

REVIEW ARTICLE

Sublingual immunotherapy in children with allergic rhinitis: quality of systematic reviews

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Keywords

systematic review; meta-analysis; methodological quality; sublingual immunotherapy; children; allergic rhinitis; assessment of multiple systematic reviews.

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Abstract

Systematic reviews have gained popularity as a way to combine the increasing amount of research information. This study assessed the quality of systematic reviews and meta-analyses of sublingual immunotherapy (SLIT) for allergic rhinitis in children, published since 2000. Eligible reviews were identified by searching Medline/Pubmed, Embase, and the Cochrane Library, from 2000 through 2008. Methodological quality was assessed using the assessment of multiple systematic reviews instrument. Ten systematic reviews were included, one of which was published in the Cochrane Library. Eight reviews gave some details about the search strategy. None of the reviews included measures to avoid selection bias. In 60% of the reviews, the methodological quality of the included studies was (partly) assessed. Four reviews pooled the results of individual studies, neglecting clinical heterogeneity. Three of the 10 reviews provided information about sources of funding or grants from industry. Of the 10 reviews, the six reviews with the highest overall score scored 5–8 points, indicating moderate quality. Systematic reviews are useful to evaluate the efficacy of SLIT in children. Although more reviews have become available, the methodological quality could be improved. SLIT for children could be promising, but methodological flaws in the reviews and individual studies are too serious to draw definite conclusions.

Background

Allergic rhinitis is a highly prevalent chronic disease in children and adults, which, despite optimal treatment, can adversely affect the quality of life (1, 2). Allergen immunotherapy can significantly reduce symptoms and medication use and prevent new sensitizations and, possibly, even the onset of asthma (3–8). The use of subcutaneous immunotherapy, with uncomfortable injections, in children and adults is limited because of the risk of severe side effects (9). Therefore, alternative routes for the delivery of allergens have been developed.

The sublingual immunotherapy (SLIT) route, consisting of drops and fast-dissolving tablets, is the most interesting and has become widely accepted in the past decade (10–12). There are several systematic reviews and meta-analyses on the efficacy of SLIT in children, but their conclusions are contradictory. For example, some concluded that there was insufficient evidence to recommend SLIT for use in clinical practice (13, 14), whereas others reported that SLIT is

effective in the treatment of allergic disease in children (15, 16).

A systematic review can be defined as using an objective and transparent approach to find and synthesize published research with the aim to minimize bias, and a meta-analysis as a systematic review that uses quantitative methods to combine the results of individual studies (17, 18). Both types of review will provide evidence-based medicine that involves tracing the best available evidence with which to answer clinical questions. Systematic reviews and meta-analyses have gained popularity as a way of combining the increasing amount of research information (19).

Systematic reviews and meta-analyses reporting the findings on SLIT in children can vary greatly in quality and have not been comprehensively appraised with respect to their methodological quality.

Rather than focusing on the content of the reviews, this review aims to identify and assess the methodological quality of the available systematic reviews and meta-analyses of SLIT (published since 2000) for allergic rhinitis in children.

Methods

Literature search and review selection

Literature searches were conducted in PubMed, Embase, and the Cochrane Library, identifying reviews or meta-analyses published between January 1, 2000, and December 31, 2008. The full search strategies can be found in Appendix 1. Additional articles were identified by manually searching references from the retrieved articles and the authors' own literature database. As the first phase of screening, two reviewers (CdB and JvdW) independently examined the titles and abstracts of the search results. The second phase of screening was based on full-text articles, which were obtained and assessed for inclusion with the predetermined selection criteria. The data from all reviews that met the selection criteria were also extracted independently by two reviewers (CdB and JvdW). Disagreements, if any, were resolved by discussion.

Inclusion criteria

The eligibility criteria for including systematic reviews and meta-analyses for step one were as follows:

- 1 'Systematic review' or 'meta-analysis' in title or abstract and/or
- 2 Literature searches described (databases, period, search terms, such as 'immunotherapy', 'allergic rhinitis', 'children')

After this first step, the additional eligibility criteria were as follows:

- 1 Reviews including randomized controlled trials (RCTs), performed in pediatric populations or in both adult and pediatric populations, assessing SLIT for allergic rhinitis

Quality of the included reviews

Methodological quality was assessed using the measurement tool 'assessment of multiple systematic reviews' (AMSTAR) (20–22). The tool consists of 11 items and has good face and content validity for measuring the methodological quality of systematic reviews (see Appendix 2). Two reviewers (CdB and JvdW) independently filled in a checklist, for every item, with detailed instructions for assessing the quality of the included studies. Each question had four possible responses: 'yes', 'no', 'can't answer', and 'not applicable'. A 'yes' gave a score of 1; any other response resulted in a score of 0. We summed the number of items that were scored positively. The maximum score on AMSTAR is 11; scores of 0–4 indicate that the review is of low quality, 5–8 of moderate quality, and 9–11 of high quality (20–23). To adjust for the number of non-applicable items, we also calculated the proportion of items scored positively divided by the total number of applicable items.

Reviews: data extraction

Data were extracted on general characteristics (publication year, source, and source of funding), clinical issues (popula-

tion, definition of allergic rhinitis, and intervention), and methodological characteristics (design and methodological quality).

None of the authors, who did the inclusion, extracted the data, and assessed the quality of the systematic reviews (CdB and JvdW), were coauthors of any of the included reviews.

Analysis

The analysis of the data was descriptive.

Results

Identification of reviews

Our primary search resulted in 541 publications (Fig. 1). After reading the abstracts, 52 full-text articles were selected and read (step 2). Most of the excluded articles did not meet the criteria of being a systematic review. Appendix 3 lists the reviews that were excluded in the last phase. Finally, we identified 10 reviews that met the inclusion criteria (13, 16, 24–31). One was a Cochrane review, which was also published as a journal article 2 yrs later (13, 31).

In the reviews, the number of included studies ranged from 7 to 46. Most of the reviews included only RCTs, and one review gave an overview of other reviews published earlier (24). Table 1 presents the characteristics of the reviews. The number of published reviews increased from one in 2003 to three in 2008.

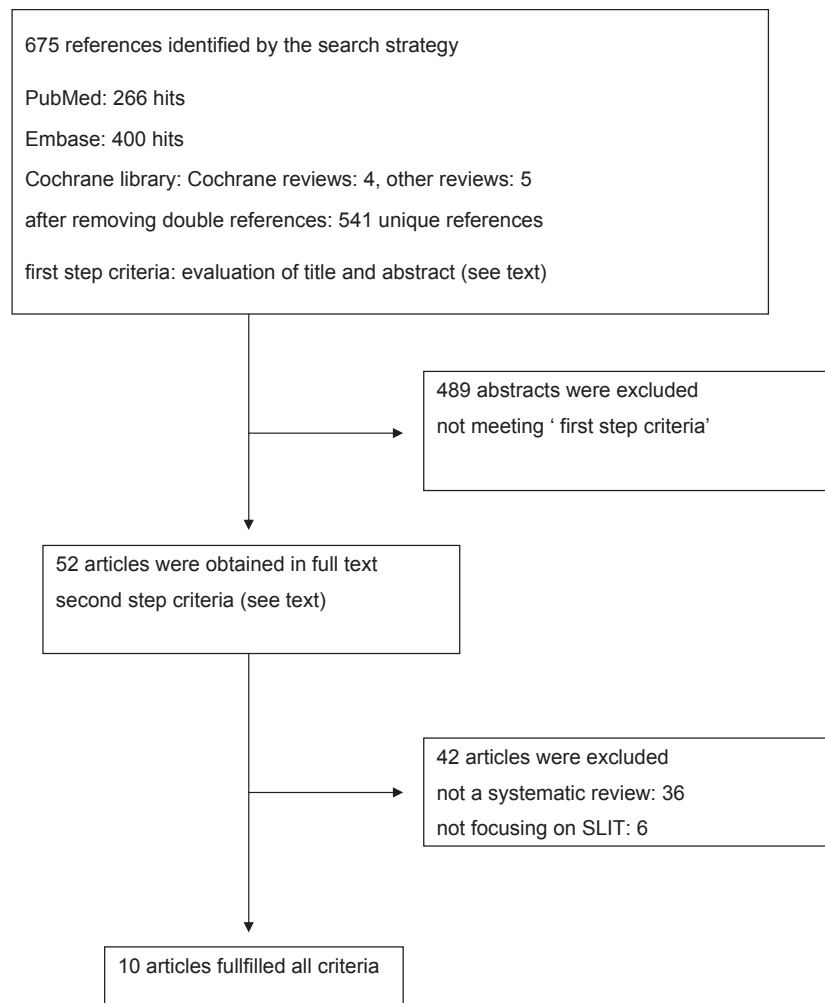
Review characteristics

Table 2 summarizes the characteristics of the included studies regarding intervention, participants, and outcomes. Nine reviews reported on the characteristics of the included studies regarding intervention, such as the number of patients who received placebo or active treatment, dosage of SLIT, and duration of the study. Eight reviews reported the characteristics of the participants in the studies; this varied from reporting only the population in the studies to describing gender, age, country, and dropout rates. Seven reviews described the characteristics of the outcomes of the included studies (ranging from 1 to 6 items); the main characteristics were AR/ nasal symptom score and rescue medication. One review reported no details on intervention, participants, or outcomes of the included studies (27).

Table 3 shows the results of the data extraction of the review process of the systematic reviews with regard to the databases used, the list of included/excluded studies, and year of publication. Four reviews used 4 databases to search for literature (13, 16, 28, 31). All reviews searched in Pubmed/Medline, followed by Embase and the Cochrane Library in six reviews. Only one review reported a list of included and excluded studies (13). In 60% of the reviews, only a list of the included studies was reported (16, 26, 28–31).

Methodological quality

Table 4 summarizes the components of the AMSTAR for the selected reviews. Only two reviews (the Cochrane review and

**Figure 1** Flow chart of the literature search and selection.**Table 1** Characteristics of the reviews

First author	Year published	Participants*	Disease†	Type of immunotherapy	Search period	Number of SLIT studies included
Wilson	2003	Children, adults	AR Asthma	SLIT	1966–2002	22
Sopo	2004	Pediatric 0–18 yrs	AR Asthma	SLIT	?–2003	8
Olaguibel	2005	Pediatric <14 yrs	Rhinitis Asthma	SLIT	?–2004	7
Wilson	2005	Children, adults	AR Asthma	SLIT	1966–2002	22
Penagos	2006	Pediatric 0–18 yrs	AR Asthma	SLIT	1966–2006	10
Cox	2007	Pediatrics <18 yrs	AR	SLIT	2005–07	19
Hoeks	2007	Children	AR Asthma	SLIT	1996–2007	13
Calderon	2008	Adults, pediatric	AR	SLIT SCIT	?–2007	46
Larenas-Linnemann	2008	Pediatric <14 yrs	AR Asthma	SLIT SCIT	1993–2008	13
Röder	2008	Pediatric 0–18 yrs	AR	SCIT SLIT LNIT OIT	1966–2006	11

AR, allergic rhinitis; SLIT, sublingual immunotherapy; SCIT, subcutaneous immunotherapy; LNIT, Local nasal immunotherapy; OIT, Oral immunotherapy.

*Described in the article.

†Included in the search strategy.

Table 2 Study characteristics as reported in the review

	Wilson (13)	Sopo (30)	Olaguibel (28)	Wilson (31)	Penagos (11)	Cox (25)	Hoeks (26)	Larenas- Linneman (27)	Calderon (24)	Röder (29)
Intervention										
Duration	x	x	x	x	x		x		x	x
Dosage		x	x		x	x	x		x	x
No of placebo/verum	x		x	x	x	x	x		x	x
Type of allergen	x	x	x	x	x	x	x		x	x
Total	3	3	4	3	4	3	4	0	4	4
Participants										
Population	x			x						
Gender	x	x				x				x
Age		x			x		x			x
Country		x								
Conditions reported										
Asthma (A)		x			x	x	x		x	x
Rhinitis (R)		x			x	x	x		x	x
Conjunctivitis (C)		x			x		x		x	
Dropouts					x				x	x
Total	2	6	0	1	5	3	4	0	4	5
Outcomes										
AR/nasal symptom score	x			x	x		x			x
Conjunctival	x									x
Rescue medication	x			x	x		x			x
(Total/specific) IgE/Ig	x						x			
Skin prick test	x						x			
Lung function tests							x			
Nasal provocation	x									
Conjunctivitis provocation test							x			
Side effects			x			x				
Total	6	0	1	2	2	1	6	0	0	3

Table 3 Review characteristics

Databases used	
PubMed/Medline	10
EMBASE	7
Cochrane Library	7
Other (i.e., ISI, CINAHL, Scisearch)	4
Number of databases used	
1	2
2	1
3	3
4	4
List of included and excluded studies	
Neither included nor excluded studies listed	3
Only included studies	6
Both included and excluded studies listed	1

the journal article based on it) provided details about their design before conducting the review as the protocol for these reviews was already published (13, 31). Other reviews did not report an *a priori* design. Of the 10 reviews, five did not report duplicate study selection and data extraction. Two reviews had only one author; thus, we assumed that no duplicate study selection and data extraction took place. In eight of the reviews, the authors provided some details about their

search strategy. This varied from providing only keywords to reporting the full search strategy, including MeSH terms and text words. The search strategies were often limited, e.g., only a few synonyms were used. In about 50% of cases, the authors also searched for 'gray' literature. Only one review reported a complete list of the included and excluded studies (13).

In six of the reviews, the methodological quality of the included studies was (partially) assessed by the authors and (some of) the results were evaluated. Different methods were used. For example, Röder et al. used the Delphi list (32), Penagos et al. and Hoeks et al. used the Jadad scale (33, 34), the review of Wilson et al. assessed the methodological quality according to the guidelines of the Cochrane Collaboration (35), and Sopo et al. used the criteria provided by the Evidence-Based Medicine Working Group (36). Only four of the 10 reviews used the results of the methodological quality for the analysis in the Conclusions section of the review (16, 26, 29, 30).

For combining the findings of studies, four reviews assessed the homogeneity with the chi-squared test for homogeneity and consequently used a random effects model to pool the data (13, 16, 28, 31). As clinical heterogeneity was present in all of these reviews and acknowledged by the

Table 4 AMSTAR quality assessment of systematic reviews

AMSTAR items	Wilson (13)	Sopo (30)	Olaguibel (28)	Wilson (31)	Penagos (11)	Cox (25)	Hoeks (26)	Larenas- Linneman (27)	Calderon (24)	Röder (29)
1. Was an 'a priori' design provided?	Yes	No	No	Yes	No	No	No	No	No	No
2. Was there duplicate study selection and data extraction?	No	Yes	Yes	No	Yes	No	Yes	No	No	Yes
3. Was a comprehensive literature search performed?	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes
4. Was the status of publication (i.e., grey literature) used as an inclusion criterion?	Yes	No	No	Yes	Yes	No	No	No	Yes	Yes
5. Was a list of studies (included and excluded) provided?	Yes	No	No	No	No	No	No	No	No	No
6. Were the characteristics of the included studies provided?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
7. Was the scientific quality of the included studies assessed and documented?	Yes	Yes	No	Yes	Yes	No	Yes	No	No	Yes
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	No	Yes	NA	No	Yes	NA	Yes	NA	NA	Yes
9. Were the methods used to combine the findings of studies appropriate?	No	NA	No	No	No	NA	NA	NA	NA	NA
10. Was the likelihood of publication bias assessed?	No	No	No	No	No	No	No	No	No	No
11. Was the conflict of interest stated?	Yes	No	No	No	Yes	No	No	No	Yes	No
Total	7	5	3	5	7	1	5	1	3	6
Proportion of applicable items	7/11	5/10	3/10	5/11	7/11	1/9	5/10	1/9	3/9	6/10

NA, not applicable; AMSTAR, assessment of multiple systematic reviews.

authors in two cases (13, 28), the reviews received a negative score on this item. The other reviews did not pool results.

None of the reviews reported measures to avoid publication bias. Three of the 10 reviews provided information about the sources of funding or receiving grants from industry (13, 16, 27).

Of the 10 reviews, six had an overall score between 5 and 8, indicating a review of moderate quality. Both the Cochrane review (2003) (13) and the review of Penagos et al. (16) scored high, with seven of 11 points, followed by Röder et al. (29) with six of 10 points. Four reviews obtained scores of 4 or less, indicating a low quality (24, 25, 27, 28). The mean AMSTAR score was 4.3 (s.d. 2.2), indicating that the quality of the systematic reviews is, on the whole, only low to moderate. Adjustment for the number of applicable items (bottom row of Table 4) yielded very similar results.

Discussion

The aim of this study was to appraise the quality of systematic reviews and meta-analyses evaluating the efficacy of SLIT in children. Between 2000 and 2008, there was an increase in published systematic reviews, with an overlap of effects and conclusions.

Strengths

Our systematic review on SLIT in children with allergic rhinitis is the first to provide insight into methodological quality of the reviews and meta-analyses measured using a validated

checklist. Two reviewers performed quality assessment and data extraction independently.

Limitations

A limitation of the AMSTAR instrument (and many others) is that it does not distinguish between an item that has not *been reported* and an item that has not actually *been done*. Because only information published in the reviews was used, we might have underrated the quality of the reviews. Also, a 'No' for an item may not necessarily be a marker of poor review quality. For example, if no list of excluded studies is reported (Item 5), this may be due to restrictions in the length of the article, rather than to poor reporting.

Although we used an extensive search strategy, our 'review of reviews' could be subject to publication bias. For example, reviews might have been conducted, but not (yet) published. In selecting a specific period (2000–08) for our search, we evidently omitted any reviews published outside this period.

From our initial search, we had to exclude many articles because they did not fulfill our inclusion criteria, a situation not uncommon in literature searches. When designing a search strategy, it is recommended not to be too restrictive in the initial search (35). Most excluded papers did not provide any details about the search strategy, nor what databases or time period was searched.

A variety of search strategies were used, which were not always clear or adequate. For example, searches using less specific terms will identify other study types or other topics (37). A systematic review should be transparent and

reproducible by providing the complete search strategy. This should include terms describing the target population and the intervention of interest. In addition, authors should use the list of synonyms that can be found in the search database (38–40).

The importance of evaluating the methodological quality of primary studies has been emphasized earlier, as it may reduce methodological problems, such as the lack of inadequate randomization methods and concealment of treatment allocation (41). In the present study, more than 50% of the authors of the reviews evaluated the methodological quality of the primary studies in an appropriate way, which is needed to assess the risk of bias in the included studies. Four different methods were used. A large variety of methods are used to evaluate the methodological quality of randomized trials (32, 34, 35). More consensus is needed to increase comparability.

Although the number of systematic reviews on the efficacy of SLIT in children has increased, many have methodological flaws. For example, some did not include unpublished and foreign-language literature. There is abundant evidence that randomized trials with 'positive' results (favoring the new treatment) are published more often and quicker than trials with negative results (finding no difference or favoring the old treatment) (42–47). None of the reviews addressed publication bias, and some did not assess the quality of the studies included in the review. These methodological limitations could have been avoided using standards such as provided in the *Cochrane Handbook for Systematic Reviews of Interventions* or *Quality of Reporting of Meta-analyses (QUOROM)* (35, 48).

To assess the quality of the systematic reviews, we considered several methods, such as the Overview Quality Assessment Questionnaire by Oxman and Guyatt (49) and AMSTAR (20–22). We chose the AMSTAR instrument, as it builds upon previous tools, empirical evidence, and expert consensus and was tested thoroughly by its developers. (20–22)

This study revealed an overall low to moderate methodological quality of systematic reviews, with 40% of the reviews having a score <4, and no reviews of high methodological quality. The mean AMSTAR score of 4.3 (s.d. 2.2) indicates that the quality of the systematic reviews is, on the whole, only low to moderate. Moreover, the quality of reviews has not improved in recent years.

Discussion continues regarding the use of individual component scores or summary scores of a checklist (50, 51). The developers of the AMSTAR aimed to develop an instrument that is pragmatic and of value to decision makers. They ensured that the components do not overlap, and validated the total score against an external standard. The component scores measure different domains of quality, and the overall score is a summary measure (20–22).

Not all systematic reviews contain a meta-analysis. Four of the included reviews pooled results (13, 16, 28, 31). Within the field of SLIT, there is a debate on heterogeneity of meta-analyses on SLIT. In general, the major barrier is that the results of a meta-analysis of heterogeneous studies are diffi-

cult to interpret (52). If significant (statistical or clinical) heterogeneity is present and can be explained, pooling of data should not be considered (35). As illustrated by Malling, heterogeneity can impair the results of meta-analyses, despite accordance with statistical guidelines (53). Given the clinical heterogeneity of the studies (different allergens, different age groups, and different durations) included in the four reviews, pooling the results was considered inappropriate (35).

Before evaluating the quality of systematic reviews and meta-analyses, we should take a step backwards and look at the fundamental elements of systematic review or meta-analyses, the included studies. Well-conducted randomized clinical trials provide the best evidence on the efficacy of medical interventions. A quality assessment of randomized clinical trials is essential in conducting meaningful systematic reviews (54). Within the field of immunotherapy, the last couple of years, the essential for proper evaluation of interventions became well defined. This resulted in guidelines and a checklist for trials with allergen-specific immunotherapy. In 2007, Bousquet et al. (55) presented a paper that critically described how to conduct clinical trials in immunotherapy. The methodology of randomized clinical trials is essential to assess and register treatment interventions. They concluded that very few trials met the criteria for pivotal studies. Also in 2007, Canonica et al. (56) made recommendations for the standardization of clinical trials with allergen-specific immunotherapy for respiratory allergy. This paper summarized the recommendations for study design, patients' selection, appropriate outcomes, and statistical treatment to be used in planning and performing clinical trials with specific immunotherapy. In the context of conducting and reporting trials in allergen-specific immunotherapy, in 2009, Bousquet et al. reflected on the items that should be included in the CONSORT checklist (57) for reporting trials in allergen-specific immunotherapy (58).

Conclusions about the effectiveness of SLIT should be regarded with caution because of the methodological limitations of the reviews and the outcome evaluations on which they are based. From this point of view, in 2009, two meta-analyses reported on SLIT for allergic respiratory diseases (59) and on specific immunotherapy for respiratory allergy (60). Although both discussed the importance of methodological issues in meta-analyses (e.g., publication bias and heterogeneity), the conclusions of the two meta-analyses differ. Nieto et al. (59) reported that the current evidence is not strong enough to support routine treatment with SLIT because the meta-analyses supporting it show features suggesting publication bias and show inconsistent and discrepant conclusions. However, Compalati et al. (60) stated that, according to evidence-based criteria, specific immunotherapy can be recommended for the treatment of respiratory allergy because of its efficacy in reducing asthma and rhinitis symptoms.

Since our search in 2008, several large randomized trials in children have been published that contribute to the overall balance of evidence for SLIT in children, mainly for grass allergens (61–65). Although we did not formally evaluate these trials, the overall reporting quality seems to be improving.

A future update of this review should answer this question in a more systematic way.

Conclusions

To evaluate the efficacy of SLIT in children, a systematic review is useful. Although the number of systematic reviews on SLIT has increased, the methodological quality remains limited and could be improved. SLIT for children could be promising, but methodological flaws in the reviews and the individual studies are too serious to draw balanced conclusions.

To ensure complete and transparent reporting of RCTs, future studies must comply with guidelines as described. This provides more valid estimates of treatment effects and may serve as a reliable basis for the development of evidence-based guidelines.

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Appendix 1: Search strategies

- ✓ The search strategy for PubMed was ('immunotherapy'[MeSH Terms] OR 'immunotherapy'[All Fields] OR 'Desensitization'[All Fields]) OR 'Desensitisation'[All Fields] AND (rhinoconjunctivitis[All Fields] OR ('rhinitis, allergic, seasonal'[MeSH Terms] OR ('rhinitis'[All Fields] AND 'allergic'[All Fields] AND 'seasonal'[All Fields]) OR 'seasonal allergic rhinitis'[All Fields] OR ('hay'[All Fields] AND 'fever'[All Fields]) OR 'hay fever'[All Fields]) OR (perennial[All Fields] AND ('rhinitis'[MeSH Terms] OR 'rhinitis'[All Fields])) OR (allergic[All Fields] AND ('rhinitis'[MeSH Terms] OR 'rhinitis'[All Fields])) AND ('2000/01/01'[PDAT] : '2008/12/31'[PDAT] AND English[lang] AND (Meta-Analysis[ptyp] OR Review[ptyp])) AND English[lang]
- ✓ The search strategy for Embase was ('rhinoconjunctivitis'/exp OR 'perennial rhinitis'/exp OR 'hay fever'/exp OR 'allergic rhinitis'/exp) AND ('active immunization'/exp OR 'immunotherapy'/exp OR 'desensitization'/exp) AND [english]/lim AND [humans]/lim AND [embase]/lim AND ('meta analysis':it,it OR 'review':it,it AND [2000–08]/py)
- ✓ The search strategy for the Cochrane Library was (immunotherapy OR desensitization) AND (rhinoconjunctivitis OR allergic rhinitis OR hay fever) in title, abstract, or keywords

Appendix 2: AMSTAR with additional information per item

AMSTAR

- | | |
|---|---|
| 1. Was an ' <i>a priori</i> ' design provided?
The research question and inclusion criteria should be established before the conduct of the review | ☐ Yes
☐ No
☐ Can't answer
☐ Not applicable |
| 2. Was there duplicate study selection and data extraction?
There should be at least two independent data extractors and a consensus procedure for disagreements should be in place | ☐ Yes
☐ No
☐ Can't answer
☐ Not applicable |
| 3. Was a comprehensive literature search performed?
At least two electronic sources should be searched. The report must include years and databases used (e.g., Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study and by reviewing the references in the studies found | ☐ Yes
☐ No
☐ Can't answer
☐ Not applicable |
| 4. Was the status of publication (i.e., gray literature) used as an inclusion criterion?
The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc. | ☐ Yes
☐ No
☐ Can't answer
☐ Not applicable |
| 5. Was a list of studies (included and excluded) provided?
A list of included and excluded studies should be provided | ☐ Yes
☐ No
☐ Can't answer
☐ Not applicable |
| 6. Were the characteristics of the included studies provided?
In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g., age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported | ☐ Yes
☐ No
☐ Can't answer
☐ Not applicable |
| 7. Was the scientific quality of the included studies assessed and documented?
' <i>A priori</i> ' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo-controlled studies, or allocation concealment as inclusion criteria); for other types of studies, alternative items will be relevant | ☐ Yes
☐ No
☐ Can't answer
☐ Not applicable |
| 8. Was the scientific quality of the included studies used appropriately in formulating conclusions?
The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review and explicitly stated in formulating recommendations | ☐ Yes
☐ No
☐ Can't answer
☐ Not applicable |

Appendix 2 (Continued)

AMSTAR

9. Were the methods used to combine the findings of studies appropriate?	☐ Yes
For the pooled results, a test should be carried out to ensure the studies were combinable to assess their homogeneity (i.e., chi-squared test for homogeneity, P). If heterogeneity exists, a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e., is it sensible to combine?)	☐ No ☐ Can't answer ☐ Not applicable
10. Was the likelihood of publication bias assessed?	☐ Yes
An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test)	☐ No ☐ Can't answer ☐ Not applicable
11. Was the conflict of interest stated?	☐ Yes
Potential sources of support should be clearly acknowledged in both the systematic review and the included studies	☐ No ☐ Can't answer ☐ Not applicable

Appendix 3: Excluded reviews

Title	First author	Year
Safety of sublingual-swallow immunotherapy in children and adults	Andre C	2000
Overview of allergic rhinitis	Berger WE	2003
Economic studies of immunotherapy: A review	Berto P	2008
Current concepts and therapeutic strategies for allergic rhinitis in school-age children	Blaiss M	2004
The safety of sublingual-swallow immunotherapy: An analysis of published studies: Commentary	Bollinger MB	2006
Specific immunotherapy in rhinitis and asthma	Bousquet J	2001
Efficacy of sublingual immunotherapy in asthma: systematic review of randomized clinical trials using the Cochrane Collaboration method	Calamita Z	2006
Allergen injection immunotherapy for seasonal allergic rhinitis	Calderon MA	2007
Accelerated immunotherapy schedules: review of efficacy and safety	Cox L	2006
Sublingual immunotherapy: A comprehensive review	Cox L	2006
Sublingual immunotherapy in pediatric allergic rhinitis and asthma: efficacy, safety, and practical considerations	Cox L	2007
Sublingual immunotherapy and allergic rhinitis	Cox LS	2008
Duration of allergen immunotherapy in respiratory allergy: when is enough, enough?	Cox L	2007
Sublingual immunotherapy, part 1: Review of clinical efficacy	Cox LS	2007
Sublingual immunotherapy in allergic rhinitis and asthma: A review of recent clinical evidence	Erny-Albrecht K	2007
Mite immunotherapy	Fernandez-Caldas E	2006
Sublingual immunotherapy in children	Gerth van Wijk R	2008
The safety of sublingual-swallow immunotherapy: an analysis of published studies	Gidaro GB	2005
Caring for patients with allergic rhinitis	Hayden ML	2007
Allergic rhinitis: epidemiological aspects, diagnosis, and treatment	Ibiapina C	2008
Allergic rhinitis in children: Management guidelines	Jones NS	2004
Sublingual immunotherapy for asthma: Need for high-quality meta-analyses to prove the concept (1)	Larenas-Linnemann D	2007
Allergen Immunotherapy efficacy in rhinitis and asthma	Malling HJ	2004
Immunotherapy for allergic rhinoconjunctivitis	Malling HJ	2004
Subcutaneous immunotherapy for allergic rhinoconjunctivitis, allergic asthma, and prevention of allergic diseases	Malling HJ	2008
Efficacy and safety of allergen immunotherapy in children	Nelson HS	2006
Sublingual immunotherapy: the optimism and the issues	Pajno GB	2007
Allergic rhinitis and its impact on asthma update: allergen immunotherapy	Passalacqua G	2007
An update on sublingual immunotherapy	Passalacqua G	2005
Non-injection routes for allergen immunotherapy: focus on sublingual immunotherapy	Passalacqua G	2006
Oral and sublingual immunotherapy in pediatric patients	Passalacqua G	2003
Non-injection immunotherapy	Passalacqua G	2004

Appendix 3 (Continued)

Title	First author	Year
Meta-analysis of the efficacy of sublingual immunotherapy in the treatment of allergic asthma in pediatric patients, 3–18 yrs of age	Penagos M	2008
Evidence-based strategies for treatment of allergic rhinitis	Portnoy JM	2004
Update on sublingual immunotherapy	Potter PC	2006
Allergen immunotherapy for allergic rhinitis	Railey MD	2008
Sublingual immunotherapy for allergic rhinoconjunctivitis – the seeming and the real	Reider N	2005
Effectiveness of specific immunotherapy in the treatment of allergic rhinitis: an analysis of randomized, prospective, single- or double-blind, placebo-controlled studies	Ross RN	2000
Update on efficacy of allergen immunotherapy for allergic rhinitis and asthma	Saltoun CA	2002
Sublingual immunotherapy: a novel, albeit not so new, immunotherapy treatment modality	Saporta D	2008
Specific allergen immunotherapy for allergic rhinitis and asthma	Vinuya RZ	2000
Efficacy of sublingual immunotherapy in grass pollen allergy	Wessner D	2003