Chapter 2. Methodology

The basis of this evidence report is a comprehensive, systematic review of the literature. This chapter describes the basic methodology for conducting the literature review, from the refinement of the key research questions through the literature search, screening, and data abstraction process. Included are descriptions of the literature search strategies and results, literature sources, screening and grading criteria, and quality control procedures.

Topic Assessment and Refinement

The American Association of Health Plans (AAHP) proposed the original topic for this report, "Seasonal Allergies, Effect on Working Populations." An eight-member national advisory panel of technical experts, which included a representative of AAHP, was convened to work with the Duke research team to refine the key research questions and to review literature search strategies, inclusion and exclusion criteria, the causal pathway or evidence model, quality scoring criteria, interventions to be assessed, and specific outcomes to be reported in the evidence tables. The panel also assisted in identifying key research issues, advised on the scope of the project and methods, nominated peer reviewers, and reviewed preliminary drafts of research findings. Specialties represented on the panel included allergy and immunology, family medicine, general internal medicine, occupational medicine, otolaryngology, and pharmacology. Two meetings of the full panel were conducted via conference calls.

During its first conference call, the panel was presented with the five key research questions specified in the task order:

1) What is the appropriate treatment protocol for diagnosing and managing seasonal allergic rhinitis in a timely and cost-effective manner?

2) What measures can healthcare providers take to help prevent complications or reduce the severity of complications associated with chronic allergic rhinitis?

3) What is the role of new therapies such as anti-immunoglobulin E (anti-IgE) therapy and cytokine antagonists?

4) Can early interventions by allergy specialists reduce the rate of complications associated with chronic allergic rhinitis and lower costs?

5) Do treatment outcomes vary according to a patient's race or ethnicity?

Based on Duke's preliminary assessment of the literature and individual and group discussion with the advisory panel and the task order officer at the Agency for Healthcare Research and Quality (AHRQ), all parties agreed to refine the questions as follows:

1) How do currently clinically available treatments for allergic rhinitis affect costs and work performance?

2) What is the relationship between symptom outcomes or disease-specific quality-of-life measures and work performance among adults with allergic rhinitis? Can data on symptomatic outcome or quality of life be reliably translated into work performance measures?

3) How effective are (a) environmental measures, (b) immunotherapy, and (c) combined treatments, such as with antihistamines and nasal steroids or antihistamines and oral decongestants, for relief of symptoms in adults with allergic rhinitis?

4) How do different types of healthcare providers (generalists, allergy specialists, and otolaryngologists) treat adults with allergic rhinitis, and how do treatment outcomes vary by provider?

5) In adult patients with symptoms of allergic rhinitis, does the prevalence, treatment patterns or response to treatment vary according to a patient's race or ethnicity?

Given the changes in the research questions, after the second conference call and with the panel's agreement, we requested that the title of the task order be changed to "Management of Allergic Rhinitis in the Working-Age Population" to more accurately reflect the contents of the evidence report. This request was approved by AHRQ.

Causal Pathway

Figure 1 represents the causal pathway underlying our analysis of the key research questions related to specific therapies. It illustrates the effects of specific treatments on cellular mechanisms, on symptoms, and ultimately on health status, costs, and work performance. This report focuses on the effects of treatments or combinations of treatments on symptoms, health status, costs, and work performance (outcomes represented on the right side of Figure 1). We do not describe evidence regarding the mechanisms by which the various treatments exert their clinical effects (outcomes represented on the left side of Figure 1).

Literature Search and Review

The comprehensive review of the literature, from identification of databases through abstraction of individual articles into evidence tables, was a multi-step, sequential process.

Literature Sources

The primary sources of literature are six of the most widely used computerized bibliographic databases: MEDLINE (1966-January 2002), CINAHL (1983-January 2002), the Cochrane Database of Systematic Reviews (CDSR) (Issue 4, 2001), the Database of Abstracts of Reviews of Effectiveness (DARE), International Pharmaceutical Abstracts, EconLit (1969-August 2002), and EMBASE (1980-February 2002). Searches of these databases were supplemented by searching the reference lists of review articles and meta-analyses, and by scanning current issues of journals not yet indexed in the computerized bibliographic databases. Specialty journals regularly scanned included Allergy; Annals of Allergy, Asthma & Immunology; Clinical & Experimental Allergy; and

the Journal of Allergy & Clinical Immunology. General interest journals regularly scanned included Annals of Internal Medicine, BMJ, JAMA, Lancet, and the New England Journal of Medicine.

Search Strategy

We developed the basic search strategy using the National Library of Medicine's MeSH key word nomenclature developed for MEDLINE. The same strategy was used to search the other databases listed above. A Duke University Medical Center librarian checked the strategies and assisted with their translation to the key word structure used by EMBASE.

The initial searches, conducted in October 2001, were performed in MEDLINE, updated in MEDLINE in January 2002, and duplicated in additional databases in January 2002. All years of each database were searched – the periods covered by the searches are given above. The searches were limited to the English language and to human subjects. For topics concerning treatment efficacy, search terms focused on identifying randomized controlled trials, except in the case of the environmental measures topic, where the search strategy used additional, less restrictive, search terms, including "controlled trials" and "clinical trials." Suggestions regarding search terms and specific articles were solicited from the advisory panel and resulted in additions to the literature database.

The basic search strategies used are reproduced in Tables 3 to 6.

Screening Criteria

Inclusion and exclusion criteria were developed for the literature searches so that the yield of articles would be appropriately focused. Citations were *excluded* based on the following criteria:

- Article was not original research;
- Article did not address allergic rhinitis or was not applicable to the key research questions;
- The study design was a single case report;
- The study design was a small case series with 20 or fewer subjects.

Empirical studies were *included* based on the following criteria:

- The study population must address allergic rhinitis;
- All original research or relevant reviews must relate to at least one of the five key research questions;
- Included study designs varied depending on the key research question being addressed (Table 7). Randomized controlled trials (RCTs) were included for all questions. For question 3a (environmental measures), we also included non-randomized prospective cohort comparisons. For questions 3b (immunotherapy) and 3c (combined treatments), we included RCTs and pseudo-randomized placebo-controlled trials. We defined "pseudo-randomized" to mean using some unbiased but non-random method of allocation, such as enrollment order, identification

number, or date of birth. For question 1 (costs and work performance), question 2 (relationship between symptom outcomes or disease-specific quality of life and work performance), question 4 (clinician specialty differences), and question 5 (racial and ethnic variation), we included RCTs, large case series (> 20 subjects), cohort studies, non-randomized comparison studies, and articles reporting data from surveys and secondary data analyses.

The final version of the abstract and full-text screening criteria is shown in Table 8.

Screening Results

The literature search yielded 1,593 articles. The titles and abstracts of these articles were reviewed against the inclusion/exclusion criteria by the investigators. Two investigators reviewed each abstract. When no abstract was available, the title, source, and keywords were screened. At this stage, articles were included if requested by one investigator. The full text of each article passing the title-and-abstract screen was retrieved from the library for further review.

At the full-text screening stage, each article was independently reviewed by two investigators, who forwarded their decisions to the task order manager for recording and comparison. If indicated, reviewers were asked to reconcile differences of opinion and return a reconciled final decision to the task order manager. Overall, the teams reconciled about 40 percent of their decisions. If team members had difficulty reaching agreement on decisions, or submitted indecisive codes, the principal investigator was the arbiter. This situation arose in about 10 percent of the reconciled decisions, largely when "include" or "exclude" decisions were at variance with the study design (e.g., an RCT coded as "exclude").

The records in the literature database were coded at each screening stage. A summary of the results of the title-and-abstract and full-text screenings is provided in Table 9. A more detailed accounting of the screening process is provided in Table 10.

Data Abstraction

Not all of the "included" articles mentioned above were abstracted into evidence tables. Some of these studies were included as background and supporting evidence and may be cited in the text, but were not abstracted into evidence tables (see bottom of Table 8 for categories of articles summarized in evidence tables).

We determined that the data from the included articles could be abstracted directly into an evidence table template, which served as a data abstraction "form." To facilitate the development of the evidence tables and to use everyone's particular skills and time to their best advantage, the senior writer/editor began the data abstraction process with a partial abstraction of each article. This partial abstraction included a description of the study design, description of the intervention, number of subjects at the start of the study, and types of outcomes data that were collected (see Table 11 for a sample). The partial evidence table was forwarded to an investigator for completion. It was pre-formatted so that the investigator could easily see which additional data needed to be inserted and where. The completed evidence table was returned to the writer/editor who checked it for completeness and consistency of information and then forwarded the table to another investigator for over-reading. The over-reader returned the table to the writer/editor for final review of the completeness of the content and for editing and formatting.

In the partial abstraction performed by the senior writer/editor, all outcomes reported were listed, and the outcomes meeting our criteria were selected for abstraction. We required patient-assessed symptom outcomes for efficacy questions; we also reported quality of life, functional status, adverse events, and patient global assessments for these questions. For all questions, we recorded work performance and cost outcomes. Specifically, outcomes abstracted for each key research question were as follows:

Question 1:
- Work performance
- Costs (direct medical or non-medical)
- Costs (indirect)

Question 2:
- Association between symptoms and work performance
- Association between quality-of-life and work performance

Question 3:
- Symptoms, assessed by patients
- Quality of life
- Functional status
- Global assessments by patients
- Adverse events

Question 4:
- Practice patterns by provider specialty (referral, drug and other treatment use, case mix)
- Drug and other treatment response by provider specialty

Question 5:
- Allergic rhinitis prevalence by racial/ethnic groups
- Severity of allergic rhinitis by racial/ethnic groups
- Provider consultation by racial/ethnic groups
- Drug and other treatment use by racial/ethnic groups
- Drug and other treatment response by racial/ethnic groups

Grading of Articles (Quality Scoring)

We evaluated each article included in the evidence tables for factors affecting internal and external validity. The quality scoring criteria are given below:

Internal validity:

1) What is the level of evidence (Oxford Centre for Evidence-based Medicine, 2001; see Table 12)?

2) Were the main outcomes of interest measured in a way that has been demonstrated empirically to be valid and reliable (e.g., using a standardized scale such as the

Rhinoconjunctivitis Quality of Life Questionnaire [RQLQ] or the Medical Outcome Study Short-Form Health Survey [SF-36])?

External validity:

3) Was the study population described and reasonably similar to an adult working US population? (Based mostly on age of study population.)

4) Were the intervention protocols referenced or described in sufficient detail to replicate?

5) Was the presence of comorbid asthma (or other upper respiratory conditions) described in the study population?

6) Was the diagnosis of allergic rhinitis based on physician diagnosis?

7) If physician-diagnosed, was the diagnosis supported by objective evidence of allergy (e.g. skin prick or serum IgE antibody testing)?

Additional quality criteria were applied to studies on environmental measures, immunotherapy, and combination therapy:

1) Was the study described as "randomized"?

2) If the method for concealing allocation from the investigators was described, was it adequate (table of random numbers, computer generated, coin toss, etc.) or inadequate (alternating, date of birth, hospital number, etc.)?

3) Was the study described as "double-blind"?

4) If the method of double-blinding was described, was it adequate (e.g., identical placebo, active placebo, injection vs. tablet with double dummy) or inadequate (e.g., tablet vs. injection with no double dummy)?

5) Did the study describe dropouts and withdrawals so that all patients entering the trial could be accounted for?

6) Was the analysis performed according to the intention-to-treat principle? (Did the analysis in some way consider all patients that were allocated to treatment, including dropouts and withdrawals?)

We did not aggregate these items into an overall quality score; rather, we considered and reported them individually. We favored this approach for several reasons:

- Previous work has shown that numeric grading systems may not discriminate well between "high" and "low" quality studies, even for randomized trials (Jüni, Witschi, Bloch, et al., 1999; Moher, Cook, Jadad, et al., 1996).

- Development and use of a new quality score would require additional work for validation, for which there is no time or budget allocation in the task order.

- Identification of specific weaknesses in each study will be helpful in identifying trends, which in turn will assist with our recommendations for future research.

- Describing key design components, rather than assigning a single aggregate score, is also consistent with recent recommendations from an expert panel on meta-analysis of observational studies (Stroup, Berlin, Morton, et al., 2000).

Summaries of each quality evaluation are provided in the far right column of the evidence tables. Grades were assigned by the primary abstractor and confirmed by the over-reader. When required, additional notes were made in the same column of the evidence table.

Quality Control Procedures

We employed quality-monitoring checks at every phase of the literature search, review, and data abstraction process to reduce bias, enhance consistency, and check the accuracy of screening. The quality checks included:

- Medical librarian review of the literature search strategy;

- Review of literature search strategies by advisory panel of technical experts;

- Check on completeness of the literature search results through reference list checks by the screener of each article;

- Reconciliation of all differences of opinion by reviewers on all full-text articles;

- Agreement of two reviewers for all eligible studies;

- Data abstractions completed by one investigator and reviewed (over-read) by another;

- Additional checks of evidence table entries for completeness and accuracy by a non-physician abstractor;

- Solicitation of advice at key decision points from the advisory panel of technical experts;

- Expert peer review of complete draft evidence report.

Figure 1. Causal Pathway

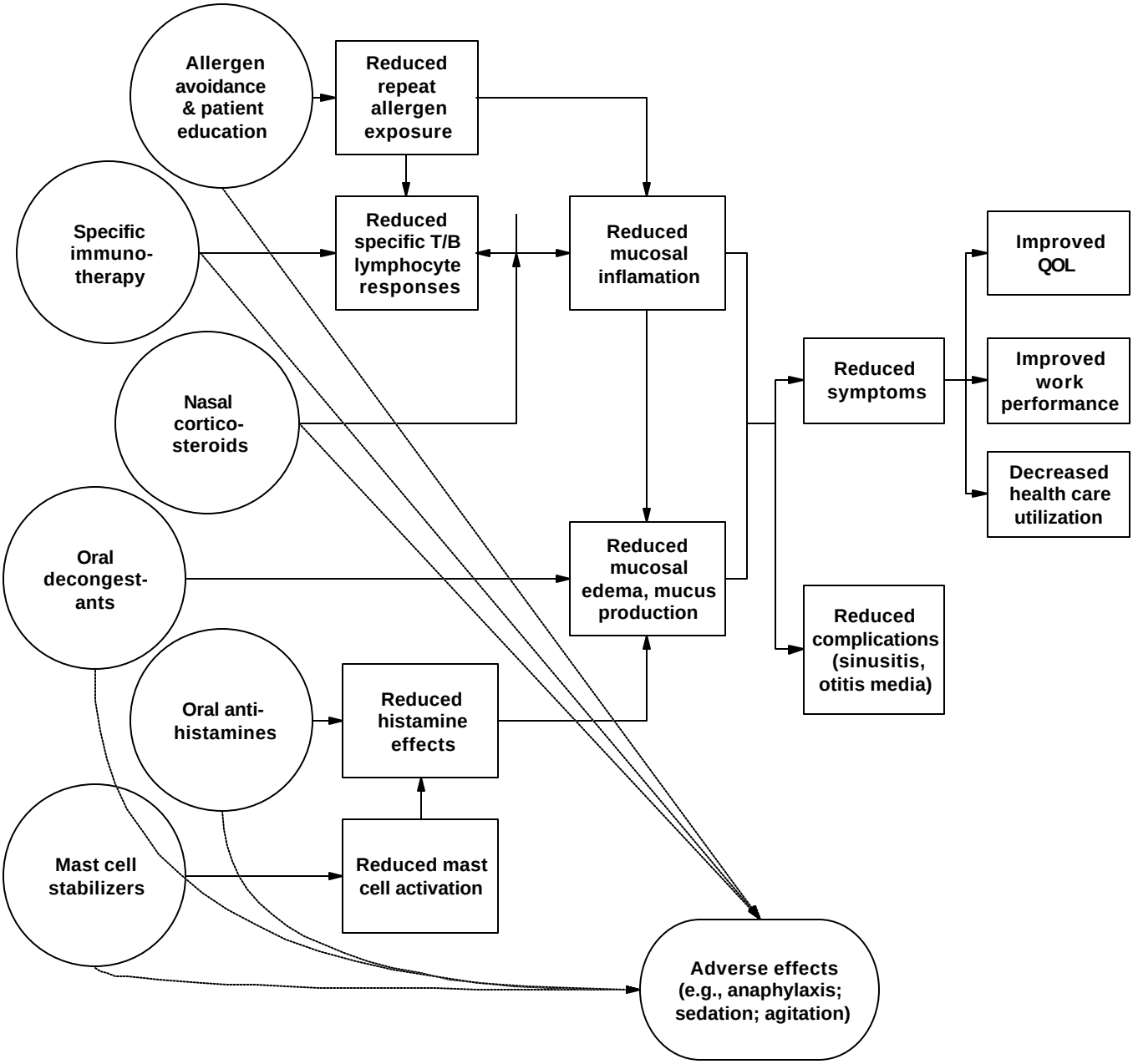

Table 3. Search strategy – preliminary general search, MEDLINE, 1966 through September 2001

Set	Search term	Results
1	exp rhinitis/	12649
2	pollinosis.tw.	842
3	hay fever.tw.	1215
4	rhinitis.tw.	8000
5	or/1-4	15475
6	desensitization, immunologic/	4765
7	immunotherapy.tw.	15633
8	desensitization.tw.	11430
9	or/6-8	29720
10	and/5,9	1679
11	limit 10 to human	1647
12	limit 11 to english language	1128
13	limit 12 to randomized controlled trial	159
14	exp filtration/	21390
15	air conditioning/	1546
16	air pollution, indoor/	2810
17	dust/	11250
18	“bedding and linens”/	2461
19	mites/	5942
20	environmental control.tw.	696
21	mite$.tw.	6141
22	or/14-21	45324
23	5 and 22	1312
24	limit 23 to human	1280
25	limit 24 to english language	930
26	limit 25 to randomized controlled trial	66
27	drug therapy, combination/	65666
28	5 and 27	142
29	limit 28 to human	138
30	limit 29 to english language	104
31	limit 30 to randomized controlled trial	54
32	exp psychology, industrial/	36848
33	exp “costs and cost analysis”/	110582
34	burden of illness.tw	188
35	or/32-34	144427
36	5 and 35	72
37	limit 36 to human	71
38	limit 37 to english language	68
39	leukotriene antagonists/tu	241
40	interleukin-4/tu	141
41	antibodies, anti-idiotypic/	9499
42	or/39-41	9879
43	5 and 42	106
44	limit 43 to human	103
45	limit 44 to english language	92
46	limit 45 to randomized controlled trial	17
47	quality of life/	28524
48	health status/	17994
49	karnofsky performance status/	404
50	activities of daily living/	21523
51	or/47-50	62587
52	5 and 51	117
53	limit 52 to human	117
54	limit 53 to english language	107
55	limit 54 to abstracts	94
56	exp anti-inflammatory agents, steroidal/tu	45608
57	5 and 56	619

(continued on next page)

Set	Search term	Results
58	limit 57 to human	614
59	limit 58 to english language	505
60	limit 59 to randomized controlled trial	190
61	cetirizine/tu	194
62	fexofenadine/tu	0
63	loratadine/tu	145
64	terfenadine/tu	168
65	or/61-64	441
66	exp histamine h1 antagonists/tu	7227
67	66 not 65	6786
68	5 and 65	225
69	limit 68 to human	223
70	limit 69 to english language	198
71	limit 70 to randomized controlled trial	127
72	limit 67 to human	6094
73	limit 72 to english language	4250
74	limit 73 to randomized controlled trial	787
75	71 or 74	914

Table 4. Search strategy – clinician specialty differences, MEDLINE, 1966 to October Week 3 2001

Set	Search term	Results
1	physicians,family/	8358
2	exp physician's practice patterns/	11285
3	family practice/	38292
4	internal medicine/	9345
5	"referral and consultation"/	29576
6	specialties, medical/	11701
7	specialties, surgical/	935
8	surgery/	17749
9	exp attitude of health personnel/	55556
10	exp "outcome and process assessment (health	151936
11	"allergy and immunology"/	2635
12	or/1-11	310954
13	exp rhinitis/	12676
14	pollinosis.tw.	843
15	hay fever.tw.	1217
16	rhinitis.tw.	8034
17	or/13-16	15518
18	and/12,17	450
19	from 18 keep 28,43-44,50,52,63,66,108,110,1	18
20	limit 18 to yr=1966-1998	289
21	limit 20 to yr=1966-1997	217
22	from 21 keep 30,33,40,43,88,99,107,156,205,	10

Table 5. Search strategy – environmental measures (1), MEDLINE, 1966 to October Week 1 2001

Set	Search term	Results
1	exp rhinitis/	12654
2	air pollutants, Environmental/ip	49
3	Allergens/ip	972
4	MITES/	5946
5	1 or 2 or 3 or 4	18967
6	Rhinitis/pc	64
7	air pollution/pc	2146
8	respiratory hypersensitivity/pc	206
9	dust/pc	288
10	Micropore Filters/	1779
11	FILTRATION/	11554
12	INSECTICIDES/	7545
13	Insect Control/	3225
14	air-cleaning.tw.	48
15	(air adj filter).tw.	96
16	(air adj cleaner$).tw.	48
17	acaricide.tw.	343
18	acardust.tw.	3
19	hepa.tw.	582
20	(allergen adj avoidance).mp. [mp=title, abstract, registry number word, mesh subject heading]	216
21	(allergen adj control).mp. [mp=title, abstract, registry number word, mesh subject heading]	27
22	(environmental adj control$).mp. [mp=title, abstract, registry number word, mesh subject heading]	811
23	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22	27516
24	5 and 23	543
25	randomized-controlled-trial (pt)	151353
26	meta-analysis (pt)	5987
27	controlled-clinical-trial (pt)	58987
28	clinical-trial (pt)	319348
29	random$.ti,ab,sh.	254436
30	(meta-anal$ or metaanaly$ or meta analy$).ti,ab,sh.	9346
31	((doubl$ or singl$) and blind$).ti,ab,sh.	67067
32	exp Clinical trials/	127044
33	crossover.ti,ab,sh.	18070
34	25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33	501236
35	24 and 34	89

Table 6. Search strategy – environmental measures (2), MEDLINE, 1966 to October Week 1 2001

Set	Search term	Results
1	exp rhinitis/	12654
2	air pollutants, Environmental/ip	49
3	Allergens/ip	972
4	MITES/	5946
5	1 or 2 or 3 or 4	18967
6	Rhinitis/pc	64
7	air pollution/pc	2146
8	respiratory hypersensitivity/pc	206
9	dust/pc	288
10	Micropore Filters/	1779
11	FILTRATION/	11554
12	INSECTICIDES/	7545
13	Insect Control/	3225
14	air-cleaning.tw.	48
15	(air adj filter).tw.	96
16	(air adj cleaner$).tw.	48
17	acaricide.tw.	343
18	acardust.tw.	3
19	hepa.tw.	582
20	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19	26537
21	Randomized Controlled Trials/	20303
22	5 and 20	421
23	21 and 22	1
24	pollinosis.tw.	842
25	hay fever.tw.	1216
26	rhinitis.tw.	8011
27	mite$.tw.	6147
28	5 or 24 or 25 or 26 or 27	23563
29	exp filtration/	21404
30	air conditioning/	1548
31	air pollution, indoor/	2815
32	dust/	11255
33	“bedding and linens”/	2463
34	20 or 29 or 30 or 31 or 32 or 33	51223
35	randomized-controlled-trial (pt)	151353
36	meta-analysis (pt)	5987
37	controlled-clinical-trial (pt)	58987
38	clinical-trial (pt)	319348
39	random$.ti,ab,sh.	254436
40	(meta-anal$ or metaanaly$ or meta analy$).ti,ab,sh.	9346
41	((doubl$ or singl$) and blind$).ti,ab,sh.	67067
42	exp Clinical trials/	127044
43	crossover.ti,ab,sh.	18070
44	35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43	501236
45	28 and 34	2799
46	44 and 45	291
47	limit 46 to (human and english language)	224

Table 7. Included study designs, by key research question

Question	Topic	Included study designs
1 2	Costs and work performance Relationship between symptom outcomes or disease-specific quality of life and work performance	Any empirical study involving more than 20 patients with allergic rhinitis. Includes randomized controlled trials (RCTs), case series, cohort studies, non-randomized comparison studies, surveys, and secondary data analyses.
3a	Environmental measures	RCTs, non-randomized prospective cohort comparisons
3b 3c	Immunotherapy Combination drug therapy	RCTs, pseudo-randomized placebo-controlled trials
4 5	Clinician specialty differences Racial and ethnic variation	Any empirical study involving more than 20 patients with allergic rhinitis. Includes RCTs, case series, cohort studies, non-randomized comparison studies, surveys, and secondary data analyses.

Table 8. Abstract and full-text screening criteria

Key research questions:

1. How do currently clinically available treatments for allergic rhinitis affect costs and work performance?
2. What is the relationship between symptom outcomes or disease-specific quality-of-life measures and work performance among adults with allergic rhinitis? Can data on symptomatic outcome or quality of life be reliably translated into work performance measures?
3. How effective are (a) environmental measures, (b) immunotherapy, and (c) combined treatments, such as with antihistamines and nasal steroids or antihistamines and oral decongestants, for relief of symptoms in adults with allergic rhinitis?
4. How do different types of healthcare providers (generalists, allergy specialists, and otolaryngologists) treat adults with allergic rhinitis, and how do treatment outcomes vary by provider?
5. In adult patients with symptoms of allergic rhinitis, does the prevalence, treatment patterns or response to treatment vary according to a patient's race or ethnicity?

Inclusion/exclusion criteria:

1 Not original research or relevant review
2 Not allergic rhinitis or allergic rhinitis not applicable to research questions
3 Case report
4 Small case series (≤ 20 patients, no controls)
5 Large case series (> 20 patients, no controls)
6 Non-randomized assignment to treatment (comparison group, but not randomly assigned)
7 Randomized controlled trial
8 Relevant review
9 Original research on other aspects (for use as background or in model, e.g., prevalence, natural history, diagnostic testing)
10 Basic science
11 Survey and secondary data

Inclusion rules:

Question 1:	codes 5-9,11:	Evidence tables for codes 5, 6 7, 11
Question 2:	codes 5-9,11:	Evidence tables for codes 5, 6, 7, 11
Question 3a:	codes 6-9,11:	Evidence tables for codes 6, 7
Question 3b:	codes 7-9,11:	Evidence tables for code 7
Question 3c:	codes 7-9,11:	Evidence tables for code 7
Question 4:	codes 5-9,11:	Evidence tables for codes 5, 6, 7, 11
Question 5:	codes 5-9,11:	Evidence tables for codes 5 ,6, 7,11

Table 9. Summary of results of abstract and full-text screening

Articles identified	1593
Abstracts:	
Included	546
Excluded	1089
Full-text articles:	
Included	258
Excluded	288

Table 10: Full-text screening results, by key research question and by inclusion/exclusion criteria

INCLUDED ARTICLES (ET = included in evidence tables)	
Question 1 (Note: one article screened for this question reported results of both an RCT and a large case series)	**54**
5-large case series (> 20 patients, no controls): ET	14
6-non-randomized controlled trials: ET	0
7-randomized controlled trial: ET	7
8-relevant review	11
9-original research on other aspects for use in background or model	13
11-survey or secondary data: ET	11
Question 2 (screened with Question 1 articles)	**6**
5-large case series (> 20 patients, no controls): ET	0
6-non-randomized controlled trials: ET	0
7-randomized controlled trial: ET	3
8-relevant review	2
9-original research on other aspects for use in background or model	0
11-survey or secondary data: ET	1
Question 3a (environmental measures)	**40**
6-non-randomized controlled trials: ET	1
7-randomized controlled trial: ET	26
8-relevant review	9
9-original research on other aspects for use in background or model	0
11-survey or secondary data	4
Question 3b (immunotherapy)	**80**
7-randomized controlled trial: ET	62
8-relevant review	11
9-original research on other aspects for use in background or model	4
11-survey or secondary data	3
Question 3c (combination treatments)	**32**
7-randomized controlled trial: ET	31
8-relevant review	0
9-original research on other aspects for use in background or model	1
Question 4	**26**
5-large case series (> 20 patients, no controls): ET	4
6-non-randomized controlled trials: ET	0
7-randomized controlled trial: ET	0
8-relevant review	12
9-original research on other aspects for use in background or model	6
11-survey or secondary data: ET	1
Question 5	**8**
5-large case series (> 20 patients, no controls)	1
6-non-randomized controlled trials	0
7-randomized controlled trial	0
8-relevant review	3
9-original research on other aspects for use in background or model	0
11-survey or secondary data	4

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EXCLUDED ARTICLES

Question 1	**82**
1-not original research or relevant review	24
2-not allergic rhinitis or not applicable to study questions	48
3-case report	0
4-small case series (≤ 20 patients, no controls)	1
10-basic science	0
Excluded during data abstraction (e.g., no relevant data reported)	9
Question 2 (screened with Question 1 articles)	**15**
1-not original research or relevant review	6
2-not allergic rhinitis or not applicable to study questions	5
3-case report	0
4-small case series (≤ 20 patients, no controls)	0
5-large case series (> 20 patients, no controls)	0
10-basic science	1
Excluded during data abstraction (no relevant data)	3
Question 3a (environmental measures)	**41**
1-not original research or relevant review	10
2-not allergic rhinitis or not applicable to study questions	10
3-case report	0
4-small case series (≤ 20 patients, no controls)	0
5-large case series (> 20 patients, no controls)	3
6-non-randomized controlled trials	0
10-basic science	11
Excluded during data abstraction (e.g., no relevant data, insufficient data, no symptom outcomes or other relevant outcomes, only atopic dermatitis)	7
Question 3b (immunotherapy):	**87**
1-not original research or relevant review	5
2-not allergic rhinitis or not applicable to study questions	71
3-case report	0
4-small case series (≤ 20 patients, no controls)	0
5-large case series (> 20 patients, no controls)	1
6-non-randomized controlled trials	4
10-basic science	2
Excluded during data abstraction (e.g., no separate results for allergic rhinitis, asthma data only, no symptom outcomes)	4
Question 3c (combination treatments)	**25**
1-not original research or relevant review	5
2-not allergic rhinitis or not applicable to study questions	14
3-case report	0
4-small case series (≤ 20 patients, no controls)	0
10-basic science	0
Excluded during data abstraction (no relevant data)	6
Question 4	**30**
1-not original research or relevant review	6
2-not allergic rhinitis or not applicable to study questions	9
3-case report	0
4-small case series (≤ 20 patients, no controls)	1

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10-basic science	1
Excluded during data abstraction (e.g., no relevant allergic rhinitis data; no data on provider differences)	13
Question 5	**21**
1-not original research	2
2-not allergic rhinitis or not applicable to study questions	18
3-case report	0
4-small case series (≤ 20 patients, no controls)	0
10-basic science	0
Excluded during data abstraction (e.g., no relevant data)	1

Table 11. Partial data abstraction – sample

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score/Notes
Andri, Senna, Betteli, et al., 1992 **#210**	Design: RCT, parallel-group, method of randomization not described Interventions: 1) Terfenadine 60 mg bid + nimesulide 100 mg bid (n = 15) 2) Terfenadine 60 mg bid + placebo (n = 15) Duration of study treatment: 30 days No other drugs "likely to affect hay fever" permitted No pre-trial washout period described Dates: **Location:** **Setting:** **Type(s) of providers:**	No. of subjects at start: 30 Dropouts/withdrawals: No. of subjects at end: Inclusion criteria: Exclusion criteria: Age: Sex: Race: [IF RESULTS ARE BROKEN DOWN BY RACE/ETHNICITY, PLEASE MAKE THIS CLEAR IN "RESULTS" COLUMN] Other:	1) Investigator-assessed symptom severity 2) Patient-assessed symptom severity: nasal itching, nasal obstruction, sneezing, running nose, eye irritation, and eye watering graded daily by patients scale of 0 (none) to 3 (severe) 3) Patient global assessment of efficacy: recorded once at end of trial – categorical scale keyed to perceived degree of improvement in symptoms (< 50%, 50-80%, > 80%) 4) Adverse events: Not clear how reported/ recorded	1) Investigator-assessed symptom severity: DO NOT ABSTRACT 2) Patient-assessed symptom severity: 3) Patient global assessment of efficacy: 4) Adverse events:	[IF ARTICLE SHOULD BE EXCLUDED, PLEASE EXPLAIN WHY HERE] Quality Scoring: Notes: Local pollen counts conducted daily during trial.

Table 12. Oxford Centre for Evidence-based Medicine levels of evidence (May 2001)[1]

Level	Therapy/prevention, aetiology/harm	Prognosis	Diagnosis	Differential diagnosis/symptom prevalence study	Economic and decision analyses
1a	Systematic review (SR) (with homogeneity*) of RCTs	SR (with homogeneity*) of inception cohort studies; CDR† validated in different populations	SR (with homogeneity*) of Level 1 diagnostic studies; CDR† with 1b studies from different clinical centres	SR (with homogeneity*) of prospective cohort studies	SR (with homogeneity*) of Level 1 economic studies
1b	Individual RCT (with narrow Confidence Interval‡)	Individual inception cohort study with ≥ 80% follow-up; CDR† validated in a single population	Validating** cohort study with good††† reference standards; or CDR† tested within one clinical centre	Prospective cohort study with good follow-up****	Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses
1c	All or none§	All or none case-series	Absolute SpPins and SnNouts††	All or none case-series	Absolute better-value or worse-value analyses ††††
2a	SR (with homogeneity*) of cohort studies	SR (with homogeneity*) of either retrospective cohort studies or untreated control groups in RCTs	SR (with homogeneity*) of Level >2 diagnostic studies	SR (with homogeneity*) of 2b and better studies	SR (with homogeneity*) of Level >2 economic studies
2b	Individual cohort study (including low quality RCT; e.g., <80% follow-up)	Retrospective cohort study or follow-up of untreated control patients in an RCT; Derivation of CDR† or validated on split-sample§§§ only	Exploratory** cohort study with good†††reference standards; CDR† after derivation, or validated only on split-sample§§§ or databases	Retrospective cohort study, or poor follow-up	Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses
2c	"Outcomes" Research; Ecological studies	"Outcomes" Research		Ecological studies	Audit or outcomes research
3a	SR (with homogeneity*) of case-control studies		SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies
3b	Individual Case-Control Study		Non-consecutive study; or without consistently applied reference standards	Non-consecutive cohort study, or very limited population	Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations.
4	Case-series (and poor quality cohort and case-control studies§§)	Case-series (and poor quality prognostic cohort studies***)	Case-control study, poor or non-independent reference standard	Case-series or superseded reference standards	Analysis with no sensitivity analysis
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on economic theory or "first principles"

[1] Produced by Bob Phillips, Chris Ball, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, Martin Dawes since November 1998. Available at: http://163.1.96.10/docs/levels .html#levels. Accessed May 30, 2002.

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Users can add a minus-sign "-" to denote the level of that fails to provide a conclusive answer because of:
· EITHER a single result with a wide Confidence Interval (such that, for example, an ARR in an RCT is not statistically significant but whose confidence intervals fail to exclude clinically important benefit or harm)
· OR a Systematic Review with troublesome (and statistically significant) heterogeneity.
· Such evidence is inconclusive, and therefore can only generate Grade D recommendations.

*	By homogeneity we mean a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all systematic reviews with statistically significant heterogeneity need be worrisome, and not all worrisome heterogeneity need be statistically significant. As noted above, studies displaying worrisome heterogeneity should be tagged with a "-" at the end of their designated level.
†	Clinical Decision Rule. (These are algorithms or scoring systems which lead to a prognostic estimation or a diagnostic category.)
‡	See note #2 for advice on how to understand, rate and use trials or other studies with wide confidence intervals.
§	Met when all patients died before the Rx became available, but some now survive on it; or when some patients died before the Rx became available, but none now die on it.
§§	By poor quality cohort study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both exposed and non-exposed individuals and/or failed to identify or appropriately control known confounders and/or failed to carry out a sufficiently long and complete follow-up of patients. By poor quality case-control study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both cases and controls and/or failed to identify or appropriately control known confounders.
§§§	Split-sample validation is achieved by collecting all the information in a single tranche, then artificially dividing this into "derivation" and "validation" samples.
††	An "Absolute SpPin" is a diagnostic finding whose Specificity is so high that a Positive result rules-in the diagnosis. An "Absolute SnNout" is a diagnostic finding whose Sensitivity is so high that a Negative result rules-out the diagnosis.
‡‡	Good, better, bad and worse refer to the comparisons between treatments in terms of their clinical risks and benefits.
†††	Good reference standards are independent of the test, and applied blindly or objectively to applied to all patients. Poor reference standards are haphazardly applied, but still independent of the test. Use of a non-independent reference standard (where the 'test' is included in the 'reference', or where the 'testing' affects the 'reference') implies a level 4 study.
††††	Better-value treatments are clearly as good but cheaper, or better at the same or reduced cost. Worse-value treatments are as good and more expensive, or worse and the equally or more expensive.
**	Validating studies test the quality of a specific diagnostic test, based on prior evidence. An exploratory study collects information and trawls the data (e.g. using a regression analysis) to find which factors are 'significant'.
***	By poor quality prognostic cohort study we mean one in which sampling was biased in favour of patients who already had the target outcome, or the measurement of outcomes was accomplished in <80% of study patients, or outcomes were determined in an unblinded, non-objective way, or there was no correction for confounding factors.
****	Good follow-up in a differential diagnosis study is >80%, with adequate time for alternative diagnoses to emerge (eg 1-6 months acute, 1-5 years chronic)

Grades of Recommendation

A	consistent level 1 studies
B	consistent level 2 or 3 studies ***or*** extrapolations from level 1 studies
C	level 4 studies ***or*** extrapolations from level 2 or 3 studies
D	level 5 evidence ***or*** troublingly inconsistent or inconclusive studies of any level

"Extrapolations" are where data is used in a situation which has potentially clinically important differences than the original study situation.
"Extrapolations" are where data is used in a situation which has potentially clinically important differences than the original study situation.

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1. Canadian Task Force on the Periodic Health Examination: The periodic health examination. CMAJ 1979;121:1193-1254.
2. Sackett DL. Rules of evidence and clinical recommendations on use of antithrombotic agents. Chest 1986 Feb; 89 (2 suppl.):2S-3S.
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4. Yusuf S, Cairns JA, Camm AJ, Fallen EL, Gersh BJ. Evidence-Based Cardiology. London: BMJ Publishing Group, 1998.