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- Analyses of implementation, pharmaceutical sales patterns and expenditures

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Göteborg 2006

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by
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ABSTRACT

Background: Over the last few decades in many western countries, the sales of prescription drugs have increased dramatically; however, this increase requires individuals and society to bear larger economic consequences. To improve cost control for pharmaceuticals, several reforms attempt to reconcile the economic responsibility of the patients, prescribers and third party payers.

Aims: The purpose was to investigate effects of policy changes concerning reimbursed pharmaceuticals in Sweden with focus on the latest reform comprising mandatory generic substitution. Specifically this thesis analyses effects of policy changes on development of expenditure and volume of pharmaceuticals, prescribers' opinions on the latest reform and how prescribers, patients and pharmacy personnel acted during implementation of generic substitution.

Methods: One study analysed pharmacy invoice data comprising expenditure and volume between 1986 and 2002 for five drug groups and all pharmaceuticals in total. A questionnaire was distributed to 1388 physicians working in Region Västra Götaland. Logistic regression was used to analyse associations between opinions and background characteristics. Three studies comprised data on reimbursed dispensed prescription drugs. One study examined data on the dispensing procedure for Region Västra Götaland between October 2002 and September 2003. Another study analysed expenditure data for each county council and the whole country during the period January 2000 to December 2004. One study examined data on volumes sold for the whole country between January 2000 and June 2005. In two studies, interrupted time series analysis was used to analyse the effects of policy changes.

Results: Increased patient co-payment was not associated with any significant effects on expenditure and volume. Introduction of co-payments for pharmaceuticals that previously were free and co-payment based on the price of the products were associated with a temporary decline in cost increase. Reference-based pricing was associated with decreased cost per volume. After its introduction, generic substitution was implemented rapidly and the key actors acted in accordance with the reform. A large percentage of the prescribers were positive to the reform. Sales of prescribed substitutable pharmaceuticals increased proportionally more than sales of non-substitutable pharmaceuticals in the same therapeutic group after introduction of generic substitution. The patients were price sensitive and chose substitution to cheaper alternatives when the price differences were high. Generic substitution was associated with decreased average patient co-payment, subsidised cost and total cost.

Conclusions: Mandatory generic substitution effectively reduced overall expenditure. Policies that increase competition limited growth in pharmaceutical expenditures more effectively than co-payment reforms.

Key words: pharmaceutical policy, health care reform, reimbursement, co-payment, reference-based pricing, generic substitution, drug cost, cost sharing

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Svensk sammanfattning

Bakgrund: Försäljningen av läkemedel på recept har ökat dramatiskt i västvärlden under de senaste decennierna. Läkemedel möjliggör behandling av många sjukdomar men medför också ekonomiska konsekvenser för den enskilde patienten och samhället. För att förbättra kostnadskontrollen har ett flertal reformer införts i Sverige och andra länder.
Syfte: Det övergripande syftet var att analysera effekter av policyförändringar vilka berör läkemedelsförmånen i Sverige med fokus på den senaste läkemedelsreformen som omfattade generiskt utbyte på apotek. Specifika syften var att analysera effekter på kostnads- och volymsutvecklingen för läkemedel, att undersöka förskrivares uppfattningar om den senaste läkemedelsreformen och undersöka hur förskrivare, patienter och apotekspersonal agerade vid införandet av generiskt utbyte.
Metod: Inleveransdata från apoteken omfattande kostnad och volym för fem läkemedelsgrupper samt alla läkemedel sammantaget för perioden 1986-2002 analyserades i en studie. En enkät som skickades ut till 1388 läkare verksamma i Västra Götalandsregionen i april 2003. Samband mellan uppfattningar om reformen och bakgrundsvariabler analyserades med logistisk regression. Data över sålda receptläkemedel användes i tre delstudier. En omfattade data över expedierade recept i Västra Götalandsregionen under perioden oktober 2002 till september 2003. I en delstudie användes kostnadsdata för samtliga landsting och hela riket. Studieperioden omfattade januari 2000 till december 2004. En delstudie omfattade data över sålda volymer för hela riket för perioden januari 2000- juni 2005. I två delstudier användes tidserieanalys för att analysera effekter av införda reformer.
Resultat: Ökade egenavgifter var inte associerade med minskade kostnader och volym för läkemedel. Policyändringar där egenavgifter infördes för läkemedel som tidigare varit kostnadsfria och introduktion av egenavgifter baserade på produktens pris var associerade med en temporär sänkning av kostnadsökningen. Det fanns ett samband mellan införandet av referensprissystem och sänkt kostnad per volym. Generiskt utbyte implementerades snabbt och nyckelaktörerna agerade i enlighet med reformens syfte. En stor andel av förskrivarna var positiva till reformen och andelen recept där förskrivarna motsatte sig utbyte var liten. Försäljningen av utbytbara receptläkemedel ökade proportionerligt mer än försäljningen av ej utbytbara receptläkemedel med samma terapeutiska effekt. Patienterna agerade priskänsligt och valde utbyte till billigare alternativ då prisskillnaden var stor. Generiskt utbyte var associerat med reducerade läkemedelskostnader för både samhället och patienterna.
Slutsats: Generiskt utbyte reducerade effektivt de samlade läkemedelskostnaderna. Policys som syftade till ökad priskonkurrens begränsade kostnadsökningen mer effektivt än reformer som syftade till att öka patienternas egenavgifter.
Nyckelord: läkemedelspolicy, hälso- och sjukvårdsreform, subvention, egenavgift, referensprissystem, generiskt utbyte, läkemedelsförmån
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ORIGINAL PAPERS

The thesis is based on the following papers:

I Karolina Andersson, Max Gustav Petzold, Christian Sonesson, Knut Lönnroth and Anders Carlsten. Do policy changes in the pharmaceutical reimbursement schedule affect drug expenditures? Interrupted time series analysis of cost, volume and cost per volume trends in Sweden 1986-2002. Health Policy (In Press).

II Karolina Andersson, Tove Jörgensen and Anders Carlsten. Physicians' opinions and experiences of the Pharmaceutical Benefits Reform. Scandinavian Journal of Public Health (In Press).

III Karolina Andersson, Christian Sonesson, Max Petzold, Anders Carlsten and Knut Lönnroth. What are the obstacles to generic substitution? An assessment of the behaviour of prescribers, patients and pharmacies during the first year of generic substitution in Sweden. Pharmacoepidemiology and Drug Safety 2005;14:341-8.

IV Karolina Andersson, Gina Bergström, Max G. Petzold and Anders Carlsten. Impact of a generic substitution reform on patients' and society's expenditure for pharmaceuticals. Accepted for publication in Health Policy.

V Karolina Andersson, Max G. Petzold, Peter Allebeck and Anders Carlsten. Influence of generic substitution on drug sales pattern. Submitted.

The papers will be referred to in the text by their Roman numerals.

The papers have been printed in this thesis with permission from the publishers.

CONTENTS

ABBREVIATIONS

ATC	Anatomical Therapeutic Chemical classification system
DDD	Defined Daily Dose
DDD/tid	Defined Daily Doses per 1000 inhabitants per day
MPA	Medical Products Agency
OTC	Over the counter
PBB	Pharmaceuticals Benefits Board
PBS	Pharmaceutical Benefits Scheme
RBP	Reference-based pricing
SEK	Swedish krona
VAT	Value added tax
WHO	World Health Organization

DEFINITIONS AND EXPLANATIONS

Anatomical Therapeutic Chemical classification system (ATC)		A classification system of drugs administered by the WHO. Assigns a unique code to each pharmacological substance.
Construction of ATC-code, example of diclofenac		
	M	1st level , anatomical main group Musculo-skeletal system
	M01	2nd level, therapeutic subgroup Anti-inflammatory and anti-rheumatic products
	M01A	3rd level, pharmacological subgroup. Anti-inflammatory and anti-rheumatic products non-steroids
	M01AB	4th level, chemical subgroup Acetic acid derivatives and related substances
	M01AB05	5th level, chemical substance Diclofenac
Brand-name drug		The original patented pharmaceutical product.
Defined Daily Dose		The assumed daily maintenance dose for a drug used for its main indication in adults. Technical unit administered and decided by WHO.
Generic drug		A pharmaceutical product containing the same active substance as the brand-name drug. Can be launched when the patent of the brand-name drug has expired.
Over the counter drug		A pharmaceutical product sold without prescription.

INTRODUCTION

In most western countries, the drug market has demonstrated remarkable growth during the last decades. Drug expenditure has escalated as drug use has increased since the 1980s. The increase has been especially pronounced for prescribed pharmaceuticals in outpatient care. Several countries reported annual increases in pharmaceutical expenditure of 6-20% in the 1990s [1-9]. Cost of drugs within the Swedish Pharmaceutical Benefits Scheme (PBS) increased 8-15% annually during the 1990s and the early 2000s [10-12]. An increase in the overall volume of existing pharmaceuticals, a shift towards more expensive drugs and costs associated with the introduction of new pharmaceuticals are important elements explaining escalating expenditures [9,10,12].

Many countries have introduced major health care reforms during the last decades, several addressed the use of pharmaceuticals [13]. The escalating costs of drugs required new policies. If costs were not addressed, there was a fear that restraints in other health care would be inevitable. To contain costs pharmaceutical benefit reforms have moved from mainly increasing patient co-payments to expand price competition between manufacturers and introducing incentives for prescribers [13,14]. These measures have been reported more effective than increasing the economic pressure on patients [14,15].

Sweden has introduced several policy changes concerning reimbursed pharmaceuticals during the last decades. During the 1990s, these changes included increased co-payments and a new structure of the co-payment for pharmaceuticals as well as reference-based pricing in order to increase price competition. In the late 1990s, policies were introduced that made county councils rather than the national government responsible for the cost of prescribed drugs. Despite these policies, costs still increased for drugs within the PBS and in 2002 a new reform was introduced to encourage price competition through the introduction of mandatory generic substitution. In addition, policy makers introduced a new authority responsible for determining which pharmaceuticals are qualified for reimbursement and at what price.

Restructuring pharmaceutical benefits schemes can be expensive. It encompasses both development of a feasible regulatory framework, implementation of necessary changes in administrative and computer systems on a central as well as a local level, education of health care practitioners and pharmacy staff, as well as informing the public about the new system. Thus it is essential to investigate the effects of policy changes on

health care utilisation and expenditures as well as potential effects on the population's health. Before implementing such policy changes, policy makers should study the economic and health outcomes from other settings.

This thesis aims to assess effects of pharmaceutical benefit reforms in Sweden with main focus on the reform introduced in 2002. This thesis also examines how earlier reforms affected pharmaceutical expenditure and utilisation. In addition, this thesis examines the implementation and effects of the latest reform from several aspects. The results may be useful for future decision-making concerning reimbursement of prescribed pharmaceuticals and planning of new interventions in this area.

The following background section describes trends in health care reforms and policy tools concerning reimbursement of pharmaceuticals as well as the mechanisms of the policies and international experiences. Then concepts and statistics of drug use is described followed by an introduction to Swedish pharmaceutical policy and pharmaceutical benefits scheme. The final part describes the contents and mechanisms of policy changes concerning the Swedish pharmaceutical benefits scheme.

1 BACKGROUND

1.1 Health Policy

Health policy guides decision-making aimed at maintaining and improving the population's health. Thus health policy goes beyond health care by also focusing on determinants of health. Health policy deals with actions and intended actions by public, private and voluntary organizations that influence health [16].

Health systems have three essential goals: improving health, fairness, and responsiveness influenced by the Health for All declaration [17]. The core values include equity, solidarity and participation. Health for All was first mentioned in 1977 in a call for national governments and World Health Organization to work towards one goal: to enable all the world's citizens to enjoy a level of health that would allow them to lead a socially active and economically productive life by 2000 [18]. Health for All has been further developed and renewed since 1977. The third value, participation, has become increasingly important [17]. Participation encompasses active participation of both organizations and individuals to improve the quality of public health decision-making.

1.2 Health care reforms

In many countries, the need for reforming health systems derives from the dramatic increase of health care expenditure during the last decades. Reasons for rising health care costs include an increased number of elderly, changed patterns of disease, and increased demand for quality health care services. Furthermore, health care inflation has exceeded the inflation in the general economy [19]. Health care reform is defined as a change with the purpose to increase efficiency and equity in performance and access to health care [20-23] by defining priorities, refining policies and reforming institutions through which policies are implemented [22].

Four integrated themes that policymakers have used to reach their objectives can be observed across the European region: 1) changed roles of the government and the market in health care; 2) increased decentralisation to lower levels of public sector or to the private sector of some state functions; 3) increased choice and empowerment for patients; and 4) an evolving role of public health [13]. In addition, some countries have decentralised certain state functions by placing more responsibility on regional or municipal governments and by transferring some functions to the private sector [13]. Some countries where the government traditionally had a less central role have seen an increase in regulatory interventions. An increased use of

market-incentives combined with continued ownership and operation of facilities by the public sector have been applied in some instances. This model, however, has received some criticism. This criticism addresses several conceptual and practical dilemmas regarding whether health is a social good or whether it can be seen as an ordinary good in a market theory model. In addition, how to pay for health care has become a central point of discussion. Some European countries have switched from insurance-based financing to tax-based financing and some have switched from tax-based financing to insurance-based financing. Furthermore, some countries that used to rely on central planning intend to or have already implemented some version of insurance-based financing.

The dynamics of the reform process are critical for its success. The dynamics involve how reforms are implemented and who is likely to oppose them [24]. Successful implementation of health care reforms requires interaction in the government and between government and the parties concerned. These include professionals, citizens, policy-makers and interest groups [13,25]. Health care providers (professionals) are an important part of the implementation of health care reforms as they play an important role in the development and implementation of health policy. Previous studies of physicians' opinions on health care reforms have reported that many physicians agree that the health care system needs revision, although they do not believe that the proposed reforms will meet required needs [26-29]. Furthermore, several studies reported that physicians perceive reforms as a threat to their autonomy [28-32], especially for changes in the financing structures for medical services that were thought to impair clinical freedom [30-32]. Resistance among physicians towards reforms can obstruct implementation, which might lead to unintended effects [33,34]. Investigating health care professionals' attitudes about the components of health care reform can provide information on areas that need further interventions in order to be implemented. Such interventions can include enhanced information on specific topics and discussion with the professionals.

1.3 Pharmaceutical policy

Pharmaceutical policy covers a wide range of issues such as access to pharmaceuticals, health targets, evidence based medicine, resource allocation, rationing, innovation and quality of products [35]. Among others pharmaceutical policy addresses the following issues: regulation on quality requirements for pharmaceuticals to be approved for sale; surveillance of pharmacovigilance; financing and construction of reimbursement schemes for pharmaceuticals; and treatment guidelines.

Before the thalidomide incident in the 1960s, most governments relied on the pharmaceutical industry to regulate its own quality and safety. After discovering an association between thalidomide use by pregnant women and congenital malformations in their offspring, governments concluded that the pharmaceutical industry needed more stringent governmental oversight [36]. To restore the public confidence in pharmaceuticals, governments took the responsibility to assess drug efficacy and safety before products were made available to customers.

National pharmaceutical policies focus on access to relevant and safe pharmaceuticals including ensuring the quality of available pharmaceuticals and interdicting counterfeit drugs [37]. They also focus on to ensure local clinics have access to the drugs they need and to ensure access to affordable medicines (issues concerning prescribing and distributing pharmaceuticals as well as reimbursement of pharmaceuticals) [37]. In addition, pharmaceutical policy ensures appropriate use of pharmaceuticals, rational drug use – the correct use of pharmaceuticals relevant for the clinical needs at the lowest cost to patients and their community. Finally, national pharmaceutical policy aims to ensure a viable and appropriate domestic pharmaceutical industry.

Some argue that pharmaceutical policy should be fully incorporated within health policy, and some argue that it should not. Traulsen and Almarsdóttir pointed out several differences between health policy and pharmaceutical policy [35]. Examples of discrepancies include that the actors – policy makers and pharmaceutical companies – have different and sometimes conflicting interests. The power relations as well as business and political nature of the actors are different. That is, the pharmaceutical profession does not always share the same interests as the health care profession. In addition, the pharmaceutical industry has a great deal of influence on the development of health care and third party payers pay a significant part of the pharmaceutical bill.

1.3.1 Pharmaceutical benefits schemes

Pharmaceutical benefits schemes (PBS), also referred to as pharmaceutical reimbursement schemes, focuses on making relevant pharmaceuticals affordable to ensure a certain level of equity [14,37]. One important part of national health policy and pharmaceutical policy are pharmaceutical benefit schemes. Almost all countries have some type of PBS either through insurance-based or tax-based systems. Benefits schemes comprise issues relating to which drugs should be reimbursed and pricing of reimbursed pharmaceuticals. Reimbursement schemes also encompass issues relating to payment of subsidised pharmaceuticals – how much is paid by the patient

and the benefit scheme as well as financing of the benefit scheme through insurance-based, tax-based, or other source of financing.

1.3.2 Statistics of drug use

The volume of prescribed drugs sold has increased over the last decades both in Sweden [10,12,38] and elsewhere [4,39]. Studies from the 1980s reported that approximately 60% of the population in Finland and Australia purchased at least one prescription drug [39,40]. A similar estimate, 66%, was reported from Canada during the late 1990s [41]. The reported average number of prescriptions redeemed per patient varied between 1.9 to 8.9 prescriptions per patient [40,41]. According to data from a Swedish county, the volume of prescribed pharmaceuticals – measured in DDDs per inhabitant – increased by 90% from 1988 to 2002, and the number of prescriptions increased by almost 60% during this period [38]. This indicates that the average volume of drugs prescribed per prescription has increased during this period.

Important predisposing factors for drug use include age, gender, and presence of chronic disease [38,39,41-47]. In general, drug use increases with increasing age and females tend to have higher rates of use. Furthermore, increasing number of symptoms [42,43] and number of physician visits [39,48] are associated with high drug use. Cardiovascular drugs, drugs for treatment of conditions related to the nervous and alimentary system, and anti-infective drugs are the most frequently used drug groups [38,39,41,45,48]. Sex hormones have been reported as one of the most frequently prescribed drug groups for women [38,45].

1.4 Pharmaceutical benefit reforms in an international perspective

Generally, drug sales are divided into three types of sales segments: 1) drugs sold to hospitals; 2) drugs sold on prescriptions; and 3) drugs sold over the counter (OTC). On average, hospital sales account for 10-15% of the total pharmaceutical expenditure, OTC drugs account for 6-10%, and prescribed drugs account for 75-84% of the total pharmaceutical expenditure in Europe [13,49,50]. Costs for pharmaceuticals sold to hospitals are paid by the ordering clinics. OTC drugs are paid out of pocket by patients. A large part of the costs (often between 50-80%) for prescription drugs are paid by third party payers [13]. Changes in pharmaceutical policy with the purpose to control pharmaceutical expenditure are concerned generally with this segment. According to Rietveld and Haijer-Ruskamp [51], there are three essential ways to control pharmaceutical expenditure: 1) controlling prices of pharmaceutical products at different levels; 2) influencing demand through

implementation of financial measures such as reimbursement and budgeting; or 3) influencing demand through implementing professional measures.

Pharmaceutical policy reforms can be directed towards patients (i.e., consumers), prescribers, pharmacies, manufacturers (pharmaceutical industry), or other agents. Several measures affect more than one of these actors. Attempts to decrease patients' access to medicines include restricting products that are reimbursed (usually referred to as listing) and introduce or increase co-payments for pharmaceuticals. To reduce patient demand for medicines, health care providers can educate patients about life style choices and non-pharmacologic treatments for prevention and treatment of diseases. Attempts to reduce patient demand are usually one of the first steps in pharmaceutical policy changes. Prescribers act on both sides. They are suppliers of health care as well as agents for the patients. Measures that can be directed towards the prescribers include guidelines (professional measures) and budgeting. Furthermore, changes in pharmaceutical regulation of certain products affect prescribers. For example, policies can limit the amount of opioids (a class of addictive analgesics) that can be prescribed on one prescription. Reforms concerning pricing of reimbursed pharmaceutical products primarily affect the manufacturers.

1.4.1 Patient co-payments

In this thesis, co-payment is defined as the direct cost paid by a patient when purchasing a dispensed prescription drug that is included in the PBS [13,23]. According to economic framework, the patient will consume an optimal amount of a drug given his or her preferences and income constraints if the patient is informed about the full price of a prescription drug and is provided enough information to assess benefits and adverse effects of the drug [52]. In theory, an increased co-payment should ration the patient's demand and should primarily affect the volume of drugs purchased thereby reducing costs [13,53,54]. Assuming that patients are well-informed about benefits and risks of prescribed pharmaceuticals products, increased cost sharing should decrease the demand for drugs with limited value more than it would decrease demand for drugs with high therapeutic value. There are, however, concerns regarding equity. For example, poor and vulnerable patients may refrain from essential medicines because they cannot afford the co-payments.

Co-payments can be constructed in several ways. It can either be a proportion of the total price of the dispensed product, a fixed fee per dispensed item, an annual deductible, or a combination of these [50]. Co-payment can also be differentiated for different types of drugs either based on the necessity of treatment or on type of product dispensed. An annual

maximum co-payment can also be applied to restrict the patient's expenses. Then paid co-payments for dispensed pharmaceuticals are summed and co-payments are zero for purchases during the remaining period when the maximum has been reached.

Reforms concerning introduction of co-payment for drugs that have been free of charge and the limitation of the amount of drugs reimbursed have been studied in several countries [53,55-59]. Reduced levels of use for non-essential [5,6,56,58,59] and essential drugs [59,60] are associated with such reforms. The effects on expenditure following introduction of co-payment are less clear. Some studies report an unclear effect on costs [56,58], whereas others report decreased average drug cost per patient [6] and decreased average drug cost per prescription [55]. Increased rates of emergency department visits have also been reported after introduction of co-payment for essential drugs [59]. More knowledge on the influence of the introduction of co-payment on drug utilisation is needed to assess the character of initial effects and their longevity.

Several studies have investigated the effects of increased co-payments [5,6,54-56,58-67]. Some report associations between increased co-payment for pharmaceuticals and decreased utilisation [6,55,58,59,61,63,65,67,68], costs, as well as reduced rate of increase of costs and reduced cost per prescription [5,6,55,56,63,65]. Other studies report no effect on drug utilisation by increased co-payments [60,62,66]. Johnson et al. found that a large co-payment increase reduced the use of essential drugs and had a negative influence on health although costs were not reduced [60]. Most of these studies concerned co-payments with a flat fee that was not related to the price of the product. Few studies have investigated the effects on utilisation and costs from different types of co-payment construction. More knowledge is needed to evaluate effects of increased co-payments on health care utilisation and health.

1.4.2 Listing of pharmaceutical products

Limiting reimbursement of products is another way to reduce a patient's demand for drugs, a strategy that should primarily affect the volumes of purchased pharmaceuticals [50,57,69,70]. It entails definition of a list of either pharmaceutical products reimbursed, usually referred to as a positive list, or a list of pharmaceutical products not reimbursed, usually referred to as a negative list. Several factors are important when considering which products to include on a positive list. Such factors include what indications are suitable for reimbursement and the therapeutic value of the drug [50,71,72]. An important criterion for the selection of indications suitable for reimbursement is seriousness of the disease. Furthermore, the negative

effects of the pharmaceutical product should not outweigh the positive effects. Costs associated with use of the pharmaceutical product should be reasonable from a medical, humanitarian, and public finance perspective. Thus listing and price control are often closely related to each other.

Removing drugs lacking efficacy documentation from the reimbursement scheme have shown to be associated with an immediate drop in the prescribing of these drugs [57]. This was followed by an increase in prescribing of substitute drugs that exceeded the drop. Costs remained unchanged. However, several areas related to listing need further assessment. These include how listing and de-listing affects the use of similar pharmaceuticals and utilisation of other health care. Other areas comprise whether de-listing and listing affect patients' and society's pharmaceutical costs and patients' health status.

1.4.3 Guidelines

Two of the three measures that Rietveld and Haijer-Ruskamp pointed out are targeted towards physicians: implementation of financial measures such as drug budgets and implementation of professional measures such as therapeutic guidelines [14]. Both measures aim to influence prescribers' demands when acting as an agent for the patient. Therapeutic guidelines focus on each disease rather than the pharmaceutical products and contain information on appropriate treatment for each disease. Thus therapeutic guidelines include both non-pharmacologic treatment, such as diet and physical exercise, and pharmacologic treatments. Therapeutic guidelines can be either local or national and are in best cases evidence-based and comprising aspects of cost-effectiveness [14]. Grimshaw and Russell found that the size of the effects of guidelines varied considerably and that the most effective strategies involved local rather than national guideline development and distribution [73]. Attributes of guidelines that have been highlighted as important for acceptance and use include that the guidelines were compatible with the physicians existing values, clear and simple to use, evidence-based, and did not demand too many changes in existing routines [74,75]. Different types of support systems in prescribing, such as automatic reminders when prescribing specific drugs, have also been implemented in several settings [76]. These include, for example, reminders to avoid inappropriate prescribing of antibiotics by requiring results from bacteriological tests before prescribing antibiotics.

Active interventions, such as academic detailing and group discussions, and reinforced interventions have been reported to be more likely to be associated with improved prescribing than passive interventions. The evidence, however, is poor since few well-controlled studies have proven

effects on prescribing quality [76]. Automatic reminders in prescribing software have shown to have a positive effect on prescribing [76]. Positive effects on prescribing did not remain when reminders were removed. Thus it is difficult to assess the effects of guidelines and interventions to increase prescribing quality. More well-controlled studies are needed to investigate both short-term and long-term influence of such interventions on prescribing.

1.4.4 Decentralised drug budgets

Some countries have transferred the financial responsibility of prescribed drugs within the PBS from a third party payer to the prescribers [50,51,77]. There are two major types of drug budgets – global and individual budgets. Global budgets refer to budgets on the regional or local level. This was applied in Germany in the 1990s in an attempt to make general practitioners more cost conscious and to reduce the steep increase of pharmaceutical expenditure [78-80]. Each region was allocated a budget for prescribed pharmaceuticals. Deficits should be compensated in the subsequent year. If deficit was not compensated, the regional physician organisation was obliged to cover the remaining deficits. The system has been questioned, especially by physicians. The reform was associated with a temporary decrease in pharmaceutical expenditure [80] and cost shifting as patients requiring expensive pharmaceuticals to a large extent were referred to tertiary clinics in hospitals [78,79]. Hard budgets were replaced by soft budgets in 1998, and in 1999 hard budgets were reintroduced. Finally, in 2001 hard budgets were abolished and replaced by target budgets for individual physicians [77].

Individual drug budgets refer to a system where each prescriber or clinic has their own budget for prescribed reimbursed pharmaceuticals. One of the most well-documented examples is the fundholding scheme introduced in United Kingdom in the 1990s [80]. A voluntary scheme where large and medium-sized primary care practices could apply for discretionary budgets was implemented. Fundholding practices were allowed to keep any surplus but did not have to cover any deficit. Fundholding practices decreased the cost per unit for prescribed pharmaceuticals, which was mainly achieved through increased prescribing of generics [81,82]. The effects noted during the five first years were diluted during the late 1990s and fund holding ceased in 1999 [77].

Experiences of global and individual budgets are restricted to few countries, and it is difficult to do comparisons between these settings due to different systems and incentives for prescribers. Previous studies indicate that sustainability has been an issue so far. More knowledge on how budgets

affect prescribing and pharmaceutical expenditure is needed in order to assess potential benefits and downsides of drug budgets.

1.4.5 Price control of reimbursed pharmaceuticals

There are three major types of pricing policies for reimbursed pharmaceuticals: direct control of product price, indirect control of product price, and profit control. The two first types of pricing policies are most widely applied, but few countries apply profit control. Several countries use a mix of direct and indirect price control depending on whether the patent of the products have expired [70-72,77].

Direct price control

Under direct control of product price, the government or a governmental agency decides on the price of pharmaceutical products encompassed by the PBS. One or more of the following factors are often considered in price fixing: health economic evaluations with reference to existing products, international price comparisons, and the contribution of the pharmaceutical to the economy [50,71,72,77,83]. Direct price control of pharmaceuticals within the PBS is applied in several countries. Primarily this is used for new pharmaceuticals where there are no interchangeable products available on the market.

Indirect price control

Indirect price control aims to introduce price competition between pharmaceutical companies either through reference-based pricing, RBP, or generic substitution [13,50,84]. These policies seek to affect the price – i.e., the cost per unit – for drugs where there are interchangeable equivalent products available containing the same or a similar active ingredient [84]. Manufacturers are free to set any price, but risk to lose market shares if the price exceeds the reimbursement level. Thus it creates incentives for the manufacturers to lower prices.

Within RBP reimbursement ceilings for interchangeable drugs, reference prices, are set by payers [50,84]. Thus the reimbursement covers drugs priced at or below the reference price. Above this ceiling, the patient has to pay the difference between the reference price and the actual price out of pocket or have a supplementary private insurance. Manufacturers risk losing market shares if the price exceeds the reimbursement level. Thus it creates incentives for the manufacturers to lower prices to the reimbursement level.

RBP has been introduced in several countries both within [13,50,64,70,84-89] and outside Europe [84,90-94]. Introduction of RBP has been associated with a decline in price for products covered by reference pricing [83,88].

However, it was noted that the introduction of RBP in both Germany and the Netherlands was followed by an increase in the price of the products not covered by RBP [83]. RBP has been reported to be associated with decreased use of cost-shared antihypertensive drugs, but unchanged overall utilisation of antihypertensive drugs in Canada where it also was associated with substantial monetary savings [91-93]. Few studies have investigated effects other than price effects of RBP outside the Canadian province British Columbia. Thus more data is needed on how RBP affects use and costs.

Generic substitution is similar to RBP with some differences. The major difference is that generic substitution gives the pharmacies the authority to substitute products exceeding the reimbursement level to the cheapest available interchangeable product. The reimbursement level usually corresponds to the price of the cheapest interchangeable product. This further sharpens the incentives for manufacturers to decrease prices as they will lose market shares unless their product has the lowest price.

Several countries have introduced generic substitution, both within [14,86,95-97] and outside Europe [84,90-94]. Previous studies have shown that pharmacies substituted a large proportion of the substitutable medicines to cheaper alternatives and that prescribers restrict substitution to varying extent in different settings [98-100]. Generic substitution has shown to be associated with notable monetary savings for the society in several settings [1,90,99,101-104]. It has also been reported that the size of the price signal had an effect on behaviour, and products with large price differences were more likely to be switched [90]. Providing positive incentives for pharmacists to dispense generic products has been reported to be associated with increased substitution rates and monetary savings [101]. In general, most studies have investigated effects of generic substitution on costs, but few have dealt with sales patterns and how patients act and how generic substitution affects patients' costs.

1.5 Opinions on pharmaceutical benefit reforms - international experiences

1.5.1 Among prescribers

Health care practitioners are important actors in the implementation of health care reforms as they play an important role in the development and implementation of health policy. This is also true for pharmaceutical policy where physicians and pharmacists can affect the outcome as they are the ones prescribing and distributing the pharmaceuticals to the patients. Few studies have investigated what physicians think about pharmaceutical benefit reforms.

Whynes and Baines [105] investigated primary care physicians' opinions regarding drug budgets in the UK. They reported that physicians with budget responsibility for prescribed drugs perceived increased cost-awareness compared to physicians that did not have budget responsibility for prescribed drugs. These opinions remained even after the fundholding scheme had been abandoned.

General practitioners' opinions on generic substitution have been investigated in Denmark [106], New Zealand [107], and USA [108]. The majority of the Danish and New Zealand physicians reported that they were negative to generic substitution. However, physicians reported they were cost conscious when prescribing [106,108] and actively prescribed generic drugs when appropriate [107,108]. Conflicting opinions were found on whether generic substitution would decrease the physician's credibility as perceived from the patient or not [106,108]. Some physicians reported that generic substitution would increase the workload [106,107]. This was mainly attributed to patients' worries and problems related to substituted pharmaceuticals. The proportion of physicians reporting that generic substitution had caused problems for their patients varied depending on the time frame for reported problems [106,107]. Forty percent of the Danish physicians responded that the system of generic substitution should be removed; the proportion was higher for males than females [106]. Because the samples in these studies were rather small, the results should be interpreted with some caution.

Sample sizes in studies investigating physicians' opinions to reforms have in general been rather small and restricted to general practitioners. Thus the generalisability to other settings and physicians working in hospitals is limited.

1.5.2 Among pharmacists

In France, the majority (90%) of responding pharmacists reported that they favoured generic substitution [109]. In Denmark, 27% of responding pharmacists reported that they favoured generic substitution; half of the Danish respondents had a negative view of the system [110]. Difficulties in implementing the system systematically – for example, adjustment of stock keeping – and need for support and further education were noted by pharmacists in both countries. The French pharmacists thought that generic substitution would have a positive effect on the health care system as well as the relationship between pharmacists and patients and the pharmacists' image [109]. However, only half of the French pharmacist considered the financial compensation for substitution to be satisfactory [109]. There was

no information on how the Danish pharmacists perceived the financial compensation. The Danish pharmacists reported that generic substitution required extra workload, on average 50 minutes per day and employee [110]. Half of the respondents claimed that the system of generic substitution should continue although the system could be improved [110]. More data on pharmacists' opinions on different aspects of generic substitution are needed as they are a key actor and can influence the outcome of the policy. Data on pharmacists' opinions can also reveal areas that need to be changed to increase sustainability and avoid problems for patients.

1.5.3 Among patients

Few studies have investigated patients' opinions on pharmaceutical benefit reforms; however, one Danish and one Norwegian study assessed patients' opinions on generic substitution [111,112]. A large proportion of the patients in Norway and Denmark were positive to generic substitution in pharmacies [111,112]. Patients considered monetary savings from substitutions important [112]. Half of the Norwegian patients and more than 80% of the Danish patients noted that their medicines were substituted. Half of the Norwegian patients that had experienced substitution would not accept substitution for certain types of pharmaceuticals, such as cardiac and asthmatic drugs [112], and one-third had negative experiences of substituted pharmaceuticals [112]. Difficulties in handling the generic medicine and perceived weaker effect of the generic medicine were the most frequently reported problems [112]. Weaker effect of generic medicine and side effects were the two most frequently reported problems among Danish patients [111]. A majority of the Danish patients thought that the system should continue [111]. More studies on patients' experiences and opinions on pharmaceutical benefit reforms are needed to find and refine systems that are safe and acceptable by patients.

1.6 Pharmaceutical policy in Sweden

Pharmaceutical policy involves several authorities and actors in Sweden. The Ministry of Health and Social Affairs is responsible for people's financial security, social services, health and medical care, public health, and the right of children and persons with disabilities. Thus the responsibility of Ministry of Health and Social Affairs includes both medical services and pharmaceuticals. A pharmaceutical product must be registered and approved for sale before it can be sold in Sweden. The Medical Products Agency, MPA, is responsible for regulation and surveillance of the development, manufacturing, and sale of drugs and other medicinal products. The MPA regulates sale and registration of pharmaceutical products in Sweden. The authority also has the responsibility to monitor adverse effects of approved pharmaceuticals. The MPA can also withdraw a pharmaceutical product

from the market if it proves to have serious adverse effects not known upon registration. Furthermore, MPA can provide a temporary sales approval for a pharmaceutical not approved for sale in Sweden for treatment of a specific patient.

Pharmaceuticals approved for sale are not reimbursed by default when approved for sale. The Pharmaceutical Benefits Board, PBB, decides which products should be included in the Swedish PBS. PBB makes decisions based on good health and care on equal terms and ethical principles that apply to health and medical care. Issues considered in the PBB's decision-making on reimbursement are suitability of the drug, cost-effectiveness, and marginal utility. The human value principle and the solidarity principle form the basis for the decisions. The PBB also has the responsibility for pricing of reimbursed pharmaceuticals in Sweden. To be included in the Swedish PBS, a pharmaceutical product needs to be approved for inclusion in the PBS and have an accepted price.

On the regional level, the 21 county councils have the responsibility to finance and organise health care services for their citizens [113]. The county councils operate most of the hospitals and primary health care centres. The county councils' financial responsibility includes both pharmaceuticals used in in-patient care and reimbursed pharmaceuticals in outpatient care. The county councils are free to choose a model for handling of the financial responsibility for pharmaceuticals within the PBS that they find appropriate: both how the financial responsibility is organised (i.e., after prescriber or in which area the patient resides) and to which level it is decentralised.

1.6.1 The Swedish Pharmaceutical Benefits Scheme

Before 1998, the Swedish National Insurance Board had the financial responsibility for drugs covered by the reimbursement scheme on behalf of the government. Since January 2005, the financial responsibility for pharmaceuticals and medical items within the PBS lies with the county councils.

The PBS entails a subsidised reduction of the individual's costs for drugs and medical items [114]. It applies to drugs included in the PBS prescribed for human use by an authorised prescriber to prevent, identify, alleviate, or cure disease or symptoms of disease, or for a similar purpose, and provided that the prescription is labelled with a workplace code that identifies the prescriber's place of work. The subsidy of pharmaceuticals is increased on a stepwise scale. The cost for drugs and medical items during a twelve-month period are summarised as shown in Table 1. The subsidy granted for each purchase is based on the total cost (i.e., retail price) of products purchased

before that date and the products purchased on that occasion. The out of pocket maximum per twelve month period is set to SEK 1800 (approximately Euro 180) (SEK 1= USD 0.13 and Euro 0.11 July 21, 2006). After SEK 1800, reimbursed pharmaceuticals and non-durables are free for the remainder of the twelve-month period. For families with more than one child under the age of 18, provisions apply commonly to the children.

Table 1. The annual patient co-payment and subsidy for pharmaceuticals encompassed by the Swedish Pharmaceutical Benefits Scheme in 2006. Costs expressed in Swedish krona (SEK).

Patient co-payment (SEK)	Total drug cost (SEK)	Subsidy (% of total drug cost)
0-900	900	0
901-1300	901-1700	50
1301-1700	1701-3300	75
1701-1800	3301-4300	90
-	4301-	100

1.7 Swedish pharmaceutical benefit reforms over time

Pharmaceuticals for treatment of disease have been reimbursed since the public health insurance was introduced in 1955. Through health insurance, pharmaceuticals for treatment of disease were discounted and pharmaceuticals were free for treatment of some selected diseases. In July 1981, the health insurance was further regulated when a joint high cost protection for pharmaceuticals, physician visits, and medical services for treatment of disease was introduced. Table 2 shows reforms within the Swedish pharmaceutical benefits scheme during the years 1981 to 2006.

1.7.1 Patient co-payments

In 1981, the reimbursement of pharmaceuticals was based on a maximum fee per dispensing occasion rather than a maximum co-payment per year, and payment of several prescriptions dispensed at the same occasion were coordinated. Furthermore, for people with a great need of health care and pharmaceuticals, the co-payment could be exempted for a limited period. The minimum dispensing fee was SEK 30 per occasion and a maximum of SEK 55 (the patient paid 50% between SEK 30 and 80). Children from the same family up to the age of 16 were given a joint maximum co-payment. A short description of changes in co-payments and co-payment structure from 1981 and onwards is included in Table 2.

An annual maximum co-payment was introduced as a complement to the dispensing fee in 1 January 1991. According to this, a patient who has paid a

total of SEK 1500 in co-payments is entitled to free medical care and pharmaceuticals for the rest of the twelve-month period, calculated from the date of the first consultation.

Table 2. Policy changes concerning prescribed pharmaceuticals within the Swedish reimbursement scheme between 1981 and 2005.

Month-Year	Elements of policy changes
July 1981	Introduction of high cost threshold for pharmaceuticals and health care based on the number of dispensing occasions and consultations
January 1991	Annual maximum co-payment of SEK 1500 for pharmaceuticals and health care replaced the previous high cost threshold
January 1993	Introduction of reference based pricing Increased annual co-payment level to SEK 1600
January 1995	Change of co-payment structure: SEK 125 for one prescription and SEK 25 for each additional prescription dispensed on the same occasion Increased annual maximum co-payment to SEK1700
January 1997	New pharmaceutical benefits scheme - co-payment introduced for pharmaceutical previously free (except insulin) - a stepwise scale for pharmaceutical co-payments. The patients pays 100% of the price up to SEK 400, 50% between SEK 400 and SEK 1200, 25% of the price between SEK 1200 and SEK 2800, and 10% of the price between SEK 2800 and SEK 3800 - annual maximum co-payment was SEK 1300 for pharmaceuticals - only the amount needed for 90 days treatment could be dispensed at the same dispensing occasion Obligation for county councils to have Drug and Therapeutics Committees Decision to transfer the financial responsibility for prescribed drugs from the government to the county councils
June 1999	Increased annual maximum co-payment for pharmaceuticals to SEK 1800 and adjusted levels within the scale (100% of the price up to SEK 900, 50% of the price between SEK 900 and SEK 1700, 25% of the price between SEK 1700 to SEK 3300 and 10% of the price between SEK 3300 and SEK 4300)
October 2002	Introduction of mandatory generic substitution, mandatory work place codes for drugs within the pharmaceutical benefits scheme and the Pharmaceutical Benefits Board Prescriber codes mandatory on prescriptions containing narcotic drugs, valid from February 2003

SEK 1= USD 0.13 and Euro 0.11 July 21, 2006

In January 1997, a new PBS was introduced when the reimbursement schemes for health care and pharmaceuticals were separated (Table 2) [115]. A stepwise scale was introduced for the discount of pharmaceuticals in which the cost for pharmaceuticals, contraceptives, and consumables for stoma care during a twelve-month period was introduced. Drugs that previously were free for certain diseases became subject to co-payment, with the exception of insulin that continued to be free. Consumables required for administering a drug to the body or for self-checking of medication were free when prescribed by an authorised professional. Joint co-payment for children in the same family was extended up to 18 years of age. The 90-days rule for dispensing was tightened. A month later pharmaceuticals for birth control was exempted from the 90-days rule, and a prescription could not be dispensed unless at least half of the period that the previously dispensed drugs had passed. The 90-days rule was further refined in April 1999, requiring that at least two-thirds of the treatment time had to pass before the prescription could be dispensed again with reimbursement. The possibility to alter the starting date of the period was removed.

Very few studies have investigated effects of increased co-payment for pharmaceuticals in Sweden. Ong et al. investigated effects of the co-payment increases in 1995 and 1997 on use of three classes of psychotropic drugs in Sweden [62]. The authors reported a permanent decrease in level for one of the classes for females after the 1997 reform. However, the trend continued to rise after the shift in level. The study did not assess how other pharmaceuticals and total pharmaceutical sales were affected. More knowledge is needed on effects of increased co-payment in other therapeutic groups and overall utilisation and expenditure.

1.7.2 Listing of pharmaceutical products

In the 1980s, subsidy of pharmaceuticals was only given for treatment of disease and a selection of drugs were free for treatment of certain serious and chronic diseases. From 1993, in general all pharmaceuticals that the MPA had approved for sale in Sweden were included in the PBS if the price were approved by the National Social Insurance Board. There were two exceptions: nicotine substitution products for smoking cessation and pharmaceuticals to prevent loss of hair. In 2000, pharmaceuticals used to reduce obesity and erectile dysfunction were removed from the benefits scheme by the government.

In October 2002, a positive list was introduced [114]. A new government agency, the Pharmaceutical Benefits Board (PBB), was assigned to handle the list. The Board decides which drugs should be included in the PBS as well as pricing of pharmaceuticals and other medical items within the scheme.

1.7.3 Guidelines

For many years, most county councils have had Drug and Therapeutics Committees working with issues related to prescribing of pharmaceuticals and use of pharmaceuticals in inpatient care. In addition to the new structure of the reimbursement scheme, the reform in 1997 contained an obligation for all county councils to have a Drug and Therapeutics Committee [116]. The purpose was that the Drug and Therapeutics Committees should promote rational prescribing and increase cost awareness among prescribers. The Drug and Therapeutics Committees prepared lists of recommended drugs for first and second line treatment for many diseases and conditions. These recommendation lists vary between the county councils.

1.7.4 Decentralised drug budgets

As described in Table 2, the 1997 reform also comprised a decision to transfer the budget responsibility for prescribed drugs from the government to the county councils to integrate pharmaceutical treatment with other health care interventions [114,117]. The transfer of the responsibility for costs of reimbursed prescription medicines was initiated in January 1998, further realised in January 2002, and fully implemented in January 2005. The county councils have been free to decide how, when, and to what extent the responsibility of costs should be decentralised, e.g., at the facility level. The county councils have chosen different ways to handle and decentralise the responsibility of costs for prescribed pharmaceuticals. According to a Swedish report, two main models have been identified based. One is based on where the prescription was issued and the other is based on where the patient resides [118]. Workplace codes became mandatory for prescriptions if the drug were included in the benefits scheme from 1 October 2002. This strategy was intended to link costs of prescribed pharmaceuticals to the prescribing provider [114]. The workplace codes identify the prescribers' place of work, and the county councils decide on how these are organised within the county councils.

Jansson and Anell [119] reported that physicians with budget responsibility for prescribed drugs perceived increased cost-awareness compared to physicians that did not have budget responsibility for prescribed drugs. When deciding on a treatment strategy, clinical aspects – such as, therapeutic effect, adverse effects, and compliance – were rated higher than costs. In addition, physicians thought that cost-effectiveness was more relevant than budget impact [119]; however, it remains unclear whether this had an impact on prescribing. A study from the county council of Västerbotten did not find any differences in prescribing between health care centres with hard and indicative budgets [120]. In Sweden, research on the

effects of drug budgets is scarce. More studies are needed on the effects of drug budgets after the responsibility for costs of prescribed medicines was fully transferred to the county councils in 2005.

1.7.5 Price control of reimbursed pharmaceuticals

RBP was introduced on 1 January 1993. The reference price was 15% above the price of the cheapest product in each reference group. Reference groups comprised pharmaceuticals containing the same substance. If the patient were prescribed a pharmaceutical with a higher price than the reference price, the patient had to pay the price difference. Patients that had reached the maximum co-payment level did not have to pay extra. Pharmacists were not allowed to substitute a cheaper equivalent without contacting the prescriber. For pharmaceuticals not encompassed by RBP, the price had to be approved by the National Social Insurance Board to be included in the pharmaceutical reimbursement scheme [121].

Jönsson reported increased market share of generics and lowered prices during the first year after the introduction of RBP in Sweden [89]. The proportion of co-payment was also increased during this period. Ljungkvist et al. reported that RBP generated substantial savings during the first year and that savings were recorded for the second year although not as large as during the first year [10]. These studies showed lowered prices and savings following introduction of RBP in Sweden. However, no studies have investigated whether the initial effects lasted. More information on this is needed to determine whether this was a sustainable policy.

On 1 October 2002, several new elements were introduced [114]. The PBB was assigned to decide on pricing of pharmaceuticals and other medical items within the PBS instead of the National Social Insurance Board. Furthermore, RBP was replaced by mandatory generic substitution.

According to the law on generic substitution, pharmacy personnel are obliged to offer the patient the cheapest available medically equivalent drug according to the MPA's list of substitutable products unless substitution is restricted [114]. This applies for all prescriptions issued after 1 October 2002 included in the PBS. Prescribers can restrict substitution by marking 'substitution not allowed' on the prescription. Substitution can also be restricted for other reasons; for example, because of divided doses, such as divided tablets, or differences in taste. The pharmacist makes this decision. If substitution is restricted by the physician or the pharmacist, the total cost of the prescribed drug is added to the patient's accumulated cost of drugs purchased within the PBS. The patient can oppose substitution if he or she pays the price difference between the prescribed and cheapest product. In

this case, the cost of the cheapest product is added to the patient's accumulated cost of drugs purchased within the PBS. To assess whether this was a successful policy, knowledge on the implementation process and effects on patterns of drug utilisation and expenditures for pharmaceuticals is needed.

International research on policy changes in pharmaceutical benefit schemes has mainly addressed effects on costs of increased co-payments, indirect pricing systems, and drug budgets. Increased knowledge on effects of co-payment changes, RBP, and generic substitution on drug use and health is needed to assess the character and persistence of effects. In addition, more studies on different types of co-payment structures are needed to analyse whether these affect health and drug use differently. Increased knowledge on how key actors act and perceive policy changes are needed to make health systems sustainable. More well-controlled studies are needed to investigate both short-term and long-term influence of therapeutic guidelines and drug budgets on prescribing. It is important to study effects of policy changes internationally to gain further knowledge on how these affect use and cost.

There has been a series of reforms concerning the Swedish PBS over the last decades. This offers the possibility of analysing effects of different policy changes in the pharmaceutical reimbursement scheme over a long period. Pharmaceutical benefit reforms implemented during the last decades in Sweden includes increased co-payments and changed co-payment structure, decentralised drug budgets, and reference-based pricing and generic substitution.

2 AIMS OF THE THESIS

The aim of this thesis was to analyse effects of pharmaceutical policy changes concerning reimbursed pharmaceuticals. The main focus is on the Pharmaceutical Benefits Reform introduced in Sweden on 1 October 2002 comprising the introduction of mandatory generic substitution.

Specific aims were:

- to analyse whether policy changes in the pharmaceutical reimbursement scheme during the years 1986 to 2002 were associated with changes in cost, volume, and cost per volume;
- to examine opinions and experiences concerning the new Pharmaceutical Benefits Reform among physicians working in Region Västra Götaland;
- to investigate obstacles to generic substitution at prescriber, patient, and pharmacy level and achieved as well as potential savings in the first year following introduction of generic substitution;
- to assess whether the implementation of generic substitution was associated with changes in development of patients' expenses and reimbursed cost for prescribed medicines; and
- to study the development of sales patterns for substitutable and non-substitutable drugs after the introduction of generic substitution.

3 METHODS

3.1 General design

3.1.1 Measuring effects of policy changes

Policy changes are often characterised as natural experiments; that is, the investigator has not created the experimental setting [122]. Because policy changes often include a whole country, an unexposed control group is seldom available. Therefore, it is not possible to undertake a randomised controlled trial to investigate the effects of such policy changes. Instead other types of study designs – such as, interrupted time series analysis – can be used to study the effects of such policy changes.

Interrupted time series studies comprise data collected at multiple occasions over time before and after the intervention (interruption) [123]. The observations before the intervention constitute historical controls to investigate whether the intervention had an effect that is significantly greater than the underlying (secular) trend. Suitable statistical methods are needed to investigate potential biases in interrupted time series studies. Two examples are time series regression techniques, also referred to as linear segmented regression, and autoregressive integrated moving average (ARIMA) models [123]. This thesis uses linear segmented regression to analyse time series. In linear segmented regression analysis, the trend of the segment before the event of interest is used as a control in order to investigate whether there was any association between changes in the trend and the intervention [57,124]. Two effect sizes are estimated: change in level and change in slope between the pre- and post-intervention lines [123,124]. Linear segmented regression can be used to estimate the nature and the size of an effect of an intervention at different time points.

3.1.2 Drug utilisation studies

According to the World Health Organisation, drug utilisation is defined as "the marketing, distribution, prescription and use of drugs in a society, with special emphasis on the resulting medical, social and economical consequences" [125]. Factors influencing and events involved in prescribing, dispensing, administration and taking of medicines are thus the focus of studies of drug utilisation [126].

Drug utilisation data can be used for several purposes: to measure effects of informational and regulatory measures and policies and to define areas for further investigation on absolute and relative efficacy and safety of drug therapy [125]. In addition, drug utilisation data can help in determination of

risk/benefit and cost-effectiveness and to indicate overuse, under-use or misuse of single drugs or therapeutic classes when properly interpreted [125]. Drug utilisation data can be derived from several sources. Disparities in drug utilisation data might depend on whether it is based on physicians' prescribing, processed prescriptions or sold prescription pharmaceuticals in pharmacies [14,36,126,127].

3.1.3 Pharmaceutical sales and delivery data in Sweden

Data on delivered and sold pharmaceuticals used in Study I and III-V were obtained from the National Corporation of Swedish Pharmacies (Apoteket AB).

Data on pharmaceuticals delivered to pharmacies, invoice data, available between the years 1977 and 2002, comprises the ATC-code, the volume in number of DDDs and packages, cost in pharmacy buying and retail prices as well as to which pharmacy the drug was delivered. Invoice data was available on a quarterly basis between 1977 and 1992 and on monthly basis between 1993 and 2002. The data source comprises data on all pharmaceuticals delivered to all Swedish pharmacies.

Since 1998, data on dispensed prescription drugs covering the whole country is available. Data comprise details on the prescription's date of issue, the prescriber, the patient (age, sex, residential area), dispensing date, characteristics and amount of the product prescribed and dispensed product (ATC-code, volume as number and type of packages, and DDDs per package). In addition, the total expenditure separated on patient co-payment and subsidised cost is included in the data. Sales data are available on a monthly basis.

In this thesis, drugs are classified according to the ATC-system. Data used on pharmaceuticals are on either 4th level (chemical subgroups, Study I) or on the 5th level (chemical substance, Study III and V). In study V, data on chemical substances were grouped together in chemical subgroups, referred to as therapeutic groups. Because the defined daily doses are adjusted regularly, they might differ over time. In the present studies, DDDs were adjusted to the last year of the study period in each study.

Data on prices and expenditures are expressed in Swedish krona, SEK, in all studies (SEK 1= USD 0.13 and Euro 0.11 July 21, 2006). Retail prices are excluding value added tax, VAT. In studies using data on costs where the study period is longer than one year (I, IV) costs have been inflation adjusted on yearly basis using the Swedish Consumer Price Index with the last year of the study period as a base [128].

3.2 Paper I-V

Table 3 shows a summary of design and methods of each study.

Table 3. Summary of design, data, sample, study period, outcome measurements, and statistical methods used in each study.

Study	Study design and data used	Sample	Study period	Outcome Measurements	Statistical analyses
I	Interrupted time series analysis. Invoice data of pharmaceuticals for the whole country	All pharmaceuticals and case studies of five chemical subgroups	1/1/ 1986 - 31/12 /2002	Changes in level and slope of volume, costs and cost per volume at introduction of five reforms	Linear segmented regression
II	Cross-sectional questionnaire survey	1388 physicians working in Region Västra Götaland	April 2003	Opinions on and experiences of the PBR	Logistic regression
III	Case study of pharmaceuticals. Data on dispensed prescription drugs in Region Västra Götaland	Six substitutable substances	1/10/ 2002 - 30/9/ 2003	Distribution of end points in the process of generic substitution (Figure 1, p. 37), achieved and possible savings of substitution	None
IV	Interrupted time series analysis. Data on dispensed PBS prescription drugs on county council and country level	1. All prescribed pharmaceuticals within PBS 2. Regular prescriptions within PBS	1/1/ 2000 - 31/12 /2004	Changes in level and slope of patient co-payment and subsidised cost at introduction of generic substitution	Linear segmented regression
V	Descriptive case study. Data on dispensed prescription drugs within PBS for the whole country	Substances within five therapeutic groups	1/1/ 2000 - 30/6/ 2005	Sales pattern of volumes substitutable and non-substitutable pharmaceuticals	None

PBS- Pharmaceutical Benefits Scheme, PBR- Pharmaceutical Benefits Reform

3.2.1 Effects of pharmaceutical policy changes 1986-2002 (I)

Study I analyses the effects of five reforms concerning the pharmaceutical reimbursement scheme during the period 1986 - 2002.

Three reforms concerned increased patient co-payment. One reform addressed the introduction of reference-based pricing and increased co-payment. One reform presented a new structure of the reimbursement schedule. At the beginning of the study period, some drugs were subject to co-payment and some were free. All registered pharmaceuticals for human use and five chemical subgroups (indicator groups) that were differently affected by the reforms were analysed. For the indicator groups, the selection criteria were that the group had to be widely used and mainly sold on outpatient prescriptions. As shown in Table 4, three groups were free before 1997 when they became subject to co-payment. Two groups comprised drugs where the patents had expired that became subject to reference-based pricing when it was introduced (Table 4). Data on pharmaceuticals delivered to all Swedish pharmacies comprising volumes as number of defined daily doses (DDD) and costs as retail prices were used. Costs were inflation adjusted with 2002 as a base. Three outcome variables were analysed: cost (in SEK), volume (number of DDD), and cost per volume (SEK/DDD). Linear segmented regression was used to analyse whether any shifts in level (intercept) or slope in costs, number of DDD, and cost per DDD occurred that were associated in time with the reforms. Shifts with $p<0.01$ were considered as statistically significant. October 1996 to March 1997 were excluded from the analysis due to extreme values following stockpiling related to the reform introduced 1 January 1997.

Table 4. Overview of how the indicator groups in Study I were affected by changes in co-payment reference-based pricing.

ATC-code	Description	Subject to co-payment		Subject to reference-based pricing 1993
		Before 1997	After 1997	
M01AB	Acetic acid derivatives and related substances	X	X	X
N06AB	Selective serotonin reuptake inhibitors	X	X	-
M04AA	Preparations inhibiting uric acid production	-	X	X
R03CA	Selective beta-2-adrenoreceptor agonists	-	X	-
A10A	Insulin and analogues	-	-	-

3.2.2 Physicians' opinions and experiences (II)

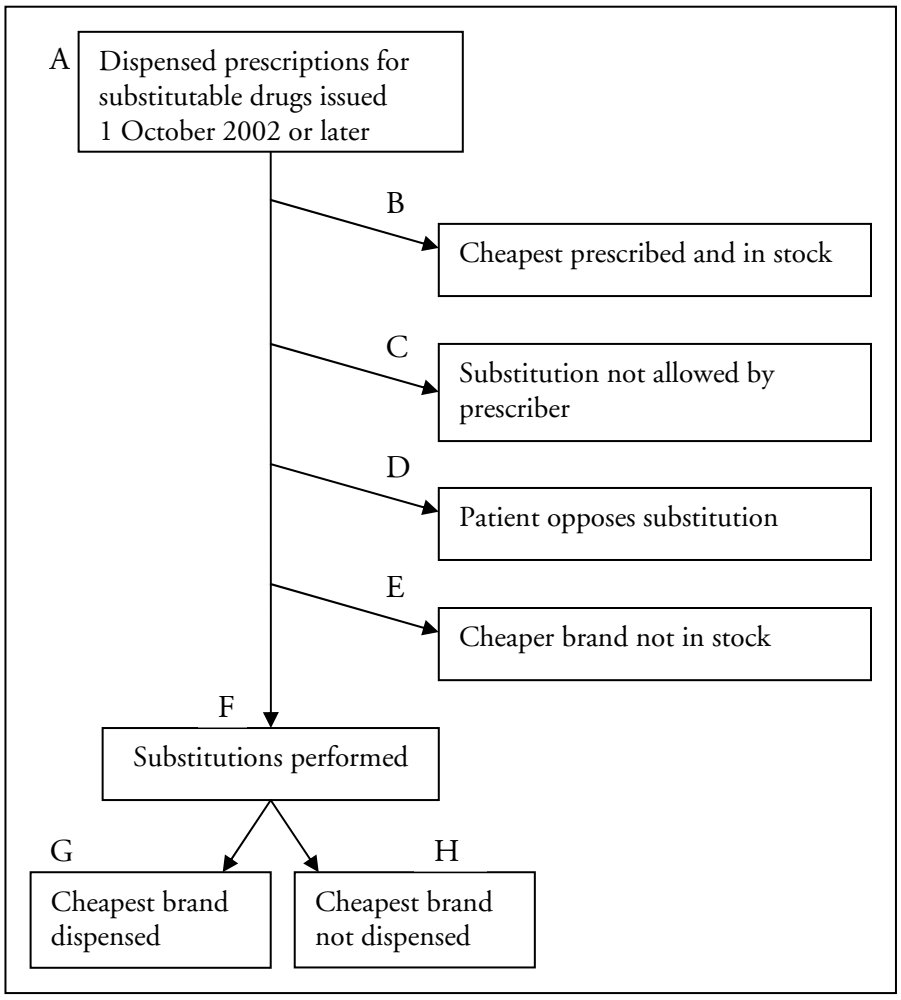
Physicians' opinions and experiences of the latest pharmaceutical benefits reform, introduced in October 2002, were assessed in a cross-sectional study performed in Region Västra Götaland.

A questionnaire was used. It was developed by the authors and based on the results of two focus group discussions with physicians. The focus groups were performed in August/September 2002; one comprised primary care physicians (n=4) and the other physicians working in hospitals (n=3) in Göteborg. Convenience sample was used to recruit physicians to group discussions. Initially, two group discussions with physicians working in primary care and hospitals respectively were planned although not possible due to difficulties to recruit enough participants. The focus group discussions were structured. A topic guide for the discussion that comprised ten questions was developed in advance and presented by the moderator during the discussions. The discussions were tape recorded and transcribed verbatim. A content analysis of the material was undertaken to identify themes and frequency, specificity, emotions, and extent was considered [129].

Based on the content analysis, seven themes, each comprising several issues, were identified that differed somewhat from the questions in the topic guide [130]. The themes were information about the reform, discussions about the reform at the workplace, drug budgets, the PBB, generic substitution, mandatory workplace codes, and prescriber codes. The primary care and hospital physicians had diverging opinions on several issues and themes. Themes that had a considerable frequency and extent were considered during the development of the questionnaires. The final questionnaire comprised questions on how the physicians had received information about the pharmaceutical benefits reform and opinions on the introduction of generic substitution in pharmacies, workplace codes, individual prescriber codes, and the PBB. Some background questions were also included (age, sex, type of workplace, employer, and sphere of activity).

The study population consisted of all private practitioners who had contracts with the county council of region Västra Götaland (n=320) and a random sample of 25% of the doctors employed by the same county council (n=1068). In April 2003, the questionnaire and two reminders were sent by mail. Associations between opinions and experiences regarding the reform and background variables were analysed with logistic regression generating odds ratios with 95% confidence intervals (OR (95%CI)). Interactions between age and background variables were investigated through age stratification.

Figure 1. A schematic description of the process of generic substitution with different end points depending on the choices made by the various actors involved.



3.2.3 Obstacles and savings of generic substitution (III)

This study investigates obstacles to generic substitution at prescriber, patient, and pharmacy level in the first year following introduction of generic substitution and assesses achieved and potential savings during this period. A descriptive approach was used.

Three different categories of pharmacological substances were studied. The categories were based on when substitutable generics were introduced, each represented by two drug substances. Sales data comprising dispensed

prescription drugs sold in Region Västra Götaland between 1/10/2002 and 31/9/2003 were used. Regular prescriptions issued on 1 October 2002 or later were included. In total, 501400 prescriptions were included in the study. Figure 1 shows the possible end points in the dispensing process that constituted outcome measurements. These outcome measurements comprised to what extent the cheapest product was dispensed and prescribers and patients opposed substitution. Furthermore, the average saving per substitution performed was calculated and the total possible savings in an ideal situation as well as the proportion of actual savings achieved out of the total possible savings were explored. The ideal situation was defined as a situation where the pharmacy offered the patient the cheapest product available on the market in all occasions where substitution was not restricted for regulatory reasons.

3.2.4 Effects of generic substitution on expenditures (IV)

Study IV investigates whether the implementation of generic substitution was associated with changes in patients' expenses and reimbursed costs for prescribed pharmaceuticals encompassed by the PBS.

Effects were analysed both for Sweden in total and each county council. Sales data comprising dispensed prescription pharmaceuticals within PBS were used. Two different data sets were analysed: all dispensed outpatient prescription pharmaceuticals encompassed by PBS and a subset that contained only pharmaceuticals on regular prescriptions (i.e., exclusion of multidose dispensed drugs). Main outcome measurements were changes in patient co-payment per 1000 inhabitants and working day and changes in subsidised cost per 1000 inhabitants and working day; both were expressed in constant SEK (2004). Working days were used instead of days since sales (both volume and expenditure) were affected by the number of working days in each month. On average, each month comprised approximately 21 working days. Linear segmented regression was used to analyse effects on costs associated with the introduction of generic substitution. A one-level random coefficient regression model with identity link was used to analyse whether any shifts in intercept and slope occurred following the introduction of generic substitution on 1 October 2002 on county council level. On the national level, an ordinary least-square regression model was used. The intercept and slope were included as random variables in both models. A fixed dummy variable for each calendar month was included in the regression models to take seasonality effects into account. Shifts where $p<0.05$ were considered as statistically significant.

3.2.5 Sales pattern and generic substitution (V)

Study V investigates the development of sales patterns for substitutable and non-substitutable pharmaceuticals after the introduction of mandatory generic substitution in Sweden and explores whether the sales patterns differ between different groups of the population based on patients' age and gender.

Five therapeutic groups were selected for case studies. Inclusion criteria were that the group had to contain both substitutable and non-substitutable substances. Selection of therapeutic groups was performed on basis of their use and the cost they generate for society and to represent pharmaceuticals used for both short- and long-term treatment with emphasis on long-term treatments. Three groups were mainly used for long-term treatment (i.e. > 6 months treatment), one was mainly used for short-term treatment, and one therapeutic group included both short- and long-term treatment. Volumes sold (expressed as defined daily doses) of each substance for Sweden in total for each age and gender group were obtained on monthly basis for the period 1 January 2000 to 30 June 2005. Defined daily doses per 1000 inhabitants per day (DDD/tid) were calculated. The following comparisons were made: the total volume of non-substitutable drugs versus substitutable drugs in each drug group; the volumes of non-substitutable versus substitutable drug substances in each drug group; and the volume of the included drugs (both separate and in total of substitutable versus non-substitutable drugs) stratified by age and gender.

4 RESULTS

4.1 Effects of pharmaceutical policy changes 1986-2002 (I)

Volumes doubled and costs increased by 2.5 times for all drugs and cost per DDD increased from SEK 3.60 to SEK 5.50 over the study period. Cost and volume increased in three of the five indicator groups as well (M01AB, N06AB and A10A). Cost per DDD increased over the period in indicator groups where products were protected by patent, but levelled out or decreased in indicator groups where the patents expired or had expired before the study period commenced.

Figure 2 shows changes in volume, cost, and cost per volume associated with the introduction of the investigated reforms. The arrows from the top indicate statistically significant shifts in intercept, I, and slope, S, as well as the direction of the shift associated with the introduction of the reforms. As shown in Figure 2 increased co-payments were not associated with any changes in level or slope in any of the outcome variables. Some shifts were indicated following the increased co-payments in 1999. These were probably due to the changes after the new reimbursement scheme was introduced in 1997 rather than a change in trend from increased co-payment (Figure 2).

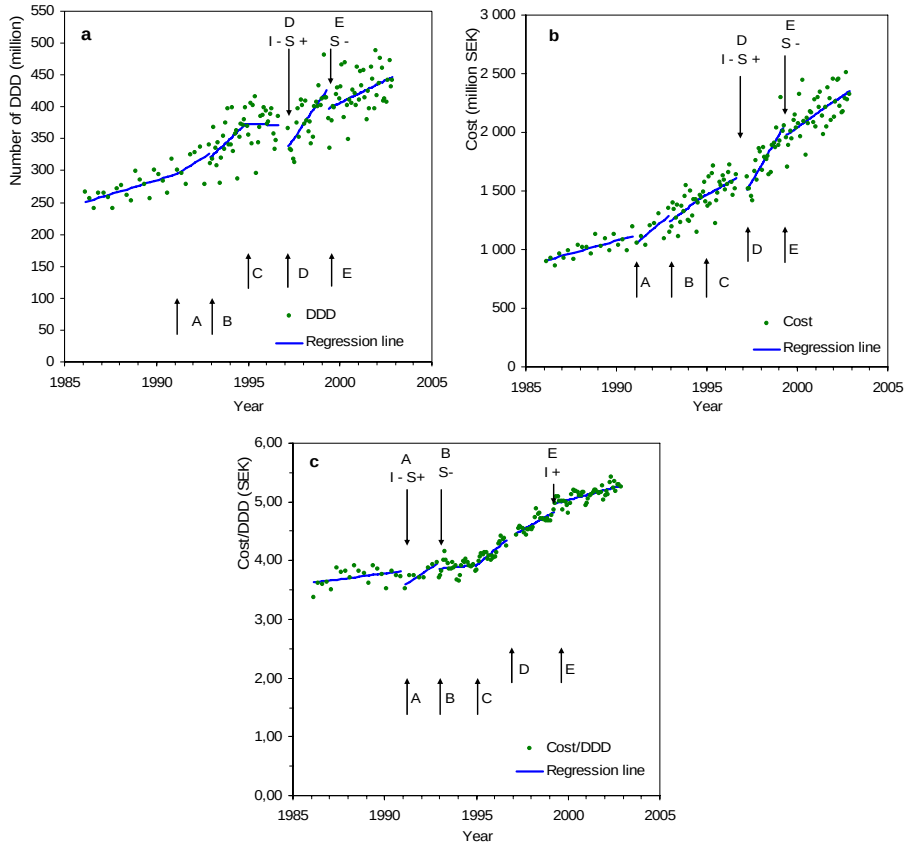
The new pharmaceutical reimbursement scheme in 1997 was associated with either decreased level or slope or both in all indicator groups and for all pharmaceuticals (Figure 2). Reference-based pricing was associated with reduced level or slope of cost per DDD in all indicator groups and all pharmaceuticals. The slope changed direction from an increase into a decrease in one of the groups, although products were covered by patents and in theory should not have been affected by reference-based pricing (N06AB).

4.2 Physicians' opinions and experiences (II)

The response rate was 65%. Two-thirds of the respondents were male. Two-thirds of the respondents worked in hospitals. The majority (66%) was employed by the county council and one-fourth were private practitioners. Age was evenly distributed over working age (25-65 years). Family medicine was the most frequently reported sphere of activity followed by surgery. Most respondents had received enough information about the new reform to perform their work. The employer was the most frequently reported source of information followed by the Drug and Therapeutics Committee.

More than half of the respondents were positive to the introduction of generic substitution. Those that were employed by the county council were

Figure 2. Changes in volume (a), cost (b), and cost per volume (c) associated with the introduction of increased patient co-payment (A, C, E), reference-based pricing (B) and a new reimbursement schedule (D).



The arrows from the bottom of the figure mark introduction of each reform. The arrows from the top indicate statistically significant shifts in intercept, I, and slope, S, as well as the direction of the shift (+ for increase, - for decrease) ($p<0.01$).

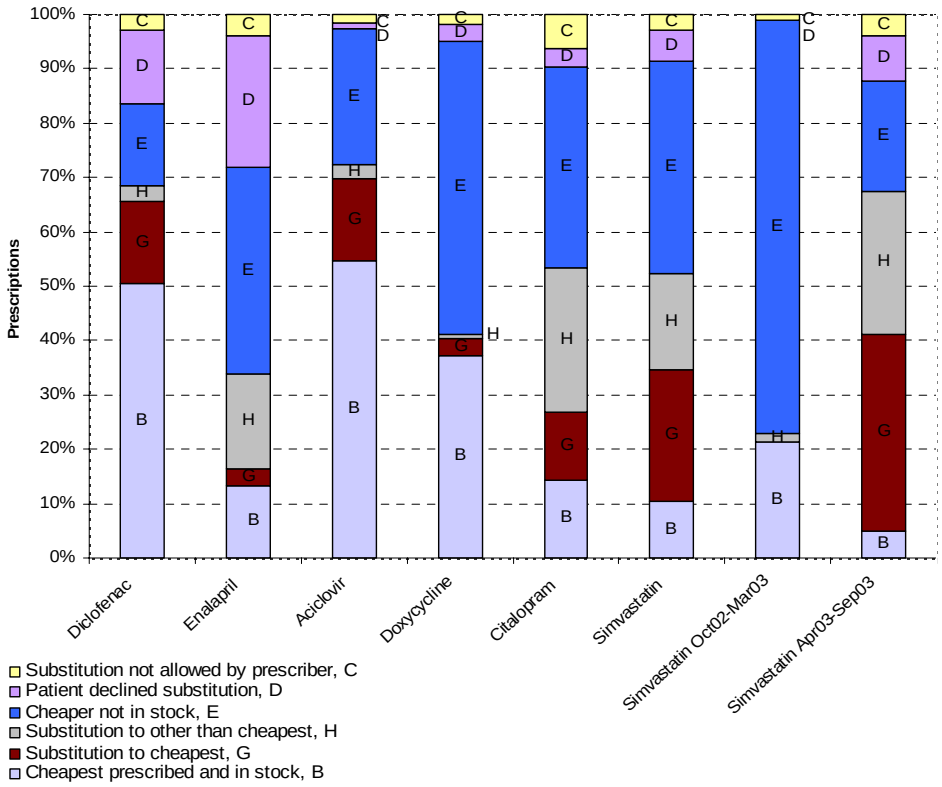
positive to a higher extent compared to private practitioners and physicians employed by the municipalities. Younger respondents were more likely to be positive. Those that reported a negative view on generic substitution encountered problems for patients to higher extent than those that expressed a positive view on generic substitution. The same was reported for private practitioners and respondents working in family medicine.

Seventy percent of the respondents reported that they thought that generic substitution could decrease society's cost for medicines. To a lesser degree, private practitioners and those negative to generic substitution reported that generic substitution could decrease society's cost for medicines. Those reporting a negative view on generic substitution reported that it could affect the right to prescribe freely to a higher degree than those that expressed a

positive view on generic substitution. This was also reported for private practitioners and those working in surgery.

A majority of the respondents reported that they considered the cost of medicines when deciding on treatment although to varying extent. Respondents working in the hospital reported that they considered the cost of medicines less often compared to respondents working in primary care.

Figure 3. The average distribution of the possible outcomes in the substitution process for the indicator drugs used in Study III. For simvastatin both the mean value for the whole period and the mean values for before and after the drug became substitutable are shown. Cheapest brand sold = G + B.



4.3 Obstacles and savings of generic substitution (III)

The distribution of the outcome variables for each included substance during the study period is shown in Figure 3. This includes the proportion of prescriptions where the prescriber and patient opposed substitution as well as the proportion of performed substitutions both to the cheapest available product and other than cheapest, and the proportion of prescriptions where the cheapest product was prescribed. As shown in Figure 3, the prescriber

opposed substitution in 1% to 8% of the dispensed prescriptions, varying between the indicator drugs. Patients declined substitution more frequently when the average saving per substitution was low. Substitution occurred most frequently in indicator drugs where the average saving per substitution was high.

The actual saving achieved by substitution was SEK 15.6 million. On average, 60% of the total possible savings was achieved; this largely depended on the extent to which the pharmacies kept the cheapest brand in stock. The proportion of achieved savings of the total possible savings was largest in the groups where the average saving per substitution was highest. The total possible saving was SEK 26 million for all the indicator drugs.

4.4 Effects of generic substitution on expenditures (IV)

The introduction of generic substitution was associated with a significant change in slope for patient co-payment in all prescribed pharmaceuticals as well as for pharmaceuticals on regular prescriptions for Sweden in total. The slope shifted direction from a slight increase before the reform to a decline after the reform was implemented. Similar results were found for the average slope of patient co-payment for all county councils where the shift in patient co-payment was statistically significant for both data sets.

The introduction of the reform was also associated with a statistically significant shift in slope for subsidised cost for Sweden in total. The slope shifted from a monthly increase before October 2002 to a monthly decline for all prescribed pharmaceuticals. A similar result was found for the average slope of subsidised cost for all county councils. The shift in subsidised cost was statistically significant both for all prescribed pharmaceuticals and pharmaceuticals on regular prescriptions. The subsidised cost for all prescribed drugs increased in all county councils before the introduction of generic substitution. After October 2002, the pattern differed between the county councils; some declined and others levelled out.

4.5 Sales pattern and generic substitution (V)

In most therapeutic groups, the sales of substitutable drugs increased after the introduction of generic substitution, whereas the sales of non-substitutable drugs levelled out or started to decline. The exception was the therapeutic group mainly used for short-term treatment where both substitutable and non-substitutable drugs increased. Thus sales of substitutable drugs have developed more strongly than non-substitutable drugs in most of the selected groups, a trend that indicates that lowered prices have contributed to an increased prescribing of substitutable drugs. The changes were most dramatic for therapeutic groups where the patents

expired during the implementation period of the reform, whereas the changes were not as distinct for groups where the patent had expired before the reform was introduced. Sales patterns varied more when the substances were compared.

Differences in sales patterns between different age groups were more often observed than between the genders. Recently introduced non-substitutable pharmaceuticals were more frequently sold to the youngest age groups.

5 DISCUSSION

This thesis analysed effects of policy changes that aim to increase control over pharmaceutical expenditures through changes in the reimbursement scheme. The thesis covers several changes in pharmaceutical benefits to give an overall view of effects of different policy tools in the Swedish setting. Emphasis, however, is on the latest pharmaceutical benefits reform introduced in 2002. Previous studies that examined the effects of policy changes concerning the reimbursement scheme concentrated on single reforms rather than relating current policy changes to earlier reforms in the same setting [62,89,131].

Previous research has estimated that between 60% and 75% of the population redeem at least one pharmaceutical prescription each year in Europe and Canada. Changes in the reimbursement affect access to pharmaceuticals and financial aspects of drug use; therefore, such policy changes will have a considerable influence on the public and could influence public health.

5.1 Main findings

This thesis showed that policies that aim to increase price competition that includes a clear, credible and transparent legislation with distinct incentives for the key actors increase the likelihood of desired effects on costs and utilisation both for patients and society.

Reference-based pricing and generic substitution increased price competition to a high extent, reflected by decreased cost per volume. Generic substitution was rapidly implemented after its introduction and the key actors acted in accordance with the intention of the reform. A large proportion of the prescribers were positive about the reform. Prescribers seldom opposed substitution of substitutable pharmaceuticals, and sales of prescribed substitutable pharmaceuticals increased proportionally more than sales of non-substitutable pharmaceuticals. The pharmacies offered the patients cheaper alternatives to a large extent from the beginning despite unclear incentives for the pharmacies to substitute. The patients were influenced by price, choosing substitution when the price differences were high. The lowered prices were also reflected by a decrease in the average patient co-payment and subsidised cost after the reform was introduced.

Reforms comprising only increased co-payments were not associated with any effects on expenditure and volume sold. Policy changes where co-payments were introduced for pharmaceuticals that previously were free of cost and introduction of co-payment based on the price of the products were

associated with an initial decline followed by a rapid return to the previous pattern.

5.1.1 Co-payments

The introduction of a new co-payment structure based on price and co-payments for pharmaceuticals that previously were free in the late 1990s was associated with a temporary decrease in both volume and expenditure. This agrees with some studies from Europe and North America that showed that introduction of co-payment was associated with decreased drug use [5,6,56,58-60].

Studies investigating effects of increased co-payments show contradictory results. Some reported effects on costs and use [5,6,55,63,65], whereas others reported no effect [60,62,66]. The co-payment structures investigated differed between the studies. Several studies investigated effects of increased flat fees [6,63,65], whereas others investigated co-payments related to the price of the product [5,55] or both [60]. We found limited effects of increased co-payments irrespective of the co-payment structure, a finding that agrees with Johnson et al. [60].

A major shortcoming of increased co-payments is the potential negative effects on equity; therefore, it is important to have safety nets for those with limited economic means. In the Swedish system, children within the same family are added together to protect for high pharmaceutical expenses. There is also an annual maximum co-payment of SEK 1800 to protect patients that use several medicines from high expenses. There are, however, no other reductions in co-payments for elderly or chronically ill as some countries apply [50]. Thus in Sweden pharmaceuticals within the PBS can pose a considerable economic burden on less wealthy groups. Studies of increased co-payments in public and private insurance plans in USA reported a negative influence on health in vulnerable groups [60,68]. This was not found when the whole study population was investigated [60,68]. These findings urge for closer analysis of equity issues before increasing patient cost sharing to avoid negative health impact in vulnerable groups. To our knowledge, no such studies have been undertaken in Sweden.

5.1.2 Indirect pricing

Supportive legislation and regulation, reliable quality assurance, professional and public acceptance, and economic incentives have been reported to be major factors needed to achieve a high level of generic coverage and a sustainable generic market [24,97]. Possible reasons for the rapid implementation of generic substitution were that it was a stepwise process where reference-based pricing was the first step. Furthermore, it comprised a

distinct legislation, and the reform coincided with patent expiration of several top-selling products, a situation that highlighted the potential economic benefits of the system. Reference-based pricing created awareness of cheaper generic equivalents among physicians, pharmacy personnel, and patients by introduction of a mutual reimbursement level for equivalent products. Thus the step towards generic substitution was not that great. The MPA has also played an important role in quality assurance of generic products and assessment of substitutability. Substitutable products were compiled on a list that was integrated in the pharmacies' software system for dispensing prescriptions to avoid substitution between products that were not considered substitutable with respect to quality, safety, and efficacy.

Effects on price competition

The increased price competition entailed significantly lowered prices on generic equivalents of several top-selling products following the introduction of generic substitution. One important factor was clear economic incentives for the manufacturers to cut the prices as the reimbursement level corresponded to the lowest price. Another was that the patents expired for several top-selling products during the first year of the reform, a factor that contributed to large price cuts. This was reflected in marked effects concerning savings and increased prescribing for pharmaceuticals where the patent expired close to the introduction of the reform. Increased price competition after introduction of generic substitution has also been reported from other countries [96,99,104].

Findings from Australia where RBP was introduced in 1990 and generic substitution was introduced four years later showed that the price competition was enhanced after introduction of substitution [90]. Sweden had a comparable implementation process with similar effects on prices on generic equivalents of several top-selling products following the introduction of generic substitution. RBP was associated with increased price competition both in Sweden [83,132] and elsewhere [83,92,93,133-135]. This might have made prescribers aware of lowered prices since physicians were contacted by patients or the pharmacies when the price of the prescribed products exceeded the reference price and the patient did not want to pay the extra cost. Increased sales of generic brands have also been reported following the introduction of RBP in Sweden and Canada [132,133].

Prescribers

Many of the responding physicians positively accepted the introduction of generic substitution and thought that it could lower pharmaceutical expenditure. This result was somewhat different than results from other settings where physicians expressed more negative opinions toward generic

substitution [106-108]. Male respondents were more negative to generic substitution than female respondents in Denmark [106], although gender did not influence the view on generic substitution in Study II. It is possible that the positive view of potential beneficial effects of generic substitution and the regulation might have influenced prescribing behaviour. Regulation and economic incentives have been reported to affect prescribing [136-140]. Other factors that have been reported to affect drug prescribing practices include perceived and actual benefits and risks of treatment, acquired habits, peers, access to unbiased information, patient demand, advertising, and education [136-140].

Our data indicated that the prescribers aligned with rather than worked against generic substitution, although the policy incurred potential problems and difficulties for patients as well as increased workload due to questions and reports on substituted medicines that had to be recorded. This is in accordance with international studies that reported that prescribers rarely restricted substitution [99,100] and frequently prescribed the cheapest or close to cheapest product [99]. Other studies reported that the prescribing of generic drugs was unchanged after the introduction of generic substitution although the dispensing of generics increased substantially [90,100]. Furthermore, the ministries and authorities refer suggestions on health policy changes to authorities, professional organisations, and patient organisations for consideration. These include professional organisations for physicians and pharmacists. Thus the parties involved have the opportunity to comment on potential problems before a reform is launched.

According to our data, three out of ten responding physicians reported problems for patients associated with generic substitution; however, we have no data on the types of problems that physicians had experienced. New Zealand GPs reported a similar frequency of problems [107]. Danish GPs reported that they estimated that generic substitution entailed patient confusion about the drug and what it was equivalent to in 6-10% of the substituted prescriptions [106]. The Danish GPs reported on patient complaints related to package differences in 15% of the substituted prescriptions [106]. We do not know whether the character of the problems reported by the Swedish physicians are similar to those reported by the Danish GPs.

Pharmacies

Several studies have highlighted that pharmacies play a central role in the implementation of generic substitution [90,98-100]. Pharmacies contribute to the outcome by what alternatives are kept in stock and to which extent patients are offered cheaper equivalents. However, generic substitution also

increases the workload in pharmacies due to intensified stock management, increased time for counselling to explain substitution, and to discuss economic aspects with patients [99,109,110]. Development of administrative support systems for stock management and dispensing can enable implementation of such reforms.

International studies have highlighted the importance for policies to provide incentives for pharmacists to substitute to create a sustainable generic market [97,141]. Previous studies reported that clear incentives for pharmacists were associated with a high rate of substitutions to cheaper alternatives [98,101]. Remuneration systems based on a fixed percentage of the price provide disincentives for dispensing cheaper equivalents as the pharmacists will make less money if dispensing a cheaper generic product compared to when dispensing a more expensive brand name product. Thus remuneration system should be constructed in such a way that it provides positive or neutral incentives for the pharmacists to dispense generics [97]. We found that pharmacies contributed to savings by offering the patients cheaper alternatives to a large extent despite unclear incentives since the remuneration system, based on a percentage of the price, was not changed on the introduction of the reform. A legislation where substitution was mandatory for pharmacies might have contributed to high substitution rates. Similar findings were reported from Finland that introduced mandatory generic substitution in April 2003 [99]. There is a potential that high substitution rates in a situation where the remuneration is based on price might have a negative impact on the pharmacies' economy. This might lead to reductions in pharmacies' expenses, which might have negative impact on access to pharmacies for patients.

Apoteket AB has the exclusive right to distribute pharmaceuticals to patients in Sweden and the corporation is owned by the state. It is possible that the monopoly situation could have contributed to the high substitution, although high substitution rates also have been noted in countries that do not have a pharmacy monopoly [98,99,101]. Introducing generic substitution in a setting without a pharmacy monopoly requires a plan for development of required technical support systems for dispensing and stock keeping and information transfer on substitutable products and prices between the different authorities. Technical support systems are required to achieve a high proportion of substitutions and to enable that stocks are readily updated in accordance with cheapest available alternatives. Support systems are also important for credibility and safety in the system. In Sweden, this was to a large extent developed by Apoteket AB and the authorities concerned.

Patients

The results showed that patients accepted substitution to a high extent in drug groups where the price differences were high, a finding that agrees with other studies [99,100]. International studies have shown that price sensitivity increased among patients after introduction of generic substitution and that notable savings were important for the patient [90,99,112]. The increased price competition contributed to lowered prices on substitutable products that contributed to a decrease in patient co-payments after generic substitution was introduced. Important reasons contributing to increased price sensitivity among patients were clear incentives for patients as the reimbursement level corresponded to the price of the cheapest available product and that prices dropped on many pharmaceuticals. Incentives for patients to choose generics have been reported to be important for sustainable generics market [97]. Such incentives include higher co-payments for brand name drugs or lower co-payments for those who agree on substitution. In addition, the price difference required for the patient to accept substitution have been reported to be based on the perceived risk of the disease [112,142-144]. Studies have also reported that patients were positive to generic drugs [143,145] and to generic substitution [111,112].

Possible savings from generic substitution have to be balanced against patient safety regarding drug use. Although generic drugs have comparable quality, safety and efficacy problems might occur for patients. Frequent switching of medicines might cause problems and difficulties to remember how to use certain medicines and how to manage treatment. Difficulties in managing treatment can cause overuse or under-use, which can lead to increased hospitalisation rates related to incorrect medication use. This can produce new costs in other parts of the health care system. The Swedish system is designed to maximise price competition by applying the lowest price as the reimbursement level independent of the product previously dispensed unless the prescriber restricts substitution for medical reasons (e.g., perceived threatened compliance after substitution). However, low rates of prescriptions where substitution was restricted indicate that this seldom was a concern. Other countries – such as, Finland and Belgium – have a slightly different system focusing on continuity for patients where the previously dispensed product should be dispensed if the price difference is minor [97,99]. Such systems might lead to somewhat less price competition, but might require less work in pharmacies and make it easier for patients with many substitutable medicines. Other measures to simplify for patients include changing how pharmaceuticals are marked so the active ingredient is stated more clearly on the package as well as noting the active ingredient on the prescription.

Other potential problems related to generic substitution are perceived differences in effect and adverse effects between the generic and brand name drugs. Perceived weaker effect of generic medicines was the most frequently reported reason related to generic substitution among Norwegian and Danish patients [111,112]. Between 6% and 10% of the responding patients had encountered problems related to generic medicines [111,112]. A Swedish report from the National Board of Health and Welfare found that 7.5% of the responding patients that had switched to a cheaper equivalent had encountered problems following generic substitution [146]. The types of problems reported were similar to those reported by Danish and Norwegian patients.

5.2 Methodological considerations

5.2.1 Pharmacy data

National pharmacy invoice and sales data were used. Pharmacy sales data is readily available, has an extensive coverage in terms of time, geographical area, and the amount of data collected concerning both characteristics of the patient purchasing the drug as well as the dispensed drug and economic data on the dispensed drug. However, pharmacy sales data is aggregated and analysis and interpretation of results is therefore on the group level. Making inferences from associations on aggregated data to the individual data can cause spurious results [147,148]. Ecological data can be used to create hypotheses and to evaluate effectiveness of population interventions (e.g., introduction of vaccine or health insurance) [148]. In this thesis, ecological data of drug sales have been used to explore drug sales patterns and to analyse whether reforms were associated with changes in pharmacy sales on a national and regional level.

In this thesis, pharmacy sales data on national and regional level – i.e., county council – was used. Data on regional level has been based on pharmacy location – i.e., where the pharmaceutical was sold and registered place of residence of the patient. A previous study showed little discrepancy between these on the county council level [127]. Thus comparisons can be made for regional data based on place of residence and place of purchase.

To measure changes in amounts of pharmaceuticals delivered and sold, volumes were expressed in defined daily doses, DDD. Other volume measurements not used in this thesis include number of prescriptions and packages. DDD is a technical unit corresponding to the average daily dose for an adult when the pharmaceutical is used for its main indication of use. Thus the DDD seldom reflects the prescribed doses since the drug often is used for several indications with varying dosages and since recommended

dosages often vary between different settings. DDD should not be used to estimate the number of users, but it can be used to describe a drug's therapeutic intensity. A major advantage of DDD is that it allows comparison over time and between countries. Previous studies have found a discrepancy between volumes measured as number of prescriptions and as DDD/tid both in Sweden and elsewhere [38,41,149,150]. The amount of drugs prescribed on each prescription often depends on the reimbursement scheme and varies over time and between settings. Defined daily doses have consistently been used in this study to express volumes since these are less prone to changes in reimbursement or altered package sizes.

Expenditures were expressed as retail prices – i.e., pharmacy selling prices – to reflect the price paid by the patient or subsidised. To avoid distortions in data caused by inflation, costs were inflation-adjusted on annual basis using the Consumer Price Index [128]. The Consumer Price Index was used instead of the Drug Price Index as the purpose was to study development of costs in relation to other consumption from the consumer's point of view rather than just drug prices. Furthermore, the Drug Price Index (for both outpatient and hospital sales) have increased less than Consumer Price Index during the last decades [151].

5.2.2 Selection of substances and drug groups

Cases, substances, and drug groups studied were chosen on the basis of whether and how these were expected to be affected by the reforms. To be eligible for case studies, the drug groups or the substances should be widely used in outpatient care and generate a substantial cost to society. Studies of a few case groups allow for closer examination of the circumstances, dynamics, and complexity. This can contribute to an understanding of a wider situation although the material generated may not be generalisable [122]. Closer studies of selected drug groups have been applied in studies of pharmaceutical policy changes in other countries [62,90,93,104,133-135]. Case studies allow for investigation of whether the policy affected the targeted groups. Studies encompassing all pharmaceuticals will give cruder pictures because the intention of most policies is to affect specific segments of the market rather than all pharmaceuticals. Case studies were used to investigate effects in drug groups that were differently affected by introduced policy changes.

5.2.3 Analyses of time series

Quasi-experimental research designs – such as, before and after studies and interrupted time series designs – have been reported to be appropriate for evaluation of certain types of interventions such as pharmaceutical policy changes [122-124,152,153]. Before and after studies hold methodological

problems especially if there is no unexposed comparison group. With pre-post design it is difficult to assess whether the observed differences would have occurred anyway as there is only one observation before and one after the intervention. Interrupted time series designs are seen as a stronger study design that is well-controlled when a comparison group is included and that is partially controlled when no comparison group is available [123,124,152]. Interrupted time series analysis enables description of the secular trend since measuring the outcome variable is done at several time points.

One of the advantages of interrupted time series analysis is that it allows for statistical investigation of potential biases when investigating the effect of the intervention. Potential biases include secular trends, cyclic or seasonal variations, autocorrelation, random fluctuations, and the duration of the intervention (how long the effect of the intervention will last). Expected extreme values – such as, those observed during the three last months of 1996 and the three first months of 1997 – were excluded from the analysis, as these would have distorted the analysis otherwise. This has been mentioned as an appropriate way to handle expected extreme values [124]. Residual plots were reviewed to check whether there were any signs of serial autocorrelation. There were few signs of autocorrelation in the performed analyses of volumes and costs. Seasonal trends appear commonly in pharmacy sales data and data used to investigate effects of generic substitution on costs was no exception. A dummy variable for each calendar month was included in the regression model to take seasonality into account. At least 12 data points are recommended in each segment to examine data for seasonality [123,124]. The segments analysed in this thesis comprised at least 24 months before and after the interventions. Seasonal effects were taken into account in the analysis where needed. In this thesis segmented linear regression analysis was used to analyse interrupted time series as linear models were found to fit data adequately.

5.2.4 Questionnaire data

The response rate in our study was quite high compared to other studies examining physicians' opinions [28,105,108,154]. There were no differences in sex, age, or employment between those who completed the questionnaire and those who answered only the background questions, although it is possible that those who chose not to return the questionnaires differed.

A self-administered questionnaire was used to assess opinions on and experiences of the last pharmaceutical benefit reform among physicians. The questions in the questionnaire were based on the results from the content analysis of two focus group sessions. Focus groups were undertaken to investigate topics related to the reform that were considered important by

prescribers. The questionnaire was structured and comprised of 20 questions concerning current opinions to specific elements of the reform and potential benefits and risks with pre-coded response choices. Structured questionnaires have been reported to be useful for short questionnaires with clear questions [122]. Questions about experiences were posed in a recent time frame to avoid recall bias.

6 CONCLUSIONS

We found that reforms comprising increased co-payments had limited influence on expenditure and utilisation of prescribed pharmaceuticals in Sweden. Introduction of co-payment for pharmaceuticals that previously were free and changed structure of co-payment based on price instead of a flat rate were associated with a temporary decline followed by a rapid return to the previous pattern.

Policies introducing indirect pricing for pharmaceuticals, reference-based pricing, and generic substitution were associated with decreased cost per volume. For generic substitution, increased price competition was especially noted in pharmacologic groups where the patent recently had expired.

We analysed several aspects of the introduction of the latest pharmaceutical benefits reform where generic substitution was the main element. The key actors – manufacturers, physicians, pharmacies, and patients – were found to align with rather than act against the reform. Sales of substitutable pharmaceuticals increased proportionally more than sales of non-substitutable pharmaceuticals. Generic substitution was also associated with a decrease of total pharmaceutical expenditure.

7 IMPLICATIONS FOR RESEARCH

Few studies have assessed effects of changes in pharmaceutical benefits schemes on drug utilisation and on public health. According to a recent Cochrane review on pharmaceutical pricing and purchasing policies, research should more fully investigate effects of policy changes [153]. Furthermore, the review recommended that research should strive to investigate long-term outcomes of policy changes and that use of well-controlled research design in policy analysis should be encouraged. This thesis is in line with these suggestions. Effects of policy changes during almost twenty years were assessed and time series analysis was used to evaluate effects of these changes where suitable. Furthermore, we investigated several aspects of generic substitution to provide a comprehensive analysis of the implementation of this policy.

Future research on pharmaceutical policy should investigate effects within different segments of the pharmaceutical market and different patient populations using as well-controlled designs as possible and based on available data. The new Swedish registry with individual data on dispensed prescriptions held by the National Board of Health and Welfare provide new opportunities for future research of pharmaceutical policy changes.

In addition, future studies should assess potentially negative effects of generic substitution on patient safety and health care use. It is important to investigate how patients perceive and manage frequent substitutions of generic drugs used for treatment of chronic conditions. Such studies could increase knowledge on how legislation affects adherence and patient outcomes – such as, quality of life.

The relation between price developments for patented drugs compared to price development for drugs with expired patents needs to be explored. This could provide information about hidden effects of indirect pricing for drugs with expired patents on prices – such as, increased prices on new pharmaceutical entities.

Multidisciplinary approaches should be encouraged to undertake comprehensive analyses of policy changes from several aspects. In addition economic outcomes, health and attitudes are other areas that need to be assessed. Such an approach would require collaboration between different occupational groups.

8 IMPLICATIONS FOR POLICY

Based on the results from this study and international experiences, the following implications have been identified:

Introduction of co-payment and changing structure of co-payment have initial effects on utilisation and costs. However, these effects often have a temporary character. Increased co-payments have limited effect on utilisation and expenditure. Co-payments should strive to make patients aware of the prices without being an obstacle for purchasing necessary medicines.

Reference-based pricing and generic substitution have been associated with decreased prices of pharmaceuticals especially for pharmaceuticals with newly expired patents. It is essential that the policy include a transparent system for determination of requirements to consider products as substitutable.

Generic substitution combined with clear incentives for key actors to provide and purchase cheaper alternatives have positive effects on development of pharmaceutical expenditure as well as sales of substitutable products. Thus indirect pricing can be an efficient tool to decrease prices of products where patents have expired and curb rising costs in these segments.

It is crucial to ensure that the policy change has the support of both professionals involved and patients. This can be done by asking professional and patient organisations to make suggestions about policy changes or to review potential policy changes.

Patients act price sensitively when provided incentives to choose cheaper alternatives. Means to avoid potential problems for patients following substitutions should be explored and introduced. Misunderstandings following substitutions can be avoided through regulations that encourage continuity for patients and improved markings on pharmaceutical packages that highlight the active ingredient rather than the product name. Generic prescribing has been discussed as a possible way to increase transparency for patients in Sweden.

Prescribers and pharmacies usually work in accordance with introduced reforms but require education on the new policy as well as administrative and technical support systems to cope with increased workload caused by new policies. Introducing generic substitution require a plan for development of required technical support systems for dispensing and stock

management as well as information transfer on substitutable products and prices between the involved authorities.

Taking these experiences into account in the development of new policies increases the probability of positive effects on drug utilisation. It is essential to incorporate incentives for both the supply (i.e., manufacturers) and demand (i.e., physicians, pharmacists, and patients) side to achieve sustainable policy changes. Evaluation of new policies should be a routine part of the policy process and carefully considered before introducing a plan.

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