

REVIEW ARTICLE

The cost-effectiveness of immunotherapy for respiratory allergy: a review

S. Simoens

Research Centre for Pharmaceutical Care and Pharmaco-Economics, Leuven, Belgium

To cite this article: Simoens S. The cost-effectiveness of immunotherapy for respiratory allergy: a review. *Allergy* 2012; DOI: 10.1111/j.1398-9995.2012.02861.x.

Keywords

cost-effectiveness; economic evaluation;
immunotherapy; respiratory allergy.

Correspondence

Prof. Dr. Steven Simoens, Research Centre
for Pharmaceutical Care and Pharmaco-
Economics, KU Leuven, Onderwijs en
Navorsing 2, Herestraat 49, P.O. Box 521,
3000 Leuven, Belgium.
Tel.: +32 0 16 323465
Fax: +32 0 16 323468
E-mail: steven.simoens@pharm.kuleuven.be

Accepted for publication 22 May 2012

DOI:10.1111/j.1398-9995.2012.02861.x

Edited by: Pascal Demoly

Abstract

This article reviews the international literature on the cost-effectiveness of immunotherapy for respiratory allergy. Included studies conducted an economic evaluation of immunotherapy for allergic rhinoconjunctivitis, allergic conjunctivitis, allergic rhinitis, asthma or allergic rhinitis in combination with asthma. Although there were few economic evaluations and these suffered from methodological shortcomings, the evidence appears to support the cost-effectiveness of immunotherapy as compared with pharmacotherapy for allergic rhinoconjunctivitis, subcutaneous immunotherapy as compared with pharmacotherapy for allergic rhinitis and immunotherapy as compared with pharmacotherapy for allergic rhinitis and asthma. One economic evaluation suggested that immunotherapy as compared with pharmacotherapy is unlikely to be cost-effective for asthma. The questions of the cost-effectiveness of sublingual *vs* subcutaneous immunotherapy and of the cost-effectiveness of immunotherapy for allergic conjunctivitis have not been resolved to date. The cost-effectiveness of immunotherapy depends on the duration of the clinical benefit of immunotherapy following treatment cessation, and on the break-even point of cumulative costs between immunotherapy and pharmacotherapy. There is a need for economic evaluations based on high-quality prospective and long-term clinical studies comparing immunotherapy with pharmacotherapy in real-life practice and comparing sublingual with subcutaneous immunotherapy.

Respiratory allergy places a substantial health and economic burden on society because of its prevalence; its impact on quality of life, social life, school performance, productivity at work and absence from work; and its association with sleep disturbance, impaired cognitive function, depression and anxiety (1, 2). For instance, allergic rhinitis is estimated to affect 30–60 million individuals annually in the United States at a total societal cost of \$11 billion in 2005 (3). Total costs of allergic rhinitis exceeded those associated with asthma, cancer, diabetes mellitus and migraines (4). In a Swedish study, productivity loss associated with allergic rhinitis was estimated at 5.1 days per worker per year, amounting to a total cost of €2.7 billion per year (5).

Immunotherapy for respiratory allergy consists of the administration of gradually increasing doses of allergen extracts, which aims to improve the quality of life and reduce symptoms when the patient is subsequently exposed to the allergen, remains effective following treatment cessation and is able to modify the natural history of respiratory allergy

(6, 7). Administration routes have evolved over time from the initial subcutaneous route to the sublingual route in the recent years. This change in administration route follows the occurrence of adverse events such as systemic reactions and the need for regular injections at the physician's office with subcutaneous immunotherapy (6). Subcutaneous as well as sublingual immunotherapy has proven to be effective in the treatment for respiratory allergy (1).

At a time of scarce resources and increasing healthcare costs, there is a need to explore the cost-effectiveness of immunotherapy for respiratory allergy. Cost-effectiveness data can be used for decision-making purposes by a variety of stakeholders (8). Policy makers draw on cost-effectiveness data to inform the allocation of scarce healthcare resources with a view to maximizing population health. Healthcare payers apply evidence about cost-effectiveness to inform pricing and/or reimbursement decisions in health care. Physicians rely on economic evaluation to shed light on whether immunotherapy is a cost-effective treatment option for a particular

indication. Finally, companies can employ techniques of economic evaluation to demonstrate the cost-effectiveness of their immunotherapy.

The aim of this article is to review the international literature on the cost-effectiveness of immunotherapy for respiratory allergy. To this effect, the review provides a synthesis of economic evaluations of immunotherapy for respiratory allergy. Methodological issues surrounding the evaluation of the cost-effectiveness of immunotherapy for respiratory allergy are also explored. This literature review was carried out on the demand of the National Institute for Health and Disability Insurance with a view to inform Belgian consensus-based guidelines on the cost-effective treatment of respiratory allergy.

Methods

Search strategy

Studies were identified by searching Medline (PubMed), Centre for Reviews and Dissemination databases (Database of Abstracts of Reviews of Effects, NHS Economic Evaluation Database, and Health Technology Assessments Database), Cochrane databases (Database of Technology Assessments and Database of Economic Evaluations) and EconLit (OVID) up to and including February 2012.

Search terms included 'allergy', 'respiratory', 'allergic rhinoconjunctivitis', 'allergic conjunctivitis', 'allergic rhinitis', 'asthma', 'seasonal', 'perennial', 'intermittent', 'persistent', 'immunotherapy', 'oral', 'subcutaneous', 'sublingual', 'health economics', 'pharmaco-economics', 'economic evaluation', 'cost-effectiveness', 'cost-minimization', 'cost-consequence', 'cost-utility' and 'cost-benefit' alone and in combination with each other.

The literature search focused on primary economic evaluations of immunotherapy for respiratory allergy. The bibliography of literature reviews was checked for relevant primary economic evaluations. Literature reviews were incorporated if they discussed the selected primary economic evaluations.

Inclusion/exclusion criteria

Evidence about cost-effectiveness was derived from economic evaluations. An economic evaluation was defined as a study contrasting an intervention with a comparator in terms of both costs and health outcomes (9). An economic evaluation can take the form of a cost-effectiveness analysis, cost-utility analysis or cost-benefit analysis.

In a cost-effectiveness analysis, the intervention and comparator are evaluated in terms of costs and a single outcome measure quantified in a natural unit (e.g. percentage of patients who respond to treatment or for whom treatment is successful). There are two specific cases of a cost-effectiveness analysis: (i) a cost-minimization analysis evaluates costs only provided that health outcomes have been shown to be equal between intervention and comparator; and (ii) a cost-consequence analysis evaluates intervention and comparator in terms of costs and multiple outcome measures.

A cost-utility analysis evaluates intervention and comparator in terms of costs and a health-related quality of life measure, such as quality-adjusted life years. This outcome measure considers both the quantity and quality of life. Quality of life is measured by means of utilities on a scale of 0 (reflecting death) to 1 (reflecting perfect health). Quality of life estimates are multiplied by the time period for which the health benefits last to calculate quality-adjusted life years.

In a cost-benefit analysis, both costs and outcomes are valued in monetary terms. A monetary value can be assigned to outcomes by means of, for example, the willingness-to-pay technique. Monetary outcomes (the so-called benefits) can then be directly compared with costs, and the net worth (benefits minus costs) of the intervention *vs* the comparator can be calculated.

The intervention was immunotherapy. The comparator could be 'do nothing', placebo, alternative immunotherapy, pharmacotherapy or other health technology (e.g. surgery, acupuncture). The literature review considered studies that enrolled patients suffering from allergic rhinoconjunctivitis, allergic conjunctivitis, allergic rhinitis, asthma or allergic rhinitis in combination with asthma.

Inclusion was restricted to articles published in peer-reviewed journals. Congress abstracts were not considered because they do not provide sufficient details of methodology and results. Articles were excluded if studies examined an intervention other than immunotherapy, if studies analysed a single intervention without a comparator, if studies measured costs only, if studies did not report data on costs or outcomes and if studies measured resource use (but not costs) and outcomes.

Articles could be published in English, Dutch or French. The review was limited to studies published between January 1995 and February 2012. Earlier articles were considered of limited relevance because changes in the organization and financing of healthcare systems over time are likely to influence cost-effectiveness estimates.

The selection of studies to be included/excluded was performed independently by two reviewers. Any disagreements between the two reviewers were resolved through discussion.

Assessment of methodological quality

The quality of economic evaluations was assessed by considering the perspective, study design (trial- or model-based economic evaluation); source of cost and outcome data; cost and outcome measures; time horizon; and allowance for uncertainty (9).

Data analysis

Economic evaluations were summarized by focusing on the study country, type of economic evaluation (i.e. cost-effectiveness analysis, cost-consequence analysis, cost-utility analysis and cost-benefit analysis) (9), sample, intervention, comparator, cost and outcome results. Because of the

heterogeneity of the primary studies, a descriptive synthesis of the extracted data was made. The characteristics and the results of the included studies were summarized via tabulation.

Results

Search results

Of the 107 articles identified, 23 articles were included in the review: 15 primary economic evaluations (10–24) and eight literature reviews (6, 7, 25–30) (see Fig. 1). The findings of economic evaluations of immunotherapy are summarized in Table 1 for allergic rhinoconjunctivitis, in Table 2 for allergic rhinitis, in Table 3 for asthma and in Table 4 for allergic rhinitis and asthma. One economic evaluation was included twice in Table 4 because this study calculated the cost-effectiveness of subcutaneous immunotherapy and of sublingual immunotherapy for patients suffering from allergic rhinitis and asthma (21).

Immunotherapy for allergic rhinoconjunctivitis

Two economic evaluations have assessed the cost-effectiveness of sublingual immunotherapy to treat grass pollen-induced allergic rhinoconjunctivitis in European countries (see Table 1) (12, 16). The economic evaluations used the same study design, intervention and comparator; were based on the same randomized controlled trial (RCT); employed the same data sources, cost and outcome measures; had the same time horizon; but differed in terms of countries

included. These studies found that sublingual immunotherapy is likely to be a cost-effective intervention as compared to pharmacotherapy in each of the selected countries. However, the cost-effectiveness of sublingual immunotherapy was established in comparison with symptomatic rather than prophylactic use of an oral histamine in combination with a nasal corticosteroid (7). The observation that sublingual immunotherapy is likely to be cost-effective was also confirmed in a more recent paper pertaining to Denmark (31). However, the cost-effectiveness depended on the annual cost of sublingual immunotherapy. Furthermore, there is a need for research on the long-term effectiveness of sublingual immunotherapy and its potential effect on preventing allergic asthma (32). For instance, a recent 5-year RCT found a significant decrease in a combined score of asthma daily symptoms and daily medications in patients treated with sublingual immunotherapy as compared to pharmacotherapy (33).

Two economic evaluations examined the cost-effectiveness of subcutaneous immunotherapy in the treatment for allergic rhinoconjunctivitis in European countries (18, 22). Effectiveness data in both economic evaluations were primarily derived from a single clinical trial.

The first study showed that subcutaneous immunotherapy for seasonal allergic rhinoconjunctivitis is likely to have an acceptable cost-effectiveness ratio from the healthcare system perspective and that it may be more effective and less expensive than pharmacotherapy from the societal perspective when costs of productivity loss are considered in the selected countries (18). The cost-effectiveness of subcutaneous immunotherapy is likely to improve when future healthcare costs

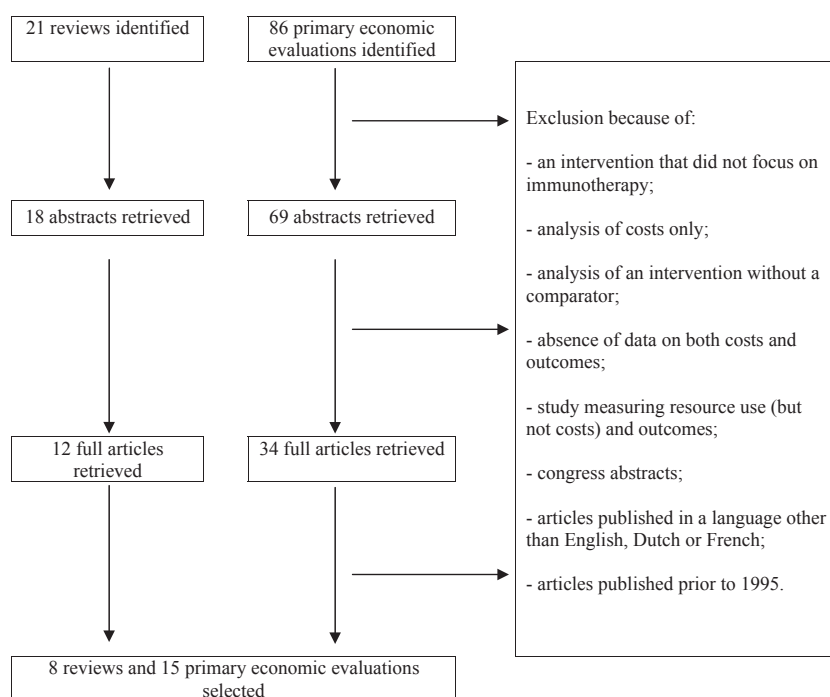


Figure 1 Flow chart of literature search.

Table 1 Economic evaluations of immunotherapy for allergic rhinoconjunctivitis

Country	Type	Perspective	Sample	Comparators	Design	Data source	Time horizon	Results	Ref/Ref*
UK, DE, NL, SE, DK, NO, FI	CUA	Society	Patients with moderate to severe seasonal grass pollen-induced allergic rhinoconjunctivitis	Sublingual immunotherapy with grass allergen tablet plus drugs as needed; pharmacotherapy	Model-based study	One double-blind, multi-centre RCT; patient diaries; literature; EuroQol-5D patient questionnaire; authors' extrapolations	9 years	Patients receiving grass allergen tablets showed a 30% reduction in rhinoconjunctivitis symptom score and a 38% reduction in rhinoconjunctivitis medication score ($P < 0.0001$) compared with pharmacotherapy. Patients treated with the grass allergen tablets gained on average 0.0287 additional QALYs per season compared with patients receiving pharmacotherapy ($P < 0.001$). There was a higher usage of rescue medications loratadine and budesonide ($P < 0.001$), and more hours missed from work ($P < 0.001$) in the pharmacotherapy group. Using 1500€ as an example for an annual treatment cost of the grass allergen tablet, the cost per QALY gained was between €12 930 (in NL) and €18 263 (in DE). The cost per QALY gained was similar in each of the seven countries	Bachert et al. (12)(7, 25–27, 29)

Table 1 (continued)

Country	Type	Perspective	Sample	Comparators	Design	Data source	Time horizon	Results	Ref/Ref*
ES, IT, FR, AT	CUA	Society	Patients with moderate to severe seasonal grass pollen-induced allergic rhinoconjunctivitis	Sublingual immunotherapy with grass allergen tablet plus drugs as needed; pharmacotherapy	Model-based study	One double-blind, multi-centre RCT; patient diaries; literature; EuroQol-5D patient questionnaire; authors' assumptions and extrapolations	9 years	Patients receiving grass allergen tablets showed a 30% reduction in rhinoconjunctivitis symptom score and a 38% reduction in rhinoconjunctivitis medication score ($P < 0.0001$) compared with pharmacotherapy. Patients treated with the grass allergen tablets gained on average 0.0167 additional QALYs per season compared with patients receiving pharmacotherapy ($P = 0.017$). There was a higher usage of rescue medications loratadine and budesonide ($P = 0.0001$), and more hours missed from work ($P < 0.0001$) in the pharmacotherapy group. Using 1200€ as an example for an annual treatment cost of the grass allergen tablet, the cost per QALY gained was €13 870 (in FR); €20 690 (in IT); €20 955 (in AT); and €21 659 (in ES). The cost-effectiveness of the grass allergen tablet improved when including future healthcare costs and costs of productivity loss owing to allergic asthma.	Canonica et al. (16)/(7, 25–27, 29)

Table 1 (continued)

Country	Type	Perspective	Sample	Comparators	Design	Data source	Time horizon	Results	Ref/Ref*
AT, DK, FI, DE, NL, SE	CEA, CUA	Healthcare system, society	Patients with grass pollen-induced seasonal allergic rhinoconjunctivitis who did not respond adequately to anti-allergic drugs	Subcutaneous immunotherapy with SQ allergen extract for 3 years plus drugs as needed; pharmacotherapy	Model-based study	One double-blind, multi-centre RCT; patient diaries; quality of life patient questionnaire; literature	9 years	The cost-effectiveness of subcutaneous immunotherapy vs pharmacotherapy was in the range of 10 000€–25 000€ per QALY from the perspective of the healthcare system. Subcutaneous immunotherapy was more effective and less expensive from the societal perspective. Cost-effectiveness differences between countries resulted from different practices in the up-dosing phase. Sensitivity analyses confirmed the robustness of findings	Keiding et al. (18)/(25, 27)
DK	CEA	Society	Two hundred and fifty-three 16- to 60-year-old patients (with higher education level than that of Danish population) with grass pollen and mite allergy	Subcutaneous allergy-specific immunotherapy for 3–5 years plus drugs as needed; pharmacotherapy	Evaluation based on before-and-after study	National Health Service records, patient questionnaire (subject to recall bias owing to long time delay)	9 years	Immunotherapy was associated with additional costs of DKK 13 676 per patient as compared to pharmacotherapy. When indirect costs of sick days were also included, immunotherapy was less expensive than pharmacotherapy. The cost per patient year of improved well-being of immunotherapy vs pharmacotherapy was in the range of DKK 16 408 to DKK 2784 depending on the time horizon	Petersen et al. (22)/

Table 1 (continued)

Country	Type	Perspective	Sample	Comparators	Design	Data source	Time horizon	Results	Ref/Ref*
CZ	CEA	Society, third-party payer	Patients with a history of seasonal allergic rhinoconjunctivitis who were uncontrolled with symptomatic medication for at least 2 years	Sublingual allergen immunotherapy with grass pollen extract (drops); subcutaneous allergen immunotherapy with grass pollen extract for 3 years	Trial-based study	RCT, hospital patient questionnaire, literature	3 years	After 3 years, the percentage of clinically improved patients as measured by the Rhinoconjunctivitis Quality of Life questionnaire did not differ: 41% with sublingual immunotherapy vs 48% with subcutaneous immunotherapy; $P > 0.75$. Healthcare costs over 3 years amounted to €416 with sublingual immunotherapy and €482 with subcutaneous immunotherapy per patient ($P < 0.001$). Total healthcare and indirect costs over 3 years amounted to €684 with sublingual immunotherapy and €1004 with subcutaneous immunotherapy per patient ($P < 0.001$). Around 82% vs 68% of total costs were attributed to healthcare costs in the sublingual immunotherapy and subcutaneous immunotherapy groups, respectively (€492 vs €542; $P < 0.001$). Sensitivity analyses confirmed the robustness of findings	Pokladnikova et al. (23)/(6)

CEA, cost-effectiveness analysis; CUA, cost-utility analysis; QALY, quality-adjusted life year; RCT, randomized controlled trial; AT, Austria; CZ, Czech Republic; DE, Germany; DK, Denmark; ES, Spain; FI, Finland; FR, France; IT, Italy; NL, Netherlands; NO, Norway; SE, Sweden; UK, United Kingdom; US, United States.

*Reference to primary economic evaluation/reference to literature review(s) (if applicable).

Table 2 Economic evaluations of immunotherapy for allergic rhinitis

Country	Type	Perspective	Sample	Comparators	Design	Data source	Time horizon	Results	Ref/Ref*
DE	CEA	Society, healthcare system, third-party payer	Patients with seasonal pollen and perennial mite allergic rhinitis	Subcutaneous immunotherapy lasting 3 years for pollen allergy and for mite allergy, continuous pharmacotherapy	Model-based study	Clinical trials, observational studies, epidemiological studies, survey, expert opinion, literature	10 years	The break-even point of cumulative costs between the treatment alternatives (i.e. cumulative costs of immunotherapy equal cumulative costs of pharmacotherapy) was reached in the seventh year. From this point in time, the cumulative difference was in favour of immunotherapy, ending up with savings per patient after 10 years of DM1100–1190 from the societal perspective; DM580-670 from the healthcare system perspective; and DM590-650 from the third-party payer perspective. Over 10 years, 161 additional patients free from asthma symptoms were gained through immunotherapy as compared with pharmacotherapy per 1000 patients. This corresponded to an increment of 0.161 per patient. Therefore, immunotherapy was more effective and less expensive than pharmacotherapy over a 10-year period. The sensitivity analysis demonstrated the robustness of the results. The costs of pharmacotherapy had the highest influence on cost-effectiveness results	Schadlich et al. (24) (25, 28, 30)

Table 2 (continued)

Country	Type	Perspective	Sample	Comparators	Design	Data source	Time horizon	Results	Ref/Ref*
IT	CEA	Society	Adults with persistent allergic rhinitis owing to mites for at least 2 years	Accelerated build-up schedule of subcutaneous immunotherapy with mite extract lasting 3 weeks, traditional build-up schedule of subcutaneous immunotherapy with mite extract lasting 13 weeks	Trial-based study	A prospective, observational, open RCT; physician records; literature; authors' assumptions	1 year	There was no difference between treatments in occurrence of side effects per patient and per injection. Total costs per patient in the build-up phase amounted to 184.40 € with accelerated immunotherapy and 429.35 € with traditional immunotherapy. Accelerated immunotherapy saves costs at equal safety	Mauro et al. (19)

CEA, cost-effectiveness analysis; RCT, randomized controlled trial.

*Reference to primary economic evaluation/reference to literature review(s) (if applicable).

Table 3 Economic evaluations of immunotherapy for asthma

Country	Type	Perspective	Sample	Comparators	Design	Data source	Time horizon	Results	Ref/Ref*
US	CCA	Healthcare system	Patients with at least 1 year of asthma exacerbated by seasonal ragweed exposure	Subcutaneous immunotherapy with ragweed pollen for 2 years plus drugs as needed, pharmacotherapy	Trial-based study	A double-blind, multicentre RCT; patient diaries; literature; authors' assumptions	2 years	During the two treatment years, the mean peak expiratory flow rate was higher in the immunotherapy group (489 ± 16 l/min vs 453 ± 17 in the pharmacotherapy group, $P = 0.06$ during the first year; and 480 ± 12 l/min vs 461 ± 13 in the pharmacotherapy group, $P = 0.03$ during the second year). Medication use was lower in the immunotherapy group than in the pharmacotherapy group during the first treatment year ($P = 0.01$) but did not differ in the two groups during the second year ($P = 0.7$). Asthma symptom scores were similar in the two groups ($P = 0.08$ in year 1 and $P = 0.3$ in year 2). A combined test of peak flow measurements, medication use and asthma symptoms was significant in the first year ($P = 0.003$); results for the second year were not significant. Therefore, the clinical effects of immunotherapy were limited, and many were not sustained for 2 years. The costs of medication were \$597 per season for the pharmacotherapy group and \$420 for the immunotherapy group. The costs for immunotherapy were \$314 the first year and \$213 the second year. Thus, the increased costs of immunotherapy did not offset the reduced medication costs.	Creticos et al. (17)

CEA, cost-effectiveness analysis; RCT, randomized controlled trial.

*Reference to primary economic evaluation/reference to literature review(s) (if applicable).

Table 4 Economic evaluations of immunotherapy for allergic rhinitis and asthma

Country	Type	Perspective	Sample	Comparators	Design	Data source	Time horizon	Results	Ref/Ref*
IT	CCA	Healthcare system	Patients with allergic rhinitis and asthma who were sensitized to house dust mites	Specific sublingual immunotherapy (drops) for 3 years plus drugs as needed, pharmacotherapy	Trial-based study	A prospective RCT, patient and physician diaries, literature	5 years	There was a difference in favour of immunotherapy in terms of bronchial, nasal and global symptom scores after 3 years ($P < 0.001$). Mean patient costs per year with immunotherapy were higher in year 1, the same in year 2 and lower in years 3–5 than with pharmacotherapy. For asthmatic patients, total costs at year 5 amounted to €3881 with immunotherapy and €5020 with pharmacotherapy. Savings increased with disease severity. Thus, immunotherapy was more effective and less expensive than pharmacotherapy in the long run	Ariano et al. (11)
IT	CCA	Healthcare system, society	Young adults with pollen-induced allergic rhinitis and asthma (60% of patients had rhinitis only, 40% had rhinitis and asthma)	Specific sublingual immunotherapy (drops) for 3 years plus drugs as needed, pharmacotherapy	Model-based study	A retrospective, multi-centre cohort study; patient records; literature; authors' assumptions	6 years	For a cohort of 1000 patients, the number of improved patients was 631 with immunotherapy and 232 with pharmacotherapy throughout 6 years. The number of asthma cases avoided was 518 with immunotherapy and 289 with pharmacotherapy. Mean costs per patient over 6 years were €6426 with pharmacotherapy and €4313 with immunotherapy from the societal perspective. Mean costs per patient over 6 years were €2408 with pharmacotherapy and €1901 with immunotherapy from the healthcare system perspective. Immunotherapy was more effective and less expensive than pharmacotherapy from both perspectives and for both effectiveness measures. The sensitivity analysis demonstrated the robustness of results	Berto et al. (14)/(6, 7, 25, 26, 29)

Table 4 (continued)

Country	Type	Perspective	Sample	Comparators	Design	Data source	Time horizon	Results	Ref/Ref*
FR	CEA	Society	Adults and juveniles with dust mite and pollen allergic rhinitis with or without allergic asthma	Specific sublingual immunotherapy (drops) for 3 years for adults and for 4 years for juveniles plus drugs as needed, pharmacotherapy	Model-based study	Literature; expert opinion	6 years for adults 7 years for juveniles	In adults, the costs per asthma case avoided with sublingual immunotherapy were €3158 and €1708 for dust mite and pollen allergy, respectively, as compared with pharmacotherapy. In children, the costs per asthma case avoided with sublingual immunotherapy were €3938 and €824 for dust mite and pollen allergy, respectively, as compared with pharmacotherapy. The sensitivity analysis demonstrated the robustness of results: sublingual immunotherapy is a cost-effective treatment in pollen and dust mite-induced allergic rhinitis and asthma as compared to pharmacotherapy	Omnes et al. (21)/(25, 28, 29)
IT	CEA	Healthcare system, society	Children and adolescents with allergic rhinitis and asthma	Specific sublingual immunotherapy (drops) for 3 years, pharmacotherapy for 1 year	Evaluation based on before-and-after study	A retrospective before-and-after study, patient records, literature	3 years	The mean number of exacerbations was 45.0 with pharmacotherapy and 6.9 with immunotherapy. The mean number of nursery/school days lost was 37.9 with pharmacotherapy and 7.3 with immunotherapy. Mean annual healthcare costs per patient amounted to €506 with pharmacotherapy and €224 with immunotherapy. Mean annual indirect costs per patient amounted to €2166 with pharmacotherapy and €406 with immunotherapy. Mean annual total costs per patient amounted to €2672 with pharmacotherapy and €629 with immunotherapy. Thus, immunotherapy was more effective and less expensive than pharmacotherapy	Berto et al. (13)/(6, 26, 29)

Table 4 (continued)

Country	Type	Perspective	Sample	Comparators	Design	Data source	Time horizon	Results	Ref/Ref*
UK	CUA	Society	Patients with grass pollen-induced allergic rhinitis and asthma	Sublingual immunotherapy with grass allergen tablet for 3 years plus drugs as needed, pharmacotherapy	Trial-based study	A prospective, double-blind, multi-centre RCT; patient diaries; literature	9 years	Mean total costs per patient amounted to £2578 with pharmacotherapy and £3429 with immunotherapy. The number of QALYs gained was 7.198 with pharmacotherapy and 7.395 with immunotherapy. Immunotherapy had an incremental cost-effectiveness ratio of £4319 per QALY as compared to pharmacotherapy. If costs of productivity loss were excluded, the ratio increased to £8816 per QALY. A reduction in the time horizon of the analysis had a negative impact on the cost-effectiveness of immunotherapy. The sensitivity analysis did not alter results. Thus, immunotherapy was cost-effective as compared to pharmacotherapy for patients with allergic rhinitis and asthma	Nasser et al. (20)/(7, 27)
FR	CEA	Society	Adults and juveniles with dust mite and pollen allergic rhinitis with or without allergic asthma	Specific subcutaneous immunotherapy for 3 years for adults and for 4 years for juveniles plus drugs as needed, pharmacotherapy	Model-based study	Literature; expert opinion	6 years for adults 7 years for juveniles	In adults, the incremental costs per asthma case avoided with subcutaneous immunotherapy were €393 and €1327 for dust mite and pollen allergy, respectively, as compared with pharmacotherapy. In children, the incremental costs per asthma case avoided with subcutaneous immunotherapy were €583 and €597 for dust mite and pollen allergy, respectively, as compared with pharmacotherapy. The sensitivity analysis demonstrated the robustness of the results: subcutaneous immunotherapy is a cost-effective treatment in pollen and dust mite-induced allergic rhinitis and asthma as compared to pharmacotherapy.	Omnes et al. (21)/(6, 25, 28, 29)

Table 4 (continued)

Country	Type	Perspective	Sample	Comparators	Design	Data source	Time horizon	Results	Ref/Ref*
IT	CCA	Healthcare system	Patients suffering from seasonal allergic rhinitis and asthma caused by sensitization to <i>Parietaria</i> pollen	Specific subcutaneous Immunotherapy with <i>Parietaria judaica</i> extract for 3 years plus drugs as needed, pharmacotherapy	Evaluation based on cohort study	A prospective cohort study, patient diaries, literature	6 years	There was a significant difference in symptom scores and drug consumption in favour of immunotherapy starting from the first year of treatment and maintaining until the end of the sixth year. Mean annual costs were significantly lower with immunotherapy as compared to pharmacotherapy from the third year of treatment onwards. Annual costs with immunotherapy progressively decreased during the 6-year period (indicating that the need for pharmacotherapy was diminishing with time), whereas annual costs of pharmacotherapy remained unchanged during the 6-year period	Ariano et al. (10)

Table 4 (continued)

Country	Type	Perspective	Sample	Comparators	Design	Data source	Time horizon	Results	Ref/Ref*
DE	CUA	Third-party payer, society	Patients with allergic rhinitis and asthma	Specific subcutaneous immunotherapy for 3 years plus drugs as needed, pharmacotherapy	Model-based study	Literature; expert opinion	15 years	After 15 years, patients with immunotherapy were more likely to have no symptoms, less likely to develop asthma and more likely to avoid more severe disease stages than patients with pharmacotherapy. Total societal costs after 15 years amounted to €26 100 with pharmacotherapy and €24 000 with immunotherapy. The break-even point of cumulative costs between treatment alternatives was reached in the tenth year. From a third-party payer's perspective, annual costs per patient were €750 with immunotherapy and €690 with pharmacotherapy. From the societal perspective, the difference in annual costs and in QALYs was €97 and 0.00764 QALYs for children, respectively; €112 and 0.00760 QALYs for adolescents; €159 and 0.00718 QALYs for adults; and €144 and 0.00730 QALYs for all patients in favour of immunotherapy. From the third-party payer perspective, immunotherapy had a cost-effectiveness ratio of €8874 per QALY for children; €8212 per QALY for adolescents; €8194 per QALY for adults; and €8308 per QALY for all patients as compared to pharmacotherapy. Cost-effectiveness was influenced by the costs of immunotherapy, the target population and the model duration. Thus, immunotherapy was more effective and less expensive than pharmacotherapy from the societal perspective and was cost-effective from the third-party payer perspective	Bruggenjurgen et al. (15)

CCA, cost-consequences analysis; CEA, cost-effectiveness analysis; CUA, cost-utility analysis; QALY, quality-adjusted life year; RCT, randomized controlled trial.

*Reference to primary economic evaluation / reference to literature review(s) (if applicable).

and costs of productivity loss owing to allergic asthma are considered.

Although the authors of the second study claimed to conduct a cost-benefit analysis, they compared healthcare costs with savings from a reduction in sick days only. They did not value health gains by means of, for example, the willingness-to-pay technique (22). Therefore, they carried out a cost-effectiveness analysis using a disease-specific measure (i.e. cost per patient year of improved well-being). This makes it difficult to judge whether subcutaneous immunotherapy is cost-effective. Indeed, it is not possible to compare the cost-effectiveness of subcutaneous immunotherapy in this study with the results from other studies that evaluate immunotherapy in terms of other effectiveness measures. Finally, if the costs of drugs other than those associated with allergy and asthma had been considered by this economic evaluation, the cost-effectiveness of subcutaneous immunotherapy may have been better.

One study conducted an economic evaluation comparing sublingual with subcutaneous allergen immunotherapy for seasonal allergic rhinoconjunctivitis in the Czech Republic (23). The economic evaluation was based on an open-label RCT which suffered from the following limitations: absence of placebo arm, absence of double-blind method and a small sample size. As a result, the statistical analysis had limited validity. The authors observed comparable clinical effectiveness of sublingual immunotherapy and subcutaneous immunotherapy. However, subcutaneous immunotherapy patients showed slightly better improvements in all clinical outcomes. Such improvements may become statistically significant in a study with more patients. The literature indicates that sublingual immunotherapy is associated with less serious systemic adverse effects than subcutaneous immunotherapy (34). However, the sample size of the RCT was too small to observe such a difference between sublingual immunotherapy and subcutaneous immunotherapy. Treatment with sublingual immunotherapy was less expensive than with subcutaneous immunotherapy from the third-party payer perspective and from the societal perspective. The time horizon was limited to 3 years of treatment, and the potential lasting effectiveness following the end of treatment was not considered. No conclusion about the cost-effectiveness of sublingual immunotherapy *vs* subcutaneous immunotherapy can be drawn because of the methodological limitations of this study.

Immunotherapy for allergic conjunctivitis

No articles examining immunotherapy for allergic conjunctivitis were included.

Immunotherapy for allergic rhinitis

Few data are available on the cost-effectiveness of immunotherapy of allergic rhinitis (see Table 2). One economic evaluation showed that subcutaneous immunotherapy is likely to be cost-effective as compared with pharmacotherapy for seasonal as well as perennial allergic rhinitis (24). This economic

evaluation was based on an observational study enrolling 38 patients only. A second economic evaluation found that an accelerated schedule of subcutaneous immunotherapy during the build-up phase offered the same safety, but at lower costs than the traditional schedule (19).

Immunotherapy for asthma

Only one economic evaluation focused on the cost-effectiveness of subcutaneous immunotherapy with ragweed pollen for asthma (see Table 3) (17). This study found that the clinical effects of subcutaneous immunotherapy (in terms of, for example, asthma symptom scores) were limited, and many were not sustained for 2 years. Also, the increased costs of immunotherapy did not offset the reduced medication costs. Therefore, immunotherapy for asthma was not considered to be cost-effective as compared with pharmacotherapy.

Immunotherapy for allergic rhinitis and asthma

Five (11, 13, 14, 20, 21) and three (10, 15, 21) economic evaluations have investigated the cost-effectiveness of sublingual and subcutaneous immunotherapy, respectively, as compared to pharmacotherapy for patients suffering from allergic rhinitis and asthma (see Table 4). These economic evaluations have attempted to explore the cost-effectiveness of immunotherapy under real-life practice circumstances.

The literature consistently finds that immunotherapy for 3 years is cost-effective as compared to pharmacotherapy. This result applies to children, adolescents and adults; seasonal and perennial allergic rhinitis; and different types of allergy. The cost-effectiveness of immunotherapy *vs* pharmacotherapy improves if the lasting effect following cessation of immunotherapy is considered. Immunotherapy becomes more cost-effective when a societal perspective is taken and costs of productivity loss are taken into account. In general, the cost-effectiveness of immunotherapy *vs* pharmacotherapy depends on the target population, the costs of immunotherapy, the model duration and the costs of productivity loss. No economic evaluations have compared sublingual with subcutaneous immunotherapy for allergic rhinitis and asthma.

Discussion

This literature review has summarized the evidence about the cost-effectiveness of immunotherapy for respiratory allergy. On the one hand, the current evidence provides support for the cost-effectiveness of immunotherapy as compared with pharmacotherapy for allergic rhinoconjunctivitis, subcutaneous immunotherapy as compared with pharmacotherapy for allergic rhinitis and immunotherapy as compared with pharmacotherapy for allergic rhinitis and asthma. On the other hand, one economic evaluation suggested that immunotherapy as compared with pharmacotherapy is unlikely to be cost-effective for asthma. To date, the cost-effectiveness of immunotherapy for allergic conjunctivitis has not been investigated.

The cost-effectiveness literature underlines the relevance of the time horizon of an economic evaluation with respect to the consideration of clinical benefits and costs associated with immunotherapy.

With respect to clinical benefits, economic evaluations on immunotherapy as compared with pharmacotherapy indicated that the cost-effectiveness of immunotherapy primarily depends on the duration of the clinical benefit of immunotherapy following treatment cessation (7). For instance, one study showed that a reduction in the time horizon of the analysis had a negative impact on the cost-effectiveness of immunotherapy (20). Data on the duration of clinical benefit of immunotherapy used in economic evaluations were derived from clinical trials or observational studies, the literature, expert opinion or authors' assumptions. For instance, two studies of sublingual immunotherapy for allergic rhinoconjunctivitis were based on the assumption of a clinical benefit lasting at least 6 years following cessation of treatment during 3 years (12, 16). Although assumptions were informed by clinical trials, the quality of the clinical evidence can be questioned and uncertainty surrounds the quantitative estimate of the duration of clinical benefit following cessation of immunotherapy (27).

With respect to costs, the cost-effectiveness of immunotherapy as compared with pharmacotherapy depends on the break-even point of cumulative costs between treatment alternatives (i.e. point in time when cumulative costs of immunotherapy equal cumulative costs of pharmacotherapy). Immunotherapy (plus drugs as needed) tends to be more expensive during the first years of treatment, but cumulative costs of pharmacotherapy start to exceed those associated with immunotherapy at a later stage when immunotherapy has stopped, but its clinical benefit is maintained. The break-even point tends to differ between economic evaluations and cannot be transferred given that, for instance, cost estimates reported in economic evaluations are specific to the study setting and unlikely to be generalizable.

No economic evaluation involved a direct comparison of sublingual with subcutaneous immunotherapy, except for one study that did not give a conclusive answer because of methodological limitations (23). Therefore, the question of the cost-effectiveness of sublingual *vs* subcutaneous immunotherapy has not been resolved to date. The literature does suggest that any future economic evaluation needs to consider such aspects as safety profile, compliance rate and administration costs, which may affect the cost-effectiveness of sublingual *vs* subcutaneous immunotherapy (6).

The literature on the cost-effectiveness of immunotherapy for respiratory allergy consisted of studies conducted in Europe and in the United States. The results of these studies should be interpreted with care when assessing their generalizability to another country. This is because, amongst other things, the patient population and the specific types of immunotherapy used are likely to vary between countries. Also, the funding, organization, regulation and real-life practices governing immunotherapy for respiratory allergy vary between countries.

Some economic evaluations included direct healthcare costs from the perspective of the third-party payer or the

healthcare system. As a result, these studies focused on the costs of immunotherapy and examined the cost impact of immunotherapy on the use of medicines, physician consultations and hospitalization. However, such studies did not consider the impact of immunotherapy on time off work or time off school. This is especially relevant in the case of respiratory allergy as the literature shows that respiratory allergy harms work and school performance (35, 36). The evidence consistently demonstrates that the cost-effectiveness of immunotherapy for respiratory allergy improves when indirect costs of productivity loss are considered from the societal perspective. The impact of immunotherapy on school performance has not been considered in economic evaluations to date.

Existing economic evaluations employed a variety of outcome measures, such as the peak expiratory flow rate, symptom scores, the number of symptom-free days, the number of patients free from symptoms and the number of exacerbations. This makes it difficult to compare cost-effectiveness results between studies. Existing economic evaluations of respiratory allergy have shown that improvement in these outcome measures resulting from immunotherapy translate into better quality of life (12, 15, 16, 18, 20). However, there is a need for additional economic evaluations that consider quality of life by means of instruments such as the Rhinoconjunctivitis Quality of Life Questionnaire (37) or the EuroQol-5D (38). The latter instrument can be used to calculate quality-adjusted life years and to express the cost-effectiveness of immunotherapy in terms of the additional costs per quality-adjusted life year gained as compared to the alternative. The cost-effectiveness of immunotherapy can then be assessed by comparing it with the threshold value set by the healthcare payer. For instance, the National Institute for Health and Clinical Excellence in England and Wales uses a threshold value of £20 000–£30 000 per quality-adjusted life year (39), which determines which health technologies will be recommended for use by the National Health Service.

Economic evaluations of immunotherapy for respiratory allergy were carried out alongside clinical studies or drew on decision-analytic modelling techniques. Analyses based on RCTs provide a degree of internal validity, while analyses based on observational studies reflect real-life practice. Alternatively, the use of modelling techniques critically depends on the study design and the quality of data that are extracted from the literature or other sources and are used as input in the cost-effectiveness model (9).

Existing economic evaluations suffered from a number of methodological limitations including small sample sizes, short time horizon, lack of standardized effectiveness measures and restricted scope of costs. More attention needs to be paid by researchers to set up economic evaluations that are appropriately designed to explore the cost-effectiveness of immunotherapy for respiratory allergy. In many existing model-based economic evaluations, extensive sensitivity analyses have been carried out to examine the impact of changes in input parameters on cost-effectiveness results. These sensitivity analyses have corroborated the robustness of cost-effectiveness results.

When setting up future economic evaluations of immunotherapy for respiratory allergy, there is a need for economic

evaluations based on high-quality prospective and long-term clinical studies comparing immunotherapy with pharmacotherapy in real-life practice, especially for allergic conjunctivitis. Future studies also need to validate the few current results on the cost-effectiveness of immunotherapy for allergic rhinitis and for asthma. Additional research is required to calculate the cost-effectiveness of sublingual vs subcutaneous immunotherapy for respiratory allergy.

Conclusions

The international literature suggests that immunotherapy is cost-effective as compared with pharmacotherapy for allergic rhinoconjunctivitis and for allergic rhinitis in combination with asthma. Subcutaneous immunotherapy appears to be cost-effective for allergic rhinitis. One economic evaluation suggested that immunotherapy as compared with pharmacotherapy is unlikely to be cost-effective for asthma. The reader should note that this evidence originated from a limited number of economic evaluations that suffered from a number of methodological shortcomings. The question of the

cost-effectiveness of sublingual vs subcutaneous immunotherapy has not been resolved to date. No economic evaluation has examined the cost-effectiveness of immunotherapy for allergic conjunctivitis.

Acknowledgments

Financial support for this study was received from the Belgian National Institute for Health and Disability Insurance. The author would like to thank Valérie Storms for her contribution to the identification of relevant studies.

Author contributions

SS designed and carried out the literature review and wrote the manuscript.

Conflict of interest

The author has no conflicts of interest that are directly relevant to the content of this manuscript.

References

1. Brozek JL, Bousquet J, Baena-Cagnani CE, Bonini S, Canonica GW, Casale TB et al. Allergic rhinitis and its impact on asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol* 2010;**126**:466–476.
2. Simoens S, Laekeman G. Pharmacotherapy of allergic rhinitis: a pharmaco-economic approach. *Allergy* 2009;**64**:85–95.
3. Meltzer EO, Bukstein DA. The economic impact of allergic rhinitis and current guidelines for treatment. *Ann Allergy Asthma Immunol* 2011;**106**:S12–S16.
4. Goetzel RZ, Long SR, Ozminkowski RJ, Hawkins K, Wang S, Lynch W. Health, absence, disability, and presenteeism cost estimates of certain physical and mental health conditions affecting U.S. employers. *J Occup Environ Med* 2004;**46**:398–412.
5. Hellgren J, Cervin A, Nordling S, Bergman A, Cardell LO. Allergic rhinitis and the common cold—high cost to society. *Allergy* 2010;**65**:776–783.
6. Incorvaia C, Masieri S, Berto P, Scurati S, Frati F. Specific immunotherapy by the sublingual route for respiratory allergy. *Allergy Asthma Clin Immunol* 2010;**6**:29.
7. Walker SM, Durham SR, Till SJ, Roberts G, Corrigan CJ, Leech SC et al. Immunotherapy for allergic rhinitis. *Clin Exp Allergy* 2011;**41**:1177–1200.
8. Drummond M, Brown R, Fendrick AM, Fullerton P, Neumann P, Taylor R et al. Use of pharmacoeconomics information—report of the ISPOR Task Force on use of pharmacoeconomic/health economic information in health-care decision making. *Value Health* 2003;**6**:407–416.
9. Drummond M, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. *Methods for the Economic Evaluation of Health Care Programmes*, edn 3. Oxford: Oxford University Press, 2005.
10. Ariano R, Berto P, Tracci D, Incorvaia C, Frati F. Pharmacoeconomics of allergen immunotherapy compared with symptomatic drug treatment in patients with allergic rhinitis and asthma. *Allergy Asthma Proc* 2006;**27**:159–163.
11. Ariano R, Berto P, Incorvaia C, Di CG, Boccardo R, La GS et al. Economic evaluation of sublingual immunotherapy vs. symptomatic treatment in allergic asthma. *Ann Allergy Asthma Immunol* 2009;**103**:254–259.
12. Bachert C, Vestenbaek U, Christensen J, Griffiths UK, Poulsen PB. Cost-effectiveness of grass allergen tablet (GRAZAX) for the prevention of seasonal grass pollen induced rhinoconjunctivitis – a Northern European perspective. *Clin Exp Allergy* 2007;**37**:772–779.
13. Berto P, Bassi M, Incorvaia C, Frati F, Puccinelli P, Giaquinto C et al. Cost effectiveness of sublingual immunotherapy in children with allergic rhinitis and asthma. *Eur Ann Allergy Clin Immunol* 2005;**37**:303–308.
14. Berto P, Passalacqua G, Crimi N, Frati F, Ortolani C, Senna G et al. Economic evaluation of sublingual immunotherapy vs symptomatic treatment in adults with pollen-induced respiratory allergy: the Sublingual Immunotherapy Pollen Allergy Italy (SPAII) study. *Ann Allergy Asthma Immunol* 2006;**97**:615–621.
15. Bruggenjurgen B, Reinhold T, Brehler R, Laake E, Wiese G, Machate U et al. Cost-effectiveness of specific subcutaneous immunotherapy in patients with allergic rhinitis and allergic asthma. *Ann Allergy Asthma Immunol* 2008;**101**:316–324.
16. Canonica GW, Poulsen PB, Vestenbaek U. Cost-effectiveness of GRAZAX for prevention of grass pollen induced rhinoconjunctivitis in Southern Europe. *Respir Med* 2007;**101**:1885–1894.
17. Creticos PS, Reed CE, Norman PS, Khoury J, Adkinson NF Jr, Buncher CR et al. Ragweed immunotherapy in adult asthma. *N Engl J Med* 1996;**334**:501–506.
18. Keiding H, Jorgensen KP. A cost-effectiveness analysis of immunotherapy with SQ allergen extract for patients with seasonal allergic rhinoconjunctivitis in selected European countries. *Curr Med Res Opin* 2007;**23**:1113–1120.
19. Mauro M, Russello M, Alesina R, Sillano V, Alessandrini A, Dama A et al. Safety and pharmacoeconomics of a cluster administration of mite immunotherapy compared to the traditional one. *Eur Ann Allergy Clin Immunol* 2006;**38**:31–34.
20. Nasser S, Vestenbaek U, Beriot-Mathiot A, Poulsen PB. Cost-effectiveness of specific immunotherapy with Grazax in allergic rhinitis co-existing with asthma. *Allergy* 2008;**63**:1624–1629.
21. Omnes LF, Bousquet J, Scheinmann P, Neukirch F, Jasso-Mosqueda G, Chicoye A et al. Pharmacoeconomic assessment of specific immunotherapy versus current symptomatic treatment for allergic rhinitis and

- asthma in France. *Eur Ann Allergy Clin Immunol* 2007;**39**:148–156.
22. Petersen KD, Gyrd-Hansen D, Dahl R. Health-economic analyses of subcutaneous specific immunotherapy for grass pollen and mite allergy. *Allergol Immunopathol (Madr)* 2005;**33**:296–302.
 23. Pokladnikova J, Krcmova I, Vlcek J. Economic evaluation of sublingual vs subcutaneous allergen immunotherapy. *Ann Allergy Asthma Immunol* 2008;**100**:482–489.
 24. Schadlich PK, Brecht JG. Economic evaluation of specific immunotherapy versus symptomatic treatment of allergic rhinitis in Germany. *Pharmacoeconomics* 2000;**17**:37–52.
 25. Berto P, Frati F, Incorvaia C. Economic studies of immunotherapy: a review. *Curr Opin Allergy Clin Immunol* 2008;**8**:585–589.
 26. Ciprandi G, Agostinis F, Amoroso S, Ariano R, Barbato A, Bassi M et al. Economic evaluation of sublingual immunotherapy: an analysis of literature. *Eur Ann Allergy Clin Immunol* 2007;**39**:21–26.
 27. Hagen A, Gorenio V, Schonermark MP. Specific immunotherapy (SIT) in the treatment of allergic rhinitis. *GMS Health Technol Assess* 2010;**6**:Doc01.
 28. Incorvaia C, Agostinis F, Amoroso S, Ariano R, Barbato A, Bassi M et al. Pharmacoeconomics of subcutaneous allergen immunotherapy. *Eur Ann Allergy Clin Immunol* 2007;**39**:17–20.
 29. Incorvaia C, Ariano R, Berto P, Ciprandi G, Leo G, Boccardo R et al. Economic aspects of sublingual immunotherapy. *Int J Immunopathol Pharmacol* 2009;**22**:27–30.
 30. Reed SD, Lee TA, McCrory DC. The economic burden of allergic rhinitis: a critical evaluation of the literature. *Pharmacoeconomics* 2004;**22**:345–361.
 31. Poulsen PB, Pedersen KM, Christensen J, Vestenbaek U. Economic evaluation of a tablet-based vaccination against hay fever in Denmark. *Ugeskr Laeger* 2008;**170**:138–142.
 32. Valovirta E, Berstad AK, de BJ, Bufe A, Eng P, Halken S et al. Design and recruitment for the GAP trial, investigating the preventive effect on asthma development of an SQ-standardized grass allergy immunotherapy tablet in children with grass pollen-induced allergic rhinoconjunctivitis. *Clin Ther* 2011;**33**:1537–1546.
 33. Durham SR, Emminger W, Kapp A, de Monchy JG, Rak S, Scadding GK et al. SQ-standardized sublingual grass immunotherapy: confirmation of disease modification 2 years after 3 years of treatment in a randomized trial. *J Allergy Clin Immunol* 2012;**129**:717–725.
 34. Wilson DR, Lima MT, Durham SR. Sublingual immunotherapy for allergic rhinitis: systematic review and meta-analysis. *Allergy* 2005;**60**:4–12.
 35. Blaiss MS. Allergic rhinitis and impairment issues in schoolchildren: a consensus report. *Curr Med Res Opin* 2004;**20**:1937–1952.
 36. Blanc PD, Trupin L, Eisner M, Earnest G, Katz PP, Israel L et al. The work impact of asthma and rhinitis: findings from a population-based survey. *J Clin Epidemiol* 2001;**54**:610–618.
 37. Juniper EF, Guyatt GH. Development and testing of a new measure of health status for clinical trials in rhinoconjunctivitis. *Clin Exp Allergy* 1991;**21**:77–83.
 38. The EuroQol Group. EuroQol—a new facility for the measurement of health-related quality of life. *Health Policy* 1990;**16**:199–208.
 39. Raftery J. Review of NICE's recommendations, 1999–2005. *BMJ* 2006;**332**:1266–1268.