*Original submission to Allergy*

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

1Sangeeta Dhami, 2Artemisia Kakourou, 3 Felix Asamoah, 4 Ioana Agache, 5Susanne Lau, 6,7Marek Jutel,  8Antonella Muraro, 9Graham Roberts, 10Cezmi A. Akdis, 11Matteo Bonini, 12Ozlem Cavkaytar, 13Breda Flood, 6Pawel Gajdanowicz, 14Kenji Izuhara, 15Ömer Kalayci, 16Ralph Mosges,, 17Oscar Palomares, 18,19Oliver Pfaar, 6,7Sylwia Smolinska, 10Milena Sokolowska, 20Miqdad Asaria, 21Gopal Netuveli, 22Hader Zaman, 23Ather Akhlaq 24Aziz Sheikh

1Evidence-Based Health Care Ltd, UK; 2Department of Hygiene and Epidemiology, University of Ioannina School of Medicine, Ioannina, Greece; 3Centre for Environmental and Preventive Medicine, Wolfson Institute of Preventive Medicine Barts and the London School of Medicine and Dentistry Queen Mary University of London; 4Transylvania University Brasov, Faculty of Medicine, Department of Allergy and Clinical Immunology, Brasov, Romania; 5Department of Pediatric Pneumology and Immunology, Charité Universitätsmedizin, Berlin, Germany; 6Wroclaw Medical University, Poland; 7ALL-MED Medical Research Institute; 8Food Allergy Referral Centre Veneto Region, University Hospital of Padua, Italy; 9The David Hide Asthma and Allergy Research Centre, St Mary’s Hospital, Newport Isle of Wight, NIHR Respiratory Biomedical Research Unit, University Hospital Southampton NHS Foundation Trust, Southampton, UK, and Faculty of Medicine, University of Southampton, Southampton, UK; 10Swiss Institute for Allergy and Asthma Research, Christine Kühne-Center for Allergy Research and Education (CK-CARE), Davos, Switzerland; 11National Heart and Lung Institute, Imperial College London, UK; 12 Sami Ulus Women’s & Children’s Diseases Training and Research Hospital, Department of Allegy and Clinical Immunology, Ankara, TurkeyUlus Women’s & Children’s Diseases Training and Research Hospital, Department of Pediatric Allergy and Immunology, Ankara, Turkey; 13European Federation of Allergy and Airways Diseases Patients Association; 14Saga Medical School, Japan; 15Hacettepe University, Ankara, Turkey; 16Institute of Medical Statistics, Informatics and Epidemiology (IMSIE), University of Cologne, Germany; 17Department of Biochemistry and Molecular Biology, Complutense University of Madrid, Spain; 18Department of Otorhinolaryngology, Head and Neck Surgery, Universitätsmedizin Mannheim, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany; 19.Center for Rhinology and Allergology, Wiesbaden, Germany.; 20Centre for Health Economics, University of York; 21Institute for Health and Human Development, University Of East London; 22Bradford School of Pharmacy; 23Health and Hospital Management Institute of Business Management, Korangi Creek, Karachi, Pakistan; 24Asthma UK Centre for Applied Research, The University of Edinburgh, Edinburgh.

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

**Abstract**

**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.

**Keywords:** allergy, allergen immunotherapy, asthma, cost-effectiveness, desensitization, effectiveness, exacerbations, lung function, quality of life, safety.

**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 phenotypesof 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 undertook a systematic review of primary studies on the effectiveness, cost-effectiveness and safety of AIT for allergic asthma in order 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 (see Appendix 1, Supplementary file). 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

|  |  |
| --- | --- |
| **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. |

**Box 1. Inclusion and exclusion criteria**

**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, 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 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)

**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 2, Supplementary file).

**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 (see 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 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, 1b, 1c and S1a, S1b, S1c (Supplementary file).

**Quality assessment**

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

**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 metaanalysis 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) (Figure S2a, Supplementary file).

*Publication bias*

The funnel plot showed possible publication bias as evidenced by an excess of small studies with large effect sizes (Figures S2b, Supplementary file). 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 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 (Figure S2c, Supplementary file), 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) (Figure S2d, Supplementary file)
* 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). (Figure S2e, Supplementary file)
* Monosensitized/mono-allergic versus polysensitized: there is evidence of AIT benefit in monosensitized/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) (Figure S2f, Supplementary file),

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 effect sizes (Figures S2g, Supplementary file), 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) (Figure S2h, Supplementary file), 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 andSMD -1.29 (95%CI -2.00, -0.59) for those receiving ≥3 years of treatment (Figure S2i, Supplementary file), 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) (Figure S2j, Supplementary file).
* Monosensitized and mono-allergic versus polysensitized: SMD -1.18 (95%CI -1.16, 0.13) in mono-sensitized and mono-allergic and the polysensitized group (SMD -0.36 (95%CI -2.11, 0.25)) in the polysensitized group (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 (2012) had a three year SLIT tablets or placebo treatment period in grass pollen allergic patients followed by a two-year blinded observation period when no active treatment was administered. 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 (see 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 (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), showeda large treatment effect with an SMD of -0.83 (95%CI -1.19, -0.47) in favor of SCIT (Figure 9).

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 2). 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 (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) (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) (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) (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) (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 (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 (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). (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) (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 (Leng 1990). 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) (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 (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 (Figure S4d)

**Cost-effectiveness**

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

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 (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) (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.(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) (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) . (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) (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) (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) (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 (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. 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.

**Interpretaion 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.

**Acknowledgments:** We would like to thank Debra De Silva, The Evidence centre for their assistance with data extraction and quality assessments; Z Sheikh for technical support. This study is part of the EAACI AIT guidelines project, chaired by Antonella Muraro and coordinated by Graham Roberts.

**Funding:** EAACI and BM4SIT project (grant number 601763) in the European Union's Seventh Framework Programme FP7.

**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:** **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, grants from Shino-test Co. Ltd,  outside the submitted work; Ö Kalayci: has nothing to disclose;Ralph 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; O Palomares: received research grants from Inmunotek S.L. under public collaborative projects from Spanish Ministry (MINECO)/CDTI: IPT-2012-0639-090000, IDI-20110410 and IDI-20141131,has received fees for giving scientific lectures from:Allergic Therapeutics, Amgen, Inmunotek S.L, Stallergenes and Novartis, has participated in advisory boards from Novartis; 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; S Smolinska: has nothing to disclose; M.Sokolowska: research fellowships and grants from European Academy of Allergy and Clinical Immunology (EAACI) and European Respiratory Society (ERS); M Asaria: reports payment from Evidence-Based Health Care Ltd during the conduct of the study; G Netuveli: has nothing to disclose; H Zaman: reports payment from Evidence-Based Health Care Ltd during the conduct of the study; A Akhlaq: has nothing to disclose; A Sheikh: reports grants from EAACI, during the conduct of the study.

**Additional material:**

Figures and tables for main paper

Appendix 1: Search strategy

Appendix 2: PRISMA Checklist

S1: Supplementary tables

S2: Supplementary figures for primary outcomes

S3: Safety tables and figures

S4: Supplementary figures for secondary outcomes

**References**

1. The Global Asthma Report 2014 http://www.globalasthmareport.org/burden/burden.php. 2014;

2. World Health Organization. Global surveillance, prevention and control of chronic respiratory diseases: a comprehensive approach, 2007.

3. Haldar P, Pavord I, Shaw D, Berry M, Thomas M, Brightling C. Cluster analysis and clinical asthma phenotypes. Am J Respir Crit Care Med. 2008 Aug;178(3):218–24.

4. Lötvall J, Akdis C, Bacharier L, Bjermer L, Casale T, Custovic A. Asthma endotypes: a new approach to classification of disease entities within the asthma syndrome. J Allergy Clin Immunol. 2011 Feb;127(2):355–60.

5. Gough H, Grabenhenrich L, Reich A, Eckers N, Nitsche O, Schramm D. Allergic multimorbidity of asthma, rhinitis and eczema over 20 years in the German birth cohort MAS. Pediatr Allergy Immunol. 2015;26(5):431–437.

6. Dhami S, Nurmatov U, Agache I, Lau S, Muraro A, Jutel M, Roberts G, Akdis C, Bonini M, Calderon M, Casale T, Cavkaytar O, Cox L, Demoly P, Flood B, Hamelmann E, Izuhara K, Kalayci Ö, Kleine-Tebbe J, Nieto A, Papadopoulos N, Pfaar O, Rosenwasser L, Ryan D, Schmidt-Weber C, Szefler S, Wahn U, van Wijk RG, Wilkinson J, Sheikh A. Allergen immunotherapy for allergic asthma: protocol for a systematic review. [Clin Transl Allergy.](https://www.ncbi.nlm.nih.gov/pubmed/26862389) 2016 Feb 9;6:5. doi: 10.1186/s13601-016-0094-y. eCollection 2015.

7. Passalacqua G, Baena-Cagnani CE,Bousquet J, Canonica GW, Casale TB, et al. Grading local side effects of sublingual immunotherapy for respiratory allergy: Speaking the same language http://www.jacionline.org/article/S0091-6749(13)00528-9/pdf.

8. World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System https://www.aaaai.org/Aaaai/media/MediaLibrary/PDF%20Documents/Immunotherapy%20Forms/7b-World-Allergy-Organization-Systemic-Reaction-Grading-systemx.pdf.

9. Cochrane Risk of bias tool http://handbook.cochrane.org/chapter\_8/table\_8\_5\_a\_the\_cochrane\_collaborations\_tool\_for\_assessing.htm.

10. CASP checklist for Economic evaluations http://media.wix.com/ugd/dded87\_3b2bd5743feb4b1aaac6ebdd68771d3f.pdf Last accessed on 3rd September 2015.

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

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

13. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. 1994;50(1088):101.

14. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. 1997;315(629):34.

15. Aas K. Hyposensitization in house dust allergy asthma. A double-blind controlled study with evaluation of the effect on bronchial sensitivity to house dust. Acta Paediatr Scand. May 1971;60(3):264–8.

16. Adkinson NF, Eggleston PA, Eney D, Goldstein EO, Schuberth KC, Bacon JR, et al. A controlled trial of immunotherapy for asthma in allergic children. N Engl J Med. 1997;336(5):324–31.

17. Alvarez-Cuesta E,Cuesta-Herranz J, Puyana-Ruiz J,Cuesta-Herranz C, Blanco-Quiros A. Monoclonal antibody-standardized cat extract immunotherapy: risk-benefit effects from a double-blind placebo study. J Allergy Clin Immunol. Mar 1994;93(3):556–66.

18. Alvarez MJ, Echechipia S, Garcia B, Tabar AI, Martin S, Rico P, et al. Liposome-entrapped D. pteronyssinus vaccination in mild asthma patients: effect of 1-year double-blind, placebo-controlled trial on inflammation, bronchial hyperresponsiveness and immediate and late bronchial responses to the allergen. Clin Exp Allergy. Nov 2002;32(11):1574–82.

19. Ameal A, Vega-Chicote JM, Fernandez S, Miranda A,Carmona MJ, Rondon MC, et al. Double-blind and placebo-controlled study to assess efficacy and safety of a modified allergen extract of Dermatophagoides pteronyssinus in allergic asthma. Allergy. Sep 2005;60(9):1178–83.

20. Armentia-Medina A, Tapias JA, Martin JF,Ventas P,Fernandez A. Immunotherapy with the storage mite Lepidoglyphus destructor. Allergol Immunopathol (Madr). 1995;23(5):211–23.

21. Arvidsson MB,Lowhagen O, Rak S. Allergen specific immunotherapy attenuates early and late phase reactions in lower airways of birch pollen asthmatic patients: a double blind placebo-controlled study. Allergy. Jan 2004;59(1):74–80.

22. Basomba A, Tabar AI, de Rojas DH, Garcia BE, Alamar R, Olaguibel JM, et al. Allergen vaccination with a liposome-encapsulated extract of Dermatophagoides pteronyssinus: a randomized, double-blind, placebo-controlled trial in asthmatic patients. J Allergy Clin Immunol. Jun 2002;109(6):943–8.

23. Blumberga G,Groes L,Haugaard L,Dahl R. Steroid-sparing effect of subcutaneous SQ-standardised specific immunotherapy in moderate and severe house dust mite allergic asthmatics. Allergy. Jul 2006;61(7):843–8.

24. Bodtger U, Poulsen LK, Jacobi, HH,Malling J. The safety and efficacy of subcutaneous birch pollen immunotherapy - a one-year, randomised, double-blind, placebo-controlled study. Allergy. Apr 2002;57(4):297–305.

25. Bousquet J, Calvayrac P, Guérin B, Hejjaoui A, Dhivert H, Hewitt B, et al. Immunotherapy with a standardized Dermatophagoides pteronyssinus extract. I. In vivo and in vitro parameters after a short course of treatment. J Allergy Clin Immunol. 1985;76(5):734–44.

26. Bousquet J, Hejjaoui A, Soussana M, et al. Double-blind, placebo-controlled immunotherapy with mixed grass-pollen allergoids IV. Comparison of the safety and efficacy of two dosages of a high-molecular-weight allergoid. J. Allergy Clin. Immunol. February 1990; volume 85 number 7

27. Cantani A, Ragno V, Monteleone MA, Lucenti P, Businco L. Enzyme potentiated desensitisation in children with asthma and mite allergy: a double blind study. Journal of Investigational Allergology and Clinical Immunology 1996;6: 270–6.

28. Chakraborty P, Roy I, Chatterjee S, Chanda S, Gupta-Bharracharya S. Phoenix sylvestris Roxb pollen allergy: a 2-year randomized controlled trial and follow-up study of immunotherapy in patients with seasonal allergy in an agricultural area of West Bengal, India. J Investig Allergol Clin Immunol. 2006;16(6):377–84.

29. Creticos PS, Reed CS, Norman PS, Khoury J, Adkinson NF, Buncher CR, et al. immunotherapy in adult asthma. New England Journal of Medicine 1996;334:501–6.

30. Dreborg S, Agrell B, Foucard T, Kjellman NI, Koivikko A, Nilsson S. A double-blind, multicenter immunotherapy trial in children, using a purified and standardized Cladosporium herbarum preparation. I. Clinical results. Allergy. 1986;41(2):131–40.

31. Dolz I, Martinez-Cocera C, Bartolome JM,Cimarra M. A double-blind, placebo-controlled study of immunotherapy with grass-pollen extract Alutard SQ during a 3-year period with initial rush immunotherapy. Allergy. Jul 1996;51(7):489–500.

32. D’Souza MF, Pepys J, Wells ID, Tai E, Palmer F, Overell BG, et al. Hyposensitisation with Dermatophagoides pteronyssinus in house dust allergy: a controlled study of clinical and immunological effects. Clinical Allergy 1973;3: 177–93.

33. Franco C, Barbadori S, Freshwater LL, Kordash TR. A double-blind, placebo controlled study of Alpare mite D. pteronyssinus immunotherapy in asthmatic patients. Allergologia et Immunopathologia 1995;23:58–66.

34. Gaddie J, Skinner C, Palmer KN. Hyposensitisation with house dust mite vaccine in bronchial asthma. Br Med J. Sep 1976; 4;2(6035):561–2.

35. Garcia-Robaina JC, Sanchez I, de la Torre F, Fernandez-Caldas E, Casanovas M. Successful management of mite-allergic asthma with modified extracts of Dermatophagoides pteronyssinus and Dermatophagoides farinae in a double-blind, placebo-controlled study. J Allergy Clin Immunol. Nov 2006;118(5):1026–32.

36. Haugaard L, Dahl R. Immunotherapy in patients allergic to cat and dog dander. I. Clinical results. Allergy. 1992;47(3):249–54.

37. Hedlin G, Willen S, Browaldh H, Hildebrand H, Holmgren D, Lindfors A. Immunotherapy in children with allergic asthma: effect on bronchial hyperreactivity and pharmacotherapy. Journal of Allergy and Clinical Immunology 1999;103(4):609–14.

38. Hui Y, Li L, Qian J, Guo Y, Zhang X. Efficacy analysis of three-year subcutaneous SQ-standardized specific immunotherapy in house dust mite-allergic children with asthma. Exp Ther Med. Mar 2014;7(3):630–4.

39. Kuna P, Alam R,Kuzminska B, Rozniecki J. The effect of preseasonal immunotherapy on the production of histamine-releasing factor (HRF) by mononuclear cells from patients with seasonal asthma: Results of a double-blind, placebo-controlled, randomized study. J Allergy Clin Immunol. 1989;83(4):816–24.

40. Kuna P, Kaczmarek J, Kupczyk M. Efficacy and safety of immunotherapy for allergies to Alternaria alternata in children. J Allergy Clin Immunol. Feb 2011;127(2):502-508-6.

41. Lewis H. Hyposensitisation in mite asthma. The Lancet. 1971 May

42. Leynadier F, Herman D, Vervloet D, Andre C. Specific immunotherapy with a standardized latex extract versus placebo in allergic healthcare workers. J Allergy Clin Immunol. 2000 Sep;106(3).::585-90.

43. Maestrelli P, Zanolla L, Pozzan M, Fabbri LM, asthma Regione Veneto Study Group on the "Effect of immunotherapy in allergic. Effect of specific immunotherapy added to pharmacologic treatment and allergen avoidance in asthmatic patients allergic to house dust mite. J Allergy Clin Immunol. Apr 2004;113(4):643–9.

44. Malling HJ, Dreborg S, Weeke B. Diagnosis and immunotherapy of mould allergy. V. Clinical efficacy and side effects of immunotherapy with Cladosporium herbarum. Allergy. Sep 1987;41(7):507–19.

45. Marques AR, Avila R. Results of a clinical trial with a Dermatophagoides pteronyssinus tyrosine adsorbed vaccine. Allergol Immunopathol (Madr). May 1978;6(3):231–5.

46. Mosbech H, Dreborg S,Frølund L, Ljungstedt-Påhlman I, Svendsen UG, Søborg M, et al. Hyposensitization in asthmatics with mPEG modified and unmodified house dust mite extract. I. Clinical effect evaluated by diary cards and a retrospective assessment. Allergy. 1989;44(7):487–98.

47. Mosbech H, Dirksen A, Dreborg S, Frolund L, Heinig JH, Svendsen UG, et al. Hyposensitization in asthmatics with mPEG-modified and unmodified house dust mite extract. IV. Occurrence and prediction of side effects. Allergy. Feb 1990;45(2):142–50.

48. Ohman JL, Findlay SR, Leitermann KM. Immunotherapy in cat-induced asthma. Double-blind trial with evaluation of in vivo and in vitro responses. J Allergy Clin Immunol. Sep 1984;74(3 Pt 1):230–9.

49. Olsen OT, Frølund L, Heinig J, Jacobsen L, Svendsen UG. A double-blind, randomized study investigating the efficacy and specificity of immunotherapy with Artemisia vulgaris or Phleum pratense/betula verrucosa. Allergol Immunopathol (Madr). 1995;23(2):73–8.

50. Newton DA, Maberley DJ,Wilson R. House dust mite hyposensitization. Br J Dis Chest. 1978;72(1):21–8.

51. Ortolani C, Pastorello E, Moss RB, Hsu YP, Restuccia M, Joppolo G, et al. Grass pollen immunotherapy: a single year double-blind, placebo-controlled study in patients with grass pollen-induced asthma and rhinitis. J Allergy Clin Immunol. Feb 1984;73(2):283–90.

52. Pauli G, Bessot JC, Bigot H, Delaume G, Hordle DA, Hirth C, et al. Clinical and immunologic evaluation of tyrosine-adsorbed Dermatophagoides pteronyssinus extract: a double-blind placebo-controlled trial. J Allergy Clin Immunol. 1984;74(4 Pt 1):524–35.

53. Pene J, Desroches A, Paradis L, Lebel B, Farce M, Nicodemus C. Immunotherapy with Fel d 1 peptides decreases IL-4 release by peripheral blood T cells of patients allergic to cats. J Allergy Clin Immunol. 1998 Oct;102(4).

54. Price JF, Warner JO, Hey EN, Turner MW, Soothill JF. A controlled trial of hyposensitization with adsorbed tyrosine Dermatophagoides pteronyssinus antigen in childhood asthma: in vivo aspects. Clin Allergy. May 1984;14(3):209–19.

55. Rak S, Heinrich C, Jacobsen L, Scheynius A, Venge P. A double-blinded, comparative study of the effects of short preseason specific immunotherapy and topical steroids in patients with allergic rhinoconjunctivitis and asthma. J Allergy Clin Immunol. Dec 2001;108(6):921–8.

56. Reid MJ, Moss RB, Hsu YP, Kwasnicki JM, Commerford TM, Nelson BL. Seasonal asthma in northern California: allergic causes and efficacy of immunotherapy. J Allergy Clin Immunol. Oct 1986;78(4 Pt 1):590–600.

57. Roberts G, Hurley C, Turcanu V, Lack G. Grass pollen immunotherapy as an effective therapy for childhood seasonal allergic asthma. J Allergy Clin Immunol. Feb 2006;117(2):263–8.

58. Sabbah A, Bonnaud F, Sonneville A, Bonneau JC, Pinon H. [Specific immunotherapy using Alpha-Fraction-Retard-D. pteronyssinus. Double-blind study in asthma]. Allerg Immunol (Leipz). Feb 1991;23(2):58–60.

59. Smith AP. Hyposensitisation with Dermatophagoides pteronyssinus antigen: trial in asthma induced by house dust. British Medical Journal 1971;4:204–6.

60. Sundin B, Lilja G, Graff-Lonnevig V, Hedlin G, Heilborn H, Norrlind K, et al. Immunotherapy with partially purified and standardized animal dander extracts. I. Clinical results from a double-blind study on patients with animal dander asthma. J Allergy Clin Immunol. 1986;77(3):478–87.

61. Tabar AI, Lizaso MT, Garcia BE, Gomez B, Echechipia S, Aldunate MT, et al. Double-blind, placebo-controlled study of Alternaria alternata immunotherapy: Clinical efficacy and safety. Pediatr Allergy Immunol. Feb 2008;19(1):67–75.

62. Taylor WW, Ohman JL, Lowell FC. Immunotherapy in cat-induced asthma. Double-blind trial with evaluation of bronchial responses to cat allergen and histamine. J Allergy Clin Immunol. May 1978;61(5):283–7.

63. Taylor B, Sanders SS, Norman AP. A double blind controlled trial of house mite fortified house dust vaccine in childhood asthma. Clin Allergy. 1974 Jan;4(1):35.

64. Valovirta E, Koivikko A, Vanto T, Viander M, Ingeman L. Immunotherapy in allergy to dog: a double-blind clinical study. Ann Allergy. 1984;53(1):85–8.

65. Valovirta E, Viander M, Koivikko A, Vanto T, Ingeman L. Immunotherapy in allergy to dog. Immunologic and clinical findings of a double-blind study. Annals of Allergy 1986;57(3):173–9.

66. Van Bever HP, Stevens WJ. Effect of hyposensitization upon the immediate and late asthmatic reaction and upon histamine reactivity in patients allergic to house dust mite (Dermatophagoides pteronyssinus). Eur Respir J. Mar 1992;5(3):318–22.

67. Van Metre TE, Marsh DG, Adkinson NF, Kagey-Sobotka A, Khattignavong A, Norman PS, et al. Immunotherapy for cat asthma. J Allergy Clin Immunol. Dec 1988;82(6):1055–68.

68. Vidal C, Tabar AI, Figueroa J, Navarro JA, Sanchez C, Orovitg A, et al. Assessment of short-term changes induced by a Dermatophagoides pteronyssinus extract on asthmatic patients. Randomised, double-blind, placebo-controlled trial. Curr Drug Deliv. Mar 2011;8(2):152–8.

69. Wang H, Lin X, Hao C, Zhang C, Sun B, Zheng J, et al. A double-blind, placebo-controlled study of house dust mite immunotherapy in Chinese asthmatic patients. Allergy. 2006;61(2):191–7.

70. Warner J, Price J, Soothill J, Hey E. Controlled trial of hyposensitisation to Dermatophagoides pteronyssinus in children with asthma. The Lancet. Oct 1978;

71. Alvarez-Cuesta E, Berges-Gimeno P, Gonzalez-Mancebo E, Fernandez-Caldas E, Cuesta-Herranz J, Casanovas M. Sublingual immunotherapy with a standardized cat dander extract: evaluation of efficacy in a double blind placebo controlled study.[Erratum appears in Allergy. Sep 2007;62(9):1100 Note: Mancebo, E G [corrected to Gonzalez-Mancebo, E]]. Allergy. Jul;62(7):810–7.

72. Bahçeciler NN, Isik U, Barlan IB, Basaran MM. Efficacy of sublingual immunotherapy in children with asthma and rhinitis: a double-blind, placebo-controlled study. Pediatr Pulmonol. 2001;32(1):49–55.

73. Bousquet J, Scheinmann P, Guinnepain MT, Perrin-Fayolle M, Sauvaget J, Tonnel AB, et al. Sublingual-swallow immunotherapy (SLIT) in patients with asthma due to house-dust mites: a double-blind, placebo-controlled study. Allergy. Mar 1999;54(3):249–60.

74. Caffarelli C, Sensi LG, Marcucci F, Cavagni G. Preseasonal local allergoid immunotherapy to grass pollen in children: a double-blind, placebo-controlled, randomized trial. Allergy. Dec 2000;55(12):1142–7.

75. Cao LF, Lu Q, Gu HL, Chen YP, Zhang Y, Lu M, et al. [Clinical evaluation for sublingual immunotherapy of allergic asthma and atopic rhinitis with Dermatophagoides Farinae Drops]. Zhonghua Erke Zazhi. Oct 2007;45(10):736–41.

76. Dahl R, Stender A, Rak S. Specific immunotherapy with SQ standardized grass allergen tablets in asthmatics with rhinoconjunctivitis. Allergy. Feb 2006;61(2):185–90.

77. de Blay F, Kuna P, Prieto L, Ginko T, Seitzberg D, Riis B, et al. SQ HDM SLIT-tablet (ALK) in treatment of asthma--post hoc results from a randomised trial. Respir Med. Oct 2014;108(10):1430–7.

78. Devillier P, Fadel R, Beaumont O. House dust mite sublingual immunotherapy is safe in patients with mild-to-moderate, persistent asthma: a clinical trial. Allergy [Internet]. 2015; Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/168/CN-01096168/frame.html

79. Drachenberg KJ, Pfeiffer P, Urban E. Sublingual immunotherapy - Results from a multi-centre, randomised, double-blind, placebo-controlled study with a standardised birch and grass/rye pollen extract. [German]. Allergologie. 2001;24(11):525–34.

80. Gomez Vera J, Flores Sandoval G, Orea Solano M, Lopez Tiro J, Jimenez Saab N. Safety and efficacy of specific sublingual immunotherapy in patients with asthma and allergy to Dermatophagoides pteronyssinus. Rev Alerg Mex. 2005 Dec;231–6.

81. Ippoliti F, De Santis W, Volterrani A, Lenti L, Canitano N, Lucarelli S, et al. Immunomodulation during sublingual therapy in allergic children. Pediatr Allergy Immunol. Jun 2003;14(3):216–21.

82. Leng X, Fu YX, Ye ST, Duan SQ. A double-blind trial of oral immunotherapy for Artemisia pollen asthma with evaluation of bronchial response to the pollen allergen and serum-specific IgE antibody. Annals of Allergy 1990;64(1):27–31.

83. Lewith GT, Watkins AD, Hyland ME, Shaw S, Broomfield JA, Dolan G, et al. Use of ultramolecular potencies of allergen to treat asthmatic people allergic to house dust mite: double blind randomised controlled clinical trial.[Summary for patients in J Fam Pract. 2002 Jul;51(7):602; PMID: 12160495]. BMJ. Mar 2002 2;324(7336):520.

84. Lue KH, Lin YH, Sun HL, Lu KH, Hsieh JC, Chou MC. Clinical and immunologic effects of sublingual immunotherapy in asthmatic children sensitized to mites: a double-blind, randomized, placebo-controlled study. Pediatr Allergy Immunol. 2006;17(6):408–15.

85. Ma CX, Lu MF, Ge LP, Qian XM, Zhang MZ. Clinical evaluation of sublingual allergen specific immunotherapy in treatment to children with bronchial asthma and allergic rhinitis. [Chinese]. J Shanghai Jiaotong Univ Med Sci. Jun 2014;34(6):873–6.

86. Ma X, Duolikun. Efficacy of sublingual immunotherapy in children with dust mite allergic asthma. [Chinese]. Chin J Contemp Pediatr. May 2010;12(5):344–7.

87. Moreno-Ancillo A, Moreno C, Ojeda P, Domínguez C, Barasona MJ, García-Cubillana A, et al. Efficacy and quality of life with once-daily sublingual immunotherapy with grasses plus olive pollen extract without updosing. J Investig Allergol Clin Immunol. 2007;17(6):399–405.

88. Mosbech H, Canonica GW, Backer V, de Blay F, Klimek L, Broge L, et al. SQ house dust mite sublingually administered immunotherapy tablet (ALK) improves allergic rhinitis in patients with house dust mite allergic asthma and rhinitis symptoms. Ann Allergy Asthma Immunol. Feb 2014;114(2):134–40.

89. Mosges R, Graute V, Christ H, Sieber HJ, Wahn U, Niggemann B. Safety of ultra-rush titration of sublingual immunotherapy in asthmatic children with tree-pollen allergy. Pediatr Allergy Immunol. Dec 2010;21(8):1135–8.

90. Niu CK, Chen WY, Huang JL, Lue KH, Wang JY. Efficacy of sublingual immunotherapy with high-dose mite extracts in asthma: A multi-center, double-blind, randomized, and placebo-controlled study in Taiwan. Respir Med. Aug 2006;100(8):1374–83.

91. Pajno GB, Morabito L, Barberio G, Parmiani S. Clinical and immunologic effects of long-term sublingual immunotherapy in asthmatic children sensitized to mites: a double-blind, placebo-controlled study. Allergy. Sep 2000;55(9):842–9.

92. Pajno GB, Vita D, Parmiani S, Caminiti L, La Grutta S, Barberio G. Impact of sublingual immunotherapy on seasonal asthma and skin reactivity in children allergic to Parietaria pollen treated with inhaled fluticasone propionate. Clin Exp Allergy. Dec 2003;33(12):1641–7.

93. Pham-Thi N, Scheinmann P, Fadel R, Combebias A, Andre C. Assessment of sublingual immunotherapy efficacy in children with house dust mite-induced allergic asthma optimally controlled by pharmacologic treatment and mite-avoidance measures. Pediatr Allergy Immunol. 2007;18(1):47–57.

94. Reilly D, Taylor MA, Beattie NG, Campbell JH, McSharry C, Aitchison TC, et al. Is evidence for homoeopathy reproducible? Lancet. Dec 1994 10;344(8937):1601–6.

95. Reinert M, Reinert U. Oral hyposensitization with pollen solutions and placebos. [German]. Prax Klin Pneumol. 1983;37(6):228–31.

96. Stelmach I, Kaczmarek-Wozniak J, Majak P, Olszowiec-Chlebna M, Jerzynska J. Efficacy and safety of high-doses sublingual immunotherapy in ultra-rush scheme in children allergic to grass pollen. Clin Exp Allergy. Mar 2008;39(3):401–8.

97. Tian M, Wang Y, Lu Y, Jiang YH, Zhao DY. Effects of sublingual immunotherapy for Dermatophagoides farinae on Th17 cells and CD4(+) CD25(+) regulatory T cells in peripheral blood of children with allergic asthma. Int Forum Allergy Rhinol. May 2014;4(5):371–5.

98. Virchow J, Backer V, Kuna P, Prieto L, Nolte H, Villesen H. Efficacy of a House Dust Mite Sublingual Allergen Immunotherapy Tablet in Adults With Allergic Asthma: A Randomized Clinical Trial. JAMA. Apr 2016 26;315(16).

99. Vourdas D, Syrigou E, Potamianou P, Carat F, Batard T, Andre C, et al. Double-blind, placebo-controlled evaluation of sublingual immunotherapy with standardized olive pollen extract in pediatric patients with allergic rhinoconjunctivitis and mild asthma due to olive pollen sensitization. Allergy. Jul 1998;53(7):662–72.

100. Wang L, Yin J, Fadel R, Montagut A, de Beaumont O, Devillier P. House dust mite sublingual immunotherapy is safe and appears to be effective in moderate, persistent asthma. Allergy. Sep 2013;69(9):1181–8.

101. Wood RA, Togias A, Wildfire J, Visness CM, Matsui EC, Gruchalla R, et al. Development of cockroach immunotherapy by the Inner-City Asthma Consortium. J Allergy Clin Immunol. 2014;133(3):846–852e.6.

102. Zhang Q, Yasin A, Qu YM, Yong J, Yalkun Y. Efficacy and safety of dust mite sublingual immunotherapy for pediatric allergic rhinitis: A meta-analysis. [Chinese]. Chin J Evid-Based Med. 2014;14(11):1373–9.

103. Zhang X, Jiang D, Liu R, Fang G, Guo Z. Long-term efficacy of Dermatophagoides farina drop specific immunotherapy on children with acarid allergic asthma. Pharm Care Res. 2015;4.

104. Zheng B, Wang G, Yang S. Efficacy of specific sublingual immunotherapy with dermatophagoides farinae drops in the treatment of cough variant asthma in children]. Zhongguo Dang Dai Er Ke Za Zhi Chin J Contemp Pediatr. 2012;14(8):585–8.

105. Cohen J. Statistical Power Analysis for the Behavioral Sciences. Vol. 2nd ed. Hillsdale, NJ: Erlbaum; 1988.

106. Kuna P, Kaczmarek J, Kupczyk M. Efficacy and safety of immunotherapy for allergies to Alternaria alternata in children. J Allergy Clin Immunol. Feb 2011;127(2):502-508-6.

107. Basomba A, Tabar AI, De Rojas DHF, Garcia BE, Alamar R, Olaguibel JM, et al. Allergen vaccination with a liposome-encapsulated extract of Dermatophagoides pteronyssinus: A randomized, double-blind, placebo-controlled trial in asthmatic patients. J Allergy Clin Immunol. 2002;109(6):943–8.

108. Olsen OT, Larsen KR, Jacobsen L, Svendsen UG. A 1-year, placebo-controlled, double-blind house-dust-mite immunotherapy study in asthmatic adults. Allergy Eur J Allergy Clin Immunol. 1997;52(8):853–9.

109. Pajno GB, Passalacqua G, Vita D, Caminiti L, Parmiani S, Barberio G. Sublingual immunotherapy abrogates seasonal bronchial hyperresponsiveness in children with Parietaria-induced respiratory allergy: a randomized controlled trial. Allergy. Aug 2004;59(8):883–7.

110. Arvidsson MB, Löwhagen O, Rak S. Allergen specific immunotherapy attenuates early and late phase reactions in lower airways of birch pollen asthmatic patients: a double blind placebo-controlled study. Allergy. 2004;59(1):74–80.

111. Reinhold T, Ostermann J, Thum-Oltmer S, Bruggenjurgen B. Influence of subcutaneous specific immunotherapy on drug costs in children suffering from allergic asthma (Provisional abstract). Clin Transl Allergy. 2013;3(1):30.

112. Nasser S, Vestenbaek U, Beriot-Mathiot A, Poulsen PB. Cost-effectiveness of specific immunotherapy with Grazax in allergic rhinitis co-existing with asthma. Allergy. Dec 2008;63(12):1624–9.

113. Ariano R, Berto P, Incorvaia C, Di Cara G, Boccardo R, La Grutta S, et al. Economic evaluation of sublinimal immunotherapy vs symptomatic treatment in allergic asthma. Ann Allergy Asthma Immunol. Sep 2009;103(3):254–9.