation of SCIT for grass pollen and found that the number of subjects who did not develop new sensitizations were higher in the group exposed to SCIT (20/26; 77%) compared to the placebo group (3/13; 23%; P-value not given) (28).

In an RCT at high risk of bias, Song followed patients with AR two years after cessation of SCIT for HDMs compared to patients receiving pharmacotherapy only (17). In the SCIT group, the occurrence of new

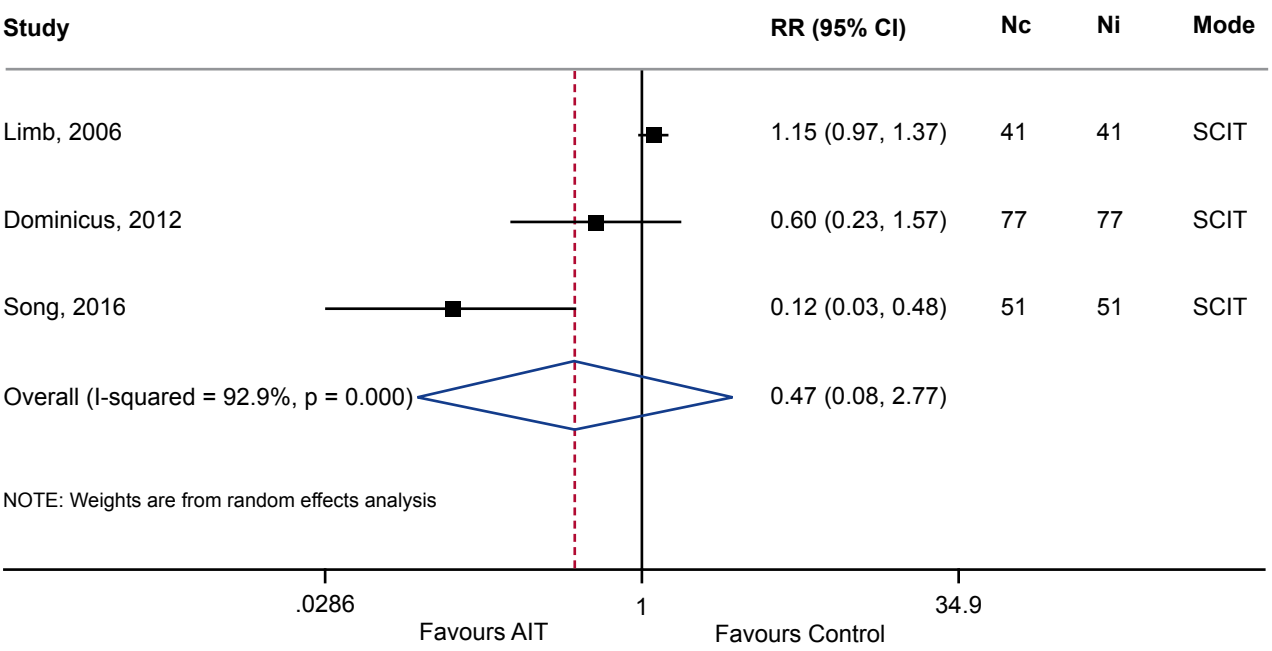

Figure 7 Random-effects meta-analysis of effectiveness of AIT in long-term prevention of allergic sensitization. Nc = number in control group; Ni = number in intervention group; mode = route of administration of AIT.

sensitizations was 2/43 (4.7%) compared to 17/41 (41.5%) among controls (P<0.01).

Meta-analyses of these studies showed no evidence of a reduction in the long-term risk of allergic sensitization: RR=0.47 (95% CI 0.08 to 2.77) (Figure 7). The Eggar test showed no evidence of publication bias (P=0.23).

CBAs

Among the seven CBAs investigating long-term preventive effects of AIT, one SLIT study by Di Rienzo found no significant differences in onset of new sensitizations among intervention and control groups during the 10 years of follow-up (27). Five studies, four SCIT and one SLIT, found reduced onset of new sensitizations among subjects exposed to AIT (7, 29, 34, 37, 39).

In contrast to these findings, a SCIT CBA by Gulen found a significantly higher occurrence of new sensitization among children with asthma who were monosensitized to HDM exposed to AIT compared to controls (32).

Cost-effectiveness

We found no studies investigating the cost-effectiveness of AIT for the prevention of allergy.

Safety

We identified a total of seven studies, six SLIT (five of these RCTs and one CBA), and one SCIT RCT, that reported on adverse events (8, 15, 22, 36, 37, 40, 42).

In the SLIT studies, an RCT at low risk of bias investigating effects of SLIT administered as drops to infants reported no differences in numbers or type of adverse reactions between intervention and control groups (8), and a further RCT with low risk of bias among children between 2-5 years of age also reported no relevant side effects in 21,170 single applications (42). The incidence of generalized itching was reported in three SLIT studies assessed to be at high risk of bias: one RCT finding that 4/271 (1.5%) of the children exposed to SLIT experienced one episode of generalized itching that resolved without therapy (36), another RCT reported one incidence of systemic itching after SLIT among 144 children in the SLIT group (22), and a CBA reported that 5/57 adult patients exposed to SLIT had transient oral itching (37). In an RCT, assessed to be at medium risk of bias, the safety of SCIT was assessed among children aged 6-14 years (40). It reported no major local or systemic effects of AIT during three years of treatment among the 15 patients randomized to SCIT (40).

DISCUSSION

Statement of principal findings

We found no consistent evidence from the limited body of RCT evidence that AIT can prevent the first onset of allergic disease over the short-term and no RCTs investigating the long-term preventive effects of AIT. We did however find clear evidence of a substantial reduced risk of developing asthma in those with pre-existing AR over the short-term, although it is unclear if this benefit was maintained over the longer-term. There was some evidence to indicate that the risk of allergic sensitization can be reduced over the short-term, but this was not confirmed in the pre-specified sensitivity analysis. There was no evidence of a long-term reduction in the risk of allergic sensitization. These risks were however in many cases imprecisely estimated and so need to be interpreted with caution. Overall, the safety profile of AIT appeared acceptable, but we found no data on cost-effectiveness considerations and so are unable to comment on this outcome.

Strengths and limitations

The strengths of this study include the comprehensive literature search that was undertaken and adherence to a pre-published protocol with clearly defined objectives and a detailed pre-specified analysis plan. The main limitations relate to the possibility of not uncovering the total body of evidence on this subject and the challenges of interpreting a heterogeneous body of relatively small-scale trial evidence.

Implications for policy, practice and research

This review has highlighted the inconsistent evidence-base and the lack of robust evidence, in particular for long-term preventive effects of AIT and in terms of detailed subgroup analysis, which impedes our ability to tease out clear implications for healthcare policy and clinical practice. In terms of research, there is a need for high quality well powered RCTs with long-term follow-up and well defined diagnostic criteria to answer the above research questions. Furthermore, there is a need for studies with more robust assessment of adherence to AIT to ascertain the dose received and take into consideration the effect of non-adherence to treatment on preventive effectiveness. Future studies should also include possible effect modification caused by measures taken to alter behaviours and/or environmental triggers of allergy (e.g. exposure to passive smoking in childhood, presence of pets) as this may modify the effect of AIT on onset of allergy.

Conclusions

This systematic review found only limited evidence to support the use of AIT in a preventive capacity. Based on the current evidence, we are unable to conclude that AIT prevents the development of first allergic disease. There appears to be short-term benefit in preventing asthma in those with AR, particularly if AIT is started in childhood with this benefit being seen for SCIT and SLIT. It is however unclear if this benefit is maintained over several years post-discontinuation of AIT or indeed whether AIT is a cost-effective intervention.

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Contributorship

A Sheikh conceived this review. This paper was drafted by M Kristiansen and S Dhami. It was revised following critical review initially by A Sheikh, S Halken, M Calderon and D Larenas-Linnemann and then by all the co-authors. This paper is part of the EAACI AIT guidelines project, chaired by Antonella Muraro and coordinated by Graham Roberts.

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Ethical approval

Not required.

Conflicts of interest

M Kristiansen: support to undertake the systematic review; S Dhami: support to co-ordinate the undertaking of the systematic review; S Halken: in the Grazax Asthma prevention study steering committee (ALK-Abello); M A Calderon: lectures honorarium (ALK, Stallergens, Merck and Allergopharma), consultancy honorarium (ALK, Stallergenes and Hal);

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2

ALLERGEN IMMUNOTHERAPY FOR INSECT VENOM ALLERGY

A SYSTEMATIC REVIEW AND META-ANALYSIS

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***Background**: The European Academy of Allergy and Clinical Immunology (EAACI) is developing EAACI Guidelines on Allergen Immunotherapy (AIT) for the management of insect venom allergy. To inform this process, we sought to assess the effectiveness, cost-effectiveness and safety of AIT in the management of insect venom allergy.*

***Methods**: We undertook a systematic review, which involved searching nine international biomedical databases for published and unpublished evidence. Studies were independently screened and critically appraised using established instruments. Data were descriptively summarized and, where possible, meta-analysed.*

***Results**: Our searches identified a total of 16,950 potentially eligible studies of which 17 satisfied our inclusion criteria. The available evidence was limited both in volume and in quality but suggested that venom immunotherapy (VIT) could substantially reduce the risk of subsequent severe systemic sting reactions (OR=0.08, 95% CI 0.03-0.26); meta-analysis showed that it also improved disease specific quality of life (risk difference= 1.41, 95% CI 1.04 to 1.79). Adverse effects were experienced in both the build-up and maintenance phases but most were mild with no fatalities being reported. The very limited evidence found on modeling cost-effectiveness suggested that VIT was likely to be cost-effective in those at high risk of repeated systemic sting reactions and/or impaired quality of life.*

***Conclusions**: The limited available evidence suggested that VIT is effective in reducing severe subsequent systemic sting reactions and in improving disease specific quality of life. VIT proved to be safe and no fatalities were recorded in the studies included in this review. The cost-effectiveness of VIT needs to be established.*

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Introduction

Hymenoptera venom allergy is a potentially life-threatening allergic reaction following a bee, wasp (i.e. paper wasp, yellow jacket or hornet) or ant (i.e. fire ants) sting. The risk of anaphylaxis to hymenoptera stings is greater in adults compared to children due to increased sting exposure, co-morbidities and concomitant medication use. Systemic reactions have been reported in up to 3% of adults, but in less than 1% of children (1, 2).

Symptoms range from large local reactions at the sting site to mild, moderate and severe systemic reactions. Mild systemic reactions usually manifest as generalized skin symptoms including flush, urticaria and angioedema. Typically, dizziness, dyspnea and nausea are examples of moderate reactions, while shock and loss of consciousness, or even cardiac or respiratory arrest all define a severe sting reaction. Seemingly mild reactions can progress into more severe reactions with little warning. The fear of future severe systemic reactions usually greatly impairs quality of life. Around a quarter of fatalities from anaphylaxis are caused by venom allergy (3-5).

Patients are advised to carry an emergency kit comprising of adrenaline (epinephrine), H_1-antihistamines, and corticosteroids depending on the severity of their previous sting reaction(s) (6). The only treatment that can potentially prevent further systemic sting reactions is venom immunotherapy (VIT). This may result in long-term clinical benefits and improved quality of life (7, 8). However, despite these possible advantages, VIT is still not commonly used by physicians across all European countries (9). This is likely to reflect uncertainty about the clinical benefits and risks associated with use of VIT as well as the practical and economic implications associated with this treatment.

The European Academy of Allergy and Clinical Immunology (EAACI) is in the process of developing guidelines for AIT. This systematic review is one of five inter-linked evidence syntheses that were undertaken in order to provide a state-of-the-art synopsis of the current evidence base in relation to evaluating AIT for the treatment of insect venom allergy, allergic rhinoconjunctivitis, food allergy, allergic asthma, and allergy prevention (10-14). These will be used to inform the formulation of key clinical recommendations for subsequent clinical practice guidelines.

AIMS

We assessed the effectiveness, safety and cost-effectiveness of VIT for the treatment of insect venom allergy.

METHODS

The detailed methods for this review have already been described in our published protocol (10). Here, we provide a more succinct account of the methods employed.

Search strategy

A highly sensitive search strategy was developed, and validated study design filters were applied to retrieve all articles pertaining to the use of VIT for insect venom allergy from electronic bibliographic databases (Appendix 2.1). We conceptualized the searches to incorporate the four elements below as shown in Figure 1.

To retrieve systematic reviews, we used the systematic review filter developed at McMaster University Health Information Research Unit (HIRU) (http://hiru.mcmaster.ca/hiru/HIRU_Hedges_MEDLINE_Strategies.aspx#Reviews).http://hiru.mcmaster.ca/hiru/HIRU_Hedges_MEDLINE_Strategies.aspx#Reviews). To retrieve randomized controlled trials (RCTs), we applied the Cochrane highly sensitive search strategy for identifying RCTs in MEDLINE (15). To retrieve non-randomized studies, i.e. controlled clinical trials (CCT), controlled before-and-after (CBA) and interrupted time-series (ITS) studies, we used the Cochrane Effective Practice and Organisation of Care (EPOC) filter Version 2.4, available on request from the EPOC Group (16, 17). 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).

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), Clinicaltrialsregister.eu,

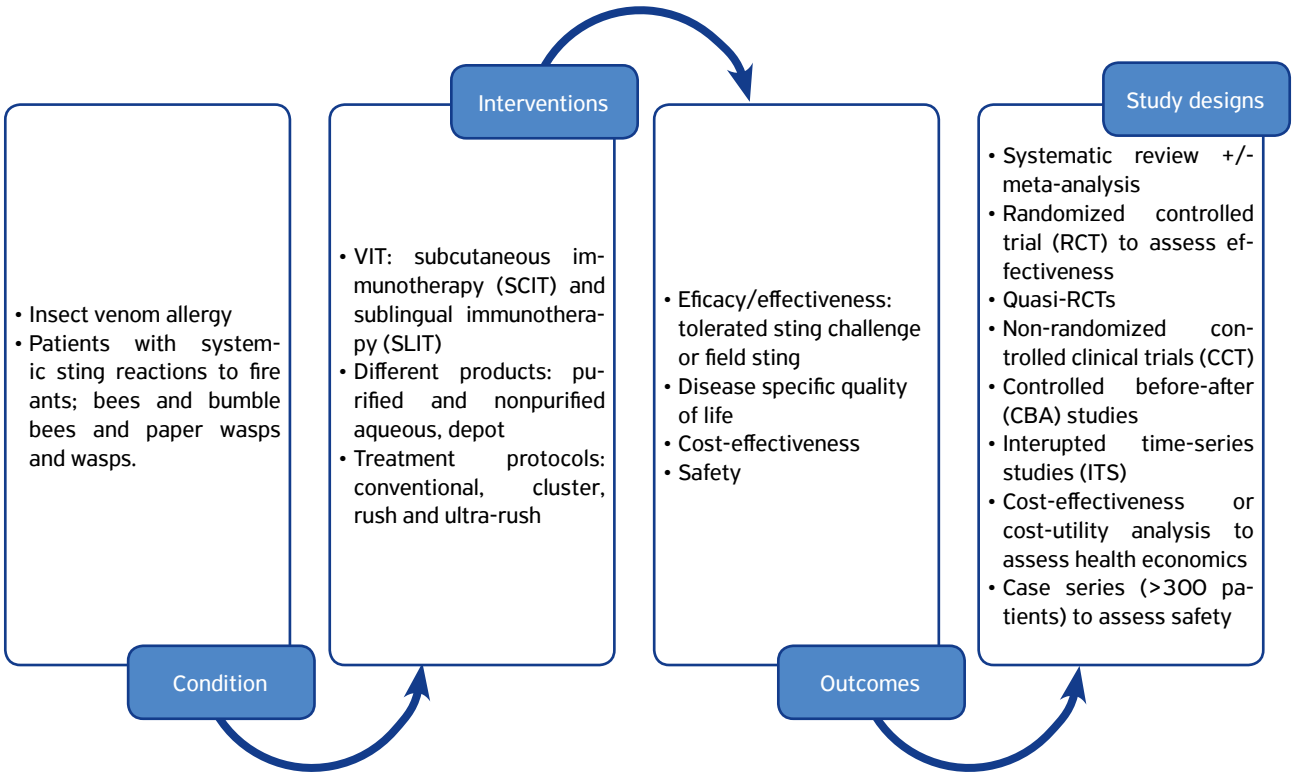

Figure 1 Conceptualization of systematic review of allergen immunotherapy for insect venom allergy (10).

Current controlled trials (www.controlled-trials.com), and the Australian and New Zealand Clinical Trials Registry (http://www.anzctr.org.au).

The search strategy was developed on OVID MEDLINE and then adapted for the other databases (Appendix 2.1). In all cases, the databases were searched from inception to October 31, 2015. Additional references were included through searching the references cited by the identified studies, and unpublished work and research in progress was identified through discussion with experts in the field (see online supplement). We invited a panel of interdisciplinary external experts in the field from different regions to add to the list of included studies by identifying additional published and unpublished papers they are aware of and research in progress (Appendix 2.2). There were no language restrictions employed; where possible, all relevant literature was translated into English.

Inclusion criteria

Patient characteristics

We were interested in identifying studies conducted on patients of any age with a physician confirmed diagnosis of systemic sting reaction to a venom sting from bees, wasps (i.e. paper wasp, yellow jacket or hornet) or fire ants.

Interventions of interest

We considered VIT using different products (purified and non-purified, aqueous or depot IT) and different treatment protocols (conventional, cluster, rush and ultra-rush) (18) administered through the subcutaneous (SCIT) or sublingual (SLIT) routes.

Comparators

We were interested in studies comparing VIT with placebo or no treatment (i.e. the natural course of the disease).

Study designs

Systematic reviews of RCTs and RCTs were used to investigate effectiveness; health economic analyses were used to assess cost-effectiveness; and systematic reviews, RCTs and case series, with a minimum of 300 patients, were used to assess safety. We appraised the evidence by looking at higher levels of evidence such as systematic reviews and/or meta-analyses of RCTs, together with individual RCTs. However, as we were expecting to find only a limited number of RCTs, we also searched for and included quasi-RCTs (i.e. non-randomized controlled clinical trials (CCTs), controlled before and after (CBA) studies and interrupted time series (ITS) analyses). Given the high inherent risk of bias in making inferences from quasi-RCTs, our main conclusions in relation to effectiveness have been based on the findings of systematic reviews and RCTs; findings from the quasi-RCTs have only been used to guide suggestions on which areas need to be prioritized in future research (19).

Our exclusion criteria were: narrative reviews, discussion papers, non-research letters and editorials, animal studies, before-after studies, qualitative studies and case series (involving less than 300 patients).

Outcomes

Primary

- Our primary outcome measure of interest was short- and long-term efficacy assessed by tolerated sting challenge or field sting; long-term was defined as sustained clinical efficacy after discontinuation of VIT.

Secondary

Our secondary outcome measures of interest were:

- Assessment of disease specific quality of life
- Safety as assessed by local and systemic reactions in accordance with the World Allergy Organization's (WAO) grading system of side-effects (20, 21)
- Health economic analysis from the perspective of the health system/payer.

Study selection

All references were uploaded into the systematic review software DistillerSR and de-duplication was undertaken. Study titles were independently checked by two reviewers (SD and HZ) 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 studies as above. Any discrepancies were resolved through discussion and, when necessary, a third reviewer arbitrated (AS). Full text copies of all potentially relevant studies were obtained and their eligibility for inclusion independently assessed. 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 (SD and HZ) using the relevant version of the Critical Appraisal Skills Programme (CASP) quality assessment tool for systematic reviews and health economic evaluations (22). We assessed the risk of bias of experimental studies using the criteria suggested by the Cochrane EPOC Group (23). RCTs, CCTs and CBAs 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 tool (24). For ITS designs, we planned to assess the independence of the intervention from secular trends, the pre-specified shape of the intervention and if the intervention may have had an impact on data collection. These methodological assessments drew on the principles incorporated into the Cochrane EPOC guidelines for assessing intervention studies (25). We used the quality assessment form produced by the National Institute for Health and Care Excellence (NICE) to critically appraise case series (26). Any discrepancies were resolved by discussion or, if agreement could not be reached, by arbitration by the third reviewer (AS).

Analysis, data synthesis and reporting

Data were independently extracted onto a customized data extraction sheet in DistillerSR by two reviewers (SD or AK and HZ), and any discrepancies were resolved. To minimize the risk of bias, reviewers were not involved in the quality appraisal of their own studies.

A descriptive summary with data tables was produced to summarize the literature. A narrative synthesis of the data was undertaken. Where possible, and appropriate, meta-analysis was undertaken using random-effects modeling using Stata (version 14) (15).

Sensitivity and subgroup analyses, and assessment for publication bias

We planned to undertake sensitivity analyses by comparing the summary estimates obtained by excluding studies judged to be at high risk of bias, but were unable to do this because of insufficient data.

We planned to perform the following subgroup analyses, but were unable to undertake any of these due to insufficient data:

- Children (5-11 years) versus adolescents (12-17 years) versus adults (≥18 years)
- Conventional versus cluster versus rush versus ultra-rush protocols in SCIT
- Conventional in SLIT versus SCIT
- Three versus five years of treatment
- Different allergen doses (50 µg versus 100 µg versus 200 µg of maintenance VIT)
- Bee versus wasp versus fire ant venom
- Patients with and without co-existent mast cell disorders (27).

We were unable to assess publication bias through the creation of funnel plots due to the small number of studies but were able to use Begg's rank correlation test (28).

Registration and reporting

This review has been registered with the International Prospective Register of Systematic Reviews (PROSPERO): http://www.crd.york.ac.uk/prospero/.http://www.crd.york.ac.uk/prospero/. The registration number is CRD42016035374. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was used to guide the reporting of the systematic review: http://www.prisma-statement.org/ (Appendix 2.3).

RESULTS

Overview of results

Our searches identified a total of 16,950 potentially eligible studies of which 17 satisfied our eligibility criteria and were therefore included in this review (Figure 2). The key characteristics and main findings of all included studies are detailed in Table 1 and the quality assessment of these studies is summarized in Tables 2-4. The main findings are discussed in more detail below.

Of the 17 included articles, five were systematic reviews (29-33); two of these systematic reviews undertook meta-analyses (29, 33). The remaining 12 studies comprised of five RCTs (34-38), three CBAs (39-41) and four case series (42-45).

Four of the systematic reviews looked at the effectiveness of VIT (29-31, 33), two at safety (29, 32), and one at cost-effectiveness (31) and one at disease specific quality of life (29). Two of the RCTs looked at both effectiveness and disease specific quality of life related issues in adults (35, 36). Two RCTs looked at the effectiveness of VIT in children (37, 38); and a further RCT studied both children and adults (33). One CBA solely focused on the safety of rush VIT protocol in adults (40), a second CBA looked at the long-term follow-up of children following VIT (39) and the third looked at the effect of VIT on anaphylactic sting reactions (41). Finally, four case studies investigated safety considerations (42-45). All of the primary studies included in this review investigated SCIT.

Effectiveness of VIT as judged by the risk of systemic sting reactions

Twelve studies looked at the effectiveness of VIT. Four of these were systematic reviews, all of which were assessed to be of high quality (29-31, 33). The remaining studies were RCTs (n=5) (34-38) and CBAs (n=3) (39-41).

Systematic reviews

Boyle *et al.*'s systematic review included six RCTs and one quasi-RCT (29). Three of the RCTs studied in this review also satisfied our eligibility criteria and these are therefore considered in detail below (34, 37, 38). The others were excluded because they did not meet our inclusion criteria. These included: Brown *et al.* (46), which looked at the jack jumper ant, which was not an insect of interest in the protocol; Oude Elberink *et al.* (47), which focussed on the burden of treatment of carriage of an adrenaline (epinephrine) auto-injector compared to VIT, which was not an outcome of interest; and Golden *et al.* (48) and Severino *et al.* (49), which both included patients who had experienced large local reactions rather than a systemic reaction to an insect sting.

The primary outcome of interest in Boyle *et al.* (29) was systemic reaction rates to a 'field' or a challenge sting in patients during the follow-up period of VIT

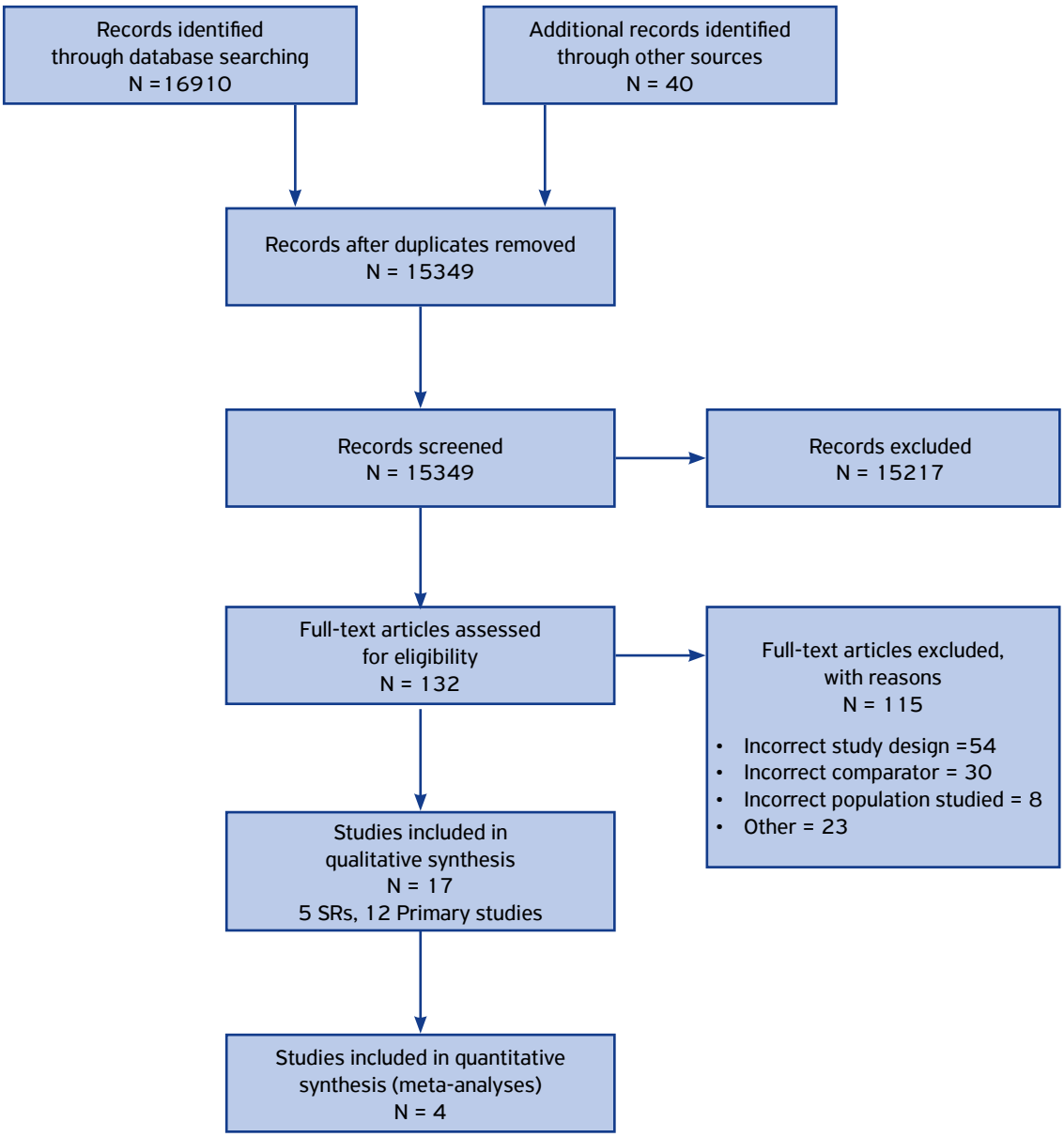

Figure 2 PRISMA diagram: allergen immunotherapy for insect venom allergy

treatment. The review concluded that VIT was effective in preventing subsequent systemic reactions to insect stings (risk ratio [RR]=0.10, 95% confidence interval (CI) 0.03 to 0.28). They also found that VIT prevented large local reactions to a sting (RR=0.41, 95% CI 0.24 to 0.69).

The systematic review conducted by Dhami *et al.* (30) on the management of anaphylaxis studied the effectiveness of VIT in preventing venom-triggered anaphylaxis. This review included four systematic reviews (29, 31, 33, 50) and 23 individual studies of varying quality. It concluded that, although much of the evidence is of a low quality, the evidence did consistently suggest that VIT can significantly reduce the risk of systemic reactions in subsequent stings.

The systematic review by Hockenhull *et al.* concluded that VIT reduced the likelihood of future systemic reactions (31). This review assessed the clinical

Table 1 Characteristics of included studies

Author/ year/ Article title/ country	Study design	Number of studies (N)/ subjects included(n)/ age	Participants - physician confirmed diagnosis of systemic sting reaction to a venom sting from	Outcome of interest	Comparators (intervention / controls) / route of administration	VIT using different products	Quality	Main outcome	Comment
PRIMARY OUTCOME: EFFICACY OF VIT									
Boyle *et al.*, 2012 (29) Venom, immunotherapy for preventing allergic reactions to insect stings: A Cochrane Systematic review Worldwide	SR of RCT's and quasi-RCT's	All ages eligible N=7 n=392	Physician confirmed diagnosis of systemic reaction to bees, wasps or fire ants	Primary: Systemic reaction to a 'field' insect sting or a sting challenge during treatment. Fatal SR due to a field or challenge insect sting over the same period. Secondary: Large local reactions to a field sting or sting challenge during treatment or during the 10 years following treatment. Quality of life or anxiety score, assessed using a published scale	Standardized venom extract vs placebo, no treatment or back-up treatment	SLIT 1 trial SCIT 6 trials	High	6 RCT's and 1 quasi-RCT included ant, bee, and wasp immunotherapy in children and adults with previous systemic or large local reactions to a sting, using sublingual (one trial) or subcutaneous (six trials) VIT is effective in preventing systemic allergic reaction to an insect sting. Fewer patients treated with VIT had a severe systemic reaction to a subsequent sting compared with untreated patients risk ratio [RR] 0.10 (95%CI 0.03, 0.28). Unable to confirm whether VIT prevents fatal reactions to insect stings Increased risk of systemic adverse reactions to treatment: RR=8.16 (95%CI 1.53, 43.46)	Undertook additional analysis of 11 observational studies to estimate risk of adverse events
Dhami *et al.*, 2013 (30) Management of anaphylaxis: a systematic review Worldwide	SR RCTs, quasi-RCTs, CBAs, ITS and case series	N=55; but only 16 relevant to VIT	Patients with an anaphylaxis reaction to venom	Long term management of venom anaphylaxis by use of VIT			High	VIT reduces the risk of subsequent systemic reactions to venom stings	

Table 1 Continued

Author/ year/ Article title/ country	Study design	Number of studies (N)/ subjects included(n)/ age	Participants - physician confirmed diagnosis of systemic sting reaction to a venom sting from	Outcome of interest	Comparators (intervention / controls) / route of administration	VIT using different products	Quality	Main outcome	Comment
Golden *et al.*, 2004 (39) Outcomes of allergy to insect stings in children, with and without venom immunotherapy USA	CBA	n=1033	Allergy to bees or paper wasps	Outcome of allergic reactions to stings 10 to 20 years after VIT or no VIT in children	VIT versus no VIT	SCIT	Low	Between 1978-85, 1033 of children, 356 received VIT. 1997-2000 postal and telephone surveys were used to assess the long term outcome.512 (50%) patients replied. VIT results in significantly lower sting reactions. This prolonged benefit seen is children 10 to 20 years after Rx is greater than that seen in adults	
Hunt *et al.*, 1978 (34) A controlled trial of immunotherapy in insect hypersensitivity USA	RCT Single blind	n=59 Age= 15-59 years	Physician confirmed diagnosis of systemic sting reaction to a venom sting from Honey bee or, yellow jacket. Patients with a history of a generalized allergic reaction to a sting included, some had a previous anaphylactic reaction to a sting.	Tolerance to a challenge sting of the insect they were most sensitive to if they tolerated a venom dose greater than that found in a sting.	Standardized venom extract vs placebo or whole body extract. Three matched groups were given placebo, whole-body extract or venom immunotherapy.	SCIT; semi-rush protocol	Low	Venom group after receiving a dose of 100mcg were sting challenged. 18 stung, one had mild urticaria. 1 patient was not challenged as failed to tolerate treatment Whole-body extract group, of 11 patients 7 were stung, 64% had systemic symptoms to the challenge. Placebo group, of 12 patients 7 were challenged and 58% had systemic symptoms to the sting. Last two groups no statistical difference but significantly greater than the venom treated group, P<0.01. Control arm of study was aborted when second patients experienced a severe systemic reaction 14 patients who were treatment failures from the placebo and whole-body extract group and a further 17 patients who were not challenged were then given venom and stung. Of these 1 patient had urticaria following sting challenge.	Of 59 patients 58 successfully achieved desensitization with venom immunotherapy. Advocate use of Venom immunotherapy over whole-body extract for the prevention of life-threatening reactions to insect stings.

Table 1 Continued

Author/ year/ Article title/ country	Study design	Number of studies (N)/ subjects included(n)/ age	Participants - physician confirmed diagnosis of systemic sting reaction to a venom sting from	Outcome of interest	Comparators (intervention / controls) / route of administration	VIT using different products	Quality	Main outcome	Comment
Park *et al.*, 2015 (32) Risk Associated with Bee Venom Therapy: A Systematic Review and Meta-Analysis South Korea	SR	N=145 20 RCTs, 79 audits and cohort studies, 33 single case-studies, 13 case -series	Any user of bee venom therapy	Frequency and type of adverse event to bee venom therapy	Safety considerations, all study types included	Bee venom acupuncture, bee sting acupuncture, conventional VIT, cluster VIT, rush VIT, ultra-rush VIT, SIT, rush specific immunotherapy.	Low	2 RCTs included which look at VIT, Oude Elberink 2002 and 2006, no systemic AEs are reported. 63 case series/cohort studies looked at VIT and showed prevalence of AEs ranged from 0.0% to 90.63%. In the 46 VIT studies the median AEs was 28.7%, these include SRs (50.37%), LR (35.8%), LLR (9.99%)	Most of the studies in this SR do not meet our inclusion criteria and did not look at VIT.
Pasaoglu *et al.*, 2006 (40) Rush Hymenoptera venom immunotherapy is efficacious and safe Turkey	CBA	n=18 Age 18-53 7 treated with vespula venom, 7 treated with honey bee venom, 4 control group	Physician confirmed diagnosis of a systemic sting reaction to yellow jacket or honeybee	Side-effects of Rush VIT Clinical response	VIT versus control group	SCIT; rush	Low	7 day rush VIT protocol followed as inpatients. 14 patients received 469 injections in 1 year, 240 for bee venom, 229 for yellow jacket. 4 systemic reactions occurred(0.85%) in 1 patient to bee venom during the build-up phase. Reactions treated with adrenaline corticosteroids, antihistamines, bronchodilators. 11 late local reactions occurred (2.34%) during the maintenance period, 8 to bee venom 3 to yellow jacket. No Rx was needed or dose reduction. No fatal or life threatening reactions. Rush VIT is safe and effective	2 patients experienced field stings, one patient a bee keeper experienced multiple stings, no systemic reactions occurred.

Table 1 Continued

Author/ year/ Article title/ country	Study design	Number of studies (N)/ subjects included(n)/ age	Participants - physician confirmed diagnosis of systemic sting reaction to a venom sting from	Outcome of interest	Comparators (intervention / controls) / route of administration	VIT using different products	Quality	Main outcome	Comment
Reisman *et al.*, 1985 (41) Stinging insect allergy: Natural history and modification with venom immunotherapy USA	CBA	n= 271 Age= 4 -83	Sting anaphylaxis to honeybee, yellow jacket, bald-faced hornet and Polistes venoms	The natural history of sting anaphylaxis and its modification with VIT	VIT or no VIT or premature discontinuation of VIT	SCIT conventional of rush		127 patients received VIT for 6 months to 9 years. 39 (31%) honeybee venom, 51(40%) yellow jacket venom, 26 (20%) honeybee and yellow jacket venoms, 7 (5%) multiple vespid venoms, 2 received multiple vespid and honeybee venoms, 1 hornet venom, and 1 Polistes venom. Most received 50ug maintenance dose at 4-6weeks. 87 re-stings in 48 patients, 2 SRs. No VIT group (n=56), 2 months to 12 years after index sting, 40 re-stings in 28 patients, 14 SRs. 88 patients discontinued VIT prematurely, after 1 month to 6.5 years. 61 re-stings in 41 patients, 11 SRs 1 month to 6 years after stopping VIT. Conclusion: VIT almost completely protective of a subsequent anaphylactic reaction. Re-sting SR, 1% in VIT group, 35% in no VIT group, 17% in premature discontinued VIT group.	Maintenance dose 50 µg Not sure of identity of insects in re-stings as accidental
Schuberth *et al.*, 1983 (37) Epidemiologic study of insect allergy in II. Effect of accidental stings in allergic children USA	Comprehensive cohort design includes an RCT	n=181 Age=3-16	Non -life threatening systemic reactions to: Bees, wasps, yellow jackets, yellow and white faced hornets	Blood samples for antibody titres, yearly skin tests and toxicity studies, skin tests, antibody measurements and accidental stings	VIT or no treatment	SCIT	Moderate	Children were randomised to VIT or no VIT, ratio of 1:1.5. Those who didn't want to be randomised chose their own Rx. The results for randomised and non- randomised are not presented separately. Accidental field stings in 2 years: 28 in 17 VIT patients and 74 in 47 no VIT patients. SRs were low in both groups and no statistical difference shown. No reaction was more serious than the index reaction. 7 of 9SRs resolved without epinephrine.	Children only included with non-life threatening systemic reactions. Those with respiratory or cardiovascular symptoms were given VIT. Accidental stings not sure if stung by insect they were allergic to

Table 1 Continued

Author/ year/ Article title/ country	Study design	Number of studies (N)/ subjects included(n)/ age	Participants - physician confirmed diagnosis of systemic sting reaction to a venom sting from	Outcome of interest	Comparators (intervention / controls) / route of administration	VIT using different products	Quality	Main outcome	Comment
								Results indicate that most children with cutaneous manifestations after a sting reaction will not get a re-sting so VIT is not indicated	
Valentine *et al.*, 1990 (38) The value of immunotherapy with venom in children with allergy to insect stings USA	Comprehensive cohort design includes an RCT	n=242 Children age 2-16 68 VIT, 174 did not About half were randomized others parent/ patient chose treatment	Physician confirmed diagnosis of a systemic sting reaction to bees or wasps	Accidental stings during 4 years were evaluated	VIT versus no VIT	SCIT	Moderate/ Low	Randomisation ratio of 1.5 to 1.Group1a no VIT=61, 1ba VIT=45. Non randomised: 2a no VIT=113, 2b VIT=23. VIT group of 45 there were 55 stings in 45 patients, 1SR. NRVIT of 23 there were 29 stings in 12 patients, no SRs. Rno VIT of 61 there were 68 stings in 21 patients, 7SRs. NR no VIT group of 113, there were128 stings in 59 patients, 11 SRs. Conclude that using VIT for children with mild systemic reactions is not justified but should be used in those with life threatening reactions	Systemic reaction confined to the skin Only 18.6% of children who were not treated went on to have subsequent systemic sting reactions.
Watanabe *et al.*, 2010 (33) Specific immunotherapy using Hymenoptera venom: systematic review Brazil	SR	N=4, n=2273 Children and adults	Anaphylaxis to sting reaction plus positive skin test to any hymenoptera insects	Change in clinical reaction following sting or field challenge	Venom immunotherapy vs. placebo or no treatment		High	Risk of systemic reactions after specific immunotherapy was evaluated using odds ratios plus their 95% confidence intervals. It was appropriate to do meta-analysis of 2 trials in children which showed OR=0.29 (95%CI 0.10,0.87) for systemic reactions after further accidental stings in VIT treated children. No indication for VIT in children who have only had a cutaneous reaction following a sting. Conclude that specific VIT should be recommended for children with previous moderate-severe reactions and adults with previous systemic reactions.	Lack of allocation concealment and the act that the trials were not double-blind may have contributed to over-estimation of the treatment effect

Table 1 Continued

Author/ year/ Article title/ country	Study design	Number of studies (N)/ subjects included(n)/ age	Participants - physician confirmed diagnosis of systemic sting reaction to a venom sting from	Outcome of interest	Comparators (intervention / controls) / route of administration	VIT using different products	Quality	Main outcome	Comment
SECONDARY OUTCOME: DISEASE SPECIFIC QUALITY OF LIFE									
Oude Elberink *et al.*, 2002 (35) Venom immunotherapy improves health-related quality of life in patients allergic to yellow jacket venom. Netherlands	Comprehensive cohort design includes an RCT	n=74 randomised; N=74 non-randomised Age: 18-65	Yellow jacket wasps	Health related quality of life	Comparison of HRQL outcomes measured with a disease specific quality of life instrument. Vespid Allergy Quality of life questionnaire in patients allergic to yellow jacket treated with VIT or adrenaline auto-injector	Semi-rush protocol	Moderate	VQLQ score calculated from mean of 14 items, range of 1, severe impairment of HRQL to 7, no impairment. Mean change in VQLQ score was calculated. Randomised group, pre-treatment scores were similar, results from 34 VIT group and 35 adrenaline auto-injector group. Mean VQLQ score improved more in the VIT group, from 3.28 to 4.35 (P<.0001) compared to the adrenaline auto-injector group, score decreased from 3.34 to 2.9, (P<.003). Mean change in VIT group is 1.07(95% CI 0.68 to 1.46), mean change in adrenaline auto-injector group is _0.43 (95% CI -0.71 to -0.16), mean difference between the 2 groups is 1.51 (95%CI 1.04-1.98) Non-randomised group: pre-treatment VQLQ scores similar. After 1 year VIT group, VQLQ score improved from 2.84 to 4.29, (P< .0001) and no significant change in the adrenaline auto-injector group. Expectation of outcome: mean pre-treatment scores similar, after 1 year R-VIT group (P<.0001), improved from 5.66 to 2.88 and NR-VIT group from 5.45 to 2.88. In the adrenaline auto-injector groups there was no change NNT=1.4 VIT results in clinically significant HRQL improvement, after 1 year of Rx, in males and females, anxious patients and not, those stung recently and more than a year before	Half of patients refused randomisation and 80% wanted to start VIT. Patients choosing VIT had greaterimprovement in scores. Patients randomised to treatment with an adrenaline auto-injector had a deterioration in score

Table 1 Continued

Author/ year/ Article title/ country	Study design	Number of studies (N)/ subjects included(n)/ age	Participants - physician confirmed diagnosis of systemic sting reaction to a venom sting from	Outcome of interest	Comparators (intervention / controls) / route of administration	VIT using different products	Quality	Main outcome	Comment
								2 patients from the VIT groups dropped out due to side-effects	
Oude Elberink *et al.*, 2009 (36) Immunotherapy improves health-related quality of life of adult patients with dermal reactions following yellow jacket stings Netherlands	Comprehensive cohort design includes an RCT	Randomised n=29, VIT=15, adrenaline auto-injector =14 Non-randomised n=26, VIT=11, adrenaline auto-injector =15	Yellow jacket wasps	Health related quality of life	Comparison of HRQL outcomes measured with a disease-specific quality of life instrument-Vespid Allergy Quality of life questionnaire (VQLQ) in patients allergic to yellow jacket venom treated with VIT or with an adrenaline auto-injector in an open label RCT.	Semi-rush protocol	Moderate	HRQL was measured using the Vespid allergy Quality of Life Questionnaire (VQLQ) Anxiety was measured using the Spielberg State Trait Anxiety Inventory (STAI) All patients were given an adrenaline auto-injector on diagnosis, those who agreed were randomised to VIT or adrenaline auto-injector and the adrenaline auto-injector in the VIT group was relinquished on reaching the maintenance dose. Those who did not want to be randomised chose VIT or adrenaline auto-injector. After 1 year of Rx the measures were retaken. VQLQ score at beginning 4.89 Responses from R-VIT=15, R-Epi=13, VIT VQLQ score improved from 5 to 5.84 (.002), R-Epi scores went from 4.95 to 4.53 (P=0.045). Mean change in VQLQ score in R-VIT 0.83 (SD 0.87, P=0.000). R-Epi mean difference 0.42 (SD 0.64) Overall difference 1.25 (95% CI 0.63-1.87) NR-VIT=10, NR-VIT=8. VQLQ in NR-VIT improved from 4.6 to 5.52 (P=0.008) and did not change significantly in the NR -Epi group (4.88 and 4.86) HRQL improves significantly with VIT compared to adrenaline auto-injector, whose HRQL deteriorated.	Systemic reaction confined to the skin Patients with mastocytosis excluded

Table 1 Continued

Author/ year/ Article title/ country	Study design	Number of studies (N)/ subjects included(n)/ age	Participants - physician confirmed diagnosis of systemic sting reaction to a venom sting from	Outcome of interest	Comparators (intervention / controls) / route of administration	VIT using different products	Quality	Main outcome	Comment
SECONDARY OUTCOME: SAFETY									
Brehler *et al.*, 2000 (42) Safety of a two-day ultra-rush insect venom immunotherapy protocol in comparison with protocols of longer duration and involving a larger number of injections. Germany	Case series	N=966 Bee VIT=122 Wasp VIT=933 Age = 2 to 84	Bee or wasp allergy	Does shortening the 7 to 9 day rush protocol to 2 days and increasing the initial administered dose increase the incidence and severity of side-effects	Safety	SCIT Rush	Low	Cohort 1 : n=317, 20 injections over 7-9 days Cohort 2: n= 335, 72.2% had 10, 11, 12 or 14 injections, mainly 3 to 5 days Cohort 3: n=403, 9 injections over 2 day protocol, No statistical difference between the cohorts at the beginning No life threatening anaphylactic reactions occurred 224 (21.2%) patients had an adverse reaction; 124 (11.8%)- generalised skin reactions; 160 (15.2%) systemic reactions: 7 (0.7%) had a drop in BP of less than 20% but did not need epinephrine Overall demonstrates the safety of a 2 day VIT protocol	

Table 1 Continued

Author/ year/ Article title/ country	Study design	Number of studies (N)/ subjects included(n)/ age	Participants - physician confirmed diagnosis of systemic sting reaction to a venom sting from	Outcome of interest	Comparators (intervention / controls) / route of administration	VIT using different products	Quality	Main outcome	Comment
Mosbech *et al.*, 2000 (45) Side-effects of insect venom immunotherapy: results from an EAACI multicentre study. Europe	Case series Multicentre	N=840 457 males and 383 females Vespula-venom 71 Honey bee venom 27% mean age 41 years (range: 5±77 years)	Honey bee, wasp or paper wasp allergy	Analyse the character and frequency of side effects and risk factors of VIT	Safety	SCIT Conventional, rush and cluster protocols. Protocols were not harmonised across centres		417 males and 365 females, were treated with one venom extract. Fifty-eight patients had two venom-extract treatments concomitantly. A total of 26,601 injections were given, 23 602 to patients receiving treatment with only one extract A total of 299 systemic side-effects were reported; of these, 280 occurred in patients treated with one venom. 20% of the patients had at least one systemic reaction and 1.2% of injections elicited reactions. The majority of systemic symptoms were mild, one-third required treatment. Oral antihistamine was the drug most frequently used. A drop in BP in 9 cases, but only one patient received adrenaline. This patient and one other patient suffered fainting/collapse. The frequency of reactions was higher during the dose-increase phase than the maintenance phase (mean: 1.9% vs 0.5% of all injections).	When analyzed separately, female sex, rapid dose-increase regimens, and treatment with bee-venom extract seemed to increase the risk of side-effects. Patients with pre-existing allergic rhinitis more often had side effects (29% vs 19%, P<0.05).The following factors did not influence the risk of systemic side-effects in either separate analyses or logistic regression: age, pre-existing asthma or urticaria, severity of original insect sting symptoms, time interval between sting and symptoms, number of systemic sting reactions, progression in sting reactions, type of extract (with or without aluminium hydroxide), and number of venom extracts used for treatment (one or two).

Table 1 Continued

Author/ year/ Article title/ country	Study design	Number of studies (N)/ subjects included(n)/ age	Participants - physician confirmed diagnosis of systemic sting reaction to a venom sting from	Outcome of interest	Comparators (intervention / controls) / route of administration	VIT using different products	Quality	Main outcome	Comment
Ruëff *et al.*, 2010 (43) Predictors of side effects during the build up phase of venom immunotherapy for Hymenoptera venom allergy: The importance of baseline serum tryptase Europe	Case series	N=680	Honeybee or vespid allergy	Emergency intervention during the build-up phase of VIT	Safety	Conventional, rush and ultra-rush	Low	27.5% had a Grade III or IV index field sting. 24.9% had prophylactic anti-allergy Rx before VIT. Conventional 10.3%; rush 55%; ultra-rush 34.7%. Emergency intervention required in 8.4%. Emergency Rx more likely with bee venom; those with positive IgE to venom; rush and ultra-rush.	Patients undergoing VIT to bee venom need closer observation
Stoevesandt *et al.*, 2014 (44) Risk stratification of systemic allergic reactions during Hymenoptera venom immunotherapy build up phase Germany	Case series	n=818 Age 7-84 Honeybee = 160 (19.6%) Vespula = 658 (80.4%)	Physician confirmed diagnosis of a systemic sting reaction to honey bees or wasps	Systematically evaluate the time course and clinical symptoms of VIT related systemic reaction	Safety	Rush	Low	In patient rush protocol. 220 (22.5%) 5 day protocol, 592(72.45%) 3 day protocol. 673 (82.3%)of 812 injections were well tolerated 35 (4.3%) LLR Rx with oral anti-histamines 71 (8.7%) subjective symptoms, 31 of whom Rx with oral or iv anti-histamines 28 had objective anaphylaxis, 23 Grade I; 3 Grade 2: 2 Grade 4. Confirmation of safety of rush protocols. 3.4% rate of objective VIT-related anaphylaxis is low if we include subjective cases then 12.1% more in line with other studies	Severity of SR correlates with severity of index reaction according to Ring classification. 23 Grade I;3 Grade II; 2 Grade III Isolated urticarial often developed 8 hours after the last injection, a case for hospitalisation during up-dosing.

Table 1 Continued

Author/ year/ Article title/ country	Study design	Number of studies (N)/ subjects included(n)/ age	Participants - physician confirmed diagnosis of systemic sting reaction to a venom sting from	Outcome of interest	Comparators (intervention / controls) / route of administration	VIT using different products	Quality	Main outcome	Comment
SECONDARY OUTCOME: HEALTH ECONOMIC ANALYSIS									
Hockenhull *et al.*, 2012 (31) A systematic review of the clinical effectiveness and cost-effectiveness of Pharmalgen(R) for the treatment of bee and wasp venom allergy UK	SR RCTs Quasi RCTs Health economic modelling	N=9 n=1065	Bee or wasp venom allergy	A systematic review of the clinical effectiveness and cost effectiveness of Pharmalgen for the treatment of bee and wasp venom allergy			High	Evidence available poor but indicates reduction of future stings following the use of Pharmalgen VIT	

Table 2 Quality assessment of systematic reviews

Author, year	Focused question	Inclusion of appropriate studies	Inclusion of eligible studies	Quality assessment of studies	Appropriateness of synthesis	Overall results of review	Applicability to local populations	Considering all relevant outcomes	Benefits vs. harms/costs	Overall quality assessment
Boyle, 2012	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Dhami, 2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Hockenhull, 2012	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Park, 2015	No	No	Yes	Yes	Yes	Unclear	No	Yes	Yes	Low
Watanabe, 2010	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High

Table 3 Quality assessment of RCTs and CBA original studies

Author, year	Design	Adequate sequence generation	Allocation concealment	Blinding/patient-related outcomes	Incomplete outcome data addressed	Free of selecting reporting	Free of other bias*	Overall quality assessment
Golden, 2004	CBA	No	No	No	Yes	Yes	No	Low
Hunt, 1978	RCT	Yes	Unclear	No	Yes	Unclear	No	Low
Oude Elberink, 2002	Comprehensive cohort design includes an RCT	Yes	Yes	No	Yes	Yes	No	Moderate
Oude Elberink, 2009	Comprehensive cohort design includes an RCT	Yes	Yes	No	Yes	Yes	No	Moderate
Pasaoglu, 2006	CBA	No	No	No	Yes	Yes	No	Low
Reisman, 1984	CBA	No	No	No	Yes	Yes	No	Low
Schuberth, 1983	Comprehensive cohort design includes an RCT	Yes	Yes	No	Yes	Yes	No	Moderate
Valentine, 1990	Comprehensive cohort design includes an RCT	Yes	Unclear	No	Yes	Yes	No	Moderate/low

and cost-effectiveness of a specific brand of VIT: Pharmalgen (ALK-Abelló). The original search strategy was to look at the effectiveness of Pharmalgen (ALK-Abelló) versus other non-VIT treatments, but this had to be modified as no studies were found matching the original objective; they therefore widened the criteria to include other forms of Pharmalgen VIT administration protocols. The quality of trials included in the review were overall judged to be at high risk of bias. The review concluded that although the evidence was poor, it suggested that Pharmalgen VIT reduced the risk of future systemic reactions.

Table 4 Quality assessment of case series studies

Author /year	Collected in more than one centre	Objective of the study clear	Clear reporting of inclusion/ exclusion criteria	Clear definition of outcomes reported	Data prospectively collected	Were patients recruited consecutively	Clear description of main study findings	Are outcomes stratified	Score out of 8 / Quality
Brehler, 2000	No	Yes	Yes	Yes	No	No	Yes	Yes	5/Low
Mosbech, 2000	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/Low
Ruëff, 2010	Yes	Yes	No	Yes	Yes	No	Yes	Yes	6/Low
Stoevesandt, 2014	No	Yes	No	Yes	No	No	Yes	Yes	4/Low

Watanabe *et al.* carried out a high quality systematic review looking at the effectiveness of VIT in patients who presented with a systemic reaction to insect stings (33). Four studies were included (34, 37, 38, 46) and a meta-analysis was performed, based on the Schuberth *et al.* and Valentine *et al.* studies, which demonstrated that there was a substantial reduction in the risk of systemic reactions occurring in children treated with VIT following an accidental sting (odds ratio (OR)=0.29 (95% CI 0.10 < OR < 0.87)). The other two studies were judged to be at low risk of bias, but because of heterogeneity between studies they could not be included in the meta-analysis. Overall, this systematic review concluded that VIT was effective and should be recommended for adults with systemic reactions and for children with moderate-to-severe reactions, but not for children who only experienced cutaneous manifestations of a systemic reaction.

In summary, the evidence from these four systematic reviews suggests that VIT is effective in reducing subsequent systemic sting reactions in both children and adults; all four reviews have however highlighted the low quality of evidence that this conclusion is based on.

RCTs

Five RCTs also focussed on the effectiveness of VIT (34-38). Hunt *et al.* was a single blind RCT of 59 patients aged 15-69 years investigating VIT versus whole body extract (WBE) immunotherapy versus placebo; it was judged to be at high risk of bias (34). After 6-10 weeks of treatment, patients were randomly selected for a sting challenge. Of the 19 patients receiving VIT, 18 were stung with only one (5%) systemic reaction. The WBE and placebo groups each had 20 patients from which 11 (55%) and 12 (60%) patients were stung, respectively. In both groups, there were seven systemic sting reactions. There were significantly more systemic reactions to the sting challenge in the WBE and placebo groups when compared with the VIT group (P<0.01). There was no difference in effectiveness between the WBE and placebo group. The authors concluded that VIT was superior to both WBE and placebo in preventing further systemic sting reactions and recommended the use of VIT to prevent life-threatening systemic sting reactions.

The two Oude Elberink *et al.* RCTs, which primarily looked at quality of life, also reported on re-sting rates. In both studies, they randomized patients to VIT or adrenaline auto-injector. In the 2002 study, two patients experienced a re-sting, one patient from the randomized control arm experienced a sting and developed a systemic reaction (1/38) which required use of an adrenaline auto-injector; one patient in the VIT group had a re-sting, but did not develop a systemic reaction. This patient was in the randomized VIT group (35). In the 2009 study, of 29 patients whose index sting reaction was confined to systemic cutaneous reactions, five patients experienced a field sting: three in the VIT group and two in the adrenaline auto-injector group (36). None of these five patients experienced a systemic sting reaction.

Schuberth *et al.* and Valentine *et al.* both looked at children with non-life-threatening sting reactions (37, 38). Both of these trials were judged to be at moderate risk of bias. They randomized children to VIT or no VIT and studied systemic sting reactions to bees and wasps

in those experiencing accidental stings. Schuberth *et al.*, who looked at 181 children with systemic sting reactions limited to cutaneous manifestations found no statistical difference in the number of systemic sting reactions following an accidental sting in the VIT and no treatment group (35). They further found that no subsequent reaction was more severe than the original and in the no-VIT group of eight systemic reactions only one was as serious as the original. This led to their conclusion that children with primarily cutaneous manifestation to a sting were unlikely to experience a further systemic reaction following a re-sting. A total of 242 children were included in the Valentine *et al.* study (38). Of 45 children who experienced 55 stings, only one child in the VIT group experienced a systemic reaction to a field sting (1.8% systemic reactions/sting) compared to seven systemic reactions from 68 stings in 61 children who did not receive VIT (10.3% systemic reactions/sting) over a period of four years (RR=0.21, 95% CI 0.03 to 1.66, P=0.14). Both studies concluded that VIT is not indicated in children with cutaneous manifestations only.

CBAs

The CBAs by Golden, Pasaoglu and Reisman *et al.* were all judged to be at moderate risk of bias (39-41). Golden *et al.* assessed the long-term effectiveness of VIT compared to no VIT in preventing systemic sting reactions in 512 children (aged 10-20) after an average of 3.5 years of VIT treatment. They found a prolonged benefit in the treatment group as the VIT group experienced less systemic sting reactions (2 of 64 patients, or 3%) than the untreated patients (19 of 111 patients, or 17%; P=0.007) (39). This study suggested VIT was effective in children with moderate-to-severe reactions, but that VIT was not recommended in children who experienced mild reactions.

In contrast, the CBA by Pasaoglu *et al.* looked at the effectiveness of a seven day rush protocol of VIT in 18 patients (40). Seven received bee VIT, seven yellow jacket VIT and four were controls. Of the 14 patients who received VIT, two experienced accidental stings (including a bee keeper who had multiple stings). No systemic sting reactions occurred. They concluded that a seven day rush protocol is effective.

The CBA by Reisman *et al.* looked at children and adults with anaphylaxis to stings from honeybee or yellow jacket or bald-faced hornets or paper wasps (41). They looked at three groups and their subsequent reactions to accidental stings over a seven year period: those who had VIT, those who started VIT, but stopped prematurely and those without VIT. The group which took VIT for the recommended duration (mean 34 months) had 87 re-stings with only two systemic reactions (1%). The group which stopped VIT prematurely (duration of VIT one month to 6.5 years) experienced 61 re-stings with 11 systemic reactions (17%). The group with no-VIT experienced 40 re-stings with 14 systemic reactions (35%). They concluded that VIT was almost 100% protective against subsequent sting triggered anaphylaxis.

Meta-analysis of the Reisman and Golden *et al.* studies demonstrated an overall substantial protective effect of VIT against subsequent systemic reactions (OR=0.08, 95% CI 0.03 to 0.26) (Figure 3).

Impact on disease specific quality of life

Systematic reviews

The systematic review by Boyle *et al.* drew on two RCTs by Oude Elberink *et al.* 2006 (47) and 2009 (36), the latter of which is also included in this review and discussed below. This systematic review found that VIT was associated with a significant improvement in disease specific quality of life after one year of VIT (RR=7.11, 95% CI 3.02 to 16.71) (29).

RCTs

Two RCTs assessed the impact of VIT on disease specific quality of life measured using the Vespid allergy Quality of Life Questionnaire (VQLQ) (35, 36). Both of these studies looked at patients allergic to yellow jackets. The Oude Elberink *et al.* (2009) RCT looked at the impact on disease specific quality of life in patients who had experienced only cutaneous manifestations of a systemic reaction; patients were randomized to VIT or an adrenaline auto-injector. The VQLQ score of patients in the VIT arm improved significantly (mean change 0.83 (SD 0.87); P<0.01), in contrast to patients randomized to an adrenaline auto-injector whose scores deteriorated (mean change -0.42 (SD 0.64)), resulting in an overall risk difference of 1.25 (95% CI 0.63 to 1.87). The study suggested that all adults, including those who only had dermal reactions as a systemic allergic reaction to yellow jacket stings, should be considered for VIT and sole treatment with an adrenaline auto-injector should be avoided (36).

A similar earlier RCT by the same research team looked at disease specific quality of life in patients who

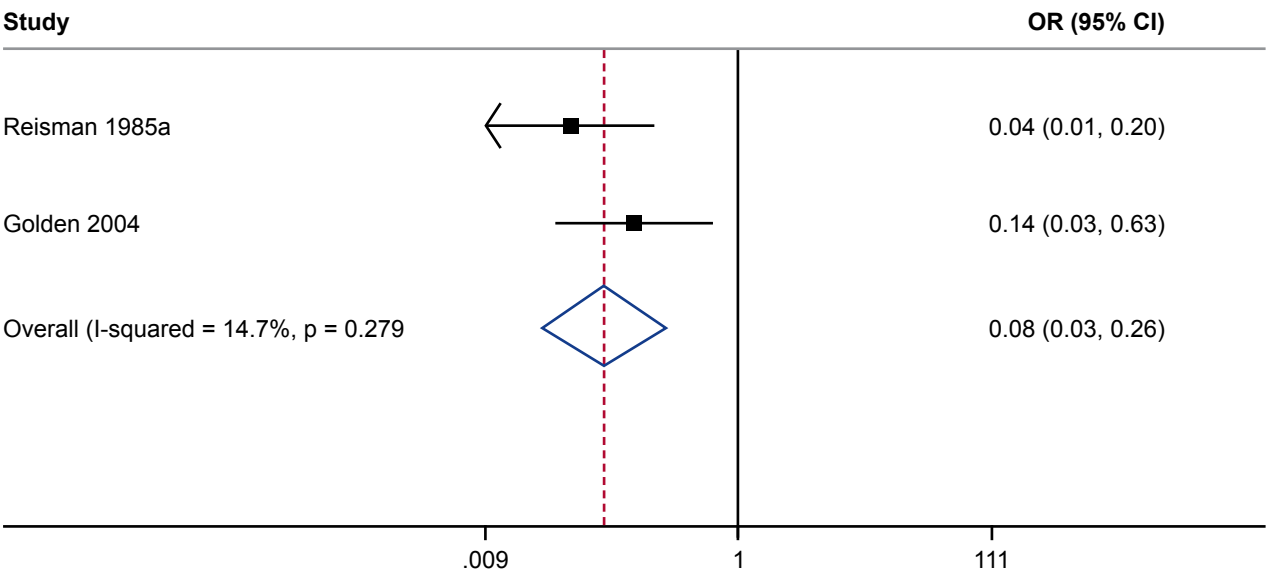

Figure 3 Meta-analysis of CBA studies investigating the effectiveness of VIT on risk of systemic sting reactions (random effects)

had experienced a systemic reaction after a yellow jacket sting that was not solely confined to the skin (35). The findings of this study were confirmed in their 2009 study, whereby there was a clinically relevant improvement in disease specific quality of life in patients treated with VIT. The mean change in VQLQ score in the group randomized to VIT was 1.07 (95% CI, 0.68 to 1.46), and this improvement was also statistically significant (P <0.0001) compared with that seen in the group randomized to the adrenaline auto-injector, in which this change was -0.43 (95% CI, -0.71 to -0.16) with a mean difference between the two groups of 1.51 (95% CI, 1.04 to 1.98). Of every three patients treated with VIT, two patients experienced a clinically relevant important improvement in their disease specific quality of life. Overall, it was found that 72% of patients benefited from VIT, this corresponding to a number needed to treat (NNT) of 1.4. Meta-analysis of these studies demonstrated an improvement in disease specific quality of life (1.41, 95% CI 1.04 to 1.79) (Figure 4). The Begg test (P=0.317) showed no evidence of publication bias.

Safety

Systematic reviews

The review by Boyle *et al.* assessed the safety of VIT, six trials reported on this outcome. They concluded that VIT carries a small but significant risk of systemic reactions (RR=8.16; 95% CI 1.53 to 43.46) (29). They further looked at 11 observational studies for safety and found that systemic adverse events occurred in 14.2% of participants treated with bee venom VIT and 2.8% of those treated with wasp venom VIT.

The systematic review by Park *et al.*, which was assessed as of a low quality, looked at identifying the frequency and types of adverse events associated with different types of bee venom therapy; in doing so they included VIT, but also acupuncture (32). It included 145 studies consisting of 20 RCTs, 79 audits and cohort studies, 33 single case studies and 13 case series. Two RCTs on VIT were included (35, 47), one of which we have included in this review (35), and 63 case series/cohort studies. From 46 VIT case series/cohort studies, the median incidence of adverse events was 28.9%. Of these, 50.4% had systemic reactions and 10.0% large local reactions. 35.8% showed just local reactions and 3.9% had "other" reactions.

RCTs

Of the RCTs included in this review two reported very limited information on safety considerations of VIT and this is included in Table 2 (34, 36).

CBAs

The CBA conducted by Pasaoglu *et al.* evaluated the safety of a rush VIT protocol lasting on average seven

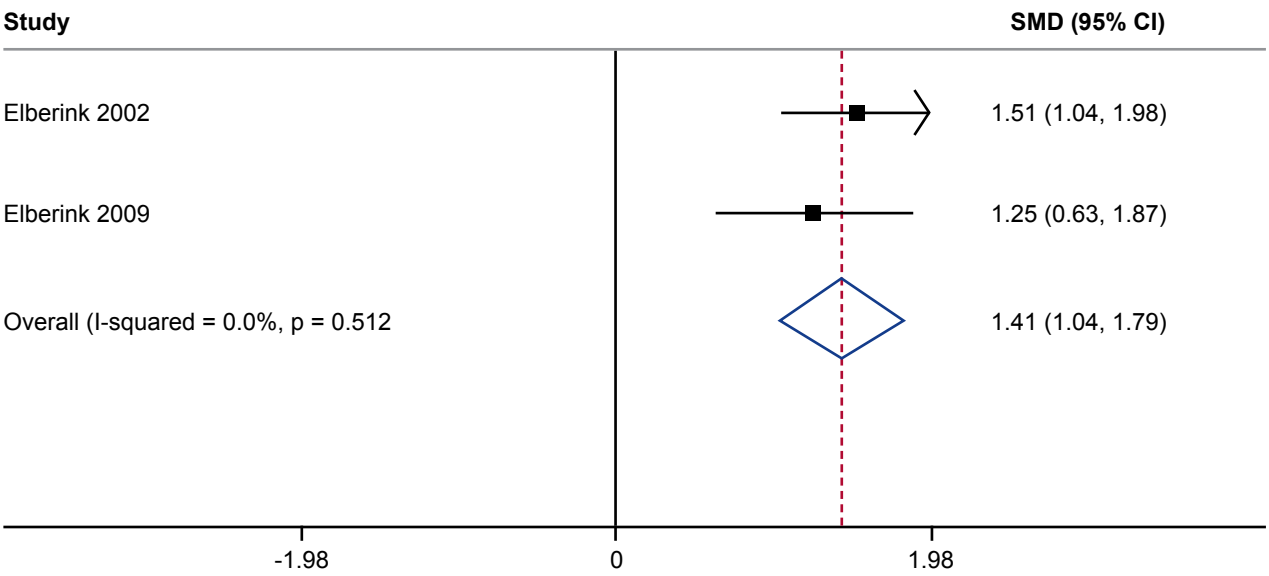

Figure 4 Meta-analysis of RCTs investigating the effectiveness of VIT on VQLQ (random effects)

days and monitored for local and systemic reactions during both the induction and maintenance phases of VIT treatment over a one year period. The study concluded that rush VIT was safe and associated with a low risk of systemic reactions (four systemic reactions from a total of 469 injections, this equating to a 0.85% risk per total number of injections) and that this treatment approach could therefore be considered for patients requiring rapid protection such as those with a high risk of subsequent stings (e.g. bee keepers and their families). The risk of systemic reaction to VIT was related to the type of venom used with vespid venom being better tolerated than bee venom (40).

Case series

Four large case series (i.e. Brehler, Mosbech, Ruëff and Stoevesandt *et al.*) met our eligibility criteria. The Brehler *et al.* study looked at the safety implication of shortening the 7-9 day rush protocol to two days as well as increasing the initial dose of venom administered. No anaphylactic reactions were seen in 1055 VIT treatments in 966 patients; most adverse events were mild and none needed treatment with adrenaline. Overall, they concluded the two day rush protocol is safe and the risk of systemic reactions is rare when the number of injections administered is reduced from 20 subcutaneous injections to nine (42).

The Mosbech *et al.* case series included 840 patients, was conducted in 10 European countries and assessed the safety of VIT in both the build-up and maintenance phases in patients allergic to honey bees, wasps and paper wasps (45). Treatment protocols were not standardised across centres and conventional, rush and cluster protocols were used. 782 patients received VIT with one venom and 58 with two venoms respectively. A total of 26,601 injections were administered and 299 systemic side-effects occurred (1.2% of injections). Most of these reactions were mild based on the Mueller grading scale (51) with only one-third needing treatment. One patient required adrenaline. Adverse events were more frequent during the dose-increase phase than the maintenance phase (mean: 1.9% vs. 0.5% of all injections). Other factors were identified that resulted in an increase in adverse events. These included female gender, rapid dose-increase regimens, and VIT with bee-venom extract. They concluded that systemic side-effects may occur in up to 20% of patients, but are usually mild.

The Ruëff *et al.* case series looked at measuring the severity of reactions according to the Ring and Meßmer (52) tool during the build-up phase of VIT, which required emergency intervention. They evaluated 680 patients in which VIT was delivered using the following protocols; conventional, rush and ultra-rush protocols for bee and vespid immunotherapy. The study identified a number of risk factors that led

to a higher frequency of adverse events requiring emergency intervention during VIT; these included bee venom immunotherapy and using rush and ultra-rush protocols. The authors concluded that patients receiving bee VIT warrant closer monitoring than those patients receiving VIT to other insects (43).

Stoevesandt *et al.* looked at the incidence of systemic reactions during 818 build-up cycles (rush five day or ultra-rush three day inpatient treatment protocol) and the severity of VIT related anaphylaxis was graded according to the WAO classification system (20). The data from this study indicated that rush protocols were safe with very low numbers of patients suffering from moderate-to-severe systemic anaphylaxis based on the WAO classification system (i.e. 673 (82.3%) of 818 documented build-up cycles were tolerated without complications). However, the authors acknowledged that due to low numbers of moderate-to-severe anaphylaxis reactions (0.8% of patients in the total cohort), robust statistical conclusions could not be drawn (44).

Health economic analysis

We found only one study, the review by Hockenhull *et al.*, that looked at the economic evaluation of VIT – a modeling study looking at the cost-effectiveness of VIT for the treatment of bee and wasp venom allergy (31). The study compared VIT with Pharmalgen plus high dose H_1-antihistamines plus adrenaline auto-injectors versus high dose H_1-antihistamines plus adrenaline auto-injectors (AAI) and avoidance advice only. It found that VIT was not cost-effective in the general population (incremental cost-effectiveness ratio (ICERs) of £18 million and £7.6 million per quality adjusted life year (QALY) against high dose H_1-antihistamines plus AAI and avoidance advice only, respectively), but more effective than other treatment options and cost saving in patients likely to be stung more than five times per year such as bee keepers. This one study, despite the fact that it was based largely on expert opinion and plausible assumptions, resulted in the suggestion that VIT for bee and wasp venom allergy is only cost-effective from a UK National Health Service (NHS) perspective for very high risk groups likely to be exposed to multiple exposures to venom per year such as bee keepers. The modelling analysis suggests plausible ranges of exposure to such events to qualify a patient as a member of a high risk group and explores a wide range of sensitivity and scenario analyses to demonstrate the robustness of its findings.

We were unable to find any primary studies assessing the cost-effectiveness of VIT for venom allergy.

DISCUSSION

Statement of principal findings

This systematic review has found a modest body of evidence of moderate quality which suggests that VIT is effective in reducing subsequent severe systemic sting reactions in both children and adults and that this treatment modality can have a significant beneficial impact on disease specific quality of life when compared with carrying an adrenaline auto-injector The available data on the safety of VIT suggests that although adverse events occurred during both the build-up and maintenance phases, the vast majority were relatively mild with adrenaline only being needed very infrequently and – importantly – no fatalities being recorded. We found no primary evidence on the cost-effectiveness of VIT; the one modelling study found that VIT would be cost-effective in high risk groups or if disease specific quality of life was taken into consideration.

Strengths and limitations

There are a number of strengths to this systematic review. In particular, we searched a broad array of databases for published and in progress research, and also consulted with a panel of international experts in an attempt to identify unpublished evidence. Furthermore, our systematic review was conducted according to a pre-defined, published protocol with no deviations from this (10).

The limitations of this review also need to be considered. Key here were the limited number of studies identified, despite the fact that we also included CBAs. The review is further limited by the low quality of the primary studies. Furthermore, two of the RCTs included in this systematic review (i.e. Valentine and Schuberth) excluded patients who had life-threatening systemic reactions to the initial sting – the group of patients who would be most likely to benefit from VIT (36, 37). Furthermore, it should be noted that in both of these studies, the definitive identification of the culprit insect responsible for the accidental sting was not possible. Thus, whether

the child was stung by the insect responsible for the index sting which resulted in a systemic reaction was unknown. This is in contrast to the Hunt trial in which patients were sting challenged by the insect they were known to be allergic to (35). As this review did not include the jack jumper species of ants the double-blind placebo controlled RCT by Brown *et al.* (2003) could not be included in this review (46). This study concluded that VIT significantly reduces the risk of serious subsequent sting reactions from the jack jumper ant (P<0.0001). Only one study assessed the cost-effectiveness of VIT and this was limited to looking only at one product and based on an economic modeling analysis (31). Finally, as with any systematic review there is the possibility that we missed some studies.

Interpreting the results of this review in the context of the wider literature

In undertaking this systematic review, we sought to identify all relevant previous systematic reviews. Our findings are broadly in accordance with these previous reviews, namely that VIT is beneficial, but that this judgement is limited by the paucity and quality of the relevant evidence base. Guidelines for the long term management of allergic reactions to venom advocate the use of VIT in patients who have experienced moderate to severe systemic reactions (53, 54). In agreement with our findings, VIT is not recommended in children whose index reaction was confined to cutaneous manifestations. SLIT remains an experimental treatment in VIT; no SLIT studies satisfied our eligibility criteria.

Implications for policy, practice and research

The results of our review indicate that people who experience moderate-to-severe systemic reactions to venom are likely to benefit from treatment with VIT. This benefit consists of a reduction in the frequency and severity of subsequent systemic reactions following future stings and/or a clinically relevant improvement in disease specific quality of life. We found very limited evidence on the cost-effectiveness of VIT for venom allergy which thus needs to be interpreted cautiously; the available evidence, from a single economic modeling study, indicated that VIT is likely to be cost-effective in patients at high risk of future sting reactions and/or if quality of life is impaired.

Given the paucity of high quality evidence uncovered, consideration needs to be given to undertaking high quality studies investigating the effectiveness and cost-effectiveness of VIT. RCTs in both adults and children would be of interest, but due to the risk of life-threatening reactions in untreated patients, RCTs may not be considered ethical by some clinicians and furthermore they may not be approved by some ethics committees. It seems unlikely therefore that there will be further placebo-controlled trials of VIT preparations in the foreseeable future. As for VIT regimens, at present many protocols for VIT are used discretionally at treatment centers with varying build-up and maintenance doses with no defined duration of treatment. These protocols vary from conventional (12 weeks) to one day ultra-rush protocols during the build-up phase. Time taken to reach the maintenance dose will be dependent on the build-up phase and varies across centers. Trials should therefore be considered comparing different VIT regimens, doses and durations of VIT. Whether trials of SLIT for venom allergy are indicated is debated (55). More standard reporting of VIT- associated adverse events is needed in order to allow comparison across studies. Primary studies of cost-effectiveness are needed

Conclusions

The limited available evidence suggests that VIT is effective in reducing subsequent severe systemic sting reactions and in improving disease specific quality of life. VIT proved to be safe and no fatalities were recorded in the studies included in this review. The cost-effectiveness of VIT needs to be established.

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Contributorship

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Conflicts of interest

[1]Sangeeta Dhami reports grants from EAACI, during the conduct of the study; [2]Hadar Zaman has nothing to disclose; [3]Eva-Maria Varga has nothing to disclose; [4]Gunter J Sturm reports grants and personal fees from ALK Abello, personal fees from Novartis, personal fees from Stallergens, personal fees from Bencard Allergy, personal fees from Leti, outside the submitted work; [5]Antonella Muraro reports personal fees from Novartis, personal fees from Meda Mylan, outside the submitted work; [6]Cezmi Akdis reports grants from Actellion, personal fees from Aventis, personal fees from Stallergenes, grants and personal fees from Allergopharma, personal fees from Circassia, grants from Novartis, grants from Christine Kuhne Center for Allergy Research and Education, outside the submitted work; [7]Darío Antolín-Amérigo reports having participated in the following: Advisory board (Merck, Novartis, Sandoz), Medical expert of the ALK web for general public (ALK-Abelló), research grant (Merck-Serono-Fundación 2000), clinical trials (Diater Laboratorios, Stallergenes), educational grants (Merck, Pfizer), speaker (Allergy Therapeutics, GlaxoSmithKline, AstraZeneca, Merck, Stallergenes), honoraria for articles (Ferrer Laboratorios, Meda, Stallergenes); [8]Beatrice Bilò has nothing to disclose; [9]Danijela Bokanovic has nothing to disclose; [10]Moises A Calderon has received honorarium in Advisory Boards for ALK and Hal-Allergy, as speaker for ALK, Merck and Stallergenes-Greer; [11]Ewa Cichocka-Jarosz has nothing to disclose; [12]Joanna N.G. Oude Elberink reports grants from ALK ABello, during the conduct of the study; [13]Radoslaw Gawlik has nothing to disclose; [14]Thilo Jakob reports non-financial support from German Society of Allergy Clinical Immunology, personal fees from Allergo Journal International, personal fees from ALK Abello, Germany, personal fees from Allergy therapeutics, grants and personal fees from Allergopharma, personal fees from Novartis, personal fees from Leti GmbH, grants and personal fees from Thermo Fisher Scientific, personal fees from Stallergenes, outside the submitted work; [15]Mitja Kosnik has nothing to disclose; [16]Joanna Lange has nothing to disclose; [17]Ervin Mingomataj has nothing to disclose; [18]Dimitris I Mitsias has nothing to disclose; [19]Holger Mosbech reports personal fees from ALK, outside the submitted work; [20]Markus Ollert reports personal fees from Thermo Fisher, outside the submitted work; and Co-Founder of the Biotech Start-up PLS-Design GmbH, Hamburg, Germany in 2004; [21] [22]Oliver 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, personal fees from Novartis Pharma, personal fees from MEDA Pharma, grants and personal fees from Anergis S.A., personal fees from Sanofi US Services, personal fees from Mobile Chamber Experts (a GA2LEN Partner), personal fees from Pohl-Boskamp, outside the submitted work; [23]Constantinos Pitsios has nothing to disclose; [24]Valerio Pravettoni has nothing to disclose; [25]Graham Roberts reports 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; [26]Franziska Ruëff has participated in clinical studies for Novartis, HAL, ALK-Abello, has received financial support for a non-interventional study from Novartis, was paid lecturer for HAL, ALK-Abello, Astra Zeneca, Novartis and a advisor for Bencard, Dr. Gerhard Mann chem.-pharm. Fabrik GmbH, Novartis, Stallergenes and ALK-Abello. These activities do not cause a conflict of interest and have no influence on the paper. [27]Betül Ayşe Sin has nothing to disclose; [28]Miqdad Asaria has nothing to disclose; [29]Gopal Netuveli has nothing to disclose; [30]Aziz Sheikh reports grants from EAACI, during the conduct of the study.

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3

ALLERGEN IMMUNOTHERAPY FOR IgE-MEDIATED FOOD ALLERGY

A SYSTEMATIC REVIEW AND META-ANALYSIS

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***Background**: The European Academy of Allergy and Clinical Immunology (EAACI) is developing Guidelines for Allergen Immunotherapy (AIT) for IgE-mediated Food Allergy. To inform the development of clinical recommendations, we sought to critically assess evidence on the effectiveness, safety and cost-effectiveness of AIT in the management of food allergy.*

***Methods**: We undertook a systematic review and meta-analysis that involved searching nine international electronic databases for randomized controlled trials (RCTs) and non-randomized studies (NRS). Eligible studies were independently assessed by two reviewers against pre-defined eligibility criteria. The quality of studies was assessed using the Cochrane Risk of Bias tool for RCTs and the Cochrane ACROBAT-NRS tool for quasi-RCTs. Random-effects meta-analyses were undertaken, with planned subgroup and sensitivity analyses.*

***Results**: We identified 1814 potentially relevant papers from which we selected 31 eligible studies, comprising of 25 RCTs and six NRS, studying a total of 1259 patients. Twenty-five trials evaluated oral immunotherapy (OIT), five studies investigated sublingual immunotherapy (SLIT) and one study evaluated epicutaneous immunotherapy (EPIT). The majority of these studies were in children. Twenty-seven studies assessed desensitization and eight studies investigated sustained unresponsiveness post-discontinuation of AIT. Meta-analyses demonstrated a substantial benefit in terms of desensitization (risk ratio (RR)=0.16, 95% CI 0.10, 0.26) and sustained unresponsiveness (RR=0.29, 95% CI 0.08, 1.13). Only one study reported on disease-specific quality of life (QoL), which reported no comparative results between OIT and control group. Meta-analyses revealed that the risk of experiencing a systemic adverse reaction was higher in those receiving AIT, with a more marked increase in the risk of local adverse reactions. Sensitivity analysis excluding those studies judged to be at high risk of bias demonstrated the robustness of summary estimates of effectiveness and safety of AIT for food allergy. None of the studies reported data on health economic analyses.*

***Conclusions**: AIT may be effective in raising the threshold of reactivity to a range of foods in children with IgE-mediated food allergy whilst receiving (i.e. desensitization) and post-discontinuation of AIT. It is however associated with a modest increased risk in serious systemic adverse reactions and a substantial increase in minor local adverse reactions. More data are needed in relation to adults, long term effects, the impact on QoL and the cost-effectiveness of AIT.*

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BACKGROUND

Food allergy may result in considerable morbidity and, in some cases, mortality (1). Epidemiological studies have demonstrated that the prevalence and severity of food allergy may be increasing, particularly in children (2-8). Food allergies can be divided into IgE-mediated acute allergic reactions manifesting as urticaria, vomiting, wheezing and anaphylaxis, and non-IgE-mediated food allergy which results from delayed, cell-mediated reactions. This systemic review is focused on IgE-mediated reactions.

Food allergies can be associated with significant reduction in disease specific quality of life (QoL) – both of individuals who suffer from food allergy and their family members (9, 10). At present, avoidance measures are the cornerstone of management (11). Difficulties in avoiding responsible food allergens can however result in accidental exposure and the risk of triggering potentially life-threatening anaphylaxis. Of concern is the increasing numbers of people being seen in emergency departments or who are hospitalized because of food-induced anaphylaxis (12, 13). Individuals with food allergy therefore need to carry adrenaline (epinephrine) auto-injectors in order to self-manage anaphylaxis. This approach is however perceived as restrictive and still leaves patients at risk if accidental exposure occurs (2, 7, 8).

Allergen immunotherapy (AIT) has been used for over a century to treat those with food allergy (14). It involves repeated administration of gradually increasing doses of the antigens to which individuals are allergic in the hope of allowing safe exposure to the food(s) in question. Whilst AIT has become an established treatment regimen in relation to the management of, for example, pollen and insect venom allergy (15), it has yet to become established in the routine management of food allergy.

The European Academy of Allergy and Clinical Immunology (EAACI) is in the process of developing the EAACI Guidelines for AIT, and this systematic review and meta-analysis is one of five inter-linked assessments of the current evidence base in relation to evaluating AIT for the treatment of food allergy, allergic rhinoconjunctivitis, venom allergy, allergic asthma and allergy prevention, which will be used to inform development of clinical recommendations. The focus of this review, which builds on our previous related reviews (16, 17), is to assess the effectiveness, safety and cost-effectiveness of AIT in the management of IgE-mediated food allergy.

METHODS

Details of the methods employed in this review, including search terms and filters, databases searched, inclusion and exclusion criteria, data extraction and quality appraisal, have been previously reported (18). We therefore confine ourselves here to a synopsis of the methods employed.

Search strategy

Nine international databases were searched for published material: Cochrane Library, which includes CENTRAL [Trials, Methods studies, Health Technology Assessments (HTA), Economic Evaluation database (EED)]; MEDLINE, EMBASE, ISI Web of Science, TRIP and CINAHL. The search strategy was developed on OVID MEDLINE and then adapted for the other databases (Appendix 3.1, search strategies 1 and 2). Our database searches covered from inception to March 31, 2016. The bibliographies of all eligible studies were scrutinized to identify additional possible studies. No language restrictions were imposed and where necessary manuscripts were translated into English.

Inclusion criteria

Patient characteristics

We focused on studies conducted on children and adults of any age with a clinician-diagnosed IgE-mediated food allergy to milk, eggs, peanuts, tree nuts and other foods with confirmation of allergic status through positive skin prick tests, specific-IgE and/or food challenge tests.

Interventions of interest and comparators

This review focused on AIT for different allergens, i.e. milk, eggs, tree nuts, peanuts and other foods, administered through the following routes: oral (OIT), sublingual (SLIT) and epicutaneous (EPIT). We were interested in studies comparing food allergy AIT with placebo or routine care (i.e. adrenaline auto-injector with or without antihistamines) or no treatment.

Outcomes

Our primary outcomes of interest were: 1) desensitization (i.e. the ability to safely consume

foods containing the allergen in question while on AIT); 2) sustained unresponsiveness (i.e. the ability to safely consume foods containing the allergen in question after discontinuing AIT) at food challenge; and 3) changes in disease specific QoL using a validated instrument. Secondary outcome measures of interest were safety as assessed by local and systemic reactions in accordance with the World Allergy Organization's (WAO) grading system of side-effects (19, 20).

Study designs

We were interested in RCTs investigating the role of OIT, SLIT or EPIT in children and adults with IgE-mediated food allergy. However, given the likelihood that we would find only a limited number of RCTs, we also searched for non-randomized studies (NRS), these including non-randomized controlled clinical trials (CCTs), controlled before-and-after (CBA) studies and interrupted time series (ITS) analyses.

Study selection

All references were uploaded into the systematic review software DistillerSR. Titles and abstracts of identified studies were checked and independently reviewed by two researchers (UN, SD). The full text of all potentially eligible studies were assessed for eligibility against the eligibility criteria (UN, SA). Any disagreements were resolved through discussion, with SD or AS arbitrating if agreement could not be reached.

Quality assessment strategy

The quality of included RCTs was independently assessed by two reviewers (UN, SA) using the methods detailed in section eight of the Cochrane Handbook for Systematic Reviews of Interventions (21). Critical appraisal of quasi-RCTs, CCTs was undertaken using the Cochrane ACROBAT tool for NRS (22). An overall assessment of quality for each trial using these categories was arrived at through consensus discussion amongst reviewers.

Data extraction, analysis and synthesis

Data were independently extracted onto a customized data extraction sheet in DistillerSR by two reviewers (UN, SA) and any discrepancies were resolved by discussion or, if agreement could not be reached, by arbitration by a third reviewer (SD or AS).

Where possible and appropriate, data were synthesized using random-effects meta-analyses following the pre-specified analysis plan. For the assessment of safety, as there were a number of studies with zero reported outcomes, in order to facilitate meta-analyses we expressed safety data as the risk of not experiencing a local or systemic reaction. All analyses were undertaken using the software Comprehensive Meta-Analysis (version 3).

Sensitivity, subgroup analyses, and assessment for publication bias

Sensitivity analyses were undertaken by focusing on results from double-blind RCTs. Subgroup analyses were undertaken to compare:

- Diagnosis of food allergy was confirmed by double-blind, placebo-controlled, food challenge (DBPCFC) versus without DBPCFC
- Route of administration: OIT versus SLIT versus EPIT
- Children (0-17 years) versus adults (≥18 years)
- Type of AIT protocol: conventional versus rush
- Allergens used for AIT.

Where possible, publication bias was assessed through the creation of funnel plots in Comprehensive Meta-Analysis (version 3).

Registration and reporting of this systematic review

This systematic review was conducted and reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. The protocol is registered in PROSPERO (International Prospective Register of Systematic Reviews) with registration number: CRD42016039384.

RESULTS

Our searches identified 1814 potentially relevant papers, from which we identified 31 trials that satisfied our inclusion criteria studying a total of 1259 patients (Figure 1: PRISMA flow diagram). There were 25 RCTs (23-46) and six NRS', all of which were CCTs (47-52). Twenty-five of these trials investigated OIT (23-27, 30, 33, 35-50, 52), one epicutaneous immunotherapy (EPIT) (28) and the remaining five

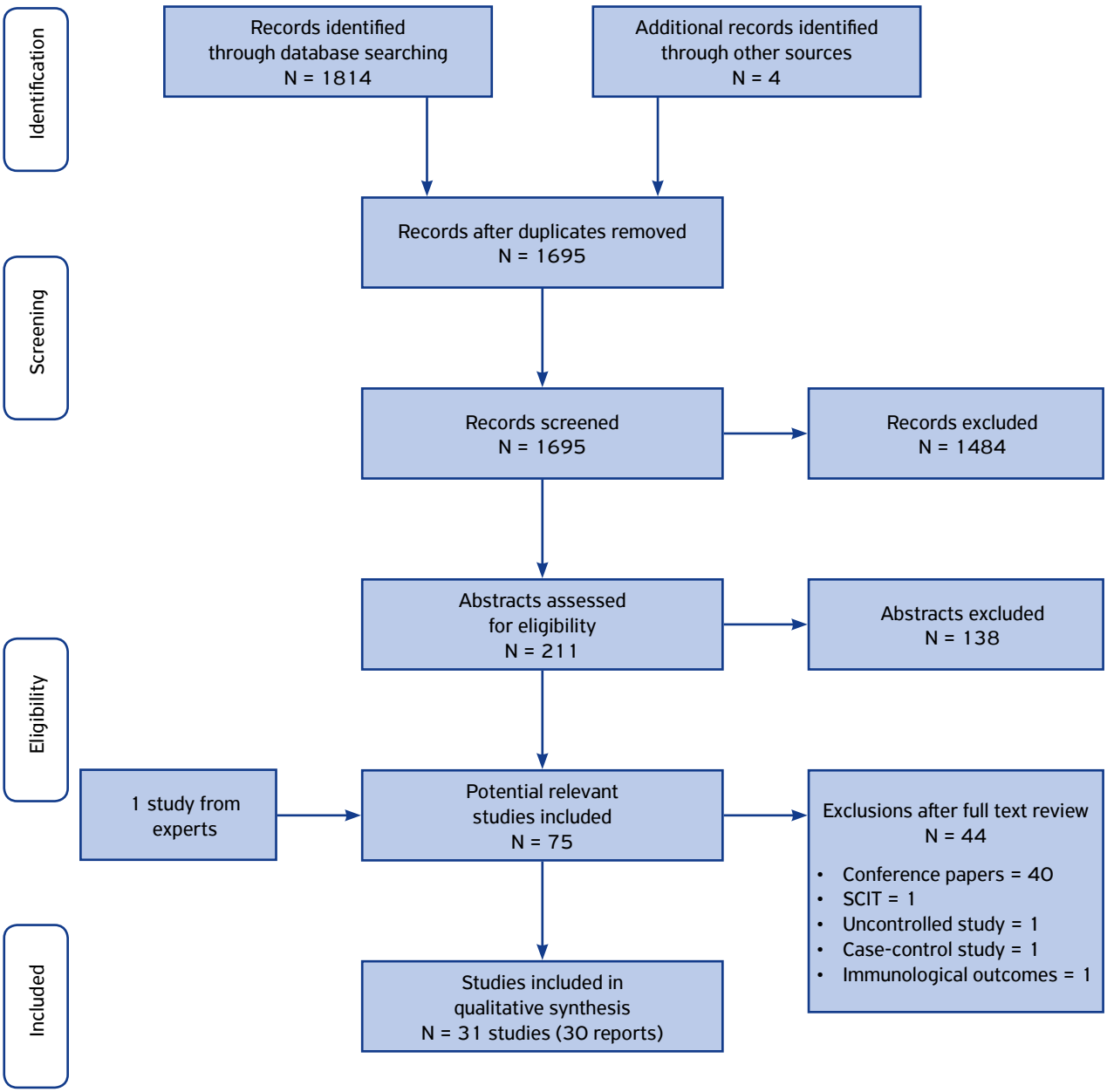


Figure 2 PRISMA flow diagram

investigated SLIT (29, 31, 32, 34, 51). One report included two independent RCTs on cow's milk (CMA) and hen's egg (HEA) (39). Sixteen studies focused on CMA, (25, 35-37, 39-44, 47-51) 11 on HEA (24, 26, 27, 30, 33, 38, 39, 41, 44, 50, 51), seven on peanut (23, 32, 34, 45, 46, 50, 52), one hazelnut (29), two peach (31, 50), three apple (41, 50, 51), three fish (41, 50, 51), and two other studies focused on a variety of food allergens including orange, corn, bean, lettuce (50), wheat and bean (51) (Table 1 and Appendix 3.2, Table S1). The trials were undertaken in Italy (n=9), Spain (n=7), the USA (n=6), France (n=3), Australia (n=1), Finland (n=1), Germany (n=1), Iran (n=1), Korea (n=1), and the UK (n=1).

Table 1 Description of the included studies (n=31)

Study (First author, year, country)	Food allergen (s)								Route AIT			Comparator		Evidence of allergy (mandatory inclusion criteria)					Clinical outcomes				
	Cow's milk	Hen's egg	Peanut	Hazelnut	Peach	Apple	Fish	Other(s)	OIT	SLIT	EPIT	Placebo	Routine care (food avoidance)	Clinical history	SPT &/ or sIgE	OFC	SBPCFC	DBPCFC	Desensitization	Sustained unresponsiveness	DR-QoL	Occurred AEs / medication use	
																						SRs	LRs
RCT (N=25)																							
Anagnostou, 2014, UK			X						X				X	X	X			X	X		X	X	X
Burks, 2012, USA		X							X			X		X	X				X	X		X	X
Caminiti, 2009, Italy	X								X			X		X	X			X	X			X	X
Caminiti, 2015; Italy		X							X			X		X	X			X	X	X		X	X
Dello Iacono, 2013, Italy		X							X				X	X	X			X	X			X	X
Dupont, 2010, France	X										X	X		X	X	X			X			X	X
Enrique, 2005, Spain				X						X[†]		X		X	X			X	X			X	X
Escudero, 2015, Spain		X							X				X	X	X			X		X		X	X
Fernandez-Rivas, 2009, Spain					X					X[‡]		X		X	X			X	X			X	X
Fleischer, 2012, USA			X							X		X							X				
Fuentes-Aparicio, 2013, Spain		X							X				X	X	X	X			X	X		X	X
Kim, 2011, USA			X							X		X		X	X				X				
Lee, 2013, Korea	X								X				X	X	X			X	X			X	X
Longo, 2008, Italy	X								X				X	X	X			X	X			X	X
Martorell, 2011, Spain	X								X				X	X	X			X	X				X
Meglio, 2013, Italy		X							X				X	X	X			X	X				X
Morisset, 2007, France [‡‡]	X	X							X				X	X	X		X		X			X	X
Pajno, 2010, Italy	X								X			X		X	X			X	X			X	X
Patriarca, 1998, Italy	X	X				X	X		X				X	X	X			X	X				X
Salmivesi, 2012, Finland	X								X			X		X	X	X			X	X		X	X
Skripak, 2008, USA	X								X			X			X			X	X			X	X
Staden, 2007, Germany	X	X							X				X	X	X			X		X		X	X
Tang, 2015, Australia			X						X[††]			X		X	X			X	X	X		X	X
Varshney, 2011, USA			X						X			X		X	X				X			X	X

Study (First author, year, country)	Food allergen (s)								Route AIT			Comparator		Evidence of allergy (mandatory inclusion criteria)					Clinical outcomes				
	Cow's milk	Hen's egg	Peanut	Hazelnut	Peach	Apple	Fish	Other(s)	OIT	SLIT	EPIT	Placebo	Routine care (food avoidance)	Clinical history	SPT &/ or sIgE	OFC	SBPCFC	DBPCFC	Desensitization	Sustained unresponsiveness	DR-QoL	Occurred AEs / medication use	
																						SRs	LRs
CCT (N=6)																							
García-Ara, 2013, Spain	X								X				X	X	X	X			X			X	X
Martınez-Botas, 2015, Spain	X								X				X	X	X			X	X	X		X	X
Mansouri, 2007, Iran	X								X				X	X	X			X	X			X	X
Patriarca, 2003, Italy	X	X	X		X	X	X	X[§]	X				X	X	X			X	X			X	X
Patriarca, 2007, Italy	X	X				X	X	X[¶]		X[‡]			X	X	X			X	X			X	X
Syed, 2014, USA			X						X				X	X	X			X		X		NR	NR

AE, adverse event; AIT, allergen specific immunotherapy; DR-QoL, disease related quality of life; LR, local reaction; NR, not reported; OIT, oral immunotherapy; OFC, open food challenge; SLIT, sublingual immunotherapy; SR, systemic reaction.

[†] sublingual-discharge technique

[‡] sublingual-swallow technique

[§] orange, corn, bean, lettuce

[¶] wheat, bean

[††] AIT and probiotics

[‡‡] one report that included two independent randomized controlled trials on cows' milk and hens' eggs

Quality assessment

Quality assessment of these studies revealed that eight of the RCTs were judged to be at low risk of bias (24, 26, 32, 34, 36, 40, 45, 46); a further five RCTs were judged as at unclear risk of bias (28, 31, 33, 37, 43), and the remaining 12 RCTs (23, 25, 27, 29, 30, 35, 38, 39, 41, 42, 44) were judged to be at high risk of bias (Appendix 3.3, Table S2). The six CCTs (47-52) were all judged to be at moderate risk of bias (Appendix 3.4, Table S3).

Primary outcomes

Desensitization

Desensitization was assessed in 18 OIT RCTs (23-27, 33, 35-43, 45, 46) and five OIT CCTs (47-51). There were also four SLIT RCTs (29, 31, 32, 34) and one SLIT CCT (51) that assessed desensitization. The efficacy of AIT was compared with placebo in 12 studies, eight of which used OIT (24-26, 42, 43, 45, 46) and four of SLIT (29, 31, 32, 34); the other 17 studies, all of OIT, employed routine care (i.e. food avoidance/strict elimination diet as the comparator) (27, 30, 33, 35-39, 41, 44, 47-52).

Meta-analysis was possible with data from 27 trials investigating a total of 1171 subjects; this revealed a substantial benefit with respect to desensitization: relative risk (RR)=0.16, 95% CI 0.10, 0.26; Figure 2(a) (23-27, 29-41, 43, 44, 46-52).

Sensitivity analyses

Sensitivity analysis of the 21 RCTs, excluding the six CCTs, also demonstrated a substantial benefit: RR=0.21, 95% CI 0.13, 0.34; Figure 2(b) (23-27, 29-41, 43, 44, 46). A further sensitivity analysis excluding all trials judged to be at high risk of bias confirmed this substantial benefit: RR=0.15, 95% CI 0.09, 0.25; Figure 2(c) (24, 26, 31-34, 36, 37, 40, 43, 46-52). A further sensitivity analysis excluding all trials (whether OIT or SLIT) judged to be at high risk of bias demonstrated a substantial average risk reduction (RR OIT=0.17, 95% CI 0.11, 0.26) (24, 26, 33, 36, 37, 40, 43, 46-50); (RR SLIT=0.31, 95% CI 0.10, 0.98) (31, 32, 34) (Appendix 3.5, Figures S1 and S2).

A final sensitivity analysis focusing on studies in which desensitization was confirmed by DBPCFC after OIT or SLIT also revealed substantial benefits (RR 0.15, 95% CI 0.09, 0.27; Appendix 3.5, Figure S3) (23, 25-27, 29-31, 35-41, 43, 44, 47-52).

Subgroup analyses

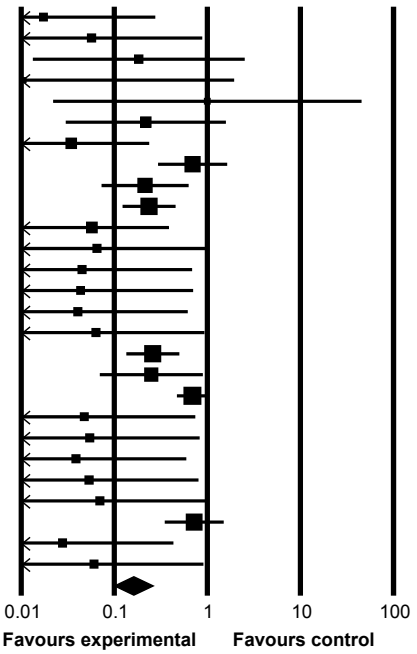
- Subgroup analysis based on the route of administration of AIT (OIT versus SLIT) revealed that both OIT (RR=0.14, 95% CI 0.08, 0.24; Figure 3) (23-27, 30, 33, 35-41, 43, 44, 46-50, 52) and SLIT were effective (RR=0.26, 95% CI 0.10, 0.64; Figure 4) (29, 31, 32, 34, 51).
- A subgroup analysis based on the age of the population studied (children aged up to 18 years old, adults ≥18 years old and mixed population that included subjects 0-55 years old) revealed a substantial average risk reduction only for children and mixed populations, but not for adults studies (RR, children's studies=0.16, 95% CI 0.09, 0.27) (23-27, 30, 32-41, 43, 44, 46-49).

  (RR, adults studies=0.56, 95% CI 0.23, 1.36) (29, 31), (RR, mixed population=0.04, 95% CI 0.01, 0.19) (50-52) (Appendix 3.5, Figures S4, S5 and S6).
- Subgroup analysis based on the type of AIT protocol (conventional versus rush) also showed a substantial average risk reduction for both methods (RR, conventional protocol=0.12, 95% CI 0.07, 0.21) (23-27, 30, 32-35, 38, 40, 43, 44, 46, 47, 49-52); (RR, rush=0.33, 95% CI 0.16, 0.65) (29, 31, 36, 37, 39, 41, 48) (Appendix 3.5, Figures S7 and S8).
- Subgroup analyses of types of allergen demonstrated that in 13 trials investigating CMA, 11 HEA and four peanut allergy OIT/SLIT substantially reduced the risk of desensitization to CMA, HEA and peanut allergy (RR CM=0.12, 95% CI 0.06, 0.25) (25, 35-37, 39-41, 43, 44, 47-51); (RR HE=0.22, 95% CI 0.11, 0.45) (24, 26, 27, 30, 33, 38, 39, 41, 44, 50, 51); (RR peanut=0.11, 95% CI 0.04, 0.31) (23, 32, 34, 46) (Appendix 3.5, Figures S9, S10 and S11). A sensitivity analysis of the 17 OIT and four SLIT RCTs found a substantial average risk reduction (RR OIT=0.18, 95% CI 0.10, 0.32) (23-27, 30, 33, 35-41, 43, 44, 46); (RR SLIT=0.31, 95% CI 0.13, 0.76) (29, 31, 32, 34) (Appendix 3.5, Figures S12 and S13).

The Funnel plot revealed evidence of potential publication bias with fewer smaller, negative studies than expected (Figure 5).

A

Study name	Statistics for each study			Events / Total		Relative weight
	Risk ratio	Lower limit	Upper limit	Control	Experimental	
Anagnostou 2014	0.017	0.001	0.277	0 / 46	24 / 39	2.25
Burks 2012	0.057	0.004	0.884	0 / 15	22 / 40	2.29
Caminiti 2009	0.183	0.013	2.528	0 / 3	7 / 10	2.44
Caminiti 2015	0.011	0.000	1.952	0 / 14	16 / 17	0.77
Dello Lacono 2013	1.000	0.022	45.635	1 / 10	1 / 10	1.33
Enrique 2005	0.218	0.030	1.588	1 / 11	5 / 12	3.58
Escudero 2015	0.035	0.005	0.238	1 / 31	28 / 30	3.71
Fernandez-Rivas 2009	0.695	0.295	1.641	5 / 19	14 / 37	7.27
Fleischer 2013	0.214	0.073	0.632	3 / 20	14 / 20	6.38
Fuentes-Aparicio 2013	0.236	0.122	0.458	7 / 32	37 / 40	8.05
Garcia-Ara 2013	0.057	0.009	0.388	1 / 19	33 / 36	3.76
Kim 2011	0.065	0.004	0.957	0 / 7	11 / 11	2.36
Lee 2013	0.045	0.003	0.688	0 / 12	14 / 16	2.31
Longo 2008	0.043	0.003	0.706	0 / 30	11 / 30	2.23
Mansouri 2007	0.041	0.003	0.619	0 / 13	18 / 20	2.31
Martinez-Botas 2015	0.064	0.004	0.933	0 / 7	25 / 25	2.36
Martorell 2011	0.259	0.134	0.501	7 / 30	27 / 30	8.06
Meglio 2013	0.250	0.070	0.897	2 / 10	8 / 10	5.65
Morisset 2007b	0.692	0.468	1.023	18 / 39	34 / 51	8.96
Pajno 2010	0.048	0.003	0.746	0 / 15	10 / 15	2.27
Patriarca 1998	0.055	0.004	0.826	0 / 10	12 / 14	2.32
Patriarca 2003	0.039	0.003	0.597	0 / 16	45 / 59	2.30
Patriarca 2007	0.054	0.004	0.806	0 / 10	36 / 42	2.33
Skripak 2008	0.070	0.005	1.031	0 / 7	12 / 13	2.35
Staden 2007	0.722	0.347	1.504	7 / 21	12 / 26	7.77
Syed 2014	0.028	0.002	0.433	0 / 20	20 / 23	2.28
Varshney 2011	0.061	0.004	0.910	0 / 9	16 / 19	2.33
	0.159	0.099	0.256	53 / 476	512 / 695	



B

Study name	Statistics for each study			Events / Total		Relative weight
	Risk ratio	Lower limit	Upper limit	Control	Experimental	
Anagnostou 2014	0.017	0.001	0.277	0 / 46	24 / 39	2.46
Burks 2012	0.057	0.004	0.884	0 / 15	22 / 40	2.50
Caminiti 2009	0.183	0.013	2.528	0 / 3	7 / 10	2.68
Caminiti 2015	0.011	0.000	1.952	0 / 14	16 / 17	0.81
Dello Lacono 2013	1.000	0.022	45.635	1 / 10	1 / 10	1.43
Enrique 2005	0.218	0.030	1.588	1 / 11	5 / 12	4.03
Escudero 2015	0.035	0.005	0.238	1 / 31	28 / 30	4.18
Fernandez-Rivas 2009	0.695	0.295	1.641	5 / 19	14 / 37	8.89
Fleischer 2013	0.214	0.073	0.632	3 / 20	14 / 20	7.64
Fuentes-Aparicio 2013	0.236	0.122	0.458	7 / 32	37 / 40	10.03
Kim 2011	0.065	0.004	0.957	0 / 7	11 / 11	2.58
Lee 2013	0.045	0.003	0.688	0 / 12	14 / 16	2.52
Longo 2008	0.043	0.003	0.706	0 / 30	11 / 30	2.43
Martorell 2011	0.259	0.134	0.501	7 / 30	27 / 30	10.03
Meglio 2013	0.250	0.070	0.897	2 / 10	8 / 10	6.64
Morisset 2007b	0.692	0.468	1.023	18 / 39	34 / 51	11.40
Pajno 2010	0.048	0.003	0.746	0 / 15	10 / 15	2.49
Patriarca 1998	0.055	0.004	0.826	0 / 10	12 / 14	2.53
Skripak 2008	0.070	0.005	1.031	0 / 7	12 / 13	2.58
Staden 2007	0.722	0.347	1.504	7 / 21	12 / 26	9.61
Varshney 2011	0.061	0.004	0.910	0 / 9	16 / 19	2.55
	0.209	0.129	0.340	52 / 391	335 / 490	

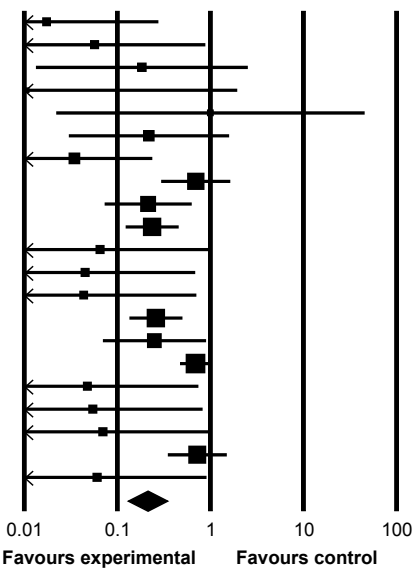


Figure 2 Risk ratios (RR) of desensitization following oral immunotherapy (OIT) or sublingual immunotherapy (SLIT) vs controls (random-effects model). A: Heterogeneity: $\tau^2 = 0.617$; $\chi^2 = 62.845$, df = 26 ($P < 0.0001$); $I^2 = 59\%$; Test for overall effect: $Z = 7.582$ ($P < 0.0001$). B: Heterogeneity: $\tau^2 = 0.498$; $\chi^2 = 47.608$, df = 20 ($P < 0.0001$); $I^2 = 58\%$; Test for overall effect: $Z = 6.318$ ($P < 0.0001$). C: Heterogeneity: $\tau^2 = 0.262$; $\chi^2 = 23.078$, df = 16 ($P < 0.112$); $I^2 = 31\%$; Test for overall effect: $Z = 7.406$ ($P < 0.0001$)

C

Study name	Risk ratio	Lower limit	Upper limit	Control	Experimental	Relative weight
Burks 2012	0.057	0.004	0.884	0 / 15	22 / 40	2.95
Caminiti 2015	0.011	0.000	1.952	0 / 14	16 / 17	0.89
Fernandez-Rivas 2009	0.695	0.295	1.641	5 / 19	14 / 37	14.43
Fleischer 2013	0.214	0.073	0.632	3 / 20	14 / 20	11.55
Fuentes-Aparicio 2013	0.236	0.122	0.458	7 / 32	37 / 40	17.43
Garcia-Ara 2013	0.057	0.009	0.388	1 / 19	33 / 36	5.40
Kim 2011	0.065	0.004	0.957	0 / 7	11 / 11	3.06
Longo 2008	0.043	0.003	0.706	0 / 30	11 / 30	2.87
Mansouri 2007	0.041	0.003	0.619	0 / 13	18 / 20	2.98
Martinez-Botas 2015	0.064	0.004	0.933	0 / 7	25 / 25	3.06
Martorell 2011	0.259	0.134	0.501	7 / 30	27 / 30	17.45
Pajno 2010	0.048	0.003	0.746	0 / 15	10 / 15	2.93
Patriarca 2003	0.039	0.003	0.597	0 / 16	45 / 59	2.96
Patriarca 2007	0.054	0.004	0.806	0 / 10	36 / 42	3.01
Skripak 2008	0.070	0.005	1.031	0 / 7	12 / 13	3.05
Syed 2014	0.028	0.002	0.433	0 / 20	20 / 23	2.95
Varshney 2011	0.061	0.004	0.910	0 / 9	16 / 19	3.01
	0.150	0.091	0.248	23 / 283	367 / 477	

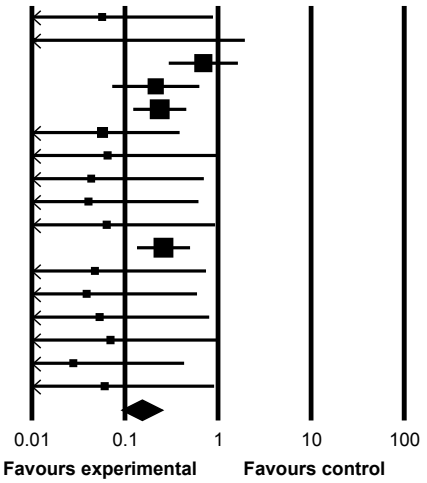


Figure 2 Continued

Study name	Risk ratio	Lower limit	Upper limit	Control	Experimental	Relative weight
Anagnostou 2014	0.017	0.001	0.277	0 / 46	24 / 39	3.04
Burks 2012	0.057	0.004	0.884	0 / 15	22 / 40	3.08
Caminiti 2009	0.183	0.013	2.528	0 / 3	7 / 10	3.28
Caminiti 2015	0.011	0.000	1.952	0 / 14	16 / 17	1.06
Dello Lacono 2013	1.000	0.022	45.635	1 / 10	1 / 10	1.83
Escudero 2015	0.035	0.005	0.238	1 / 31	28 / 30	4.86
Fuentes-Aparicio 2013	0.236	0.122	0.458	7 / 32	37 / 40	9.77
Garcia-Ara 2013	0.057	0.009	0.388	1 / 19	33 / 36	4.92
Lee 2013	0.045	0.003	0.688	0 / 12	14 / 16	3.11
Longo 2008	0.043	0.003	0.706	0 / 30	11 / 30	3.01
Mansouri 2007	0.041	0.003	0.619	0 / 13	18 / 20	3.11
Martinez-Botas 2015	0.064	0.004	0.933	0 / 7	25 / 25	3.18
Martorell 2011	0.259	0.134	0.501	7 / 30	27 / 30	9.78
Meglio 2013	0.250	0.070	0.897	2 / 10	8 / 10	7.15
Morisset 2007b	0.692	0.468	1.023	18 / 39	34 / 51	10.70
Pajno 2010	0.048	0.003	0.746	0 / 15	10 / 15	3.07
Patriarca 1998	0.055	0.004	0.826	0 / 10	12 / 14	3.12
Patriarca 2003	0.039	0.003	0.597	0 / 16	45 / 59	3.09
Skripak 2008	0.070	0.005	1.031	0 / 7	12 / 13	3.17
Staden 2007	0.722	0.347	1.504	7 / 21	12 / 26	9.48
Syed 2014	0.028	0.002	0.433	0 / 20	20 / 23	3.08
Varshney 2011	0.061	0.004	0.910	0 / 9	16 / 19	3.13
	0.135	0.076	0.237	44 / 409	432 / 573	

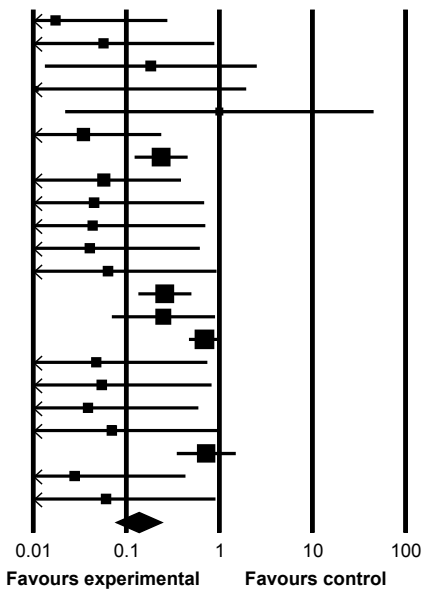


Figure 3 Risk ratios (RR) of desensitization as assessed by double-blind placebo-controlled food challenge in OIT v. controls (random-effects model). Heterogeneity: $\tau^2 = 0.735$; $\chi^2 = 56.047$, df = 21 ($P < 0.0001$); $I^2 = 62\%$; Test for overall effect: $Z = 6.967$ ($P < 0.0001$).

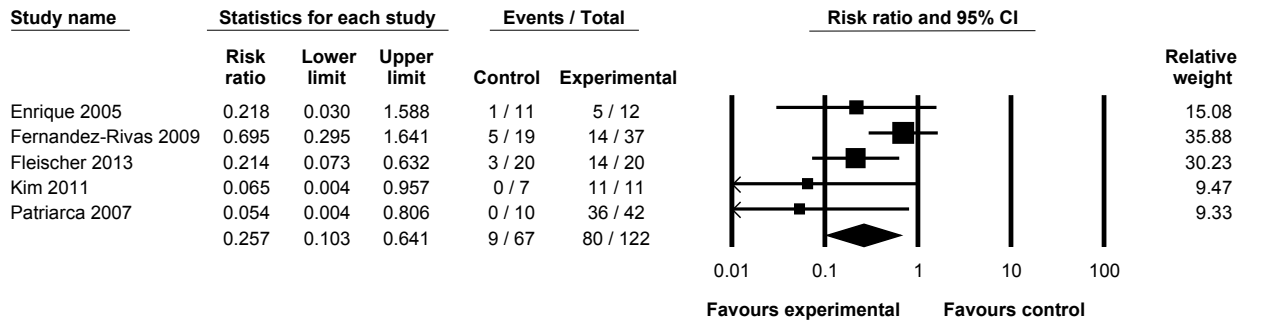


Figure 4 Risk ratios (RR) of desensitization as assessed by doubleblind, placebo-controlled food challenge in SLIT vs controls (randomeffects model). Heterogeneity: $\tau^2 = 0.41$; $\chi^2 = 6.80$, df = 4 ($P < 0.147$); $I^2 = 41\%$; Test for overall effect: $Z = 2.91$ ($P < 0.004$)

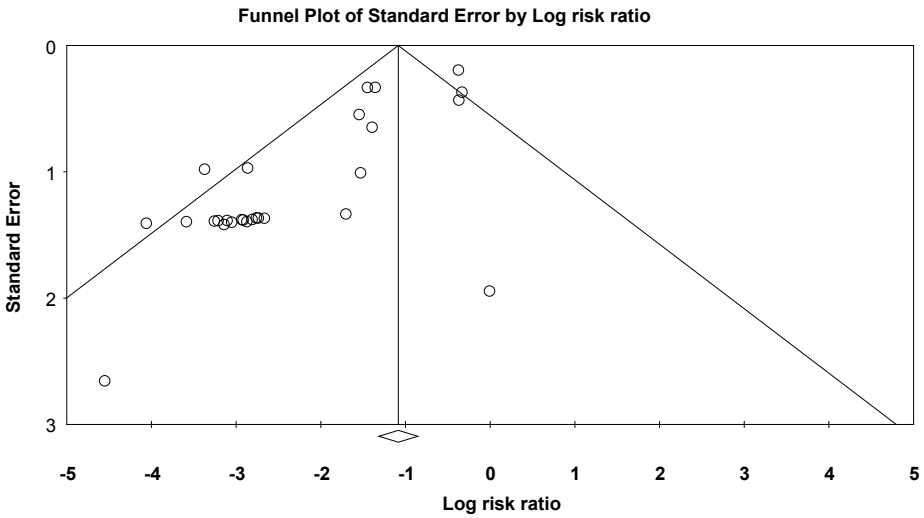


Figure 5 Funnel plot showing: risk ratios (RR) of persisting food allergy after OIT or SLIT

Sustained unresponsiveness post-discontinuation of AIT

There were seven OIT RCTs (24, 26, 30, 33, 42, 44, 45), and one OIT CCTs (52) that investigated the longer-term effects of AIT between two weeks and 36 months after discontinuation of AIT (Table 1 and Appendix 3.2, Table S1). Meta-analysis suggested, but did not confirm the benefits of OIT (RR=0.29, 95% CI 0.08, 1.13) (24, 26, 30, 33, 44, 48) (Figure 6).

The Funnel plot also revealed evidence of potential publication bias with fewer smaller, negative studies than expected (Figure 7).

Disease specific quality of life

Only one OIT RCT reported disease-specific QoL of patients and their families (23). This study used a validated questionnaire for parents, the Food Allergy Quality of Life Questionnaire Parent Form (FAQLQ-PF) however no comparative results between OIT and the control group were reported at the end of the first phase of the study. Results are reported for the end of the second phase of the study at which time the control group had also received OIT.

Secondary Outcomes

Safety

Systemic reactions

Data on the occurrence of systemic adverse reactions during AIT were available from 25 trials (23-27, 29-31, 33, 35, 36, 39, 40, 42-51) (Table 1). However, there were different formats of reporting systemic

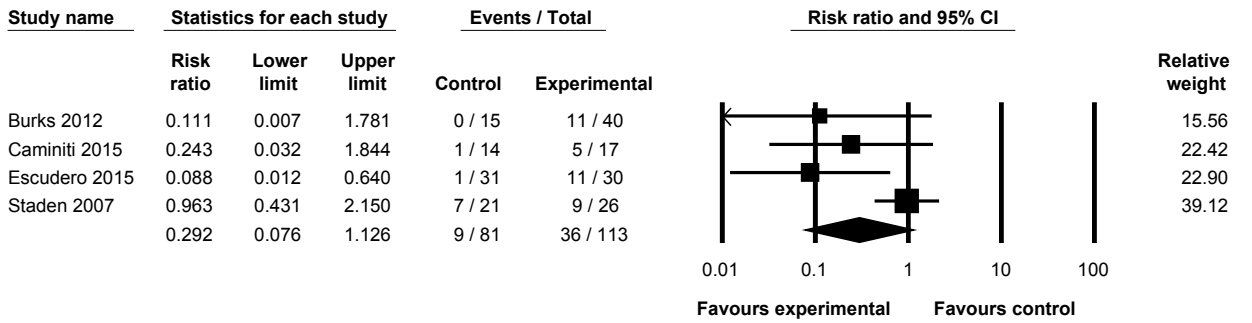


Figure 6 Risk ratios (RR) of sustained unresponsiveness as assessed by double-blind, placebo-controlled food challenge in OIT v. controls (random-effects model). Heterogeneity: $\tau^2 = 1.043$; $\chi^2 = 7.044$, df = 3 ($P < 0.071$); $I^2 = 57\%$; Test for overall effect: $Z = 1.788$ ($P < 0.074$)

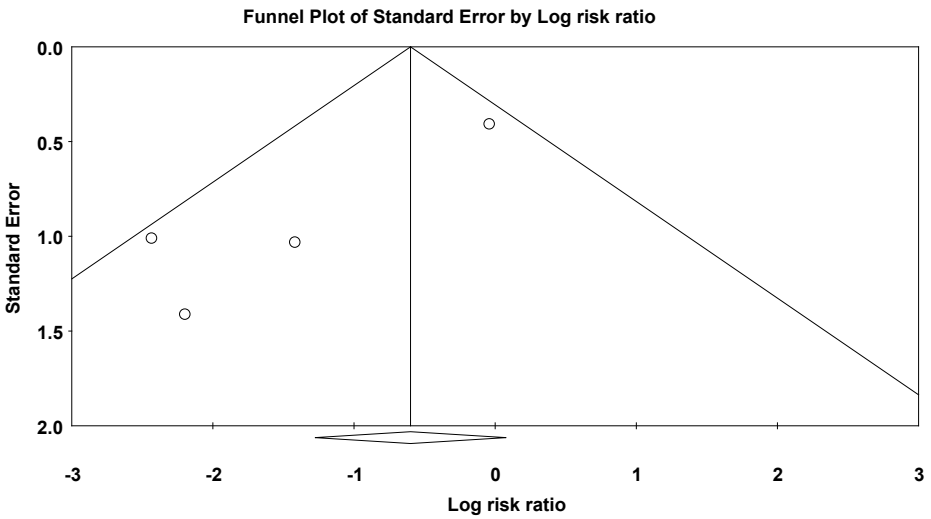


Figure 7 Funnel plot showing: risk ratios (RR) of persisting food allergy after OIT or SLIT (only RCTs)

reactions between trials, and we were therefore only able to pool data from seven studies (26, 29, 31, 35, 40, 46, 49). Meta-analyses of *not* experiencing a systemic reactions was higher in those receiving control: RR=1.09, 95% CI 1.00, 1.19) (Figure 8) (26, 29, 31, 35, 40, 46, 49).

Subgroup analysis demonstrated that the risk of experiencing a systemic reaction was higher in those receiving OIT (RR of *not* experiencing a reaction in controls=1.16, 95% CI 1.03, 1.30) (26, 35, 40, 46, 49). In contrast, data from two SLIT studies showed no difference between arms (RR of *not* experiencing a reaction in controls=0.98, 95% CI 0.85, 1.14) (29, 31) (Appendix 3.5, Figures S14 and S15).

Sensitivity analysis excluding all trials judged to be at high risk of bias after OIT or SLIT demonstrated either a borderline difference (RR of *not* experiencing a reaction in controls=1.10, 95% CI 0.99, 1.23) (26, 31, 40, 46, 49) or a significant difference in the rate of systemic reactions between the two arms after OIT (RR of *not* experiencing a reaction in controls=1.17, 95% CI 1.03, 1.33) (26, 40, 46, 49) (Appendix 3.5, Figures S16 and S17).

A subgroup analysis of CMA trials found that the risk of experiencing a systemic reaction was higher in the AIT arm (RR of *not* experiencing a reaction in controls=1.19, 95% CI 1.03, 1.37) (35, 40, 49) (Appendix 3.5, Figure S18). Subgroup analysis of

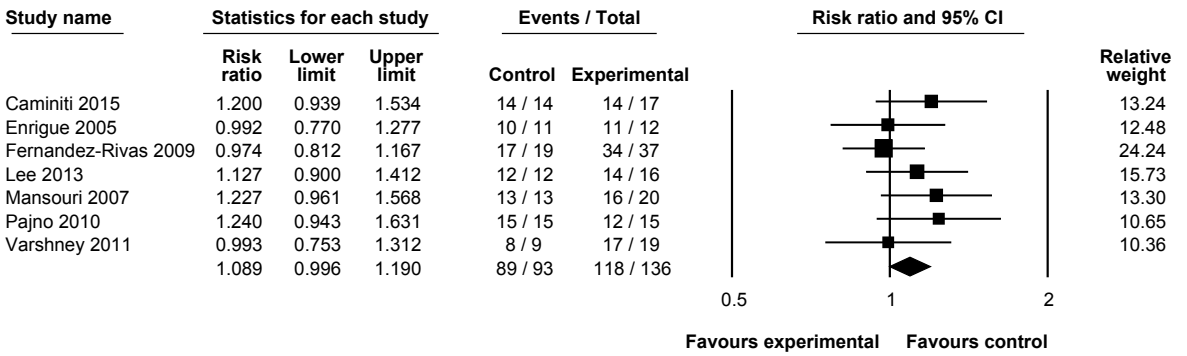


Figure 8 Safety data – absence of systemic reactions during OIT or SLIT for food allergy. RR, risk ratio (random-effects model). Heterogeneity: $\tau^2 = 0.0001$; $\chi^2 = 4.87$, df = 6 ($P < 0.56$); $I^2 = 0\%$; Test for overall effect: $Z = 1.86$ ($P < 0.06$)

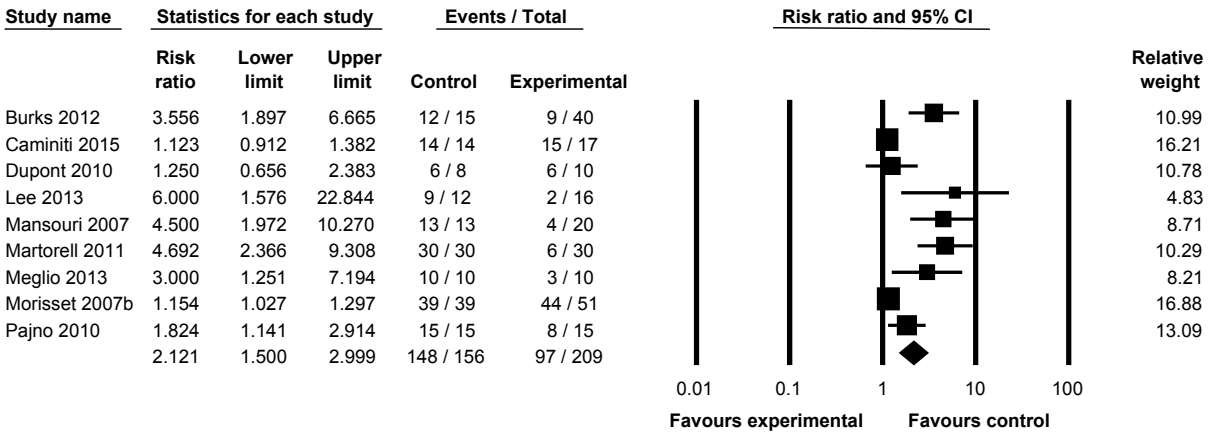


Figure 9 Safety data – absence of local reactions during OIT or EPIT for food allergy. RR, risk ratio (random-effects model). Heterogeneity: $\tau^2 = 0.182$; $\chi^2 = 48.412$, df = 8 ($P < 0.0001$); $I^2 = 83\%$; Test for overall effect: $Z = 4.253$ ($P < 0.0001$)

systemic reactions during OIT from five children's studies to cow's milk, egg or peanut showed a significant difference between the two arms, however the pooled data from the two studies with adult populations using SLIT for peach or hazelnut allergy found no clear evidence of a difference in systemic reactions between the treatment arms and the control arms (RR of not experiencing a reaction in controls, children=1.16, 95% CI 1.03, 1.30) (26, 35, 40, 46, 49); (RR of not experiencing a reaction in controls, adult=0.98, 95% CI 0.85, 1.14) (29, 31) The lack of a significant effect in adults may reflect a lack of precision (as the point estimate suggests benefit), which in turn is a function of the paucity of large trials in adult populations (Appendix 3.5, Figures S19 and S20).

Local reactions

Data on occurrence of local adverse reactions during AIT (minor oropharyngeal/gastrointestinal/ perioral rash) were available from 28 trials (23-31, 33, 35-51) (Table 1). However, there were different formats of reporting reactions between trials, and we were therefore only able to pool data from nine studies. Meta-analyses of local reactions obtained from these nine trials demonstrated that AIT was associated

with an increased risk of local reactions (RR of *not* experiencing a reaction in controls 2.12, 95% CI 1.50, 3.00) (24, 26, 28, 35, 37-40, 49) (Figure 9).

Subgroup analysis of local adverse events demonstrated higher risk of reactions in those receiving OIT (RR of *not* experiencing a reaction in controls=2.14, 95% CI 1.47, 3.12) (24, 26, 37-40, 49) (Appendix 3.5, Figure S21). A further sensitivity analysis excluding all trials judged to be at high risk of bias also showed an increased risk of local reactions in the treatment arms compared with the control arms (RR of *not* experiencing a reaction in controls=2.58, 95% CI 1.43, 3.02) (24, 26, 37, 40, 49) (Appendix 3.5, Figure S22). Local reactions during OIT from only RCTs subgroup analysis demonstrated higher risk of local reactions in the AIT group (RR of *not* experiencing a reaction in controls=2.08, 95% CI 1.43, 3.02) (24, 26, 35, 37-40) (Appendix 3.5, Figure S23). Another subgroup analysis of local reactions during OIT for CMA from either RCTs and CCTs or only RCTs also demonstrated increased risk of having local reactions in the AIT group (from RCTs and CCTs, RR of *not* experiencing a reaction in controls=3.49, 95% CI 1.89, 6.43) (35, 37, 39, 40, 49); (from RCTs, RR of *not* experiencing a reaction in controls=3.29, 95% CI 1.50, 7.23) (35, 37, 39, 40) (Appendix 3.5, Figures S24 and S25). Local reactions during OIT for HEA also found an increased risk of local reactions in the AIT arm (RR of *not* experiencing a reaction in controls= 1.55, 95% CI 1.09, 2.22) (24, 26, 38, 39) (Appendix 3.5, Figure S26).

The effect of the AIT protocol (conventional versus rush) on the occurrence of local reactions during the treatment was available only from OIT trials. Both, conventional and rush AIT protocols demonstrated an increased risk of local reactions in the treatment arm compared with the controls (RR of *not* experiencing a reaction in controls, conventional=2.58, 95% CI 1.46, 4.55) (24, 26, 35, 38, 40, 49) (RR of *not* experiencing a reaction in controls, rush=2.23, 95% CI 0.57, 8.80) (37, 39) (Appendix 3.5, Figures S27 and S28).

Health economic analysis

None of the studies reported data on cost-effectiveness.

DISCUSSION

Summary of main findings

This systematic review and meta-analysis has found evidence that AIT may be effective in raising the threshold of reactivity to a range of foods in patients with IgE-mediated food allergy whilst receiving (i.e. desensitization) and post-discontinuation of AIT. This evidence comes mainly from studies in children and it is therefore still unclear if AIT is effective for adults. Pooling of the safety data demonstrated an increased risk of local and systemic reactions with AIT. No fatalities were reported during AIT. Only one study assessed QoL (23), which reported no comparative results between OIT and the control group. We found no data investigating the cost-effectiveness of AIT in patients with food allergy.

Strengths and limitations of this work

We believe that this systematic review is the most robust investigation undertaken to date to support the use of AIT in children and adults with food allergy (53-60). A key strength of our systematic review was the comprehensiveness of the searches. We carefully identified and scrutinized the characteristics of all possible terms, including MeSH, EMTREE and free keywords for different types of food allergy and AIT. In addition, we encompassed all available bodies of evidence from all randomized and NRS, with a range of planned subgroup and sensitivity analyses.

The main limitations of this systematic review stem from the heterogeneity of included populations, interventions, outcomes, diversity of AIT protocols and treatment modalities, and definition of outcomes (e.g. adverse reactions). Due to the heterogeneity of studies, the meta-analyses need to be interpreted with caution. In an attempt to account for this heterogeneity, we undertook random-effects meta-analyses which produce more conservative assessments of benefits than would have been obtained using fixed-effects meta-analyses. That said, this is an area that will warrant further exploration of the possible sources of heterogeneity in follow-on work. We were also limited by the lack of data on long-term adverse outcomes (e.g. eosinophilic eesophagitis) and lack of data on cost-effectiveness. Studies which were published after our cut-off date 31st March 2016 are not included in this review which may have provided additional evidence to support the effectiveness and safety of OIT (61).

Conclusions

We found that AIT may be effective in raising the threshold of reactivity to a range of foods in patients with IgE-mediated food allergy whilst receiving (i.e. desensitization) and post-discontinuation of AIT, but was associated with an increased risk of local and systemic adverse events. Future trials need in particular to investigate the effectiveness of AIT in adults, long term effects,understand the impact of AIT on disease-specific QoL of patients and family members, and establish the cost-effectiveness of AIT for food allergy.

Conflicts of interest

U Nurmatov, no conflicts of interest; Sangeeta Dhami reports grants from EAACI to carry out the review; S Arasi reports other from Evidence-Based Health Care Ltd during the conduct of the study; G Pajno reports grants from Stallergenes during the conduct of the study; M Fernandez Rivas reports grants from European Union, grants from Instituto de Salud Carlos Ill, Ministerio de Ciencia, Espaha, grants from Ministerio de Economia, Espaha, personal fees from DBV, personal fees from Aimmune, Reacta Biotech, personal fees from ALK Abello, Merck, GSK, non-financial support from EAACI, personal fees and non-financial support from Fundaci6n SEAIC, other from Hospital Clinico San Carlos and Universidad Complutense de Madrid, outside the submitted work; In addition, Fernandez Rivas has a patent PT0042/2013 issued; A Muraro reports personal fees from Novartis, personal fees from Meda Mylan, outside the submitted work; G Roberts has a patent use of sublingual immunotherapy to prevent the development of allergy in at risk infants. issued and his University has received payments for activities he has 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; C Akdis reports grants from Actellion, personal fees from Aventis, personal fees from Stallergenes, grants and personal fees from Allergopharma, personal fees from Circassia, grants from Novartis, grants from Christine Kuhne Center for Allergy Research and Education, outside the submitted work; Alvaro has nothing to disclose; K Beyer reports grants from DBV, grants and personal fees from Aimmune, outside the submitted work; C Bindslev-Jensen reports grants from Anergis, grants from AImmune, grants from HAL Allergy, outside the submitted work; W Burks reports grants from Food Allergy & Anaphylaxis Network, grants from National Institutes of Health, grants from Wallace Research Foundation, during the conduct of the study; personal fees from FARE, personal fees from NIH AITC Review Panel, personal fees from NIH HAI Study Section, personal fees from World Allergy Organization, personal fees from Aimmune Therapeutics, Inc., personal fees from Epiva Biosciences, Inc., personal fees from Genentech, personal fees from Merck, non-financial support from Regeneron Pharmaceuticals, Inc., personal fees from Stallergenes, personal fees from Valeant Pharmaceuticals North America, LLC, personal fees from PPD Development, LP, personal fees from Allertein, personal fees from Sanofi US Services, outside the submitted work; G Du Toit reports income from grants from National Institute of Allergy and Infectious Diseases (NIAID, NIH), Food Allergy & Research Education (FARE), MRC & Asthma UK Centre, UK Dept of Health through NIHR, National Peanut Board (NPB), and grants from UK Food Standards Agency (FSA); these grants part funded salary over period of this submitted work; M Ebisawa has nothing to disclose; P Eigenmann reports personal fees from DBV technologies, personal fees from Mictotest DX, personal fees from Nestlé, from Gesellschaft zur Förderung der dermatologischen Forschung und Fortbildung e.V., personal fees from Danone, personal fees from Novartis, personal fees from EFSA, grants from Swiss National Science Foundation, grants from Ulrich Muller Gierock Foundation, grants from LETI, grants and personal fees from ThermoFischer, personal fees from Sodilac, personal fees from UpToDate, personal fees from Elsevier, outside the submitted work; E Knol has nothing to disclose; M Mäkelä has nothing to disclose; K C Nadeau has a patent pending; L O'Mahony reports personal fees from Alimentary Health, grants from GSK, outside the submitted work; N Papadopoulos reports personal fees from AbbvieĐ from Novartis, from GSK, from Novartis, from Faes Farma, from BIOMAY, from HAL, personal fees from MEDA, personal fees from Novartis, personal fees from Menarini, personal fees from ALK ABELLO, personal fees from Novartis, personal fees from CHIESI, personal fees from Faes Farma, personal fees from Uriach, personal fees from Novartis, personal fees from Stallergenes, personal fees from Abbvie, personal fees from MEDA,

personal fees from MSD, grants from NESTEC, grants from MERCK SHARP & DOHME, outside the submitted work; L Poulsen reports grants from EU Commission, during the conduct of the study; C Sackesen reports grants from MSD to support laboratory tests for the study 'Effects of the montelukast therapy on asthma and allergic inflammation in children with food allergy, outside the submitted work; H Sampson reports that he is employed 60% of time as Professor of Pediatrics at the Icahn School of Medicine at Mount Sinai and 40% of time as the Chief Scientific Officer at DBV Technologies, which is developing a patch for epicutaneous immunotherapy; A Santos has nothing to disclose; R van Ree reports personal fees from HAL Allergy BV, personal fees from Citeq BV, outside the submitted work; F Timmermans has nothing to disclose; A Sheikh reports grants from EAACI, during the conduct of the study.

Contributorship

AS conceived this review. This paper was drafted by UN, SD and SA. It was revised following critical review initially by AS and then by all the co-authors. This paper is part of the EAACI AIT guidelines project, chaired by Antonella Muraro and coordinated by Graham Roberts.

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Ethical approval

Not required.

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ALLERGEN IMMUNOTHERAPY FOR ALLERGIC ASTHMA

A SYSTEMATIC REVIEW AND META-ANALYSIS

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***Background**: To inform the development of the European Academy of Allergy and Clinical Immunonology's (EAACI) Guidelines on Allergen Immunotherapy (AIT) for allergic asthma, we assessed the evidence on the effectiveness, cost-effectiveness and safety of AIT.*

***Methods**: We performed a systematic review, which involved searching nine databases. Studies were screened against pre-defined eligibility criteria and critically appraised using established instruments. Data were synthesized using random-effects meta-analyses.*

***Results**: 98 studies satisfied the inclusion criteria. Short-term symptom scores were reduced with a standardized mean difference (SMD) of -1.11 (95% CI -1.66, -0.56). This was robust to a pre-specified sensitivity analyses, but there was evidence suggestive of publication bias. Short-term medication scores were reduced SMD -1.21 (95% CI -1.87, -0.54), again with evidence of potential publication bias. There was no reduction in short-term combined medication and symptom scores SMD 0.17 (95% CI -0.23, 0.58), but one study showed a beneficial long-term effect. For secondary outcomes subcutaneous immunotherapy (SCIT) improved quality of life and decreased allergen specific airways hyperreactivity (AHR) but this was not the case for sub-lingual immunotherapy (SLIT). There were no consistent effects on asthma control, exacerbations, lung function, and non-specific AHR. AIT resulted in a modest increased risk of adverse events (AEs). Although relatively uncommon, systemic AEs were more frequent with SCIT; however no fatalities were reported. The limited evidence on cost-effectiveness was mainly available for sublingual immunotherapy (SLIT) and this suggested that SLIT is likely to be cost-effective.*

***Conclusions**: AIT can achieve substantial reductions in short-term symptom and medication scores in allergic asthma. It was however associated with a modest increased risk of systemic and local AEs. More data are needed in relation to secondary outcomes, longer-term effectiveness and cost-effectiveness.*

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BACKGROUND

Asthma is a major public health problem affecting over 300 million people worldwide (1). Its prevalence and impact are particularly on the rise and it is estimated that by 2025 an additional 100 million people may develop asthma (2). Asthma is therefore set to become one of the world's most prevalent chronic diseases.

Based on the clinical history, examination and investigative procedures, different asthma phenotypes have been described (3). The pathogenesis of asthma is extremely complex and several disease endotypes have been suggested (3, 4). Allergic asthma is one of best described asthma phenotypes of primary studies. Allergic sensitization is a strong risk factor for asthma inception and severity in children and in adults (5).

Current asthma therapies can effectively control symptoms and the ongoing inflammatory process but do not affect the underlying, dysregulated immune response. Thus, they are very limited in controlling the progression of the disease. Allergen immunotherapy (AIT) is the only etiology-based treatment for allergic diseases capable of disease modification, as demonstrated by prevention of both the onset of new allergic sensitizations and disease progression.

The European Academy of Allergy and Clinical Immunology (EAACI) is in the process of developing *Guidelines on Allergen Immunotherapy (AIT) for Allergic Asthma*. We have already undertaken a systematic review of the previously systematic reviews focusing on allergic asthma (Appendix 4.1), these earlier studies are now relatively old and do not incorporate the recent large, high quality studies. A further systematic review of primary studies on the effectiveness, cost-effectiveness and safety of AIT for allergic asthma has been undertaken to inform the formulation of key clinical recommendations.

METHODS

A detailed outline of the methods have previously been published in the protocol of this review (6). We therefore confine ourseleves to a synopsis of the methods employed.

A highly sensitive search strategy was developed, and validated study design filters were applied to retrieve articles pertaining to the use of AIT for allergic asthma from electronic bibliographic databases. The search strategy was developed on OVID MEDLINE and then adapted for the other databases (Appendix 4.2). In all cases, the databases were searched from inception to October 31, 2015. Additional papers were located through searching the references cited by the identified studies, and unpublished work and research in progress was identified through discussion with experts in the field. There were no language restrictions employed.

Inclusion and exclusion criteria are detailed in Box 1.

Study selection

All references were uploaded into the systematic review software DistillerSR and underwent de-duplication. Studies were independently checked by two reviewers (SD, FA or AK) against the above inclusion criteria. Any discrepancies were resolved through discussion and, when necessary, a third reviewer was consulted (AS).

Quality assessment

Quality assessments were independently carried out on each study by two reviewers (FA, AK, DD, MA, SD or MK). We used the Cochrane Risk of Bias (ROB) tool to assess RCTs (9), the Critical Appraisal Skills Programme (CASP) Economic Evaluation Checklist for health economic studies (10), and the National Institute for Health and Clinical Excellence (NICE) quality assessment tool to critically appraise case series (11). Any discrepancies were resolved by discussion or arbitration by a third reviewer (AS).

Data extraction, analysis and synthesis

Data were independently extracted onto a customized data extraction sheet in DistillerSR by two reviewers (FA, AK, HZ, DD, MA or SD) and any discrepancies were resolved by discussion or arbitration by a third reviewer (AS). A descriptive report with summary data tables was produced to summarize the literature. Where clinically and statistically appropriate, meta-analyses were undertaken using random-effects modeling (12). Where standardized mean difference (SMD) has been used the scale used is 0.2 represents a small effect size, 0.5 a medium effect size and 0.8 a large effect size (105).

Box 1 Inclusion and exclusion criteria

Patient characteristics	Studies conducted on patients of any age with a physician confirmed diagnosis of asthma, plus evidence of clinically relevant allergic sensitization as assessed by an objective biomarker (e.g., skin prick test or specific-IgE), in combination with a history of asthma symptoms due to allergen exposure.
Interventions of interest	AIT for different allergens (e.g. pollens, house dust mites (HDM), animal dander, cockroach and molds), administered through either subcutaneous (SCIT) or sublingual (SLIT) routes.
Comparator	Placebo or any active comparator.
Study designs	*Effectiveness*: Double-blind randomized controlled trials (RCTs). Originally, we planned to include data from any RCT, irrespective of whether there was blinding. This was changed due to the large volume of RCT studies. This decision was made prior to any analyses being undertaken. *Cost-effectiveness*: Health economic analysis. *Safety*: Double-blind RCTs and large case series (≥300 patients).
Outcomes	*Primary outcomes*: 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. *Secondary outcomes*: Asthma control; asthma specific quality of life (QoL); exacerbations; lung function; response to environmental exposure chamber or bronchial allergen challenge; health economic analysis from the perspective of the health system/payer; and safety as assessed by local and systemic reactions (7,8).
Exclusion criteria	Reviews, discussion papers, non-research letters and editorials, animal studies and studies not employing double-blind RCT designs.

Sensitivity and assessment for publication bias

Sensitivity analyses were, where possible, undertaken by comparing the summary estimates obtained by excluding studies judged to be at high ROB with those judged to be at low or moderate ROB.

Where possible, publication bias was assessed through the creation of funnel plots, and tested by Begg's rank correlation test and Egger's regression test (13, 14).

Subgroup analyses

A number of sub-group analyses were undertaken, details of which are in the protocol.

Registration and reporting

This review has been registered with the International Prospective Register of Systematic Reviews (PROSPERO): CRD42016035372. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was used to guide the reporting of the systematic review (Appendix 4.3).

RESULTS

Our search strategy yielded 7,490 papers of which 98 studies were eligible; these comprised of 89 double-blind RCTs (reported in 94 papers), three cost-effectiveness studies and six case series (Figure 1).

Effectiveness

Description of studies

The RCTs enrolled a total of 7,413 patients. The route of administration of AIT was SCIT (n=54), SLIT (n=34), and SCIT versus SLIT (n=1). The majority of trials reported on the short-term effectiveness of AIT with only one SLIT trial reporting on long-term effectiveness. The 54 SCIT trials (reported in 57 papers) included 2,305 patients (15-70). and the 34 SLIT trials (71-104) (reported in 36 papers) included

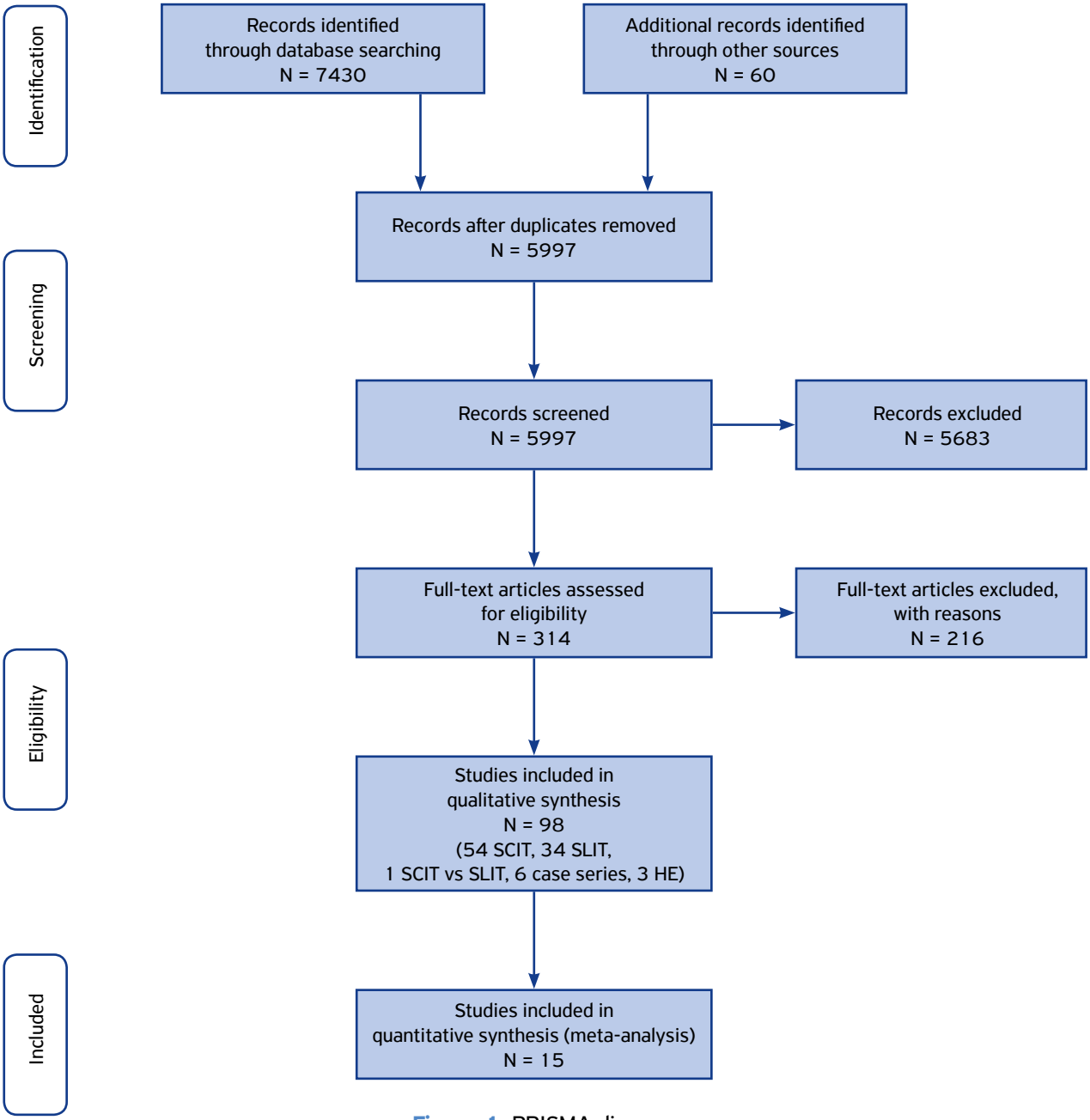


Figure 1 PRISMA diagram

5,108 patients. SCIT studies included adults (n=24), both children and adults (n=17), and children (n=13). SLIT studies included children (n=20), both children and adults (n=10), and adults (n=4). Allergen extracts administered included HDM, grass, cat, dog, trees, molds, latex and weeds. Various AIT protocols were utilized. The severity of asthma tended to be mild-to-moderate. Further details are included in Tables 1a-c and S1a-c (Appendix 4.4).

Quality assessment

The majority of SCIT trials (n=32) were judged as unclear ROB, seven low ROB and 15 studies as at high ROB (Appendix 4.4, Table S1d). Twenty SLIT studies were assessed to be at high ROB; 13 studies were at unclear ROB; and one study at low ROB (Appendix 4.4, Table S1e). The one SCIT vs SLIT study was judged to be at a low ROB (Appendix 4.4, Table S1f).

Table 1a Overview of SCIT trials (n=54 studies in 57 papers)

Study Author, year, country	Allergen(s) type							Aller-gen no.		Compar-ator			AIT Protocol											Short-term effective-ness			Long-term effective-ness						
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mould(s)	HDM	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 (manufacture)	Symptom score	Medication score	Combined score	Symptom score	Medication score	Combined score	Safety	Quality of life	Lung function	Corticosteroid use	Asthma exacerbations EX	Bronchial tests
Aas, 1971, Norway					X				X		X						X					3 y	Two house dust extracts from Nyegaard et Co., Oslo (house dust group A), and from Allergologisk Laboratorium, Copenhagen (House dust B), respectively.										X	X
Adkinson, 1997, US	X	X		X	X			X		X	X						X					2 y	SCIT mixture of seven aeroallergens (HDM ragweed, grass mix, Bermuda grass, white oak, *Alternaria, cladosporium, aspergillus*) prepared by ALK Laboratories, Copenhagen, Denmark, vs placebo	X	X					X		X	X		X
Alvarez-Cuesta, 1994, Spain						X			X		X						X					1 y	The allergen extract was obtained from Alergia e Inmunologia (Abell6, S.A., Madrid, Spain) and prepared by extracting the raw material (cat dander supplied by Allergon AB Engelholm, Valinge, Sweden)	X	X					X			X	X
Alvarez, 2002, Spain					X				X		X											1y	*D. pteronyssinus D. pteronyssinus* extract at 10 biological units /mL contained 4µg/mL of Der p1 and 2 µg/mL of Der p2, entrapped in liposomes vs placebo								X			X
Ameal, 2005, Spain					X				X		X						X					1 y	The active group received a modified allergen extract of *D. pteronyssinus*. The modified extract was adsorbed onto aluminium hydroxide.	X	X					X	X		X	X
Armentia-Medina, 1995, Spain								X	X		X						X					1 y	Standardised extract of storage mite *Lepidoglyphus* destructor with an activity of 100BU/ml. Concentration 18%	X									X	X

Table 1a Continued

Study Author, year, country	Allergen(s) type								Allergen no.		Comparator			AIT Protocol												Short-term effectiveness			Long-term effectiveness						
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mould(s)	HDM	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 (manufacture)	Symptom score	Medication score	Combined score	Symptom score	Medication score	Combined score	Safety	Quality of life	Lung function	Corticosteroid use	Asthma exacerbations EX	Bronchial tests
Arvidsson, 2004, Sweden		X							X		X											1 y	Standardized birch pollen extract (Alutard SQ *Betula verrucosa*; ALK-Abello) vs dilute histamine dihydrochloride.								X			X	X
Basomba, 2002, Spain					X				X		X						X					1 y	*D pteronyssinus* encapsulated in liposomes containing 0.025, 0.05, 0.1, 0.2, 0.4, 0.8, 1.6, and 3.2 μg of *Der p 1*.	X	X					X				X	X
Blumberga, 2006, Denmark					X				X		X						X					3 y	Subcutaneous SIT with Alutard SQ D.							X		X		
Bødtger, 2002, Denmark		X							X		X							X				1 y	High dose birch pollen extract, commercially available and produced by ALK-Abello, Hørsholm, Denmark. The content of the major birch pollen allergen *Bet v 1* was 12 mg/100 000 SQ-U.	x	x					x					
Bousquet, 1985, France					X				X		X									X		7 w	Standardized *Dermatophagoides pteronyssinus* extract							x		X		X	X
Bousquet, 1990, France	X								X		X		X							X		1 y	High and low dose grass extract.	X						X					
Cantani, 1996 Italy	X			X	X	X	X			X	X											3m	Mixture of grass, other pollen, mould, house dust mite and cat and dog dander	X	X										X
Chakraborty, 2006, India		X							X		X						X					2 y	*P sylvestris* pollen extract standardized with one of its principal allergenic fraction	X	X					X		X			
Creticos, 1996, US			X						X		X						X					2 y	Lyophilized extract of short ragweed pollen (Greer Laboratories, Lenoir, N.C.)	X	X					X					

Table 1a Continued

Study Author, year, country	Allergen(s) type								Allergen no.		Comparator			AIT Protocol													Short-term effectiveness			Long-term effectiveness						
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mould(s)	HDM	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 (manufacture)	Symptom score	Medication score	Combined score	Symptom score	Medication score	Combined score	Safety	Quality of life	Lung function	Corticosteroid use	Asthma exacerbations EX	Bronchial tests
Dolz, 1996, Spain	X								X		X								X			3 y	The grass-pollen allergen extract Alutard SQ. aluminium hydroxide-adsorbed allergens PDL (*Phleum, Dactylis, Lolium*), was used.												X
Dreborg, 1986, Sweden & Finland				X					X		X							X				10 m	Purified and standardised *Cladosporium herbarum* allergen preparation.	X	X					X					X
D'Souza, 1973, UK					X				X		X						X					3 m	The *D. pteronyssinus* extract was prepared by Beecham Research Laboratories.	X	X					X					
Franco, 1995, Italy					X				X		X						X					15 m	Alum absorbed Alpare *D pteronyssinus* extract	X	X					X				X	X
Gaddie, 1976, UK					X				X		X						X					1 y	Tyrosine-adsorbed depot form of *D pteroniyssinus* vaccine (Migen, Bencard)	X	X					X	X				
Garcia-Robaina, 2006, Spain					X				X		X						X					54 w	The active group received a mixture of modified allergen extracts containing 50% *D pteronyssinus* and 50% *D farinae*	X	X					X	X			X	X
Haugaard, 1992, Denmark						X	X			X	X						X					5 m	Extracts used for diagnosis and treatment were Pharmalgen® cat epithelium extract and dog dander extract (Pharmacia AB, Uppsala, Sweden. AEK, Hersholm, Denmark).							X	X			X	X
Hedlin, 1999, Denmark	X	X			X	X				X	X		X				X					3 y	Partly purified and standardized extracts of cat dander, *Dermatophagoides pteronyssinus*, timothy pollen, and birch pollen were provided by ALK (Hørsholm, Denmark).							X	X				X

Table 1a Continued

Study Author, year, country	Allergen(s) type								Allergen no.		Comparator			AIT Protocol													Short-term effectiveness			Long-term effectiveness						
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mould(s)	HDM	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 (manufacture)	Symptom score	Medication score	Combined score	Symptom score	Medication score	Combined score	Safety	Quality of life	Lung function	Corticosteroid use	Asthma exacerbations EX	Bronchial tests
Hui, 2014, China					X						X	X					X					3 y	The SCIT treatment was initiated at a dosage of 20 U/ml, and was continued weekly with an increase in the dosage each week	X						X		X	X		
Kuna, 1989, Poland	X								X		X						X					1 y	Glutaraldehyde-modified, tyrosine-adsorbed grass pollen (Pollinex, Bencard Allergy Service, Brentford, Middlesex, England).	X						X					
Kuna, 2011, Poland				X					X		X											3 y	Standardized A alternata extract (Novo-Helisen Depot, *A alternata* 100%; Allergopharma Joachim Ganzer KG, Reinbek, Germany) in a depot formulation with aluminium hydroxide	X	X					X	X				
Lewis, 1971 UK					X				X				X	X								6- 9 m	HDM D. farinae 0.002% to 0-1% w/v	X									X		
Leynadier, 2000, Germany								X	X		X									X		1 y	Standardized latex extract (Stallergènes)	X											
Maestrelli, 2004, Italy					X				X		X						X					4 y	A 1:1 mixture of *D pteronyssinus* and *D farina* extracts adsorbed to aluminium hydroxide in normal saline solution (ALKAbello, Madrid, Spain)	X	X						X				
Malling, 1986, Sweden				X					X		X							X				1 y	Lyophilized, partially purified and biologically standardized preparation of *Cladosporium herbarum* (Pharmalgen®, Pharmacia, Uppsala, Sweden)												X
Malling, 1987, Sweden 2nd paper original study 1986				X					X		X							X				1 y	Lyophilised, partially purified and biologically standardised preparation of *Cladosporium herbarum* (Pharmalgen, Pharmacia, Uppsala, Sweden) was used.												

Table 1a Continued

Study Author, year, country	Allergen(s) type							Aller-gen no.		Compar-ator			AIT Protocol													Short-term effective-ness			Long-term effective-ness						
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mould(s)	HDM	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 (manufacture)	Symptom score	Medication score	Combined score	Symptom score	Medication score	Combined score	Safety	Quality of life	Lung function	Corticosteroid use	Asthma exacerbations EX	Bronchial tests
Marques, 1978, Italy					X				X		X						X					14 m	Six syringes numbered in order of dose, each containing 0.5 ml of *D pteronyssinus* extract absorbed into tyrosine	X						X						
Mosbech, 1989, Denmark					X				X				X				X					2 y	Biologically standardized and purified unmodified Dp extract (Pharmalgen). The mPEG-modified Dp extract was produced by coupling activated mPEG-succinate to the un- modified Dp extract. A buffered solution of isotonic saline containing 0.3 mg/ml albumin, 0.4% phenol, and phosphate 0.95 mg/ml was used for mPEG-modified extract.	X	X											
Mosbech, 1990, Denmark					X				X				X									2 y	Single batch of unmodified, purified Dp-extract (Pharmalgen) biologically standardized was used. By RAST-inhibition, 10-11,000 BU of this extract equated 100,000 SQ-U of a similar mite allergen extract (Aquagen, ALK, Horsholm, Denmark). Part of this batch was modified with mPEG (3,000 Daltons). The unmodified extract was reconstituted in a diluent containing aluminiumhydroxide, whereas no such additive was present in the buffered saline used for the mPEG-modified extract.							X						
Newton, 1979, UK					X				X		X											15 m	Alum-precipitated D. farinae								X				

Table 1a Continued

Study Author, year, country	Allergen(s) type							Allergen no.		Comparator			AIT Protocol											Short-term effectiveness			Long-term effectiveness						
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mould(s)	HDM	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 (manufacture)	Symptom score	Medication score	Combined score	Symptom score	Medication score	Combined score	Safety	Quality of life	Lung function	Corticosteroid use	Asthma exacerbations EX	Bronchial tests
Ohman, 1984, US					X				X		X						X					3 m	Active-treatment vials reconstituted in 50% glycerine to a concentration of 13 units of cat allergen 1 per millilitre							X	X		X	X
Olsen,1997, Denmark				X					X		X						X					1 y	Active treatment with extracts of either *Dermatophagoides pteronyssinus* (Dpt) or *D. farinae* (Dfa) (Alutard® SQ, ALK, Denmark).	X	X					X	X			X
Ortolani, 1984, Italy	X								X		X						X					6 m	Aqueous lyophilized extract (Hollister-Stier, Spokane, Washington) of 89 velvet, 1/3 sweet vernal, and 89 timothy grass pollen	X										
Pauli, 1984, (not stated. Authors from France & UK)				X					X		X						X					1 y	Dpt tyrosine- adsorbed extract	X	X									
Pene, 1998 France					X				X		X											6 w	Fel d 1 peptides											X
Price, 1984, UK				X					X		X						X					2 y	Tyrosine glutaraldehyde modified *D. pteronyssinus* antigen, "Migen', Bencard.		X									
Rak, 2001, Sweden		X							X		X	X					X						Standardized depot preparations of birch pollen allergen extract (Alutard SQ, ALKAbelló) containing water-soluble allergen extract and aluminium hydroxide	X	X								X	X
Reid, 1986, US	X								X			X					X					8 m	Seven grass mix in serum, plus other allergens specific to individuals	X	X					X				

Table 1a Continued

Study Author, year, country	Allergen(s) type							Allergen no.		Comparator			AIT Protocol											Short-term effectiveness			Long-term effectiveness						
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mould(s)	HDM	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 (manufacture)	Symptom score	Medication score	Combined score	Symptom score	Medication score	Combined score	Safety	Quality of life	Lung function	Corticosteroid use	Asthma exacerbations EX	Bronchial tests
Roberts, 2006, UK	X								X		X							X				2 y	Alutard SQ P pratense (ALK-Abello) was used. This is an alum-adsorbed preparation of pollen from P pratense with a recommended dose of 100,000 SQ-U.	X	X					X		X	X	X		
Sabbah, 1991, France					X				X		X						X					180 d	Alpha-Fraction-Retard-D. pteronyssinus	X	X					X						
Smith, 1971, UK					X				X				X				X						HDM extract	X	X					X						
Sundlin, 1986, Sweden						X	X			X	X						X					18 m	Partially purified, standardized allergenic extracts of cat or dog dander							X					X	X
Tabar, 2008, Spain			X						X		X						X					1 y	Metabolic extract of *A. alternata* that had been biologically standardised	X	X					X		X				
Taylor, 1978, US						X			X		X						X					4 m	1.6 mg/ml cat allergen							X		X				
Taylor, 1978, UK					X				X		X						X					10 w	HDM fortified house dust vaccine							X		X				
Valovirta, 1984, Finland							X		X		X						X					1 y	Commercial standardised aluminium hydroxide bound dog dander extract (Alutard SQ)												X	X
Valovirta, 1986, Finland 2nd paper original study 1984							X		X		X						X					1 y	Commercial standardised aluminium hydroxide bound dog dander extract (Alutard SQ)	X						X						

Table 1a Continued

Study Author, year, country	Allergen(s) type								Allergen no.		Comparator			AIT Protocol													Short-term effectiveness			Long-term effectiveness						
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mould(s)	HDM	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 (manufacture)	Symptom score	Medication score	Combined score	Symptom score	Medication score	Combined score	Safety	Quality of life	Lung function	Corticosteroid use	Asthma exacerbations EX	Bronchial tests
Van Bever, 1992, Belgium					X				X		X								X			1 y	Aqueous extract of *Dermatophagoides pteronyssinus* (10 BU·ml 1)	X							X				X
Van Metre, 1988, US						X			X		X						X					2 y	Cat allergenic extract ALK 1209/229452 was supplied by Allergologisk Laboratories, Copenhagen, Denmark							X	X		X	X	X
Vidal, 2011, Spain					X				X		X											4 m	*D. pteronyssinus* extract with the major allergens Der p 1 and 2		X					X		X		
Wang 2006 China					X				X		X											52 w	*Dermatophagoides pteronyssinus* extract	X	X					X	X	X		X
Warner, 1978 UK					X				X		X											1 y	*D. pteronyssinus* absorbed into tyrosine ('Migen', Bencard).	X	X					X		X		X

AIT, allergen specific immunotherapy; d, day; HDM, house dust mite; m, month; NR, not reported; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; w, week; y, year

Table 1b Overview of SLIT trials (n=34 studies in 36 papers)

Study Author, year, country	Allergen(s) type							Allergen no		Compar-ator			AIT Protocol										Short-term effective-ness			Long-term effective-ness		
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mould(s)	HDM	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 (manufacture)	Symptom score	Medication score	Combined score	Symptom score	Medication score	Combined score
Alvarez-Cuesta, 2007, Spain					X				X		X						X					1 y	Aqueous solution of standardized semi-purified cat dander extract	X	X	X			
Bachelier, 2001, Turkey					X				X		X						X					26 w	*Dermatophagoide* (*D.pteronyssinus*)+*Dermatophagoides farinea* (*D. farinea*) 50/50 extract	X	X				
Bousquet, 1999, France					X				X		X						X					108 w	HDM SLIT	X	X	X			
Caffarelli, 2000, Italy	X								X		X						X					13 w and 9 week follow up post treatment	Grass pollen tablet (33% *Holcus lanatus*, 33% *Phleum pratense* and 33% *Poa pratensis*)	X	X	X			
Cao, 2007, China					X				X		X						X					3 m	*Dermatophagoides Farinae* Drops		X				
Dahl, 2006, Denmark & Sweden	X								X		X			X	X		X					19.5 w	Timothy grass (*Phleumpratense*) GRAZAX tablet 75,000 SQ-T once daily	X	X				
de Blay, 2014, Denmark, Germany, Italy, Spain, UK, Sweden, France & Poland					X				X		X		X				X					1 y	Oral lyophilisates containing standardized extracts of *D pteronyssinus* and *D farinae* in a 1:1 ratio. One development unit corresponds to 1 SQ-HDM			X			
Devillier, 2015, China					X				X		X						X					"52 w (+ 12 week baseline period before randomisation)"	HDM SLIT (*D. pteronyssinus* and *D. farinae*), approximately 28 mcg Der P 1 and 50mcg Der f 1 daily (300 IR)						
Drachenberg, 2001, Germany	X								X		X						X					6 m	Standardized allergen extract (ORALVAC birch n = 21 resp. grass/rye = 28)			X			

Table 1b Continued

Study Author, year, country	Allergen(s) type						Allergen no		Comparator			AIT Protocol								Short-term effectiveness			Long-term effectiveness		
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mould(s)	HDM	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 (manufacture)	Symptom score	Medication score	Combined score	Symptom score	Medication score	Combined score
Durham, 2012	X								X		X			X	X		X					5y (3 Rx, 2 followup)	Timothy grass (*Phleumpratense*) GRAZAX tablet 75,000 SQ-T once daily						x
Gomez Vera et al, 2005, Mexico				X					X		X						X					6 m	*Dermatophagoides pteronyssinus* 1 standardized allergens (IPI-ASAC, Mexico) at a total dose of 10,469 UBE		X				
Ippoliti, 2003, Italy					X				X		X						X					26 w (with 3-month run-in)	HDM SLIT (*D. pteronyssinus*), maintenance dose 5 drops of 10 BU/mL 3 times a week	X					
Leng, 1990, unclear country			X					X	X		X						x					7.14 w (13 w post-treatment follow-up)	Artemisia pollen SLIT daily up-dosing to a maximum of 16416 PNU. Cumulative dose 396,652.06 PNU						
Lewith, 2002, UK				X					X		X										X	16 w.	Homeopathic HDM SLIT administered on 3 occasions over 24 hours. Dose 30 dilutions of 1:100						
Lue, 2006, Taiwan				X					X		X						X					24 w (2 eeks post-treatment follow-up)	HDM SLIT daily with 3 week initiation phase. Maximum 20 drop dose of 300 IR/mL. Cumulative dose of 41,824 IR	X	X				
Ma, 2010, China				X					X			X	X				X					1 y	SLIT immunotherapy with Der F drops	X					
Ma, 2014, China				X					X		X						X					1 y	SLIT immunotherapy with Der F drops		X				
Moreno-Ancillo, 2007, Spain	X						X			X	X						X					248 d	biologically standardized by major allergens and quantified in micrograms, without up-dosing	X	X	X			
Mosbech, 2014, Denmark, Germany, Italy, Spain, UK, Sweden, France & Poland				X					X		X		X				X					52 w (1 y treatment duration)	Orallyophilisates containing standardized extracts of Dpteronyssinus and D farinae in a 1:1 ratio. Three active strengths were investigated: 1, 3, and 6 SQ-HDM. The units were designated in development units. One development unit corresponds to 1 SQ-HDM.	X					

Table 1b Continued

Study Author, year, country	Allergen(s) type							Allergen no		Comparator			AIT Protocol									Product type/ Name (manufacture)	Short-term effectiveness			Long-term effectiveness		
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mould(s)	HDM	Cat	Dog	Other(s)	Single	Multiple	Placebo	Routine care	Active	Pre-seasonal	Co-seasonal	Continuous	Conventional	Cluster	Semi-rush	Rush	Ultra-rush	Rx duration		Symptom score	Medication score	Combined score	Symptom score	Medication score	Combined score
Mosges et al, 2010, Germany	X								X		X										X	9 m	Standardized birch pollen (*Betula alba*) allergen extract. Ultra-rush high-dose SLIT titration regimen reaching the maintenance dose of 300 IR within 90 min (30–90–150–300 IR)						
Niu, 2006, Taiwan					X				X		X		X									24 w (+2 week off-treatment follow up)	HDM SLIT (*D. Pteronyssinus* and *D. farinae*), incremental dosing up to maintenance dose (cumulative dose ~ 41824 IR, which was equivalent to 1.7 mg D.p. and 3.0 mg D.f.)	X	X				
Pajno, 2000, Italy					X				X		X		X									104 w	HDM SLIT (*D. pteronyssinus*), incremental dosing schedule followed by maintenance 2.4 mg Der P 1 and 1.2 mg Der P 2 per week (in 3 doses/wk)		X	X			
Pajno, 2002, Italy									X		X		X									56 w (with 52 week off-treatment follow-up)	Parietaria pollen SLIT (*Parietaria judaica*), incremental dosing schedule followed by maintenance twice/wk (cumulative Par j ~ 20.3 mcg)	X	X				
Pajno, 2004, Italy		X					X		X		X						X					56 w (with 52 week off-treatment follow-up)	Parietaria pollen SLIT (*Parietaria judaica*), incremental dosing schedule followed by maintenance twice/wk (cumulative Par j ~ 20.3 mcg)						
Pham-Thi, 2007, France					X				X		X						X					78 w.	HDM SLIT (*D. Pteronyssinus* and *D.farinae*), up-dosing for 2 w up to 300 IR concentration once daily (average cumulative dose was 155,000 IR, corresponding to 6.9 mg Der P 1 and 14.7 mg Der f 1)	X	X				
Reilly, 1994, UK			X	X			X		X		X						X					4 w (with 4 w 'optional' post-treatment follow-up)	Homeopathic SLIT (allergen varied, decided on case-by-case basis; HDM (84.6% of participants); feathers (7.7%); mixed moulds (7.7%)). 3 doses in 24 hours then optionally repeated at 4 w (according to patient choice)			X			

Table 1b Continued

Study Author, year, country	Allergen(s) type							Allergen no		Comparator			AIT Protocol									Short-term effectiveness			Long-term effectiveness		
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mould(s)	HDM	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 (manufacture)	Symptom score	Medication score	Combined score	Symptom score	Medication score	Combined score
Reinert, 1983, Germany	X								X		X						X					2 y	Troponholistersteir			X			
Stelmach, 2009, Poland	X								X		X										X	104 w.	Grass pollen SLIT (*Dactylisglomerata, Anthoxanthumodoratum, Loliumperenne, Poapratensis, Phleum pretense*). Ultra-rush period (total of 24 0IR). At the beginning of the next day, every morning before breakfast, received 4 puffs (120 IR) for 6 m. Cumulative dose 43,800 IR	X	X				
Tian, 2014, China					X				X		X						X					48 w.	HDM SLIT (*D. farinae*), titrated up over the first 4 w to 333 mcg/mL once daily	X					
Virchow, 2016, Germany					X				X		X											20 m (11 August 2011 to 24 April 2013)	HDM SLIT tablet contains extract from 2 species of cultivated HDM (*D pteronyssinus* and *D farinae*), produced in a standardized process with a 1:1:1:1 ratio of the major allergens (Group 1 allergens of *D farinae* and *D pteronyssinus* and Group2 allergens of *D farinae* and *D pteronyssinus*), and formulated as rapidly dissolving oral lyophilisate for sublingual administration (ALK).	X					
Vourdas, 1998, Greece	X								X		X											104 w (2 y)	Olive pollen SLIT, daily up-dosing then each morning pre- and co-seasonally from January to July for 2 y up to a maximum of 20 drops of 300 IR (total 30,000 IR/y)	X	X				
Wang, 2014, China	X								X		X											52 w (+12 w baseline period before randomisation)	HDM SLIT (*D. pteronyssinus* and *D. farinae*), approximately 28 mcg Der P 1 and 50 mcg Der f 1 daily (300 IR)	X	X				

Table 1b Continued

Study Author, year, country	Allergen(s) type									Allergen no		Comparator			AIT Protocol										Short-term effectiveness			Long-term effectiveness		
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mould(s)	HDM	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 (manufacture)	Symptom score	Medication score	Combined score	Symptom score	Medication score	Combined score
Wood, 201, US & UK							X			X		X			X	X							13 w.	Greer German cockroach extract						
Zhang, 2013, China					X					X			X										36 m	Standard *dermatophagoides farinae* drops (1~4) usage:1~3 were for increasing period of treatment for 3 w, 1 times a day.						
Zhang, 2015, China					X					X			X										36 m	*Dermatophagoides farina* drop (1drop/time and 1 time/day)						
Zheng et al, 2012, China					X					X			X										36 months	Standard *dermatophagoides farinae* drops						

AIT, allergen specific immunotherapy; d, day; HDM, house dust mite; m, month; NR, not reported; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; w, week; y, year

Table 1c Overview of SCIT vs SLIT trials (n= 1)

Study Author, year, country	Allergen(s) type								Allergen no.		Comparator			AIT Protocol										Short-term effectiveness			Long-term effectiveness					
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mould(s)	HDM	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 (manufacture)	Symptom score	Medication score	Combined score	Symptom score	Medication score	Combined score	Safety	Quality of life	Lung function	Corticosteroid use	Asthma exacerbations EX	Bronchial tests
Yuksel-en,2012, Turkey					X				X		X		X			X							HDM (*D. pteronyssinus* and *D. farinae*) (50/50) for sublingual and subcutaneous administration.	X	X					X	X				

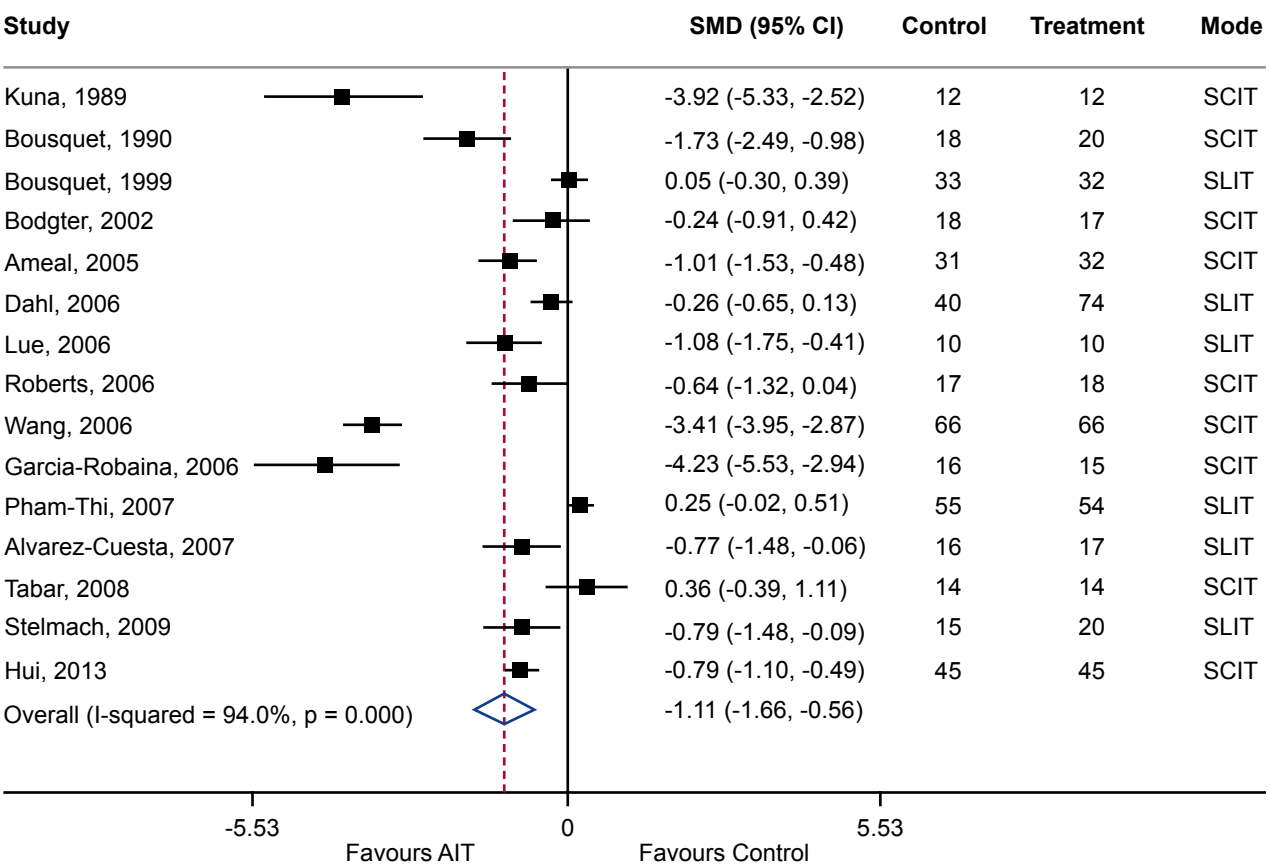


Figure 2 Meta-analysis of double-blind RCTs for symptom scores comparing AIT (SLIT and SCIT) and placebo groups (random effects model). Test of ES=0: z=3.96 p = 0.000; Heterogeneity χ^2 = 234.28 (d.f. = 14) p = 0.000; I^2 (variation in ES attributable to heterogeneity) = 94.0%; Estimate of between-study variance τ^2 = 1.0488

Primary outcomes

Symptom scores

Short-term

Fifty-eight (36 SCIT and 22 SLIT) trials reported on the effect of symptoms at the end of the AIT treatment period. We were able to pool data from 15 SCIT and SLIT trials with placebo as comparator. The meta-analysis showed that AIT improved symptom scores with a standardized mean difference (SMD) of -1.11 (95% CI -1.66, -0.56) (Figure 2), these suggesting a large effect of AIT (105).

Sensitivity analysis

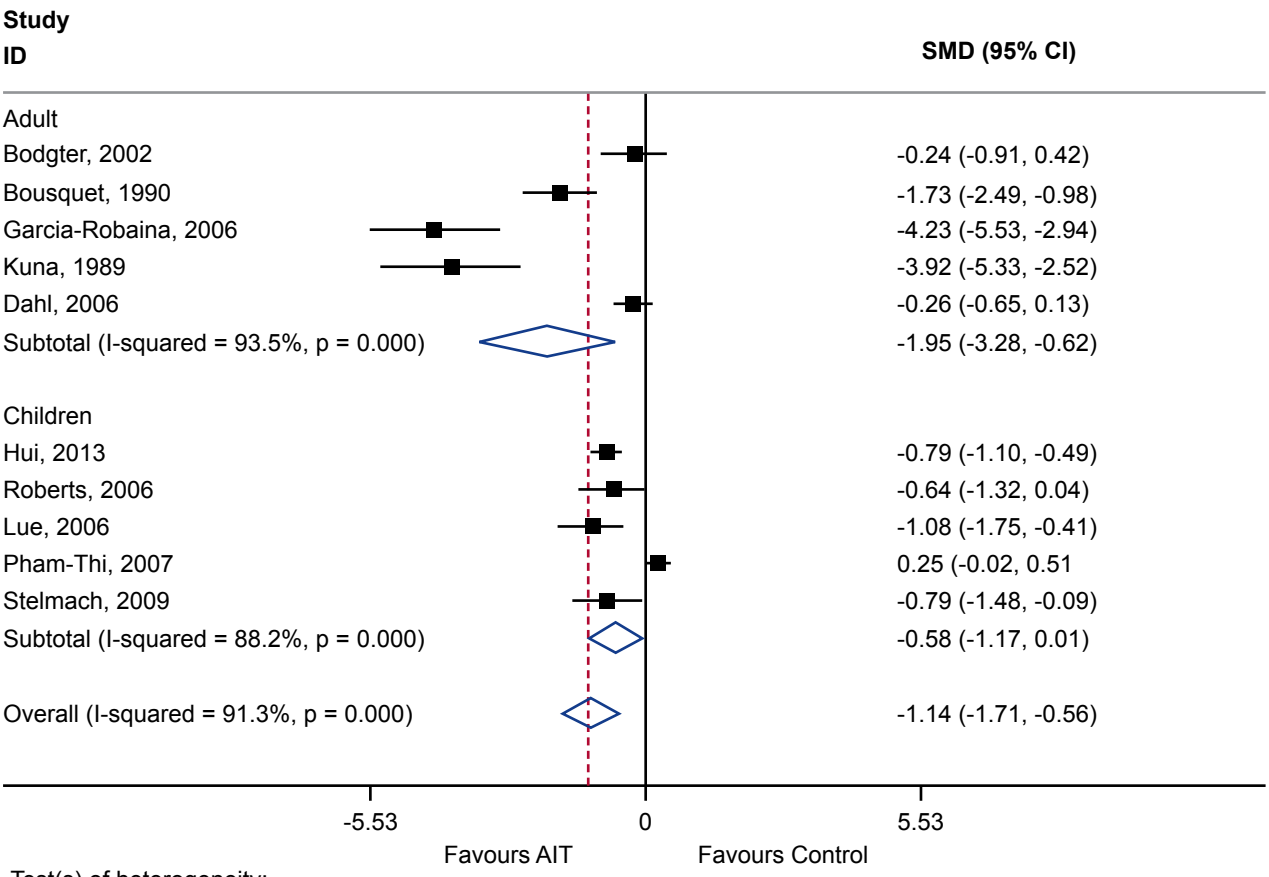
By excluding studies at high ROB sensitivity analysis confirmed the effect of AIT on asthma symptom scores: SMD -1.44 (95% CI -2.14, -0.74) (Appendix 4.5, Figure S2a).

Publication bias

The funnel plot showed possible publication bias as evidenced by an excess of small studies with large effect sizes (Appendix 4.5, Figures S2b). Publication bias was also suggested by the Egger test (P=0.024). There were insufficient studies to undertake the Begg test.

Subgroup analyses

- Children (<18 years) versus adults (≥18 years): SMD -0.58 (95% CI -1.17, -0.01) in children and SMD -1.95 (95% CI -3.28, -0.62)) in adults (Figure 3), supporting AIT effectiveness in both children and adults.
- SCIT versus SLIT: the analyses found that SCIT is effective with SMD -1.64 (95% CI -2.51, -0.78) and suggested (but did not confirm) that SLIT was effective SMD -0.35 (95% CI -0.75, 0.05) (Figure



Test(s) of heterogeneity:

	Heterogeneity Statistic	degrees of freedom	P	I^2	τ^2
Adult	61.83	4	0.000	93.5%	2.0670
Children	34.02	4	0.000	88.2%	0.3750
Overall	104.04	9	0.000	91.3%	0.7215

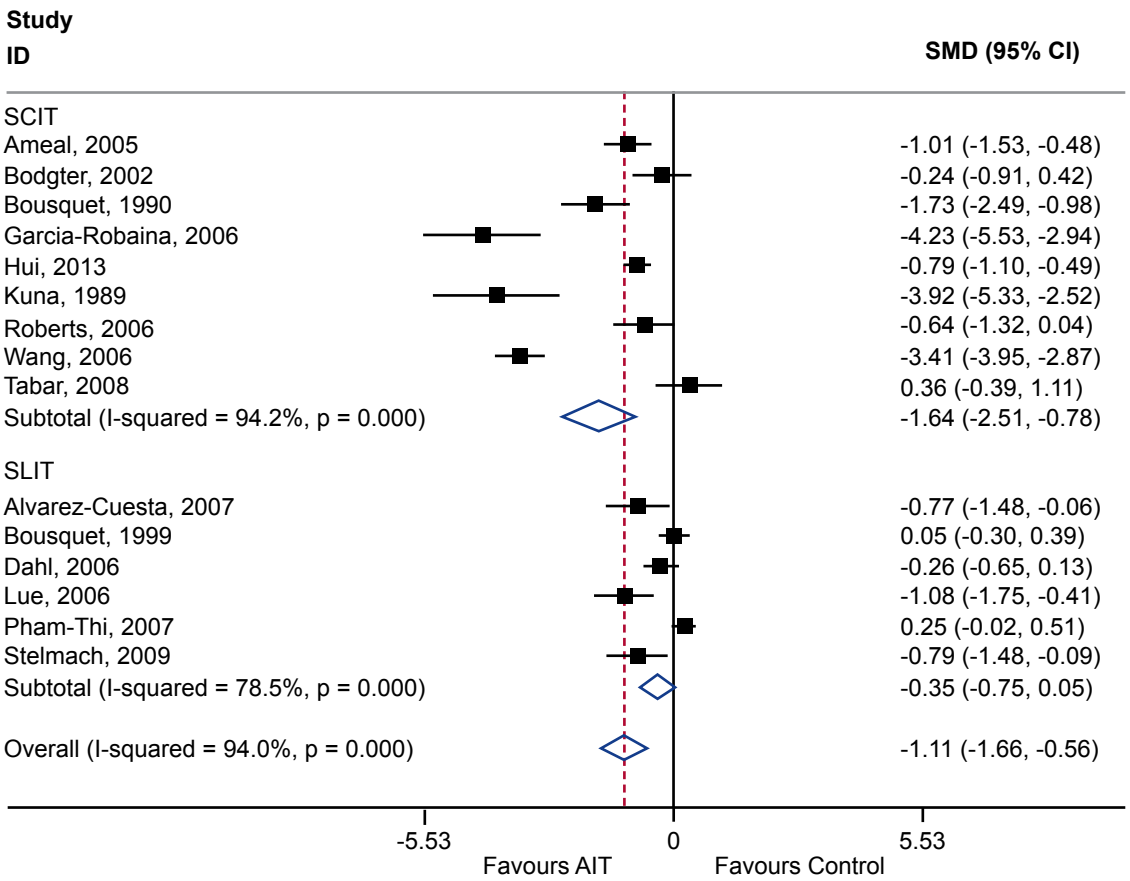
Significance test(s) of ES=0

	z	p
Adult	2.87	0.004
Children	1.93	0.054
Overall	3.87	0.000

Figure 3 Meta-analysis of double-blind RCTs, comparing symptom scores between AIT (SLIT and SCIT) and placebo groups in children <18 versus adults ≥18 years (random effects model)

4); this indirect comparison suggested that SCIT was more effective than SLIT.

- Treatment duration: SMD -1.15 (95% CI -1.77, -0.53) in those treated for <3 years and SMD -0.79 (95% CI -1.10, -0.49) in those treated for ≥3 years (Appendix 4.5, Figure S2c), these analyses finding that both treatment durations were effective.
- Mild/moderate versus moderate/severe disease: this subgroup analyses found that AIT is effective for mild/moderate asthma SMD -1.00 (95% CI -1.81, -0.19) and suggested (but did not confirm) a possible benefit in those with moderate/severe disease SMD -0.23 (95% CI -0.89, 0.43) (Appendix 4.5, Figure S2d).
- Individual allergens: this subgroup analyses found evidence of benefit for AIT with HDM SMD -1.41 (95% CI -2.27, -0.55), grass pollen SMD -1.18 (95% CI -2.17, -0.20) and cat/dog dander (SMD -0.77 (95% CI -1.48, -0.06)), suggested (but did not confirm) benefit for tree pollen SMD -0.24 (95% CI -0.91, 0.42), and found no benefit for mold SMD 0.36 (95% CI -0.39, 1.11) (Appendix 4.5, Figure S2e).
- Monosensitized/mono-allergic versus polysensitized: there is evidence of AIT benefit in monosensiti-



Test(s) of heterogeneity:

	Heterogeneity Statistic	degrees of freedom	P	I^2	τ^2
SCIT	137.11	8	0.000	94.2%	1.5937
SLIT	23.26	5	0.000	78.5%	0.1810
Overall	234.28	14	0.000	94.0%	1.0488

Significance test(s) of ES=0

	z	p
SCIT	3.71	0.000
SLIT	1.71	0.087
Overall	3.96	0.000

Figure 4 Meta-analysis of double-blind RCTs, comparing symptom scores between SCIT versus SLIT (random effects model)

zed/mono-allergic patients SMD -4.23 (95% CI -5.53, -2.94) and a suggested benefit (but not confirmed) for polysensitized patients SMD -0.31 (95% CI -0.65, 0.04) (Appendix 4.5, Figure S2f).

Long-term

No studies reported on the long-term effectiveness of AIT on symptom score.

Medication scores

Short-term

Forty-two (28 SCIT and 14 SLIT) studies reported on medication scores. Pooling of data with placebo as the comparator was possible for 10 studies. Meta-analysis found evidence that AIT improved medication scores (i.e. reduced medication use) with a SMD of -1.21 (95% CI -1.87, -0.54) (Figure 5), this corresponding to a large effect.

Sensitivity analysis

Sensitivity analysis for this outcome was not possible as no studies were found to be at high ROB.

Publication bias

The funnel plot showed possible publication bias as evidenced by an excess of small studies with large

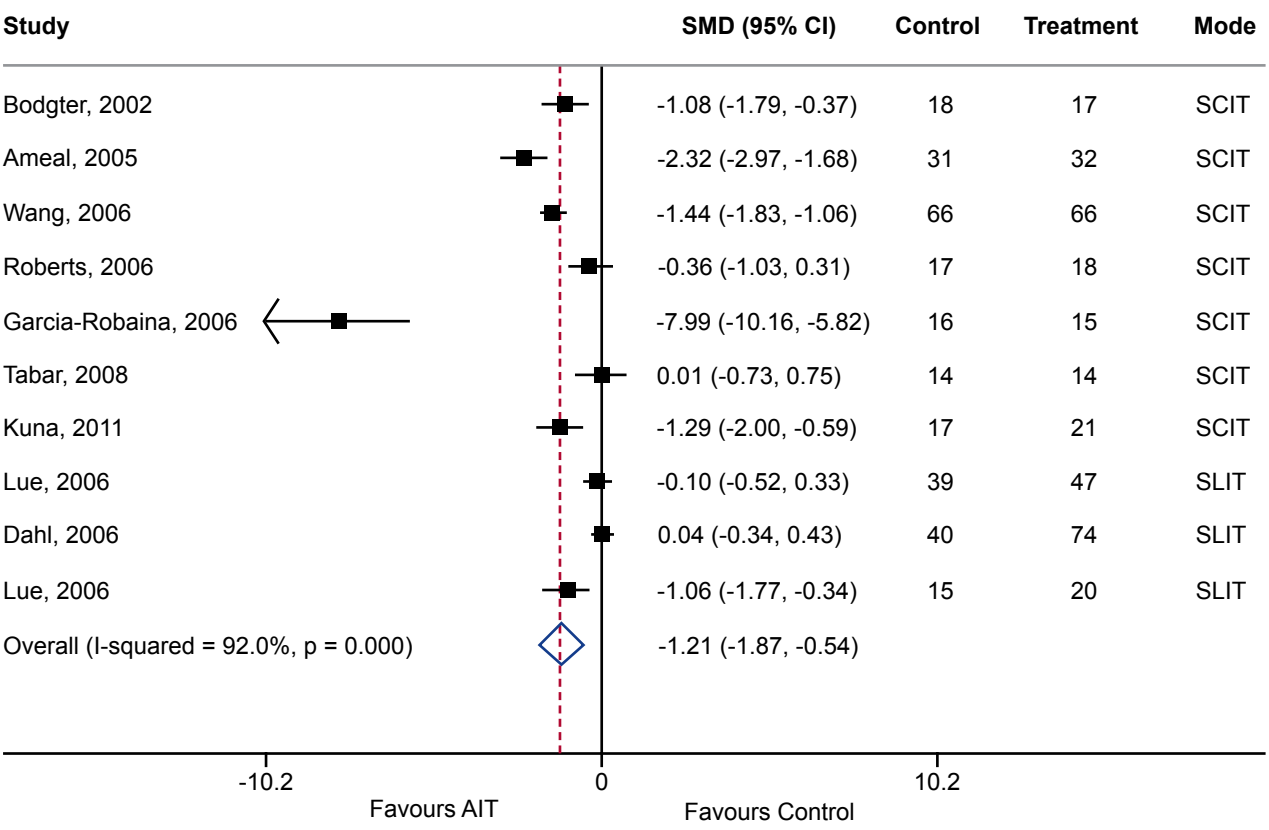
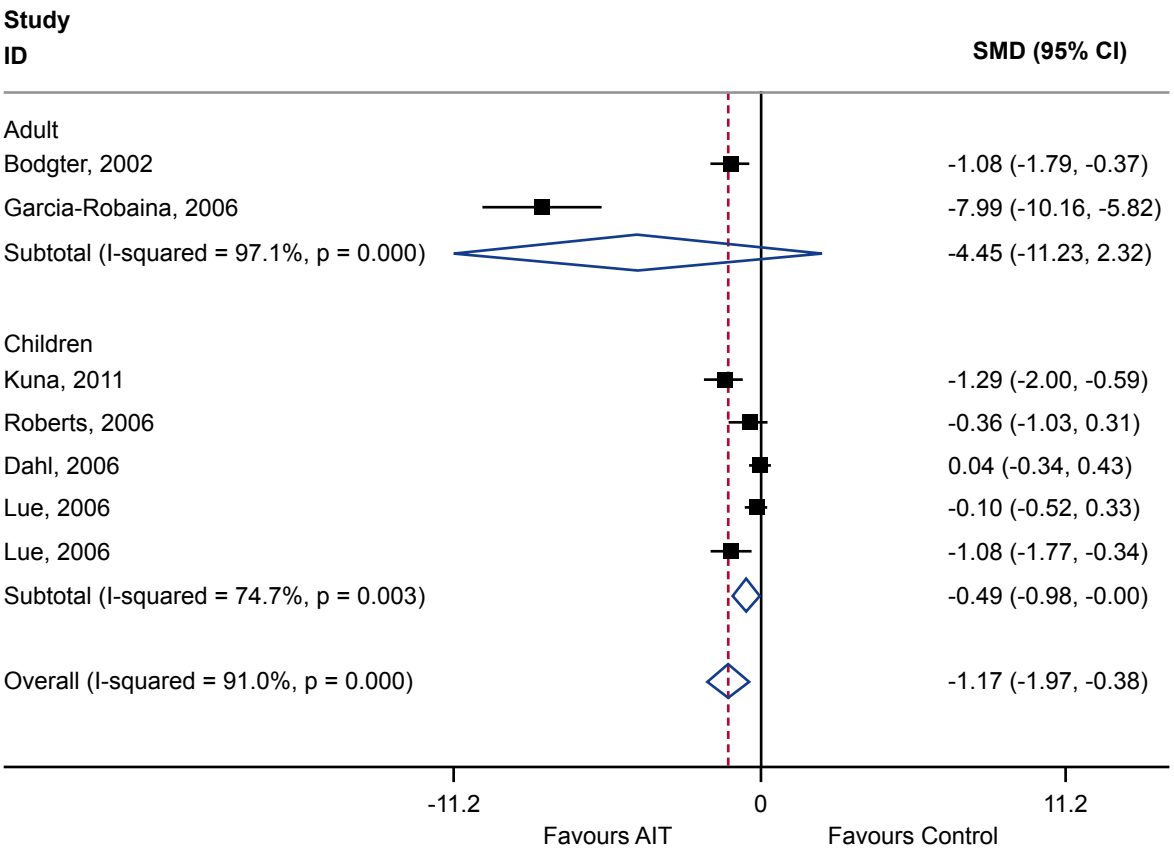


Figure 5 Meta-analysis of double-blind RCTs for symptom scores comparing AIT (SLIT and SCIT) and placebo groups (random effects model). Test of ES=0 : z= 3.56 p = 0.000; Heterogeneity χ^2 = 112.48 (d.f. = 9) p = 0.000; I^2 (variation in ES attributable to heterogeneity) = 92.0%; Estimate of between-study variance τ^2 = 0.9967

effect sizes (Appendix 4.5, Figures S2g), but this was not confirmed by the Egger test (P=0.09). There were insufficient studies to undertake the Begg test.

Subgroup analyses

- Children (<18 years) versus adults (≥18 years): there is evidence for benefit in children SMD -0.49 (95% CI -0.98, 0.00) and a suggested benefit (but not confirmed) in adults SMD -4.45 (95% CI -11.23, 2.32) (Figure 6)
- SCIT versus SLIT: SMD -1.65 (95% CI -2.52, -0.79) for SCIT and SMD -0.29 (95% CI -0.82, 0.24) for SLIT (Figure 7), these analyses showing benefit of SCIT and suggesting (but not confirming) benefit from SLIT.
- Mild/moderate versus moderate/severe disease: SMD -1.59 (95% CI -2.48, -0.70) for mild/moderate disease and SMD -0.36 (95% CI -1.03, 0.31) (Appendix 4.5, Figure S2h), these analyses showing a benefit in those with mild/moderate disease and suggesting (but not confirming) benefit in those with moderate/severe disease.
- Treatment duration: SMD -1.21 (95% CI -1.94, -0.49) for those treated for <3 years and SMD -1.29 (95% CI -2.00, -0.59) for those receiving ≥3 years of treatment (Appendix 4.5, Figure S2i), these analyses showing evidence of benefit in both groups.
- Individual allergens: this subgroup analysis demonstrated a benefit of AIT with HDM SMD -2.10 (95% CI -3.29, -0.91) and tree pollen (one study) SMD -1.08 (95% CI -1.79, -0.37) and suggested (but not confirmed) a benefit for, grass pollen SMD -0.06 (95% CI -0.41, 0.28) and molds SMD -0.65 (95% CI -1.92, 0.62) (Appendix 4.5, Figure S2j).
- Monosensitized and mono-allergic versus polysensitized: SMD -1.18 (95% CI -1.16, 0.13)



Test(s) of heterogeneity:

	Heterogeneity Statistic	degrees of freedom	P	I^2	τ^2
Adult	35.08	1	0.000	97.1%	23.2029
Children	15.79	4	0.003	74.7%	0.2244
Overall	66.41	6	0.000	91.0%	0.9722

Significance test(s) of ES=0

	z	p
Adult	1.29	0.197
Children	1.96	0.050
Overall	2.89	0.004

Figure 6 Meta-analysis of double-blind RCTs, comparing symptom scores between AIT (SLIT and SCIT) and placebo groups in children < 18 versus adults ≥ 18 years (random effects model)

in mono-sensitized and mono-allergic and the polysensitized group SMD -0.36 (95% CI -2.11, 0.25) in the polysensitized group (Appendix 4.5, Figure S2k) these analyses suggesting (but not confirming) benefit in both groups.

Long-term

No studies reported on the long-term effectiveness of AIT on medication score.

Combined symptom and medication scores

Short-term

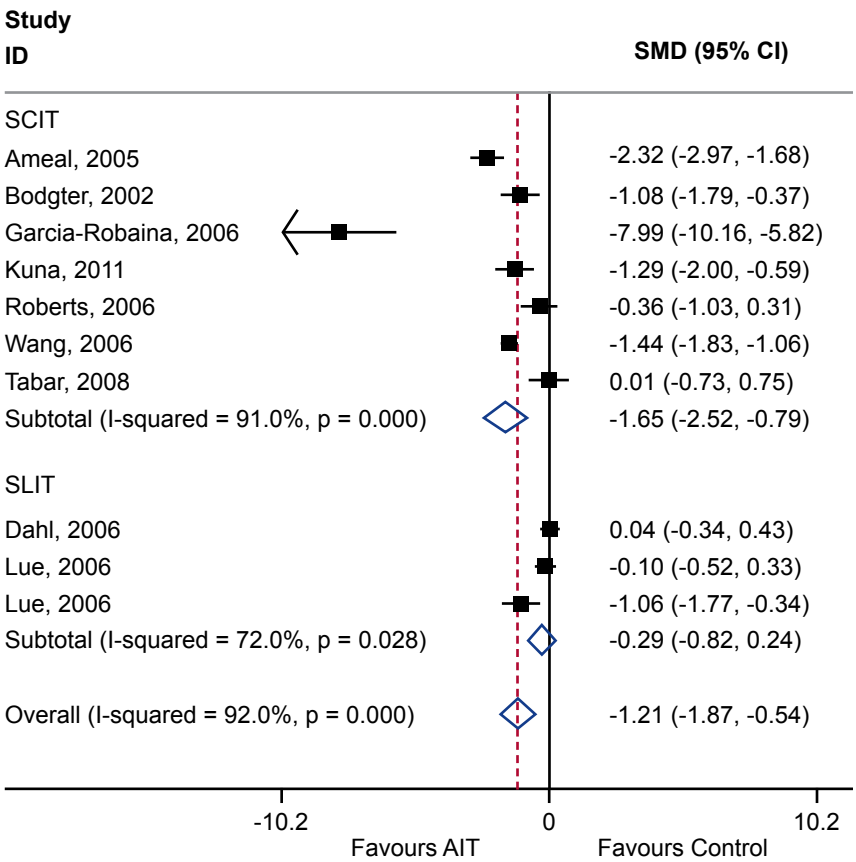
Six studies (two SCIT, three SLIT studies and one SCIT vs. SLIT) reported a combined assessment of the effectiveness of AIT on symptoms and medication usage. Pooling of data was possible for two studies, this showing a SMD of 0.17 (95% CI -0.23, 0.58) (Figure 8).

Sensitivity analysis, assessment of publication bias and subgroup analyses

These analyses were not possible for this outcome.

Long-term

One SLIT study at low ROB reported on this outcome. A five-year double blind placebo RCT by Durham (114) had a three year SLIT tablets or placebo treatment period in grass pollen allergic patients followed by a



Test(s) of heterogeneity:

	Heterogeneity Statistic	degrees of freedom	P	I^2	τ^2
SCIT	66.59	6	0.000	91.0%	1.1642
SLIT	7.14	2	0.028	72.0%	0.1533
Overall	112.48	9	0.000	92.0%	0.9967

Significance test(s) of ES=0

	z	p
SCIT	3.74	0.000
SLIT	1.06	0.287
Overall	3.56	0.000

Figure 7 Meta-analysis of double-blind RCTs, comparing medication scores between SLIT and SCIT (random effects model)

two-year blinded observation period when no active treatment was administered. At the end of the five years the group who had received SLIT were found to have a significant improvement in combined asthma symptom and medication scores when compared to placebo for the whole five-year period (p=0.049).

Secondary outcomes

Asthma control

Seven SLIT studies reported on a measure of asthma control (Appendix 4.4 Table S1g for details) (77, 78, 85, 88, 93, 98, 100). We were unable to pool data due to the differences in reporting of results. The one study at low ROB found that AIT did not improve asthma control (98) . We found no evidence to assess whether SCIT is effective in improving asthma control in allergic asthma patients.

Quality of life

Eleven AIT trials reported on a measure of disease-specific QoL (Appendix 4.4 , Table S1h).

Three SCIT studies (19, 35, 106), all judged to be at low ROB, reported significant improvements in disease-specific QoL. Pooled data from two of these trials (19, 35), showed a large treatment effect with an SMD of -0.83 (95% CI -1.19, -0.47) in favor of SCIT (Figure 9).

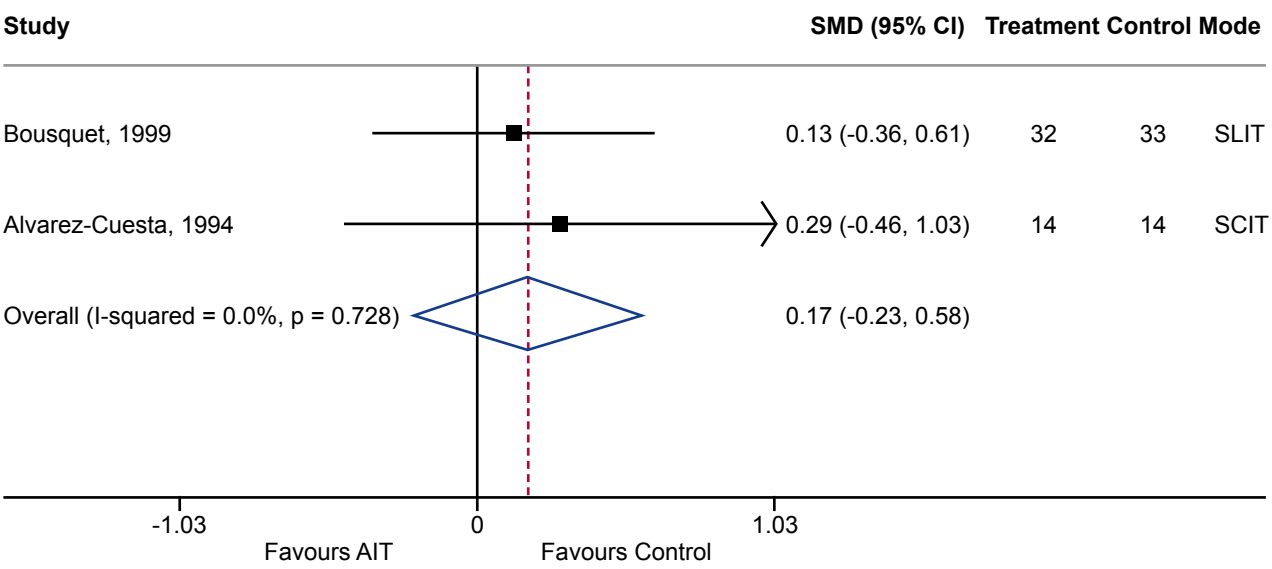


Figure 8 Meta-analysis of double-blind RCTs, comparing combined symptom medication scores between AIT (SLIT and SCIT) and placebo groups (random effects model). Test of SMD=0 : z= 0.84 p = 0.400; Heterogeneity χ^2 = 0.12 (d.f. = 1) p = 0.728; I^2 (variation in SMD attributable to heterogeneity) = 0.0%; Estimate of between-study variance τ^2 = 0.0000

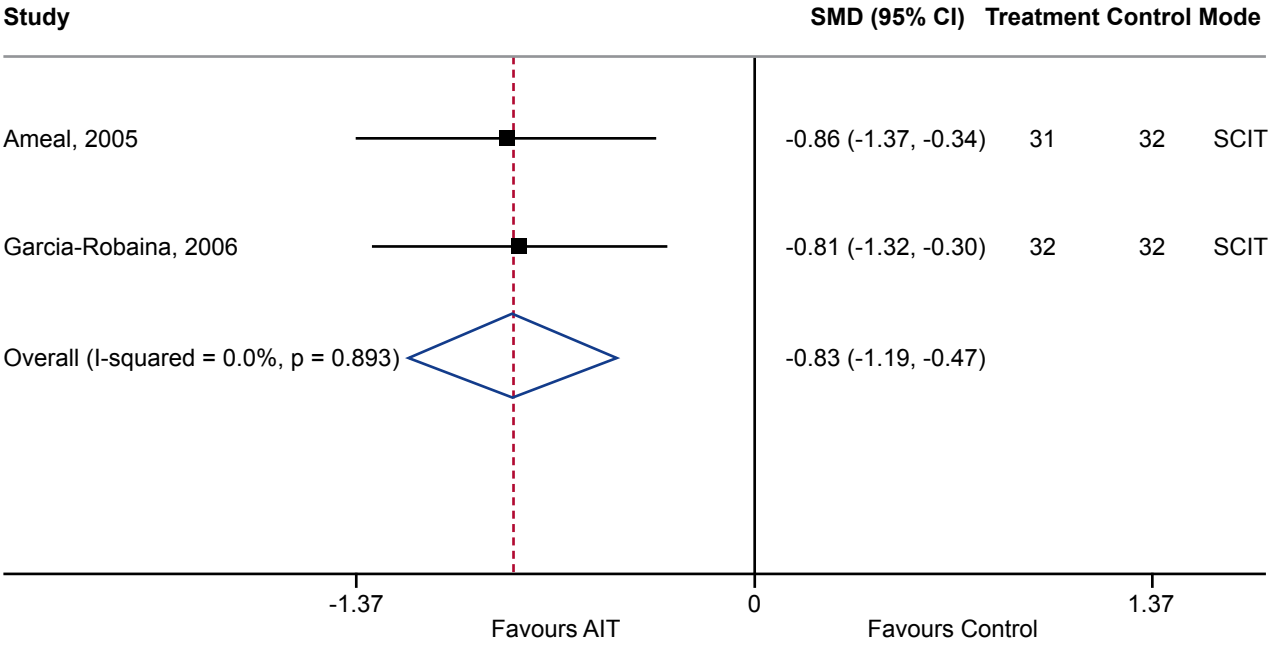


Figure 9 Meta-analysis of double blind RCTs of AIT (SCIT and SLIT) versus placebo for asthma specific quality of life (random effects model). Test of SMD=0 : z= 4.48 p = 0.000; Heterogeneity χ^2 = 0.02 (d.f. = 1) p = 0.893; I^2 (variation in SMD attributable to heterogeneity) = 0.0%;
Estimate of between-study variance τ^2 = 0.0000

Seven SLIT trials reported on disease-specific QoL (77, 78, 83, 88, 93, 98, 100). We were unable to pool data from these studies for meta-analysis due to the variable reporting of results (Table 1a). The one low ROB trial of SLIT (98) showed no significant improvement in disease-specific QoL.

Exacerbations

Six trials (69, 78, 80, 88, 91, 98) reported on asthma exacerbations, which were defined in a number of ways (Appendix 4.4, Table S1i). The one SCIT trial at low ROB (69) reported on exacerbations defined by the number of courses of oral corticosteroids required to restore asthma control found no significant difference between the SCIT and placebo groups (P-value not given). Five SLIT studies reported on exacerbations, which we were unable to pool due to variations in the ways in which trial results were reported.

In summary, focusing on the trials at low ROB, the Wang (2006) SCIT trial failed to demonstrate evidence of a reduction in exacerbations in those treated with AIT compared with those treated with placebo. Two SLIT trials reported a positive effect of AIT on asthma exacerbations, one in the context of reducing the dose of ICS.

Lung function

Twenty-five studies, of variable quality, reported on measures of lung function: peak expiratory flow rate (PEF), forced expiratory volume in 1 second (FEV1) and forced expiratory flow at 25-75% of forced vital capacity (FEF 25-75%). Data on these outcomes were recorded in a number of ways and at varying times throughout the study.

Peak expiratory flow rate (PEF)

Fourteen studies reported on this outcome (16, 29, 38, 43, 48, 50, 61, 69, 72, 73, 93, 96, 107, 108) (Appendix 4.4, Table S1j). Pooled data from six studies suggested no clear benefit of AIT with a SMD of 0.48 (95% CI -0.21, 1.18) (Appendix 4.7, Figure S4a).

Forced expiratory volume (FEV1)

Nine studies reported on FEV1. Reporting of data was varied (18, 28, 43, 57, 73, 93, 96, 108, 109) (Appendix 4.4, Table S1k). Data pooled from two studies indicated no clear evidence of benefit associated with AIT with a SMD of 0.41 (95% CI -0.46, 1.27) (Appendix 4.7, Figure S4a).

Forced expiratory flow at 25-75% of forced vital capacity (FEF25-75)

We were able to pool data on FEF 25-75 from three trials (72, 96, 109) and found an SMD of 0.83 (95% CI 0.31, 1.35), this suggesting a large beneficial effect of AIT (Appendix 4.7, Figure S4a).

In summary, the evidence identified from meta-analysis evaluating the effect of AIT on lung function in allergic asthma supports the effectiveness of AIT on small airways (FEF 25-75%), but with no clear evidence of benefit on improving PEF or FEV1.

Bronchial provocation tests

Thirty-one trials reported on bronchial provocation tests. Twenty-one trials looked at allergen specific provocation tests and 18 studies evaluated non-specific measures of bronchial hyperreactivity. There was a wide variation in reporting of outcome data (Appendix 4.4, Tables S1l and S1m).

Allergen specific airway hyperreactivity

Twenty-one trials performed allergen specific bronchial provocation tests (15, 17-20, 25, 30, 31, 35, 44, 48, 53, 60, 62, 64, 67, 70, 82, 107, 108, 110). They were of variable quality and were mainly SCIT trials (n=20), SLIT being evaluated in only one trial (82) (Appendix 4.4, Table S1l).

Pooled data from three SCIT studies, demonstrated a large effect of AIT with a SMD of 0.93 (95% CI 0.08, 1.79) (Appendix 4.7, Figure S4b). Furthermore, there was evidence from eight high quality RCTs that SCIT was effective in reducing allergen specific bronchial reactivity in patients with allergic asthma

One SLIT study reported on allergen specific bronchial responsiveness to Artemisia pollen (82). This study, at moderate ROB, found no significant difference between the SLIT and placebo groups.

Non- specific airway hyperreactivity

Eighteen studies reported on this outcome (16-18, 20, 33, 36, 48, 55, 62, 67, 69, 72, 73, 94, 96, 106, 109, 110) (Appendix 4.4, Table S1m).

Pooling of data was possible for metacholine PC20 for three studies which showed an SMD of 0.74 (95% CI -0.17, 1.66), showing no clear evidence of benefit for AIT; Histamine PC20 for two studies with an SMD of 0.33 (95% CI 0.03, 0.64) favouring AIT and for metacholine PD20 for two studies showing an SMD of 0.03 (95% CI -0.32, 0.39) showing no clear evidence in favour of AIT (Appendix 4.7, Figure S4c). We were

able to combine data from seven of these studies which showed an overall SMD of 0.33 (95% CI 0.01, 0.64) in favour of AIT (Appendix 4.7, Figure S4d).

Cost-effectiveness

One SCIT and two SLIT studies satisfied the eligibility criteria (111-113). These included children and adults with or without allergic rhinitis (Appendix 4.4, Tables S1m and S1n). The quality appraisal is detailed in Tables S1o and S1p (Appendix 4.4).

Of the three studies included only one focused on patients with allergic asthma who did not also have allergic rhinitis (111). This study was carried out in Germany and compared SCIT with standard care based on a small scale RCT (N=65) with three years of follow-up data. The study used a disease specific outcome measure (i.e. mean morning peak flow) with no attempt to convert it to a general quality of life measure such as quality adjusted life years (QALYs) making it impossible to assess the cost-effectiveness of the treatment. The study found that, over the three years, SCIT was more expensive than standard care and performed better than standard care on the disease specific outcome measure.

The remaining two studies looked at patients with both asthma and allergic rhinitis. SLIT was compared with standard care in an RCT (N=151) with one year of follow-up conducted in Austria, Denmark, Germany, Holland, Italy, Spain, Sweden and the UK, and with results evaluated from an English National Health Service (NHS) perspective (112). This study used one year of treatment data and assumed a constant treatment effect over the three year treatment period and the six years following the end of the treatment. EQ5D was used to evaluate the treatment outcome. The incremental cost-effectiveness ratio (ICER) of SLIT, as compared to standard care at 2005 prices, was calculated at £8816 (€10850) per QALY over the nine year period. The study did not attempt to characterize the uncertainty around this estimate. Updating this to 2014/15 prices using Personal Social Services Resource Unit (PSSRU) NHS inflation indices gave an ICER of £10726 (€13202) per QALY. Another RCT (N=70) with five years of follow-up conducted in Italy comparing SLIT with standard care in patients with asthma and rhinitis and found that patients on SLIT cost less and experienced less symptoms than those on standard care (113). Methods for calculationg the costs were not presented in enough detail to understand the analysis that had been performed and there was no attempt to convert the symptom score to a general quality of life scale making it impossible to assess the cost-effectiveness of SLIT.

Safety

Data from randomized controlled trials (RCTs) and case series were included to assess the safety of AIT.

RCTs

Fifty-two RCTs (36 SCIT studies and 16 SLIT) reported safety data (Appendix 4.6, Tables S3a-f). We were able to pool data from 38 of these studies (SCIT=29; SLIT=9) including both local and systemic adverse events (AEs).

Risk of patients experiencing one or more AE

AIT delivered by any route (SCIT or SLIT) increased the risk of patients experiencing one or more AE (i.e. local and systemic) with a rate ratio (RR) of 1.74 (95% CI 1.38, 2.2) (Appendix 4.6, Figure S3a). Subgroup analysis found that the increased risk was higher for SCIT RR=2.22 (95% CI 1.48, 3.33) than SLIT RR=1.49 (95% CI 1.13, 1.98), although this is an indirect comparison (Appendix 4.6, Figures S3b and S3c).

Total number of AEs reported

AIT delivered by any route (SCIT or SLIT) increased the risk of total AEs (i.e. local and/or systemic) with a RR=1.50 (95% CI 1.12, 2.02) (Appendix 4.6, Figure S3d). Subgroup analysis found increased risk both for SCIT RR=1.32 (95% CI 1.01, 1.74) and SLIT RR=1.93 (95% CI 0.95, 3.95) (Appendix 4.6, Figures S3e and S3f).

Risk of systemic AEs

AIT delivered by any route (SCIT or SLIT) increased the risk of systemic AEs with a RR of 1.85 (95% CI 1.20, 2.84) (Appendix 4.6, Figure S3g). Subgroup analysis found that there was clearly an increased risk of systemic AEs with SCIT RR=1.92 (95% CI 1.19, 3.09), but not for SLIT RR=1.39 (95% CI 0.67, 2.92) (Appendix 4.6, Figures S3h and S3i).

Risk of local AEs

AIT delivered by any route was not found to increase the risk of local AEs: RR=1.18 (95% CI 0.83, 1.67) (Appendix 4.6, Figure S3j). The available data suggested that the risk of local AEs was however substantially greater in those receiving SLIT when compared to those receiving SCIT (Appendix 4.6, Figure S3j).

Case-series

We identified six eligible case-series studies in our searches; SCIT (n=5) and SLIT (n=1). The main characteristics of these studies and quality appraisal are presented in Tables S3g and S3h (Appendix 4.6). The reported incidence of local AEs varied from 0.66 per patient and 0.33 per injection to 1.8% The reported incidence of systemic AEs varied from 0.0074% to 0.06%

No deaths from AIT were reported in any of these studies.

DISCUSSION

Statement of principal findings

This review has found a substantial body of evidence showing that administration of AIT in patients with allergic asthma can result in reductions in short-term symptom and medication scores. These findings do however need to be interpreted with caution given that the majority of trials were found to be at high or unclear ROB and the possibility of publication bias in relation to both these outcomes. Further sub-group analysis confirmed the beneficial effect for SCIT but was questionable for SLIT. There was a more modest body of evidence for the combined symptom and medication scores, which meta-analysis suggested was ineffective but this was not conclusively demonstrated on account of the wide confidence intervals. We found only one trial, judged to be at low ROB, evaluating long-term outcomes, which found a significant improvement in combined symptom and medication scores.

There is evidence for SCIT in improving asthma specific quality-of-life and reducing allergen specific airway hyperreactivity. In terms of lung function we were unable to demonstrate any significant beneficial effect on PEFR and FEV1 however SCIT does have a beneficial effect on FEV25-75. No beneficial effect of AIT could be demonstrated on asthma control. As for asthma exacerbations, no beneficial effect could be demonstrated for SCIT, but there was limited evidence in favour of SLIT.

AIT was associated with a moderate increased risk of AEs, both for SCIT and SLIT. Severe systemic AEs were observed, but these were uncommon and mainly occurred with SCIT. No fatalities were reported in the studies included in this review.

Strengths and limitations

To our knowledge, this is the most comprehensive assessment of AIT in asthma ever undertaken. We employed internationally accepted techniques to systematically identify, assess and synthesize a substantial body of evidence, which included a number of pre-specified sensitivity and subgroup analyses.

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. The results of this review, particularly for primary outcomes, are based on the trials which we were able to meta-analyse which may not be representative of all trials. For example, data for combined scores was only available for six studies of which only two could be pooled for meta-analysis the results of which had a wide confidence interval allowing no clear conclusion to be drawn. For the subgroup analyses that were undertaken, there was in some cases imprecision which impacted on our ability to draw clear conclusions. Third, because of the heterogeneity in scoring systems used, we undertook meta-analyses using random-effects modeling 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. Finally, it needs to be borne in mind that there may have been important differences between specific AIT products. Investigating this issue was however beyond the scope of this review.

Interpretation in the light of the previous literature

The findings from this review are in keeping with earlier evidence syntheses on this subject (see companion paper), which found that SCIT inproved short-term symptom amd medication scores and measures of bronchial reactivity, but the evidence for SLIT was less consistent. There was no clear improvement of lung function for either SCIT or SLIT. This present study has built on this body of work by adding a broader range of subgroup analyses, including additional studies at low ROB, and achieveing greater precision in summary results.

Implications for policy, practice and research

Our findings provide evidence that AIT may be effective in improving two of our three patient-reported primary outcomes over the short-term. Interpretation of these results is however complicated by considerations about the quality of the substantial number of studies and possible publication bias. The subgroup analyses suggest that SCIT is likely to be more effective than SLIT, and that AIT may be more effective in children than in adults

Greater standardization of trial designs, looking at the compliance of patients to AIT for the differing routes of administration, reporting and choice of outcomes and their reporting so as to facilitate evidence syntheses and key subgroup analyses would greatly help to advance the body of evidence underpinning AIT in allergic asthma. Future well conducted studies looking at the combined symptom and medication score are needed to determine whether AIT is beneficial for this outcome. 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. We anticipate that this review will report mid 2017.

Conclusions

There is evidence that AIT in allergic asthma can achieve substantial reductions in short-term symptom and medication scores, with subgroup analyses confirming a benefit from SCIT and a questionable benefit from SLIT. These findings however need to be interpreted with caution given concerns about study quality and potential publication bias. Further there is evidence showing that SCIT decreases allergen-specific airway hypereactivity and improves asthma specific quality-of-life. The effect of AIT on asthma control and exacerbations is not conclusive, neither its long-term efficacy after stopping AIT, which requires further investigation. More research is needed to establish the cost-effectiveness of AIT but evidence suggest that SLIT is cost-effective in a UK NHS environment.

AIT is associated with a modest increase in the risk of AEs, both for SCIT and SLIT. Severe systemic AEs can occur, but are uncommon and mainly associated with SCIT. No fatalities were reported in the studies included in this review.

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Contributorship

This review was drafted by Sangeeta Dhami. It was revised following critical review initially by Aziz Sheikh, Ioana Agache, Marek Jutel, Susanne Lau, and then by all the co-authors.

Conflicts of interest

S Dhami: reports grants from EAACI to carry out the review, during the conduct of the study; A Kakourou: has nothing to disclose; F Asamoah: reports payment from Evidence-Based Health Care Ltd during the conduct of the study; I Agache: consulting fee for ALK and Allergopharma; S Lau: grant from Allergopharma; drug monitoring committee immunotherapy Merck; grants and research support from Merck, Allergopharma; M Jutel: consulting fee Anergis, Allergopharma; scientific/governmental grant from NCN Poland; fee for review activities Biomag; A Muraro: consulting fee Meda, Nestle, Nutricia, Novartis, ALK; co-investigator for research protocol for Nestlé and Nutricia; G Roberts: Materials for research programme (ALK-Abello), research grant (ALK-Abello), advisory board (ALK-Abello), speaker (Allergy Therapeutics, ALK-Abelo); C Akdis: consulting fee Novartis, Boehringer-Ingelheim; stocks Davos Diagnostics, Allimentary Health Pharma Davos; research grant Novartis, Allergopharma; M Bonini: has nothing to disclose; O Cavkaytar: has nothing to disclose; B Flood: has nothing to disclose; P Gajdanowicz: has nothing to disclose; K Izuhara: reports grants and personal fees from Chugai Pharmaceutical Co. Ltd,

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5

ALLERGEN IMMUNOTHERAPY FOR ALLERGIC RHINOCONJUNCTIVITIS

A SYSTEMATIC REVIEW AND META-ANALYSIS

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***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 nine 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.*

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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 many patients.

The European Academy of Allergy and Clinical Immunology (EAACI) is in the process of developing Guidelines on AIT for Allergic Rhinoconjunctivitis. We have already undertaken a systematic review of the previously systematic reviews focusing on allergic rhinoconjuctivitis (Appendix 5.1), these earlier studies are now relatively old and do not incorporate the recent large, high quality studies. A further systematic review has been undertaken to help 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 nine electronic bibliographic databases. The search strategy was developed on OVID MEDLINE and then adapted for the other databases (Appendix 5.2 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.

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,

Box 1 Inclusion and exclusion criteria

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), intralympahtic (ILIT) or any other routes.
Comparator	Placebo or any active comparator.
Study designs	*Effectiveness*: 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. *Cost-effectiveness*: health economic analysis. *Safety*: double-blind RCTs and large case series (≥ 300 patients).
Study outcomes	*Primary outcomes*: 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. *Secondary outcomes*: 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.

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, HZ, 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 5.3).

RESULTS

Our search strategy yielded 5,932 titles of which 160 studies (reported in 166 papers) met our overall review eligibility criteria. These eligible papers included 134 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 (Appendix 5.5, Tables S2a-c). A full description of the trials is given in the online supplement (Appendix 5.5).

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 (Appendix 5.5, Table S2e). In one study, ROB could not reliably be assessed from the translation.

ILIT

Both studies had a low ROB (Appendix 5.5, Table S2f).

Primary outcomes

Data on primary outcomes are summarized in Tables S2 g-i (Appendix 5.5).

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) (Appendix 5.4, Figure S1).

Assessment for publication bias

There was evidence of potential publication bias (Appendix 5.4, Figure S2) 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 (Appendix 5.4,

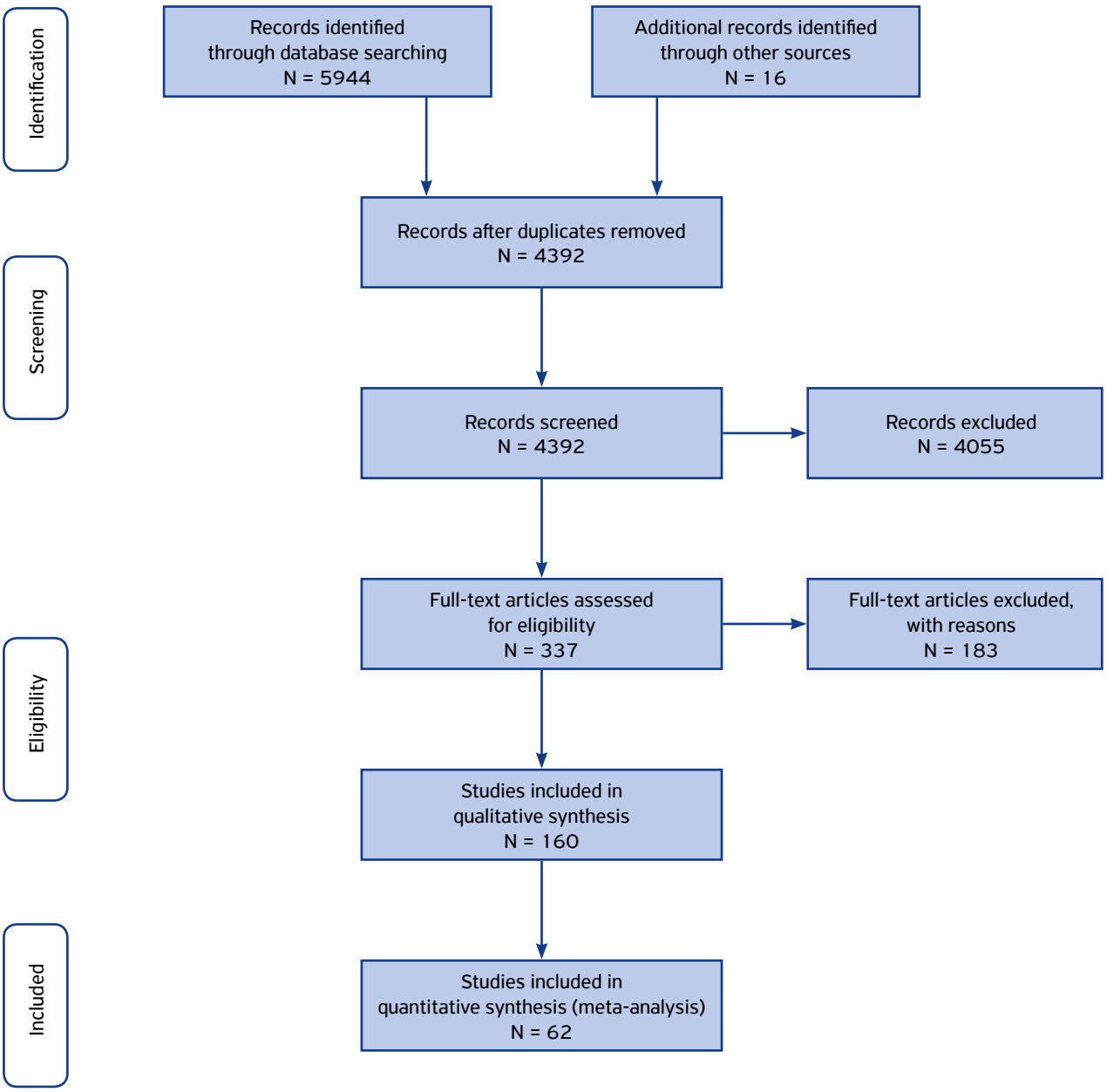


Figure 1 PRISMA flow diagram

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 (Appendix 5.4, Figures S4a and b), 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) (Appendix 5.4, Figures S5a and b), 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

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

Study (First author, year, country)	Allergen(s) type								Allergen no.		Compar-ator			AIT Protocol											Short-term effective-ness			Long-term effective-ness				
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mold(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	Safety	Quality of life
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 *Parietaria judaica* (50%) & *Parietaria officinalis* (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, Germany		X							X		X			X			X					7 w	Purified and standardized extracts composed of equal parts of *Corylus avellana*, *Alnus glutinosa*, and *Betula verrucosa* / ALK7 Frűhbltihermischűng®	X	X					X	
Bodtger, 2002, Denmark		X							X		X			X	X			X				1 y	*Betula verrucosa* extract / Soluprick SQ® (ALK-Abello´)	X	X					X	
Bousquet, 1987, France	X								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					X		8 m	SCIT with a high-molecular-weight formalinized allergoid (HMW-GOID) vs SCIT with unfractionated allergoid (GOID) vs SCIT with standardized extract vs placebo / NR	X	X					X	
Bousquet, 1990, France	X								X		X		X	X	X					X		NR	High-molecular weight mixed grass pollen allergoids / NR	X	X					X	

Table 1a Continued

Study (First author, year, country)	Allergen(s) type								Allergen no.		Comparator			AIT Protocol												Short-term effectiveness			Long-term effectiveness				
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mold(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	Safety	Quality of life
Bousquet, 1991, France	X	X	X							X	X			X						X		1 y	Standardized extracts from orchard grass (*Dactylis glomerata*), olive (*Olea europaea*), plane tree (*Platanus occidentalis*), mugwort (*Artemisia vulgaris*), and *Parietaria officinalis* pollens / NR (manifactured by Stallergenes)			X				X	
Bozek, 2016, Poland	X								X		X			X			X					3 y	Pollen mixture extract solution of grass pollens (*Agrostis stolonifera*, *A odoratum*, *Arrhenatherum elatius*, *D glomerata*, *Festuca rubra*, *Holcus lanatus*, *Lolium perenne*, *P pratense*, *P pratensis*, *Secale cereal*, and *Loe edasi*) / 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	*Phoenix sylvestris Roxb* or sugar palm allergoid extract / NR			X				X	
Charpin, 2007, France		X							X		X					X	X					15 m	Standardized, aluminum hydroxide-adsorbed *Juniperus ashei* extract/ Alustal® (Stallergenes)	X	X					X	X
Colas, 2006, Spain			X						X		X					X		X				1 y	Depigmented and glutaraldehyde polymerized extract of *Salsola kali* absorbed onto aluminium hydroxide/ NR (supplied by Laboratorios LETI, SL.)	X	X					X	X

Table 1a Continued

Study (First author, year, 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)	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		
Corrigan, 2005, UK	X								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 *Parietaria judaica* extract adsorbed onto aluminum hydroxide / Alutard SQ®	X	X					X	
Dokic, 2005, Macedonia					X				X		X						X					3 y	Aluminium hydroxide adsorbed *D.pt.* allergoid / NR (Allergopharma)	X	X					X	
Dolz, 1996, Spain	X								X		X					X				X		3 y	Grass-pollen allergen extract (*Phleum*, *Dactylis*, *Lolium*) adsorbed onto aluminum hydroxide / Alutard SQ® (ALK-Abelló)	X	X					X	
Drachenberg, 2001, Germany and Austria	X								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, Germany		X							X		X			X			X					4-7 w	L-tyrosine-adsorbed birch, alder, hazel pollen allergoids treated with glutaraldehyde plus monophosphoryl lipid-A (MPL) / Pollinex Quattro ®			X				X	
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	

Table 1a Continued

Study (First author, year, country)	Allergen(s) type								Allergen no.		Comparator			AIT Protocol											Short-term effectiveness			Long-term effectiveness				
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mold(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	Safety	Quality of life
Ewan, 1988, UK					X				X		X								X			3 m	Partially purified extract of *D. pteronysinus* / Pharmalgen®	X						X	
Fell, 1988, UK	X								X		X			X							X	1 injection	Enzyme (glucuronidase) potentiated grass pollen allergens / (Pharmacia)	X	X						
Ferrer, 2005, Spain			X						X		X					X	X					20 m	Biologically standardized extract of *Parietaria judaica* 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					>30m (UR)	Polymerized ragweed extract / NR			X			X	X	
Grammer, 1987, USA	X								X		X			X			X					4 m	Polymerized ragweed extract / NR			X				X	
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 Sl)			X				X	
Horst, 1989, France				X					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	*Phleum pratense* extract adsorbed with aluminum hydroxide / Alutard SQ ®				X		X		

Table 1a Continued

Study (First author, year, country)	Allergen(s) type								Allergen no.		Comparator			AIT Protocol											Short-term effectiveness			Long-term effectiveness				
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mold(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	Safety	Quality of life
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
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	*Alternaria alternata* extract in a depot formulation with aluminum hydroxide / Novo-Helisen Depot® A alternata 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			X					5 w	Glutaraldehyde-modified, tyosine-adsorbed short ragweed extract / NR (Beecham Laboratories)	X						X	
Mirone, 2004, Italy			X						X		X					X	X					1y (DB RCT)	*Ambrosia artemisiifolia* absorbed onto aluminium hydroxide and suspended in phenolated (0.4% w/v) saline solution / NR (ALK-Abello`)	X	X					X	

Table 1a Continued

Study (First author, year, country)	Allergen(s) type								Allergen no.		Comparator			AIT Protocol												Short-term effectiveness			Long-term effectiveness				
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mold(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	Safety	Quality of life
Olsen, 1995, Denmark	X	X	X							X			X			X	X					2 y	Aluminium hydroxide adsorbed extracts of standardized extracts of *Betula*, *Phleum* and *Artemisia* / Alutard® SQ (ALK)	X						X	
Ortolani, 1994, Italy			X						X		X					X	X					1 y	Partially purified alginate-conjugated extract of *Parietaria judaica* / Conjuvac Parietaria ® (Dome Hollister-Stier)			X				X	
Pastorello, 1992, Italy	X								X		X			X	X		X					5-12 m	Formalinized depot 6 grass allergoid absorbed onto aluminum hydroxide / NR (Allergopharma)			X				X	
Patel, 2012, Canada						X			X		X		X					X				3 m	Fel d 1–derived peptide antigen (Cat-PAD) / NR (Bachem and Patheon)	X*			X*			X	
Pauli, 2008, Austria, Denmark, France, Italy & Sweden		X							X		X		X			X	X					2 y	Aluminum hydroxide–adsorbed vaccines of birch pollen extract, *rBet v 1*, and *nBet v 1* / 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% *Corylus avellana*, 33% *Alnus glutinosa*, 34% *Betula alba*) 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					14m	Standardized depot preparations of grass pollen extract / Alutard® SQ grass pollen (ALK-Abello´)								X

Table 1a Continued

Study (First author, year, country)	Allergen(s) type								Allergen no.		Compar-ator			AIT Protocol											Short-term effective-ness			Long-term effective-ness				
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mold(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	Safety	Quality of life
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 *Alternaria alternata* / Allergovac® depot	X	X					X	X
Tari, 1997, Italy			X						X		X					X	X					2 y	Alum-adsorbed *Parietaria judaica* pollen allergoid/ Allergovit® (Allergopharma)	X	X					X	
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 *Phleum pratense* 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	

Table 1a Continued

Study (First author, year, country)	Allergen(s) type								Allergen no.		Comparator			AIT Protocol												Short-term effectiveness			Long-term effectiveness				
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mold(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	Safety	Quality of life
Walker, 2001, UK	X								X		X					X		X				2 y	Alutard SQ (ALK Abelló, Horshølm, Denmark), a standardized extract of *Phleum pratense* (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	
Zenner, 1997, Germany	X		X						X		X				X		X					4 m	Partially purified and standardized extracts of 6 grasses (50%, *Dactylis glomerata*, *Lolium perenne*, *Arena elatior*, *Phleum pratense*, *Poa pratensis*, and *Fetuca pratensis*) and rye, (50%, *Secale cereale*) 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)

	Allergen(s) type								Allergen no.		Comparator			AIT Protocol												Short-term effectiveness			Long-term effectiveness				
Study (First author, year, country)	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mold(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	Safety	Quality of life
Ahmadiafshar, 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 *Cupressus arizonica* partially purified through dialyis in a phyiological solution with 15% glycerin.	X	X					X	
Aydogan, 2013, Turkey, UK & Cyprus.					X				X		X											12 m	1:1 mixture of *D. pteronysinus* and *D. farinae* (STALORAL, Stallergenes SA, Antony, France)	X	X						
Bahçeciler, 2007, Turkey					X				X		X											6 m	*D. pteronysinus* and *D. farinea* 50/50 extract.	X							
Bergmann, 2013, Germany, France, the Netherlands & Spain					X				X		X											2 y	Oral tablets of 1:1 mixture of *D pteronysinus* and *D farinae* (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	

Table 1b Continued

Study (First author, year, country)	Allergen(s) type								Allergen no.		Comparator			AIT Protocol												Short-term effectiveness			Long-term effectiveness				
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mold(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	Safety	Quality of life
Blaiss, 2010, US & Canada	X								X		X											18 m	f 2,800 bioequivalent allergen units of grass AIT treatment (oral lyophilisate, *Phleum pratense*, 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, Canada			X						X		X			X								4 m	Ragweed allergen extract	X	X					X	
Bozek, 2012, Poland					X				X		X											3 y	Oral Staloral 300 SR Der p and Der f (1:1)	X	X					X	
Bozek, 2014, Poland	X								X		X											3 y	Oral Staloral 300 SR 5 grass pollen solution of *P. pratense*, D. *glomerata*, A. odoratum, *L. perenne*, and *P. pratensis* (Stallergenes)	X	X					X	
Bufe, 2004, Germany	X								X		X				X							3 y	Grass pollen extracts (Sublivac B.E.S.T.TM, HAL-Allergy, Haarlem, the Netherland)								
Bufe, 2009, Germany	X								X		X			X	X							8-23 w	Orodispersible, fast-dissolving, SQ-standardized grass allergen tablet (Grazax; ALK, Hørsholm, Denmark; 75,000 SQ-T/2800 bioequivalent allergen units, approximately 15 mg Phl p 5, Phleum pratense major allergen 5)	X	X					X	
Caffarelli, 2000, Italy	X								X		X			X								3 m	Mixture of monomeric grass-pollen allergens (33% Holcus lanatus, 33% Phleum pratense, and 33% Poa pratensis) in tablets (LAIS, Lofarma S.p.A, Milan, Italy)	X	X					X	
Clavel, 1998, France	X								X		X											7 m	Mixture of five major grass pollens (orchard grass, meadow grass, ryegrass, sweet vernal grass, and timothy grass	X	X					X	
Cortellini, 2010, Italy				X					X		X											10 m	Glycerinated *Alternaria alternata* extract in droplets (Anallergo, Firenze, Italy)	X	X					X	

Table 1b Continued

Study (First author, year, country)	Allergen(s) type								Allergen no.		Comparator			AIT Protocol									Short-term effectiveness			Long-term effectiveness				
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mold(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	Safety	Quality of life
Cox, 2012, US	X								X		X											6 m	300 IR SLIT tablets containing a standardized 5-grass pollen allergen obtained by means of extraction of a mixture of 5 grass pollens in equal amounts (orchard grass, *Dactylis glomerata*; Kentucky bluegrass, *Poa pratensis*; perennial rye grass, *Lolium perenne*; sweet vernal grass, *Anthoxanthum odoratum*; and timothy grass, P*hleum pratense*)	X	X	X				X	X
Creticos, 2013, US		X							X		X			X	X							20 m	Short ragweed tablets (1.5, 6, or 12 units of *Ambrosia artemisiifolia* major allergen 1 [Amb a 1-U])	X	X	X				X	
Creticos, 2013, Canada		X							X		X				X							12 w	Ragweed SAIL (RW-SAIL) Standardized glycerinated short ragweed	X		X				X	
Dahl, 2006, Denmark, Germany, Italy, the Netherlands, Sweden, Austria, Spain & UK	X								X		X			X	X							1 y	Grass pollen allergen tablet (GRAZAX) (75,000 SQ-T; 15 mg major allergen *Phleum p* 5)	X	X					X	
Dahl, 2006, Denmark & Sweden	X								X		X			X	X								Orodispersible grass allergen tablet (GRAZAX; approximately 15 mg major allergen *Phleum pretense* (75 000 SQ-T)	X	X					X	
de Blay, 2007, France	X								X		X			X	X							12 m	3-grass pollen extract (33.3% *Dactylis glomerata* [orchard grass], 33.3% *Phleum pretense* timothy grass], and 33.3% *Lolium perenne* [rye grass]) Allerbio, Varennes-en-Argonne, France) in 50% glycerin	X	X					X	X

Table 1b Continued

Study (First author, year, country)	Allergen(s) type								Allergen no.		Comparator			AIT Protocol											Short-term effectiveness			Long-term effectiveness				
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mold(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	Safety	Quality of life
De Bot, 2011, The Netherlands					X				X		X											2 y	Aqueous extract of house dust mites (*D pter*,) 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 (*D. pteronysinus* and *D. farinae*) (1:1:1:1 ratio of the major allergens *Der p 1*, *Der f 1*, *Der p 2*, and *Der f 2*)	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	X							6 m	Lyophilized vaccines of five grass pollens (orchard or cocksfoot (*Dactylis glomerata*), meadow (*Poa pratensis*), perennial rye (Lolium perenne), sweet vernal (*Anthoxanthum odoratum*) and timothy (*Phleum pratense*))	X						X	
Didier, 2013, Denmark, Austria, France, Canada & Germany	X								X		X			X	X							4 y	300 IR tablets containing mixture of 5 grasses [cocksfoot (*Dactylis glomerata*), meadow (*Poa pratensis*), rye (*Lolium perenne*), sweet vernal (*Anthoxanthum odoratum*) and timothy (*Phleum pretense*)	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 (*Phleum pratense*)	X	X					X	X

Table 1b Continued

Study (First author, year, country)	Allergen(s) type								Allergen no.		Comparator			AIT Protocol										Short-term effectiveness			Long-term effectiveness				
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mold(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	Safety	Quality of life
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 *Phleum pratense* 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 (*Phleum pratense* 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					

Table 1b Continued

Study (First author, year, country)	Allergen(s) type								Allergen no.		Comparator			AIT Protocol											Short-term effectiveness			Long-term effectiveness				
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mold(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	Safety	Quality of life
Feliziani, 1995, Italy	X								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	
Frølund, 2010, Austria, Denmark & UK	X								X		X			X	X							4 y	SQ-standardized grass allergy immunotherapy tablet (AIT), Grazax (*Phleum pratense* 75,000 SQ-T/2800 BAU; ALK, Denmark).								X
Guez, 2000, France					X				X		X											24 m	*D. pteronysinus* and *D. farinae* 50/50 extract	X	X					X	
Halken, 2010, Germany, Denmark, Poland, France & Spain	X								X		X			X	X							10 m	five-grass pollen 300IR tablets (Stallergènes SA, France)	X						X	
Hirsch, 1997, Germany					X				X		X											12 m	Purified *D. pteronysinus* extract in 50% aqueous glycerol (cumulative dose 570 jag) (Allergopharma J. Ganzer KG, Reinhek, FRG)	X	X						
Horak, 1998, Austria		X							X		X											4m	Biologically standardized *Betula Alba* Alergia e Immunologia Abello SA	X						X	
Horak, 2009, Austria	X								X		X											4m	300-IR 5 grass pollen tablet (orchard, meadow, perennial rye, sweet vernal, timothy)	X						X	
Hordijk, 1998, the Netherlands	X								X		X				X							10 m	Glycerinated (50% w/v) five-grass pollen extract (*Anthoxanthum odoratum* (Sweet vernal grass), *Cynodon dactylon* (Bermuda grass), *Dactylis glomerata* (Orchard grass), *Holcus lanatus* (Velvet grass) and *Phleum pratense* (Timothy grass)) (9,500 BU/ml) (Oralgen) (ARTU Biologicals Europe B.V., Lelytad, The Netherlands)	X						X	

Table 1b Continued

Study (First author, year, country)	Allergen(s) type								Allergen no.		Comparator			AIT Protocol											Short-term effectiveness			Long-term effectiveness				
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mold(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	Safety	Quality of life
Ibanez, 2007, Spain & Germany	X								X													28 d	Orodispersible grass allergen tablet (75,000 SQ-T; 15 Ig *P. pratense* major allergen (Phl p 5)) (Grazax) ALK-Abello A/S, Horsholm, Denmark)							X	
Ippoliti, 2003, Italy					X				X		X											6 m	*D. pteronysinus* extract	X							
Kaluzinska-Parzyzek, 2011, Poland (Polish, translated)	X								X		X			X	X			X				2 y	Staloral 300 IR (Stallergenes)								
La Rosa, 1999, Italy & France		X							X		X											2 y	*P judaica* extract (Stallergènes, Antony, France) in drops	X	X					X	
Marcucci, 2003, Italy					X				X		X											1 y	house dust mite allergens (1 ml of the top-dose vial 1000 STU/ml/4 Ig of the major mite allergen Group 1 and 2 Ig of the major mite allergen Group 2)								
Moreno-Ancillo, 2007, Spain	X									X	X			X	X							10 m	2 µg of grass Group 5 and 3 µg of Olive europaea Ole e 1 (daily)	X	X	X				X	X
Mosbech, 2014, Denmark, Italy, Germany & France					X				X		X											1 y	Oral lyophilisates containing *D. pteronysinus* and *D. farinae* in a 1:1 ratio. Three active strengths were investigated: 1, 3, and 6 SQ-HDM.			X				X	X
Mosges, 2007, Germany	X									X	X											9 m	Grass and rye pollen extract mixture solution (Staloral(r) (Stallergenes, Antony, France)) and a tablet (freeze-dried pollen extract)		X	X				X	

Table 1b Continued

Study (First author, year, country)	Allergen(s) type								Allergen no.		Comparator			AIT Protocol											Short-term effectiveness			Long-term effectiveness				
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mold(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	Safety	Quality of life
Okubo, 2008, Japan		X							X		X			X	X		X					7 m	Diluted cedar antigen extract (2 to 2000 JAU/ml)		X					X	X
Ott, 2009, Germany	X								X		X				X						X	3 y	Pollen extract mixture of five grasses (cocksfoot or orchard, meadow, perennialrye, sweet vernal and timothy grasses; Staloral, Stallergenes SA,France) (300 IR/ml, equivalent to 21 lg/ml of Phleum pratense major allergen)	X	X	X	X	X	X	X	
Nelson, 1993, US						X			X		X											105 d	Cat dander extract (total dose: 4.5 AU)	X						X	
Pajno, 2003, Italy			X						X		X	X	X	X	X							14 m	*P. judaica*, fluticasone	X	X						
Palma-Carlos, 2006, Italy	X								X		X		X	X								2 y	Mixture of carbamylated grass pollens (*Holcus lanatus* 33%, *Phleum pratense* 33%, and *Poa pratensis* 33%) in tablets	X						X	
Panzner, 2008, Czech Republic	X								X		X			X								1 y	Mixture of six grass pollen species extracts (oat grass (*Arrhenatherum elatius*), orchard grass (*Dactylis glomerata*), fescue (*Festuca sp.*), rye grass (*Lolium sp.*), timothy grass (*Phleum pratense*) and rye (*Secale cereale*)) (H-Al per os) (Sevapharma A.S., Prague, Czech Republic)	X	X					X	
Passalacqua, 1996, Italy					X				X		X											2 y	Monomeric allergoid tablets with *Dermatophagoides pteronysinus* and *D farina*	X						X	
Passalacqua, 1999, Italy	X								X		X			X					X			7 m	ALK-Abello (major allergen Par j) (0.016, 0.08, 0.4, 2, and 10 BU/mL)	X	X					X	
Passalacqua, 2006, Italy					X				X		X					X						2 y	Monomeric carbamylated grass pollen allergen (Lais)	X	X					X	X

Table 1b Continued

Study (First author, year, country)	Allergen(s) type								Allergen no.		Comparator			AIT Protocol											Short-term effectiveness			Long-term effectiveness				
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mold(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	Safety	Quality of life
Pfaar, 2008, Germany, Poland & Macedonia	X								X		X											2 y	Six-grass pollen mixture (high-dose)	X						X	
Pradalier, 1999, France	X								X		X											4.5 m	Five-grass-pollen extracts (orchard grass, meadow grass, ryegrass, sweet vernal grass, and timothy grass) (Stallerge Ánes SA, Antony, France)	X	X					X	
Purello-D'Ambrosio, 1999, Italy			X						X		X			X						X		6 m	*P. judaica* extract (five 3-ml vials: 0.016 BU/ml (vial 0), 0.08 (#1), 0.04 (#2), 2.00 (#3), and 10.00 (#4) in phyiologic saline with 50% v/v of glycerol & 0.4% w/v of phenol) (maximum concentration of major allergen Par j 1: 0.6 mg/ml)	X	X					X	
Qeuiros, 2013, Brazil & US					X				X		X		X									18 m	SLIT 1: *D. pteronysinus* extract (FDA Allergenic Ltda, Rio de Janeiro, Brazil) SLIT 2: *Dpt plus* mixed respiratory bacterial (MRB) (FDA Allergenic Ltda)			X				X	
Rak, 2006, UK	X								X		X											174 d	Grass pollen allergen tablets (2,500, 25,000, and 75,000 SQ-T)								X
Roder, 2007, The Netherlands	X								X		X					X						2 y	Aqueous extracts of 5 grass pollen (*Lollium perenne*, *Phleum pratense*, *Dactylis glomeratein*, *Anthoxantum odoratum*, *Holcus lanatus*) Oralgen grass pollen, Artu Biologicals	X	X					X	X
Rolinck-Werninghaus, 2004, Germany	X								X		X					XX						32 m	Pangramin (0.5 lg major allergens) (ALK-SCHERAX) three times weekly	X	X					X	

Table 1b Continued

Study (First author, year, country)	Allergen(s) type								Allergen no.		Comparator			AIT Protocol												Short-term effectiveness			Long-term effectiveness				
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mold(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	Safety	Quality of life
Sabbah, 1994, France	X								X		X											4 m	Five-grass pollen extracts in glycerol-saline diluent (from 1 drop of 1 IR/ml up to 20 drops of 100 IR/ml)	X	X					X	
Stelmach, 2011, Poland	X								X		X			X	X							2 y	Staloral 300 IR with five grass pollen (*Dactylis glomerata*, *Anthoxanthum odoratum*, *Lolium perenne*, *Poa pratensis* and *Phleum pretense*)	X	X					X	
Tari, 1990, Italy					X				X		X											18 m	Graded courses of aqueous mite extract with 0.4% phenol	X						X	
Valovirta, 2006, Finland		X							X		X		X									19 m	Intervention arm #1: *Betula verrucosa*, *Corylus avellana* and *Alnus glutinosa* (weekly dose: 24 000 SQ-U); intervention arm #2: *Betula verrucosa*, *Corylus avellana* and *Alnus glutinosa* (weekly dose: 200,000 SQ-U)	X	X					X	
Van Niekerk, 1987, South Africa	X								X		X											24 m	Mixture of aqueous extracts of twelve grass pollens (B2 grasses) (Bencard, UK), plus Bermuda grass pollen and maize pollen in phosphate buffered phyiological saline with 0 5% w/v phenol identical to Bencard SDV® vaccine (Beechams, UK)	X						X	
Vourdas, 1998, Greece & France		X							X		X											2 y	Olive pollen extract (major allergen Ole e 1 13.5 jig/ml (100 IR/ml)) (four concentrations: 1, 10, 100, and 300 IR/ml) (Stallergenes SA)	X	X					X	
Wang, 2013, China					X				X		X											6 m	Mixture of *D. pteronysinus* and *D. farinae* in 50% glycerol solution (Zhejiang Wolwo BioPharmaceutical Co., Ltd., China) (five treatment dosages with different concentrations: 0.75 lg/ml, 7.5 lg/ml, 75 lg/ml, 250 lg/ml, and 750 lg/ml)	X	X					X	

Table 1b Continued

Study (First author, year, country)	Allergen(s) type								Allergen no.		Comparator			AIT Protocol											Short-term effectiveness			Long-term effectiveness				
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mold(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	Safety	Quality of life
Wahn, 2012, Germany & Poland	X								X		X			X	X							8 m	Aqueous grass pollen preparation containing 6 species (*Dactylis glomerata*, *Festuca pratensis*, *Holcus lanatus*, *Lolium perenne*, *Phleum pratense*, and *Poa pratensis*) in a water/glycerol solution with phosphate-buffered saline (40 µg per maintenance dose) Allergopharma Joachim Ganzer KG, Reinbek, German			X				x	
Wahn, 2009, Denmark & France	X								X		X			X	X							Approx 5-6 m	Aqueous mixture of 5 grass pollen extracts (orchard, meadow, perennial rye, sweet vernal, and timothy; Stallergenes SA, Antony, France) (300 IR)	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.

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

Study (First author, year, country)	Allergen(s) type								Aller-gen no		Route AIT			Compar-ator			AIT Protocol												Short term effective-ness			Long term effective-ness				
	Grass pollen's	Tree pollens	Weeds	Moulds	House dust mite	cat	dog	other (s)	single	Multiple	SCIT	SLIT	ILIT	placebo	routine care	active	Pre-seasonal	Co-seasonal	Continuous	Conventional	Cluster	Semi-rush	Rush	Ultra rush	Duration of Rx	Product type/Name (manifacturer)				Symptom score	Medication score	Combined score	Symptom score	Meidication score	Combined score	Safety	Quality of life
Hylander et al, 2016, Spain	X	X							X				X	X			X				X				2 mos	aluminium hydroxide adsorbed, depot birch- or grass-pollen vaccine / Alutard (ALK Abéllo)				X	X					X	
Senti et al, 2012, Switzerland						X			X				X	X					X		X				2 mos	recombinant major cat dander allergen Fel d 1 fused to a modular antigen 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.

Study name	Std diff in means	Lower limit	Upper limit	Treatment	Control	Relative weight
Amar 2009	0.030	-0.625	0.684	19	17	1.39
Andre 2003	-0.449	-0.848	-0.050	48	51	2.13
Ariano 2001	-2.274	-3.398	-1.149	10	10	0.67
Bahceciler 2001	0.333	-0.689	1.354	8	7	0.77
Bowen 2004	-0.433	-0.888	0.022	37	39	1.94
Bufe 2004	-0.058	-0.399	0.284	68	64	2.32
Bufe 2009	-0.221	-0.476	0.034	117	121	2.62
Caffarelli 2000	-0.453	-1.134	0.228	17	17	1.33
Cortellini 2010	-1.457	-2.310	-0.604	15	12	1.00
Creticos 2014	-0.297	-0.487	-0.107	218	211	2.81
Dahl 2006a	-0.637	-1.074	-0.199	61	32	2.00
Dahl 2006b	-0.519	-0.687	-0.352	282	286	2.88
de Blay 2003	-0.167	-0.624	0.289	33	42	1.94
de Bot 2011	0.069	-0.192	0.330	110	116	2.60
Didier 2007	-0.434	-0.670	-0.198	136	148	2.68
Drachenbergh 2001	-0.268	-0.921	0.386	37	12	1.39
Durham 2006	-0.229	-0.473	0.015	131	129	2.65
Feliziani 1995	-1.028	-1.744	-0.312	18	16	1.25
Guez 2000	-0.416	-0.883	0.051	36	36	1.90
Halken 2010	-0.437	-0.680	-0.193	131	135	2.65
Hirsch 1997	0.525	-0.329	1.378	12	10	1.00
Horak 2009	-0.778	-1.208	-0.347	45	44	2.02
Hordijk 1998	-0.575	-1.050	-0.100	35	36	1.88
La Rosa 1999	-0.249	-0.934	0.437	16	17	1.32
Marcucci 2003	-0.235	-1.041	0.571	13	11	1.08
Nelson 1993	-0.570	-1.194	0.055	20	21	1.46
Ott 2009	-0.515	-0.829	-0.202	123	60	2.42
Paino 2003	-0.850	-1.638	-0.061	14	13	1.11
Palma Carlos 2006	-0.585	-1.283	0.112	17	16	1.29
Panzner 2008	-1.291	-2.025	-0.556	20	15	1.21
Passalacqua 1998	-1.327	-2.321	-0.332	10	9	0.80
Passalacqua 1999	-0.018	-0.734	0.698	15	15	1.25
Passalacqua 2006	-1.624	-2.228	-1.020	28	28	1.51
Pfaar 2008	-0.699	-1.125	-0.272	42	48	2.03
Pradalier 1999	-0.177	-0.527	0.173	63	63	2.29
Rolinck-Werninghaus 2004	0.047	-0.400	0.494	39	38	1.97
Stelmach 2012	-1.165	-1.862	-0.468	19	18	1.29
Tari 1990	-2.274	-2.935	-1.613	30	28	1.37
Valovirta 2006	-0.500	-1.032	0.032	27	29	1.71
Vourdas 1998	-0.170	-0.654	0.314	34	32	1.85
Wahn 2009	-0.435	-0.678	-0.192	131	135	2.65
Balda 1998*	-0.270	-0.655	0.115	49	56	2.17
Bodtger 2002*	-0.900	-1.616	-0.183	16	17	1.25
Bousquet 1990*	-1.371	-2.078	-0.663	20	18	1.27
Charpin 2007*	-0.694	-1.409	0.021	17	15	1.25
Corrigan 2005*	-0.410	-0.729	-0.091	77	77	2.40
Drachenberg 2001*	-0.467	-0.831	-0.104	74	50	2.25
Ferrer 2005*	-0.821	-1.451	-0.191	22	20	1.44
Frew 2006*	-0.493	-0.749	-0.238	187	89	2.61
Jutel 2005*	-0.563	-1.092	-0.033	29	28	1.71
Klimek 2014*	-0.599	-0.963	-0.234	61	60	2.24
Ortolani 1994*	-2.457	-3.335	-1.579	18	17	0.96
Tabar 2008*	0.313	-0.432	1.058	14	14	1.19
Varney 1991*	-0.466	-1.140	0.208	19	16	1.34
Varney 2003*	-1.588	-2.439	-0.737	15	13	1.00
Walker 2001*	-0.515	-1.249	0.219	17	13	1.21
Weyer 1981*	-0.554	-1.250	0.141	17	16	1.29
Zenner 1997*	-0.453	-0.894	-0.012	41	40	1.99
	-0.527	-0.631	-0.424	2978	2746	

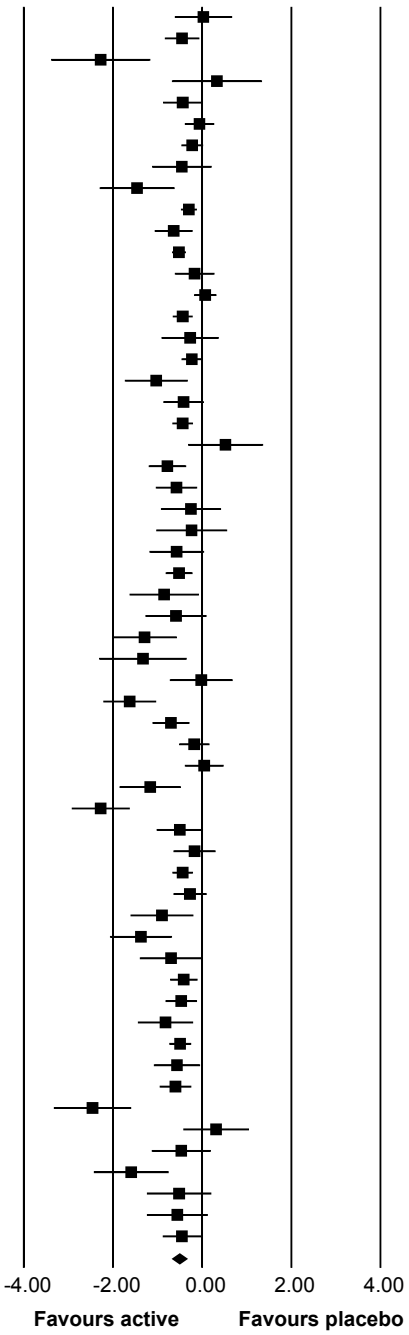


Figure 2 Meta-analysis of double-blind RCTs comparing symptom scores between AIT (SCIT or SLIT) and placebo groups (random-effects model). Heterogeneity: $\tau^2 = 0.090$; $\chi^2 = 173.586$, df = 57 (P<0.0001); $I^2 = 67\%$; Test for overall effect: Z = -9.992 (P<0.0001); *denotes SCIT studies

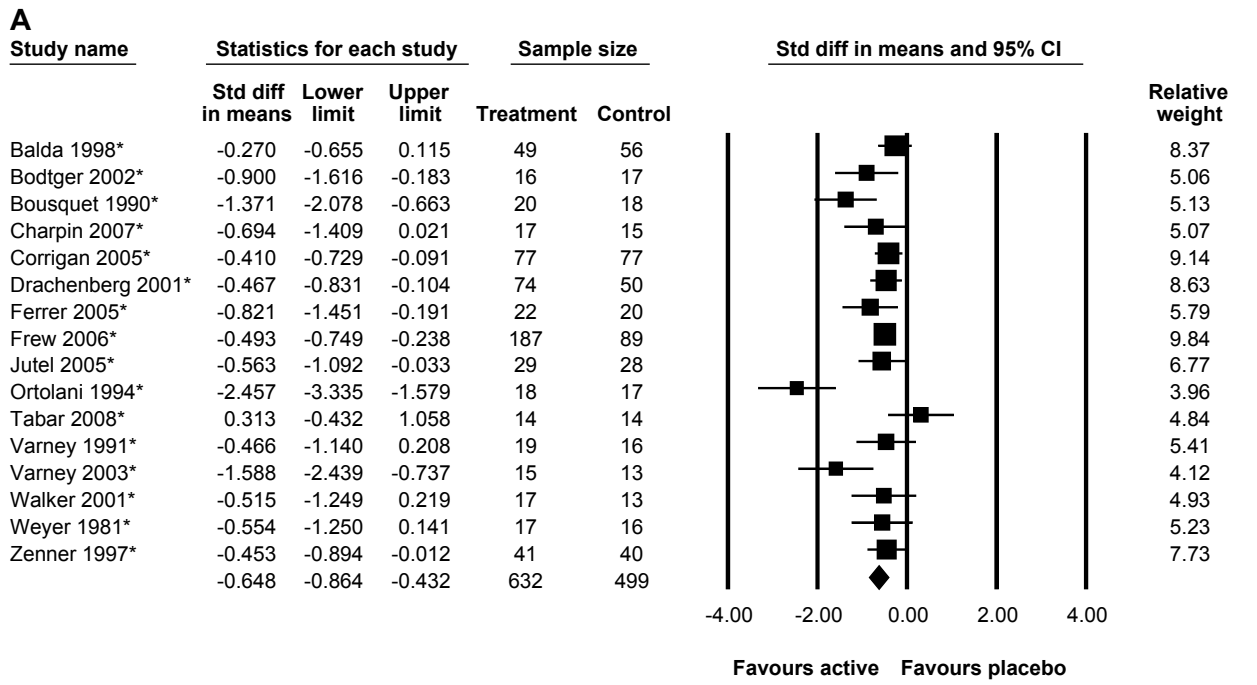


Figure 3 Meta-analysis of double-blind RCTs comparing symptom scores between (a) SCIT and placebo groups and (b) SLIT and placebo group (random-effects models). A: Heterogeneity: τ^2 = 0.106; χ^2 = 39.357, df = 15 (P<0.001); I^2 = 62%; Test for overall effect: Z = -5.875 (P<0.0001). B: Heterogeneity: τ^2 = 0.088; χ^2 = 129.171, df = 40 (P<0.0001); I^2 = 69%; Test for overall effect: Z = -7.855 (P<0.0001); *denotes SCIT studies

SMD -0.81 (95% CI -1.41, -0.20) for perennial allergens (Appendix 5.4, Figures S6a and b).

- 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) (Appendix 5.4, Figures S7a and b), 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 (Appendix 5.4, Figures S8a and b), 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) (Appendix 5.4, Figures S9a and b), 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 (Appendix 5.4, Figures S10a and b), 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 (Appendix 5.4, Figures S11a, b, c, d and e),

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.

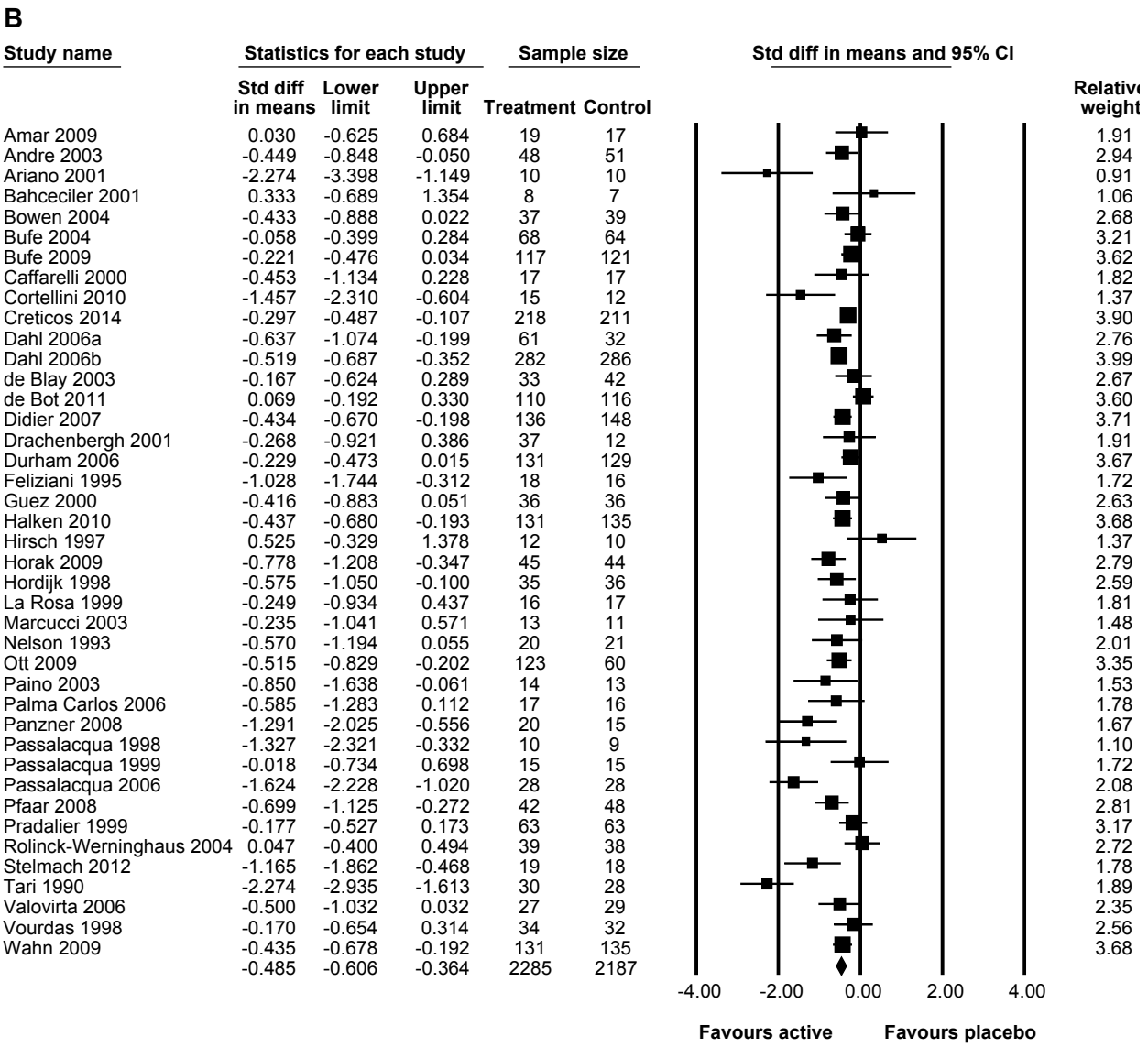


Figure 3 Continued.

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

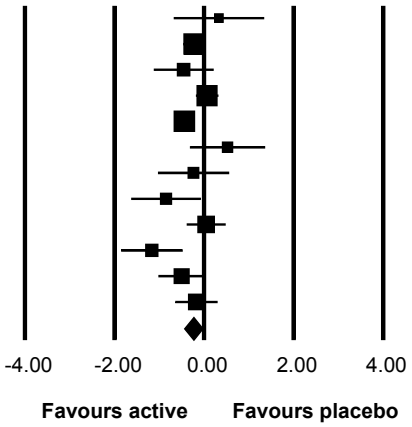
Sensitivity analysis, performed by excluding all studies at high ROB, gave an SMD of -0.35 (95% CI -0.46, -0.24) (Appendix 5.4, Figure S12).

Assessment of publication bias

The Funnel plot revealed evidence of potential publication bias (Appendix 5.4, Figure S13) which

A

Study name	Std diff in means	Lower limit	Upper limit	Treatment	Control	Relative weight
Bahceciler 2001	0.333	-0.689	1.354	8	7	3.32
Bufe 2009	-0.221	-0.476	0.034	117	121	14.38
Caffarelli 2000	-0.453	-1.134	0.228	17	17	6.10
de Bot 2011	0.069	-0.192	0.330	110	116	14.23
Halken 2010	-0.437	-0.680	-0.193	131	135	14.67
Hirsch 1997	0.525	-0.329	1.378	12	10	4.41
Marcucci 2003	-0.235	-1.041	0.571	13	11	4.81
Paino 2003	-0.850	-1.638	-0.061	14	13	4.97
Rolinck-Werninghaus 2004	0.047	-0.400	0.494	39	38	9.85
Stelmach 2012	-1.165	-1.862	-0.468	19	18	5.90
Valovirta 2006	-0.500	-1.032	0.032	27	29	8.24
Vourdas 1998	-0.170	-0.654	0.314	34	32	9.13
	-0.254	-0.459	-0.048	541	547	



B

Study name	Std diff in means	Lower limit	Upper limit	Treatment	Control	Relative weight
Amar 2009	0.030	-0.625	0.684	19	17	2.93
Creticos 2014	-0.297	-0.487	-0.107	218	211	7.45
Dahl 2006a	-0.637	-1.074	-0.199	61	32	4.62
Dahl 2006b	-0.519	-0.687	-0.352	282	286	7.70
Didier 2007	-0.434	-0.670	-0.198	136	148	6.93
Durham 2006	-0.229	-0.473	0.015	131	129	6.82
Horak 2009	-0.778	-1.208	-0.347	45	44	4.69
Hordijk 1998	-0.575	-1.050	-0.100	35	36	4.27
Nelson 1993	-0.570	-1.194	0.055	20	21	3.11
Palma Carlos 2006	-0.585	-1.283	0.112	17	16	2.68
Passalacqua 1999	-0.018	-0.734	0.698	15	15	2.59
Passalacqua 2006	-1.624	-2.228	-1.020	28	28	3.24
Balda 1998*	-0.270	-0.655	0.115	49	56	5.17
Bodtger 2002*	-0.900	-1.616	-0.183	16	17	2.59
Charpin 2007*	-0.694	-1.409	0.021	17	15	2.59
Corrigan 2005*	-0.410	-0.729	-0.091	77	77	5.92
Drachenberg 2001*	-0.467	-0.831	-0.104	74	50	5.41
Frew 2006*	-0.493	-0.749	-0.238	187	89	6.68
Klimek 2014*	-0.599	-0.963	-0.234	61	60	5.40
Ortolani 1994*	-2.457	-3.335	-1.579	18	17	1.91
Varney 1991*	-0.466	-1.140	0.208	19	16	2.81
Varney 2003*	-1.588	-2.439	-0.737	15	13	2.00
Walker 2001*	-0.515	-1.249	0.219	17	13	2.50
	-0.559	-0.696	-0.421	1557	1406	

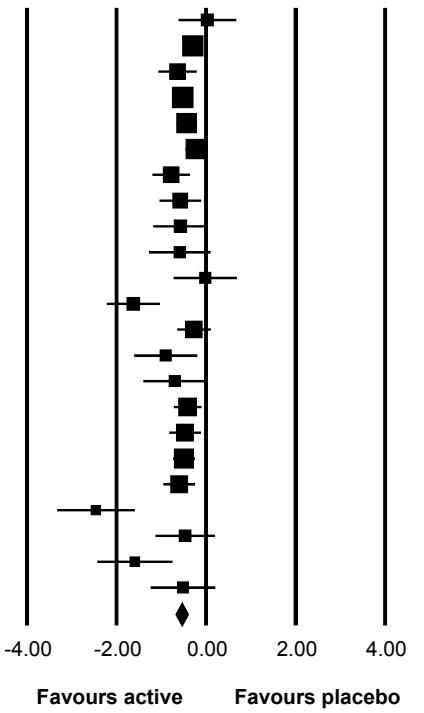


Figure 4 Meta-analysis of double-blind RCTs comparing symptom scores between AIT (SCIT or SLIT) and placebo group in (a) those <18 years old and (b) those≥18 years old (random-effects models). A: Heterogeneity: $\tau^2 = 0.059$; $\chi^2 = 24.209$, df = 11 (P<0.012); $I^2 = 54\%$; Test for overall effect: 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.

Study name	Std diff in means	Lower limit	Upper limit	Treatment	Control	Relative weight
Amar 2009	0.338	-0.321	0.997	19	17	1.77
Andre 2003	-0.502	-0.902	-0.101	48	51	2.86
Ariano 2001	-0.743	-1.649	0.163	10	10	1.15
Bahceciler 2001	-0.280	-1.300	0.739	8	7	0.96
Bowen 2004	-0.147	-0.598	0.303	37	39	2.61
Bufe 2004	0.316	-0.028	0.659	68	64	3.16
Bufe 2009	-0.123	-0.377	0.132	117	121	3.64
Caffarelli 2000	-0.135	-0.808	0.538	17	17	1.73
Dahl 2006a	-0.453	-0.886	-0.021	61	32	2.69
Dahl 2006b	-0.405	-0.571	-0.239	282	286	4.07
de Blay 2003	-0.575	-1.040	-0.109	33	42	2.54
Drachenberg 2001	-0.544	-1.204	0.116	37	12	1.77
Durham 2006	-0.278	-0.523	-0.034	131	129	3.69
Feliziani 1995	-1.322	-2.065	-0.579	18	16	1.52
Guez 2000	-0.323	-0.788	0.142	36	36	2.54
Hordijk 1998	-0.364	-0.833	0.105	35	36	2.52
La Rosa 1999	-0.020	-0.703	0.662	16	17	1.70
Marcucci 2003	-0.749	-1.579	0.081	13	11	1.31
Ott 2009	0.067	-0.242	0.375	123	60	3.34
Pajno 2003	-1.273	-2.100	-0.445	14	13	1.31
Palma Carlos 2006	-0.571	-1.268	0.125	17	16	1.65
Passalacqua 1999	-0.710	-1.448	0.028	15	15	1.54
Passalacqua 2006	-1.409	-1.994	-0.823	28	28	2.03
Pradalier 1999	-0.144	-0.493	0.206	63	63	3.12
Rolinck-Werninghaus 2004	-0.083	-0.530	0.364	39	38	2.63
Stelmach 2012	0.242	-0.405	0.889	19	18	1.81
Valovirta 2006	-0.246	-0.772	0.280	27	29	2.27
Vourdas 1998	-0.105	-0.588	0.378	34	32	2.46
Wahn 2009	-0.302	-0.544	-0.060	131	135	3.70
Balda 1998*	-0.255	-0.640	0.130	49	56	2.94
Bodtger 2002*	-0.591	-1.278	0.096	17	17	1.68
Bousquet 1990*	-0.620	-1.272	0.032	20	18	1.79
Charpin 2007*	-0.293	-0.991	0.405	17	15	1.65
Corrigan 2005*	-0.291	-0.609	0.026	77	77	3.30
Dolz 1996*	-3.663	-4.895	-2.431	18	10	0.71
Drachenber 2001*	-0.231	-0.591	0.129	74	50	3.07
Ferrer 2005*	-0.460	-1.073	0.154	22	20	1.93
Frew 2006*	-0.432	-0.687	-0.177	187	89	3.63
Jutel 2005*	-0.223	-0.744	0.298	29	28	2.29
Mirone 2004*	-0.614	-1.451	0.223	11	12	1.29
Tabar 2008*	0.341	-0.405	1.087	14	14	1.51
Varney 1991*	-1.196	-1.917	-0.474	19	16	1.58
Varney 2003*	-0.267	-1.013	0.479	15	13	1.51
Walker 2001*	-0.963	-1.736	-0.191	16	13	1.44
Weyer 1981*	-0.822	-1.533	-0.111	17	16	1.61
	-0.375	-0.487	-0.262	2098	1854	

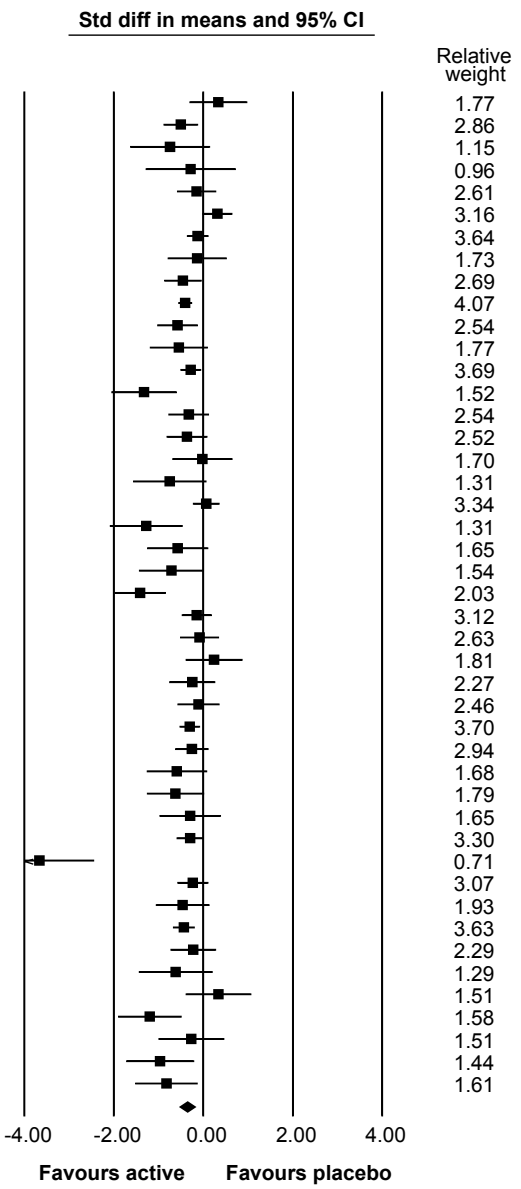


Figure 5 Meta-analysis of double-blind RCTs studies comparing medication scores between AIT (SCIT or SLIT) and placebo groups (random-effects model). Heterogeneity: $\tau^2 = 0.074$; $\chi^2 = 110.337$, df = 44 (P<0.0001); $I^2 = 60\%$; Test for overall effect: Z = -6.502 (P<0.0001) *denotes SCIT studies

was also suggested by the Begg (P=0.004) and Egger (P=0.03) tests.

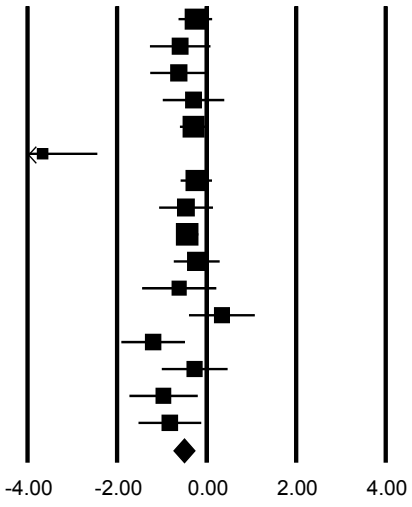
Subgroup analyses

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 (Appendix 5.4, Figure S14a and b), 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 (Appendix 5.4, Figure S15a and b).

A

Study name	Std diff in means	Lower limit	Upper limit	Sample size: Treatment	Sample size: Control	Relative weight
Balda 1998*	-0.255	-0.640	0.130	49	56	8.50
Bodtger 2002*	-0.591	-1.278	0.096	17	17	5.63
Bousquet 1990*	-0.620	-1.272	0.032	20	18	5.92
Charpin 2007*	-0.293	-0.991	0.405	17	15	5.54
Corrigan 2005*	-0.291	-0.609	0.026	77	77	9.19
Dolz 1996*	-3.663	-4.895	-2.431	18	10	2.69
Drachenber 2001*	-0.231	-0.591	0.129	74	50	8.76
Ferrer 2005*	-0.460	-1.073	0.154	22	20	6.25
Frew 2006*	-0.432	-0.687	-0.177	187	89	9.79
Jutel 2005*	-0.223	-0.744	0.298	29	28	7.12
Mirone 2004*	-0.614	-1.451	0.223	11	12	4.54
Tabar 2008*	0.341	-0.405	1.087	14	14	5.17
Varney 1991*	-1.196	-1.917	-0.474	19	16	5.35
Varney 2003*	-0.267	-1.013	0.479	15	13	5.17
Walker 2001*	-0.963	-1.736	-0.191	16	13	4.97
Weyer 1981*	-0.822	-1.533	-0.111	17	16	5.43
	-0.521	-0.753	-0.289	602	464	



B

Study name	Std diff in means	Lower limit	Upper limit	Sample size: Treatment	Sample size: Control	Relative weight
Amar 2009	0.338	-0.321	0.997	19	17	2.46
Andre 2003	-0.502	-0.902	-0.101	48	51	4.24
Ariano 2001	-0.743	-1.649	0.163	10	10	1.55
Bahceciler 2001	-0.280	-1.300	0.739	8	7	1.28
Bowen 2004	-0.147	-0.598	0.303	37	39	3.81
Bufe 2004	0.316	-0.028	0.659	68	64	4.77
Bufe 2009	-0.123	-0.377	0.132	117	121	5.67
Caffarelli 2000	-0.135	-0.808	0.538	17	17	2.40
Dahl 2006a	-0.453	-0.886	-0.021	61	32	3.96
Dahl 2006b	-0.405	-0.571	-0.239	282	286	6.52
de Blay 2003	-0.575	-1.040	-0.109	33	42	3.70
Drachenberg 2001	-0.544	-1.204	0.116	37	12	2.46
Durham 2006	-0.278	-0.523	-0.034	131	129	5.77
Feliziani 1995	-1.322	-2.065	-0.579	18	16	2.09
Guez 2000	-0.323	-0.788	0.142	36	36	3.70
Hordijk 1998	-0.364	-0.833	0.105	35	36	3.67
La Rosa 1999	-0.020	-0.703	0.662	16	17	2.35
Marcucci 2003	-0.749	-1.579	0.081	13	11	1.77
Ott 2009	0.067	-0.242	0.375	123	60	5.12
Pajno 2003	-1.273	-2.100	-0.445	14	13	1.78
Palma Carlos 2006	-0.571	-1.268	0.125	17	16	2.29
Passalacqua 1999	-0.710	-1.448	0.028	15	15	2.11
Passalacqua 2006	-1.409	-1.994	-0.823	28	28	2.87
Pradalier 1999	-0.144	-0.493	0.206	63	63	4.71
Rolinck-Werninghaus 2004	-0.083	-0.530	0.364	39	38	3.84
Stelmach 2012	0.242	-0.405	0.889	19	18	2.52
Valovirta 2006	-0.246	-0.772	0.280	27	29	3.25
Vourdas 1998	-0.105	-0.588	0.378	34	32	3.56
Wahn 2009	-0.302	-0.544	-0.060	131	135	5.80
	-0.311	-0.438	-0.184	1496	1390	

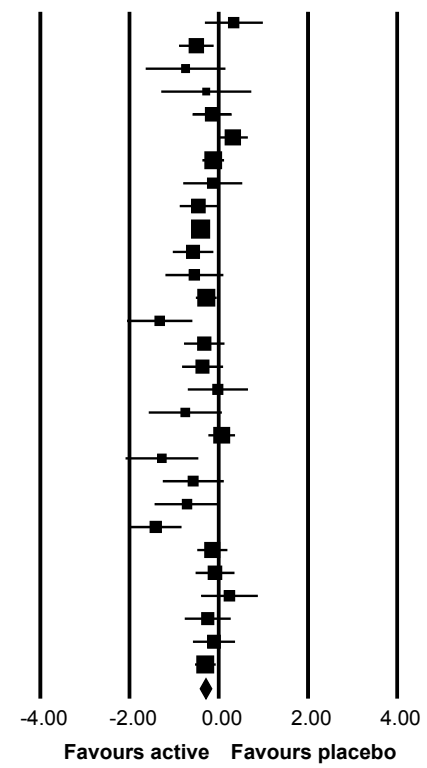


Figure 6 Meta-analysis of double-blind RCTs comparing medication scores between (a) SCIT and placebo groups and (b) SLIT and placebo groups (random-effects models). A: Heterogeneity: $\tau^2 = 0.126$; $\chi^2 = 42.241$, df = 15 (P<0.0001); $I^2 = 64\%$; Test for overall effect: Z = -4.399 (P<0.0001) *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)

- 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 (Appendix 5.4, Figure S16a and b), 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) (Appendix 5.4, Figure S17a and b).
- 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) (Appendix 5.4, Figure S18a and b), 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 (Appendix 5.4, Figure S19a and b), 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 (Appendix 5.4, Figure S20a and b), 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) (Appendix 5.4, Figure S21a and b).
- 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 (Appendix 5.4, Figure S22a and b), 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) (Appendix 5.4, Figures S23a, b, c, d and e), 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, (Appendix 5.4, Figure S24) 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 (Appendix 5.4, Figures S25a and b), 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) (Appendix 5.4, Figures S26a and b), 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

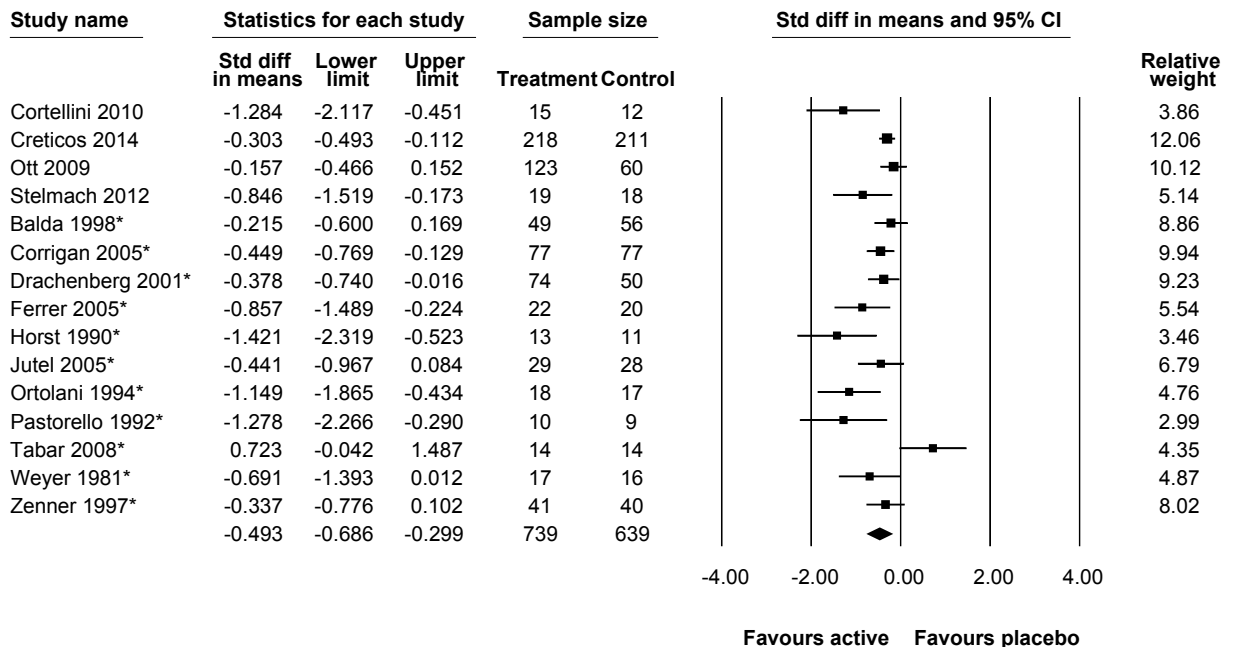


Figure 7 Meta-analysis of double-blind RCTs studies comparing combined symptom and medication scores between AIT (SCIT or SLIT) and placebo groups (random-effects model). Heterogeneity: $\tau^2 = 0.071$; $\chi^2 = 33.631$, df = 14 (P<0.002); $I^2 = 58\%$; Test for overall effect: Z = -4.997 (P<0.001) *denotes SCIT studies

(95% CI -0.79, -0.19) for allergoids and SMD -0.36 (95% CI -0.73, 0.03) (Appendix 5.4, Figures S27a and b), 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) (Appendix 5.4, Figures S28a, b, c and d), 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 (109, 159) 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 (Appendix 5.5, 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

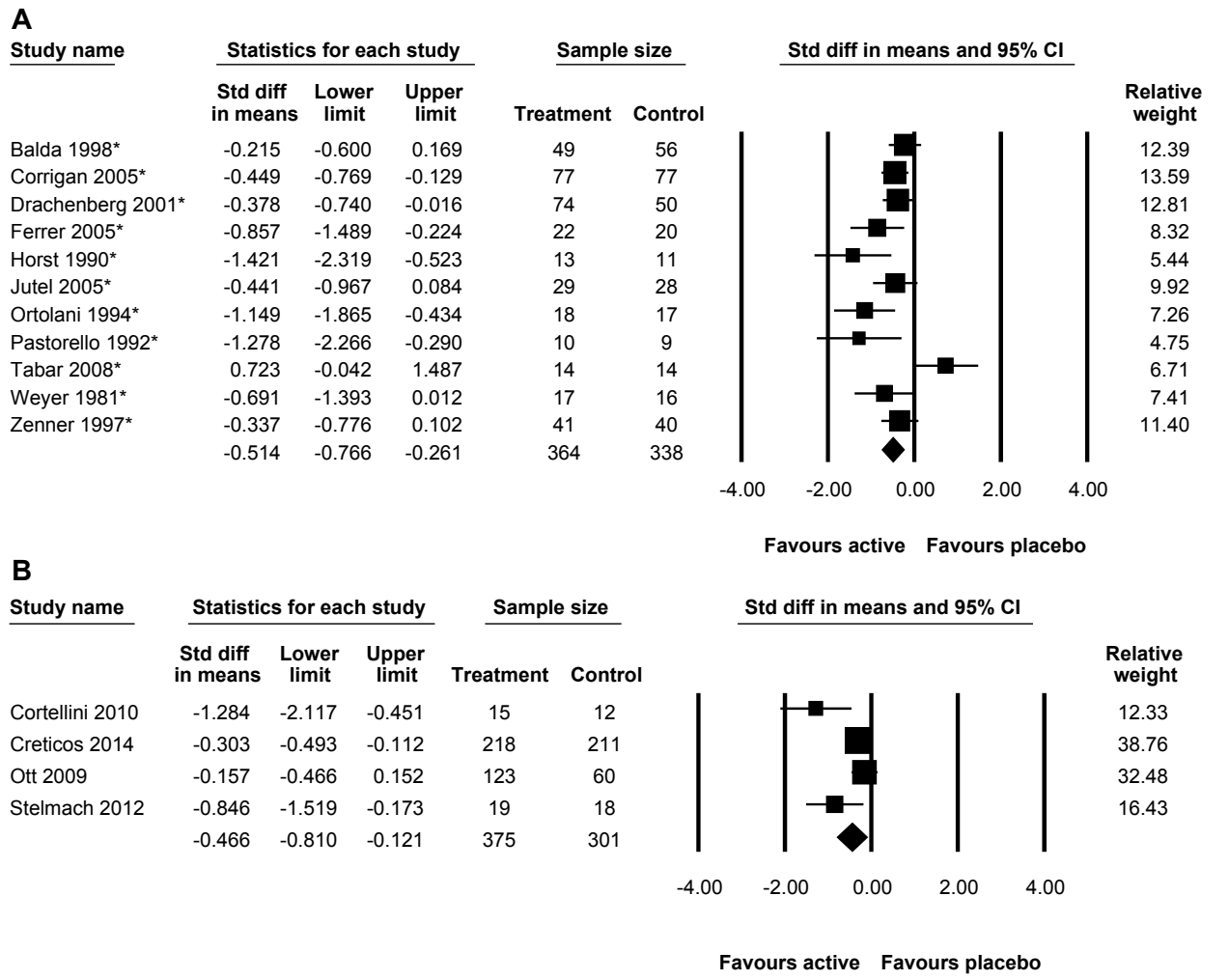


Figure 8 Meta-analysis of double-blind RCTs comparing combined symptom and medication scores between (a) SCIT and placebo groups and (b) SLIT and placebo groups (random-effects models). A: Heterogeneity: τ^2 = 0.096; χ^2 = 23.777, df = 10 (P<0.008); I^2 = 58%; Test for overall effect: Z = -3.984 (P<0.0001) *denotes SCIT studies. B: Heterogeneity: τ^2 = 0.070; χ^2 = 8.584, df = 3 (P<0.035); I^2 = 65%; Test for overall effect: Z = -2.648 (P<0.008)

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) (Appendix 5.5, 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) (Appendix 5.5, 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 (Appendix 5.5, Table S2n) (160-178). Studies were based in a range of countries. Seven of the studies reported results against disease

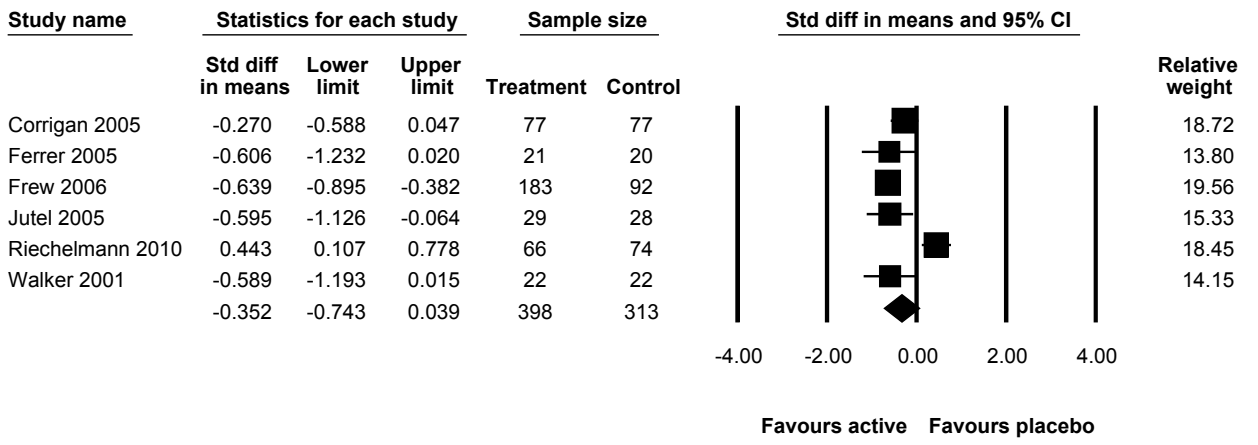


Figure 9 Meta-analysis of double-blind RCTs comparing quality of life scores between SCIT and placebo groups (random-effects models). Heterogeneity: $\tau^2 = 0.186$; $\chi^2 = 28.432$, df = 5 (P<0.0001); $I^2 = 82\%$; Test for overall effect: Z = -1.764 (P<0.078)

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 (Appendix 5.5).

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 a study in adult patients with rhino-conjunctivitis performed in the U.K. ICERs of SCIT were calculated using health care data from 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 (Appendix 5.5). 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) (Appendix 5.6, 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) (Appendix 5.6, 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) (Appendix 5.6, 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) (Appendix 5.6, 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) (Appendix 5.6, 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) (Appendix 5.6, 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) (Appendix 5.6, 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) (Appendix 5.6, Figure S3k).

Case series

Seven large case series were identified (179-185) (Appendix 5.5, 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 (Appendix 5.5). 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 fidnings 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.

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Contributorship

This review was drafted by S. Dhami, 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.

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Conflicts of interest

S. Dhami: 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 discose;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, personal fees from Novartis Pharma, personal fees from MEDA Pharma, grants and personal fees from Anergis S.A., personal fees from Sanofi US Services, 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, 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-Elberlink: 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-Alello; L. Zhang: has nothing to disclose; A. Sheikh: reports grants from EAACI, during the conduct of the study.

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