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REVIEW ARTICLE

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EAACI guidelines on allergen immunotherapy: Prevention of allergy

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Abbreviations: AD, atopic dermatitis (atopic eczema); AIT, allergen immunotherapy; AR, allergic rhinitis/allergic rhinoconjunctivitis; ARIA, allergic rhinitis and its impact of asthma; CBA, controlled before and after study; EAACI, European Academy of Allergy and Clinical Immunology; EMA, European Medicines Agency; HDM, house dust mite; OAS, oral allergy syndrome; QoL, quality of life; RCT, randomized controlled trial; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; SPT, skin prick test; SR, systematic review; WAO, World Allergy Organization.

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This Guideline published by the European Academy of Allergy and Clinical Immunology (EAACI) has drawn on data from a systematic review of the literature, more recent published studies and multi-stakeholder expert clinical opinion. This Guideline is aimed at healthcare professionals who are encouraged to take the recommendations into account in the context of delivering clinical care. This Guideline is not a substitute for professional clinical judgment, which professionals need to exercise in the context of delivering personalised healthcare.

Abstract

Allergic diseases are common and frequently coexist. Allergen immunotherapy (AIT) is a disease-modifying treatment for IgE-mediated allergic disease with effects beyond cessation of AIT that may include important preventive effects. The European Academy of Allergy and Clinical Immunology (EAACI) has developed a clinical practice guideline to provide evidence-based recommendations for AIT for the prevention of (i) development of allergic comorbidities in those with established allergic diseases, (ii) development of first allergic condition, and (iii) allergic sensitization. This guideline has been developed using the Appraisal of Guidelines for Research & Evaluation (AGREE II) framework, which involved a multidisciplinary expert working group, a systematic review of the underpinning evidence, and external peer-review of draft recommendations. Our key recommendation is that a 3-year course of subcutaneous or sublingual AIT can be recommended for children and adolescents with moderate-to-severe allergic rhinitis (AR) triggered by grass/birch pollen allergy to prevent asthma for up to 2 years post-AIT in addition to its sustained effect on AR symptoms and medication. Some trial data even suggest a preventive effect on asthma symptoms and medication more than 2 years post-AIT. We need more evidence concerning AIT for prevention in individuals with AR triggered by house dust mites or other allergens and for the prevention of allergic sensitization, the first allergic disease, or for the prevention of allergic comorbidities in those with other allergic conditions. Evidence for the preventive potential of AIT as disease-modifying treatment exists but there is an urgent need for more high-quality clinical trials.

KEYWORDS
AGREE II, allergen immunotherapy, allergic diseases, allergic rhinitis, allergy, asthma, atopic dermatitis/eczema, atopy, prevention, sensitization

1 | INTRODUCTION

Allergic diseases are among the commonest chronic diseases and encompass atopic eczema/dermatitis (AD), asthma, allergic rhinitis and allergic rhinoconjunctivitis (both from here onward referred to as AR), food allergy, and venom allergy.[1-5] They frequently start in early childhood and continue throughout adulthood. Allergies can cause a considerable burden to individuals leading to impaired quality of life.[6] At a societal level, they cause additional costs, particularly in terms of healthcare utilization, reduction in economic productivity, and impacting on activities of daily living. The latter may include loss of school days, work absence, presenteeism, and early retirement.[7,8] For allergic asthma and AR, many patients respond well to pharmacotherapy, whereas others do not or need treatment with more than 1 product.[9] However, there is good evidence for the clinical efficacy of allergen immunotherapy (AIT) for AR, allergic asthma, and moderate-to-severe venom allergy[10-12] with many patients responding to therapeutic AIT, leading to a sustained reduction in symptoms and requirement for symptomatic treatment.

AIT is considered a disease-modifying intervention in IgE-mediated allergic disease, with both a therapeutic, even beyond cessation of AIT,[10-12] and the potential for a preventive effect.[13-16] It has been

shown that children with AR have a 3-fold increased risk of developing asthma[17,18] and that childhood AD and AR are strongly associated with the incidence and persistence of adult atopic asthma and with allergic asthma persisting into adulthood.[19] Studies assessing the long-term effectiveness of AIT in children with AR indicate that AIT might reduce the risk of developing asthma.[20-23] AIT has the potential to induce immunologic changes that result in immune modification.[14] Therefore, AIT should be considered as a preventive strategy in the treatment for allergic diseases.

This guideline has been developed by the European Academy of Allergy and Clinical Immunology (EAACI) Taskforce on AIT for Allergy Prevention and forms part of the EAACI Guidelines on Allergen Immunotherapy. The aim is to provide evidence-based recommendations for the use of AIT for the prevention of (i) further allergic comorbidities in those with established allergic disease, (ii) first allergic disease, and (iii) development of allergic sensitization. This guideline does not cover prevention of symptoms, exacerbations, or progression of already-existing allergic disease as this is included in other guidelines in this series. Likewise, it does not cover weaning and dietetic strategies, which are considered in the "EAACI food allergy and anaphylaxis guidelines: Primary prevention of food allergy".[24] Definition of key terms is described in Box 1.

The primary audience for this guideline are clinical allergists (specialists and subspecialists). It may also provide guidance for other

Box 1 Key terms

Allergic asthma	Typical symptoms of asthma (wheezing, cough, dyspnea, chest tightness with evidence of reversibility) induced upon exposure to an allergen together with the proof of immunologic sensitization to that allergen
Allergic conjunctivitis	Inflammation of the conjunctiva characterized by watery, itchy, red eyes induced upon exposure to an allergen together with the proof of immunologic sensitization to that allergen
Allergic diseases	Atopic dermatitis (eczema) (AD), food allergy (FA), allergic asthma, allergic rhinitis/conjunctivitis (AR), and venom allergy at any age
Allergic rhinitis	Inflammation of the nasal mucosa resulting in at least 2 nasal symptoms: rhinorrhoea, blockage, sneezing or itching induced upon exposure to an allergen together with the proof of immunologic sensitization to that allergen
AIT (allergen immunotherapy)	Repeated allergen exposure at regular intervals to modulate immune response to reduce symptoms and need for medication for clinical allergies and to prevent the development of new allergies and asthma (adapted from European Medicines Agency [EMA]). This is also sometimes known as allergen-specific immunotherapy, desensitization, hyposensitization, and allergy vaccination[a] • Subcutaneous immunotherapy (SCIT): form of AIT where the allergen is administered as subcutaneous injections • Sublingual immunotherapy (SLIT): form of AIT where the allergen is administered under the tongue with formulation as drops or tablets
Healthy individuals	Individuals with or without IgE sensitization, but without any manifestations of current allergic disease
Prevention	Prevention of the development of a new sensitization or new allergic disease in healthy individuals without sensitizations, in healthy individuals with sensitizations, and in those who already have an allergic disease *Short-term prevention*: preventive effect assessed within a 2-y window post-AIT *Long-term prevention*: preventive effect maintained for two years and beyond AIT In this document, specific treatment effects such as effect on exacerbations and progression of the disease, including long-term effects, are not regarded as prevention.
Sensitization	Detectable specific IgE antibodies, either by means of SPT or determination of specific IgE antibody levels in a serum sample

[a]Dietary interventions in infants aimed at the prevention of food allergy are not covered in this guideline: They form part of the "EAACI food allergy and anaphylaxis guidelines. Primary prevention of food allergy" https://www.ncbi.nlm.nih.gov/pubmed/24697491.[24]

healthcare professionals, for example, physicians, nurses, and pharmacists working across a range of primary, secondary, and tertiary care settings managing patients with allergic diseases and healthy individuals at risk of developing allergic diseases.

2 | METHODS

Development of the guideline has been informed by a formal systematic review and meta-analysis of AIT for the prevention of allergy[25] with SR principles being used to identify additional evidence, where necessary.

This guideline was produced using the Appraisal of Guidelines for Research & Evaluation (AGREE II) approach.[26,27] This structured method for guideline production is designed to ensure appropriate representation of the full range of stakeholders, an exhaustive 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 began in April 2015 with detailed face-to-face discussions agreeing on the process and the key clinical areas to address, followed by face-to-face and web conferences in which professional and lay representatives participated.

2.1 | Clarifying the scope and purpose of the guidelines

The scope of this EAACI guideline is multifaceted, providing recommendations that assist clinicians in the optimal use of AIT for the prevention of development of allergic disease in the management of individuals with, or at risk for, allergic disease, and identifying gaps for further research. The guideline builds on a SR conducted to summarize the evidence base in relation to these aims (Box 2).[25]

2.2 | Ensuring appropriate stakeholder involvement

Participants in the EAACI Taskforce on AIT for Prevention represented a range of countries, with various disciplinary and clinical backgrounds, including allergists, primary care physicians, allied health professionals, public health practitioners, representatives from patient interest organizations, and methodologists who took the lead in undertaking the underpinning SR. Clinical academics took the lead in formulating recommendations for clinical care. Additionally, producers of immunotherapy products were given the opportunity to review and comment on the draft guidelines as part of the peer-review and public comment process. The Taskforce members considered these comments and revised the guideline, where appropriate.

2.3 | Systematic reviews of the evidence

The initial full range of questions that were considered important were rationalized through several rounds of iteration to agree on 1 key overarching question: "What is the effectiveness, safety, and cost-effectiveness of AIT for the prevention of allergic disease and sensitization in all populations?" This was then pursued through a formal SR of the evidence by independent methodologists as previously published.[25,28] We continued to track evidence published after our SR cutoff date October 31, 2015, and, where relevant, studies were considered by the Taskforce chairs and members.

2.4 | Formulating recommendations

We graded the strength and consistency of key findings from the SR and meta-analysis, using a random-effects model to take into account the heterogeneity of findings[25] to formulate evidence-based recommendations for clinical care, using an approach that was adapted from that proposed by the Oxford Centre for Evidence-Based Medicine (Oxford Centre for Evidence-based Medicine) (Box 3).[29] The adaptation involved providing an assessment of the risk of bias, based on the Cochrane risk of bias tool, of the underpinning evidence and highlighting other potentially relevant contextual information, formulating clear recommendations, and making clear the evidence base underpinning each recommendation. Where the systematic review did not cover the clinical area, we took a hierarchical approach reviewing other evidence until we could formulate a recommendation: (i) other systematic reviews on the subject to see whether these provided any clarity on the topic; (ii) RCTs within these systematic reviews; (iii) other RCTs known to Taskforce members; and (iv) a consensus-based approach within the Taskforce. This evidence was graded as described in Box 2 using the systematic review data and clearly labeled in the recommendation tables. In formulating the recommendations, not only possible beneficial effects, but also any possible disadvantages and harms were considered (Table 1).

2.5 | Identification of evidence gaps

The process of developing this guideline has identified a number of evidence gaps, which are prioritized in Table 2.

2.6 | Implementation of the guideline

The Taskforce members identified the resource implications, barriers, and facilitators to the implementation of each recommendation (Tables 3-5), advised on approaches to implementing the recommendations and suggested audit criteria that can help with assessing organizational compliance with each recommendation (Table 6).

2.7 | Peer-review and public comment

A draft of this guideline was externally peer-reviewed by invited external experts in this field from a range of organizations, countries, and professional backgrounds: Stephen Durham, Peter Eng, Hans Jørgen Malling, Antonio Nieto, Zsolt Szepfalusi, and Erkka

Box 2 Summary of the aim and outcomes in the supporting systematic review[25]

Aim

To provide the evidence basis for formulating clinical practice guidelines for the use of AIT as preventive therapeutic intervention in allergy. This will be based on a rigorous evaluation of current SR evidence on the effectiveness, safety, and cost-effectiveness of AIT for the prevention of allergic sensitization(s) and allergic disease(s).

Outcomes of the SR

Primary

- The development of the first allergic manifestation in healthy individuals, or of a new allergic manifestation in those with a previous allergic condition (eg, development of asthma in patients with atopic eczema/dermatitis (AD) or AR, a) is lacking here assessed over the short-term (<2 y) or the longer-term (≥2 years) post-AIT.

Secondary

- The development of new allergic sensitization(s), spreading of allergic sensitization(s) from 1 allergen to other nonrelated allergen(s), spreading of allergic sensitization(s) at molecular level, from 1 allergenic molecule to other molecules.
- The development of previously nonexistent oral allergy syndrome (OAS).
- Safety as assessed by local and systemic reactions in accordance with the World Allergy Organization's (WAO) grading systems of local and systemic side effects.[77,78]
- Health economic analysis from the perspective of the health system/payer as reported in studies.

Box 3 Assigning levels of evidence and grade and strength of recommendations (adapted from Oxford Centre for Evidence-based Medicine—Levels of Evidence and Grades of Recommendations)[29]

Level of evidence	
Level I	Systematic reviews, meta-analyses, randomized controlled trials
Level II	Two groups, nonrandomized studies (eg, cohort, case-control)
Level III	One-group, nonrandomized studies (eg, before and after, pretest and post-test)
Level IV	Descriptive studies that include analysis of outcomes (single-subject design, case series)
Level V	Case reports and expert opinion that include narrative literature, reviews, and consensus statements
Grades of recommendation	
Grade A	Consistent level I studies
Grade B	Consistent level II or III studies or extrapolations from level I studies
Grade C	Level IV studies or extrapolations from level II or III studies
Grade D	Level V evidence or troublingly inconsistent or inconclusive studies at any level
Strength of recommendations	
Strong	Evidence from studies at low risk of bias
Moderate	Evidence from studies at moderate risk of bias
Weak	Evidence from studies at high risk of bias

Recommendations are phrased according to the strength of recommendation: strong: "is recommended"; moderate: "can be recommended"; weak: "may be recommended in specific circumstances"; negative: "cannot be recommended"; or neutral: "cannot be recommended in favor or against".

Valovirta. Additionally, the draft guideline was made available on the EAACI website for a 3-week period in May 2017 for public review to allow a broader array of stakeholders to comment. All feedback was considered by the Taskforce members and, where appropriate, final revisions were made in light of the feedback received.

TABLE 1 Benefits and harms/disadvantages of AIT as preventive treatment in different populations

Population	Benefits	Harms/disadvantages
Healthy ± sensitization	Possible preventive effect remains to be documented	Daily intake of tablets/drops (SLIT/oral) or regular injections (SCIT) for 3 y Frequency of visits to the clinic (SCIT) Risk for adverse events Costs[a]
Children with AD	Possible preventive effect remains to be documented	Daily intake of tablets/drops (SLIT/oral) or regular injections (SCIT) for 3 y Frequency of visits to the clinic (SCIT) Risk of adverse events Costs[a]
Patients with AR	Documented beneficial effect on symptoms and reduction in medication on short- and long-term Possible preventive effect on development of asthma	Daily intake of tablets/drops (SLIT/oral) or regular injections (SCIT) for 3 y Frequency of visits to the clinic (SCIT) Risk for adverse events Costs[a]

AIT, allergen immunotherapy; AD, atopic dermatitis/eczema; AR, allergic rhinitis/rhinoconjunctivitis.
[a]Costs should be evaluated in relation to potential direct and indirect costs related to the development of an eventual allergic disease and other comorbidities.

2.8 | Editorial independence and managing conflict of interests

The production of this guideline was funded and supported by EAACI. The funder did not have any influence on the guideline production process, on its contents, or on the decision to publish. Taskforce members' conflict of interests were declared at the start of the process and taken into account by the Taskforce Chairs as recommendations were formulated. Methodologists, who had no conflict of interests in this area, checked final decisions about strength of evidence for recommendations.

2.9 | Updating the guideline

EAACI plans to update this guideline using the AGREE II approach in 2022 unless there are important advances before then.

3 | AIT FOR PREVENTION: EVIDENCE AND CLINICAL RECOMMENDATIONS

3.1 | Overarching considerations

This guideline is based on a comprehensive SR evaluating the evidence according to predefined well-established methods.[25] As in other SRs, heterogeneity in the populations under study, methods employed, and outcomes studied made it challenging to interpret the evidence. Factors related to the population, such as atopic heredity, play a role in the risk of development of allergic disease. In addition, children with sensitization and/or early manifestations of atopic diseases—AD and food allergy—or later manifestations such as AR have a higher risk for development of other allergic manifestations such as asthma.[17,30] The age of the population is important as the phenotypic expression may change with age and some manifestations may even disappear spontaneously.[31] The results of individual studies are difficult to compare because studies have used different populations, outcome measures, diagnostic criteria (if any, eg, the exact definition of asthma, intermittent versus persistent asthma), methods, and cutoff values for measuring sensitization. Furthermore, the mode of administration and the products used for AIT differ as regards allergens, formulation, strength,[32,33] schedules, dose, route of administration, and duration of the intervention.[34] Additionally, many studies are small without sufficient power and adjustment for confounders. Where possible, these factors are taken into consideration in the risk of bias assessment in the SR on which this guideline is based.

The significant heterogeneity seen in meta-analysis can be explained by the differences in study design, study population, products, and schedules evaluated. Therefore, an individual product-based evaluation of the evidence for efficacy is strongly recommended before treatment with a specific product is initiated.[16,35] But caution is recommended as not all AIT products used currently provide sufficient data to support their efficacy in clinical practice. We might consider that a limited class effect can be assumed when the same clinical outcomes were used to evaluate clinical efficacy (and safety) of different products only if the same route of application, similar dosing schemes, and demonstrable comparable amounts of relevant allergens and potency were used. However, it should be noted that such comparability is also dependent on standardized and validated assays and that a limited class effect does not neglect the necessity for product-specific clinical studies.

Using AIT for the prevention of development of new allergic disease or sensitization requires use of products with a high level of safety, especially in healthy individuals. However, if AIT is indicated due to treatment of an already-existing allergic disease, and the preventive effect is regarded as an additional effect, then the safety profile should be considered in that context.

TABLE 2 Gaps in the evidence

Gaps	Plan to address	Priority
AIT for prevention of asthma in children with AR due to grass pollen—long-term effects	Long-term follow-up of RCTs Further evaluation of GAP trial	High
AIT for prevention of asthma in children with AR due to HDM	RCTs[a]	High
Optimal age for introduction of AIT for prevention	RCTs[a]	High
Optimal duration of AIT for prevention	RCTs[a]	High
Optimal product, administration form, dose, and schedule of AIT for prevention	RCTs[a] and high-quality real-life studies	High
Evaluation of influence of AIT for prevention on QoI in different age groups	QoI as outcome in RCTs[a]	High
AIT for prevention of AR/asthma in children and adults with AD/food allergy	RCTs[a]	Medium
Evaluation of health economics of AIT for prevention	Cost-effectiveness analysis of RCT	Medium
Evaluation of adherence in AIT for prevention in different age groups	Adherence measured in RCTs and real-life studies	Medium
Evaluation of acceptability of AIT for prevention in different age groups	RCTs[a]	Medium
AIT for the prevention of new allergic sensitizations		
Spreading from 1 allergen to related and unrelated allergen(s)	RCTs[a]	Medium
Spreading at molecular level, from 1 allergenic molecule to other molecules		
AIT for prevention of the oral allergy syndrome	RCTs[a]	Low
AIT for prevention of first allergic disease	RCTs[a]	Low

AIT, allergen immunotherapy; AD, atopic dermatitis/eczema; AR, allergic rhinitis/rhinoconjunctivitis; HDM, house dust mites; GAP, Grazax Asthma Prevention Trial[48].

[a]Apart from new RCTs, published clinical data can be reviewed, raw data can be reanalyzed, and blood samples can be analyzed further to provide new data.

Strategies to prevent the development of a new sensitization or of a new allergic disease by AIT may vary for different populations at different stages in life. Strategies need to be pursued for different scenarios, for example, for those planning pregnancy to take measures such as AIT to reduce the likelihood of their child becoming allergic, healthy infants, and young children with early manifestations such as AD, older children with manifest allergic disease such as AR, healthy adolescents/adults, and adolescents/adults with established allergic disease.

In order to recommend AIT for the prevention of allergic diseases, evidence is required that there is a relevant and substantial beneficial effect on clinical outcomes for the individual. Furthermore, safety aspects of the treatment and of the disease to be avoided, quality of life, and evaluation of health economics should be taken into consideration. Thus, an optimal balance between benefits, harms, costs, and other possible disadvantages should be achieved (Table 1).

3.2 | AIT in individuals with AR: short- and long-term prevention of development of new asthma

3.2.1 | Short-term prevention

The SR[25] identified six RCTs investigating the preventive effect up to 2 years post-AIT on the development of asthma in individuals with AR. These RCTs included 3 SCIT studies (1 of low,[36] 1 of moderate,[37] and 1 of high risk of bias[38]), 1 of moderate risk of bias on oral AIT[39] plus 1 of high[40] and 1 moderate risk of bias SLIT study.[32] Three of these[36,37,39] were small studies with a trend toward less development of asthma in the AIT group but no significant differences. The remaining 3 studies[38,40,41] showed a significant reduction in the development of asthma in the AIT groups as compared to the control groups. The SR and meta-analysis[25] demonstrated a significant preventive effect of AIT on the development of asthma up to 2 years post-AIT in patients with AR. Subgroup analyses showed that AIT with either SLIT or SCIT was beneficial for those aged <18 years but not ≥18 years and for pollen AIT. For HDM AIT, the groups were so small that there was a nonstatistically significant impact despite an OR of 0.20. There was a high degree of heterogeneity, and therefore, the meta-analysis should be interpreted with caution although 3 RCTs demonstrated a statistically significant preventive effect. Also, the results were supported by 2 large-scale, real-life, retrospective, nonrandomized CBAs,[42,43] based on German longitudinal prescription databases, both reporting a short-term preventive effect of AIT on the progression from AR to asthma.

3.2.2 | Long-term prevention

For the long-term preventive effect, that is, 2 or more years post-AIT, the SR[25] identified 2 high risk of bias SCIT RCTs[44,45] in patients with AR. Both showed a significantly lower risk for developing asthma in the SCIT groups as compared to the controls, up to 7 years post-AIT[38,44,46] and 2 years post-AIT.[45] A large recently published low risk

TABLE 3 AIT for prevention: recommendations for school-age children, adolescents, and adults with allergic rhinitis (AR) or asthma

Recommendations for individuals with manifest allergic disease(s), eg, allergic rhinitis	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations	Key references
In children and adolescents with AR and grass/birch pollen allergy, who are suboptimally controlled despite appropriate treatment with antihistamines/nasal corticosteroids, a 3-y course of AIT (SCIT or SLIT) can be recommended for the short-term (ie, <2 y post-AIT) prevention of the onset of asthma in addition to the sustained effect on AR symptoms and medication use.	I	A	Moderate recommendation: based on consistent significant results from 2 moderate[39,41] and 2 high risk of bias[38,40] RCTs and some CBA studies	The indication should be discussed with the patients/families including the asthma preventive effect as well as the effect on AR and risk of adverse effects, costs, and preferences	Möller,[38] Novembre,[41] Marogna,[40] Kristiansen[25]
In children and adolescents with AR and grass/birch pollen allergy, no recommendation can currently be made in favor of or against the use of AIT (SCIT or SLIT) for the long-term (≥2 years post-AIT) prevention of the onset of asthma as diagnosed by symptoms combined with demonstrated reversibility.	I	B	Weak recommendation: based on consistent results from 2 high risk of bias RCTs,[44,45] nonsignificant results from 1 low risk of bias RCT,[48] and the meta-analyses being not significant due to the latter study	In the Valovirta's (2017)[48] study, no effect on the primary asthma outcome using a restrictive definition of asthma based on demonstration of reversibility. More data are needed	Jacobsen,[44] Song,[45] Valovirta,[48] Kristiansen[25]
In children and adolescents with AR and grass/birch pollen allergy, the use of AIT (SCIT or SLIT) may be recommended for the long-term (≥2 y post-AIT) prevention of the onset of asthma symptoms and medication use.	I	B	Weak-moderate recommendation: based on consistent results from 2 high risk of bias RCTs[44,45] and secondary outcomes in 1 low risk of bias RCT[48]	In the Valovirta's (2017)[48] study, a significant preventive effect on the secondary outcomes asthma symptoms and medication was found. More data are needed	Jacobsen,[44] Song,[45] Valovirta[48]
In children and adolescents with AR and allergy to house dust mites or other allergens except for birch/grass pollen, no recommendation can currently be made in favor of or against the use of AIT (SCIT or SLIT) for the short-term (ie, <2 y post-AIT) or long-term (ie, ≥2 y post-AIT) prevention of the onset of asthma.	I	B	Weak recommendation: based on inconsistent results from 1 high[40] and 1 low risk of bias RCT[36]	Only HDM, Parietaria, and mix of these and grass/birch pollen investigated. More data are needed	Marogna,[40] Crimi,[37] Grembiale,[36] Kristiansen[25]

(Continues)

TABLE 3 (Continued)

Recommendations for individuals with manifest allergic disease(s), eg, allergic rhinitis	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations	Key references
In adults with AR and house dust mite or pollen allergy, no recommendation can currently be made in favor of or against the use of AIT (SCIT or SLIT) for the short-term (ie, <2 y post-AIT) or long-term (ie, ≥2 y post-AIT prevention of the onset of asthma	I	B	Weak recommendation: based on 1 small moderate risk of bias study[37]	Only SCIT with Parietaria Judaica investigated. More data are needed	Crimi[37]
In children or adults with AR and/or asthma, AIT cannot currently be recommended for the prevention of new sensitizations.	I	B	Weak recommendation: based on inconsistent results from 4 high,[40,45,58,67] 2 moderate,[57,66] and 3 low risk of bias[53,55,56] RCTs		Marogna,[58] Marogna,[40] Dominicus,[67] Song,[45] Pifferi,[57] Limb,[66] Garcia,[55] Szepfalusi,[56] Zolkipli,[53] Kristiansen[25]

of bias RCT (Grazax Asthma Prevention Trial)[47,48] explored the effect of a 3-year course of SLIT tablets on the prevention of asthma in 812 children with AR and grass pollen allergy. This study[48] failed to demonstrate the preventive effect of AIT on the development of asthma as defined by very strict a priori criteria including reversibility to beta-2-agonists (OR = 0.91; 95% CI [0.58 to 1.41])[47,48] 2 years post-AIT. However, the number of subjects with asthma symptoms or asthma medication usage (secondary efficacy parameter) was significantly lower in the SLIT group compared to the placebo group at the end of the 5-year trial period (OR 0.66; 95% CI 0.45 to 0.97; $P < .036$), during the 2-year post-AIT follow-up and during the entire 5-year trial period. Also, AR symptoms were significantly reduced during the entire 5-year trial period. In addition, it appeared that this preventive effect was strongest for the youngest children.[48] Two high risk of bias nonrandomized studies, namely 1 with grass pollen SCIT[22,23] and 1 with HDM SCIT[49] in children with AR, also suggested a long-term effect. As published in the SR,[25] the meta-analysis showed no overall evidence of reduction in the long-term (ie, at least 2 years post-AIT) risk of developing asthma, but there was a high degree of heterogeneity so the result should be interpreted with caution. Furthermore, the negative result was due to 1 RCT with very strict diagnostic criteria for primary outcome (GAP) in which there was an effect when asthma symptoms and/or medication was considered.[48] However, some suggest that there is a long-term preventive effect on the development of asthma symptoms and the use of asthma medication although further confirmatory studies are needed.

Thus, there is a question about which asthma outcome parameter is most relevant—a diagnosis based on demonstrated reversibility or on symptoms and medication use. There is an urgent need to define and standardize the optimal clinical asthma outcomes that should be used in future clinical trials.

3.3 | Indication for AIT for treatment and prevention in patients with AR

The RCTs included in the above evaluation of asthma prevention in subjects with AR[38,40,41,44,46–48] included patients with a history of AR and the need for medication combined with documented pollen allergy for at least 1 previous season. Yet, there is no description on AR severity (mild/moderate/severe) or stratification (intermittent/persistent) in these prevention trials, and thus, these subjects may have had a milder disease than those included in studies on efficacy of AIT. However, based on baseline descriptions of the populations in these studies,[38,40,41,44,46–48] it is reasonable to assume that most of the patients included had persistent symptoms.

As discussed in another manuscript on AIT for AR of this EAACI AIT Guideline series,[10,50] many patients with AR and pollen allergy benefit from AIT in reducing AR symptoms and need for medication. Thus, AIT is recommended for the treatment of patients with moderate-to-severe pollen-induced AR if not optimally controlled on antihistamines and nasal corticosteroids.[50]

None of the studies on prevention of development of asthma in AR included preschool children, and therefore, no recommendations

TABLE 4 AIT for prevention: recommendations for individuals with early-life atopic manifestations, eg, atopic dermatitis/eczema (AD) or food allergy

Recommendations for individuals with early atopic manifestations	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations	Key references
In children with AD, no recommendations can currently be made in favor of or against the use of AIT for the prevention of onset of later allergic manifestations	I	B	Weak recommendation: based on 1 small moderate risk of bias study[51]		Holt[51]
In individuals at all ages with other early atopic manifestations, eg, food allergy, no recommendations can currently be made in favor of or against the use of AIT for the prevention of onset of other allergic manifestations	V	D	Expert opinion. No studies		

can currently be made in favor of or against AIT for this age group for prevention.

Based on an objective and clinical evaluation of the current published evidence for AIT preventive effects and considering the potential harmful effects, disadvantages, and costs associated with the use of AIT, these seem to be outweighed by the beneficial effects for this group of patients (Table 1), ultimately resulting in a favorable risk benefit profile.

Thus, there is moderate-to-high-quality evidence indicating that AIT (SCIT or SLIT) can be recommended for short-term prevention up to 2 years post-AIT of asthma in children/adolescents with moderate/severe AR and pollen allergy who are suboptimally controlled despite appropriate pharmacotherapy, and there are data suggesting that this benefit persists after 2 years post-AIT as regards asthma symptoms and medication use (Table 3). AIT may even be considered in patients with milder AR, as AIT might modify the natural disease history, including the long-term effect in AR and the preventive effect regarding the development of asthma, qualities that could never be attributed to current pharmacotherapy.

The indication and initiation of AIT should always be preceded by a discussion with the patient/family considering the possible benefits, harms, disadvantages, costs, preferential route of AIT (SCIT vs SLIT) based on the individual patient's profile, preferences, and considerations for future AIT adherence. Using AIT for preventive purposes should include all normal safety recommendations as for the treatment of AR as indicated in the corresponding guideline on AIT for AR in this EAACI AIT Guideline series.[50]

3.4 | Which products and schedules for AIT asthma prevention in individuals with AR should be used?

The products, doses, and AIT schedules used in the AIT prevention trials vary. According to the subgroup analysis in the SR,[25] it appears that SCIT and SLIT are both effective and that a 3-year AIT course is preferable to a shorter course. The studies that have demonstrated a preventive effect used 3-year courses of continuous AIT.

The SR[25] did not compare different AIT products, SLIT drops versus tablets or pre-/coseasonal versus perennial AIT. However, according to the results from 2 lower-quality, real-life nonrandomized, controlled before-after AIT treatment studies based on large German longitudinal prescription databases,[42,43] it seems that SCIT[43] and grass pollen SLIT tablets[42] with natural allergen extracts have a preventive effect on the progression from AR to asthma and that AIT for 3 or more years tended to have a stronger preventive effect than AIT for less than 3 years. Further high-quality RCTs and real-life studies are recommended to objectively confirm this.

As the indication for AIT for the prevention of asthma is linked to the indication for treatment of AR, the products, schedules, and doses used should be proven effective for AR with the relevant allergen product. Therefore, only those products registered and with the indication for AR (eg, pollen allergy at present and maybe HDM in the future) should be considered for use in allergy prevention.

3.5 | AIT in individuals with AD: short- and long-term preventive effects

The SR[25] identified 1 moderate risk of bias RCT investigating the effects of 12 months of daily SLIT with a mixture of HDM, cat, and timothy grass allergens on the prevention of asthma and new sensitizations in children with AD and sensitization to 1 or more food allergens.[51] The investigators included the absence of a difference between active/placebo groups in early immunologic changes, that is, specific IgE/IgG antibodies and associated T_H-cell responses, as a stopping rule, as this was regarded an indication of whether the treatment was delivering sufficient allergen transmucosally to trigger immunologic recognition by the infant mucosal system. As these a priori immunologic changes were not met, recruitment was interrupted and the trial reduced to a pilot study status. After 48 months of follow-up, there were no differences in asthma prevalence between the 2 groups.[51]

Based on this study, we cannot currently make any recommendations in favor of or against AIT for the prevention of the development of a first allergic disease in individuals with AD at present (Table 4) and more studies are needed.

TABLE 5 AIT for prevention: recommendations for healthy individuals

Recommendations for healthy individuals of all ages	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations	Key references
In adult allergic patients, no recommendations can currently be made in favor of or against the use of AIT for the prevention of onset of allergic diseases in their offspring	IV-V	D	Weak recommendation: based on results from 1 high risk of bias study[52]		Bozek[52]
In healthy individuals with or without sensitization, AIT cannot currently be recommended for the prevention of onset of allergic diseases	I	A	Weak recommendation: based on 1 low[53] and 1 high risk of bias RCTs[54]	One RCT with infant and 1 with adult population	Zolkipli,[53] Yamanaka[54]
In healthy children, AIT cannot currently be recommended for the prevention of new sensitizations	I	B	Weak to moderate recommendation: based on results from 2 low risk of bias RCTs[53,56]	One RCT with infant and 1 with preschool population	Zolkipli,[53] Szepfalusi[56]
In healthy adults, no recommendations can currently be made in favor of or against the use of AIT for the prevention of new sensitizations	V	D	Expert opinion. No studies		

3.6 | AIT for prevention of allergy in the offspring of allergic individuals

This topic was not included in the protocol or in the SR. However, we found 1 recent case-control study of high risk of bias comparing 194 children of parents completing AIT at least 9 months before birth with 195 controls.[52] This study found that the odds ratios of developing any allergic disease and asthma was significantly lower in children with at least 1 allergic parent after AIT compared with those having allergic parents who did not receive AIT (odds ratio: 0.73, 95% confidence interval 0.59-0.86). The authors hypothesized that AIT in allergic parents might reduce the risk of allergies in their offspring, but this requires further investigation.

Based on the very scarce and very low-quality evidence, we cannot currently make any recommendations in favor of or against AIT for allergic adults for the prevention of allergic disease in their offspring (Table 5).

3.7 | AIT in healthy individuals: short- and long-term prevention of development of new allergic disease

Two RCTs, 1 of low[53] and 1 of high risk of bias,[54] investigated the possible effect of AIT in healthy individuals on the risk for the development of their first allergic disease. The large low risk of bias study[53] found no preventive effect of oral HDM AIT on AD, wheeze, and food allergy among infants with a family history of allergic diseases, whereas the small high risk of bias study[54] reported a reduced risk of developing pollinosis among asymptomatic adults sensitized to Japanese cedar pollen in the SLIT group. Data from these 2 trials[53,54] are not comparable. No data on a long-term preventive effect were identified. Based on these results from the SR,[25] there is currently no good evidence to recommend use of AIT for the prevention of a first allergic disease in healthy individuals (Table 5).

3.8 | AIT for the prevention of the development of new allergic sensitization

3.8.1 | Short-term effects

The SR identified 3 low risk of bias RCTs[53,55,56]: 1 moderate[57] and 2 high risk of bias[40,58] RCTs investigating the short-term effects of AIT on the risk of developing new sensitizations. One low risk of bias RCT[53] on oral HDM AIT for healthy infants at high risk of developing allergic disease found a significant reduction in sensitization to any common allergen (eg, HDM, grass pollen, cat, peanut, milk, and egg) in the active group compared with the placebo group at the end of the trial, but no difference in HDM sensitization.[53] The other 2 low risk of bias RCTs found no effect of SLIT in adult patients allergic to peach[55] post-AIT and after SLIT with grass pollen or HDM extract in monosensitized children.[56] Three additional RCTs of moderate to high risk of bias[40,57,58] found a significantly lower incidence of new sensitizations among children and adults with AR treated with SLIT[40,58] and SCIT[57] as compared to controls.

Thus, these RCTs of varying quality with varying allergens and formulations showed inconsistent results. Meta-analysis showed an overall reduction in the risk of allergic sensitization but the sensitivity analyses, excluding the 2 high risk of bias studies by Marogna,[40,58] failed to confirm this risk reduction.[25] Due to the high degree of heterogeneity, the results from the meta-analysis should be interpreted with caution.

The inconsistent evidence found in RCTs was also reflected in the included high risk of bias CBA studies with 3 finding a lower occurrence of new sensitizations among AIT-treated subjects compared with controls,[59–61] 1 reporting higher occurrence in the AIT group compared with controls[62] and 3 studies reporting no differences between groups.[63–65]

3.8.2 | Long-term effects

As regards the long-term (ie, at least 2 years post-AIT) effects on prevention of new sensitivities, the SR identified 1 moderate[66] and 1 high risk of bias RCT[67] showing no preventive effect of SCIT among children with moderate-to-severe asthma followed into adulthood[66] and SCIT in adults with AR 3 years post-AIT.[67] Another high risk of bias RCT[45] found that patients with AR treated with HDM SCIT less frequently developed new sensitizations compared with controls 2 years post-AIT.[45]

Thus, there is no good evidence for a reduction in the long-term risk of allergic sensitization.

The 7 high risk of bias CBAs investigating long-term preventive effects of AIT produced inconsistent results, 1 found no difference,[68] 4 showed reduced onset,[22,60,69–71] and 1 found a significantly higher occurrence of new sensitization among AIT-treated subjects compared with controls.[72]

The development of new sensitizations may impose a higher risk for the development of further symptomatic allergies, suggesting that it might be relevant to prevent the development of new sensitizations. However, this has not been investigated sufficiently. A subgroup analysis in the SR[25] showed a tendency toward an effect in children and adolescents after 3 years of AIT, supporting the rationale of the clinical effect.

Thus, there is currently no good evidence to recommend the use of AIT for either short- or long-term prevention of development of new sensitizations in healthy individuals, children with atopic predisposition (Table 5), children with AD/food allergy (Table 4), or children and adults with AR/asthma (Table 3). Some positive data, though, suggest that this may be a good focus for future high-quality trials.

3.9 | Safety

The safety issues are fully covered by the SR and guideline for AR in this AIT Guideline series.[10,50] SCIT is occasionally associated with allergic side effects and should therefore be administered in a specialist setting. Fatalities are very rare and have not been reported with the use of SLIT. In a recent meta-analysis about the efficacy of grass pollen SLIT tablet by Di Bona et al.,[73] 7 treatment-related adverse events

TABLE 6 Recommendations for individuals with allergic rhinitis: implementation

Prevention of development of asthma in patients with AR	Barriers to implementation	Facilitators to implementation	Audit criteria	Resource implications
In children and adolescents with AR and grass/birch pollen allergy who are suboptimally controlled despite appropriate treatment with antihistamines/nasal corticosteroids, a 3-y course of AIT (SCIT or SLIT) can be recommended for short-term (ie, <2 y post-AIT) prevention of the onset of asthma in children with daily symptoms and need for medication	Lack of recognized policy in Europe about allergies and their treatment. Failure to recognize manifestations in primary care. Lack of knowledge among patients, caregivers, and primary care professionals about the benefits of AIT. Lack of communication specialists/primary care interface or specific referral criteria primary care. Lack of agreed clinical pathways Lack of access to AIT Unavailability of AIT No reimbursement Costs of travel and time of work for patients and caregivers Concerns about side effects and safety of especially SCIT Lack of health economics data	Government and European policy on allergy. Reimbursement of AIT Accessible education and training in allergy primary care. Agreed competencies in allergy for primary care and allied health workers for shared care protocols. Information among patients, caregivers, and healthcare professionals about the benefits of AIT. Integrated multidisciplinary working and service delivery. Timely advice and continuous guidance by specialists. Workforce remodeling. Agreed pathways of care with cross-boundary working	Proportion of potentially eligible patients referred from primary care for a specialist assessment. Proportion of potentially eligible patients formally considered for AIT	Identification of patients who may benefit from AIT. Thorough investigation of the patient including proper assessment of relevant allergies. AIT needs to be prescribed, made available, and administered to patients. Evaluation of effect and eventual AEs

requiring adrenaline were reported in the SLIT RCTs; however, no episode of anaphylaxis was reported. In recent real-life clinical studies of AIT, less severe systemic reactions were reported with SLIT than with SCIT, although the overall rate of adverse reactions is similar in SCIT and SCIT.[74,75] The safety profile for the present purpose is not regarded as being different from AIT for the treatment of AR. Due to its better safety profile, SLIT might be a better choice for prevention than SCIT.

4 | SUMMARY, GAPS IN THE EVIDENCE, FUTURE PERSPECTIVES, AND IMPLEMENTATION

This guideline on AIT for the prevention of allergy has been developed as part of the EAACI Guidelines on Allergen Immunotherapy Project. The recommendations in this guideline are based on a thorough SR performed by a group of experienced and independent methodologists and have been developed by a multidisciplinary EAACI Task Force representing a range of countries and disciplines and clinical backgrounds.

The guideline provides evidence-based recommendations for the use of AIT for the prevention of new allergic disease(s) and new allergic sensitization(s) in all populations. The guideline should assist all healthcare professionals as regards evaluation of AIT for the prevention of allergic disease/sensitization, and when to refer which individuals to further evaluation. The main results are summarized in Box 4.

The key limitation of this guideline is the heterogeneity and gaps in the underpinning literature. There are many areas for which there is no evidence or no high-quality evidence; these represent gaps in the current evidence (Table 2). Thus, for the preventive effect of AIT in healthy individuals or in children with early atopic manifestations such as AD or food allergy as well as for the possible long-term effect in children with AR, more high-quality data are needed. Also, we did not find studies related to spreading of allergic sensitization(s) at the molecular level, nor did we identify studies exploring the development of new OAS or health economic analyses of AIT used for prevention (Box 5).

In addition, there is a lack of evidence as regards patient selection (eg, optimal age and characteristics) for preventive AIT and for the optimal allergen preparation, mode, and duration of AIT administration; there is a need to define standardized relevant outcomes including asthma and quality of life (Qol) for future studies.

The current evidence does not allow to identify superiority between SCIT and SLIT; therefore, this choice depends on availability, patients'/family's preferences, safety, costs, routes, schedules, and patients' adherence to the AIT treatment. Only products and regimens proven effective for the treatment of AR should be used. Currently, only products with the indication for treatment of AR can be recommended for the prevention of asthma in children and adolescents with AR and pollen allergy.

Based on current evidence, AIT can be recommended for up to 2 years post-AIT prevention of development of asthma in children and adolescents with AR and pollen allergy primarily birch and grass. Some studies suggest a long-term asthma preventive effect as regards asthma symptoms and medication use, although it has to be further demonstrated if this effect can be extended to asthma as diagnosed by stricter diagnostic criteria. Such a disease-modifying effect after cessation of AIT is not achievable with pharmacotherapy. AIT should, in particular, be considered for those with moderate-severe AR as it has been shown to be effective in controlling this condition in addition to the preventive effect on the development of asthma.[10,50] Furthermore, some patients with less severe AR may prefer AIT to reduce medication use and avoid side effects of other treatments, to obtain long-term efficacy, and/or to obtain the asthma preventive effect.

Considerations should be taken when making recommendations for AIT as preventive treatment in allergy, as children and adolescents included in the prevention studies did not necessarily fulfill the criteria for proper endorsement of AIT for the treatment of AR as well as they did not necessarily meet the "Allergic Rhinitis and its Impact of Asthma" (ARIA)[9] criteria for moderate-severe AR.

At present, the indications for AIT for the prevention of allergic disease are the same as for the treatment of AR (ie, documented

Box 4 Summary

- A 3-y course of AIT (SCIT or SLIT) can be considered in children with moderate-to-severe AR and grass/birch pollen allergy, not sufficiently controlled with optimal pharmacotherapy, for:
  - Treatment of AR with a sustained effect on symptoms and use of medication beyond cessation of AIT.
  - Short-term (ie, up to 2 y post-treatment) prevention of the onset of asthma in addition to improving the control of AR. Moreover, some studies indicate that this asthma preventive effect is maintained over a longer period as evaluated by symptoms and medication use.
- Only AIT products with documented effect in patients with the relevant pollen allergy should be used and a product-specific evaluation of clinical efficacy and preventive effects is recommended.
- Before initiating AIT the possible benefits including the beneficial effects on controlling AR symptoms and the asthma preventive effect, disadvantages, potential harms, patients' preferences (SCIT or SLIT tablets/SLIT drops), patients' adherence to treatment and costs should be discussed with the patient/family on an individual basis.
- There is an urgent need for more high-quality clinical trials on prevention in AIT and more high-quality evidence.

Box 5 Key messages for primary care about referral to allergy services

- AIT has a role in delaying/preventing progression from seasonal AR/ARC to asthma.
  - Primary care teams should consider early referral of children with troublesome AR in spite of pharmacotherapy with antihistamine and/or nasal corticosteroids for a specialist assessment with a view to considering AIT to improve control of AR and also simultaneously delay/prevent asthma.
  - Patients should be considered as "individuals" during the assessment to prescribe AIT, and they all have to be aware of the potential benefits, risks, and costs of AIT.
- AIT may be indicated in those individuals with perennial AR on clinical grounds but not only for delaying/preventing progression to asthma (this preventive effect needs to have high-quality evidence).
- Recommendations cannot currently be made for AIT for prevention to (i) allergic parents who would be interested in receiving AIT to prevent allergy in their offspring; (ii) healthy infants/children; and (iii) infants/children with AD and/or food allergy.

IgE-mediated disease caused by the relevant allergens and not sufficiently controlled by antihistamines and nasal corticosteroids).[50] Contraindications are the same as for the treatment of AR.[50] The asthma preventive effect may in the future downgrade the level of severity of AR required before initiation of AIT in children and adolescents with AR and pollen allergy, especially grass pollen allergy. Therefore, AIT as a relevant treatment option for children and adolescents up to 18 years of age with less severe AR due to pollen allergy should be further investigated and discussed. Currently, there is no high-quality evidence to support AIT for prevention in HDM-allergic patients with AR, but further high-quality studies are warranted.

The products available, and registered for different indications, have varied over time and across countries. Therefore, at present, we cannot make homogeneous product-specific recommendations at a European level. In the context of the implementation of this guideline series, we plan to provide such recommendations based on each national country availability of the products,

For the implementation of this guideline (described in Table 6), there is a need to ensure that primary care healthcare professionals recognize AIT as a treatment option for some allergic diseases and have clear guidelines to aid patient selection for early referral to specialist care.[76] Patients and patient organizations need to be aware of AIT as a treatment option. Political awareness should be increased to ensure sufficient availability, knowledge, competences, skills, and resources in the healthcare system by demonstrating the economic benefits of AIT by proper assessment of its positive impact on economic productivity. In addition, methods to overcome problems with adherence should be further considered and evaluated. Finally, a plan for monitoring the audit criteria should be part of the dissemination and implementation plan, and as new evidence is published, these guidelines will be updated with appropriate revision of specific recommendations.

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AUTHORS' CONTRIBUTION

S Halken chaired the EAACI Guideline AIT for Allergy Prevention Taskforce. D Larenas-Linnemann, G Roberts, MA Calderón, M Penagos, S Bonini, G Du Toit, IJ Ansotegui, J Kleine-Tebbe, S Lau, P Maria Matricardi, G Pajno, NG Papadopoulos, O Pfaar, D Ryan, AF Santos, F Timmermans, U Wahn, M Kristiansen, S Dhami, A Sheikh, and A Muraro were all members of the Taskforce and were involved in conceptualizing the guideline, drafting of the guideline, and critically reviewed the guidelines draft and I Agache, S Arasi, M Fernandez-Rivas, M Jutel, GJ Sturm, EM Varga, R van Ree, R Gerth van Wijk, and Antonella Muraro were members of the Chairs Steering group who also critically discussed and reviewed the guideline draft. F Timmermans was also the patient group representative. All the authors satisfied the international Vancouver authorship criteria. This guideline is part of the EAACI Guidelines on Allergen Immunotherapy, chaired by Antonella Muraro and coordinated by Graham Roberts. All authors' job titles and role in the guideline development are in Table S1 in the online repository.

CONFLICTS OF INTEREST

S. Halken reports personal fees from ALK-Abelló, personal fees from different companies, for example, MEDA, Stallergenes, Allergopharma, and ALK-Abelló, outside the submitted work. D. Larenas-Linnemann reports personal fees from MSD, Grunenthal, Amstrong, and DBV; grants and personal fees from Astrazeneca, MEDA, GSK, Pfizer, Novartis, Boehringer-ingelheim, Sanofi, UCB;

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Participated in ALK conference SOSA meeting 2015. Previous paid advisory board one each for MEDA 2012, Stallergenes, 2012, Schering Plough 2009, and one paid lecture by MEDA. I. Agache has nothing to disclose. I.J. Ansotegui has nothing to disclose. S. Arasi has nothing to disclose. George 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. Prof. Du Toit is scientific advisor for the Anaphylaxis Campaign, advisor to—and holds stock in—FoodMaestro and is site investigator for Aimmune-sponsored Peanut Desensitisation Trials and is scientific advisor to Aimmune. He was Chairperson of the EAACI Paediatric Section over the period when this document was formulated. 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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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