

## ORIGINAL ARTICLES

# Health-Economic Analyses of subcutaneous Specific Immunotherapy for grass pollen and mite allergy

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### ABSTRACT

**Objective:** To investigate the health and monetary consequences of treating allergy with specific immunotherapy (SIT) compared with symptomatic treatment/standard care among patients with grass pollen or mite allergy.

**Methods:** We performed an economic analysis based on 253 grass- and/or mite allergic patients who started SIT from 1.1.1996 to 1.1.2002 at the Allergy Unit, Aarhus University Hospital and at a specialist practice in Aarhus. Relevant data were collected before, during and after SIT treatment from the national health service based on each patient's personal identification number and medical records and from a specifically designed questionnaire. A cost-benefit analysis including direct and indirect costs before, during and after SIT was performed. In addition direct costs were related to the clinical effect (improvement in well-being) in the form of a cost-effectiveness analysis.

**Results:** The direct cost per patient/year before SIT (equivalent to standard care) was DKK 2,580. The investment in SIT was DKK 27,545 (in present values) per patient over a 4-year period. After SIT the

cost was reduced to DKK 1,072 per patient/year. In the long term, prospective introduction of SIT incurred additional present-value direct costs of DKK 13,676 per patient treated and DKK 2,784 per patient/year of improved well-being. However, when indirect costs were included in the economic evaluation SIT was shown to be net beneficial.

**Conclusion:** This study reveals that SIT is associated with initial resource investments and subsequent resource savings in the long term compared with standard care. When all consequences are measured in monetary terms, and assuming that sick days are associated with a loss of productivity, this analysis suggests that SIT increases societal welfare. This conclusion also holds if there is no loss of productivity.

**Key words:** Health-economic analysis. Cost-effectiveness analysis. Cost-benefit analysis. Allergic rhinitis. Grass pollen. Mite allergy. Immunotherapy.

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### INTRODUCTION

Allergic asthma and rhino conjunctivitis are common diseases in westernised countries and the prevalence in Denmark is about 20 %<sup>1</sup>. These diseases impair both physical, psychological and cognitive functions and reduce the patient's quality of life<sup>2,3</sup>. Intervention against allergic disease can be done by pharmacological intervention in the form of symptomatic treatment in this study called Standard Care (SC), by allergen avoidance and by allergy specific immunotherapy (SIT)<sup>4</sup>. Allergy to air-

borne substances often results in multi organ manifestations and symptoms from eyes, nose and lungs. Many patients require 3-6 different drugs several times a day, which was also the case for the patients in this study. Among the advantages of SIT is its capacity to interfere with the pathophysiological mechanisms of allergic inflammation, with a potential for a prolonged effect or cure compared to pharmacological treatment, which only reduces symptoms during administration with no long-term preventive capacity<sup>5</sup>. Controlled studies have documented that SIT significantly increases the quality of life, reduces symptoms, reduces the risk of developing new allergies<sup>6,7</sup> and reduces the risk of asthma manifestations in patients with rhino conjunctivitis<sup>8,9</sup>. In addition, SIT results in significant reductions in medicine use for allergic asthma and rhino conjunctivitis<sup>8,10,11</sup>. Few studies have addressed the economic outcomes and the cost effectiveness of SIT<sup>12</sup>. The purpose of the present study is to contribute with knowledge about the relative merits of SIT and SC.

## METHODS

Data on all costs were collected irrespective of payer. Hence, the study applies a societal perspective. Resource consequences from a health care sector perspective as well as a patient perspective are also presented. Results are presented in the form of a cost-benefit analysis (CBA) and a cost-effectiveness analysis (CEA) in which measure of effect is person year of improved psychological wellbeing.

A total of 253 16-60 year old patients who had started SIT during the period 1.1.1996-1.1.2002 were retrospectively enrolled in the study from the Allergy Unit, Aarhus University Hospital (52 patients) and from a specialist practice in Aarhus (201 patients). A questionnaire was sent by post to the enrolled patients. 204 (81 %) completed and returned the questionnaire. The SIT treated patients had gone through an up dosing phase lasting approximately 15 weeks followed by a maintenance phase lasting 3-5 years. In the up dosing phase the patients were vaccinated once a week. In the maintenance phase they were vaccinated every 6-8 weeks.

In the questionnaire the respondents were asked to describe whether they had experienced a change in their quality of wellbeing (psychological) in connection with SIT (follow-up time ranged from 1 to 7 years). The quality of wellbeing was stated on a five point scale; whether the respondents thought SIT had improved their wellbeing a lot, a little, no

change, or if SIT had aggravated their wellbeing a little or a lot. The patients also had to state if they thought the advantages with SIT were greater than the disadvantages.

The following direct costs were estimated; 1. medicine use, 2. visits to medical doctors, 3. visits to emergency rooms, visits to doctors on emergency duty and hospital stays pre, per and post SIT. Patient costs associated with SIT treatment were also registered by way of 4. transportation costs and 5. time costs. Indirect costs in form of productivity costs and loss of leisure time were calculated by asking respondents to indicate how many work days and leisure days, respectively, were affected by allergy and asthma to such an extent that they could be described as sick days (6. work related sick days or 7. leisure activity sick days). Indirect costs were registered for the period's pre, per and post SIT.

## Cost of medicine

Cost of medicine use was calculated applying pharmacy recommended retail prices ultimo November 2002. The study only includes allergy and asthma medicine defined according to Anatomical Therapeutic Chemical Classification System (ATC). Medicine use was extracted from the National Health Service in the county of Aarhus based on each patient's personal identification number. The registry only included person specific data for the latest 16 months. Hence, in order to acquire information on pre SIT medicine consumption it was necessary to collect information from a different cohort: 53 persons that had started SIT for either grass-pollen or mite allergy in the period 1.11.2002-1.2.2003. This cohort's medicine use was registered for the period 1.11.2001-1.11.2002. The post SIT medicine use was based on patients who had finished SIT. Data was registered for the period 1.1.2002-1.8.2002 and subsequently extrapolated to a 12 month period.

## Cost of medical doctors

Information on the use of medical doctors (general practitioners as well as specialists) was obtained from the local county authorities of Aarhus for the period 1.1.1997-1.8.2002. This registry only stores data for a period of 5 years; hence it was not possible to register visits to doctors for those 26 patients who initiated SIT in 1996. Unit prices were based on doctor's fees as negotiated with the National Health Service year 2002.

### Cost of emergency rooms, doctor on emergency duty and hospital

In the questionnaire respondents were asked to state how many times they had been in contact with emergency rooms, doctors on emergency duty and hospitals pre, per and post SIT. Information about the incident was subsequently acquired from the hospital. Costs were estimated using the Diagnosis Related Group rate (DRG). All prices were translated to 2002 prices.

### Cost of transportation

Respondents were asked to state how many kilometres they had travelled in order to receive SIT. It was assumed that the cost per kilometre travelled was 2.84 DKK. (This figure is equivalent to the Danish mileage allowance anno 2002).

### Cost of time

Number of vaccinations in the up dosing phase was approximated to 15 and the number of vaccinations in the maintenance phase was approximated to 26. The respondents were asked to specify how much time they had used per up dosing and per maintenance vaccination. The respondents were also asked to state if they had used work time and/or leisure time for the vaccinations. The work/leisure time fragment was stated on a scale from; 100 % work time, 75 % work time and 25 % leisure time, 50 % work time and 50 % leisure time, 75 % leisure time and 25 % work time or 100 % leisure time. Leisure time and work time was valued as described in the next section.

### Cost of work related and leisure sick days

One sick day was approximated to 7.5 hours. In valuing the productivity loss associated with one work hour lost the mean gross income per hour was applied. Hours of leisure were valued equivalent to net income. The argument being that individuals choose to work until the value of their time is equal to the compensation they receive for working, which is equivalent to income net of tax. A Danish person in the labour force aged 16-60 years had a mean gross income of DKK 205 per hour and a mean net income of DKK 100 per hour in 2002 (Denmark's Statistics).

### Cost benefit analysis (CBA) and cost effectiveness analysis (CEA)

A CBA is performed which includes direct costs and indirect costs. Indirect costs encompass the monetary value of experiencing sick days. Where lost work days incur costs to society in terms of lost productivity, being sick in ones leisure time incurs loss of quality-of-life. Quality of life gains due to fewer sick days in ones leisure time can be measured in monetary terms by way of net income. Net income reflects the loss of time for performing leisure activities, but does not necessarily reflect the disutility associated with being sick per se. Patient may thus value reduction in sick days higher than is indicated by the calculations based on net income. Hence the method applied here is likely to produce a conservative estimate.

The CEA includes all direct costs and a non-monetary measure of psychological well-being. In this analysis the value of fewer sick days in ones leisure time is incorporated in the effect measure as the impact of psychological well-being of having days off work and possibly losing own net income. However, the possible loss of productivity which society experiences (i.e. the tax component) is not included. Resource consequences are related to health outcomes by way of an incremental cost effectiveness ratio (ICER):

$$ICER = \frac{CostSIT - CostSC}{EffectSIT - EffectSC} = \frac{\Delta Cost}{\Delta Effect}$$

Where effect is measured as number of patient years in which psychological well-being is improved and costs are measured from a societal perspective. ICERs are reported excluding indirect costs. Costs and outcomes are discounted by 5 % p.a. and reported in present values.

There is evidence from the literature that the effect of SIT lasts three to six years after three years of treatment<sup>5,13</sup>. Consequently, we chose to extrapolate post SIT results to a period of five years.

Statistics Package for the Social Science (SPSS 11.0) was used for analyse. When analysing the differences in the measured parameters pre/per/post SIT the distribution of answers were tested for normal distribution by use of Kolmogorov-Smirnov test. McNemar test was used for dichotomy paired data, and Wilcoxon's Signed Ranks Test was used for ordinal paired data<sup>14</sup>. Permission was obtained from the National Danish Data Inspection to establish a private research register. Ethics committee for the county of Aarhus had no objections to the study and did not find the project needed permission from the committee.

### Data from the study population

The whole study population constituted 55.3 % men and 44.7 % women. Mean age was 29.2 years, median age 28.2 years. 42.1 % had a medium-long or an academic education. Amongst those who answered the questionnaire 50.5 % were men and 49.5 % were women. There was significantly more males among non-responders OR 3.0 (C.I. 95 % 1.5-6.2) and among non-responders there were a greater proportion of individuals with a follow up time of more than 4 years OR 3.2 (C.I. 95 % 1.5- 6.7). Non-responders did not distinguish themselves from responders in any other way.

A total of 15.2 % of respondents had 1-2 years of further education, 24.0 % had further education lasting 3-4 years and 18.1 % had more than 4 years of further education

Most of the patients were vaccinated with one allergen (68.0 % grass pollen, 9.5 % house dust mites). The rest were vaccinated against either grass or mites in combination with other allergens. 94 % (95 % CI 90-97) of participants completed the up dosing phase.

## RESULTS

As much as 75 % (95 % CI 69-80) of the respondents found that the advantages of SIT were greater than the disadvantages. A total of 67.2 % of the vaccinated patients experienced improvements in their psychological wellbeing: 39.7 % of respondents stated it had improved a lot and 27.5 % stated it had improved a little. The percentage of respondents who stated that their psychological wellbeing remained unchanged was 27.5, whereas 4.4 % stated that their wellbeing was aggravated a little and 1 % stated it was aggravated a lot.

### Cost of medicine

Pre SIT median medicine use was estimated to DKK 1,925 per person per year. The medicine used for an up dosing kit was DKK 1,688 per person. The median medicine consumptions (including medication used for maintenance) per person during SIT was DKK 2,395 per patient-year during the 4 year period. 34 patients in the study had finished SIT. Those 34 persons' mean medicine use was estimated to DKK 497 per year. In Denmark direct costs of medicine are covered by the National Health System, with approximately 32 % of expenses financed through co-payment (see table I).

### Costs of medical doctors

Mean resource use pre SIT was estimated to DKK 609 per patient-year. In the 1st year of SIT the mean resource use was estimated to DKK 3,247 per patient-year. The cost was DKK 2,525, DKK 1,264 and DKK 1,041 in the 2nd, 3rd and 4th patient-year, respectively. Post SIT (5 and 6 years after SIT was initiated) the resource use was estimated to DKK 825 per patient-year. Direct costs to medical doctors are paid by the National Health Service (see table I).

### Cost of emergency rooms, doctor on emergency duty and hospital

Mean annual resource use per person was DKK. 46 pre SIT, DKK 127 per SIT and DKK 13 post SIT. All costs are covered by the National Health Service (see table I).

### Resources used for transportation

203 respondents reported that they had travelled a total of 126,420 km (mean travel per respondent: 623 km) during the up-dosing phase, 196 respondents reported the distance travelled in order to receive maintenance vaccination for the whole maintenance period. This amounted to a total of 71,032 km with a mean of 362 km per respondent over the 4 year period. The costs were estimated to DKK 2,797 for a full vaccination program per patient. The patients' mean transport cost was for the 1st year of SIT estimated to DKK 2,026 and DKK 257 for each of the following years during SIT. Transport costs are covered by the patients (see table I).

### Time costs

All 204 respondents had stated their use of time for the up dosing phase; mean time was 94.7 min (range 25-600 min.) per vaccination. In the maintenance period 197 respondents had stated their use of time; mean time was 65.9 min (range 10-600 min.) per vaccination. 202 respondents had categorised the time used. Most of the patients had used leisure time. Based on the fractions of work/leisure time and the valuations of productive and leisure time patients spent time equivalent to DKK 211.20 per up dosing and DKK 146.90 per maintenance visit. The patients' mean time cost was for the 1st year of SIT estimated to DKK 4,123, and DKK 955 for each of the following years during SIT. Direct time costs represent patient costs (see table I).

**Table I**  
**Costs per patient-year before, during and after (Pre, Per and Post) treating allergy with Specific Immunotherapy (SIT). 2002 prices**

Resource	Health care system perspective						Patient perspective				Societal perspective							
	<sup>a</sup> Pre	<sup>a</sup> 1 <sup>st</sup>	<sup>a</sup> 2 <sup>nd</sup>	<sup>a</sup> 3 <sup>rd</sup>	<sup>a</sup> 4 <sup>th</sup>	Post	<sup>a</sup> Pre	1 <sup>st</sup>	<sup>b</sup> Per	Post	<sup>a</sup> Pre	<sup>a</sup> 1 <sup>st</sup>	<sup>a</sup> 2 <sup>nd</sup>	<sup>a</sup> 3 <sup>rd</sup>	<sup>a</sup> 4 <sup>th</sup>	Per total	Post	
Direct cost																		
1. Medicine	1309	2776	1629	1629	1629	338	616	1307	766	159	1925	4083	2395	2395	2395	11268	497	
2. Doctors	609	3247	2525	1264	1041	825					609	3247	2525	1264	1041	8077	825	
3. EHD <sup>c</sup>	46	127	127	127	127	13					46	127	127	127	127	508	13	
4. Transport								2026	257			2026	257	257	257	2797		
5. Time								4123	955			4123	955	955	955	6988		
Total direct cost	1964	6150	4281	3020	2797	1176	616	7456	1978	159	2580	13606	6259	4998	4775	29638	1335	
*PV direct cost	<b>1964</b>					<b>944</b>	<b>616</b>			<b>128</b>	<b>2580</b>	13278	5817	4424	4025	<b>27545</b>	<b>1072</b>	
Indirect cost																		
6. Sick days work <sup>d</sup>							4105	984	984	907	4105	984	984	984	984	3936	907	
7. Sick days leisure time							9600	2258	2258	2205	9600	2258	2258	2258	2258	9030	2205	
Total direct + indirect cost	1964	6150	4281	3020	2797	1176	14321	10698	5220	3271	16285	16848	9501	8240	8017	42604	4447	
*PV Total	<b>1964</b>					<b>944</b>	<b>14321</b>			<b>2626</b>	<b>16285</b>	16441	8830	7293	6758	<b>39323</b>	<b>3570</b>	

<sup>a</sup>Cost during 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup> and 4<sup>th</sup> year of SIT.

<sup>b</sup>The same cost during 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup> year of SIT.

<sup>c</sup>Emergency room, hospital and doctors on emergency duty.

<sup>d</sup>This cost is in many cases not the patients but rather the employers

<sup>e</sup>Pre ~ Standard Care (SC) which is mainly symptomatic treatment.

\*Present Value

### Cost of work related and leisure sick days

There were significant reductions in the number of sick days experienced by respondents after SIT was initiated ( $P < 0.001$  Wilcoxon's Signed Rank test). Before initiating SIT respondents had on average 2.67 sick days per annum which entailed that they had to take the day off from work, whereas the annual number of days off from work amounted to 0.64 during SIT and 0.59 post SIT. In addition, respondents experienced on average 12.80 sick days per annum in their leisure time before initiation of SIT, 3.01 days during SIT and 2.94 days post SIT. The productivity loss associated with loss of work days was estimated to on average DKK 4,105 per person-year pre SIT, to DKK 984 per person-year during SIT and to DKK 907 per person-year post SIT. The value of lost leisure time was estimated to DKK 9,600 per person-year pre SIT, to DKK 2,258 per person-year during SIT and to DKK 2,205 per person-year post SIT (see table I).

The present value of the investment in SIT over the four year period excluding indirect costs was calculated to DKK 27,545. The present value of SC during the same period was estimated to be DKK 9,374.

Over the initial four years SIT is more costly and incurs an added cost of DKK 18,170 (in present value). In subsequent years following SIT annual costs fall to DKK 1,335. This represents a cost saving of 1,245 relative to the annual cost of SC. The present value of saving DKK 1,245 annually 4 years from now and over a 5 year period is DKK 4,544. A longer term perspective reduces the added direct costs of SIT, but there remains a net incurred cost of DKK 13,626.

When indirect costs are included in the calculations, the present value of the investment in SIT over the four year period is calculated to DKK 39,323 whereas the present value of SC over the same period is DKK 59,172. This means there is a net saving to society of DKK 19,849 over the initial four years after commencement of SIT. In subsequent years SIT incurs a net saving of DKK 11,838 per annum. The present value of saving DKK 11,838 annually 4 years from now and over a 5 year period is DKK 43,207. Long term consequences of SIT would be a net saving of DKK 63,056. On the basis of the CBA in which we measure the value of time spent in a sick state in monetary terms, we can conclude that the investments in SIT are justified by the incurred benefits in subsequent years.



## Change in wellbeing and CEA

67.2 % of the respondents experienced an improvement in their wellbeing over the 1 to 7 year observation period after SIT was initiated. The fraction of patients experiencing an improvement remained close to constant over the follow-up period. Direct costs per year of improved well-being was estimated for each year during and post SIT. ICER was estimated for each year during and post SIT, (see fig. 1).

## DISCUSSION

The chosen quasi experimental design was effective for this pragmatic study as it was possible in a relative short period to recruit many patients that had initiated SIT. The weakness of the design was the time delay because of a potential recall bias. Recall bias may underestimate or overestimate the effects of SIT depending on the nature of the bias. The best alternative design would have been a prospective follow up study.

The effects found in this investigation can be biased by the fact that the study included no control group (placebo effect). On the other hand many other studies indicate the same effects<sup>15-20</sup>. And in a controlled study patients are monitored and evaluated to an extent that does not occur in usual clinical practise and results are generated from an ideal setting. This bias is not influencing the present retrospective data that reflect a real world setting.

The up dosing phase which lasted only 3-4 months was almost as expensive as the maintenance phase that lasted approximately 4 years. There are several explanations for this. Firstly, a specialist doctor is more expensive than a GP. Secondly, the distance to the specialist practice was longer than to the patients GP, which both means greater transport expenses and greater use of time for the patients during the up dosing phase. The CEA estimates in this study are likely to be conservative for several reasons. The CEA used a mileage allowance of DKK 2.84. The appropriateness of applying this mileage allowance is questionable since it is not necessarily a good proxy for the actual costs incurred. It should also be noted that transportation costs are ignored both pre and post SIT. Consequently, transport costs may overestimate the costs of SIT relative to SC thus rendering SIT less cost effective.

The use of register data from the county of Aarhus' National Health System formed the basis for estimating medicine consumption. In this CEA we only included the types of medicine that according to the ATC grouping could be characterised as allergy/asthma medicine.

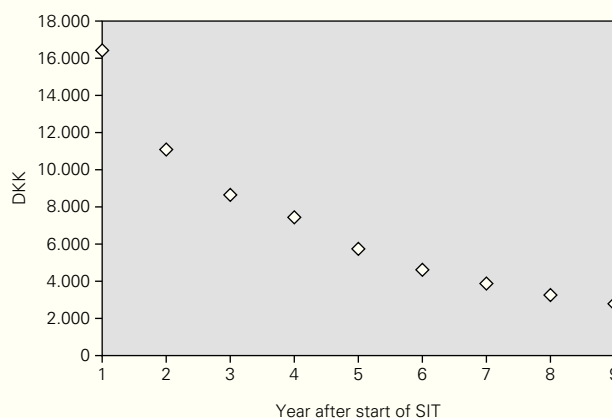


Figure 1.—Cumulated present value of ICER per year in DKK for improvement in psychological wellbeing during and after SIT. 2002 prices.

In other studies it has been proven that allergy is increasingly associated with co-morbidity<sup>2,21</sup>. Reduction in medicine consumption due to SIT may thus be underestimated in the present study, and consequently cost-effectiveness may be underestimated. Furthermore, the post SIT use of medicine was based on the period 1.1.2002-1.8.2002 and then extrapolated to 12 months. This 7 month period included the grass pollen season, which is a period in which medicine use for allergy/asthma is increased. Therefore, the estimated medicine consumption post SIT is likely to be overestimated.

Use of medical doctors increased with the initiation of SIT and continued to be greater post SIT compared to pre SIT. The difference in resource use did however decline significantly. During the fourth year of SIT the added use of medical doctors was valued to DKK 432. Post SIT the added cost was DKK 216. In our analysis we assume that in the subsequent years post SIT the use of medical doctors remains higher than for SC, but it may be that a longer observation period would disclose that the difference is annulled some years after SIT is finalised. This would improve the cost effectiveness of SIT.

In the present study we performed a CBA in which all items – including the value of productive time and leisure time were estimated in monetary terms. When calculating the value of productive time we assumed that any time away from work entails a reduction in productivity and hence a loss to society. To the extent that persons suffering from allergy manage to fulfil their obligations at work despite the sick days, the indirect costs are clearly overestimated. Excluding production gains from the CBA analysis does not, however, alter the conclusion that the benefits of SIT exceed investment costs. It is assumed that the value of leisure time is higher than zero and equivalent to the net hourly wage. This only

holds true for those individuals who are on the labour market. However, since the average age amongst the group of individuals who enter into a SIT program is relatively low it is deemed fair to assume that the majority of participant will be active on the labour market.

## CONCLUSION

When all consequences are measured in monetary terms and we assume that sick days are associated with loss of productivity this analysis suggests that SIT increases societal welfare. The conclusion also holds if there is no loss in productivity. We cannot draw the same clear conclusion from the CEA because in this type of analysis we have chosen not to monetarise all outcomes. In the CEA the cost per patient year of improved well-being lies in the range DKK 16,408 to DKK 2,784 depending on whether we are looking at the very short time horizon or the longer time horizon. As with any CEA interpretation of the ICER requires some notion of the value of the measure of outcome. What is a person year with improved psychological well-being worth? The CBA suggests that if the value of improvement in well-being is set at least equal to the monetary value of gained non-sick leisure time the SIT programme is worthwhile.

We observed a high level of compliance of 94 % (95 % CI 90-97). It is likely that compliance rates may be reduced if the socio-economic characteristics of the participants were different. In the present study as much as 42.1 % had a medium-long or an academic education. The groups of participant in the present study are clearly not representative of the Danish population (year 2002) in which 17 % of the population (15-59 years old) had a medium-long or an academic education (Denmark's statistics). If the characteristics of participant should significantly change the cost-effectiveness of SIT may be reduced.

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