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The Saudi Center for
Evidence Based Health Care

Allergic Rhinitis

Clinical Practice Guideline on Allergic Rhinitis in Asthma

April 2014

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Executive Summary

Introduction

Allergic rhinitis (AR) is defined clinically by nasal hypersensitivity symptoms induced by an immunologically mediated (most often IgE-dependent) inflammation after the exposure of the nasal mucous membranes to an offending allergen. Symptoms of rhinitis include rhinorrhea, nasal obstruction or blockage, nasal itching, sneezing, and postnasal drip that are reversible spontaneously or under treatment. Allergic conjunctivitis often accompanies allergic rhinitis.

Allergic rhinitis represents a global health problem affecting 10 to 20% of the population. This is probably an underestimate, since many patients do not recognize rhinitis as a disease and the prevalence is increasing. Although allergic rhinitis is not usually a severe disease, it affects patients' social life, school performance, and work productivity.

Given the importance of this topic, the Ministry of Health (MoH) of Saudi Arabia with the methodological support of the McMaster University working group produced clinical practice guidelines to assist health care providers in evidence-based clinical decision-making. This guideline evaluates the role of inhaled corticosteroids, inhaled antihistamines and sublingual immunotherapy in the management of allergic rhinitis in this population.

Methodology

This clinical practice guideline is a part of the larger initiative of the Ministry of Health of the Kingdom of Saudi Arabia (KSA) to establish a program of rigorous adaptation and de novo development of guidelines. The ultimate goals are to provide guidance for clinicians and reduce variability in clinical practice across the Kingdom.

The KSA guideline panel selected the topic of this guideline and all clinical questions addressed herein using a formal prioritization process. For all selected questions we updated existing systematic reviews that were used for the 2010 Allergic Rhinitis and its Impact on Asthma (ARIA).[1] We also conducted systematic searches for information that was required to develop full guidelines for the KSA, including searches for information about patients' values and preferences and cost (resource use) specific to the Saudi context. Based on the updated systematic reviews we prepared summaries of available evidence supporting each recommendation following the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach.[2] We used this information to prepare the evidence to recommendation tables that served the guideline panel to follow the structured consensus process and transparently document all decisions made during the meeting (see **Appendix 1**). The guideline panel met in Riyadh on December 3, 2013 and formulated all recommendations during this meeting. Potential conflicts of interests of all panel members were managed according to the World Health Organization (WHO) rules.[3]

How to use these guidelines

The guideline working group developed and graded the recommendations and assessed the quality of the supporting evidence according to the GRADE approach. Quality of evidence (confidence in the available estimates of treatment effects) is categorized as: high, moderate, low, or very low based on consideration of risk of bias, directness, consistency and precision of the estimates. High quality evidence indicates that we are very confident that the *true* effect lies close to that of the estimate of the effect. Moderate quality evidence indicates moderate confidence, and that the *true* effect is likely close to the estimate of the effect, but there is a possibility that it is substantially different. Low quality evidence indicates that our confidence in the effect estimate is limited, and that the *true* effect may be substantially different. Finally, very low quality evidence indicates that the estimate of effect of interventions is very uncertain, the *true* effect is likely to be substantially different from the effect estimate and

further research is likely to have important potential for reducing the uncertainty.
The strength of recommendations is expressed as either strong ('guideline panel recommends…') or conditional ('guideline panel suggests…') and has explicit implications (see **Table 1**). Understanding the interpretation of these two grades is essential for sagacious clinical decision making.

Table 1: Interpretation of strong and conditional (weak) recommendations

Implications	Strong recommendation	Conditional (weak) recommendation
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful helping individuals making decisions consistent with their values and preferences.
For policy makers	The recommendation can be adapted as policy in most situations	Policy making will require substantial debate and involvement of various stakeholders.

Key questions

1. Should intranasal glucocorticosteroids be used in patient with allergic rhinitis?
2. Should intranasal glucocorticosteroids versus intranasal H1-antihistamines be used in patients with allergic rhinitis?
3. Should sublingual specific immunotherapy be used for treatment of allergic rhinitis in adults without concomitant asthma?
4. Should sublingual specific immunotherapy be used for treatment of allergic rhinitis in children younger than 18 years old without concomitant asthma?

Recommendations

Recommendation 1:
The KSA MoH panel recommends intranasal corticosteroids for treatment of adults with seasonal or intermittent allergic rhinitis (Strong recommendation; Moderate-quality evidence).

Remarks:
Health care practitioners in the Middle East should be encouraged to explain the use of INCSs in greater depth to their patients especially about the time required to reach the desired symptom relief.

Recommendation 2:
The KSA MoH panel suggests intranasal corticosteroids for treatment of adults with perennial or persistent allergic rhinitis (Condi-

tional recommendation; Low-quality evidence).

Remarks:
Health care practitioners in the Middle East should be encouraged to explain the use of INCSs in greater depth to their patients especially about the time required to reach the desired symptom relief.

Recommendation 3:
The KSA MoH panel recommends intranasal corticosteroids rather than intranasal H1-antihistamines for treatment of adults with seasonal or intermittent allergic rhinitis (Strong recommendation; High-quality evidence).

Remarks:
In steroidphobic patients and in patients with contraindications for INCS the alternative choice may be equally reasonable.
Health care practitioners in the Middle East should be encouraged to explain the use of INCSs in greater depth to their patients especially about the time required to reach the desired symptom relief.

Recommendation 4:
The KSA MoH panel suggests intranasal corticosteroids rather than intranasal H1-antihistamines for treatment of adults with perennial or persistent allergic rhinitis (Conditional recommendation; Very low-quality evidence).

Remarks:
In steroidphobic patients the alternative choice may be equally reasonable.
Health care practitioners in the Middle East should be encouraged to explain the use of INCSs in greater depth to their patients especially about the time required to reach the desired symptom relief.

Recommendation 5:
The KSA MoH panel suggests sublingual immunotherapy for treatment of adults with seasonal or intermittent allergic rhinitis (conditional recommendation; Moderate-quality evidence).

Remarks:
The SLIT should be used only when all other regular options do not work: It is more appropriate for those with moderate to severe AR who do not respond to first line therapy.
The SLIT should not be started during pregnancy, but could be continued if the woman has already started the treatment.

Recommendation 6:
The KSA MoH panel suggests sublingual immunotherapy for treatment of adults with perennial/persistent allergic rhinitis (conditional recommendation; very low-quality evidence).

Remarks:
The SLIT should be used only when all other regular options do not work: It is more appropriate for those with moderate to severe AR who do not respond to first line therapy.
The SLIT should not be started during pregnancy, but could be continued if the woman has already started the treatment.

Recommendation 7:
The KSA MoH panel suggests sublingual immunotherapy for treatment of children younger than 18 years old with seasonal or intermittent allergic rhinitis (Conditional recommendation; Moderate-quality evidence)

Remarks:
The SLIT should be used only when all other regular options do not work: It is more appropriate for those with moderate to severe AR who do not respond to first line therapy.
The SLIT should not be started during pregnancy, but could be continued if the woman has already started the treatment.

Recommendation 8:
The KSA MoH panel suggests sublingual immunotherapy be not used for treatment of children younger than 18 years old with perennial or persistent allergic rhinitis (Conditional recommendation; very low-quality evidence)

Remarks:
In special situations, children not responding to maximal medications may be referred to an allergy specialist for evaluation of indications for immunotherapy.

Scope and purpose

The purpose of this document is to provide guidance about selected clinical questions on the treatment of allergic rhinitis. The target audience of these guidelines includes primary care physicians and allergy specialists in the Kingdom of Saudi Arabia. Other health care professionals, public health officers and policy makers may also benefit from these guidelines.

Given the importance of this topic, the Ministry of Health (MoH) of Saudi Arabia with the methodological support of the McMaster University working group produced clinical practice guidelines to assist health care providers in evidence-based clinical decision-making. This clinical practice guideline is a part of the larger initiative of the Ministry of Health of Saudi Arabia to establish a program of rigorous adaptation and de novo development of guidelines in the Kingdom; the ultimate goal being to provide guidance for clinicians and reduce variability in clinical practice across the Kingdom.

Introduction

Allergic rhinitis (AR) is defined clinically by nasal hypersensitivity symptoms induced by an immunologically mediated (most often IgE-dependent) inflammation after the exposure of the nasal mucous membranes to an offending allergen. Symptoms of rhinitis include rhinorrhea, nasal obstruction or blockage, nasal itching, sneezing, and postnasal drip that are reversible spontaneously or under treatment. Allergic conjunctivitis often accompanies allergic rhinitis.

Allergic rhinitis has been traditionally subdivided into seasonal, perennial, and occupational rhinitis. Perennial allergic rhinitis is most frequently, although not necessarily, caused by indoor allergens such as house dust mites, moulds, cockroaches, and animal dander. Seasonal allergic rhinitis is most often caused by outdoor allergens such as pollens or moulds. As in the 2010 edition of the ARIA guideline,[1] in this document we retained the terms “seasonal” and “perennial” to enable the interpretation of published studies, and we also include the terms used to classify AR according to the duration of symptoms as “intermittent” rhinitis (symptoms are present less than 4 days a week or for less than 4 weeks) or “persistent” (symptoms are present at least 4 days a week and for at least 4 weeks).

Allergic rhinitis represents a global health problem affecting 10 to 20% of the population. This is probably an underestimate, since many patients do not recognize rhinitis as a disease and the prevalence is increasing.[4] Although allergic rhinitis is not usually a severe disease, it affects patients’ social life, school performance, and work productivity.

There are few studies reporting the prevalence of the allergic rhinitis in Saudi Arabia, some of the most recent studies determine prevalence around 10-25 %.[5-7] Nevertheless, it is considered that these self-reporting studies could underestimate the prevalence (by not recognizing the symptoms as a disease or not having a medical diagnosis) or overestimate (by considering any kind of rhinitis not only allergic rhinitis). However, it is a fact that there is a lack of an appropriate database which collects this data and the panel members of this guideline, based on their clinical experience, estimate prevalence from 20% to 40% of AR in the KSA.

Nasal allergies have a big impact on patients' lives all around the world, and work productivity levels and daily activities are hugely affected in a large proportion of individuals with nasal allergies. A high percentage of patient surveyed in several regions of the world missed work or had their work performance affected by allergies in the past year, with work productivity decreasing by 30% in patients from the Middle East when allergy symptoms were at their worst (23% in America, 24% in Asia Pacific and 33% in Latin America).[6]

Methodology

To facilitate the interpretation of these guidelines; we briefly describe the methodology we used to develop and grade recommendations and quality of the supporting evidence. We present the detailed methodology in a separate publication.[8]

The KSA guideline panel selected the topic of this guideline and all clinical questions addressed herein using a formal prioritization process. The questions chosen by the guideline panel were adapted to make them applicable to the Saudi context. For all selected questions we updated existing systematic reviews that were used for the Allergic Rhinitis and its Impact on Asthma (ARIA) guideline.[1] We also conducted systematic searches for information that was required to develop full guidelines for the KSA, including searches for information about patients' values and preferences and cost (resource use) specific to the Saudi context. Based on the updated systematic reviews (see **Appendix 3**) we prepared summaries of available evidence supporting each recommendation following the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach.[2]

We assessed the quality of evidence using the system described by the GRADE working group.[9]
Quality of evidence is classified as "high", "moderate", "low", or "very low" based on decisions about methodological characteristics of the available evidence for a specific health care problem. The definition of each category is as follows:

- *High*: We are very confident that the true effect lies close to that of the estimate of the effect.
- *Moderate*: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- *Low*: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
- *Very low*: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

According to the GRADE approach, the strength of a recommendation is either strong or conditional (weak) and has explicit implications (see **Table 1**). Understanding the interpretation of these two grades – either strong or conditional – of the strength of recommendations is essential for sagacious clinical decision-making.

Based on this information and the input of KSA MoH panel members we prepared the *evidence-to-recommendation* tables that served the guideline panel to follow the structured consensus process and transparently document all decisions made during the meeting (see **Appendix 1**). The guideline panel met in Riyadh on December 3, 2013 and formulated all recommendations during this meeting. Potential conflicts of interests of all panel members were managed according to the World Health Organization (WHO) rules.[3]

How to use these guidelines

The Ministry of Health of Saudi Arabia and McMaster University Clinical Practice Guidelines provide clinicians and their patients with a basis for rational decisions in the management of Allergic Rhinitis with intranasal glucocorticosteroids, intranasal antihistamines and sublingual immunotherapy. Clinicians, patients, third-party payers, institutional review committees, other stakeholders, or the courts should never view these recommendations as dictates. No recommendation can take into account all of the often-compelling unique features of individual clinical circumstances. Therefore, nobody charged with evaluating clinicians' actions should attempt to apply the recommendations from these guidelines as rote or in a blanket fashion.

Statements about the underlying values and preferences as well as qualifying remarks accompanying each recommendation are its integral parts and serve to facilitate an accurate interpretation. They should never be omitted when quoting or translating recommendations from these guidelines.

Key questions

The following is a list of the clinical questions selected by the KSA guideline panel and addressed in this guideline. For details on the process by which the questions were selected for this guideline please refer to the separate methodology publication.[8]

1. Should intranasal glucocorticosteroids be used in patient with allergic rhinitis?
2. Should intranasal glucocorticosteroids versus intranasal H1-antihistamines be used in patients with allergic rhinitis?
3. Should sublingual specific immunotherapy be used for treatment of allergic rhinitis in adults without concomitant asthma?
4. Should sublingual specific immunotherapy be used for treatment of allergic rhinitis in children younger than 18 years old without concomitant asthma?

Recommendations

Question 1: Should intranasal glucocorticosteroids be used in patient with allergic rhinitis?

Summary of Findings:
One systematic review published in 2008, and included in the ARIA 2010 guideline,[1] investigated the effects of mometasone fuorate nasal spray compared to placebo in patients with seasonal and perennial allergic rhinitis.[10] Another systematic review from 2011, which has been added in this update, evaluated the effects of fluticasone fuorate spray.[11] We found an additional 33 randomized controlled trials eligible for quantitative analysis and published since the last search was performed in these systematic reviews (from January 2007 to October 2013) and that fulfilled the criteria for quality and entry into this update.

We based our judgements on the systematic reviews of mometasone[10] and fluticasone[11] and on the systematic review and meta-analysis that we were able to perform for this guideline with the selected six individual studies about glucocorticosteroids[12-17] (both mometasone and fluticasone) versus placebo.

Summary of the results:
Seasonal allergic rhinitis
Based on both systematic reviews of intranasal corticosteroids versus placebo,[10,11] and our own update of the evidence from individual RCTs,[12-17] in patients with seasonal/intermittent AR intranasal glucocorticosteroids moderately reduced total nasal symptoms (measured by the total nasal symptom score -TNSS) of seasonal allergic rhinitis in adults; as well as the symptoms of nasal congestion, rhinorrhea, sneezing, itching, and a small reduction on ocular symptoms. Three studies measured quality of life with a reduction in the total score in favour of the intranasal glucocorticosteroids. One study was performed in children with seasonal allergic rhinitis and found an effect of mometasone on nasal symptoms similar to that in adults.

Both systematic reviews[10,11] included patients with perennial allergic rhinitis and the information could be updated with new randomized trials. Based on this body of evidence, intranasal glucocorticosteroids moderately reduced total nasal symptoms (measured by the total nasal symptom score –TNSS) in patients with perennial / persistent AR. As in seasonal rhinitis, intranasal corticosteroids reduced the symptoms of nasal congestion, sneezing, itching, and with a smaller effect the ocular symptoms. Three studies measured quality of life with a moderate reduction in the total score in favour of the intranasal glucocorticosteroids.

Information on adverse events could be obtained from both systematic review of mometasone fuorate and fluticasone vs placebo.[10,11] The proportion of patients who experienced adverse events was similar in the intranasal corticosteroids and placebo groups in both sub-groups of seasonal and perennial allergic rhinitis.

Systematic reviews of other intranasal glucocorticosteroids compared to other active treatments reported low incidence of adverse effects. Epistaxis, headache, taste perversion, and pharyngitis were the most frequently reported side-effects of intranasal glucocorticosteroids in these reviews.[10,11] None of the short-term treatment studies analyzed in the reviews reported systemic side effects from intranasal glucocorticosteroids, although there has been concern that the prolonged use of intranasal glucocorticosteroids may be associated with systemic adverse effects including suppression of the hypothalamic-pituitary-adrenal axis and suppression of growth in children. Although these effects were observed in few studies we were not able to identify any systematic review to inform the assessment of the risk and its magnitude.

The overall quality of evidence for the effect of INCS compared with placebo was judged to be “moderate” in patients with seasonal/intermittent AR and the panel members felt that the desirable effects are probably large relative to undesirable effects. On the other hand in patients with perennial/persistent AR the overall quality of evidence was judge to be “low”, but the magnitude of the desirable effects of INCS are also considered probably large relative to undesirable effects.

Values and Preferences:
We identified two publications related with a multiattribute Rhinitis Symptom Utility Index (RSUI) which reported utility-based measures.[18,19] The first of the publication is the development and the preliminary validation of the RSUI[18,19] conducted in the USA. The second Chinese publication aims to examine similarities and differences in preference-based measures between Western and Asian respondents.[18,19] No studies were identified in the context of the KSA.

The results of a series of patient surveys conducted between 2006 and 2011, covering the United States, Asia-Pacific, Latin America, and the Middle East were published in 2013.[20] The purpose of this article was to compare the results of the Allergic in Middle East (AIME) survey[5] with those from the other landmark allergy surveys worldwide and to discuss differences and similarities with regard to the burden of allergic rhinitis, treatment outcomes, and expectations. The AIME[5] was conducted to a total of 501 patients across Egypt, Iran, Lebanon, Saudi Arabia, and the United Arab Emirates. Its results showed that the majority of survey participants with AR reported that the condition had an impact on their daily private and professional life, limiting their work/school activities and interfering with and caused them to miss work or school. The most common reasons cited for dissatisfaction with INCS medications were inadequate effectiveness, bothersome side effects (e.g., unpleasant taste and retrograde drainage into the pharynx), decreased effectiveness with chronic use, and failure to provide 24-hour relief [5].

Comparing with the results of others allergy surveys worldwide a higher proportion of patients in the Middle East reported bothersome side effects of their prescription nasal sprays, and a higher proportion of these patients strongly agreed that there were no truly effective treatments for allergic rhinitis. This suggests that health care practitioners in the Middle East should be encouraged to explain the use of INCSs in greater depth to their patients[20] and that patient education must play a central role in treatment decision making, particularly in the Middle East, to achieve higher patient satisfaction.

This recommendation places a relatively high value on the mild effect of intranasal glucocorticosteroids reducing symptoms, and a relatively low value on avoiding their possible

moderate adverse effects, for both evidence for intermittent / seasonal AR and perennial / persistent AR patients.

Resource Use:
No cost effectiveness studies were found in the context of the KSA. Nevertheless, it is considered a relatively low cost for the drug. Indirect evidence reported in a Canadian retrospective cost-effectiveness study[21] which analyse the total treatment costs based on "blocked nose" in two different INCS drugs and including the relative importance of the drug costs in the total cost shows that: The average treatment cost per patient in Canada over 12 months in fluticasone Intranasal was CAD 508.06 with a drug cost per patient of 214 CAD. In the context of Saudi Arabia and base on the official acquisition/ public price costs from the official Saudi FDA website[22] the average annual cost of intranasal corticosteroids per patient in Saudi Arabia is estimated around 600 SAR. Thus, the panel members considered that the incremental cost is probably small relative to the net benefits.

Implementation Considerations:
Health care practitioners in the Middle East should be encouraged to explain the use of INCSs in greater depth to their patients especially about the time required to reach the desired symptom relief.
Different INCS should be available to provide choice opportunity for different patient preferences related with drug characteristics, such as smell for example.

Research Priorities:
Nation-wide population-based community prevalence studies are needed to correctly estimate the AR rates. Information on patients' values and preferences and cost effectiveness studies about SLIT is also needed in the context of the KSA to inform future guidelines and stakeholders.
Further research is needed to answer the question about the efficacy and specially safety of intranasal glucocorticosteroids in children with AR.
A complete rigorously performed and reported systematic review of all individual intranasal glucocorticosteroids (budesonide, ciclesonide and beclomethasone) versus placebo that provides information on all outcomes important to patients, including adverse effects, is required.

Recommendation 1: Seasonal/intermittent Allergic Rhinitis

The KSA MoH panel recommends Intranasal corticosteroids for treatment of adults with seasonal or intermittent allergic rhinitis (Strong recommendation; Moderate-quality evidence).

Remarks:
Health care practitioners in the Middle East should be encouraged to explain the use of INCSs in greater depth to their patients especially about the time required to reach the desired symptom relief.

Recommendation 2: Perennial/persistent Allergic Rhinitis

The KSA MoH panel suggests Intranasal corticosteroids for treatment of adults with perennial or persistent allergic rhinitis (Conditional recommendation; Low-quality evidence).

Remarks:
Health care practitioners in the Middle East should be encouraged to explain the use of INCSs in greater depth to their patients especially about the time required to reach the desired symptom relief.

Question 2: Should intranasal glucocorticosteroids versus intranasal H1-antihistamines be used in adults with allergic rhinitis?

Summary of Findings:
One systematic review published in 2013 investigated the effects of intranasal corticosteroids compared with intranasal H1 antihistamines in adults with seasonal AR.[23] Another systematic review from 2002 and already included in the 2010 ARIA guideline, evaluated the effects of these same medications in patients with seasonal and perennial AR.[24] We

found additional 8 randomized controlled trials and 5 systematic reviews potentially eligible for quantitative analysis and published since the last search performed in these systematic reviews. Some of these RCTs were included in previous systematic reviews and other reasons for excluding these 13 studies can be found in appendix 3.
We analyzed seasonal and perennial AR separately. We based our judgements on Glacy et al. (1) and Yañez et al (2) systematic reviews' RCT for seasonal AR and on three RCTs[25-27] included in Yañez et al (2) for perennial AR.

Summary of the results:
The aggregation of the data from the RCTs included in both, the selected new SR[23] and the one included in ARIA 2010 guideline,[24] shows that in adults with seasonal/intermittent AR intranasal glucocorticosteroids reduced the total nasal symptoms moderately more than intranasal antihistamines. The reduction of the specific rhinitis symptoms including nasal congestion, rhinorrhea, itching and sneezing, is also bigger in with the INCS but the differences are smaller. The ocular symptoms reduction is no different with the two medication options. Studies measuring quality of life using the RQLQ instrument showed statistically no significant treatment effects in favour of intranasal corticosteroid. These results were consistent between pooled and non-pooled data, favouring intranasal corticosteroid, but they didn't exceed the minimally important difference (MID) of 0.5 points.

Three RCTs[25-27] included adults with perennial/persistent allergic rhinitis. Based on the body of this evidence, intranasal glucocorticosteroids seem to reduce the total nasal symptoms moderately more than intranasal antihistamines. This effect is mostly observed in the large reduction of nasal blockage symptoms rand on itching reduction. None these studies measured quality of life.

For patients with seasonal AR most adverse events were rated as mild or moderate, and there were no differences between groups. The most frequently reported adverse events were taste perversion, intolerance to nasal spray, infection, headache, flu-like disorders and epistaxis.
The overall quality of evidence for the effect of INCS compared with INAH was judged to be "high" in patients with seasonal/intermittent AR and the panel members felt that the desirable effects are probably large relative to undesirable effects. On the other hand in patient with perennial/persistent AR the overall quality of evidence was judge to be "very low", but the magnitude of the desirable effects of INCS are also considered probably large relative to undesirable effects and to the effects of INAH.

Values and Preferences:
This recommendation places a relatively high value on the efficacy of intranasal glucocorticosteroids and on avoiding intranasal antihistamines' adverse effects, and a relatively low value on avoiding INCS possible adverse effects.

Resource Use:
Only one study with information about the cost of the medication, conducted in Ankara, Turkey, was found.[28] In this observational study a symptom-medication score-based cost analysis calculated a mean medication costs of $20.2 ±1.1 for nasal steroids per person without a comorbid disorder during a Gramineae pollen season, while the total cost of the SAR per person was estimated in $79.0 ± 3.3. The cost of the INAH is not calculated in this study and we do not have comparable information about the cost of the INAH. In the context of Saudi Arabia the cost of INCS medication is around the half of the cost of INAH. Based on the official acquisition/ public price costs from the official Saudi FDA website [22] the average annual INCS cost per patient in Saudi Arabia is estimated around 600 SAR, while the average annual INAH cost per patient is around 1200 SAR.

Other Considerations:
It is considered that patients from the KSA usually accept what their doctors prescribe for them and that any of the options would be acceptable from a health care system perspective.

Implementation Considerations:
Clinicians should be aware that patient education is crucial, especially about the time required to reach the desired symptom relief. Different INCS should be available to provide opportunity for different patient preferences and choices related to drug characteristics, such as smell for example. At least one antihistamine should be also available for steroidphobic and for patients with contraindications for INCS.

Research Priorities:
Further research is needed to answer the question about the efficacy and safety of intranasal glucocorticosteroids in adults with perennial AR.

Recommendation 3: Seasonal/intermittent Allergic Rhinitis

The KSA MoH panel recommends Intranasal corticosteroids rather than intranasal H1-antihistamines for treatment of adults with seasonal or intermittent allergic rhinitis (Strong recommendation; High-quality evidence).

Remarks:
In steroidphobic patients and in patients with contraindications for INCS the alternative choice may be equally reasonable.
Health care practitioners in the Middle East should be encouraged to explain the use of INCSs in greater depth to their patients especially about the time required to reach the desired symptom relief.

Recommendation 4: Perennial/persistent Allergic Rhinitis

The KSA MoH panel suggests Intranasal corticosteroids rather than intranasal H1-antihistamines for treatment of adults with perennial or persistent allergic rhinitis (Conditional recommendation; Low-quality evidence).

Remarks:
In steroidphobic patients the alternative choice may be equally reasonable.

Health care practitioners in the Middle East should be encouraged to explain the use of INCSs in greater depth to their patients especially about the time required to reach the desired symptom relief.

Question 3: Should sublingual specific immunotherapy be used for treatment of allergic rhinitis in adults without concomitant asthma?

Summary of Findings:
The search strategy carried out for the update of this question, resulted in 140 review documents from which 25 were selected after the screening of titles and abstracts. The full text of these 25 reviews were assessed and one HTA report [29] and a Cochrane Systematic review [30] were selected to update this question.
The HTA report [29] published in 2013 aims to determine the comparative clinical effectiveness and cost-effectiveness of subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) for seasonal allergic rhinitis in adults and children. The Cochrane Systematic Review, published in 2010 aims to evaluate the efficacy and safety of sublingual immunotherapy for allergic rhinitis in adults and children. This last review includes studies about both seasonal or intermittent and perennial or persistent allergic rhinitis. The HTA's purpose was to update, rather than repeat, the Cochrane review published in 2010,[30] so only the results of 11 new studies published from 2009 onwards were presented, although all 44 relevant RCTs already included in the Cochrane review were included in the meta-analyses. Therefore we carried out a search for new RCTs to update the evidence for perennial or persistent AR, since the last search performed in these systematic reviews (from January 2009 to November 2013). The search resulted in 96 documents from which 5 were selected for the full text assessment. Finally, only two RCTs were selected[31,32] and included in our update because they fulfilled the quality criteria. One of the excluded studies was conducted with patients with seasonal AR and it was included in the HTA report,[33] the other did not evaluate outcomes of our interest[34]

and the last one did not provide available useful data[7].

Summary of the results:
In adults with seasonal or intermittent allergic rhinitis SLIT compared to placebo had a statistically significant small to moderate reductions in symptom scores and ocular symptoms. The medication score was also moderately decreased and the combined symptom and medication scores (SMSs). Moreover the sensitivity analysis carried out for the authors showed that these effects were largely unrelated to participant age, treatment duration or type of allergens. Adults treated with SLIT have improved quality of life, although the effect is not clinically relevant.

In adults with perennial or persistent allergic rhinitis SLIT compared to placebo had a higher reduction in symptom scores, although the results are inconsistent across studies with risk of bias and imprecise duo to low participants' number. The medication scores did not show differences between SLIT and placebo and the authors of the unique study assessing the quality of life reported that there was no statistical change in all the domains of the SF-36 questionnaire at the six time points, and that all the scores were quite high, but the magnitude and precision of this effect was impossible to assess.

There were no serious adverse effects reported in any of 42 studies of SLIT in adults with intermittent or persistent allergic rhinitis (altogether 4461 patients receiving SLIT). However, local adverse effects – most commonly oral pruritus, oral and labial oedema and gastrointestinal intolerance were frequent in the SLIT groups and significantly more often led to discontinuation of treatment in adults with intermittent AR . Six trials included in the HTA report meta-analysis, five including adults (n=938), reported systemic events by severity: The vast majority (73%) of systemic AEs in these trials were of mild intensity, 24% were of moderate intensity and 3% were graded as severe, those reported in this outcome.

The overall quality of evidence for the effect of SLIT was judged to be "moderate" in patients with seasonal/intermittent AR and the panel members felt that the desirable effects probably are not large relative to undesirable effects. On the other hand, in patients with perennial/persistent AR the overall quality of evidence was judged to be "very low", and the magnitude of the desirable effects relative to undesirable effects was uncertain.

Values and Preferences:
This recommendation places a relatively high value on alleviating the symptoms of rhinitis, and relatively low value on avoiding adverse effects and resource expenditure. Local adverse effects are relatively frequent (~35%). An alternative choice may be equally reasonable, if patients' values or preferences differ from those described here. Possibly there is important variability about how much people value its effectiveness because there is a concern that some patients in the KSA would not accept SLIT with some allergens of animal origin, however others would accept it as the last option when the symptoms do not decrease with all other regular options.

Resource Use:
There are no published or unpublished data on the cost effectiveness of SLIT in the context of Saudi Arabia. Based on the official acquisition/ public price costs from the official Saudi FDA website [22] the average annual cost per patient in Saudi Arabia is estimated around 35,000 SAR and the average cost per treatment (3 years) per patient around 100,000 SAR. On the other hand, a recent HTA report [29] with a cost-effectiveness review suggested that SLIT compared with standard therapy was just more effective or, in some cases, both more effective and cost-effective. Thus, the panel members considered that the incremental cost is not small relative to the net benefits.

Other Considerations:
If sublingual immunotherapy use were to be recommended, health inequity will increase so the indications and the applications of SLIT should be determined. The SLIT should be

used only when all other regular options do not work. Therefore only few patients will be affected. There would be uncertainty in acceptance from patients, and likely low acceptability from the health care system perspective because of cost considerations. Furthermore, the implementation would require expert personnel and resources (i.e. skin tests, specific allergen) which are not readily available in most areas.

Implementation Considerations:
SLIT should only be prescribed by allergy specialists who have expertise in diagnosis of AR, proper identification of the allergens, providing immunotherapy and treatment of potentially serious adverse effects.

Monitoring and Evaluation:
If patients receiving SLIT do not respond within 6-12 months consider discontinuation of SLIT.

Research Priorities:
RCTs which evaluate the effectiveness of SLIT in patients with perennial / persistent AR are required. Nation-wide population-based community prevalence studies are needed to correctly estimate AR rates. Information on patients' values and preferences and cost effectiveness studies about SLIT are also needed in the context of the KSA to inform future guidelines and stakeholders.

Recommendation 5: Seasonal/intermittent Allergic Rhinitis

The KSA MoH panel suggests sublingual immunotherapy for treatment of adults with seasonal or intermittent allergic rhinitis (Conditional recommendation; Moderate-quality evidence).

Remarks:
The SLIT should be used only when all other regular options do not work: It is more appropriate for those with moderate to severe AR who do not respond to first line therapy.
The SLIT Should not be started during pregnancy, but could be continued if the woman has already started the treatment.

Recommendation 6: Perennial/persistent Allergic Rhinitis

The KSA MoH panel suggests sublingual immunotherapy for treatment of adults with perennial/persistent allergic rhinitis (Conditional recommendation; Very low-quality evidence).

Remarks:
The SLIT should be used only when all other regular options do not work: It is more appropriate for those with moderate to severe AR who do not respond to first line therapy.
The SLIT Should not be started during pregnancy, but could be continued if the woman has already started the treatment.

Question 4: Should sublingual specific immunotherapy (SLIT) be used for treatment of allergic rhinitis (AR) in children younger than 18 years old without concomitant asthma?

Summary of Findings:
The search strategy carried out for the update of this question was the same as the one used to update the question about sublingual immunotherapy in adults. The two documents selected to update the evidence for this question, since its last update from the ARIA guideline in 2010, were an HTA report[29] and a Cochrane Systematic review.[30]
The HTA report [29] published in 2013 aims to determine the comparative clinical effectiveness and cost-effectiveness of subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) for seasonal allergic rhinitis in adults and also in children. The Cochrane Systematic Review, published in 2010 aims to evaluate the efficacy and safety of sublingual immunotherapy for allergic rhinitis in adults and children. This last review includes studies about both seasonal or intermittent and perennial or persistent allergic rhinitis. The HTA report updated the Cochrane systematic review for seasonal or intermittent rhinitis so we also carried out a search for new RCTs to update the evidence for perennial or persistent AR, since the last search performed in these systematic reviews (from January 2009 to November 2013). From the search, only

one RCT[31] with children with perennial or persistent AR and which fulfilled the quality criteria was selected to be included in this update.

Summary of the results:
In children with seasonal allergic rhinitis SLIT compared to placebo has small effect on nasal symptoms and probably also on ocular symptoms. The medication score seemed to be similar in both group of children with and without the treatment and the combined symptom and medication scores (SMSs) only studied in the most new study showed a small decrease with the SLIT. The study which reports the quality of life suggests a slight improvement in children treated with SLIT, although it was not clinically relevant.

Studies that used SLIT in children allergic mainly to house dust mite, hence, children with perennial or persistent AR, did not find evidence of its efficacy. There was no effect on nasal symptoms and medication scores. The studies providing these results had some methodological limitations, with some inconsistency and the results that did not exclude a small benefit or small harm. No study measured quality of life.

There were no serious adverse effects reported in any of the included studies of SLIT in children with allergic rhinitis, intermittent or persistent, which measured this outcome (altogether 550 children receiving SLIT). Other adverse effects were poorly reported in the included studies. Similar to SLIT in adults, local adverse effects (oral and labial pruritus and oedema) were frequent in the SLIT groups and more often led to discontinuation of treatment, but these estimates are very imprecise.

Cox et al. also reviewed observational studies that provided any information on safety or tolerance of SLIT in children.[35] Two observational studies (98 children) and one post-marketing survey (126 children) assessed safety of SLIT in 2-7 year old children with allergic rhinitis or asthma. In one study, children received SLIT with a monomeric allergoid (22,200 doses altogether) and were followed for 22 months. Two children had abdominal pain (1 episode each; 5% of patients; 7.1 per 100,000 doses). In a second study children received SLIT to various pollens or house dust mites for 8 months. There were 13 adverse events in 11 children (6 episodes of urticaria, 4 gastrointestinal symptoms, and 3 oral itch; all were reported to be mild or moderate, and none required discontinuation of treatment). A post-marketing survey of children treated with SLIT to various allergens for 2 years (39,000 doses) found 9 adverse events recorded by parents on diary cards in 7 children (5.6% of children; 2.3 per 10,000 doses). Of these 7 were systemic reactions (1 mild abdominal pain, 6 moderate abdominal pain with diarrhoea), and 2 were oral itching. All events occurred during the induction phase.

The overall quality of evidence for the effect of SLIT was judged to be “moderate” in children with seasonal/intermittent AR and the panel members felt that the desirable effects probably are not large relative to undesirable effects. On the other hand in children with perennial/persistent AR the overall quality of evidence was judged to be “very low”, and the magnitude of the desirable effects relative to undesirable effects uncertain.
Values and Preferences:

This recommendation to use sublingual immunotherapy in children with seasonal allergic rhinitis places a relatively high value on a small reduction in nasal symptoms and relatively low value on avoiding adverse effects and resource expenditure because studies conducted in the Middle East showed that the psychological and physical health of caregivers, who were primarily mothers, was strongly influenced by child chronic disease.[36,37] A review conducted in the United States also reported that allergic rhinitis can affect children’s learning ability and performance at school and cause somnolence and inability to concentrate in children.[38] Possibly there is important variability about how much people value its effectiveness because there is a concern that some patients in the KSA would not accept SLIT with some allergens of animal origin, however others would accept it as the

last option when the symptoms do not decrease with all other regular options.
The recommendation to use sublingual immunotherapy in children with perennial allergic rhinitis only in the context of clinical research places a relatively high value on avoiding adverse effects and resource expenditure, and relatively low value on a possible small reduction in nasal symptoms.
Local adverse effects are relatively frequent (~35%). An alternative choice may be equally reasonable, if patients' values or preferences differ from those described here.

Other Considerations:
If sublingual immunotherapy use were to be recommended, health inequity will increase so the indications and the applications of SLIT should be determined. The SLIT should be used only when all other regular options do not work. There would be uncertainty in acceptance from patients, and likely low acceptability from the health care system perspective because of cost considerations. Furthermore, the implementation would require expert personnel and resources (i.e. skin tests, specific allergen) which are not readily available in most areas.

Implementation Considerations:
If SLIT is prescribed in special situations it should be for children older than 5 years old and administered only by allergy specialists who have expertise in diagnosis of AR, proper identification of the allergens, providing immunotherapy and treatment of potentially serious adverse effects.

Monitoring and Evaluation:
If patients receiving SLIT do not respond within 6-12 months consider discontinuation of SLIT

Research Priorities:
There is a need for rigorously designed and executed randomised trials of SLIT in children younger and older than 5 years old, especially with perennial/persistent allergic rhinitis, that measure and properly report patient-important outcomes and adverse events. Further research, if done, will have important impact on this recommendation.
Nation-wide population-based community prevalence studies are needed to correctly estimate the AR rates in children. Information on patients' values and preferences and cost effectiveness studies about SLIT are also needed in the context of the KSA to inform future guidelines and stakeholders.

Recommendation 7: Seasonal/intermittent Allergic Rhinitis

The KSA MoH panel suggests sublingual immunotherapy for treatment of children younger than 18 years old with seasonal or intermittent allergic rhinitis (Conditional recommendation; Moderate-quality evidence)

Remarks:
The SLIT should be used only when all other regular options do not work: It is more appropriate for those with moderate to severe AR who do not respond to first line therapy.
The SLIT Should not be started during pregnancy, but could be continued if the woman has already started the treatment.

Recommendation 8: Perennial/persistent Allergic Rhinitis

The KSA MoH panel suggests sublingual immunotherapy be not used for treatment of children younger than 18 years old with perennial or persistent allergic rhinitis (Conditional recommendation; Very low-quality evidence)

Remarks:
In special situations in children not responding to maximal medications may be referred to an allergy specialist for evaluation of indications for immunotherapy.

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Appendices

1. Evidence-to-Recommendation Tables and Evidence Profiles
2. Forest Plots
3. Search Strategies and Results

Appendix 1: Evidence-to-Recommendation Tables and Evidence Profiles

Evidence to recommendation framework 1

Question 1: Should intranasal corticosteroids be used in patients with allergic rhinitis (AR)?

Problem: Allergic Rhinitis (seasonal and perennial)
Option: intranasal corticosteroids
Comparison: No intranasal corticosteroids
Setting: Outpatient
Perspective: Health Care system

Background: Allergic rhinitis (AR) is defined clinically by nasal hypersensitivity symptoms induced by an immunologically mediated (most often IgE-dependent) inflammation after the exposure of the nasal mucous membranes to an offending allergen. Symptoms of rhinitis include rhinorrhea, nasal obstruction or blockage, nasal itching, sneezing, and postnasal drip that are reversible spontaneously or under treatment. Allergic conjunctivitis often accompanies allergic rhinitis.

Allergic rhinitis has been traditionally subdivided into seasonal, perennial, and occupational rhinitis. Perennial allergic rhinitis is most frequently, although not necessarily, caused by indoor allergens such as house dust mites, moulds, cockroaches, and animal dander. Seasonal allergic rhinitis is most often caused by outdoor allergens such as pollens or moulds. As in a 2010 edition of ARIA guideline in this document we retained the terms “seasonal” and “perennial” to enable the interpretation of published studies, and we also include the terms used to classify AR according to the duration of symptoms as “intermittent” rhinitis (symptoms are present less than 4 days a week or for less than 4 weeks) or “persistent” (symptoms are present at least 4 days a week and for at least 4 weeks).

These guidelines do not address the issues related to diagnosis of allergic rhinitis and it is assumed that the correct diagnosis had been established before commencing treatment.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ ***Varies*** ☐	1. Overall risk of AR in adults Saudi Arabia is 90 per 1000 (79% SAR) Overall in the Middle East: • Runny nose, nasal and throat itching, postnasal drip, and nasal congestion or stuffed up nose were the most common and bothersome symptoms of AR. • 58% of participants with AR reported that the condition had an impact on their daily private and professional life. • 72% reported that limitations on their work/school activities • 35% reported that interfered with and caused them to miss work or • Sleep disturbances were shown in this survey to be extremely troubling in 15% of AR patients. (Abdulrahman H, 2012. Survey conducted in Middle East including KSA) 2. A high percentage of patients with AR surveyed missed work or had their work performance affected by allergies: work productivity decreasing by 23% in AIA, 24% in AIAP, 33% in AILA and 30% in Middle East when allergy symptoms were at their worst. Nasal allergies also interfered with many patients' sleep, and were associated with feelings of depression, anxiety, irritability and tiredness. (Blaiss 2012, America, Asia pacific, Latin America, and Middle East)	The guideline panel estimates a prevalence of 20% to 40% of AR in KSA. They consider that due to the lack of an appropiate data base with this data, the self- reporting studies could underestimate the prevalence (for not recognize the symptoms or not having a medical diagnosis) or overestimate (for considering any kind of rhinitis not only the allergic one).

Seasonal / Intermittent Allergic Rhinitis

BENEFITS & HARMS OF THE OPTIONS

CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
What is the overall certainty of this evidence?	☐ No included studies ☐ Very low ☐ Low ☒ Moderate ☐ High		
Is there important uncertainty about how much people value the main outcomes?	☐ Important uncertainty or variability ☐ Possibly important uncertainty or variability ☐ Probably no important uncertainty or variability ☒ No important uncertainty or variability ☐ No known undesirable outcomes		
Are the desirable anticipated effects large?	☐ No ☐ Probably No ☐ Uncertain ☒ Probably Yes ☐ Yes ☐ ***Varies***		
Are the undesirable anticipated effects small?	☐ No ☐ Probably No ☐ Uncertain ☒ Probably Yes ☐ Yes ☐ ***Varies***		

Outcome	Relative importance	Certainty of the evidence (seasonal AR)
Nasal symptoms	Critical	Moderate
Nasal congestion	Critical	Moderate
Rhinorrhea	Critical	Moderate
Sneezing	Important	Moderate
Nasal itching	Important	Moderate
Ocular symptoms	Important	Moderate
Quality of life	Critical	Moderate
Adverse effects	Critical	Moderate

***Summary of the evidence for patients' values and preferences*:** See aditional considerations columm.

High value on the moderate effect of intranasal glucocorticosteroids reducing symptoms, and a relatively low value on avoiding their possible moderate adverse effects.

Summary of findings: See evidence table and reference list

1. Relative importance of AR symptoms(Revicki 1998 (US), Lo 2006 (China))
Rhinitis Symptom Utility Index (RSUI):
0 –best state of symptoms-no symptoms. 1 – the worst state symptoms- 8-14 days with severity symptoms.

The mean RSUI score for this sample was 0.72 ± 0.23, with a range of 0.15–1.0. (Revicki 1998 (US), Lo 2006 (China))

2. In the treatment of nasal allergies worldwide. The allergy surveys highlight the key factors in choosing an INCS: fast, complete, and long-lasting symptom relief. Furthermore, Comparing with the results of others allergy surveys worldwide a higher proportion of patients in the Middle East reported bothersome side effects of their prescription nasal sprays, and a higher proportion of these patients strongly agreed that there were no truly effective treatments for allergic rhinitis. This suggests that health care practitioners in the Middle East should be encouraged to explain the use of INCSs in greater depth to their patients. Patient education must play a central role in treatment decision making, particularly in the Middle East, to achieve higher patient satisfaction. (Hadi, U, 2013. WordWide including KSA).

3. The most common reasons cited for dissatisfaction with INCS medications were inadequate effectiveness, bothersome side effects (e.g., unpleasant taste and retrograde drainage into the pharynx), decreased effectiveness with chronic use, and failure to provide 24-hour relief. (Abdulrahman H, 2012. Middle East including KSA).
4. Narrative satisfaction and preference for INCS: Only 19% stated the INCSs as being effective/important drugs, while 36% stated them as being dangerous drugs. In reply to the question "would you use nasal steroids if they were

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	Are the desirable effects large relative to undesirable effects?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ | ***Varies*** ☐		prescribed?", 47% of the entire study sample answered "yes, if prescribed". (Cingi 2010, Turkey) 5. Narrative satisfaction and preference for treatment: Nasal sprays were not used daily because their use was inconvenient and embarrassing. Factors such as mild disease, side-effects, cost, and lack of efficacy were of less importance. (Borres 1997, Sweden)

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
RESOURCE USE	Are the resources required small?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☒ / Yes ☐ / Varies ☐	- The average treatment cost per patient in Canada over 12 months in fluticasone Intranasal was CAD 508.06 (Ståhl 2000, Canada), with a drug cost per patient of 214 CAD, which was an average around 120 CAD more expensive than the cost of budesonide intranasal.	- **Average annual cost per patient: around 600 SAR** Average price of 120 doses Spray (a month treatment): 43 SAR.
	Is the incremental cost small relative to the net benefits?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☒ / Yes ☐ / Varies ☐	None identified	
EQUITY	What would be the impact on health inequities?	Increased ☐ / Probably increased ☐ / Uncertain ☐ / Probably reduced ☒ / Reduced ☐ / Varies ☐	None identified	
ACCEPTABILITY	Is the option acceptable to key stakeholders?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	None identified	
FEASIBILITY	Is the option feasible to implement?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	None identified	

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings
	☐	☐	☐	☐	☒

Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option
	☐	☐	☐	☒

Recommendation (text)	The KSA MoH panel recommends Intranasal corticosteroids for treatment of adults with seasonal or intermittent allergic rhinitis (Strong recommendation; Moderate-quality evidence).
Justification	The evidence, with an overall moderate certainty, shows that the desirable effects probably are large relative to undesirable effects. It is considered that there is no important uncertainty or variability about how much people value its effectiveness and its mild adverse effects. The incremental cost is probably small relative to the net benefits due to relatively low cost of the drugs. Furthermore, the use of INSC would be acceptable and feasible. Reasons to formulate a strong rather than a conditional recommendation.
Subgroup considerations	- Health care practitioners in the Middle East should be encouraged to explain the use of INCSs in greater depth to their patients especially about the time required to reach the desired symptom relief.
Implementation considerations	- Different INCS should be available to provide choice opportunity for different patient preferences related with drug characteristics, such as smell for example.
Monitoring and evaluation	

Research priorities	Nation-wide population-based community prevalence studies are needed to correctly estimate the AR rates. Patient values and preferences and cost effectiveness studies are also needed in the context of KSA to inform future guidelines and stakeholders. Further research is needed to answer the question about the efficacy and specially safety of intranasal glucocorticosteroids in children with AR. A complete rigorously performed and reported systematic review of all individual intranasal glucocorticosteroids (budesonide, ciclesonide and beclomethasone) versus placebo that provides information on all outcomes important to patients, including adverse effects, is required.

Evidence profile: Should intranasal corticosteroids be used in patients with seasonal / intermittent allergic rhinitis (SAR)?

Author(s): Carlos Cuello

Date: 2013-11

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considera-tions	intranasal cortico-steroids	no intranasal cortico-steroids	Relative (95% CI)	Absolute		
Nasal symptoms (follow up: range 1 to 10 weeks; assessed with: Total nasal symptoms score (TNSS): better indicated by lower values)												
16	randomised trials	serious [1]	not serious	not serious	not serious	not serious	2045	1975	-	SMD 0.5 lower (0.61 lower to 0.39 lower)	⊕⊕⊕O MODERATE	CRITICAL
Nasal congestion (follow up: range 1 to 10 weeks; assessed with: Symptom score: better indicated by lower values)												
13	randomised trials	serious [1]	not serious	not serious	not serious	not serious	1498	1437	-	SMD 0.41 lower (0.53 lower to 0.3 lower)	⊕⊕⊕O MODERATE	IMPORTANT
Rhinorrhea (follow up: range 1 to 10 weeks; assessed with: Symptom score: better indicated by lower values)												
13	randomised trials	serious [1]	not serious	not serious	not serious	not serious	1498	1437	-	SMD 0.47 lower (0.62 lower to 0.32 lower)	⊕⊕⊕O MODERATE	IMPORTANT
Sneezing (follow up: range 1 to 10 weeks; assessed with: Symptom score: better indicated by lower values)												
13	randomised trials	serious [1]	not serious	not serious	not serious	not serious	1498	1437	-	SMD 0.45 lower (0.58 lower to 0.33 lower)	⊕⊕⊕O MODERATE	IMPORTANT
Nasal itching (follow up: range 1 to 10 weeks; assessed with: Symptom score: better indicated by lower values)												
13	randomised trials	serious [1]	not serious	not serious	not serious	not serious	1498	1437	-	SMD 0.39 lower (0.5 lower to 0.28 lower)	⊕⊕⊕O MODERATE	IMPORTANT
Ocular and non-nasal symptoms (follow up: range 1 to 10 weeks; assessed with: Symptom score: better indicated by lower values)												
13	randomised trials	serious [1]	not serious	not serious	not serious	not serious	1866	1852	-	SMD 0.28 lower (0.34 lower to 0.21 lower)	⊕⊕⊕O MODERATE	IMPORTANT
Quality of life (follow up: 1 to 20 weeks; assessed with: Rhinoconjunctivitis Quality of Life Questionnaire [RQLQ]: better indicated by lower values)												
3	randomised trials	serious [3]	not serious	not serious	not serious	not serious	80	79	-	SMD 0.76 lower (1.09 lower to 0.44 lower)	⊕⊕⊕O MODERATE	CRITICAL
Adverse events (follow up: range 2 to 20 weeks; assessed with: clinical assessment)												
19	randomised trials	serious [1]	not serious	not serious	not serious	not serious	647/2753 (23.5)%	617/2739 (22.5)%	RR 1.05 (0.95 to 1.15)	11 more per 1000 (from 11 fewer to 34 more)	⊕⊕⊕O MODERATE	CRITICAL

1. Most studies did not describe the randomization process and did not describe allocation concealment
2. Statistical heterogeneity, especially in the fluticasone studies
3. Only studies evaluating mometasone fuorate spray

Perennial / Persistent Allergic Rhinitis

BENEFITS & HARMS OF THE OPTIONS

CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
What is the overall certainty of this evidence?	*No included studies* ☐ | *Very low* ☐ | *Low* ☒ | *Moderate* ☐ | *High* ☐		
Is there important uncertainty about how much people value the main outcomes?	*Important uncertainty or variability* ☐ | *Possibly important uncertainty or variability* ☐ | *Probably no important uncertainty or variability* ☐ | *No important uncertainty or variability* ☒ | *No known undesirable outcomes* ☐		
Are the desirable anticipated effects large?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☒ | *Yes* ☐ | ***Varies*** ☐		
Are the undesirable anticipated effects small?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☒ | *Yes* ☐ | ***Varies*** ☐		

Outcome	Relative importance	Certainty of the evidence
Nasal symptoms	Critical	Moderate
Nasal congestion	Critical	Moderate
Rhinorrhea	Critical	Moderate
Sneezing	Important	Moderate
Nasal itching	Important	Moderate
Ocular symptoms	Important	Moderate
Quality of life	Critical	Moderate
Adverse effects	Critical	Low

Summary of findings:
See evidence table and reference list

Summary of the evidence for patients' values and preferences:
high value placed on the mild effect of intranasal glucocorticosteroids reducing symptoms, and a relatively low value on avoiding their possible moderate adverse effects.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	Are the desirable effects large relative to undesirable effects?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ ***Varies*** ☐		

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
RESOURCE USE	Are the resources required small?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☒ / Yes ☐ / Varies ☐	- The average treatment cost per patient in Canada over 12 months in fluticasone Intranasal was CAD 508.06 (Ståhl 2000, Canada), with a drug cost per patient of 214 CAD, which was an average around 120 CAD more expensive than the cost of budesonide intranasal.	**Average annual cost per patient: around 600 SAR** Average price of 120 doses Spray (a month treatment): 43 SAR.
	Is the incremental cost small relative to the net benefits?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☒ / Yes ☐ / Varies ☐	None identified	
EQUITY	What would be the impact on health inequities?	Increased ☐ / Probably increased ☐ / Uncertain ☐ / Probably reduced ☒ / Reduced ☐ / Varies ☐	None identified	
ACCEPTABILITY	Is the option acceptable to key stakeholders?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	None identified	
FEASIBILITY	Is the option feasible to implement?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	None identified	

Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option
	☐	☐	☒	☐

Recommendation (text)	The KSA MoH panel suggests Intranasal corticosteroids for treatment of adults with perennial or persistent allergic rhinitis (Conditional recommendation; Low-quality evidence).
Justification	The evidence, with an overall low certainty, shows that the desirable effects probably are large relative to undesirable effects. It is considered that there is no important uncertainty or variability about how much people value its effectiveness and its mild adverse effects. The incremental cost is probably small relative to the net benefits due to relatively low cost of the drugs. Furthermore, the use of INSC would be acceptable and feasible. Reasons to formulate a strong rather than a conditional recommendation.
Subgroup considerations	- Health care practitioners in the Middle East should be encouraged to explain the use of INCSs in greater depth to their patients especially about the time required to reach the desired symptom relief.
Implementation considerations	- Different INCS should be available to provide choice opportunity for different patient preferences related with drug characteristics, such as smell for example.
Monitoring and evaluation	
Research priorities	Nation-wide population-based community prevalence studies are needed to correctly estimate the AR rates. Patient values and preferences and cost effectiveness studies are also needed in the context of KSA to inform future guidelines and stakeholders. Further research is needed to answer the question about the efficacy and specially safety of intranasal glucocorticosteroids in children with AR. A complete rigorously performed and reported systematic review of all individual intranasal glucocorticosteroids (budesonide, ciclesonide and beclomethasone) versus placebo that provides information on all outcomes important to patients, including adverse effects, is required

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings
	☐	☐	☐	☐	☒

Evidence profile: Should intranasal corticosteroids be used in patients with <u>perennial / persistent</u> allergic rhinitis (PAR)?

Author(s): Carlos Cuello

Date: 2013-11

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intranasal corticosteroids	no intranasal corticosteroids	Relative (95% CI)	Absolute		
Nasal symptoms (follow up: range 2 to 20 weeks; assessed with: Total nasal symptoms score (TNSS): better indicated by lower values)												
10	randomised trials	serious [1]	not serious [2]	not serious	not serious	not serious	1188	1186	-	SMD 0.46 lower (0.63 lower to 0.28 lower)	⊕⊕⊕O MODERATE	CRITICAL
Nasal congestion (follow up: range 2 to 20 weeks; assessed with: Symptom score: better indicated by lower values)												
8	randomised trials	serious [1]	not serious	not serious	not serious	not serious	983	978	-	SMD 0.36 lower (0.49 lower to 0.23 lower)	⊕⊕⊕O MODERATE	IMPORTANT
Rhinorrea (follow up: range 2 to 20 weeks; assessed with: Symptom score: better indicated by lower values)												
8	randomised trials	serious [1]	not serious	not serious	not serious	not serious	983	978	-	SMD 0.44 lower (0.59 lower to 0.28 lower)	⊕⊕⊕O MODERATE	IMPORTANT
Sneezing (follow up: range 2 to 20 weeks; assessed with: Symptom score: better indicated by lower values)												
8	randomised trials	serious [1]	not serious	not serious	not serious	not serious	983	978	-	SMD 0.42 lower (0.56 lower to 0.29 lower)	⊕⊕⊕O MODERATE	IMPORTANT
Nasal itching (follow up: range 2 to 20 weeks; assessed with: Symptom score: better indicated by lower values)												
8	randomised trials	serious [1]	not serious	not serious	not serious	not serious	983	978	-	SMD 0.37 lower (0.46 lower to 0.27 lower)	⊕⊕⊕O MODERATE	IMPORTANT
Ocular and non-nasal symptoms (follow up: range 2 to 20 weeks; assessed with: Symptom score: better indicated by lower values)												
7	randomised trials	serious [1]	not serious	not serious	not serious	not serious	967	961	-	SMD 0.25 lower (0.37 lower to 0.14 lower)	⊕⊕⊕O MODERATE	IMPORTANT
Quality of life (follow up: range 2 to 20 weeks; assessed with: Rhinoconjunctivitis Quality of Life Questionnaire [RQLQ]: better indicated by lower values)												
3	randomised trials	serious [1]	not serious	not serious	not serious	not serious	259	260	-	SMD 0.39 lower (0.72 lower to 0.06 lower)	⊕⊕⊕O MODERATE	CRITICAL
Adverse events (follow up: range 2 to 20 weeks; assessed with: clinical assessment)												
9	randomised trials	serious [1]	not serious	not serious	serious [3]	not serious	392/1055 (37.2)%	728/1460 (49.9)%	RR 0.95 (0.81 to 1.11)	25 fewer per 1000 (from 55 more to 95 fewer)	⊕⊕OO LOW	CRITICAL

1. Most studies did not describe randomization and/or allocation concealment
2. Although heterogeneity above 60% exists among studies, results are in the same direction
3. Wide 95% confidence intervals that might surpass a clinical significant threshold for importance

Evidence to recommendation framework 2

Question 2: Should intranasal glucocorticosteroids versus intranasal H1-antihistamines be used in adults with allergic rhinitis?

Problem: Patients with allergic rhinitis
Option: Intranasal glucocorticosteroids
Comparison: Intranasal antihistamines
Setting: Outpatient
Perspective: Health Care system

Background: Background: Allergic rhinitis (AR) is defined clinically by nasal hypersensitivity symptoms induced by an immunologically mediated (most often IgE-dependent) inflammation after the exposure of the nasal mucous membranes to an offending allergen. Symptoms of rhinitis include rhinorrhea, nasal obstruction or blockage, nasal itching, sneezing, and postnasal drip that are reversible spontaneously or under treatment. Allergic conjunctivitis often accompanies allergic rhinitis.
Allergic rhinitis has been traditionally subdivided into seasonal, perennial, and occupational rhinitis. Perennial allergic rhinitis is most frequently, although not necessarily, caused by indoor allergens such as house dust mites, moulds, cockroaches, and animal dander. Seasonal allergic rhinitis is most often caused by outdoor allergens such as pollens or moulds. As in a 2010 edition of ARIA guideline in this document we retained the terms “seasonal” and “perennial” to enable the interpretation of published studies, and we also include the terms used to classify AR according to the duration of symptoms as “intermittent” rhinitis (symptoms are present less than 4 days a week or for less than 4 weeks) or “persistent” (symptoms are present at least 4 days a week and for at least 4 weeks).
These guidelines do not address the issues related to diagnosis of allergic rhinitis and it is assumed that the correct diagnosis had been established before commencing treatment.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	Is the problem a priority?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ ***Varies*** ☐	1. Overall risk of AR in adults Saudi Arabia is 90 per 1000 (79% SAR) Overall in the Middle East: • Runny nose, nasal and throat itching, postnasal drip, and nasal congestion or stuffed up nose were the most common and bothersome symptoms of AR. • 58% of participants with AR reported that the condition had an impact on their daily private and professional life. • 72% reported that limitations on their work/school activities • 35% reported that interfered with and caused them to miss work or • Sleep disturbances were shown in this survey to be extremely troubling in 15% of AR patients. (Abdulrahman H, 2012. Survey conducted in Middle East including KSA) 2. A high percentage of patients with AR surveyed missed work or had their work performance affected by allergies: work productivity decreasing by 23% in AIA, 24% in AIAP, 33% in AILA and 30% in Middle East when allergy symptoms were at their worst. Nasal allergies also interfered with many patients' sleep, and were associated with feelings of depression, anxiety, irritability and tiredness. (Blaiss 2012, America, Asia pacific, Latin America, and Middle East)	The guideline panel estimates a prevalence of 20% to 40% of AR in KSA. They consider that due to the lack of an appropiate data base with this data, the self- reporting studies could underestimate the prevalence (for not recognize the symptoms or not having a medical diagnosis) or overestimate (for considering any kind of rhinitis not only the allergic one).

Seasonal / Intermittent Allergic Rhinitis

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
BENEFITS & HARMS OF THE OPTIONS	**What is the overall certainty of this evidence?**	*No included studies* ☐ · *Very low* ☐ · *Low* ☐ · *Moderate* ☐ · *High* ☒		**Comments from the panel members:** 1. How the symptoms affect the QoL of the patients: Difficulty falling asleep, wake up at night and lack of a good night's sleep. Fatigue, reduced productivity, reduced concentration, frustration/restless/irritability
	Is there important uncertainty about how much people value the main outcomes?	*Important uncertainty or variability* ☐ · *Possibly important uncertainty or variability* ☒ · *Probably no important uncertainty or variability* ☐ · *No important uncertainty or variability* ☐ · *No known undesirable outcomes* ☐		
	Are the desirable anticipated effects large?	*No* ☐ · *Probably No* ☐ · *Uncertain* ☐ · *Probably Yes* ☒ · *Yes* ☐ · ***Varies*** ☐		
	Are the undesirable anticipated effects small?	*No* ☐ · *Probably No* ☐ · *Uncertain* ☐ · *Probably Yes* ☒ · *Yes* ☐ · ***Varies*** ☐		

Outcome	Certainty of the evidence (Seasonal AR)
Total nasal symptom score	High
Sneezing	High
Rhinorrhea	High
Itching	High
Nasal blockage/ congestion	High
Ocular symptoms	Low
Quality of life	Low
Adverse effects	-

Summary of the evidence/for patients' values and preferences:

See question INSCS vs. placebo for AR

This recommendation places a relatively high value on the efficacy of intranasal glucocorticosteroids, and a relatively low value on avoiding their possible adverse effects.

Summary of findings:

See evidence table and reference list

	Are the desirable effects large relative to undesirable effects?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☒ *Yes* ☐ ***Varies*** ☐		

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
RESOURCE USE	**Are the resources required small?**	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☒ Yes ☐ **Varies** ☐	1. SAR cost per person without a comorbid disorder during a Gramineae pollen season for Ankara was $79.0 ± 3.3 (Celik 2004, Turkey, symptom-medication score-based cost analysis) 1. Mean medication costs were $20.2 ±1.1 for nasal steroids steroids (Nasonex, $22.8 ±1.8 [n = 19]; Flixonase, $21 ± 0.5 [n = 5]; and Rhinocort, $15.7 ± 0.4 [n = 10]) and $14.5 ± 2.2 for oral antihistamines (Telfast, $18.1 ± 3.8 [n = 18]; Zyrtec, $7.3 ± 6.5 [n = 9]; and Claritin, $14.6 ± 3.9 [n = 7]). (Celik 2004, Turkey) 2. The average cost of AR intranasal medication for the 1-year of follow up for INS cohort was $177.42 and $130.06 for OAH cohort	**- Average annual INCS cost per patient: around 600 SAR** Average price of 120 doses Spray (a month treatment): 43 SAR. **- Average annual INAH cost per patient: around 1200 SAR** Average price of 10 ml Spray (10 days treatment): 34 SAR. Annual cost: 34 X 3 X 12= 1225
	Is the incremental cost small relative to the net benefits?	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☒ Yes ☐ **Varies** ☐	NONE IDENTIFIED	
EQUITY	**What would be the impact on health inequities?**	Increased ☐ Probably increased ☐ Uncertain ☐ Probably reduced ☒ Reduced ☐ **Varies** ☐	NONE IDENTIFIED	
ACCEPTABILITY	**Is the option acceptable to key stakeholders?**	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ☒ **Varies** ☐	NONE IDENTIFIED	
FEASIBILITY	**Is the option feasible to implement?**	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☒ Yes ☐ **Varies** ☐	NONE IDENTIFIED	

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings
	☐	☐	☐	☐	☒

Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option
	☐	☐	☐	☒

Recommendation (text)	The KSA MoH panels recommend Intranasal corticosteroids rather than intranasal H1-antihistamines for treatment of adults with seasonal or intermittent allergic rhinitis (Strong recommendation; High-quality evidence).
Justification	The evidence, with an overall high certainty, shows that the desirable effects probably are large relative to undesirable effects. There is possibly an important uncertainty or variability about how much people value its effectiveness. The incremental cost is probably small relative to the net benefits, and the use of INSC rather than INAH would be acceptable and feasible. Reasons to formulate a strong rather than a conditional recommendation.
Subgroup considerations	- In steroidphobic patients and in patient with contraindications for INCS the alternative choice may be equally reasonable. - Health care practitioners in the Middle East should be encouraged to explain the use of INCSs in greater depth to their patients especially about the time required to reach the desired symptom relief.
Implementation considerations	- The choice of different INCS should be available because of patient preferences for smell etc. and at least one antihistamine should be available for steroidphobic and patient with contraindications for INCS.
Monitoring and evaluation	
Research priorities	

Evidence profile: Intranasal corticosteroids vs intranasal antihistamines in patients with <u>seasonal / intermittent</u> allergic rhinitis

Author(s): Juan José Yepes-Nuñez.

Date: 2013-11-18

Quality assessment							Summary of findings				Quality	Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Publication Bias	Intranasal corticosteroids	Intranasal antihistamines	Relative (95% CI)	Absolute		
Total nasal symptom score (follow-up 2 to 5 weeks; Better indicated by less)												
9	Randomised trial	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Not detected	2313[1]		-	SMD -0.42 (-0.63 to -0.19)	⊕⊕⊕⊕ HIGH	CRITICAL
Sneezing (follow-up 2 to 4 weeks; Better indicated by less)												
8	Randomised trial	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Not detected	2180[1]		-	SMD -0.21(-0.32 to -0.10)	⊕⊕⊕⊕ HIGH	CRITICAL
Rhinorrhea (follow-up 2 to 5 weeks; Better indicated by less)												
8	Randomised trial	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Not detected	2180[1]		-	SMD -0.25 (-0.36 to -0.15)	⊕⊕⊕⊕ HIGH	CRITICAL
Itching (follow-up 2 to 5 weeks; Better indicated by less)												
7	Randomised trial	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Not detected	2180[1]		-	SMD -0.24 (-0.35 to -0.14)	⊕⊕⊕⊕ HIGH	IMPORTANT
Nasal congestion (follow-up 2 and 4 weeks; Better indicated by less)												
6	Randomised trial	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Not detected	2000[1]		-	SMD -0.23 (-0.34 to -0.12)	⊕⊕⊕⊕ HIGH	IMPORTANT
Ocular symptoms (follow-up 2 weeks; Better indicated by less)												
5	Randomised trial	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Not detected	2052[1]		-	SMD -0.03 (-0.21 to 0.15)	⊕⊕⊕⊕ HIGH	IMPORTANT
Quality of life (follow-up 2 weeks; Better indicated by less)												
2[2]	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Not detected	–[3]	–[3]	Not pooled[15]	SMD 0.26 in both studies[4]	⊕⊕OO LOW	CRITICAL
Adverse effects[14]												
8[5]	Randomised trial	-	No serious inconsistency	No serious indirectness	serious	Not detected	-	-	Not pooled[5]	Not pooled[16]	-	IMPORTANT

[1] Total participant included in the meta-analyzed studies. There is no enough information in all studies to report the participant number in each of the treatment groups.
[2] two good quality studies presented of 5, which reported the outcome in a total of 1693 patients. The rest of the 3 studies yielded a pooled effect estimate of 0.1 favouring intranasal corticosteroid. This result is consistent with the treatment effects reported in the meta-analysis.
[3] 24%of patients reporting that outcome (n= 404)
[4] SMD calculated from 3 studies. The 2 studies not meta-analyzed reported an effect favouring the INSC.
[5] Eight of nine trials that reported efficacy outcomes also reported adverse events narratively.
Sedation: reported by three (N=1330) with risk differences ranging from no risk difference to 1.5 percent favouring intranasal corticosteroid to avoid sedation; none were statistically significant (medium RoB)
headache: reported by four trials (N=1998) with risk differences ranging from 0.7 percent in favour of intranasal corticosteroid to 2.6 percent in favour of nasal antihistamine; none were statistically significant. (Low RoB) nasal discomfort: reported by four trials (N=1153) with risk differences ranging from 8 percent in favour of intranasal corticosteroids to 0.7 percent in favour of nasal antihistamine; none statistically significant (medium RoB) bitter aftertaste: Bitter aftertaste was reported by six trials (N=2178) with risk differences ranging from 2 percent to 6.7 percent favouring intranasal corticosteroid. Effects were statistically significant in two trials in the same publication (medium RoB)

Perennial / Persistent Allergic Rhinitis

BENEFITS & HARMS OF THE OPTIONS

CRITERIA	JUDGEMENTS
What is the overall certainty of this evidence?	*No included studies* ☐ | *Very low* ☒ | *Low* ☐ | *Moderate* ☐ | *High* ☐
Is there important uncertainty about how much people value the main outcomes?	*Important uncertainty or variability* ☐ | *Possibly important uncertainty or variability* ☒ | *Probably no important uncertainty or variability* ☐ | *No important uncertainty or variability* ☐ | *No known undesirable outcomes* ☐
Are the desirable anticipated effects large?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☒ | *Yes* ☐ | ***Varies*** ☐
Are the undesirable anticipated effects small?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☒ | *Yes* ☐ | ***Varies*** ☐

RESEARCH EVIDENCE

Outcome	Certainty of the evidence (Perennial AR)
Total nasal symptom score	Very Low
Sneezing	Low
Rhinorrhea	Low
Itching	Very Low
Nasal blockage	Low
Ocular symptoms	Very Low
Quality of life	-
Adverse effects	-

Summary of the evidence/for patients' values and preferences:

See question INSCS vs. placebo for AR

This recommendation places a relatively high value on the efficacy of intranasal glucocorticosteroids reducing the symptoms, and a relatively low value on avoiding their possible adverse effects.

Summary of findings: *see evidence table and reference list*

ADDITIONAL CONSIDERATIONS

Comments from the panel members:

1. How the Symptoms affect the QoL of the patients:
Difficulty falling asleep, wake up at night and lack of a good night's sleep. Fatigue, reduced productivity, reduced concentration, frustration/restless/irritability

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	Are the desirable effects large relative to undesirable effects?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☒ *Yes* ☐ ***Varies*** ☐		

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
RESOURCE USE	**Are the resources required small?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☒ *Yes* ☐ ***Varies*** ☐	1. Mean medication costs were $20.2 ±1.1 for nasal steroids steroids (Nasonex, $22.8 ±1.8 [n = 19]; Flixonase, $21 ± 0.5 [n = 5]; and Rhinocort, $15.7 ± 0.4 [n = 10]) and $14.5 ± 2.2 for oral antihistamines (Telfast, $18.1 ± 3.8 [n = 18]; Zyrtec, $7.3 ± 6.5 [n = 9]; and Claritin, $14.6 ± 3.9 [n = 7]). (Celik 2004, Turkey) 2. The average cost of AR intranasal medication for the 1-year of follow up for INS cohort was $177.42 and $130.06 for OAH cohort.	**- Average annual INCS cost per patient: around 600 SAR** Average price of 120 doses Spray (a month treatment): 43 SAR. **- Average annual INAH cost per patient: around 1200 SAR** Average price of 10 ml Spray (10 days treatment): 34 SAR. Annual cost: 34 X 3 X 12= 1225
	Is the incremental cost small relative to the net benefits?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☒ *Yes* ☐ ***Varies*** ☐	NONE IDENTIFIED	
EQUITY	**What would be the impact on health inequities?**	*Increased* ☐ *Probably increased* ☐ *Uncertain* ☐ *Probably reduced* ☒ *Reduced* ☐ ***Varies*** ☐	NONE IDENTIFIED	
ACCEPTABILITY	**Is the option acceptable to key stakeholders?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ ***Varies*** ☐	NONE IDENTIFIED	
FEASIBILITY	**Is the option feasible to implement?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☒ *Yes* ☐ ***Varies*** ☐	NONE IDENTIFIED	

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings
	☐	☐	☐	☒	☐

Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option
	☐	☐	☒	☐

Recommendation (text)	The KSA MoH panel suggests Intranasal corticosteroids rather than intranasal H1-antihistamines for treatment of adults with perennial or persistent allergic rhinitis (Conditional recommendation; Very low -quality evidence).
Justification	There is an overall low confidence in the currently available estimates of effects, so it is uncertain that the desirable effects could be large relative to undesirable effects. There is an important variability about how much people value its effectiveness .The incremental cost is probably small relative to the net benefits, and the use of INSC rather than INAH would be acceptable and feasible. Even though the quality of evidence for direct comparison is low, the indirect comparison of INCS versus INAH against placebo suggests net benefit with INCS and no effect with antihistamines, furthermore the INAH are suggested not to be used for adults with perennial rhinitis, in the 2010 ARIA guideline. Reasons to formulate a conditional rather than a strong recommendation
Subgroup considerations	- In steroidphobic patients and in patient with contraindications for INCS the alternative choice may be equally reasonable. - Health care practitioners in the Middle East should be encouraged to explain the use of INCSs in greater depth to their patients especially about the time required to reach the desired symptom relief.
Implementation considerations	- Different INCS should be available to provide choice opportunity for different patient preferences related with drug characteristics, such as smell for example. At least one antihistamine should be also available for steroidphobic and patient with contraindications for INCS.
Monitoring and evaluation	

Research priorities	Further research is needed to answer the question about the efficacy and safety of intranasal glucocorticosteroids in adults with perennial AR. Researches for the effectiveness and adverse effects of the INSC comparing against INAH in children. with perennial / persistent AR are required.

Evidence profile: Intranasal corticosteroids vs intranasal antihistamines in patients with perennial / persistent allergic rhinitis

Author(s): Juan José Yepes-Nuñez

Date: 2013-11-18

Quality assessment							Summary of findings				Quality	Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Publication Bias	Intranasal corticosteroids	Intranasal antihistamines	Relative (95% CI)	Absolute		
Total nasal symptom score (follow-up 2 to 5 weeks; Better indicated by less)												
1	Randomised trial	Serious [1]	No serious inconsistency	No serious indirectness	Very serious[2]	Non detected	65[3]	65[3]	-	SMD -0.33 (-0.73 to 0.07) [2]	⊕OOO VERY LOW	CRITICAL
Sneezing (follow-up 2 to 4 weeks; Better indicated by less)												
2	Randomised trial	Serious[4]	No serious inconsistency	No serious indirectness	Serious[2]	Non detected	90[5]	74[5]	-	SMD -0.43 (-0.78 to 0.08) [5]	⊕⊕OO LOW	CRITICAL
Rhinorrhea (follow-up 2 to 5 weeks; Better indicated by less)												
2	Randomised trial	Serious[4]	No serious inconsistency	No serious indirectness	Serious[2]	Non detected	90[5]	74[5]	-	SMD -0.32 (-0.66 to 0.03) [5]	⊕⊕OO LOW	CRITICAL
Itching (follow-up 2 to 6 weeks)												
1	Randomised trial	Serious[6]	No serious inconsistency	No serious indirectness	Very Serious[2]	Non detected	45[7]	45[7]	-	SMD -0.43 (-0.91 to -0.05) [7]	⊕OOO VERY LOW	IMPORTANT
Nasal blockage (follow-up 2 and 4 weeks; Better indicated by less)												
2	Randomised trial	Serious[8]	No serious inconsistency	No serious indirectness	Serious[2]	Non detected	110[9]	110[9]	-	SMD -0.94 (-1.27 to -0.62) [9]	⊕⊕OO LOW	CRITICAL
Ocular symptoms (follow-up 2 weeks; Better indicated by less)												
1	Randomised trial	Serious[10]	No serious inconsistency	No serious indirectness	Very Serious[2]	Non detected	25[11]	19[11]	-	SMD -0.28 (-0.92 to 0.36) [11]	⊕OOO VERY LOW	IMPORTANT
Quality of life – not measured[13]												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Adverse effects [12]												
2	Randomised trial	-	-	-	-	Non detected	-	-	Not pooled	Not pooled	-	IMPORTANT

[1] There was 26% of lost to of follow up.
[2] Small number size
[3] Total number of participants in this study was 130 but the SMD calculated from only 96 patients.
[4] There was 23% of lost to of follow up.
[5] Total number of participants in the 2 studies was 174 but the SMD calculated from only 134 patients.
[6] There was 21% of lost to of follow up
[7] Total number of participants in the study was 90 but the SMD calculated from only 71 patients.
[8] There was 24% of lost to of follow up.
[9] Total number of participants in the 2 studies was 220, SMD calculated from 167.
[10] There was 13% of lost to of follow up
[11] Total number of participants in the study was 44, SMD calculated from 38.
[12] None of the studies measured quality of life.[13] Two of three trials that reported efficacy outcomes also reported adverse events. Authors not reported whether evidence was insufficient to support the use of either intranasal corticosteroid or nasal antihistamine to avoid any of the following adverse events reported: taste perversion, intolerance to nasal spray, infection, headache, flu-like disorders and epistaxis.

Evidence to recommendation framework 3

Question 3: Should sublingual specific immunotherapy be used for treatment of allergic rhinitis in adults without concomitant asthma?

Problem: Adults with Allergic Rhinitis
Option: sublingual specific immunotherapy
Comparison: No treatment
Setting: Outpatient
Perspective: Health Care system

Background: Background: Allergic rhinitis (AR) is defined clinically by nasal hypersensitivity symptoms induced by an immunologically mediated (most often IgE-dependent) inflammation after the exposure of the nasal mucous membranes to an offending allergen. Symptoms of rhinitis include rhinorrhea, nasal obstruction or blockage, nasal itching, sneezing, and postnasal drip that are reversible spontaneously or under treatment. Allergic conjunctivitis often accompanies allergic rhinitis.
Allergic rhinitis has been traditionally subdivided into seasonal, perennial, and occupational rhinitis. Perennial allergic rhinitis is most frequently, although not necessarily, caused by indoor allergens such as house dust mites, moulds, cockroaches, and animal dander. Seasonal allergic rhinitis is most often caused by outdoor allergens such as pollens or moulds. As in a 2010 edition of ARIA guideline in this document we retained the terms “seasonal” and “perennial” to enable the interpretation of published studies, and we also include the terms used to classify AR according to the duration of symptoms as “intermittent” rhinitis (symptoms are present less than 4 days a week or for less than 4 weeks) or “persistent” (symptoms are present at least 4 days a week and for at least 4 weeks).
These guidelines do not address the issues related to diagnosis of allergic rhinitis and it is assumed that the correct diagnosis had been established before commencing treatment.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?**	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ☑ Varies ☐	1. Overall risk of AR in adults Saudi Arabia is 90 per 1000 (79% SAR) Overall in the Middle East: • Runny nose, nasal and throat itching, postnasal drip, and nasal congestion or stuffed up nose were the most common and bothersome symptoms of AR. • 58% of participants with AR reported that the condition had an impact on their daily private and professional life. • 72% reported that limitations on their work/school activities • 35% reported that interfered with and caused them to miss work or • Sleep disturbances were shown in this survey to be extremely troubling in 15% of AR patients. (Abdulrahman H, 2012. Survey conducted in Middle East including KSA) 2. A high percentage of patients with AR surveyed missed work or had their work performance affected by allergies: work productivity decreasing by 23% in AIA, 24% in AIAP, 33% in AILA and 30% in Middle East when allergy symptoms were at their worst. Nasal allergies also interfered with many patients' sleep, and were associated with feelings of depression, anxiety, irritability and tiredness. (Blaiss 2012, America, Asia pacific, Latin America, and Middle East)	The guideline panel estimates a prevalence of 20% to 40% of AR in KSA. They consider that due to the lack of an appropiate data base with this data, the self- reporting studies could underestimate the prevalence (for not recognize the symptoms or not having a medical diagnosis) or overestimate (for considering any kind of rhinitis not only the allergic one).

Seasonal / Intermittent Allergic Rhinitis

BENEFITS & HARMS OF THE OPTIONS

CRITERIA	JUDGEMENTS
What is the overall certainty of this evidence?	*No included studies* ☐ | *Very low* ☐ | *Low* ☐ | *Moderate* ☒ | *High* ☐
Is there important uncertainty about how much people value the main outcomes?	*Important uncertainty or variability* ☐ | *Possibly important uncertainty or variability* ☒ | *Probably no important uncertainty or variability* ☐ | *No important uncertainty or variability* ☐ | *No known undesirable outcomes* ☐
Are the desirable anticipated effects large?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☒ | *Probably Yes* ☐ | *Yes* ☐ | ***Varies*** ☐
Are the undesirable anticipated effects small?	*No* ☐ | *Probably No* ☒ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☐ | ***Varies*** ☐

RESEARCH EVIDENCE

Outcome	Relative importance	Certainty of the evidence (SAR)
Nasal symptoms	Critical	Moderate
Ocular symptoms	Important	Low
Medication score	Important	Moderate
Symptom-medication score	Important	Moderate
Quality of life	Critical	Moderate
Serious adverse effects	Important	High
Withdrawal due to adverse effect	Critical	High
Oral pruritus or burning	Critical	High
Oral oedema	Critical	High
Gastrointestinal adverse effects	Critical	Moderate

Summary of the evidence for patients' values and preferences:
This recommendation places a relatively high value on alleviating the symptoms of rhinitis, and relatively low value on avoiding adverse effects and resource expenditure.

Local adverse effects are relatively frequent (~35%). An alternative choice may be equally reasonable, if patients' values or preferences differ from those described here.

Summary of findings: see evidence table and reference list

ADDITIONAL CONSIDERATIONS

- There is a concern that some patients in KSA would not accept SLIT with some allergens of animal origin.

- Also considered that most people initially do not accept SLIT but when the symptoms do not decrease with all other regular options, they accept this medication with its adverse effects.

- It is considered that the lack of adherence with the medication use is not related with its adverse effects but with the long duration of treatment.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	Are the desirable effects large relative to undesirable effects?	*No* ☐ *Probably No* ☒ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☐ ***Varies*** ☐		

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
RESOURCE USE	**Are the resources required small?**	No ☒ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☐ / Varies ☐	1. SLIT was compared with standard therapy, It was (just) more effective or, in some cases, both more effective and cost-effective - SLIT is likely to be cost-effective at thresholds of £20,000; (Meadows A, 2013. SR) - These studies did not, however, report all of the utility data in a disaggregated form and all were funded by a manufacturer of SIT products (Meadows A, 2013. SR)	**- Average annual cost per patient: around 35 K SAR** **- Average cost per treatment (3 years) and patient: around 100K SAR** Average maintenance vial/ allergen/ month =707 SAR. Average 4 allergens/patient: Annual cost= 707 X 4 X 12 = 33, 936 SAR
RESOURCE USE	**Is the incremental cost small relative to the net benefits?**	No ☒ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☐ / Varies ☐		
EQUITY	**What would be the impact on health inequities?**	Increased ☒ / Probably increased ☐ / Uncertain ☐ / Probably reduced ☐ / Reduced ☐ / Varies ☐		**Comments from the panel members:** 1. If sublingual immunotherapy use were to be recommended, the health inequity will increase so the indications and the applications of SLIT should be determined: The SLIT should be used only when all other regular options do not work 2. Impact: Few patients will be affected
ACCEPTABILITY	**Is the option acceptable to key stakeholders ?**	No ☐ / Probably No ☐ / Uncertain ☒ / Probably Yes ☐ / Yes ☐ / Varies ☐		Uncertain acceptance from patients and likely not for health care system because of cost consideration reasons
FEASIBILITY	**Is the option feasible to implement?**	No ☐ / Probably No ☒ / Uncertain ☐ / Probably Yes ☐ / Yes ☐ / Varies ☐		Implementation would require expertise and resources (i.e. skin tests, relevant allergen) not readily available in most areas.

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings
	☐	☐	☒	☐	☐

Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option
	☐	☐	☒	☐

Recommendation (text)	The KSA MoH panel suggests sublingual immunotherapy for treatment of adults with seasonal or intermittent allergic rhinitis (conditional recommendation; Moderate-quality evidence).
Justification	The evidence, with an overall moderate certainty, shows that the desirable effects probably are not large relative to undesirable effects. Furthermore, possibly there is an important variability about how much people value its effectiveness because there is a concern that some patients in KSA would not accept SLIT with some allergens of animal origin, however others would accept it as the last option when the symptoms do not decrease with all other regular options. On the other hand the incremental cost is not small relative to the net benefits, and the implementation would require personnel experts and resources (i.e. skin tests, specific allergen) which are not readily available in most areas. Reasons to formulate a conditional rather than a strong recommendation. It is considered that the lack of adherence with the medication use is not related with its adverse effects but with the long duration of treatment. For this reason in the cases when the SLIT would be the treatment of choice clinicians should provide an adequate educational instruction to the patient.
Subgroup considerations	The SLIT should be used only when all other regular options do not work: It is more appropriate for those with moderate to severe AR who does not respond to first line therapy. The SLIT Should not be started during pregnancy, but could be continued if the woman has already started the treatment.

Implementation considerations	SLIT should only be prescribed by allergy specialists who have expertise in diagnosis of AR, proper identification of the allergens, providing immunotherapy and treatment of potentially serious adverse effects.
Monitoring and evaluation	If patients receiving SLIT do not respond within 6-12 m consider discontinuation SLIT
Research priorities	Nation wide population-based community prevalence studies are needed to correctly estimate the AR rates. Patient values and preferences and cost effectiveness studies are also needed in the context of KSA to inform future guidelines and stakeholders.

Evidence profile: Sublingual immunotherapy vs usual care in adults with <u>seasonal/intermittent</u> AR

Author(s): Itziar Etxeandia

Date: 2013-11-16

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLIT	Control	Relative (95% CI)	Absolute		
Allergic rhinitis symptom scores (SS) (follow-up median 7 months[1]) (Better indicated by lower values)												
33	randomised trials	No serious[2]	Serious[3]	no serious indirectness	no serious imprecision	none	1768	1708	-	SMD 0.38 lower (0.49 to 0.27 lower) [4]	⊕⊕⊕O MODERATE	CRITICAL
Ocular symptoms (follow-up median 7 months[5]; Better indicated by lower values)												
8	randomised trials	serious[6]	no serious inconsistency[7]	no serious indirectness	serious	none	597	616	-	SMD 0.26 lower (0.06 to 0.46 lower)	⊕⊕OO LOW	IMPORTANT
Medication scores (MS) (follow-up median 7 months[1]) (Better indicated by lower values)												
27	randomised trials	No serious[2]	Serious[3]	no serious indirectness	no serious imprecision	none	1353	1438	-	SMD 0.35 lower (0.47 to 0.23 lower) [9]	⊕⊕⊕O MODERATE	IMPORTANT
Combined SS and MS (SMS) (follow-up median 7 months[10]) (Better indicated by lower values)												
5	randomised trials	No serious	Serious[11]	no serious indirectness	no serious imprecision	none	541	546	-	SMD 0.44 lower (0.62 to 0.27 lower) [12]	⊕⊕⊕O MODERATE	IMPORTANT
QoL (disease specific RQLQ) (follow-up median 7 months[10]) (Better indicated by lower values)												
6	randomised trials	No serious	Serious[13]	no serious indirectness	no serious imprecision	none	818	840	-	SMD 0.36 lower (0.46 to 0.26 lower) [14]	⊕⊕⊕O MODERATE	CRITICAL
Serious adverse effects (follow-up median 7 months[1])												
36	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/2253 (0%)	0/1906 (0%)	not pooled[15]	not pooled	⊕⊕⊕⊕ HIGH	IMPORTANT
Withdrawal due to adverse effect (follow-up median 7 months[1])												
25	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[16]	none	70/1691 (4.1%)	16/1430 (1.1%)	RR 2.91 (1.72 to 4.92)	21 more per 1000 (from 8 more to 44 more)	⊕⊕⊕O MODERATE	CRITICAL
Oral pruritus or burning (follow-up median 7 months[1]) [17]												
19	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	strong association[18]	481/1304 (36.9%)	73/1152 (6.3%)	RR 4.92 (3.16 to 7.67)	248 more per 1000x (from 137 more to 423 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Oral oedema (follow-up median 8 months[1,19])												
7	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	Serious[20]	very strong association[21]	113/763 (14.8%)	4/702 (0.6%)	RR 11.47 (4.66 to 28.24)	60 more per 1000 (from 21 more to 155 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Gastrointestinal adverse effects (follow-up median 7 months[1]; nausea, vomiting, stomach upset, diarrhoea)												
9	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[22]	none	40/482 (8.3%)	10/413 (2.4%)	RR 2.85 (1.44 to 5.65)	45 more per 1000 (from 11 more to 113 more)	⊕⊕⊕O MODERATE	CRITICAL

[1] The duration of maintenance treatment and the period of follow up varied considerably between studies, largely reflecting pre-seasonal, co-seasonal and perennial administration. Range of follow-up was 1 to 48 months

[2] Most studies were at low or unclear risk of bias, mostly because they did not report the sequence generation and in some cases allocation concealment. Majority of studies did not report following intention-to-treat principle and was analysed per-protocol.
[3] There was some inconsistency in the results with I2= -48%49%.
[4] Moderate effect sizes favouring active SLIT in the adults subgroup analysis, and these did not differ significantly in the subgroups analysis of the 42 studies with age (children and adults together (SMD: -0.33 (95%IC -0.42 to-0.25)) , study duration (42 studies) (<6 months, 6-12 months,>12monts), major allergen content (31 studies) (5µg, 5-20 µg, >20 µg) or type of allergen (42 studies) (Grass, Ragweed, Parietaria, tree).
[5] Range: 3.5 to 18 months.
[6] In all studies but one between 10% and 20% of patients withdrew from the study. Majority of studies did not report following intention-to-treat principle and was analysed per-protocol.
[7] There was some inconsistency in results, but removing the studies with extreme results did not substantially change the estimate of effect.
[9] Combined SMD of the 35 studies which included Children and adults was –0.27 (95% CI –0.37 to –0.17) but MSs in children were not significantly better than with placebo treatment (see GRADE profile in the next question).On the other hand small to moderate effect sizes favouring active SLIT were found in all subgroup analyses of the 35 studies, study duration (<6 months, 6-12 months,>12monts), MAC (5µg, 5-20 µg, >20 µg) and type of allergen (Grass, Ragweed, Parietaria, tree).
[10] Range of follow-up was 3 to 10 months
[11] Some heterogeneity between Studies I2: 41%.
[12] When all 6 studies of Children and adults are taking together the combined SMD was similar (–0.40 (95% CI –0.55 to –0.25)), furthermore moderate effect sizes favouring active SLIT were found in all subgroup analyses of those 6 studies conducted in children and adults [study duration (6 studies) (<6 months, 6-12 months,>12monts), MAC (3 studies) (5-20 µg) or type of allergen (4 studies) (Grass)], and these were similar between studies.
[13] Some heterogeneity between Studies I2: 69%. Four of the included studies used the full version of the disease-specific RQLQ to measure QoL, the others an alternative version. Nevertheless the subgroup analysis of those four studies showed a similar combined SMD – 0.34 (95%IC -0.49 to -0.18).
[14] When all 7 studies of Children and adults are taking together the combined SMD was similar -0.37 (95%IC -0.52 to -0.22), moderate effect sizes favouring active SLIT were found in all subgroup analyses of those 7 studies conducted in children and adults [study duration (6 studies) (<6 months, >12monts) or MAC (4 studies) (5-20 µg, >20 µg).
15 There were no serious adverse observed in any of the 36 studies and five new trials added in the Meadows et al. meta-analysis reported a total of 20 SAEs in a total of 1565 study participants, of which only one, abdominal pain in a placebo-treated patient, was considered likely to be treatment related.
[16] Only 86 events
[17] In the new RCT added in the Meadows et al. meta-analysis the numbers of adverse events were generally not reported. The most commonly reported local reactions were itching, swelling and burning in the oral cavity. Four trials (n = 890), one in children (n= 307) and three in adults (n=583) reported oral pruritus (39% in active group vs. 5% placebo); two trials (n = 782) reported throat irritation (33% active vs. 4% of control), and mild erythema (11% active vs. 1% control); and three trials (n = 863) reported oral paraesthesia (10% in SLIT vs. 2% in placebo) and mouth oedema (9% in SLIT vs. 1% in placebo).
[18] Lower confidence limit was 3.16.
[19] Range: 4 to 24 months.
[20] Only 117 events.
[21] Lower confidence limit was 4.66 21
[22] Only 50 events.

Note about AE:
Five trials of the new RCTs added in the Meadows et al. meta-analysis reported a total of 20 SAEs in a total of 1565 study participants, of which only one, abdominal pain in a placebo-treated patient, was considered likely to be treatment related.
Six trials included in the Meadows et al. meta-analysis, five including adults (n=938) and one children (n=307), reported systemic events by severity: The vast majority (73%) of systemic AEs in these trials were of mild intensity, 24% were of moderate intensity and 3% were graded as severe, those reported in this outcome.

Perennial / Persistent Allergic Rhinitis

BENEFITS & HARMS OF THE OPTIONS

CRITERIA	JUDGEMENTS
What is the overall certainty of this evidence?	*No included studies* ☐ | *Very low* ☒ | *Low* ☐ | *Moderate* ☐ | *High* ☐
Is there important uncertainty about how much people value the main outcomes?	*Important uncertainty or variability* ☒ | *Possibly important uncertainty or variability* ☐ | *Probably no important uncertainty or variability* ☐ | *No important uncertainty or variability* ☐ | *No known undesirable outcomes* ☐
Are the desirable anticipated effects large?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☒ | *Probably Yes* ☐ | *Yes* ☐ | ***Varies*** ☐
Are the undesirable anticipated effects small?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☒ | *Probably Yes* ☐ | *Yes* ☐ | ***Varies*** ☐

RESEARCH EVIDENCE

Outcome	Relative importance	Certainty of the evidence (PAR)
Nasal symptoms	Critical	Low
Ocular symptoms	Important	-
Medication score	Important	Very low
Symptom-medication score	Important	-
Quality of life	Critical	Low
Serious adverse effects	Important	High
Withdrawal due to adverse effect	Critical	Very low
Oral pruritus or burning	Critical	Moderate
Oral oedema	Critical	-
Gastrointestinal adverse effects	Critical	-

Summary of the evidence for patients' values and preferences:
This recommendation places a relatively high value on alleviating the symptoms of rhinitis, and relatively low value on avoiding adverse effects and resource expenditure.

Local adverse effects are relatively frequent (~35%). An alternative choice may be equally reasonable, if patients' values or preferences differ from those described here.
Summary of findings: see evidence table and reference list

ADDITIONAL CONSIDERATIONS

- There is a concern that some patients in KSA would not accept SLIT with some allergens of animal origin.

- Also considered that most people initially do not accept SLIT but when the symptoms do not decrease with all other regular options, they accept this medication with its adverse effects.

- It is considered that the lack of adherence with the medication use is not related with its adverse effects but with the long duration of treatment..

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	Are the desirable effects large relative to undesirable effects?	No ☐ Probably No ☐ Uncertain ☒ Probably Yes ☐ Yes ☐ Varies ☐		

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
RESOURCE USE	**Are the resources required small?**	No ☒ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☐ / Varies ☐	1. SLIT was compared with standard therapy, It was (just) more effective or, in some cases, both more effective and cost-effective - SLIT is likely to be cost-effective at thresholds of £20,000; (Meadows A, 2013. SR) - These studies did not, however, report all of the utility data in a disaggregated form and all were funded by a manufacturer of SIT products (Meadows A, 2013. SR)	**- Average annual cost per patient: around 35 K SAR** **- Average cost per treatment (3 years) and patient: around 100K SAR** Average maintenance vial/ allergen/ month =707 SAR. Average 4 allergens/patient: Annual cost= 707 X 4 X 12 = 33, 936 SAR
	Is the incremental cost small relative to the net benefits?	No ☒ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☐ / Varies ☐		
EQUITY	**What would be the impact on health inequities?**	Increased ☒ / Probably increased ☐ / Uncertain ☐ / Probably reduced ☐ / Reduced ☐ / Varies ☐		**Comments from the panel members:** 1. If sublingual immunotherapy use were to be recommended, the health inequity will increase so the indications and the applications of SLIT should be determined: The SLIT should be used only when all other regular options do not work 2. Impact: Few patients will be affected
ACCEPTABILITY	**Is the option acceptable to key stakeholders?**	No ☐ / Probably No ☐ / Uncertain ☒ / Probably Yes ☐ / Yes ☐ / Varies ☐		Uncertain acceptance from patients and likely not for health care system because of cost consideration reasons
FEASIBILITY	**Is the option feasible to implement?**	No ☐ / Probably No ☒ / Uncertain ☐ / Probably Yes ☐ / Yes ☐ / Varies ☐		Implementation would require expertise and resources (i.e. skin tests, relevant allergen) not readily available in most areas.

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings
	☐	☐	☒	☐	☐

Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option
	☐	☐	☒	☐

Recommendation (text)	The KSA MoH panel suggests sublingual immunotherapy for treatment of adults with perennial/persistent allergic rhinitis (conditional recommendation; very low-quality evidence).
Justification	There is a very low confidence in the currently available estimates of effects, so it is uncertain that the desirable effects could be large relative to undesirable effects. Furthermore, there is an important variability about how much people value its effectiveness because there is a concern that some patients in KSA would not accept SLIT with some allergens of animal origin, however others would accept it as the last option when the symptoms do not decrease with all other regular options. On the other hand the incremental cost is not small relative to the net benefits, and the implementation would require personnel experts and resources (i.e. skin tests, specific allergen) which are not readily available in most areas. Reasons to formulate a conditional rather than a strong recommendation. It is considered that the lack of adherence with the medication use is not related with its adverse effects but with the long duration of treatment. For this reason in the cases when the SLIT would be the treatment of choice clinicians should provide an adequate educational instruction to the patient.
Subgroup considerations	The SLIT should be used only when all other regular options do not work: It is more appropriate for those with moderate to severe AR who does not respond to first line therapy. The SLIT Should not be started during pregnancy, but could be continued if the woman has already started the treatment.
Implementation considerations	SLIT should only be prescribed by allergy specialists who have expertise in diagnosis of AR, proper identification of the allergens, providing immunotherapy and treatment of potentially serious adverse effects.

Monitoring and evaluation	If patients receiving SLIT do not respond within 6-12 m consider discontinuation SLIT
Research priorities	Research for the effectiveness and adverse effects of SLIT in patients with perennial / persistent AR are required. Nation wide population-based community prevalence studies are needed to correctly estimate the AR rates. Patient values and preferences and cost effectiveness studies are also needed in the context of KSA to inform future guidelines and stakeholders.

Evidence profile: Sublingual immunotherapy vs usual care in adults with <u>perennial/persistent</u> AR
Author(s): Itziar Etxeandia
Date: 2013-11-16

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLIT	Control	Relative (95% CI)	Absolute		
Allergic rhinitis symptom scores (follow-up 3 to 24 months[1]; Better indicated by lower values)												
6	randomised trials	Serious[2]	Serious[3]	no serious indirectness	no serious imprecision	none	151	154	-	SMD 1.14 lower (1.83 to 0.44 lower)	⊕⊕OO LOW	CRITICAL
Medication scores (follow-up 28 months; Better indicated by lower values)												
4	randomised trials	Serious[4]	Serious[3]	no serious indirectness	Serious[5]	none	121	124	-	SMD 0.83 lower (1.69 lower to 0.04 higher)	⊕OOO VERY LOW	IMPORTANT
Quality of life (follow-up 24 months; Better indicated by lower values)												
1	randomised trials	Serious[6]	no serious inconsistency	no serious indirectness	Serious[7]	none	28	28	-	not pooled[8]	⊕⊕OO LOW	CRITICAL
Withdrawal due to adverse effects (follow-up 24 months)												
1	randomised trials	Serious[9]	no serious inconsistency	no serious indirectness	very serious[10]	none	1/15 (6.7%)	0/15 (0%)	RR 3.0 (0.13 to 68.26)	0 more per 1000 (from 0 fewer to 0 more)	⊕OOO VERY LOW	CRITICAL
Serious adverse effects (follow-up 3 to 24 months[1])												
6	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/151 (0%)	0/151 (0%)	not pooled	not pooled	⊕⊕⊕⊕ HIGH	IMPORTANT
Oral pruritus/burning/oedema												
4[11,12]	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[13]	none	5/76 (6.6%)	1/74 (1.4%)	RR 2.31 (0.53 to 10.09)	18 more per 1000 (from 6 fewer to 123 more)	⊕⊕⊕O MODERATE	CRITICAL

[1] The oldest study followed the patient only for 65 days the other 5 studies did for an average of 24-28 months.
[2] no one of the studies describes a clear allocation concealment and 5 of 6 neither an adequate sequence generation
[3] I2=87%-90%. Differences in the effect sizes.
[4] no one of the studies describes a clear allocation concealment and 2 of 4 neither an adequate sequence generation
[5] The estimation include benefits and also no effect
[6] method of analysis was not reported and 18% did not complete treatment. Only one study with poor reporting of this outcome.
[7] Only one study with 56 patients. No measure of variability in results.
[8] Authors did not report a summary score or any variability in the results. They stated that 'there was no statistical change in all the domains of the SF-36 questionnaire at the six time points, and all the scores were quite high'.
[9] Only one study reported measuring this outcome
[10] One very small study, only one event, but results do not exclude an important harm.
[11] Two studies did not mention adverse effects at all.
[12] Studies in patients allergic to cat dander did not mention adverse effects at all.
[13] Only 6 events. Results do not exclude a very large harm or no effect.

Evidence to recommendation framework 4

Question 4: Should sublingual specific immunotherapy (SLIT) be used for treatment of allergic rhinitis (AR) in children younger than 18 years old without concomitant asthma?

Problem: *Children with Allergic Rhinitis*
Option: *Sublingual specific immunotherapy*
Comparison: *No sublingual specific immunotherapy*
Setting: *Outpatient*
Perspective: *Health Care system*

Background: Background: Allergic rhinitis (AR) is defined clinically by nasal hypersensitivity symptoms induced by an immunologically mediated (most often IgE-dependent) inflammation after the exposure of the nasal mucous membranes to an offending allergen. Symptoms of rhinitis include rhinorrhea, nasal obstruction or blockage, nasal itching, sneezing, and postnasal drip that are reversible spontaneously or under treatment. Allergic conjunctivitis often accompanies allergic rhinitis.

Allergic rhinitis has been traditionally subdivided into seasonal, perennial, and occupational rhinitis. Perennial allergic rhinitis is most frequently, although not necessarily, caused by indoor allergens such as house dust mites, moulds, cockroaches, and animal dander. Seasonal allergic rhinitis is most often caused by outdoor allergens such as pollens or moulds. As in a 2010 edition of ARIA guideline in this document we retained the terms “seasonal” and “perennial” to enable the interpretation of published studies, and we also include the terms used to classify AR according to the duration of symptoms as “intermittent” rhinitis (symptoms are present less than 4 days a week or for less than 4 weeks) or “persistent” (symptoms are present at least 4 days a week and for at least 4 weeks).

These guidelines do not address the issues related to diagnosis of allergic rhinitis and it is assumed that the correct diagnosis had been established before commencing treatment.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ ***Varies*** ☐	1. Overall risk of AR in adults Saudi Arabia is 90 per 1000 (79% SAR) Overall in the Middle East: • Runny nose, nasal and throat itching, postnasal drip, and nasal congestion or stuffed up nose were the most common and bothersome symptoms of AR. • 58% of participants with AR reported that the condition had an impact on their daily private and professional life. • 72% reported that limitations on their work/school activities • 35% reported that interfered with and caused them to miss work or • Sleep disturbances were shown in this survey to be extremely troubling in 15% of AR patients. (Abdulrahman H, 2012. Survey conducted in Middle East including KSA) 2. A high percentage of patients with AR surveyed missed work or had their work performance affected by allergies: work productivity decreasing by 23% in AIA, 24% in AIAP, 33% in AILA and 30% in Middle East when allergy symptoms were at their worst. Nasal allergies also interfered with many patients' sleep, and were associated with feelings of depression, anxiety, irritability and tiredness. (Blaiss 2012, America, Asia pacific, Latin America, and Middle East)	The guideline panel estimates a prevalence of 20% to 40% of AR in KSA. They consider that due to the lack of an appropiate data base with this data, the self- reporting studies could underestimate the prevalence (for not recognize the symptoms or not having a medical diagnosis) or overestimate (for considering any kind of rhinitis not only the allergic one).

Seasonal / Intermittent Allergic Rhinitis

BENEFITS & HARMS OF THE OPTIONS

CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

What is the overall certainty of this evidence?

No included studies	Very low	Low	Moderate	High
☐	☐	☐	☒	☐

Is there important uncertainty about how much people value the main outcomes?

Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability	No known undesirable outcomes
☒	☐	☐	☐	☐

Are the desirable anticipated effects large?

No	Probably No	Uncertain	Probably Yes	Yes	Varies
☐	☒	☐	☐	☐	☐

Are the undesirable anticipated effects small?

No	Probably No	Uncertain	Probably Yes	Yes	Varies
☐	☒	☐	☐	☐	☐

Outcome	Relative importance	Certainty of the evidence (SAR)
Nasal symptoms	Critical	High
Ocular symptoms	Important	Moderate
Medication score	Important	Moderate
Symptom-medication score	Important	Moderate
Quality of life	Critical	Moderate
Serious adverse effects	Important	High
Withdrawal due to adverse effect	Critical	Moderate
Oral pruritus/ oedema or burning	Critical	High

Summary of findingsevidence for patients' values and preferences:

1. Anxiety scores in mother of children with allergic rhinitis were significantly higher than the ones in the control group, and might be associated with child disease and the functioning of the entire family rather than features of the mother alone. (Emin 2009, Turkey)
2. The psychological and physical health of caregivers, who were primarily mothers, was strongly influenced by child chronic disease. The mean scores of the SF-36 subscales, were higher in schoolar children with AR than in patients without AR, with no statistically significance in different domains but in physical functioning and bodily pain. (Amizade 2013, Iran)

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	Are the desirable effects large relative to undesirable effects?	*No* ☐ *Probably No* ☐ *Uncertain* ☒ *Probably Yes* ☐ *Yes* ☐ ***Varies*** ☐	3. Sleep quality: Allergic rhinitis can affect children's learning ability and performance at school and cause somnolence and inability to concentrate in children. (Lunn 2011, review from US) This recommendation places a relatively high value on alleviating the symptoms of rhinitis, and relatively low value on avoiding adverse effects and resource expenditure. ***Summary of findings:*** Please see evidence table and reference list	

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
RESOURCE USE	Are the resources required small?	No [X] / Probably No [ ] / Uncertain [ ] / Probably Yes [ ] / Yes [ ] / Varies [ ]	None identified	
	Is the incremental cost small relative to the net benefits?	No [X] / Probably No [ ] / Uncertain [ ] / Probably Yes [ ] / Yes [ ] / Varies [ ]	None identified	
EQUITY	What would be the impact on health inequities?	Increased [X] / Probably increased [ ] / Uncertain [ ] / Probably reduced [ ] / Reduced [ ] / Varies [ ]	None identified	**Comments from the panel members:** 1. If sublingual immunotherapy use were to be recommended, the health inequity will increase so the indications and the applications of SLIT should be determined: The SLIT should be used only when all other regular options do not work 2. Impact: Few patients will be affected
ACCEPTABILITY	Is the option acceptable to key stakeholders?	No [ ] / Probably No [X] / Uncertain [ ] / Probably Yes [ ] / Yes [ ] / Varies [ ]	None identified	**Comments from the panel members:** 1. Uncertain acceptance from patients and likely not for health care system because of cost consideration reasons
FEASIBILITY	Is the option feasible to implement?	No [ ] / Probably No [X] / Uncertain [ ] / Probably Yes [ ] / Yes [ ] / Varies [ ]	None identified	Implementation would require expertise and resources (i.e. skin tests, relevant allergen) not readily available in most areas.

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings
	☐	☐	☒	☐	☐

Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option
	☐	☐	☒	☐

Recommendation (text)	The KSA MoH panel suggests sublingual immunotherapy for treatment of children younger than 18 years old with seasonal or intermittent allergic rhinitis (Conditional recommendation; Moderate-quality evidence)
Justification	A moderate certainty of evidence shows that the desirable effects probably are not large relative to undesirable effects. Furthermore, there is an important uncertainty or variability about how much patients' families value its effectiveness because there is a concern that some patients in KSA would not accept SLIT with some allergens of animal origin, however others would accept it as the last option when the symptoms do not decrease with all other regular options. On the other hand the incremental cost is not small relative to the net benefits, and the implementation would require personnel experts and resources (i.e. skin tests, specific allergen) which are not readily available in most areas. Reasons to formulate a conditional rather than a strong recommendation.
Subgroup considerations	The SLIT should be used only when all other regular options do not work: It is more appropriate for those with moderate to severe AR who does not respond to first line therapy. The SLIT Should not be started during pregnancy, but could be continued if the woman has already started the treatment.
Implementation considerations	SLIT should be prescribed only for children ≥5 years old and by allergy specialists who have expertise in diagnosis of AR, proper identification of the allergens, providing immunotherapy and treatment of potentially serious adverse effects.
Monitoring and evaluation	If patients receiving SLIT do not respond within 6-12 months consider discontinuation SLIT

Research priorities	Research for the use of the SLIT in children younger than 5yers old are needed. Nation wide population-based community prevalence studies are needed to correctly estimate the AR rates in children. Patient values and preferences and cost effectiveness studies are also needed in the context of KSA to inform future guidelines and stakeholders.

Evidence profile: Sublingual immunotherapy in children with seasonal/intermittent AR

Author(s): Itziar Etxeandia

Date: 2013-11-17

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLIT	Control	Relative (95% CI)	Absolute	Quality	Importance
Allergic rhinitis symptom scores (follow up mean 18 months[1]) (Better indicated by lower values)												
9	randomised trials	no serious[2]	no serious inconsistency[3]	no serious indirectness	no serious imprecision	none	672	671	-	SMD 0.24 lower (0.35 to 0.13 lower)	⊕⊕⊕⊕ HIGH	CRITICAL
Ocular symptoms (follow-up median 12 months[4]; Better indicated by lower values)												
4	randomised trials	no serious limitations	no serious inconsistency[5]	no serious indirectness	Serious[6]	none	208	206	-	SMD 0.18 lower (0.44 lower to 0.08 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Medication scores (follow up mean 12 months[7]) (Better indicated by lower values)												
8	randomised trials	no serious[2]	no serious inconsistency	no serious indirectness	Serious[8]	none	581	594	-	SMD 0.11 lower (0.24 lower to 0.03 higher)	⊕⊕⊕O MODERATE	IMPORTANT
SMS (Combined SS and MS) (follow up 23 weeks) (Better indicated by lower values)												
1	randomised trials	Serious[9]	-	no serious indirectness	no serious imprecision	none	149	158	-	SMD 0.26 lower (0.49 to 0.04 lower)	⊕⊕⊕O MODERATE	IMPORTANT
QoL (disease specific RQLQ) (Better indicated by lower values)												
1	randomised trials	Serious[9]	-	no serious indirectness	no serious imprecision	none	109	111	-	SMD 0.31 lower (0.57 to 0.04 lower)	⊕⊕⊕O MODERATE	CRITICAL
Serious adverse effects (follow-up median 24 months[10])												
7	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/516 (0%)	0/500 (0%)	not pooled[11]	not pooled[11]	⊕⊕⊕⊕ HIGH	IMPORTANT
Withdrawal due to adverse effects (follow-up median 24 months[12])												
8	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[13]	none	19/620 (3.1%)	8/543 (1.5%)	RR 2.07 (0.89 to 4.84)	16 more per 1000 (from 2 fewer to 57 more)	⊕⊕⊕O MODERATE	CRITICAL
Oral pruritus/oedema (follow-up median 18 months[12])												
5	randomised trials	Serious[14]	no serious inconsistency	no serious indirectness	no serious imprecision	strong association[19]	157/446 (35.2%)	38/438 (8.7%)	RR 4.03 (1.64 to 9.93)	263 more per 1000 (from 56 more to 775 more)	⊕⊕⊕⊕ HIGH	CRITICAL

[1] The duration of maintenance treatment and the period of follow up varied considerably between studies. Range of follow-up was less than 6 months to 48 months
[2] Most studies were at low or unclear risk of bias, mostly because they did not report the sequence generation and the allocation concealment. Majority of studies did not report following intention-to-treat principle and was analysed per-protocol.
[3]Although only nine paediatric studies have been included here, compared with 15 in the Cochrane review, total participant numbers were very similar (1343 vs 1392 children, respectively) and heterogeneity was significantly reduced (I2 = 0%, compared with 92% in the Cochrane review).
[4] Range of follow-up was less than 6 months to 32 months.
[5] There was inconsistency with results, but could be explained by one study (Caffarelli 2000) explicitly including patients with allergic conjunctivitis. This study showed a larger effect (ES: -0.68, 95% CI: -0.07 to -1.29) than the other three studies together (SMD: -0.11, 95% CI: -0.32 to 0.09). Inclusion of one additional study that enrolled children with asthma some of whom had also rhinitis did not substantially change the results (SMD: -0.18, 95% CI: -0.39 to 0.03). 12 Results do not exclude a moderate benefit with SLIT or no difference.
[6] Results do not exclude a moderate benefit with SLIT or no difference
[7] Range: 3 to 32 months [8] The estimation includes both benefits and harms. Finding consistent with the earlier Cochrane Review and the effect size was decreased further with the addition of the more recent studies. Of the eight included studies, only one favouring placebo treatment was statistically significant.
[9] Only one study not following intention-to-treat principle and reporting analysis per-protocol.
[10] Range: 3 to 36 months
[11] There were no serious adverse events related to the treatment in these studies
[12] Range: 5 to 36 months [13] Results do not exclude appreciable harm with SLIT or no difference.
[14] Most studies poorly reported this and other adverse effects (e.g. stating the total number of events in the study but not reporting in which group they occurred).
[15] Lower confidence limit is 1.64 and all plausible biases as well as the results from studies in adults suggest that the effect is larger than estimated.

Perennial / Persistent Allergic Rhinitis

BENEFITS & HARMS OF THE OPTIONS

CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

What is the overall certainty of this evidence?

☐ No included studies ☒ Very low ☐ Low ☐ Moderate ☐ High

Is there important uncertainty about how much people value the main outcomes?

☒ Important uncertainty or variability ☐ Possibly important uncertainty or variability ☐ Probably no important uncertainty or variability ☐ No important uncertainty or variability ☐ No known undesirable outcomes

Are the desirable anticipated effects large?

☐ No ☒ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ☐ Varies

Are the undesirable anticipated effects small?

☐ No ☒ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ☐ Varies

Outcome	Relative importance	Certainty of the evidence (PAR)
Nasal symptoms	Critical	Low
Ocular symptoms	Important	-
Medication score	Important	Low
Symptom-medication score	Important	-
Quality of life	Critical	-
Serious adverse effects	Important	Moderate
Withdrawal due to adverse effect	Critical	Very low
Oral pruritus/ oedema or burning	Critical	Very low

Summary of findingsevidence for patients' values and preferences:

1. Anxiety scores in mother of children with allergic rhinitis were significantly higher than the ones in the control group, and might be associated with child disease and the functioning of the entire family rather than features of the mother alone. (Emin 2009, Turkey)
2. The psychological and physical health of caregivers, who were primarily mothers, was strongly influenced by child chronic disease. The mean scores of the SF-36 subscales, were higher in schoolar children with AR than in patients without AR, with no statistically significance in different domains but in physical functioning and bodily pain. (Amizade 2013, Iran)

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	Are the desirable effects large relative to undesirable effects?	*No* ☐ *Probably No* ☐ *Uncertain* ☒ *Probably Yes* ☐ *Yes* ☐ ***Varies*** ☐	3. Sleep quality: Allergic rhinitis can affect children's learning ability and performance at school and cause somnolence and inability to concentrate in children. (Lunn 2011, review from US) This recommendation places a relatively high value on avoiding adverse effects and resource expenditure, and relatively low value on possible small reduction in nasal symptoms. ***Summary of findings:*** Please see evidence table and reference list	

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
RESOURCE USE	**Are the resources required small?**	*No* ☒ / *Probably No* ☐ / *Uncertain* ☐ / *Probably Yes* ☐ / *Yes* ☐ / ***Varies*** ☐	None identified	
	Is the incremental cost small relative to the net benefits?	*No* ☒ / *Probably No* ☐ / *Uncertain* ☐ / *Probably Yes* ☐ / *Yes* ☐ / ***Varies*** ☐	None identified	
EQUITY	**What would be the impact on health inequities?**	*Increased* ☒ / *Probably increased* ☐ / *Uncertain* ☐ / *Probably reduced* ☐ / *Reduced* ☐ / ***Varies*** ☐	None identified	**Comments from the panel members:** 1. If sublingual immunotherapy use were to be recommended, the health inequity will increase so the indications and the applications of SLIT should be determined: The SLIT should be used only when all other regular options do not work 2. Impact: Few patients will be affected
ACCEPTABILITY	**Is the option acceptable to key stakeholders ?**	*No* ☐ / *Probably No* ☒ / *Uncertain* ☐ / *Probably Yes* ☐ / *Yes* ☐ / ***Varies*** ☐	None identified	**Comments from the panel members:** 1. Uncertain acceptance from patients and likely not for health care system because of cost consideration reasons
FEASIBILITY	**Is the option feasible to implement?**	*No* ☐ / *Probably No* ☒ / *Uncertain* ☐ / *Probably Yes* ☐ / *Yes* ☐ / ***Varies*** ☐	None identified	Implementation would require expertise and resources (i.e. skin tests, relevant allergen) not readily available in most areas.

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings
	☐	☐	☒	☐	☐

Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option
	☐	☒	☐	☐

Recommendation (text)	The KSA MoH panel suggests sublingual immunotherapy be not used for treatment of children younger than 18 years old with perennial or persistent allergic rhinitis (Conditional recommendation; very low-quality evidence)
Justification	There is a very low confidence in the currently available estimates of effects and a lack of evidence about adverse events, so it is uncertain that the desirable effects could be large relative to undesirable effects. Furthermore, there is an important variability about how much people value its effectiveness because there is a concern that some patients in KSA would not accept SLIT with some allergens of animal origin, however others would accept it as the last option when the symptoms do not decrease with all other regular options. On the other hand the incremental cost is not small relative to the net benefits, and the implementation would require personnel experts and resources (i.e. skin tests, specific allergen) which are not readily available in most areas. Reasons to formulate a conditional rather than a strong recommendation.
Subgroup considerations	In special situations in children not responding to maximal medications may be referred to an allergy specialist for evaluation of indications for immunotherapy.
Implementation considerations	If SLIT is prescribed in special situations it should be for children older than 5 years old and administered only by allergy specialists who have expertise in diagnosis of AR, proper identification of the allergens, providing immunotherapy and treatment of potentially serious adverse effects.
Monitoring and evaluation	If patients receiving SLIT do not respond within 6-12 months consider discontinuation SLIT

Research priorities	Research for the effectiveness and adverse effects of the SLIT in children younger and older than 5years old are needed. Nation-wide population-based community prevalence studies are needed to correctly estimate the AR rates in children. Patient values and preferences and cost effectiveness studies are also needed in the context of KSA to inform future guidelines and stakeholders.

Evidence profile: Sublingual immunotherapy in children with perennial/persistent AR

Author(s): Itziar Etxeandia

Date: 2013-11-18

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLIT	Control	Relative (95% CI)	Absolute		
Allergic rhinitis symptom scores (follow-up 5 to 12 months; Better indicated by lower values)												
6	randomised trials	serious[1]	serious[2]	no serious indirectness	no serious imprecision[3]	none	155	156	-	SMD 0.78 lower (2.09 lower to 0.53 higher)	⊕⊕OO LOW	CRITICAL
Medication scores (follow-up 5 to 12 months; Better indicated by lower values)												
4	randomised trials	serious	no serious inconsistency	no serious indirectness	serious[3]	none	113	118	-	SMD 0.22 lower (0.48 lower to 0.04 higher)	⊕⊕OO LOW	IMPORTANT
Withdrawal due to adverse effects (follow-up 12 months)												
2	randomised trials	Serious[4]	no serious inconsistency	no serious indirectness	very serious[5]	none	2/23 (8.7%)	0/25 (0%)	RR 3.32 (0.37 to 29.75)	0 more per 1000 (from 0 fewer to 0 more)	⊕OOO VERY LOW	CRITICAL
Serious adverse effects (follow-12 months)												
1	randomised trials	Serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/34 (0%)	0/32 (0%)	not pooled[7]	not pooled	⊕⊕⊕O MODERATE	IMPORTANT
Oral pruritus/oedema (follow-up 12 months)												
1	randomised trials	Serious[8]	no serious inconsistency	no serious indirectness	very serious[9]	none	5/15 (33.3%)	1/15 (6.7%) 2%[10]	RR 5.0 (0.66 to 37.87)	267 more per 1000 (from 23 fewer to 2458 more) 80 more per 1000 (from 7 fewer to 737 more)	⊕OOO VERY LOW	CRITICAL

1 3 of 6 studies with unclear sequence generation and allocation concealment
2 I2=95%. 2 of 6 studies with high effect size (favour SLIT) in contrast with the rests.
3 The estimation interval includes possible benefits and harms or no effect
4 Only two studies reported measuring this outcome, which did not follow an intent-to-treat analysis.
5 very small studies, only two events, but results do not exclude an important harm.
6 Only one of six studies reported measuring serious adverse effects.
7 There were no serious adverse effects in the study that reported measuring them.
8 Only one study reported measuring this outcome.
9 One small study. Very few events, but results do not exclude important harm.
13 low (2%) assumed baseline risk was estimated based on 2 most recent studies of SLIT in children allergic

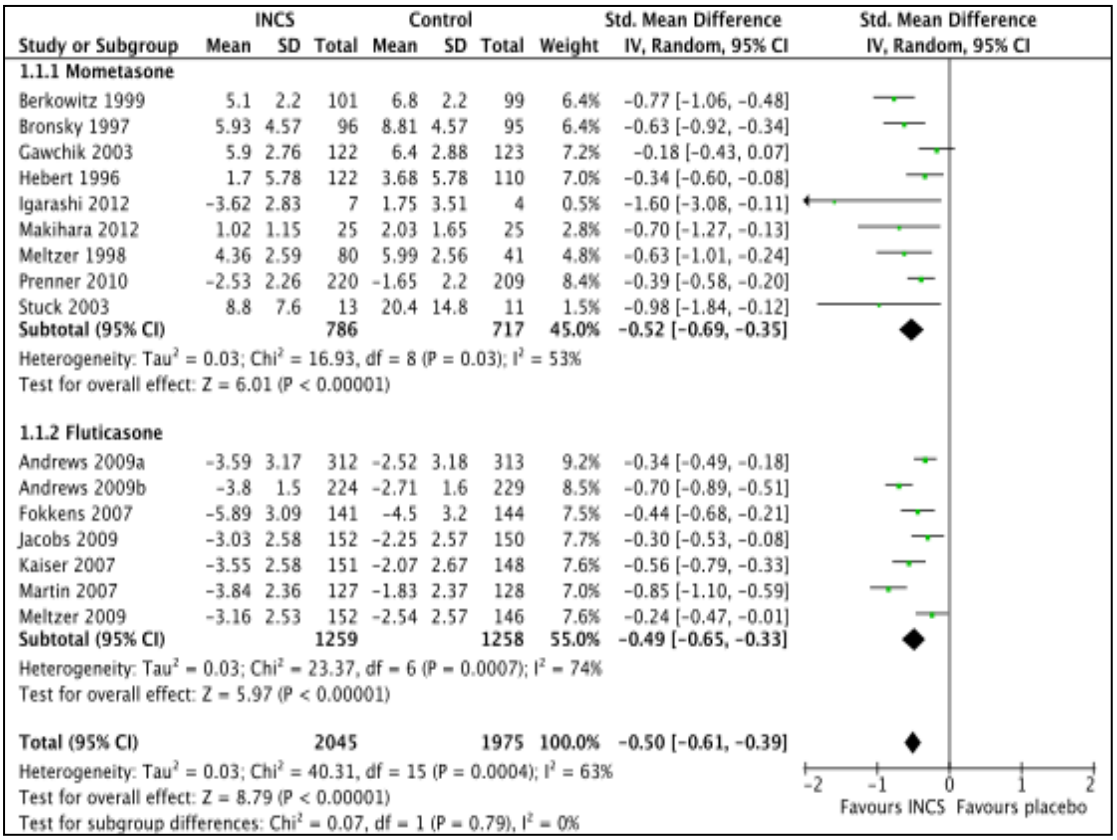
Appendix 2: Forest Plots

Question 1: Should intranasal corticosteroids be used in patients with allergic rhinitis (AR)?

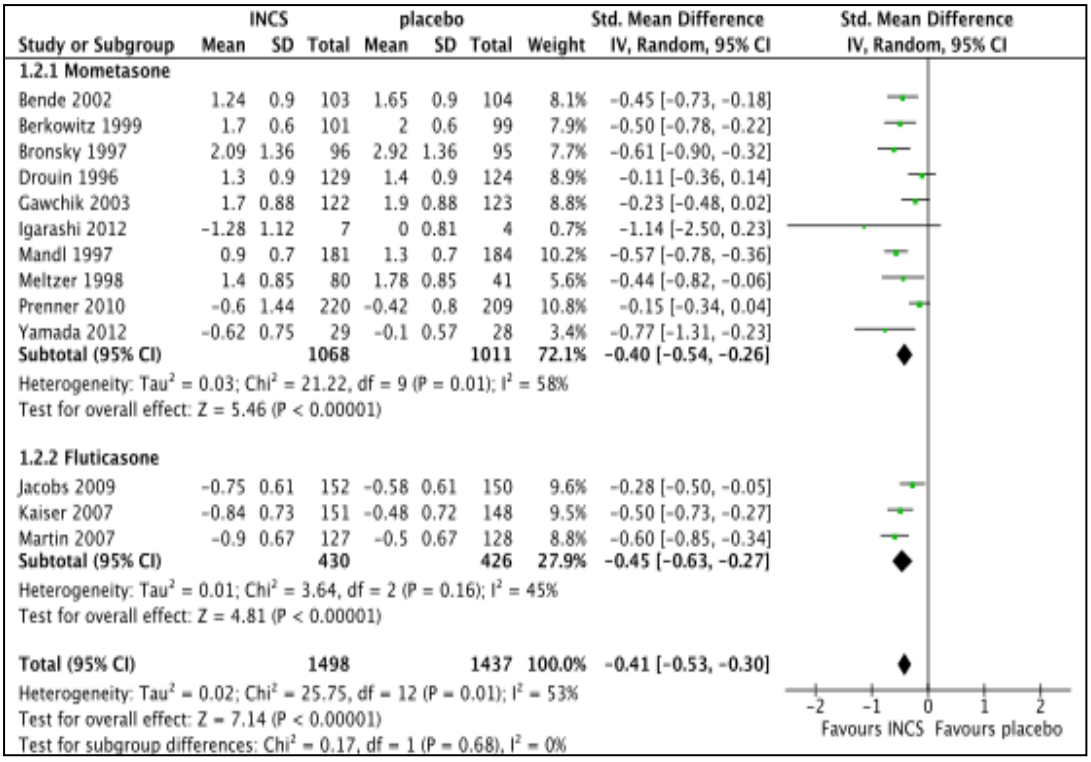
Seasonal / Intermittent Allergic Rhinitis

Forest plot of comparison: 1 Intranasal corticosteroids (INCS) vs placebo (seasonal), out-come:

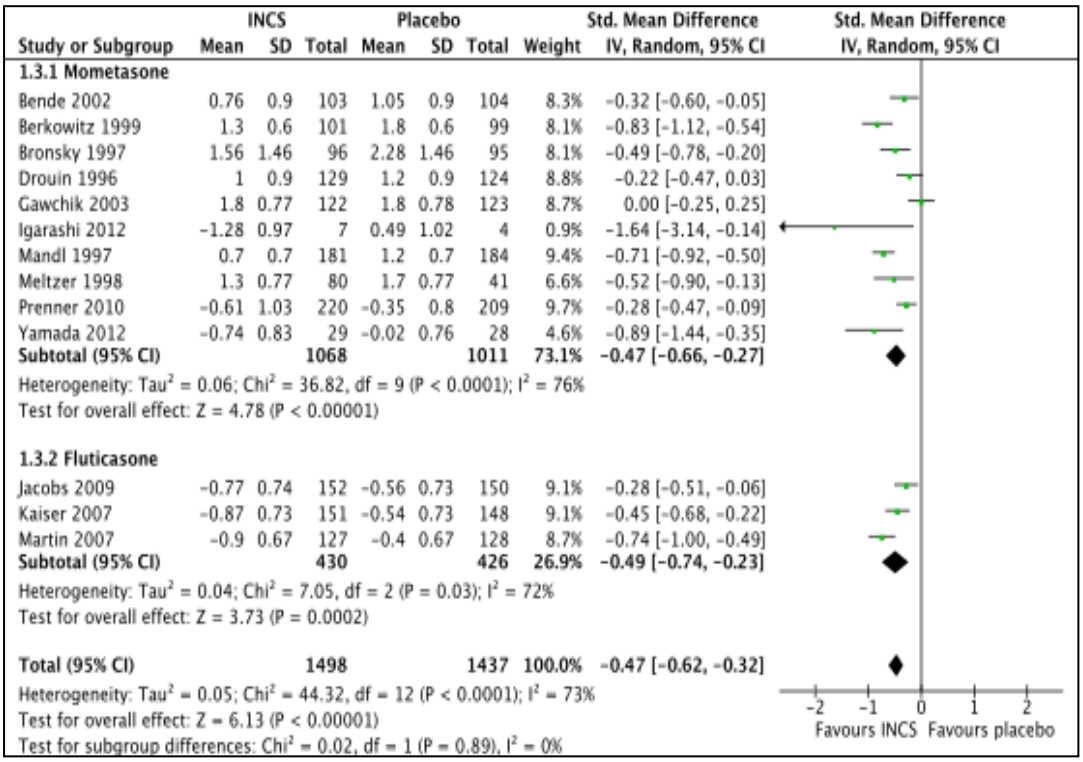
1.1 Nasal symptoms (Total nasal symptom score –TNSS).



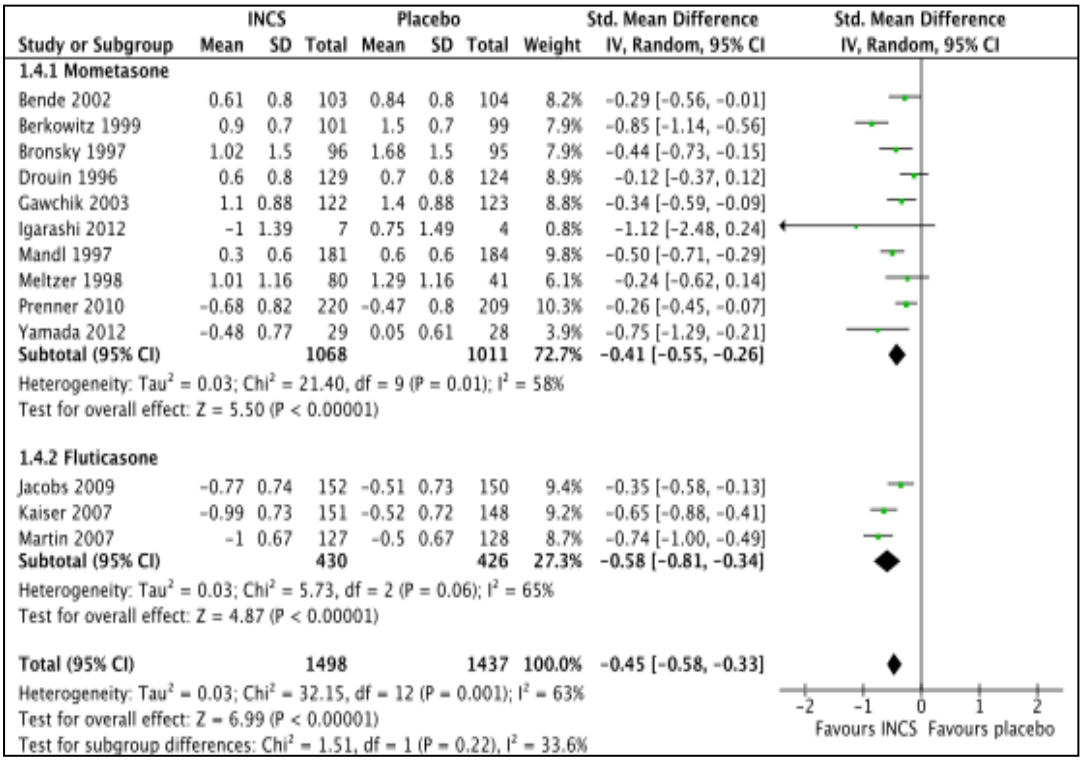
1.2 Nasal congestion.



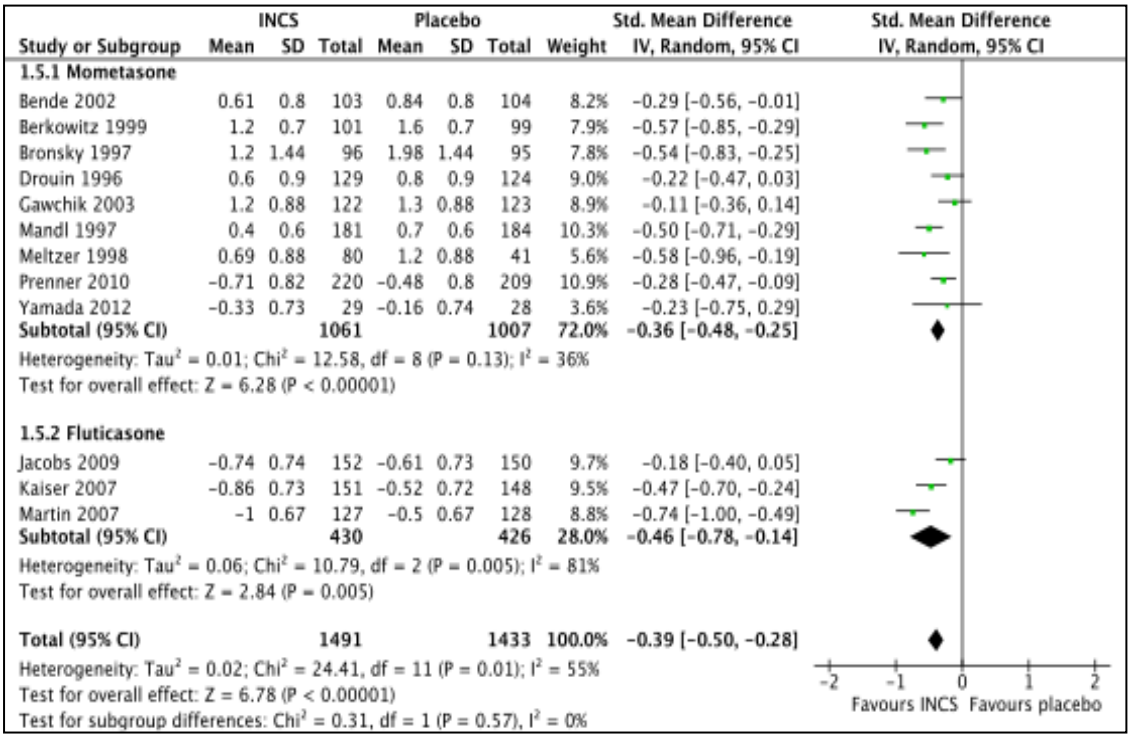
1.3 Rhinorrhea.



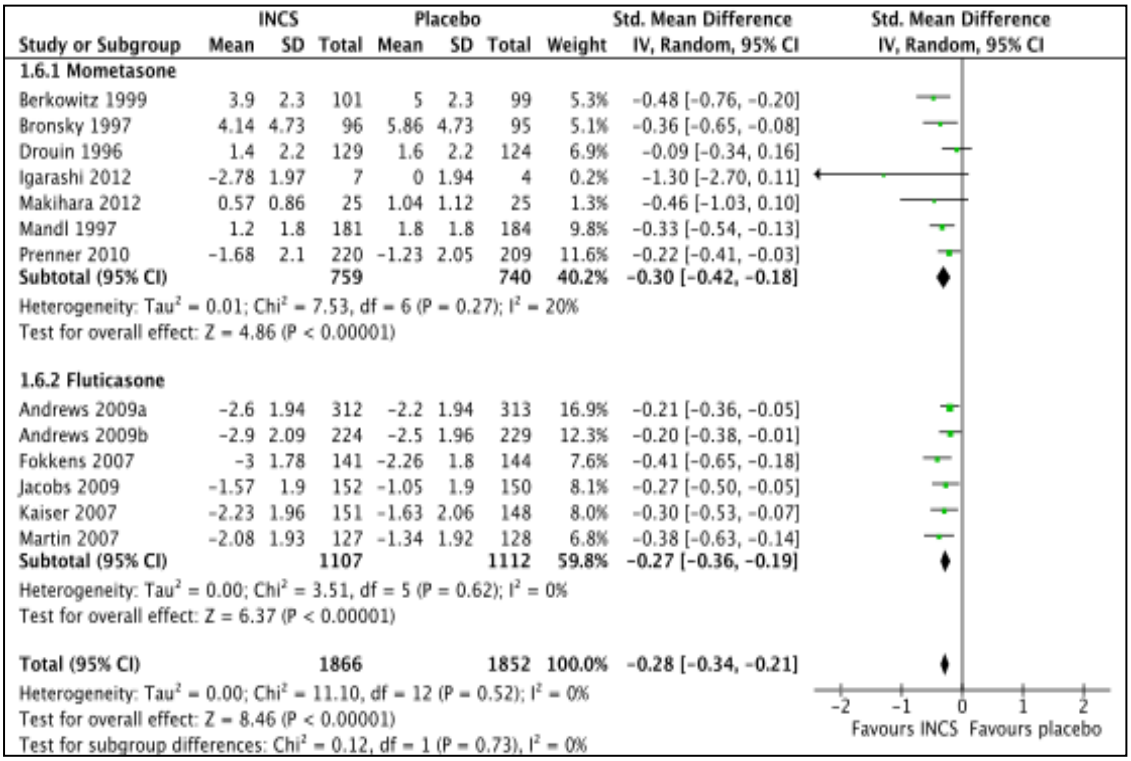
1.4 Sneezing.



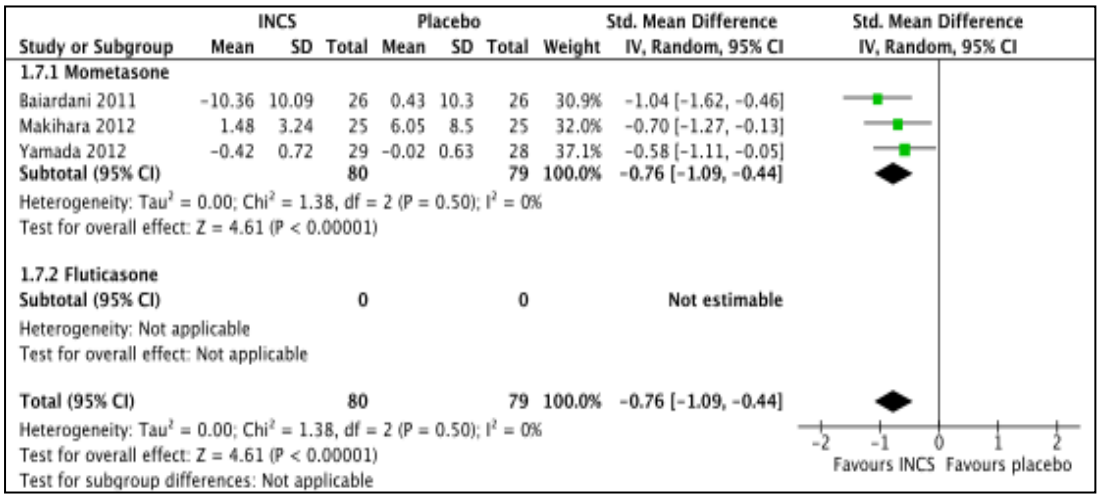
1.5 Nasal itching.



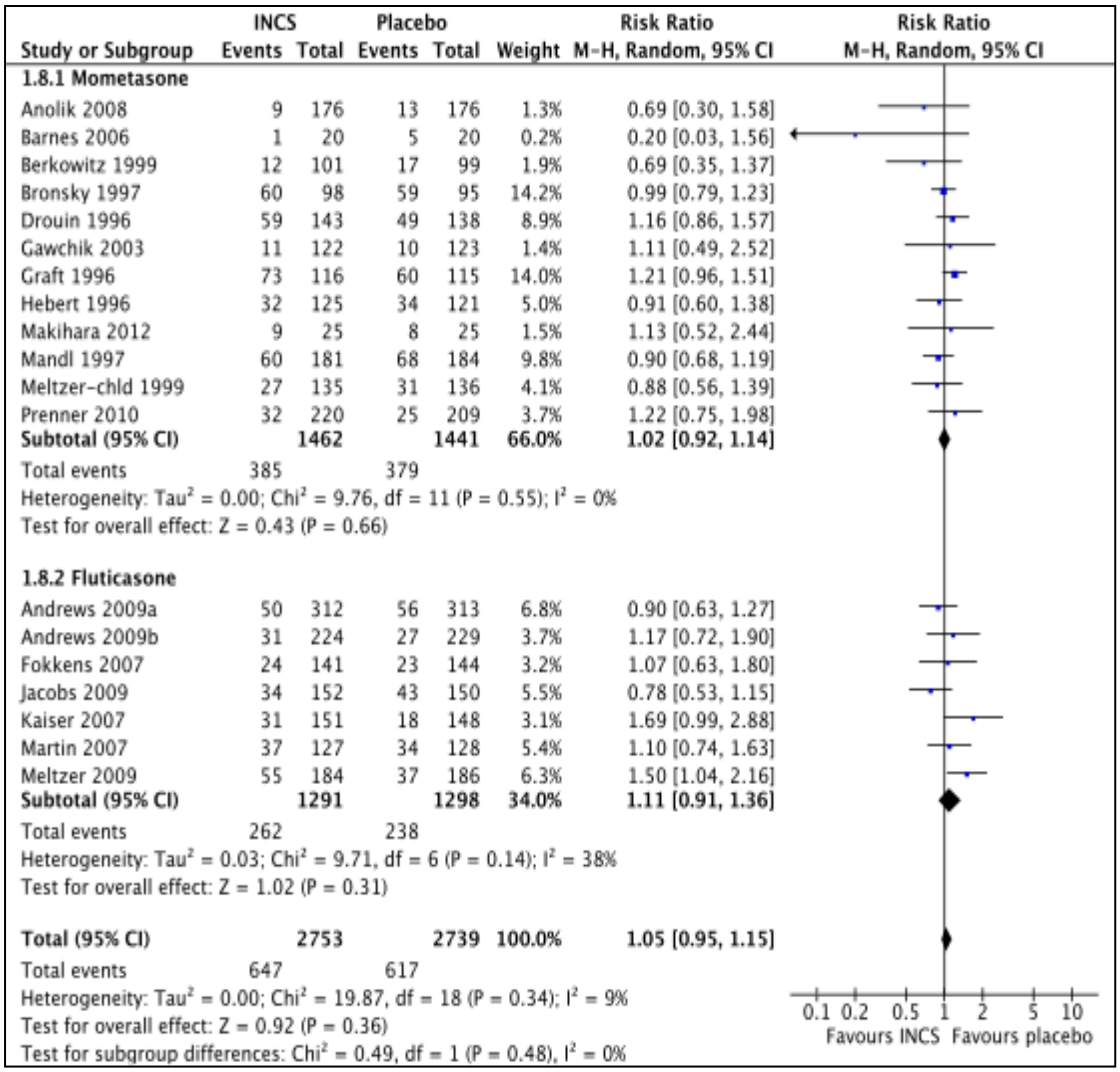
1.6 Non-nasal (ocular) symptoms (i.e., eye tearing, itching, eye redness)



1.7 Quality of life.



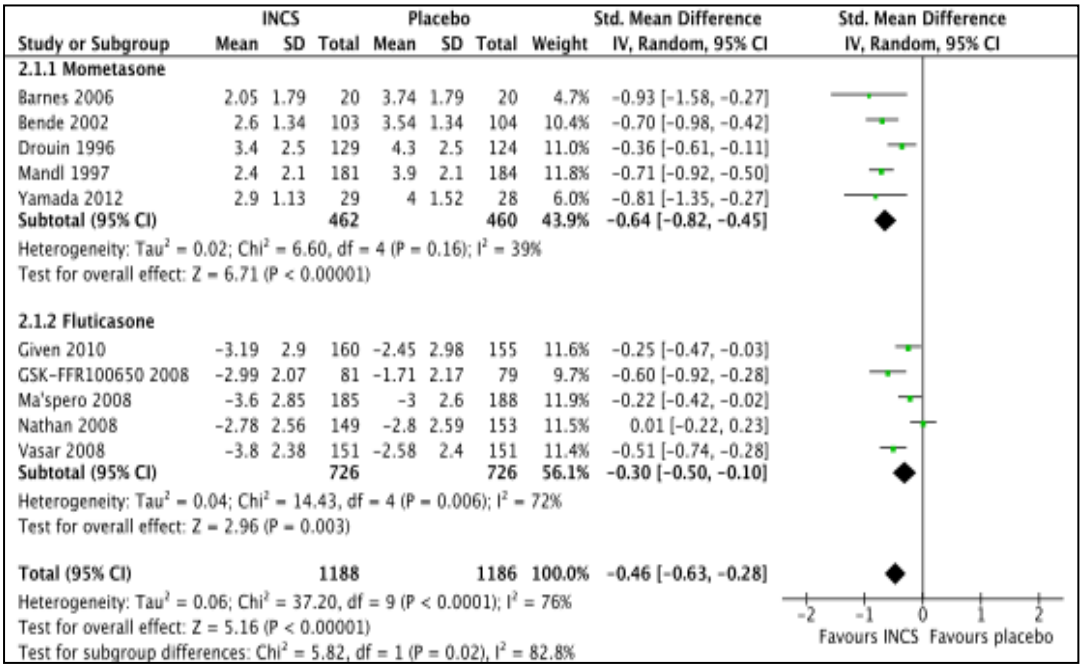
1.8 Adverse events of any kind.



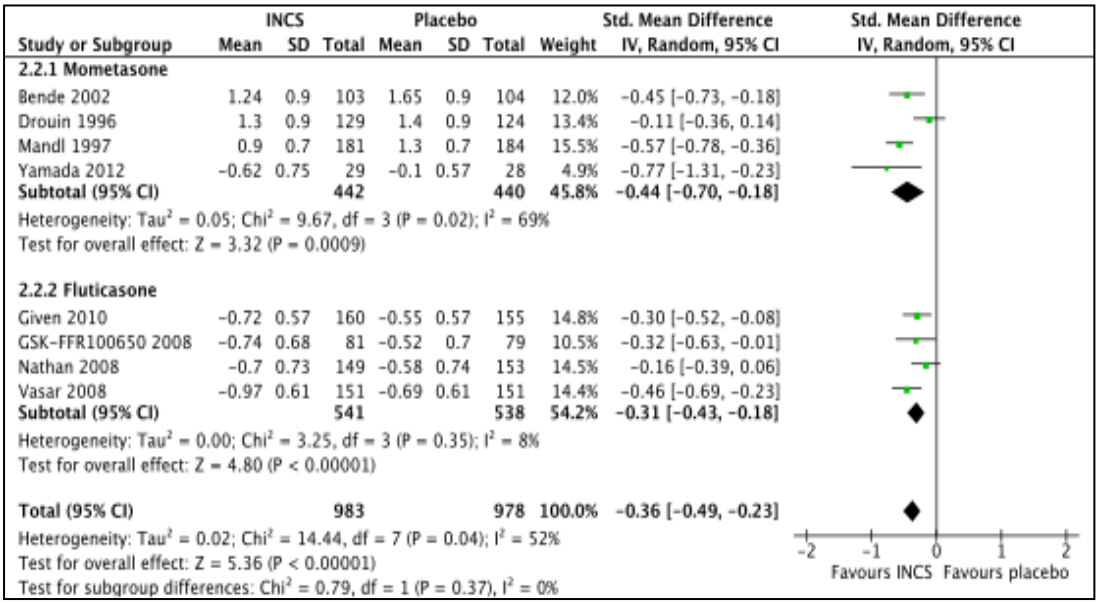
Perennial / persistent Allergic Rhinitis

Forest plot of comparison: 2 Intranasal corticosteroids (INCS) vs placebo (perennial), out-come:

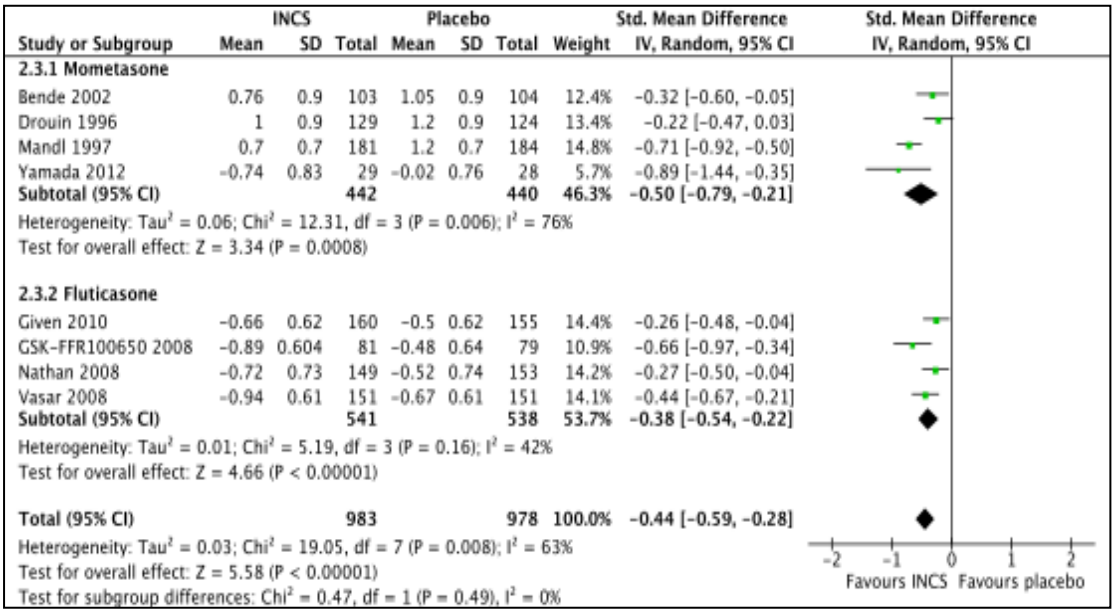
2.1 Total nasal symptoms (Total nasal symptom score –TNSS).



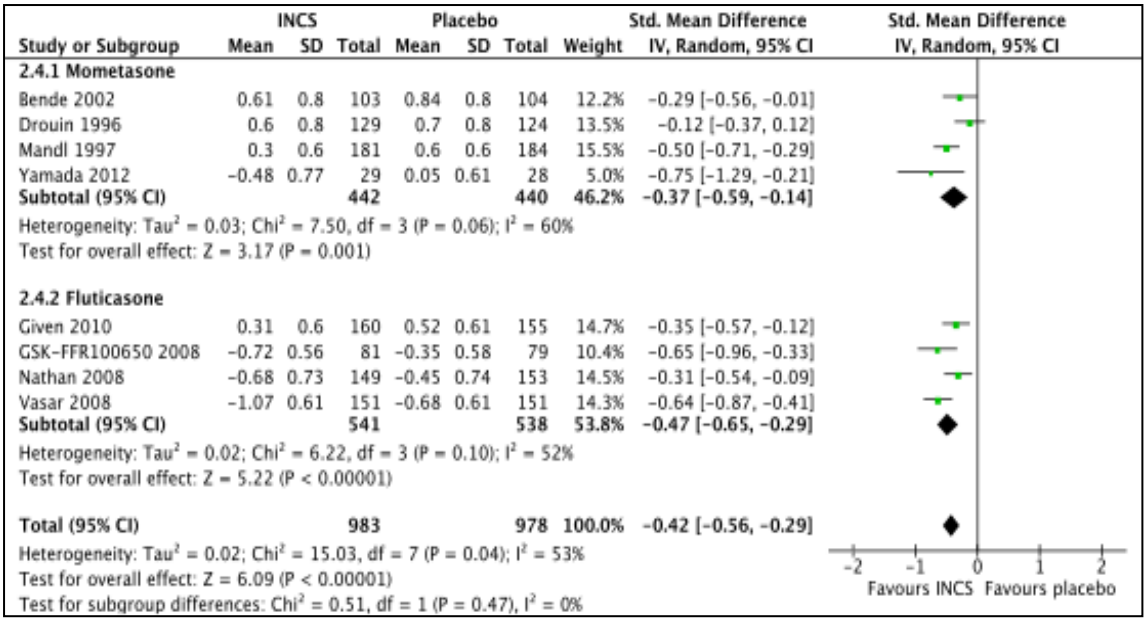
2.2 Nasal congestion.



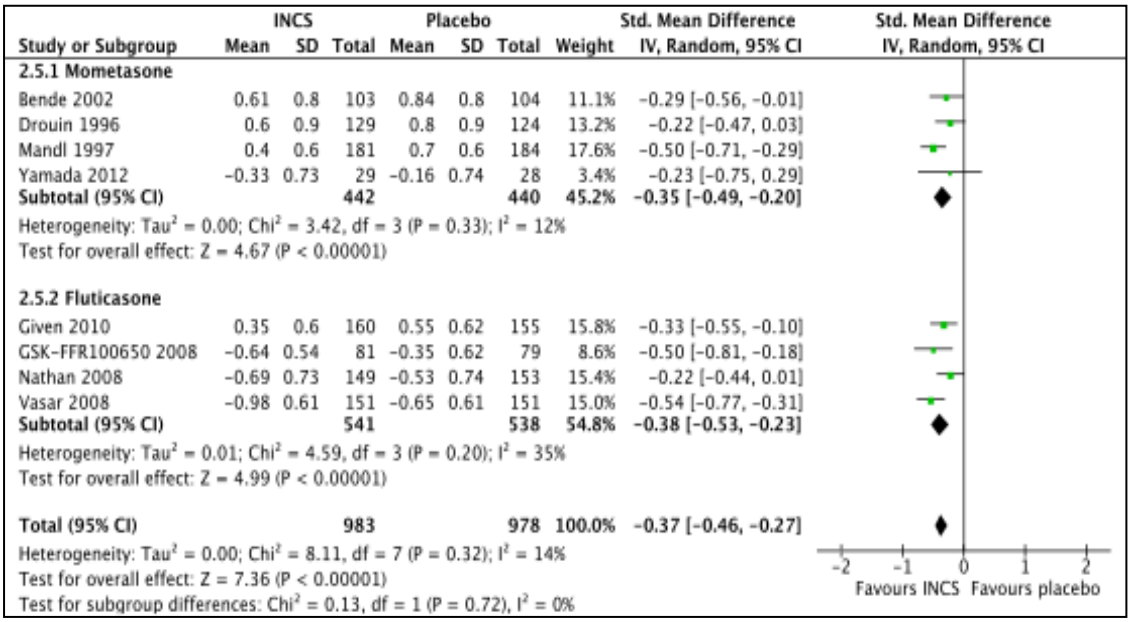
2.3 Rhinorrhea.



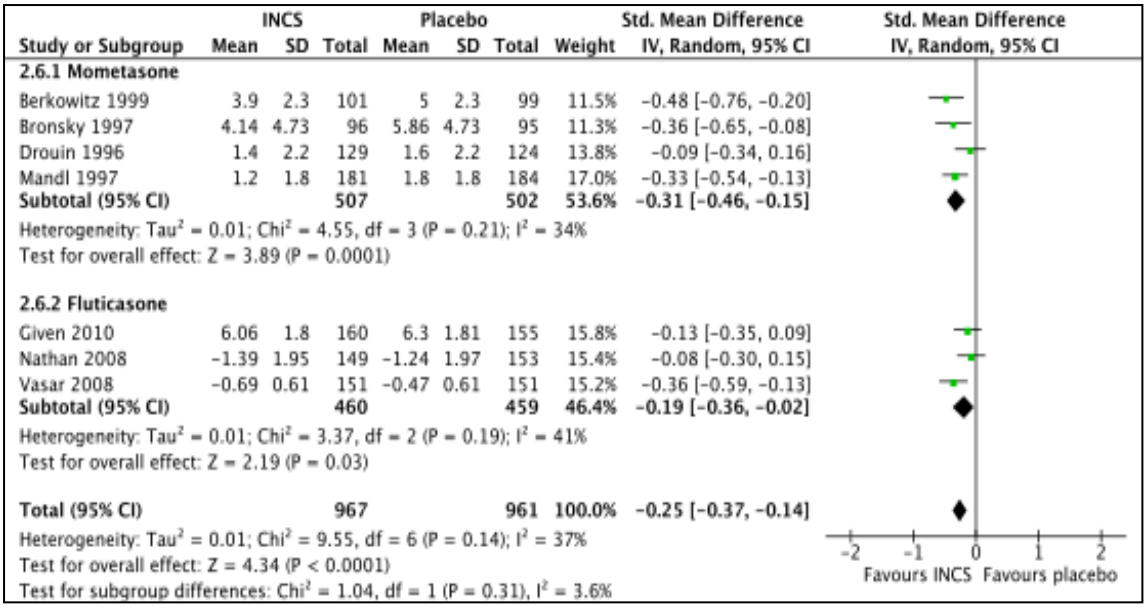
2.4 Sneezing.



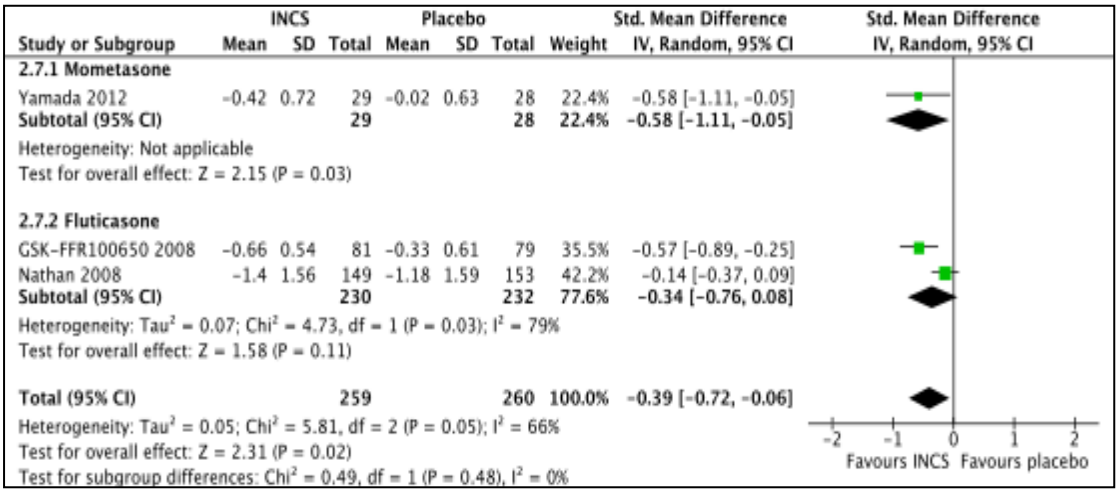
2.5 Nasal itching.



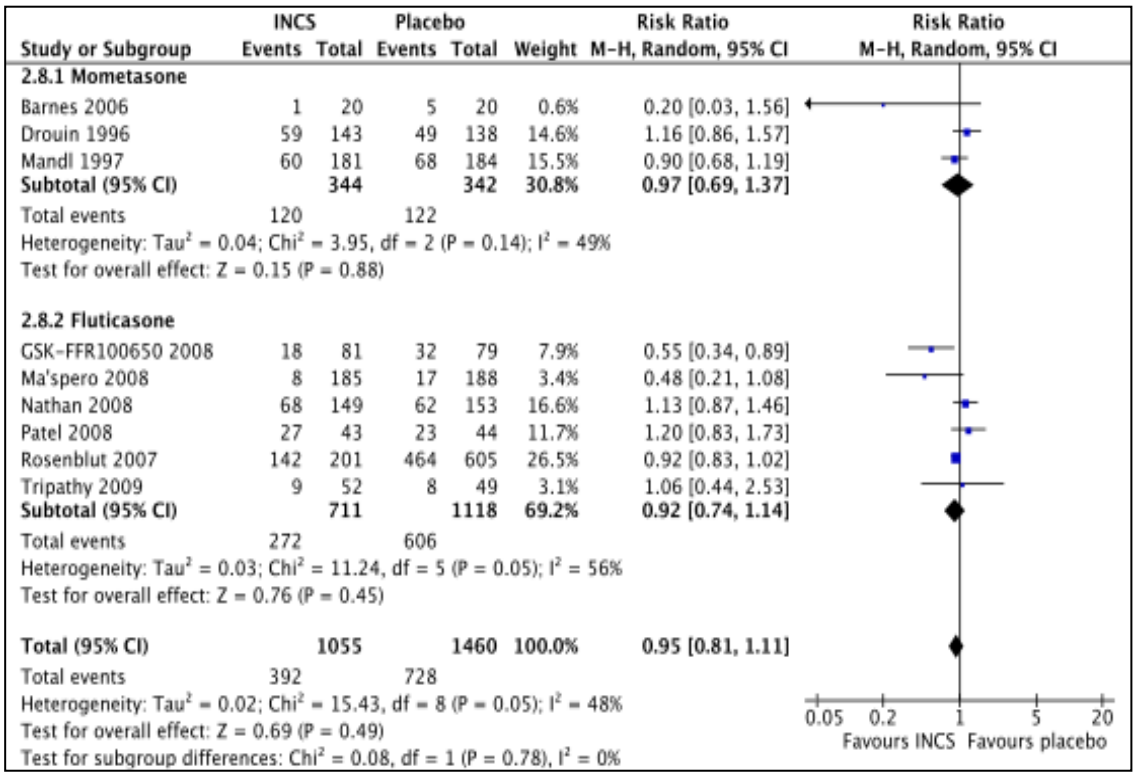
2.6 Non-nasal symptoms.



2.7 Quality of life.



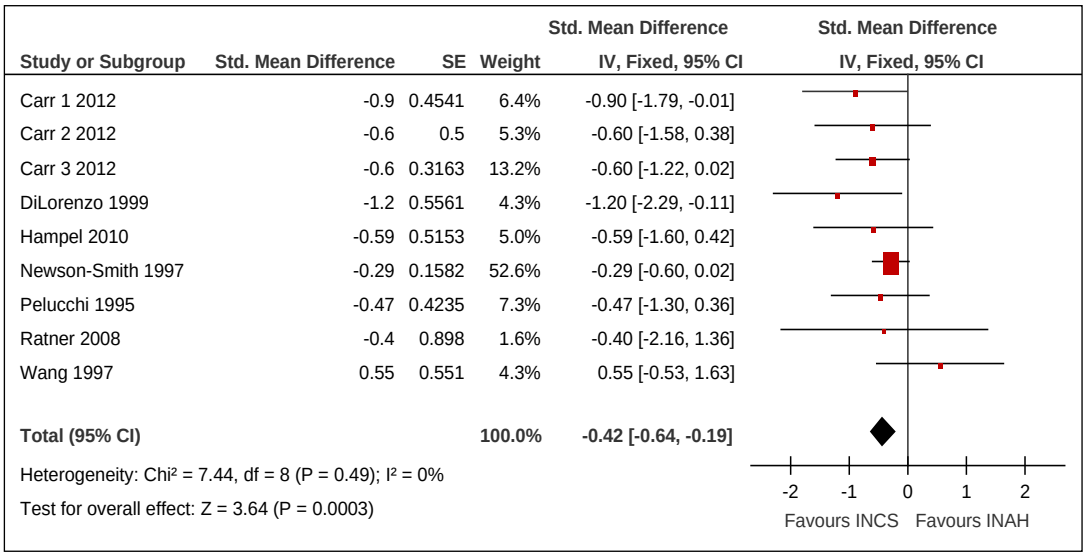
2.8 Adverse events.



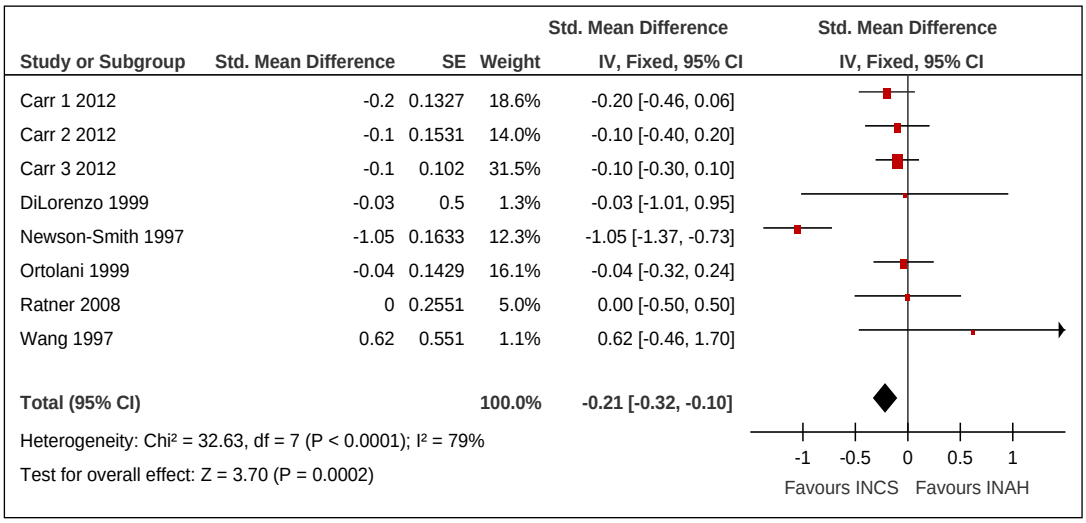
Question 2: Should intranasal glucocorticosteroids versus intranasal H1-antihistamines be used in adults with allergic rhinitis?

Seasonal Allergic Rhinitis (adults and younger over 12 years old)

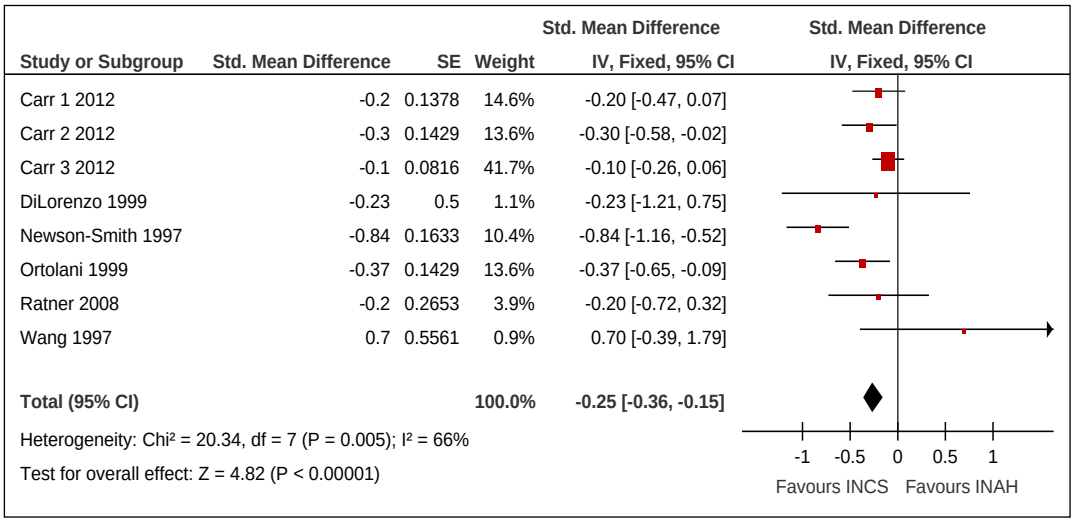
Total nasal symptoms



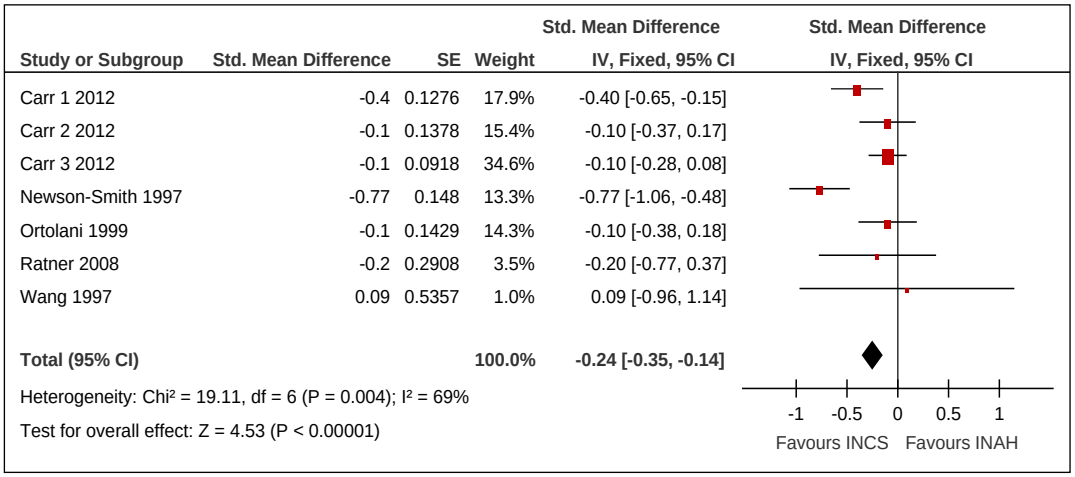
Sneezing



Rhinorrhea



Itching

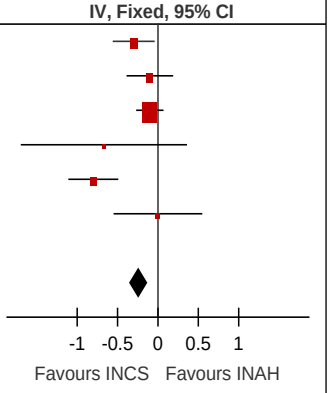


Nasal congestion

Study or Subgroup	Std. Mean Difference	SE	Weight	Std. Mean Difference IV, Fixed, 95% CI
Carr 1 2012	-0.3	0.1276	19.2%	-0.30 [-0.55, -0.05]
Carr 2 2012	-0.1	0.1429	15.3%	-0.10 [-0.38, 0.18]
Carr 3 2012	-0.1	0.0816	46.9%	-0.10 [-0.26, 0.06]
DiLorenzo 1999	-0.67	0.5204	1.2%	-0.67 [-1.69, 0.35]
Ortolani 1999	-0.8	0.1531	13.3%	-0.80 [-1.10, -0.50]
Ratner 2008	0	0.2755	4.1%	0.00 [-0.54, 0.54]
Total (95% CI)			**100.0%**	**-0.23 [-0.34, -0.12]**

Heterogeneity: Chi² = 18.93, df = 5 (P = 0.002); I² = 74%

Test for overall effect: Z = 4.19 (P < 0.0001)

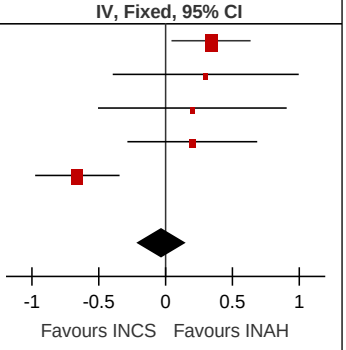


Ocular symptoms

Study or Subgroup	Std. Mean Difference	SE	Weight	Std. Mean Difference IV, Fixed, 95% CI
Ortolani 1999	0.34	0.148	38.6%	0.34 [0.05, 0.63]
Carr 2 2012	0.3	0.352	6.8%	0.30 [-0.39, 0.99]
Carr 1 2012	0.2	0.3571	6.6%	0.20 [-0.50, 0.90]
Carr 3 2012	0.2	0.2449	14.1%	0.20 [-0.28, 0.68]
Newson-Smith 1997	-0.66	0.1582	33.8%	-0.66 [-0.97, -0.35]
Total (95% CI)			**100.0%**	**-0.03 [-0.21, 0.15]**

Heterogeneity: Chi² = 24.28, df = 4 (P < 0.0001); I² = 84%

Test for overall effect: Z = 0.32 (P = 0.75)



QoL

Outcome	Variance	SS Favors Nasal AH MD	NSS Favors/NR Nasal AH MD	Favors Neither MD=0	NSS Favors/NR INCS MD	SS Favors INCS MD
2-week RQLQ						
Hampel, 2010[117]					0.26 (NR)	
Ratner, 2008[121]	SD				0.26 (NR)	
Carr, 2012[115]					0.1[a] (NR)	

AH = antihistamine; INCS = intranasal corticosteroid; MD = mean difference between group mean changes from baseline; NR = p-value not reported; NSS = not statistically significant; RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire; S-AH = selective antihistamine; SS = statistically significant.

Variance/confidence interval reported: CI = confidence interval; SD = standard deviation; SE = standard error.

[a]Meta-analysis estimate of Carr, 2012 trials 1, 2 and 3.

Adverse effects

Outcome	Severity	Citation	Favors[a] INCS RD	Favors[a] Neither RD = 0	Favors[a] Nasal AH RD	USPSTF	Active?[b]	Pt Blind?	Assessor Blind?	Risk of Bias	Cons	Dir	Prec	SOE
Sedation	Unspecified	Carr, 2012 (Trial 3)[115]	0.4			G	Y	Y	Y					
		Hampel, 2010[117]		0		G	N	Y	Y					
		Kaliner, 2009[118]	1.5			P	N	Y	Y					
										Med	Incons	Dir	Imprec	Insuf
Headache	Unspecified	Carr, 2012 (Trial 1)[115]			1.9	G	Y	Y	Y					
		Carr, 2012 (Trial 2)[115]		0		G	Y	Y	Y					
		Carr, 2012 (Trial 3)[115]	0.7			G	Y	Y	Y					
		Hampel, 2010[117]			2.6	G	N	Y	Y					
		Newson-Smith, 1997[119c]			4.8	P	Int	Y	Y					
		Ratner, 2008[121b]	0.1			G	Y	Y	Y					
										Low	Incons	Dir	Imprec	Insuf
Nasal discomfort	Unspecified	Carr, 2012 (Trial 1)[115]	0.9			G	Y	Y	Y					
		Carr, 2012 (Trial 2)[115]	1.0			G	Y	Y	Y					
		Ghimire, 2007[116]	8.0			P	N	Y	Y					
		Hampel, 2010[117]			0.7	G	N	Y	Y					
		Newson-Smith, 1997[119c]			1.2	P	Int	Y	Y					
										Med	Incons	Dir	Imprec	Insuf
Bitter aftertaste	Unspecified	Carr, 2012 (Trial 1)[115]	2.4			G	Y	Y	Y					
		Carr, 2012 (Trial 2)[115]	6.7*			G	Y	Y	Y					
		Carr, 2012 (Trial 3)[115]	4.8*			G	Y	Y	Y					
		Ghimire, 2007[116]	4.0			P	N	Y	Y					
		Hampel, 2010[117]	2.0			G	N	Y	Y					
		Kaliner, 2009[118]	3.1			P	N	Y	Y					
		Newson-Smith, 1997[119c]	6.0			P	Int	Y	Y					
		Ratner, 2008[121b]	6.2			G	Y	Y	Y					
										Med	Cons	Dir	Imprec	Insuf
Nosebleeds	Unspecified	Carr, 2012 (Trial 1)[115]			1.4	G	Y	Y	Y					
		Carr, 2012 (Trial 2)[115]		0		G	Y	Y	Y					
		Carr, 2012 (Trial 3)[115]		0		G	Y	Y	Y					
		Hampel, 2010[117]			1.9	G	N	Y	Y					
		Kaliner, 2009[118]	4.6			P	N	Y	Y					
		Newson-Smith, 1997[119c]	1.2			P	Int	Y	Y					
										Low	Incons	Dir	Imprec	Insuf

Cons = consistent; Dir = direct; G = good; Incons = inconsistent; Imprec = imprecision; Insuf = insufficient; INCS = intranasal corticosteroid; Int = intermediate; Mod = moderate; N = no; P = poor; Pt = patient; RD = risk difference; S-AH = selective antihistamine; SOE = strength of evidence; USPSTF = U.S. Preventive Services Task Force; Y = yes.

[a] Statistical significance as indicated.

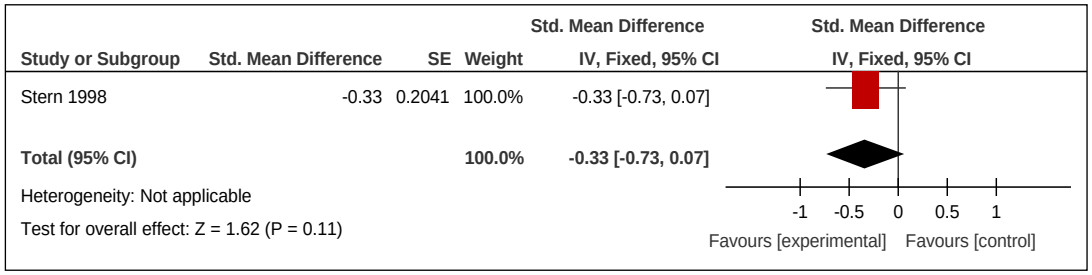
[b] The process of harms ascertainment was characterized as active, passive, or intermediate as defined in the Methods section.

[c] Denominator was reports, not patients. Confidence limits not calculated to assess strength of evidence.

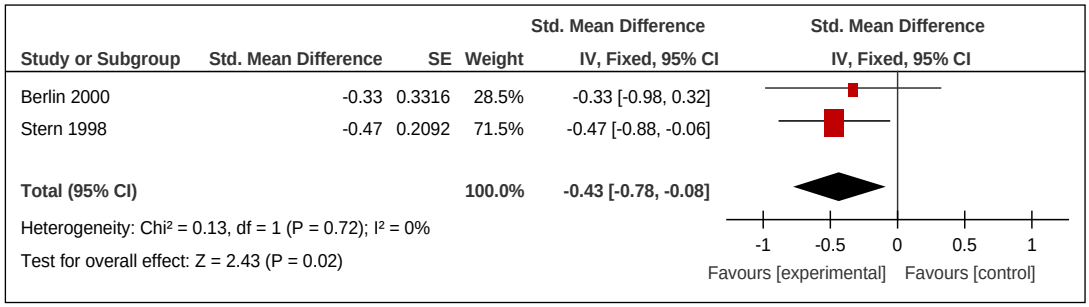
* $p<0.05$, calculated by CER authors.

Perennial Allergic Rhinitis (adults and younger over 12 years old)

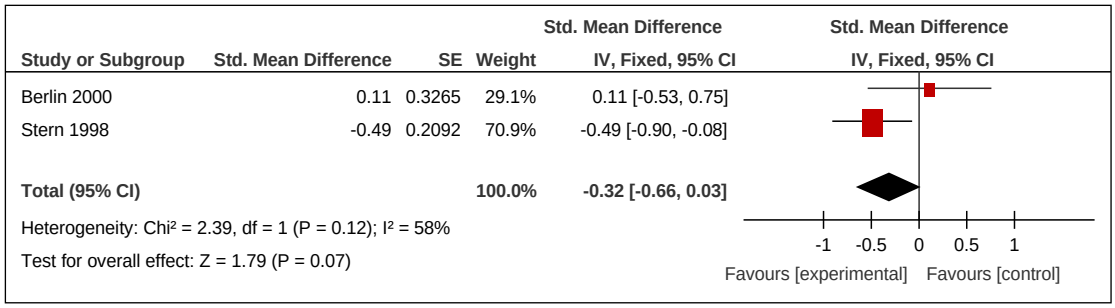
Total nasal symptoms



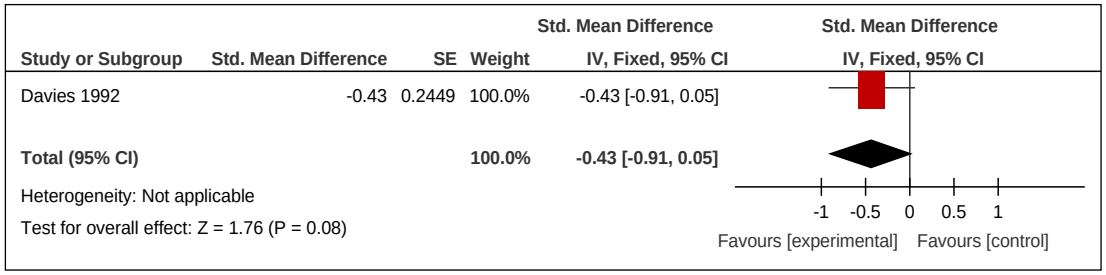
Sneezing



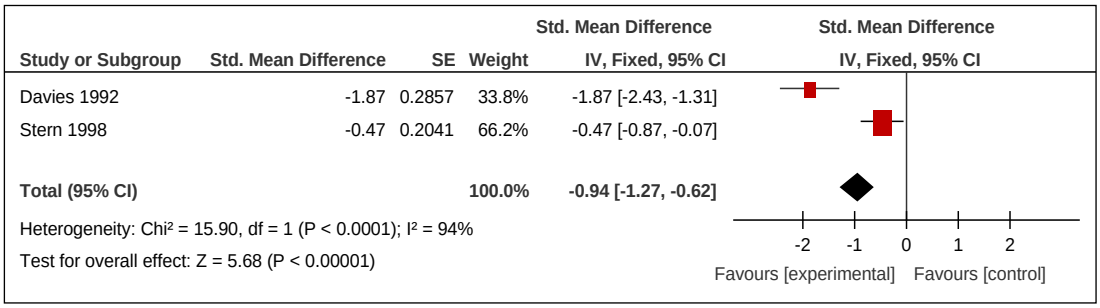
Rhinorrhea



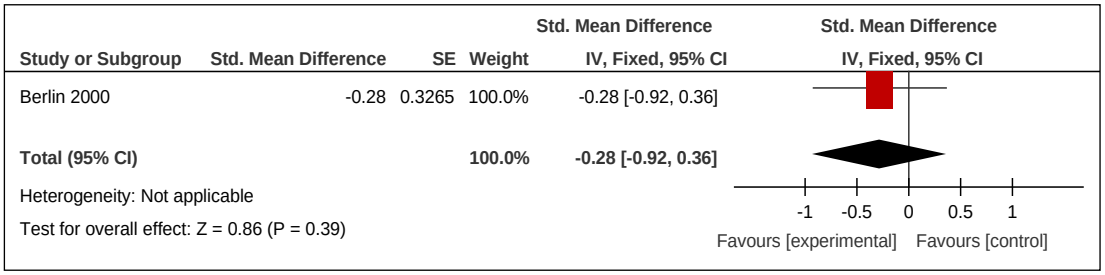
Itching



Nasal blockage



Ocular symptoms



Quality of Life

None

Adverse effects

None

Question 3: Should sublingual specific immunotherapy be used for treatment of allergic rhinitis in adults without concomitant asthma?

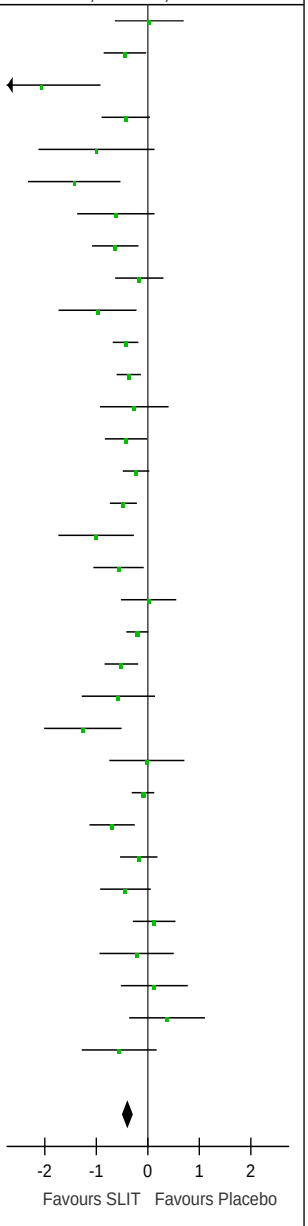
Adults with seasonal/intermittent AR:

Allergic rhinitis symptom scores

	SLIT			Placebo				Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Amar 2009	3.83	4.9	19	3.71	2.7	17	2.0%	0.03 [-0.63, 0.68]	
Andre 2003	2.27	1.42	48	3.09	2.14	51	3.7%	-0.45 [-0.84, -0.05]	
Ariano 2001	1.8	1.75	10	5.38	1.57	10	0.8%	-2.06 [-3.19, -0.93]	
Bowen 2004	3.95	2.45	37	5.03	2.54	39	3.2%	-0.43 [-0.88, 0.03]	
Casanovas 1994	5.46	3.56	9	10.98	7.1	6	0.8%	-1.00 [-2.11, 0.12]	
Cortellini 2010	182	67	15	315	115	11	1.2%	-1.43 [-2.31, -0.54]	
D'Ambrosio 1999	509	514.2	14	897.06	678.2	16	1.7%	-0.62 [-1.36, 0.12]	
Dahl 2006a	2.1	1.7	61	3.3	2.2	32	3.3%	-0.63 [-1.07, -0.19]	
de Blay 2003	20.55	15.88	33	23.49	18.76	42	3.2%	-0.17 [-0.62, 0.29]	
Di Rienzo 2006	0.4	0.3	18	0.8	0.5	14	1.6%	-0.98 [-1.72, -0.23]	
Didier 2007	3.58	2.976	136	4.93	3.229	148	5.5%	-0.43 [-0.67, -0.20]	
Didier 2011	2.67	3.63	149	4.03	3.71	165	5.7%	-0.37 [-0.59, -0.15]	
Drachenberg 2001	29.5	24.2	37	36.4	30.4	12	2.0%	-0.26 [-0.92, 0.39]	
Dubakiene 2003	0.48	0.3	47	0.64	0.43	53	3.7%	-0.42 [-0.82, -0.03]	
Durham 2006	2.48	2.1	131	2.96	2.09	129	5.4%	-0.23 [-0.47, 0.02]	
Durham 2010	2.7	2.1	142	3.7	2.1	115	5.4%	-0.47 [-0.72, -0.23]	
Feliziani 1995	109.7	92.46	18	215.8	114.2	16	1.7%	-1.00 [-1.72, -0.28]	
Hordijk 1998	3.21	3.05	35	5.13	3.6	36	3.0%	-0.57 [-1.04, -0.09]	
Lima 2002	2,494	2,326	28	2,465	1,537	28	2.7%	0.01 [-0.51, 0.54]	
Nelson 2011	3.83	4.07	184	4.69	4.32	207	6.0%	-0.20 [-0.40, -0.01]	
Ott 2009	-1.02	4.54	123	1.32	4.54	60	4.6%	-0.51 [-0.83, -0.20]	
Palma Carlos 2006	31.15	32.61	17	55.86	50.48	16	1.8%	-0.57 [-1.27, 0.13]	
Panzner 2008	111.35	114.91	20	321.6	211.22	15	1.6%	-1.26 [-2.00, -0.52]	
Passalacqua 1999	189	113	15	191	108	15	1.7%	-0.02 [-0.73, 0.70]	
Peter 2009	0.732	0.483	176	0.78	0.544	189	5.9%	-0.09 [-0.30, 0.11]	
Pfaar 2008	146.2	123	42	236.2	133.6	48	3.4%	-0.69 [-1.12, -0.27]	
Pradalier 1999	2.33	1.6	63	2.65	2	63	4.2%	-0.18 [-0.53, 0.17]	
Skoner 2010	0.19	1.16	33	1	2.3	36	3.0%	-0.43 [-0.91, 0.04]	
Smith 2004	2.58	2.48	45	2.32	1.67	51	3.7%	0.12 [-0.28, 0.52]	
Troise 1995	87	76	15	102	58	16	1.8%	-0.22 [-0.92, 0.49]	
Vervloet 2006	2.68	1.64	19	2.44	2.06	19	2.1%	0.13 [-0.51, 0.76]	
Voltolini 2001	130	154	15	83	79	15	1.7%	0.37 [-0.35, 1.10]	
Wessner 2001	0.32	0.26	14	0.51	0.38	18	1.7%	-0.56 [-1.27, 0.16]	
Total (95% CI)			**1768**			**1708**	**100.0%**	**-0.38 [-0.49, -0.27]**	

Heterogeneity: Tau² = 0.04; Chi² = 62.78, df = 32 (P = 0.0009); I² = 49%

Test for overall effect: Z = 6.94 (P < 0.00001)

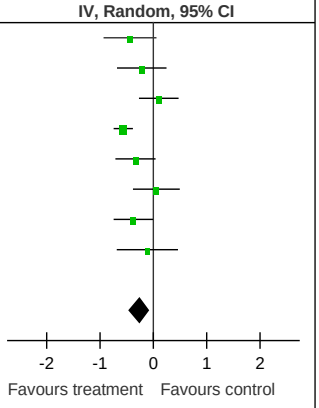


Ocular Symptoms

Study or Subgroup	Treatment Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Andre 2003	1.11	0.91	26	1.69	1.48	48	9.9%	-0.44 [-0.92, 0.04]
Bowen 2004	1.96	1.9	37	2.38	1.92	39	10.7%	-0.22 [-0.67, 0.23]
Clavel 1998	53	107.9	62	43	84.5	58	13.3%	0.10 [-0.26, 0.46]
Dahl 2006 B	0.7	0.6	282	1.1	0.8	286	19.9%	-0.56 [-0.73, -0.40]
de Blay 2007	7.79	9.28	61	11.18	10.82	57	13.2%	-0.34 [-0.70, 0.03]
Moreno-Ancillo 2007	0.48	0.39	41	0.46	0.31	44	11.4%	0.06 [-0.37, 0.48]
Pradalier 1999	1.06	1.02	62	1.55	1.53	61	13.4%	-0.38 [-0.73, -0.02]
Torres Lima 2002	462	891.9	26	550	596.3	23	8.3%	-0.11 [-0.67, 0.45]
Total (95% CI)			**597**			**616**	**100.0%**	**-0.26 [-0.46, -0.06]**

Heterogeneity: Tau² = 0.05; Chi² = 17.02, df = 7 (P = 0.02); I² = 59%

Test for overall effect: Z = 2.55 (P = 0.01)

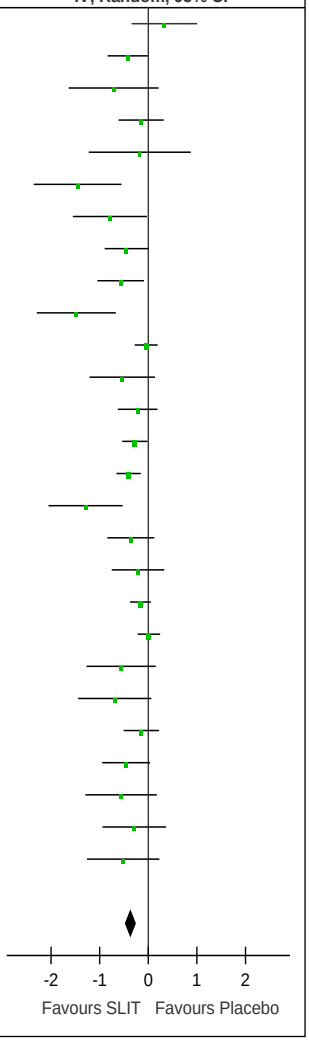


Medication scores

Study or Subgroup	SLIT Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Amar 2009	0.44	1.2	19	0.14	0.24	17	2.5%	0.33 [-0.33, 0.99]
Andre 2003	2.41	3.09	48	4	4.24	51	4.7%	-0.42 [-0.82, -0.02]
Ariano 2001	2.5	2.1	10	5.3	4.9	10	1.5%	-0.71 [-1.62, 0.20]
Bowen 2004	1.05	1.6	37	1.26	1.24	39	4.1%	-0.15 [-0.60, 0.30]
Casanovas 1994	1.69	2.46	9	2.13	2.22	6	1.2%	-0.17 [-1.21, 0.86]
Cortellini 2010	41	34	15	94	37	11	1.5%	-1.45 [-2.34, -0.57]
D'Ambrosio 1999	48.1	46.6	14	124.37	121	16	2.0%	-0.79 [-1.54, -0.04]
Dahl 2006a	2.4	3.9	61	4.2	4.1	32	4.3%	-0.45 [-0.88, -0.02]
de Blay 2003	3.48	5.37	33	7.57	8.23	42	3.9%	-0.57 [-1.03, -0.10]
Di Rienzo 2006	3.2	0.7	18	4.9	1.5	14	1.8%	-1.48 [-2.28, -0.68]
Didier 2011	0.31	3.63	149	0.47	3.71	165	7.2%	-0.04 [-0.26, 0.18]
Drachenberg 2001	12.5	18.7	37	23.8	26.4	12	2.4%	-0.54 [-1.20, 0.12]
Dubakiene 2003	0.13	0.17	47	0.17	0.19	53	4.7%	-0.22 [-0.61, 0.17]
Durham 2006	1.4	2.13	131	2.03	2.39	129	6.9%	-0.28 [-0.52, -0.03]
Durham 2010	1.82	3.01	160	3.04	3.01	127	7.0%	-0.40 [-0.64, -0.17]
Feliziani 1995	24.06	25.72	18	75.9	50.3	16	2.0%	-1.29 [-2.04, -0.54]
Hordijk 1998	0.16	0.37	35	0.31	0.45	36	3.9%	-0.36 [-0.83, 0.11]
Lima 2002	2,334	2,616	28	2,837	2,052	28	3.4%	-0.21 [-0.74, 0.31]
Nelson 2011	1.25	2.71	184	1.7	2.88	207	7.6%	-0.16 [-0.36, 0.04]
Ott 2009	-0.28	11.55	123	-0.92	60	247	7.3%	0.01 [-0.20, 0.23]
Palma Carlos 2006	15.38	32.98	17	44.57	65.05	16	2.3%	-0.56 [-1.26, 0.14]
Passalacqua 1999	42	49.5	15	83	65	15	2.1%	-0.69 [-1.43, 0.05]
Pradalier 1999	1.77	2.3	63	2.13	2.7	63	5.3%	-0.14 [-0.49, 0.21]
Skoner 2010	0.0003	1.64	33	0.63	1.06	36	3.8%	-0.46 [-0.93, 0.02]
Troise 1995	17	21	15	33	33	16	2.1%	-0.56 [-1.28, 0.16]
Vervloet 2006	3.39	3.94	19	4.71	5	19	2.6%	-0.29 [-0.93, 0.35]
Voltolini 2001	22	30	15	39	34	15	2.1%	-0.52 [-1.25, 0.21]
Total (95% CI)			**1353**			**1438**	**100.0%**	**-0.35 [-0.47, -0.23]**

Heterogeneity: Tau² = 0.04; Chi² = 49.79, df = 26 (P = 0.003); I² = 48%

Test for overall effect: Z = 5.74 (P < 0.00001)

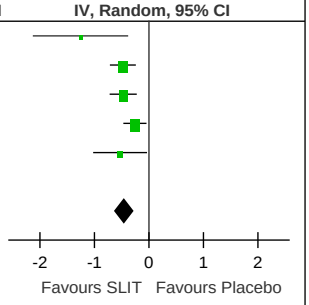


SMS (Combined SS and MS)

Study or Subgroup	SLIT Mean	SLIT SD	SLIT Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
Cortellini 2010	231	113	15	414	173	11	3.8%	-1.26 [-2.12, -0.39]
Didier 2011	3.46	3.625	149	5.28	3.942	165	28.0%	-0.48 [-0.70, -0.25]
Durham 2010	0.17	0.19	160	0.26	0.19	127	26.7%	-0.47 [-0.71, -0.24]
Nelson 2011	5.08	5.4	184	6.39	4.8	207	31.0%	-0.26 [-0.46, -0.06]
Skoner 2010	0.19	2.32	33	1.63	2.99	36	10.5%	-0.53 [-1.01, -0.05]
Total (95% CI)			**541**			**546**	**100.0%**	**-0.44 [-0.62, -0.27]**

Heterogeneity: Tau² = 0.02; Chi² = 6.82, df = 4 (P = 0.15); I² = 41%

Test for overall effect: Z = 4.98 (P < 0.00001)

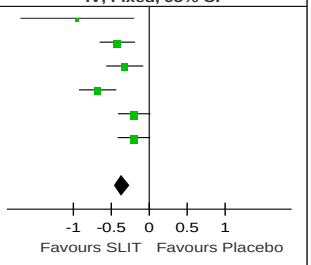


QoL

Study or Subgroup	SLIT Mean	SLIT SD	SLIT Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Di Rienzo 2006	0.5	1.52	18	1.83	1.14	14	1.7%	-0.95 [-1.69, -0.21]
Didier 2011	-0.43	1.02	149	0	1.02	165	18.9%	-0.42 [-0.64, -0.20]
Durham 2010	0.78	0.71	160	1.01	0.71	127	17.3%	-0.32 [-0.56, -0.09]
Horak 2009	-0.3	0.44	143	0	0.44	148	17.0%	-0.68 [-0.92, -0.44]
Nelson 2011	1.3	1.31	172	1.57	1.4	197	22.6%	-0.20 [-0.40, 0.01]
Peter 2009	-1.127	1.531	176	-0.81	1.601	189	22.4%	-0.20 [-0.41, 0.00]
Total (95% CI)			**818**			**840**	**100.0%**	**-0.36 [-0.46, -0.26]**

Heterogeneity: Chi² = 14.48, df = 5 (P = 0.01); I² = 65%

Test for overall effect: Z = 7.19 (P < 0.00001)

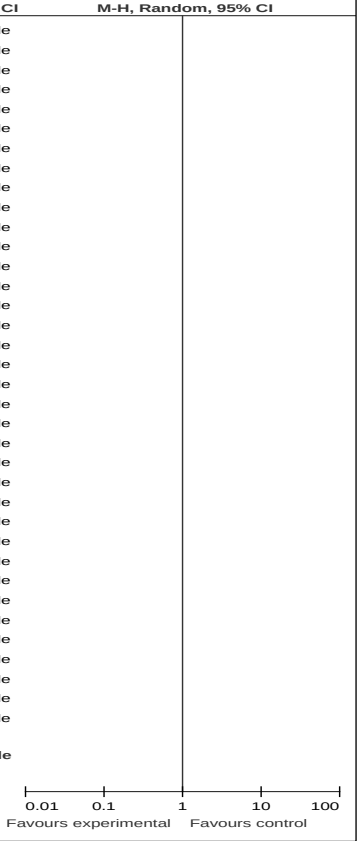


Serious Adverse events

Study or Subgroup	SLIT Events	SLIT Total	placebo Events	placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Andre 2003	0	53	0	53		Not estimable
Ariano 2001	0	10	0	10		Not estimable
Bowen 2004	0	43	0	40		Not estimable
Casanovas 1994 (W)	0	9	0	6		Not estimable
Clavel 1998	0	62	0	58		Not estimable
D'Anneo 2008	0	24	0	21		Not estimable
Dahl 2006 A	0	61	0	32		Not estimable
Dahl 2006 B	0	316	0	318		Not estimable
de Blay 2007	0	61	0	57		Not estimable
di Rienzo 2006	0	19	0	15		Not estimable
Didier 2007	0	155	0	156		Not estimable
Drachenberg 2001	0	49	0	19		Not estimable
Durham 2006	0	139	0	136		Not estimable
Feliziani 1995 (W)	0	18	0	16		Not estimable
Hordijk 1998	0	27	0	30		Not estimable
Horiguchi 2008	0	43	0	24		Not estimable
Khinchi 2004	0	23	0	24		Not estimable
Marogna 2004	0	319	0	192		Not estimable
Marogna 2005	0	29	0	23		Not estimable
Marogna 2007 birch	0	36	0	12		Not estimable
Moreno-Ancillo 2007	0	52	0	53		Not estimable
Mosges 2007	0	48	0	53		Not estimable
Okubo 2008	0	37	0	22		Not estimable
Palma-Carlos 2006	0	17	0	16		Not estimable
Passalacqua 1999 (W)	0	15	0	15		Not estimable
Pokladnikova 2008	0	17	0	20		Not estimable
Pradalier 1999	0	63	0	63		Not estimable
Purello D'Ambrosio 1996 W	0	15	0	15		Not estimable
Purello D'Ambrosio 1999 W	0	14	0	16		Not estimable
Sabbah 1994	0	29	0	29		Not estimable
Sambugaro 2003	0	43	0	10		Not estimable
Smith 2004	0	121	0	59		Not estimable
Torres Lima 2002	0	26	0	23		Not estimable
Troise 1995 (W)	0	15	0	16		Not estimable
Voltolini 2001	0	15	0	15		Not estimable
Worm 2006	0	94	0	91		Not estimable
Total (95% CI)		**2117**		**1758**		**Not estimable**
Total events	0		0			

Heterogeneity: Not applicable

Test for overall effect: Not applicable

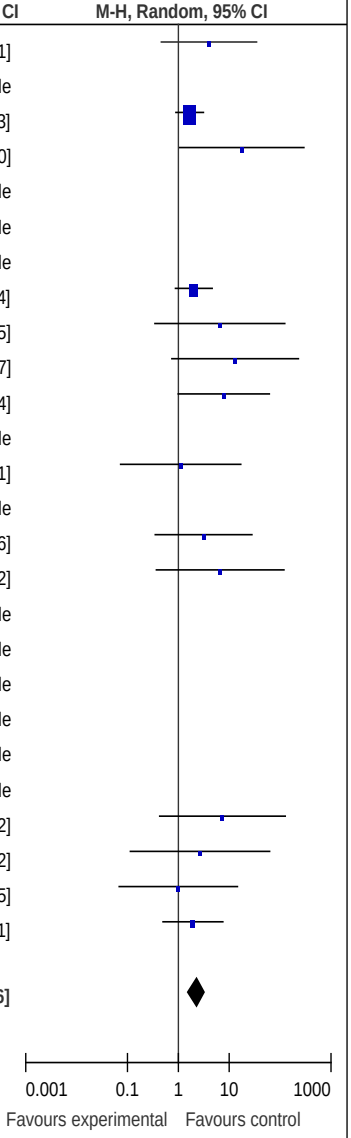


Withdrawal due to adverse effect (follow-up median 7 months1)

Study or Subgroup	SLIT Events	SLIT Total	placebo Events	placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Andre 2003	4	53	1	53	3.5%	4.00 [0.46, 34.61]
Ariano 2001	0	10	0	10		Not estimable
Blai/cor/Nel/Pfa/Rei 2011	30	879	14	686	41.3%	1.67 [0.89, 3.13]
Bowen 2004	9	43	0	40	2.1%	17.70 [1.06, 294.60]
Casanovas 1994 (W)	0	9	0	6		Not estimable
Clavel 1998	0	62	0	58		Not estimable
D'Anneo 2008	0	24	0	21		Not estimable
Dahl 2006 B	16	316	8	318	23.3%	2.01 [0.87, 4.64]
de Blay 2007	3	61	0	57	1.9%	6.55 [0.35, 124.05]
Didier 2007	6	155	0	156	2.0%	13.08 [0.74, 230.27]
Durham 2006	8	139	1	136	3.8%	7.83 [0.99, 61.74]
Feliziani 1995 (W)	0	18	0	16		Not estimable
Hordijk 1998	1	27	1	30	2.2%	1.11 [0.07, 16.91]
Horiguchi 2008	0	43	0	24		Not estimable
Khinchi 2004	3	23	1	24	3.4%	3.13 [0.35, 27.96]
Marogna 2004	5	319	0	192	1.9%	6.63 [0.37, 119.32]
Palma-Carlos 2006	0	17	0	16		Not estimable
Passalacqua 1999 (W)	0	15	0	15		Not estimable
Purello D'Ambrosio 1996 W	0	15	0	15		Not estimable
Purello D'Ambrosio 1999 W	0	14	0	16		Not estimable
Sabbah 1994	0	29	0	29		Not estimable
Sambugaro 2003	0	43	0	10		Not estimable
Smith 2004	7	121	0	59	2.0%	7.38 [0.43, 127.02]
Torres Lima 2002	1	26	0	23	1.6%	2.67 [0.11, 62.42]
Voltolini 2001	1	15	1	15	2.3%	1.00 [0.07, 14.55]
Worm 2006	6	94	3	91	8.8%	1.94 [0.50, 7.51]
Total (95% CI)		**2570**		**2116**	**100.0%**	**2.31 [1.55, 3.46]**
Total events	100		30			

Heterogeneity: Tau² = 0.00; Chi² = 9.15, df = 13 (P = 0.76); I² = 0%

Test for overall effect: Z = 4.08 (P < 0.0001)

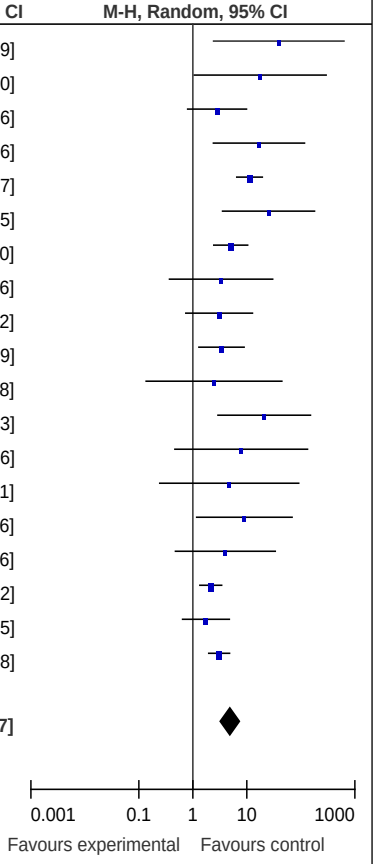


Oral pruritus or burning (follow-up median 7 months1)

Study or Subgroup	SLIT Events	SLIT Total	placebo Events	placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Andre 2003	19	53	0	53	2.1%	39.00 [2.42, 629.69]
Bowen 2004	9	43	0	40	2.1%	17.70 [1.06, 294.60]
Clavel 1998	9	62	3	58	6.2%	2.81 [0.80, 9.86]
Dahl 2006 A	32	61	1	32	3.7%	16.79 [2.40, 117.26]
Dahl 2006 B	145	316	13	318	10.5%	11.22 [6.50, 19.37]
de Blay 2007	27	61	1	57	3.6%	25.23 [3.54, 179.65]
Didier 2007	40	155	8	156	9.4%	5.03 [2.44, 10.40]
Hordijk 1998	3	27	1	30	3.1%	3.33 [0.37, 30.16]
Horiguchi 2008	11	43	2	24	5.5%	3.07 [0.74, 12.72]
Khinchi 2004	13	23	4	24	7.9%	3.39 [1.29, 8.89]
Marogna 2007 birch	3	36	0	12	2.0%	2.46 [0.14, 44.48]
Mosges 2007	19	48	1	53	3.6%	20.98 [2.92, 150.83]
Okubo 2008	6	37	0	22	2.1%	7.87 [0.46, 133.26]
Palma-Carlos 2006	2	17	0	16	1.9%	4.72 [0.24, 91.41]
Pradalier 1999	9	63	1	63	3.4%	9.00 [1.17, 68.96]
Sabbah 1994	4	29	1	29	3.2%	4.00 [0.48, 33.66]
Smith 2004	66	121	15	59	11.0%	2.15 [1.35, 3.42]
Voltolini 2001	7	15	4	15	7.7%	1.75 [0.64, 4.75]
Worm 2006	57	94	18	91	11.1%	3.07 [1.97, 4.78]
Total (95% CI)		**1304**		**1152**	**100.0%**	**4.92 [3.16, 7.67]**
Total events	481		73			

Heterogeneity: Tau² = 0.41; Chi² = 44.68, df = 18 (P = 0.0005); I² = 60%

Test for overall effect: Z = 7.04 (P < 0.00001)

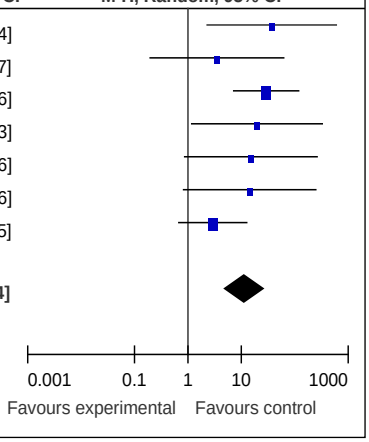


Oral oedema (follow-up median 8 months1,18)

Study or Subgroup	SLIT Events	SLIT Total	placebo Events	placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Andre 2003	18	53	0	53	9.4%	37.00 [2.29, 598.54]
Casanovas 1994 (W)	2	9	0	6	8.8%	3.50 [0.20, 62.27]
Dahl 2006 B	58	316	2	318	28.2%	29.18 [7.19, 118.46]
de Blay 2007	10	61	0	57	9.2%	19.65 [1.18, 327.73]
Didier 2007	7	155	0	156	9.0%	15.10 [0.87, 262.06]
Mosges 2007	6	48	0	53	9.0%	14.33 [0.83, 247.76]
Smith 2004	12	121	2	59	26.5%	2.93 [0.68, 12.65]
Total (95% CI)		**763**		**702**	**100.0%**	**11.47 [4.66, 28.24]**
Total events	113		4			

Heterogeneity: Tau² = 0.24; Chi² = 7.15, df = 6 (P = 0.31); I² = 16%

Test for overall effect: Z = 5.31 (P < 0.00001)

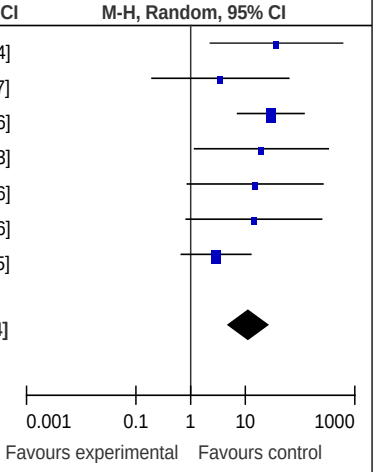


Gastrointestinal adverse effects (follow-up median 7 months1; nausea, vomiting, stomach upset, diarrhoea)

Study or Subgroup	SLIT Events	SLIT Total	placebo Events	placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Andre 2003	18	53	0	53	9.4%	37.00 [2.29, 598.54]
Casanovas 1994 (W)	2	9	0	6	8.8%	3.50 [0.20, 62.27]
Dahl 2006 B	58	316	2	318	28.2%	29.18 [7.19, 118.46]
de Blay 2007	10	61	0	57	9.2%	19.65 [1.18, 327.73]
Didier 2007	7	155	0	156	9.0%	15.10 [0.87, 262.06]
Mosges 2007	6	48	0	53	9.0%	14.33 [0.83, 247.76]
Smith 2004	12	121	2	59	26.5%	2.93 [0.68, 12.65]
Total (95% CI)		**763**		**702**	**100.0%**	**11.47 [4.66, 28.24]**
Total events	113		4			

Heterogeneity: Tau² = 0.24; Chi² = 7.15, df = 6 (P = 0.31); I² = 16%

Test for overall effect: Z = 5.31 (P < 0.00001)



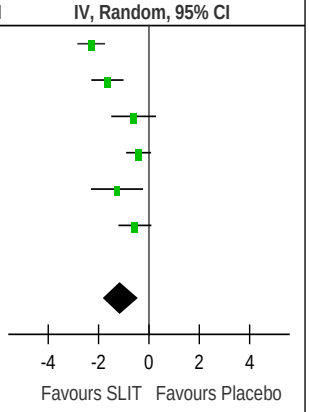
Adults with perennial/persistent AR:

Allergic rhinitis symptom scores

Study or Subgroup	SLIT Mean	SLIT SD	SLIT Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bozek 2013	2.656	0.634	47	3.975	0.501	48	17.9%	-2.29 [-2.81, -1.77]
Passalacqua 2006	1.82	0.23	28	2.18	0.2	28	17.3%	-1.65 [-2.26, -1.04]
Tonnel 2004	2.74	2.14	10	4.11	2.19	12	15.3%	-0.61 [-1.47, 0.25]
Guez 2000	2.3	1.9	36	3.2	2.4	36	18.3%	-0.41 [-0.88, 0.06]
Passalacqua 1998	59.6	27.8	10	109.1	45.7	9	14.1%	-1.27 [-2.28, -0.26]
Nelson 1993	12.15	8.68	20	18.67	13.56	21	17.2%	-0.56 [-1.18, 0.07]
Total (95% CI)			**151**			**154**	**100.0%**	**-1.14 [-1.83, -0.44]**

Heterogeneity: Tau² = 0.63; Chi² = 35.54, df = 5 (P < 0.00001); I² = 86%

Test for overall effect: Z = 3.21 (P = 0.001)

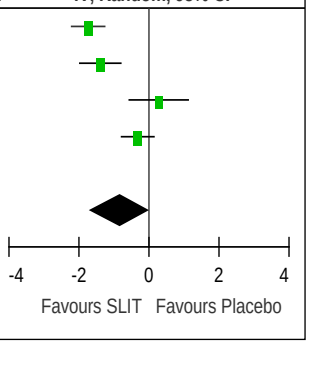


Medication scores

Study or Subgroup	SLIT Mean	SLIT SD	SLIT Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bozek 2013	0.345	0.076	47	0.467	0.063	48	26.2%	-1.74 [-2.21, -1.26]
Passalacqua 2006	110	44	28	166	35	28	25.1%	-1.39 [-1.98, -0.80]
Tonnel 2004	18.16	22.37	10	12.6	16.14	12	22.4%	0.28 [-0.57, 1.12]
Guez 2000	4.1	5.5	36	6.1	6.8	36	26.3%	-0.32 [-0.79, 0.15]
Total (95% CI)			**121**			**124**	**100.0%**	**-0.83 [-1.69, 0.04]**

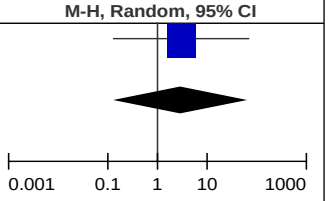
Heterogeneity: Tau² = 0.68; Chi² = 27.84, df = 3 (P < 0.00001); I² = 89%

Test for overall effect: Z = 1.88 (P = 0.06)



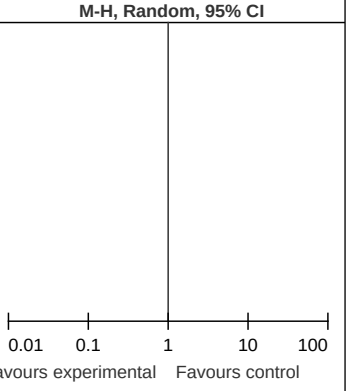
Withdrawal due to adverse effects (follow-up 24 months)

Study or Subgroup	SLIT Events	SLIT Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Bozek 2013	1	15	0	15	100.0%	3.00 [0.13, 68.26]
Total (95% CI)		**15**		**15**	**100.0%**	**3.00 [0.13, 68.26]**
Total events	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						



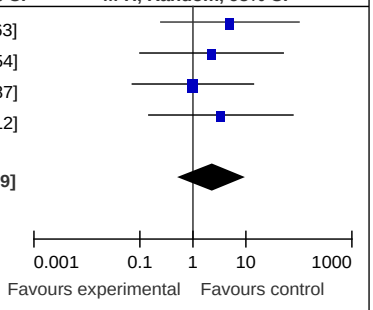
Serious adverse effects (follow-up 3 to 24 months[1])

Study or Subgroup	SLIT Events	SLIT Total	placebo Events	placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Bozek 2013	0	47	0	48		Not estimable
Guez 2000	0	36	0	36		Not estimable
Nelson 2011	0	20	0	21		Not estimable
Passalacqua 1998	0	10	0	9		Not estimable
Passalacqua 2006	0	28	0	28		Not estimable
Tonnel 2004	0	10	0	12		Not estimable
Total (95% CI)		**151**		**154**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						



Oral pruritus/burning/oedema

Study or Subgroup	SLIT Events	SLIT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Guez 2000	2	36	0	36	24.1%	5.00 [0.25, 100.63]
Mungan 1999 (W)	1	15	0	11	22.4%	2.25 [0.10, 50.54]
Passalacqua 1998	1	10	1	10	31.4%	1.00 [0.07, 13.87]
Tonnel 2004	1	15	0	17	22.2%	3.38 [0.15, 77.12]
Total (95% CI)		**76**		**74**	**100.0%**	**2.31 [0.53, 10.09]**
Total events	5		1			
Heterogeneity: Tau² = 0.00; Chi² = 0.71, df = 3 (P = 0.87); I² = 0%						
Test for overall effect: Z = 1.12 (P = 0.26)						



Question 4: Should sublingual specific immunotherapy (SLIT) be used for treatment of allergic rhinitis (AR) in children younger than 18 years old without concomitant asthma?

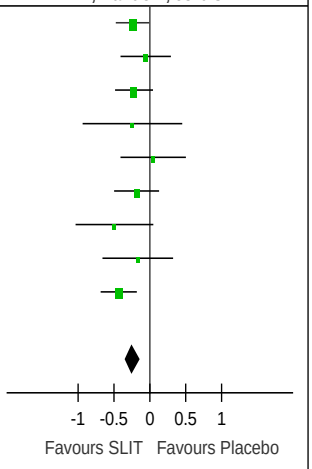
Children with seasonal/intermittent AR:

Allergic rhinitis symptom scores (SS)

	SLIT			Placebo				Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Blaiss 2011	3.71	4.88	149	4.91	5.03	158	22.9%	-0.24 [-0.47, -0.02]	
Bufe 2004	1.54	0.77	68	1.59	0.96	64	9.9%	-0.06 [-0.40, 0.28]	
Bufe 2009	2.67	2.38	117	3.17	2.14	121	17.8%	-0.22 [-0.48, 0.03]	
La Rosa 1999	1.21	1.66	16	1.61	1.56	17	2.5%	-0.24 [-0.93, 0.44]	
Rolinck-Werninghaus 2004	13.71	23.12	39	12.66	21.65	38	5.8%	0.05 [-0.40, 0.49]	
Röder 2007	2.45	1.48	91	2.74	1.66	77	12.5%	-0.18 [-0.49, 0.12]	
Valovirta 2006	1.5	1.4	27	2.2	1.4	29	4.1%	-0.49 [-1.03, 0.04]	
Vourdas 1998	1.07	1.63	34	1.38	2.01	32	4.9%	-0.17 [-0.65, 0.32]	
Wahn 2009	3.25	2.86	131	4.51	2.931	135	19.6%	-0.43 [-0.68, -0.19]	
Total (95% CI)			**672**			**671**	**100.0%**	**-0.24 [-0.35, -0.13]**	

Heterogeneity: Tau² = 0.00; Chi² = 6.22, df = 8 (P = 0.62); I² = 0%

Test for overall effect: Z = 4.37 (P < 0.0001)

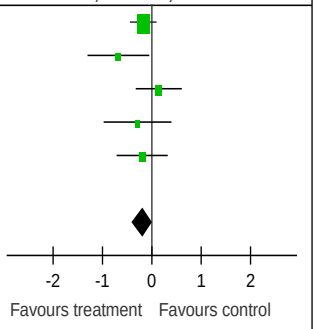


Ocular symptoms

	Treatment			Placebo				Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Bufe 2009	0.66	0.76	114	0.79	0.73	120	45.9%	-0.17 [-0.43, 0.08]	
Caffarelli 2000	2.9	1.4	24	4	1.8	20	10.9%	-0.68 [-1.29, -0.07]	
Rolinck-Werninghaus 2004	6.83	13.63	38	5.15	9.81	37	18.7%	0.14 [-0.31, 0.59]	
Stelmach 2008	1.31	3.03	20	2.12	2.29	15	9.1%	-0.29 [-0.96, 0.38]	
Valovirta 2006	0.9	1.1	32	1.1	0.9	29	15.5%	-0.20 [-0.70, 0.31]	
Total (95% CI)			**228**			**221**	**100.0%**	**-0.18 [-0.39, 0.03]**	

Heterogeneity: Tau² = 0.01; Chi² = 4.56, df = 4 (P = 0.34); I² = 12%

Test for overall effect: Z = 1.72 (P = 0.09)

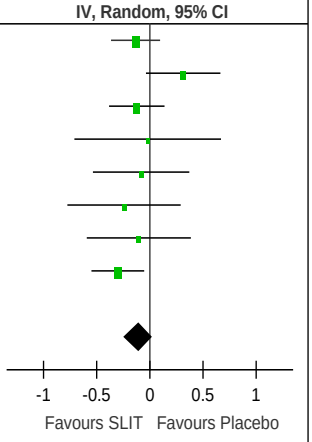


Medication scores (MS)

Study or Subgroup	SLIT Mean	SLIT SD	SLIT Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
Blaiss 2011	0.91	3.66	149	1.33	2.51	158	23.2%	-0.13 [-0.36, 0.09]
Bufe 2004	0.24	0.19	68	0.18	0.19	64	12.3%	0.31 [-0.03, 0.66]
Bufe 2009	2.13	3.48	117	2.53	3.03	121	19.5%	-0.12 [-0.38, 0.13]
La Rosa 1999	2.28	3.89	16	2.36	3.95	17	3.6%	-0.02 [-0.70, 0.66]
Rolinck-Werninghaus 2004	2.54	3.58	39	2.85	3.87	38	7.8%	-0.08 [-0.53, 0.36]
Valovirta 2006	2.9	3.4	27	3.9	4.6	29	5.8%	-0.24 [-0.77, 0.28]
Vourdas 1998	1.39	3.41	34	1.77	3.85	32	6.8%	-0.10 [-0.59, 0.38]
Wahn 2009	0.6	0.611	131	0.79	0.647	135	20.9%	-0.30 [-0.54, -0.06]
Total (95% CI)			**581**			**594**	**100.0%**	**-0.11 [-0.24, 0.03]**

Heterogeneity: Tau² = 0.01; Chi² = 8.62, df = 7 (P = 0.28); I² = 19%

Test for overall effect: Z = 1.59 (P = 0.11)

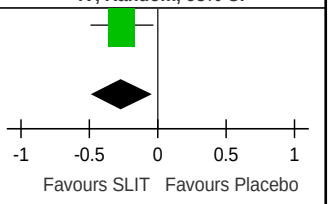


SMS (Combined SS and MS)

Study or Subgroup	SLIT Mean	SLIT SD	SLIT Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
Blaiss 2011	4.62	6.1	149	6.25	6.3	158	100.0%	-0.26 [-0.49, -0.04]
Total (95% CI)			**149**			**158**	**100.0%**	**-0.26 [-0.49, -0.04]**

Heterogeneity: Not applicable

Test for overall effect: Z = 2.29 (P = 0.02)

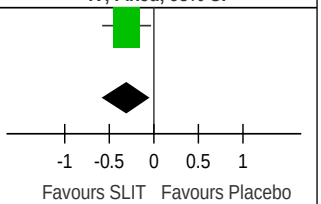


QoL

Study or Subgroup	SLIT Mean	SLIT SD	SLIT Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Blaiss 2011	1.45	1.04	109	1.77	1.05	111	100.0%	-0.31 [-0.57, -0.04]
Total (95% CI)			**109**			**111**	**100.0%**	**-0.31 [-0.57, -0.04]**

Heterogeneity: Not applicable

Test for overall effect: Z = 2.25 (P = 0.02)

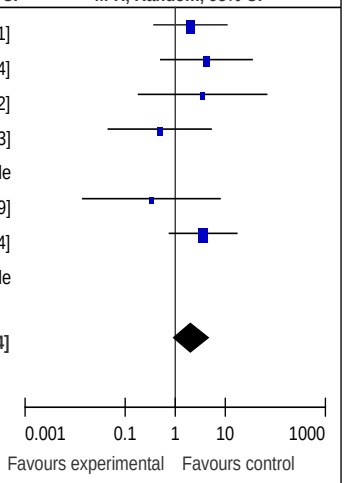


Withdrawal due to adverse effects

Study or Subgroup	Experimental Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bufe 2009	4	126	2	127	25.5%	2.02 [0.38, 10.81]
La Rosa 1999 (P)	4	20	1	21	16.3%	4.20 [0.51, 34.44]
Marogna 2008	3	144	0	72	8.3%	3.52 [0.18, 67.32]
Rolinck-Werninghaus 2004	1	49	2	48	12.9%	0.49 [0.05, 5.23]
Röder 2007	0	108	0	96		Not estimable
Valovirta 2006	0	32	1	32	7.2%	0.33 [0.01, 7.89]
Wahn 2009	7	131	2	135	29.9%	3.61 [0.76, 17.04]
Wuthrich 2003 (P)	0	10	0	12		Not estimable
Total (95% CI)		**620**		**543**	**100.0%**	**2.07 [0.89, 4.84]**
Total events	19		8			

Heterogeneity: Tau² = 0.00; Chi² = 3.76, df = 5 (P = 0.59); I² = 0%

Test for overall effect: Z = 1.68 (P = 0.09)



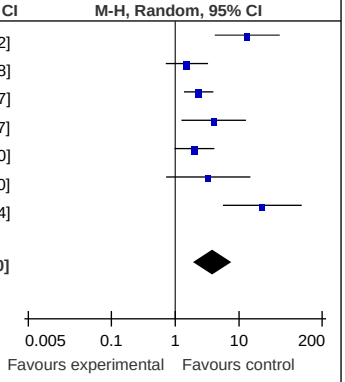
Oral pruritus/oedema

Study or Subgroup	Experimental Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bufe 2009	40	126	3	127	13.1%	13.44 [4.27, 42.32]
Rolinck-Werninghaus 2004	14	49	9	48	16.6%	1.52 [0.73, 3.18]
Röder 2007	42	108	16	96	18.4%	2.33 [1.41, 3.87]
Stelmach 2008 (1)	12	25	3	25	13.2%	4.00 [1.28, 12.47]
Valovirta 2006	16	32	8	32	17.0%	2.00 [1.00, 4.00]
Vourdas 1998 A	7	34	2	32	10.5%	3.29 [0.74, 14.70]
Wahn 2009	45	131	2	135	11.2%	23.19 [5.74, 93.64]
Total (95% CI)		**505**		**495**	**100.0%**	**3.84 [1.91, 7.70]**
Total events	176		43			

Heterogeneity: Tau² = 0.62; Chi² = 24.90, df = 6 (P = 0.0004); I² = 76%

Test for overall effect: Z = 3.79 (P = 0.0002)

(1) asthma

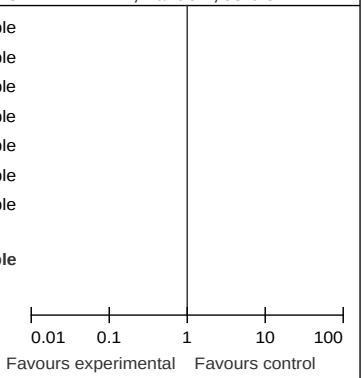


Serious adverse effects

Study or Subgroup	Experimental Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bufe 2004	0	83	0	78		Not estimable
Bufe 2009	0	126	0	127		Not estimable
Caffarelli 2000	0	24	0	20		Not estimable
Röder 2007	0	108	0	96		Not estimable
Vourdas 1998	0	34	0	32		Not estimable
Wahn 2009	0	131	0	135		Not estimable
Wutrich 2003	0	10	0	12		Not estimable
Total (95% CI)		**516**		**500**		**Not estimable**
Total events	0		0			

Heterogeneity: Not applicable

Test for overall effect: Not applicable



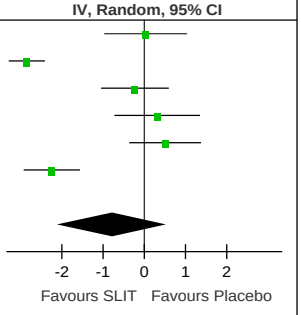
Children with perennial/persistent AR:

Allergic rhinitis symptom scores

Study or Subgroup	SLIT Mean	SLIT SD	SLIT Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
Aydogan 2013	3.4	2.7	7	3.3	3	9	16.2%	0.03 [-0.95, 1.02]
Cao 2007	0.65	0.88	85	2.64	0.46	91	17.5%	-2.85 [-3.27, -2.43]
Marcucci 2005	412.92	332.55	13	517.27	548.18	11	16.7%	-0.23 [-1.03, 0.58]
Bahceciler 2001	0.53	0.4	8	0.4	0.38	7	16.1%	0.31 [-0.71, 1.34]
Hirsch 1997	0.99	1.13	12	0.52	0.47	10	16.6%	0.50 [-0.35, 1.36]
Tari 1990	8	1.5	30	12	2	28	17.0%	-2.24 [-2.91, -1.58]
Total (95% CI)			**155**			**156**	**100.0%**	**-0.78 [-2.09, 0.53]**

Heterogeneity: Tau² = 2.51; Chi² = 95.65, df = 5 (P < 0.00001); I² = 95%

Test for overall effect: Z = 1.17 (P = 0.24)

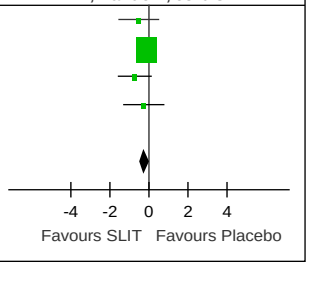


Medication scores

Study or Subgroup	SLIT Mean	SLIT SD	SLIT Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
Aydogan 2013	0.2	0.4	7	0.8	1.4	9	6.6%	-0.52 [-1.53, 0.49]
Cao 2007	0.01	0.1	85	0.18	1.92	91	77.2%	-0.12 [-0.42, 0.17]
Marcucci 2005	21.92	30.45	13	67.45	83.77	11	9.7%	-0.72 [-1.56, 0.11]
Bahceciler 2001	1.25	1.04	8	1.57	1.25	7	6.5%	-0.26 [-1.28, 0.76]
Total (95% CI)			**113**			**118**	**100.0%**	**-0.22 [-0.48, 0.04]**

Heterogeneity: Tau² = 0.00; Chi² = 2.16, df = 3 (P = 0.54); I² = 0%

Test for overall effect: Z = 1.63 (P = 0.10)

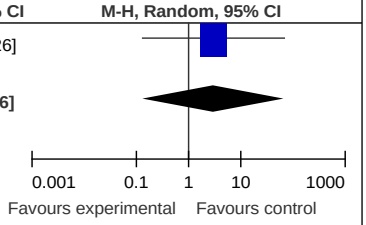


Serious adverse effects (follow-up 6 to 18 months)

Study or Subgroup	Experimental Events	Experimental Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Hirsh 1997 (PP)	1	15	0	15	100.0%	3.00 [0.13, 68.26]
Total (95% CI)		**15**		**15**	**100.0%**	**3.00 [0.13, 68.26]**
Total events	1		0			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.69 (P = 0.49)

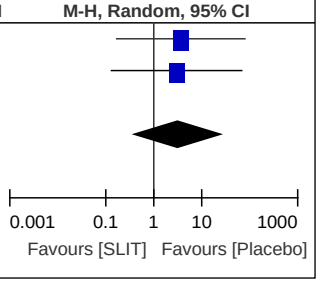


Withdrawal due to adverse effects

Study or Subgroup	SLIT Events	SLIT Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Aydogan 2013	1	8	0	10	50.8%	3.67 [0.17, 79.54]
Hirsh 1997 (PP)	1	15	0	15	49.2%	3.00 [0.13, 68.26]
Total (95% CI)		**23**		**25**	**100.0%**	**3.32 [0.37, 29.75]**
Total events	2		0			

Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.93); I² = 0%

Test for overall effect: Z = 1.07 (P = 0.28)

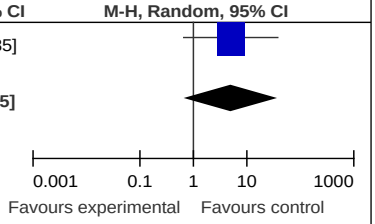


Oral pruritus/oedema (follow-up 12 months)

Study or Subgroup	Experimental Events	Experimental Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Hirsh 1997 (PP)	5	15	1	15	100.0%	5.00 [0.66, 37.85]
Total (95% CI)		**15**		**15**	**100.0%**	**5.00 [0.66, 37.85]**
Total events	5		1			

Heterogeneity: Not applicable

Test for overall effect: Z = 1.56 (P = 0.12)



Appendix 3: Search Strategies and Results

(1) Update of main benefits/harms search

Question 1: Should intranasal corticosteroids be used in patients with allergic rhinitis (AR)?

Data base: **Cochrane Library**	
Search strategy:	**Date of search: 11/2013**
1. steroid* 2. steroids 3. corticosteroid* 4. glucocorticoid* 5. beclomethasone 6. fluticasone 7. triamcinolone 8. budesonide 9. mometasone 10. flunisolide 11. ciclesonide 12. “Anti-Inflammatory Agents”[pa] 13. “Anti-Inflammatory Agents, Non-Steroidal”[pa] 14. #12 NOT #13 15. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #14 16. "allergic rhinitis" 17. "hay fever" 18. “hayfever” 19. “nasal allergy” 20. “nasal allergies” 21. “nasal congestion” 22. “nasal itching” 23. rhinorrhea 24. 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 25. 15 AND 24 Date limit: 01/2007 - 11/2013 Study Types: Cochrane SR, Other SR, HTA and Economic Evaluation	

Data base: **MEDLINE**	
Search strategy:	**Date of search: 11/2013**
1 steroid* 2 steroids 3 corticosteroid* 4 glucocorticoid* 5 beclomethasone 6 fluticasone 7 triamcinolone 8 budesonide 9 mometasone 10 flunisolide 11 ciclesonide 12 “Anti-Inflammatory Agents”[pa]	

13	“Anti-Inflammatory Agents, Non-Steroidal”[pa]
14	#12 NOT #13
15	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #14
16	"allergic rhinitis"
17	"hay fever"
18	“hayfever”
19	“nasal allergy”
20	“nasal allergies”
21	“nasal congestion”
22	“nasal itching”
23	rhinorrhea
24	16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23
25	Cochrane Database Syst Rev [ta]
26	search* [tiab]
27	meta-analysis [pt]
28	medline [tiab]
29	systematic review [tiab]
30	25 OR 26 OR 27 OR 28 OR 29
31	15 AND 24 AND 30

Date limit: 01/2007 - 11/2013
Study Types: SR

Data base: **Cochrane Library**	
Search strategy:	**Date of search: 11/2013**

1.	steroid*
2.	steroids
3.	corticosteroid*
4.	glucocorticoid*
5.	beclomethasone
6.	fluticasone
7.	triamcinolone
8.	budesonide
9.	mometasone
10.	flunisolide
11.	ciclesonide
12.	“Anti-Inflammatory Agents”[pa]
13.	“Anti-Inflammatory Agents, Non-Steroidal”[pa]
14.	#12 NOT #13
15.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #14
16.	"allergic rhinitis"
17.	"hay fever"
18.	“hayfever”
19.	“nasal allergy”
20.	“nasal allergies”
21.	“nasal congestion”
22.	“nasal itching”
23.	rhinorrhea
24.	16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23
25.	15 AND 24

Date limit: 01/2007 - 11/2013
Study Types: Trials

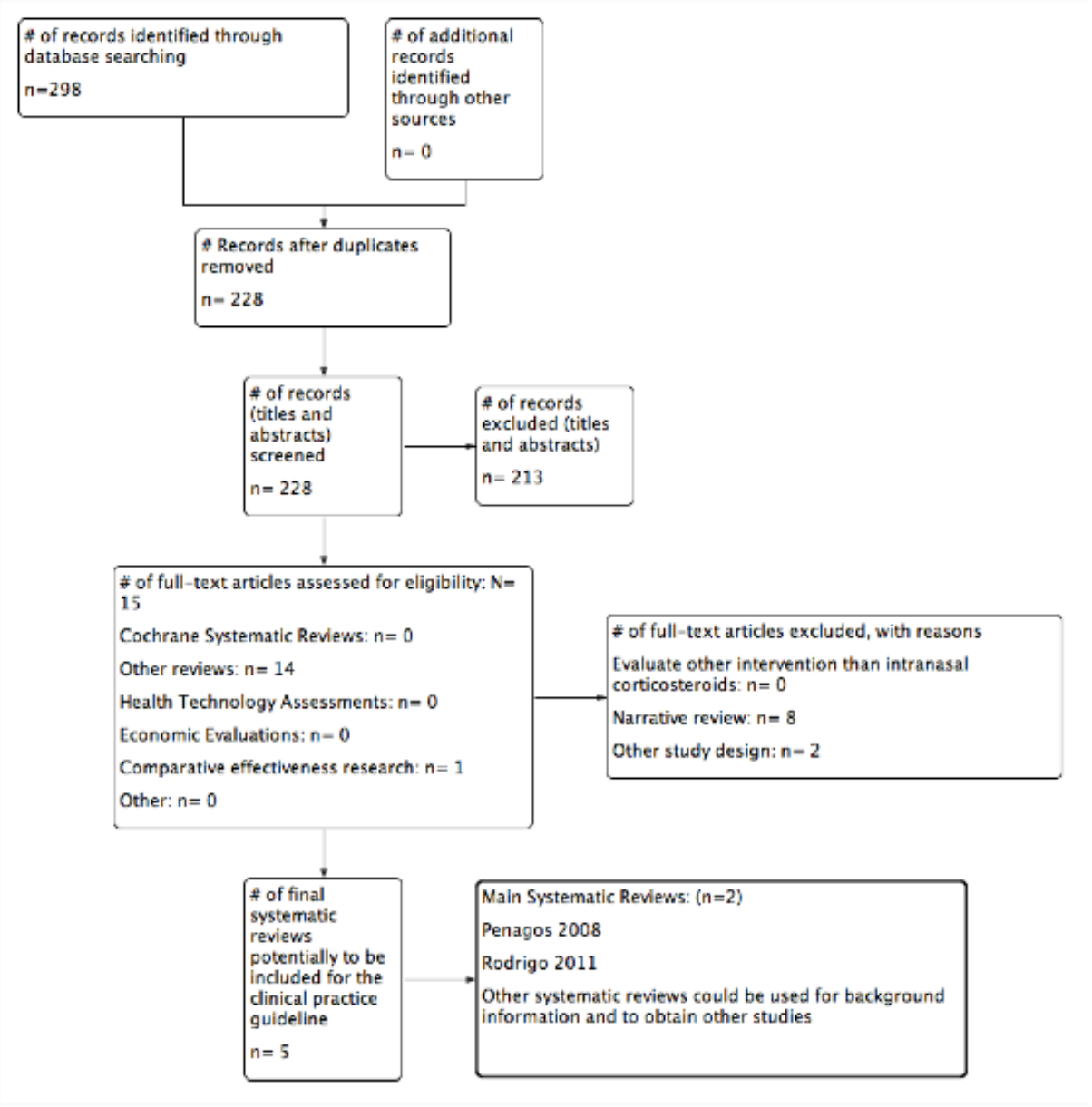
Data base: **MEDLINE**	
Search strategy:	**Date of search: 11/2013**

1	steroid*
2	steroids
3	corticosteroid*
4	glucocorticoid*
5	beclomethasone
6	fluticasone
7	triamcinolone
8	budesonide
9	mometasone
10	flunisolide
11	ciclesonide
12	“Anti-Inflammatory Agents”[pa]
13	“Anti-Inflammatory Agents, Non-Steroidal”[pa]
14	#12 NOT #13
15	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #14
16	"allergic rhinitis"
17	"hay fever"
18	“hayfever”
19	“nasal allergy”
20	“nasal allergies”
21	“nasal congestion”
22	“nasal itching”
23	rhinorrhea
24	16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23
25	randomized controlled [tiab]
26	controlled clinical trial [pt]
27	randomized [tiab]
28	placebo [tiab]
29	clinical trials as topic [mesh: noexp]
30	randomly [tiab]
31	trial [ti])
32	25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31
33	animals [mh] NOT humans [mh]
34	32 NOT 33
35	15 AND 24 AND 34

Date limit: 01/2007 - 11/2013

Study Types: RCT

Summary of Searches:



Question 2: Should intranasal glucocorticosteroids versus intranasal H1-antihistamines be used in adults with allergic rhinitis?

Data base: **MEDLINE**	
Search strategy:	**Date of search: 10/2013**
(steroid* OR steroids OR corticosteroid* OR glucocorticoid* OR beclomethasone OR fluticasone OR triamcinolone OR budesonide OR mometasone OR dexamethasone OR flunisolide OR ciclesonide OR ("Anti-Inflammatory Agents"[pa] NOT "Anti-Inflammatory Agents, Non-Steroidal"[pa])) AND (((antihistamine* OR "Histamine H1 Antagonists"[mh]) AND (nasal OR intranasal OR topical)) OR azelastine OR levocabastine OR olopatadine) AND (Cochrane Database Syst Rev [ta] OR search* [tiab] OR meta-analysis [pt] OR medline [tiab] OR systematic review [tiab]) Filters: Publication date from 2007/08/01 to 2013/12/31	
Date limit: 08/2007 - 12/2013 Study Types: **Systematic review**	
Records Retrieved	41

Data base: **Cochrane Database**	
Search strategy:	**Date of search: 10/2013**
(steroid* OR steroids OR corticosteroid* OR glucocorticoid* OR beclomethasone OR fluticasone OR triamcinolone OR budesonide OR mometasone OR dexamethasone OR flunisolide OR ciclesonide OR ("Anti-Inflammatory Agents" NOT "Anti-Inflammatory Agents, Non-Steroidal")) AND ((antihistamine* OR "Histamine H1 Antagonists") AND (nasal OR intranasal OR topical)) OR azelastine OR levocabastine OR olopatadine)	
Date limit: 08/2007 - 12/2013 Study Types: **Systematic review**	
Records Retrieved	208

Data base: **Cochrane Central Register of Controlled Trials (Search strategy ARIA 2010)**	
Search strategy:	**Date of search: 10/2013**
#1 antihistamine* or "Histamine H1 Antagonists" [mh] or mepyramine or pyrilamine or antazoline or diphenhydramine or carbinoxamine or doxylamine or clemastine or dimenhydrinate or pheniramine or chlorphenamine or chlorpheniramine or brompheniramine or triprolidine or hydroxyzine or promethazine or cyproheptadine or azatadine or ketotifen or acrivastine or cetirizine or loratadine or mizolastine or fexofenadine or levocetirizine or desloratadine #2 steroid* or steroids or corticosteroid* or glucocorticoid* or beclomethasone or fluticasone or triamcinolone or budesonide or mometasone or flunisolide or ciclesonide or ("Anti-Inflammatory Agents" not "Anti-Inflammatory Agents, Non-Steroidal") #3 "allergic rhinitis" or "hay fever" or hayfever or "nasal allergy" or "nasal allergies" or "nasal congestion" or "nasal itching" or rhinorrhea #1 and #2 and #3 Filters: Publication date from 2007/08/01 to 2013/12/31	
Date limit: 08/2007 - 12/2013 Study Types: **RCT**	
Records Retrieved	54

Data base: **MEDLINE (Search strategy ARIA 2010)**	
Search strategy:	**Date of search: 10/2013**
(steroid* OR steroids OR corticosteroid* OR glucocorticoid* OR beclomethasone OR fluticasone OR triamcinolone OR budesonide OR mometasone OR dexamethasone OR flunisolide OR ciclesonide OR ("Anti-Inflammatory Agents"[pa] NOT "Anti-Inflammatory Agents, Non-Steroidal"[pa])) AND (((antihistamine* OR "Histamine H1 Antagonists"[mh]) AND (nasal OR intranasal OR topical)) OR azelastine OR levocabastine OR olopatadine) AND (randomized controlled trial[Publication Type] OR (randomized[Title/Abstract] AND controlled[Title/Abstract] AND trial[Title/Abstract])) Filters: Publication date from 2007/08/01 to 2013/12/31	
Date limit: 08/2007 - 12/2013 Study Types: **RCT**	
Records Retrieved	43

Summary of Searches – Systematic Reviews

Total No. Retrieved:	**249**
Cochrane:	208
Medline:	41
Duplicates:	98
No. Total without duplicates**:**	**151**
Screening (Title and Abstract Review)	
No. Excluded:	144
Included for Full Text review:	7
Selection (Full Text Review)	
No. Excluded:	See table of exclusions below

Summary of Searches – RCTs

Total No. Retrieved:	**97**
Cochrane:	54
Medline:	43
Duplicates:	41
No. Total without duplicates**:**	**56**
Screening (Title and Abstract Review)	
No. Excluded:	48
Included for Full Text review:	8
Selection (Full Text Review)	
No. Excluded:	See table of exclusions below

Flowchart of study selection process

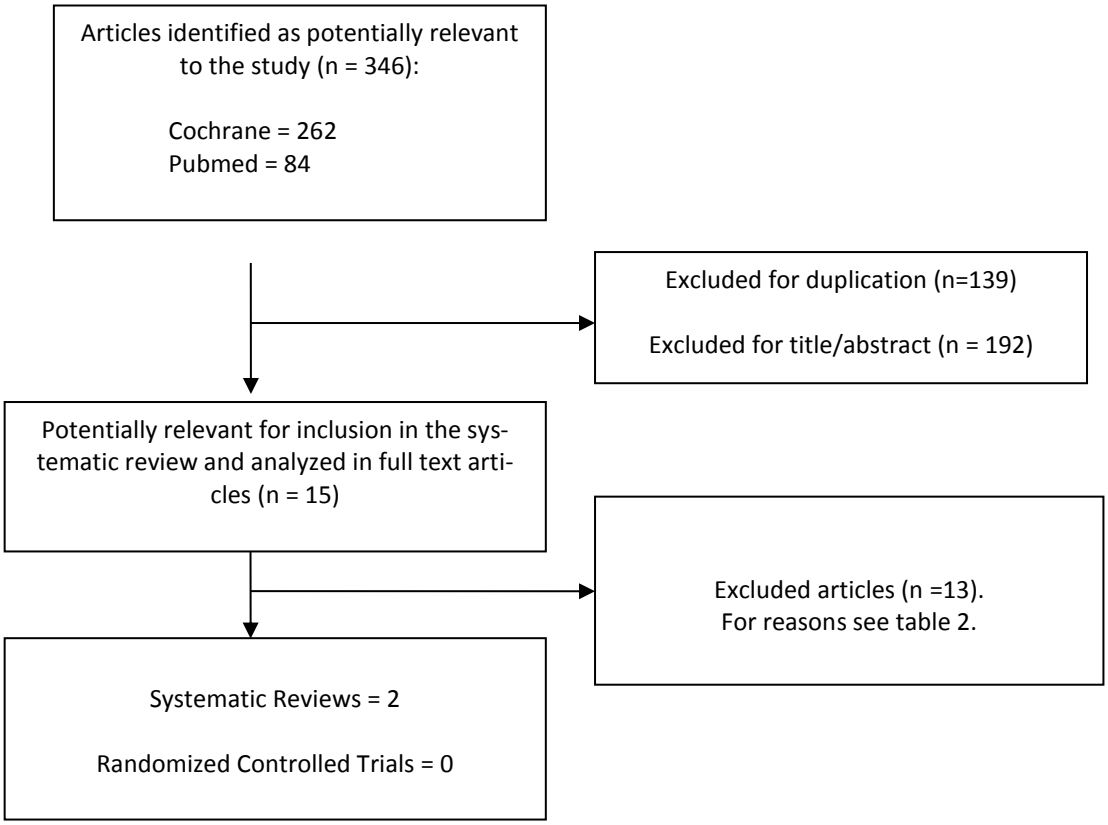


Table: Reasons for exclusion of full-text articles reviewed

Rather et al., 2008 [39]	RCT included in Glacy et al [23].
Al Sayyad [40]	Systematic review only with intranasal steroids vs other steroids or placebo.
Patel et al., 2007 [41]	RCT simple bind and one dose only.
Bernstein JA et al., 2007 [42]	It's a narrative review.
Lange B et al., 2005 [43]	It's an open RCT and doesn't describe randomization method.
Kaliner et al., 2011 [44]	Narrative review from which cannot be obtained details INCS vs INAH group.
Hong et al., 2011 [45]	Study included in Systematic Review from Yañez et al.[24]
Kalpaklioglu et al., 2010 [46]	RCT of patients with allergic and non- allergic rhinitis, does not specify whether they are perennial or seasonal.
Nasser et al., 2010 [47]	Cochrane Systematic Review includes only the analysis of a study to compare the results and antihistamine + vs glucocorticoid glucocorticoid only.
Benninger M et al., 2010 [48]	Systematic review that doesn't correspond to PICO
Kulapaditharom et al., 2010 [49]	RCT which could not be obtained in full text and abstract does not specify whether levocitirizina was administered orally or intranasally.
Sheikh et al., 2009 [50]	Study is included in Yañez et al [24] and Glacy et al. [23].
Kaliner et al., 2009 [51]	RCT included in Glacy et al [23].

Question 3: Should sublingual specific immunotherapy be used for treatment of allergic rhinitis in adults without concomitant asthma?

Question 4: Should sublingual specific immunotherapy (SLIT) be used for treatment of allergic rhinitis in children younger than 18 years old without concomitant asthma?

Data base: **Cochrane Library**	
Search strategy:	**Date of search: 24/10/2013**
#1 (immunotherapy or desensiti* or hyposensiti*) and ("allergic rhinitis" or "hay fever" or hayfever or "nasal allergy" or "nasal allergies" or "nasal congestion" or "nasal itching" or rhinorrhea) 552 #2 (immunotherapy or desensiti* or hyposensiti*) and ("allergic rhinitis" or "hay fever" or hayfever or "nasal allergy" or "nasal allergies" or "nasal congestion" or "nasal itching" or rhinorrhea) and (subling*) 142 Date limit: 01/2009 - 11/2013 Study Types: Cochrane SR, Other SR, HTA and Economic Evaluation	
Records Retrieved	26 Cochrane Reviews (All: Review + Protocol) (11) Other Reviews (8) Technology Assessments (2) Economic Evaluations (5)

Data base: **MEDLINE**	
Search strategy:	**Date of search: 07/11/2013**
1 Rhinitis, Allergic, Perennial/ or Rhinitis, Allergic, Seasonal/ or Rhinitis/ (25661) 2 (Rhinitis, Allergic, Perennial or Rhinitis, Allergic, Seasonal or Rhinitis).mp. (33012) 3 (Rhin$ or 'hay fever' or hayfever or 'nasal allergy' or 'nasal allerg$' or "nasal congestion" or 'nasal itching' or rhinorrhea).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (66840) **4 1 or 2 or 3 (66840)** 5 Desensitization, Immunologic/ (8523) 6 ('Desensitization, Immunologic' or desensiti$ or hyposensiti$).mp. (33308) 7 Immunotherapy/ (30643) 8 (Immunotherapy or immunother$).mp. (65276) **9 5 or 6 or 7 or 8 (95019)** 10 Administration, Sublingual/ (2345) 11 ('Administration, Sublingual' or sublingu$).mp. (8729) **12 10 or 11 (8729)** 13 4 and 9 (4021) 14 4 and 9 and 12 (678) 15 limit 14 to yr="2009 -Current" (343) 16 ('Cochrane Database Syst Rev' or search* or meta-analysis or 'systematic review').mp. (288246) 17 15 and 16 (46) 18 limit 15 to "reviews (maximizes sensitivity)" (191) 19 limit 15 to "reviews (maximizes specificity)" (30) 20 limit 15 to ("review" or systematic reviews) (135) Date limit: 01/2009 - 11/2003 Study Types: SR	
Records Retrieved	46

Data base: **EMBASE**	
Search strategy:	**Date of search: 11/2013**
1 allergic rhinitis/ or rhinitis/ (24000) 2 ('Rhinitis Allergic' or Rhinit$).mp. (31412) 3 (Rhin$ or 'hay fever' or hayfever or 'nasal allergy' or 'nasal allerg$' or "nasal congestion" or 'nasal itching' or rhinorrhea).mp. (71330) 4 1 or 2 or 3 (71330) 5 desensitization/ (9559) 6 ('Desensitization Immunologic' or desensiti$ or hyposensiti$).mp. (21424) 7 immunotherapy/ (36420) 8 (Immunotherapy or immunother$).mp. (79252) 9 5 or 6 or 7 or 8 (98995) 10 sublingual drug administration/ (1281) 11 sublingual immunotherapy/ (633) 12 ('sublingual administration' or sublingu$ or 'sublingual immunotherapy' or 'subling$ immunothe$').mp. (7790) 13 10 or 11 or 12 (7790) 14 4 and 9 and 13 (1339) 15 limit 14 to (embase and yr="2009 -Current") (767) 16 ('Cochrane Database Syst Rev' or search* or meta-analysis or 'systematic review').mp. (347442) 17 15 and 16 (97) 18 limit 15 to "reviews (maximizes specificity)" (43) 19 limit 15 to "reviews (maximizes sensitivity)" (413) 20 limit 15 to "review" (178) Date limit: 01/2009 - 11/2013 Study Types: SR	
Records Retrieved	97

Data base: **Cochrane Library**	
Search strategy:	**Date of search: 24/10/2013**
#1 (immunotherapy or desensiti* or hyposensiti*) and ("allergic rhinitis" or "hay fever" or hayfever or "nasal allergy" or "nasal allergies" or "nasal congestion" or "nasal itching" or rhinorrhea) and (subling*) 67 Date limit: /2009 - /2013 Study Types: Trals	
Records Retrieved	46 Trials (46)

Data base: **PUBMED -**	
Search strategy:	**Date of search: 13/11/2013**
#19,"Search (#17 AND #18)",50,11:16:31 #18,"Search (randomized controlled trial[Publication Type] OR (randomized[Title/Abstract] AND controlled[Title/Abstract] AND trial[Title/Abstract])",374260,11:16:31 #17,"Search (#16) AND (""2009""[Date - Publication] : ""3000""[Date - Publication])",222,11:16:31 #16,"Search (#9 AND #12 AND #15)",519,11:14:44	

#15,"Search (#13 OR #14)",73306,11:14:15
#12,"Search (#10 OR #11)",253050,11:14:15
#9,"Search (#7 or #8)",20911,11:14:15
#14,"Search (""Administration, Sublingual"" or sublingu*)",8884,11:13:31
#13,"Search ((""administration, sublingual""[MeSH Terms] OR ""administration, topical""[MeSH Terms]))",66753,11:13:31
#10,"Search (""desensitization, immunologic""[MeSH Terms]) OR (""Desensitization, Immunologic"" or desensiti* or hyposensiti*)",32049,11:11:42
#11,"Search (""immunotherapy""[MeSH Terms]) OR (Immunotherapy or immunother*)",229446,11:11:42
#8,"Search (Rhin$ or 'hay fever' or hayfever or 'nasal allergy' or 'nasal allerg$' or ""nasal congestion"" or 'nasal itching' or rhinorrhea)",18570,11:09:04
#7,"Search ((""rhinitis/drug therapy""[MeSH Terms] OR ""rhinitis, allergic, perennial/drug therapy""[MeSH Terms]))",5572,11:09:04

Date limit: 01/2009 - 11/2013

Study Types: RCT

Records Retrieved	50

Summary of Searches - Systematic Reviews

Total No. Retrieved:	**169**
Cochrane:	26
Medline:	46
Embase:	97
Duplicates:	29
No. Total without duplicates**:**	**140**
Screening (Title and Abstract Review)	
No. Excluded:	115
Included for Full Text review:	25
Selection (Full Text Review)	
No. Excluded:	22
Reasons for exclusions:	
1. duplicates (6) 2. descriptive or narrative (3) 3. not available (1) 4. include only one kind of allergy type (grass,tree, only conjuntivitis,...) or subgroup (seasonal,) (5) 5. SR with RCT included in the latest SR (2) 6. S.type, language (2) 7. comparator diferent to placebo (3)	

Summary of Searches – RCTs

Total No. Retrieved:	**96**
Cochrane:	46
Medline:	50
Duplicates:	8
No. Total without duplicates**:**	**88**
Screening (Title and Abstract Review)	

No. Excluded:	83
Included for Full Text review:	5
Selection (Full Text Review)	
No. Excluded:	3
Reasons for exclusions:	
1. Seasonal AR (2) 2. No useful data provided (1)	

(2) Values and preferences search

Data base: **MEDLINE**	
Search strategy:	**Date of search: 23/11/2013**
1. ("allergic rhinitis" or "hay fever" or hayfever or "nasal allergy" or "nasal allergies" or "nasal congestion" or "nasal itching" or rhinorrhea).mp. (21155) 2. exp Rhinitis/ or Nasal Provocation Tests/ or Nasal Obstruction/(30685) 3. 1 or 2(39705) 4. patient$ participation.mp. or exp patient participation/(19349) 5. patient$ satisfaction.mp. or exp patient satisfaction/(73751) 6. attitude to health.mp. or exp Attitude to health/(376205) 7. (patient$ preference$ or patient$ perception$ or patient$ decision$ or patient$ perspective$ or er$ view$ or patient$ view$ or patient$ value$).mp. (24381) 8. (patient$ utilit$ or health utilit$).mp. (1438) 9. health related quality of life.mp. or exp "quality of life"/(127462) 10. (health stat$ utilit$ or health stat$ indicator$ or (health stat$ adj 2 valu$)).mp. or exp Health Status Indicators/(205657) 11. 4 or 5 or 6 or 7 or 8 or 9 or 10(683718) 12. Saudi Arab$.mp,in. or Saudi Arabia/(27221) 13. Riyadh.mp,in. (14468) 14. Jeddah.mp,in. (2832) 15. Kh*bar.mp,in. (722) 16. Dammam.mp,in. (1164) 17. 12 or 13 or 14 or 15 or 16(27593) 18. Kuwait$.mp,in. or Kuwait/(6640) 19. United Arab Emirates.mp,in. or United Arab Emirates/(4008) 20. Qatar$.mp,in. or Qatar/(1873) 21. Oman$.mp,in. or Oman/(3485) 22. Yemen$.mp,in. or Yemen/(1841) 23. Bahr*in$.mp,in. or Bahrain/(1180) 24. 18 or 19 or 20 or 21 or 22 or 23(18294) 25. Middle East$.mp,in. or Middle East/(11372) 26. Jordan$.mp,in. or Jordan/(9648) 27. Libya$.mp,in. or Libya/(1778) 28. Egypt$.mp,in. or Egypt/(36899) 29. Syria$.mp,in. or Syria/(10616) 30. Iraq$/ or Iraq.mp,in. (7565) 31. Morocc$.mp,in. or Morocco/(8133) 32. Tunisia$.mp,in. or Tunisia/(11835) 33. Leban$.mp,in. or Lebanon/(14064) 34. West Bank.mp,in. (715) 35. Iran$.mp,in. or Iran/(52911) 36. Turkey/ or (Turkey or Turkish).mp,in. (137094) 37. Algeria$.mp,in. or Algeria/(4006) 38. Arab$.mp,in. or Arabs/(124336) 39. 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37(296861) 40. 38 or 39(413555) 41. 17 or 24 or 40(425008) 42. "journal of epidemiology and global health".jn. (66) 43. "journal of infection and public health".jn. (278)	

44. "saudi journal of kidney diseases & transplantation".jn. (2156) 45. saudi medical journal.jn. (4874) 46. saudi pharmaceutical journal.jn. (178) 47. "annals of saudi medicine".jn. (3576) 48. "saudi journal of gastroenterology".jn. (1102) 49. 42 or 43 or 44 or 45 or 46 or 47 or 48(12230) 50. 41 or 49(428217) 51. 11 and 50(16989) 52. 3 and 51(129) 53. (immunotherapy or desensiti* or hyposensiti*).mp. (94703) 54. exp Immunotherapy/(219022) 55. 53 or 54(263397) 56. 51 and 55(153) 57. nasal.mp. or nasal sprays/(96745) 58. intranasal.mp. or Administration, Intranasal/(21848) 59. topical.mp. or Administration, Topical/(88416) 60. 57 or 58 or 59(195398) 61. (steroid* or steroids or corticosteroid* or glucocorticoid* or beclomethasone or fluticasone or triamcinolone or budesonide or mometasone or flunisolide or ciclesonide).mp. (404817) 62. (Anti-Inflammatory Agents not (Anti-Inflammatory Agents adj2 Non-Steroidal)).mp. or exp Adrenal Cortex Hormones/(378183) 63. 61 or 62(631089) 64. (antihistamine* or (Histamine adj2 Antagonists) or mepyramine or pyrilamine or antazoline or diphenhydramine or carbinoxamine or doxylamine or clemastine or dimenhydrinate or pheniramine or chlorphenamine or chlorpheniramine or brompheniramine or triprolidine or hydroxyzine or promethazine or cyproheptadine or azatadine or ketotifen or acrivastine or cetirizine or loratadine or mizolastine or fexofenadine or levocetirizine or desloratadine).mp. (46807) 65. exp Histamine Antagonists/(56375) 66. 64 or 65(64874) 67. 60 and 63(26473) 68. 51 and 67(70) 69. 51 and 66(46) 70. 52 or 56 or 68 or 69(362) 71. limit 70 to english language(345) Date limit: No date limit (1946-current) Study Types: No limit on study types
Records Retrieved 345

Data base: **EMBASE**	
Search strategy:	**Date of search: 23/11/2013**
1. exp Rhinitis/ or Nasal Provocation Tests/ or Nasal Obstruction/ or hay fever/ or nose allergy/ or nasal pruritus/(69066) 2. ("allergic rhinitis" or "hay fever" or hayfever or "nasal allergy" or "nasal allergies" or "nasal congestion" or "nasal itching" or "nasal obstructionor rhinorrhea").mp. (34468) 3. 1 or 2(72773) 4. patient$ participation.mp. or exp patient participation/(18266) 5. patient$ satisfaction.mp. or exp patient satisfaction/(91620)	

6. attitude to health.mp. or exp Attitude to health/(82875)
7. (patient$ preference$ or patient$ perception$ or patient$ decision$ or patient$ perspective$ or user$ view$ or patient$ view$ or patient$ value$).mp. (34889)
8. (patient$ utilit$ or health utilit$).mp. (1864)
9. health related quality of life.mp. or exp "quality of life"/(259480)
10. (health stat$ utilit$ or health stat$ indicator$ or (health stat$ adj 2 valu$)).mp. or exp Health Status Indicators/(5368)
11. 4 or 5 or 6 or 7 or 8 or 9 or 10(459140)
12. Saudi Arab$.mp,in. or Saudi Arabia/(44088)
13. Riyadh.mp,in. (24452)
14. Jeddah.mp,in. (5572)
15. Kh*bar.mp,in. (1211)
16. Dammam.mp,in. (1751)
17. 12 or 13 or 14 or 15 or 16(44371)
18. Kuwait$.mp,in. or Kuwait/(10766)
19. United Arab Emirates.mp,in. or United Arab Emirates/(9072)
20. Qatar$.mp,in. or Qatar/(3968)
21. Oman$.mp,in. or Oman/(5183)
22. Yemen$.mp,in. or Yemen/(2449)
23. Bahr*in$.mp,in. or Bahrain/(2904)
24. 18 or 19 or 20 or 21 or 22 or 23(32551)
25. Middle East$.mp,in. or Middle East/(14295)
26. Jordan$.mp,in. or Jordan/(29511)
27. Libya$.mp,in. or Libya/(2821)
28. Egypt$.mp,in. or Egypt/(63291)
29. Syria$.mp,in. or Syria/(16714)
30. Iraq$/ or Iraq.mp,in. (9909)
31. Morocc$.mp,in. or Morocco/(17427)
32. Tunisia$.mp,in. or Tunisia/(24059)
33. Leban$.mp,in. or Lebanon/(25675)
34. West Bank.mp,in. (1044)
35. Iran$.mp,in. or Iran/(96928)
36. Turkey/ or (Turkey or Turkish).mp,in. (239455)
37. Algeria$.mp,in. or Algeria/(7443)
38. Arab$.mp,in. or Arabs/(149134)
39. 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37(531902)
40. 38 or 39(662105)
41. 17 or 24 or 40(680304)
42. "journal of epidemiology and global health".jn. (66)
43. "journal of infection and public health".jn. (275)
44. "saudi journal of kidney diseases & transplantation".jn. (0)
45. saudi medical journal.jn. (6623)
46. saudi pharmaceutical journal.jn. (569)
47. "annals of saudi medicine".jn. (3529)
48. "saudi journal of gastroenterology".jn. (390)
49. 42 or 43 or 44 or 45 or 46 or 47 or 48(11452)
50. 41 or 49(682257)
51. (immunotherapy or desensiti* or hyposensiti*).mp. (141272)
52. exp Immunotherapy/(127458)
53. 51 or 52(179563)
54. (steroid* or steroids or corticosteroid* or glucocorticoid* or beclomethasone or fluticasone or tri-

amcinolone or budesonide or mometasone or flunisolide or ciclesonide).mp. (612196) 55. (Anti-Inflammatory Agents not (Anti-Inflammatory Agents adj2 Non-Steroidal)).mp. (6175) 56. corticosteroid/(182513) 57. 54 or 55 or 56(616445) 58. intranasal.mp. or intranasal drug administration/(25486) 59. topical.mp. or topical drug administration/(149855) 60. (nasal spray or nose spray).mp. or nose spray/(3786) 61. 58 or 59 or 60(175708) 62. 57 and 61(30973) 63. (antihistamine* or (Histamine adj2 Antagonists) or mepyramine or pyrilamine or antazoline or diphenhydramine or carbinoxamine or doxylamine or clemastine or dimenhydrinate or pheniramine or chlorphenamine or chlorpheniramine or brompheniramine or triprolidine or hydroxyzine or promethazine or cyproheptadine or azatadine or ketotifen or acrivastine or cetirizine or loratadine or mizolastine or fexofenadine or levocetirizine or desloratadine).mp. (78735) 64. exp Histamine Antagonists/(172267) 65. 63 or 64(176765) 66. 11 and 50 and 3(189) 67. 11 and 50 and 53(64) 68. 11 and 50 and 62(54) 69. 11 and 50 and 65(142) 70. 52 or 56 or 68 or 69(371) 71. limit 70 to english language(342) Date limit: No date limit (1974-current) Study Types: No limit on study types
Records Retrieved 342

Data base: **PsychInfo**	
Search strategy:	**Date of search: 23/11/2013**
1. client$ participation.mp. or exp client participation/(1463) 2. client$ satisfaction.mp. or exp client satisfaction/(4889) 3. exp Health Attitudes/(8014) 4. (patient$ preference$ or patient$ perception$ or patient$ decision$ or patient$ perspective$ or user$ view$ or patient$ view$ or patient$ value$ or patient$ attitude$).mp. (8449) 5. (patient$ utilit$ or health utilit$).mp. (457) 6. health related quality of life.mp. or exp "quality of life"/(27163) 7. (health stat$ utilit$ or health stat$ indicator$ or (health stat$ adj 2 valu$)).mp. (138) 8. (standard gambl$ or time trade off or willingness to pay or visual analog scale or (VAS or "visual analog$ adj 2 scal$")).mp. (4421) 9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8(52193) 10. (rhinitis or "allergic rhinitis" or "hay fever" or hayfever or "nasal allergy" or "nasal allergies" or "nasal congestion" or "nasal itching" or rhinorrhea or nose provocation test or nose obstruction).mp. (472) 11. exp Hay Fever/(22) 12. 10 or 11(472) 13. 9 and 12(27) 14. (immunotherapy or desensiti* or hyposensiti*).mp. (7066)	

15. exp Immunotherapy/(2916)
16. 14 or 15(9574)
17. (antihistamine* or (Histamine adj2 Antagonists) or mepyramine or pyrilamine or antazoline or diphenhydramine or carbinoxamine or doxylamine or clemastine or dimenhydrinate or phenira-mine or chlorphenamine or chlorpheniramine or brompheniramine or triprolidine or hydroxyzine or promethazine or cyproheptadine or azatadine or ketotifen or acrivastine or cetirizine or lo-ratadine or mizolastine or fexofenadine or levocetirizine or desloratadine).mp. (1525)
18. exp Antihistaminic Drugs/(960)
19. 17 or 18(2046)
20. 9 and 19(37)
21. (steroid* or steroids or corticosteroid* or glucocorticoid* or beclomethasone or fluticasone or triamcinolone or budesonide or mometasone or flunisolide or ciclesonide).mp. (13013)
22. (Anti-Inflammatory Agents not (Anti-Inflammatory Agents adj2 Non-Steroidal)).mp. (138)
23. exp Corticosteroids/(9814)
24. 21 or 22 or 23(20342)
25. intranasal.mp. (811)
26. topical.mp. (3160)
27. (nasal spray or nose spray).mp. (221)
28. 25 or 26 or 27(4170)
29. 24 and 28(97)
30. 9 and 29(10)
31. Saudi Arab$.mp,in. or Saudi Arabia/(1570)
32. Riyadh.mp,in. (541)
33. Jeddah.mp,in. (133)
34. Kh*bar.mp,in. (22)
35. Dammam.mp,in. (60)
36. 31 or 32 or 33 or 34 or 35(1584)
37. Kuwait$.mp,in. or Kuwait/(1027)
38. United Arab Emirates.mp,in. or United Arab Emirates/(1233)
39. Qatar$.mp,in. or Qatar/(340)
40. Oman$.mp,in. or Oman/(377)
41. Yemen$.mp,in. or Yemen/(226)
42. Bahr*in$.mp,in. or Bahrain/(256)
43. 37 or 38 or 39 or 40 or 41 or 42(3227)
44. Middle East$.mp,in. or Middle East/(2900)
45. Jordan$.mp,in. or Jordan/(3070)
46. Libya$.mp,in. or Libya/(150)
47. Egypt$.mp,in. or Egypt/(2964)
48. Syria$.mp,in. or Syria/(934)
49. Iraq$/ or Iraq.mp,in. (2427)
50. Morocc$.mp,in. or Morocco/(1228)
51. Tunisia$.mp,in. or Tunisia/(687)
52. Leban$.mp,in. or Lebanon/(3251)
53. West Bank.mp,in. (264)
54. Iran$.mp,in. or Iran/(5755)
55. Turkey/ or (Turkey or Turkish).mp,in. (15670)
56. Algeria$.mp,in. or Algeria/(491)
57. Arab$.mp,in. or Arabs/(8952)
58. 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56(36849)
59. 57 or 58(43538)
60. 36 or 43 or 59(44812)

61. "journal of epidemiology and global health".jn. (0) 62. "journal of infection and public health".jn. (0) 63. "saudi journal of kidney diseases & transplantation".jn. (0) 64. saudi medical journal.jn. (0) 65. saudi pharmaceutical journal.jn. (0) 66. "annals of saudi medicine".jn. (0) 67. "saudi journal of gastroenterology".jn. (0) 68. 61 or 62 or 63 or 64 or 65 or 66 or 67(0) 69. Saudi Arab$.in. (983) 70. 60 or 68 or 69(44812) 71. 9 and 16 and 70(8) 72. 13 or 20 or 30 or 71(72) Date limit: No date limit (1806-current) Study Types: No limit on study types	
Records Retrieved	72

Summary of Searches:

Total No. Retrieved:	**749**
Medline:	345
Embase:	342
PsychInfo:	72
Duplicates:	103
No. Total without duplicates**:**	**656**
Screening (Title and Abstract Review)	
No. Excluded:	540
Included for Full Text review:	116
Selection (Full Text Review)	
No. Excluded:	22

(3) Cost-effectiveness search

Data base: **MEDLINE**	
Search strategy:	**Date of search: 23/11/2013**
1 ("allergic rhinitis" or "hay fever" or hayfever or "nasal allergy" or "nasal allergies" or "nasal congestion" or "nasal itching" or rhinorrhea).mp. (19921)	
2 exp Rhinitis/ or Nasal Provocation Tests/ or Nasal Obstruction/ (30489)	
3 1 or 2 (38357)	
4 economics/ or exp economics, hospital/ or exp economics, medical/ or economics, nursing/ or economics, pharmaceutical/ (65625)	
5 exp "Costs and Cost Analysis"/ (183636)	
6 Value-Based Purchasing/ (99)	
7 exp "Fees and Charges"/ (27124)	
8 budget$.mp. or Budgets/ (22996)	
9 (low adj cost).mp. (20604)	
10 (high adj cost).mp. (7647)	
11 (health?care adj cost$).mp. (4072)	
12 (cost adj estimate$).mp. (1388)	
13 (cost adj variable$).mp. (103)	
14 (unit adj cost$).mp. (1536)	
15 (fiscal or funding or financial or finance).tw. (78277)	
16 (economic$ or pharmacoeconomic$ or price$ or pricing).tw. (164760)	
17 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 (457169)	
18 Saudi Arab$.mp,in. or Saudi Arabia/ (21560)	
19 Riyadh.mp,in. (11619)	
20 Jeddah.mp,in. (2202)	
21 Kh*bar.mp,in. (509)	
22 Dammam.mp,in. (786)	
23 18 or 19 or 20 or 21 or 22 (21834)	
24 Kuwait$.mp,in. or Kuwait/ (6174)	
25 United Arab Emirates.mp,in. or United Arab Emirates/ (3604)	
26 Qatar$.mp,in. or Qatar/ (1485)	
27 Oman$.mp,in. or Oman/ (2460)	
28 Yemen$.mp,in. or Yemen/ (1647)	
29 Bahr*in$.mp,in. or Bahrain/ (1053)	
30 24 or 25 or 26 or 27 or 28 or 29 (15777)	
31 Middle East$.mp,in. or Middle East/ (10376)	
32 Jordan$.mp,in. or Jordan/ (8728)	
33 Libya$.mp,in. or Libya/ (1543)	
34 Egypt$.mp,in. or Egypt/ (33575)	
35 Syria$.mp,in. or Syria/ (10138)	
36 Iraq$/ or Iraq.mp,in. (6898)	
37 Morocc$.mp,in. or Morocco/ (7258)	
38 Tunisia$.mp,in. or Tunisia/ (10875)	
39 Leban$.mp,in. or Lebanon/ (13379)	
40 West Bank.mp,in. (667)	
41 Iran$.mp,in. or Iran/ (40971)	
42 Turkey/ or (Turkey or Turkish).mp,in. (129288)	
43 Algeria$.mp,in. or Algeria/ (3650)	
44 Arab$.mp,in. or Arabs/ (111356)	

45	31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 (268369)
46	44 or 45 (372693)
47	23 or 30 or 46 (382255)
48	"journal of epidemiology and global health".jn. (0)
49	"journal of infection and public health".jn. (227)
50	"saudi journal of kidney diseases & transplantation".jn. (1438)
51	saudi medical journal.jn. (4585)
52	saudi pharmaceutical journal.jn. (0)
53	"annals of saudi medicine".jn. (1361)
54	"saudi journal of gastroenterology".jn. (628)
55	48 or 49 or 50 or 51 or 52 or 53 or 54 (8239)
56	47 or 55 (384556)
57	3 and 17 and 56 (22)

Date limit: No date limit (1946-current)
Study Types: No limit on study types

Records Retrieved	22

Data base: **EMBASE**

Search strategy:	**Date of search: 23/11/2013**

1	exp Rhinitis/ or Nasal Provocation Tests/ or Nasal Obstruction/ or hay fever/ or nose allergy/ or nasal pruritus/ (69066)
2	("allergic rhinitis" or "hay fever" or hayfever or "nasal allergy" or "nasal allergies" or "nasal congestion" or "nasal itching" or "nasal obstructionor rhinorrhea").mp. (34468)
3	Saudi Arab$.mp,in. or Saudi Arabia/ (44088)
4	Riyadh.mp,in. (24452)
5	Jeddah.mp,in. (5572)
6	Kh*bar.mp,in. (1211)
7	Dammam.mp,in. (1751)
8	3 or 4 or 5 or 6 or 7 (44371)
9	Kuwait$.mp,in. or Kuwait/ (10766)
10	United Arab Emirates.mp,in. or United Arab Emirates/ (9072)
11	Qatar$.mp,in. or Qatar/ (3968)
12	Oman$.mp,in. or Oman/ (5183)
13	Yemen$.mp,in. or Yemen/ (2449)
14	Bahr*in$.mp,in. or Bahrain/ (2904)
15	9 or 10 or 11 or 12 or 13 or 14 (32551)
16	Middle East$.mp,in. or Middle East/ (14295)
17	Jordan$.mp,in. or Jordan/ (29511)
18	Libya$.mp,in. or Libya/ (2821)
19	Egypt$.mp,in. or Egypt/ (63291)
20	Syria$.mp,in. or Syria/ (16714)
21	Iraq$/ or Iraq.mp,in. (9909)
22	Morocc$.mp,in. or Morocco/ (17427)
23	Tunisia$.mp,in. or Tunisia/ (24059)
24	Leban$.mp,in. or Lebanon/ (25675)
25	West Bank.mp,in. (1044)
26	Iran$.mp,in. or Iran/ (96928)
27	Turkey/ or (Turkey or Turkish).mp,in. (239455)
28	Algeria$.mp,in. or Algeria/ (7443)

29	Arab$.mp,in. or Arabs/ (149134)
30	16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 (531902)
31	29 or 30 (662105)
32	8 or 15 or 31 (680304)
33	"journal of epidemiology and global health".jn. (66)
34	"journal of infection and public health".jn. (275)
35	"saudi journal of kidney diseases & transplantation".jn. (0)
36	saudi medical journal.jn. (6623)
37	saudi pharmaceutical journal.jn. (569)
38	"annals of saudi medicine".jn. (3529)
39	"saudi journal of gastroenterology".jn. (390)
40	33 or 34 or 35 or 36 or 37 or 38 or 39 (11452)
41	economic evaluation$.mp. or exp economic evaluation/ (211549)
42	fee$.mp. or exp fee/ (587575)
43	health care cost$.mp. or exp "health care cost"/ (205196)
44	hospital cost$.mp. or exp "hospital cost"/ (28398)
45	pharmacoeconomics.mp. or exp pharmacoeconomics/ (173058)
46	health economics.mp. or health economics/ (35641)
47	budget$.mp. or budget/ (35268)
48	socioeconomics.mp. or socioeconomics/ (112286)
49	41 or 42 or 43 or 44 or 45 or 46 (1050639)
50	47 or 49 (1072732)
51	48 or 50 (1167708)
52	(low adj cost).mp. (28430)
53	(high adj cost).mp. (9207)
54	(health?care adj cost$).mp. (12388)
55	(cost adj estimate$).mp. (1973)
56	(cost adj variable$).mp. (153)
57	(unit adj cost$).mp. (2420)
58	(fiscal or funding or financial or finance).tw. (103249)
59	(economic$ or pharmacoeconomic$ or price$ or pricing).tw. (225414)
60	52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 (359936)
61	51 or 60 (1392272)
62	50 or 60 (1315070)
63	49 or 60 (1297165)
64	1 or 2 (72773)
65	32 or 40 (682257)
66	61 and 64 and 65 (174)

Date limit: No date limit (1974-current)
Study Types: No limit on study types

Records Retrieved	174

Summary of Searches:

Total No. Retrieved:	**223**
Cochrane:	22
Medline:	174
Others: NHS EED	27
Duplicates:	19
No. Total without duplicates**:**	**204**
Screening (Title and Abstract Review)	
No. Excluded:	199
Included for Full Text review:	5


المركز السعودي للرعاية الصحية المبنية على البراهين
The Saudi Center for Evidence Based Health Care
وزارة الصحة
Ministry of Health