

Economic impact of drug-related morbidity in Sweden

– Estimated using experts' opinion,
medical records and self-reports

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UNIVERSITY OF GOTHENBURG

Gothenburg 2014

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ISBN 978-91-628-9030-8 (print)

ISBN 978-91-628-9033-9, <http://hdl.handle.net/2077/35203> (e-publication)

Printed in Gothenburg, Sweden 2014

Ineko AB

‘...An error, sir, is worse than a sin, the reason being that a sin is often of opinion or viewpoint or even of timing but an error is a fact and it cries out for correction. ...’

Terry Pratchett, *Making Money* (p. 74-75)

For something to exist, it has to be observed, ... And if you want the story, then remember that a story does not unwind. It weaves. Events that start in different places and different times all bear down on that one tiny point in space-time...

Terry Pratchett, *Thief of Time* (p. 11)

‘As far as I can tell,’ he reported, ‘it’s a way of making up stories that work. It’s a way of finding things out and thinking about them ... *psy-ence*, you see? “Psy” means “mind” and “ence” means, er, *esness*,...

Terry Pratchett, *The Globe* (p. 223)

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ABSTRACT

Drug-related morbidity is an important public health concern, but knowledge about its economic impact is limited to hospitals. Thus, important consequences to the general public may have been overlooked. The aim of the thesis is to estimate the economic impact of drug-related morbidity in Sweden. Specific aims are to estimate the cost-of-illness of drug-related morbidity in Sweden based on pharmacists' and physicians' expert opinions. Moreover, to estimate the direct costs resulting from adverse drug events, identified from medical records or self-reported in a population-based survey, and to estimate the cost-of-illness of these individuals.

Healthcare professionals' expert opinions were used to estimate probabilities for clinical outcomes of drug-related morbidity. For adverse drug events and resource-use identified from medical records, costs were assigned using Cost Per Patient register data. Resource-use reported by survey respondents and expert panels were assigned unit costs based on national costs statistics. Furthermore, indirect costs were measured by the human capital approach. Cost estimates were prevalence-based and measured from a societal perspective.

Both pharmacists and physicians view drug-related morbidity to be common, and to cause considerable healthcare resource use representing up to 20% of all costs to the healthcare system. The adverse drug events identified from medical records were estimated to cause 1.5% of all drug costs and 9.5% of healthcare costs. Two types of self-reported adverse drug events - adverse drug reactions and sub-therapeutic effect of medication therapy - caused

0.5% of all drug costs, 6.1% of all healthcare costs, informal care, lost leisure time, and sick-leave. It can be concluded that drug-related morbidity causes resource use and harm in all parts of the Swedish healthcare system and the Swedish general public. It appears that sub-therapeutic effects of medication therapy are equally as costly as adverse drug reactions, but there were also costs resulting from other categories (e.g. drug intoxications). Moreover, this group of individuals had high overall resource use and costs; resulting from drug use, healthcare encounters, transportation, productivity loss from both short-term sick-leave and disability pension, and informal care. For patients with repeated encounters and prolonged episodes of drug-related morbidity, there appears to be potential for improving care and saving resources by rapid detection of occurring adverse drug events.

Keywords: drug-related morbidity, adverse drug event, cost-of-illness

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SVENSK SAMMANFATTNING

Det är idag väl känt att läkemedelsbehandling inte bara botar utan också orsakar sjukdom. Läkemedelsrelaterad sjuklighet orsakar både lidande och ökade vårdkostnader, men forskning om kostnader för läkemedelsrelaterad sjuklighet har hittills varit begränsad till patienter på sjukhus. Konsekvenser som uppstår i andra delar av vården och i övriga samhället är delvis outforskade, och vi riskerar därför att underskatta kostnaden för läkemedelsrelaterad sjuklighet i samhället. Avsikten med studierna i den här avhandlingen var att undersöka kostnaden för läkemedelsrelaterad sjuklighet i Sverige. För att ge en bred bild av problematiken samlades information till de olika delstudierna in från olika källor: I-II) apotekare och läkare, vårdgivare som ofta jobbar med läkemedel och läkemedelsrelaterad sjuklighet, III) patientjournaler, och IV) en befolkningsenkät.

Utifrån studierna beräknades de direkta kostnaderna för läkemedelsrelaterad sjuklighet. Direkta kostnader är kostnader för en specifik vara eller tjänst. Resursförbrukningen rapporterad av vårdgivarna och i befolkningsenkäten översattes till kostnader genom nationell kostnadsstatistik, medan journalerna var kopplade till ett register över kostnader för specifika vårdträffar och åtgärder. Förutom direkta kostnader för läkemedelsrelaterade sjukligheter beräknades också direkta och indirekta kostnaderna för all sjuklighet (oavsett orsak). Indirekta kostnader är produktionsbortfall, exempelvis sjukskrivning. Tack vare studiedesignen i respektive delstudie går resultaten att överföra till en befolkningsnivå.

Både apotekare och läkare uppgav att läkemedelsrelaterad sjuklighet är vanlig (50-60% av alla patienter i vården) och leder till stor vårdförbrukning. Utifrån deras skattningar av förekomst och kliniska konsekvenser beräknades kostnaden till 7000-15000 per patient med läkemedelsrelaterad sjuklighet, beroende på vilken del av vården som studerades. Enligt apotekarnas skattningar orsakar läkemedelsrelaterad sjuklighet 20% av den totala kostnaden för hälso- och sjukvård i Sverige. Läkemedelsrelaterad sjuklighet som identifierades från journaler beräknades orsaka 1,5% av läkemedelskostnaderna och 10% av vårdkostnaderna i Sverige. Läkemedelsbiverkningar och otillräcklig effekt av läkemedelsbehandling - två underkategorier av läkemedelsrelaterad sjuklighet - rapporterades i befolkningsenkäten tillsammans orsaka 0,5% av läkemedelskostnaderna, 6% av vårdkostnaderna, samt produktionsbortfall för anhörigvård, förlorad fritid och sjukfrånvaro. Om man utgår från de totala årliga kostnaderna i Sverige så

motsvarar detta läkemedel för 130-380 miljoner kronor och vårdkostnader på 12-19 miljarder kronor. De som drabbas av läkemedelsrelaterad sjuklighet har hög vårdkonsumtion även till följd av annan sjukdom, och orsakar högt produktionsbortfall, både jämfört med den allmänna befolkningen och om man begränsar jämförelsen till andra patienter i vården.

Tillsammans visar delstudierna att kostnaderna för läkemedelsrelaterad sjuklighet är spridda i hela vårdkedjan, och att ungefär hälften av kostnaden verkar uppstå utanför sjukhusen. Det finns en potential att minska lidandet och kostnaderna för den läkemedelsrelaterade sjukligheten, genom förebyggande åtgärder och genom att snabbare än idag upptäcka och åtgärda den sjuklighet som ändå uppstår.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

- I. Gyllensten, H, Hakkarainen, KM, Jönsson, AK, Andersson Sundell, K, Hägg, S, Rehnberg, C, Carlsten, A.
Modelling drug-related morbidity in Sweden using an expert panel of pharmacists.
Int J Clin Pharm. 2012; 34(4): 538-46.
- II. Hakkarainen, KM, Ahlström, D, Hägg, S, Carlsten, A, Gyllensten, H.
Modelling drug-related morbidity in Sweden using an expert panel of physicians.
Eur J Clin Pharmacol. 2012; 68(9): 1309-19.
- III. Gyllensten, H, Hakkarainen, KM, Hägg, S, Carlsten, C, Petzold, M, Rehnberg, C, Jönsson, AK.
Economic impact of adverse drug events – A retrospective population-based cohort study of 4970 adults.
PLoS One 2014; 9(3): e92061.
- IV. Gyllensten, H, Rehnberg, C, Jönsson, AK, Petzold, M, Carlsten, A, Andersson Sundell, K.
Cost of illness of patient-reported adverse drug events: A population-based cross-sectional survey.
BMJ Open 2013; 3(6): e002574.

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DEFINITIONS IN SHORT

- Adverse drug event** An injury resulting from medical intervention related to a drug.^[1]
- Adverse drug reaction** A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function,^[2] excluding drug dependence.^[3]
- Drug abuse** A maladaptive pattern of drug* use leading to clinically significant impairment or distress as manifested by one (or more) of the following, occurring within a 12-month period:
1. Recurrent substance use resulting in a failure to fulfil major role obligations at work, school, or home (such as repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school; or neglect of children or household).
 2. Recurrent substance use in situations in which it is physically hazardous (such as driving an automobile or operating a machine when impaired by substance use)
 3. Recurrent substance-related legal problems (such as arrests for substance related disorderly conduct)
 4. Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (for example, arguments with spouse about consequences of intoxication and physical fights).^[4]
- Drug dependence** A maladaptive pattern of use of an addictive drug[#] leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring any time in the same 12-month period:
1. Tolerance, as defined by either of the following: (a) A need for markedly increased amounts of the substance to achieve intoxication or the desired effect; or (b) Markedly diminished effect with continued use of the same amount of the substance.
 2. Withdrawal, as manifested by either of the following: (a) The characteristic withdrawal syndrome for the substance; or (b) The same (or closely related) substance is taken to relieve or avoid withdrawal symptoms.
 3. The substance is often taken in larger amounts or over a longer period than intended.
 4. There is a persistent desire or unsuccessful efforts to cut down or control substance use.
 5. A great deal of time is spent in activities necessary to obtain the substance,

use the substance, or recover from its effects.

6. Important social, occupational, or recreational activities are given up or reduced because of substance use.

7. The substance use is continued despite knowledge of having a persistent physical or psychological problem that is likely to have been caused or exacerbated by the substance.^[4]

Drug intoxication from overdose	A noxious, intended or unintended drug reaction that occurs at higher doses than normally used in man for prophylaxis, diagnosis or treatment. The intention for administrating the drug(s) may or may not be therapeutic. ^[3]
Drug-related untreated indication	A clinical condition that under normal circumstances requires pharmacological therapy but the person is not receiving any drug therapy for the condition. ^[3]
Sub-therapeutic effect of medication therapy	An absence of therapeutic response that could be linked causally either to dose that was too low, drug non-compliance, recent dose reduction/discontinuation or inadequate monitoring, and sub-optimal therapeutic effect due to improper drug selection or when treatment has been rational (e.g. first line treatment not effective). ^[3]
Drug-related morbidity	The illness resulting from an adverse drug event [§] .
New medical problem	Effects beyond the wanted effects of the drugs; including ADRs, drug dependence and intoxications by overdose (papers I-II).
Therapeutic failure	Insufficient effects of drugs due to erroneous therapy, such as sub-therapeutic dose, underuse, interaction or untreated indication, and sub-therapeutic effects with rational use of drugs (papers I-II).

* Licit drugs

Drugs classified as narcotics in the Swedish Medicines Information Engine (FASS), and five additional drugs with evidence on addictive properties: caffeine, codeine, nicotine, pregabalin, and dextropropoxyphene.

\$ Own definition used in this thesis.

ABBREVIATIONS

ADE	Adverse drug event
ADR	Adverse drug reaction
COI	Cost-of-illness
DRUMS	Drug-related morbidity in Sweden [project]
EUR	Euro, currency of European Union euro zone
Max	Maximum [estimation]
Min	Minimum [estimation]
NMP	New medical problem
SEK	Krona, currency of Sweden
STE	Sub-therapeutic effect of medication therapy
TF	Therapeutic failure
USD	Dollar, currency of United States of America
WHO	World Health Organization

PREFACE

My pre-understanding of public health in relation to drug therapy was based on both my background as a pharmacist and my own experiences of using medicines and experiencing their side-effects. In the pharmacy program I realised pharmacists can make a difference and help patients achieve better outcomes from their drug therapy. My Master's thesis involved interviewing hospitalised patients about their drug treatments, opinions and beliefs about drugs, and their experiences with side-effects. I have thereafter worked both in community pharmacies and as a ward pharmacist, always motivated by my desire to meet with the drug users and discussing their therapy.

This thesis is part of a national project exploring prevalence, preventability and costs of drug-related morbidity, the *Drug-related morbidity in Sweden* (DRUMS) project. The DRUMS project aims to identify drug-related morbidity in the Swedish general public, independent of how and where it occurs. The hypothesis is that drug-related morbidity causes harm and increases healthcare use, which is explored using quantitative data. Throughout the project, drug-related morbidity is acknowledged to affect a large group within the population. Thus, the consequences of drug-related morbidity are likely to affect several actors and payers in society, and the studies within the DRUMS project were therefore designed to identify drug-related morbidity and its consequences in the general public. By using data from several different sources - experts' opinion of healthcare professionals, medical record reviews, and a population-based survey - more information can be collected and drug-related morbidity can be studied from different perspectives. Because of the personal identity numbers and population-based registers available in Sweden, the project has unique opportunities to study drug-related morbidity in the general public and to include register data for each individual.

The DRUMS project will result in a project report, a number of articles, and two Doctoral theses. One thesis focuses on the prevalence and preventability of drug-related morbidity, while this thesis examines the economic impact of drug-related morbidity in Sweden. By estimating costs from the perspective of society, I intend to position the economic impact of drug-related morbidity in relation to other public health concerns.

1 INTRODUCTION

1.1 From case reports to global concerns

Drug safety and pharmacovigilance has developed over the last 60 years: In 1961, a short letter from W.G. McBride was published in the *Lancet*,^[5] addressing an observed increased incidence of severe abnormalities in newborn babies to mothers who had used thalidomide. Already in 1968, the global drug monitoring programme had started, aiming for early detection of pharmacovigilance signals.^[6] Today it is well known that all medicines have the potential to cause side-effects.^[7] Recently, the Global Burden of Disease report from the World Health Organization (WHO) reported that adverse effects of medical treatment corresponded to 83700 deaths^[8] and 1090000 years lived with disability during 2010.^[9] The researchers involved acknowledge that the figures presented, from the WHO Mortality database, appear to be underestimates.^[10]

Pharmacovigilance is “the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems”. It includes collection of spontaneous reports of adverse drug reactions (ADR) and other methods to evaluate drug safety in society.^[11] Methods include signal detection and data mining from spontaneous reports of ADRs, intensive monitoring through non-interventional cohort and case-control studies of users of specific drugs, and data mining of healthcare databases.^[12] The spontaneous ADR reporting has been based on the following definition: “a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function”,^[2] thus limited to therapeutic doses of the drugs. Since 2012, spontaneous reporting includes all “suspected ADRs”, including overdose, misuse, abuse and medication errors, and suspected adverse reactions associated with occupational exposure (Directive 2010/84/EU^[13]).

Since the early 1990s, research on adverse drug events (ADE), including both ADRs and the clinical consequences of medication errors, has developed.^[14] With the 1999 Institute of Medicine report “To err is human – building a safer health system”,^[15] increased attention was directed towards healthcare quality and errors. The report stated that 44000-98000 deaths annually in the United States were caused by adverse events in healthcare, and drug-related events were among the most common. The report was succeeded by a shift

towards a systems perspective on patient safety, with demands for multiple stakeholder involvement.^[16]

Part of this approach to patient safety is pharmaceutical care, a suggested new professional role for pharmacists. It focuses on interventions to identify and solve drug-related problems in order to resolve preventable drug-related morbidity and mortality.^[17] Pharmacist-led medication reconciliations in hospitals and emergency departments have been suggested to be a cost-effective method for solving drug-related morbidity.^[18,19] Another aspect is the identification and resolution of drug-related problems in community pharmacies. A large proportion of identified problems can be solved in the pharmacy without needing to contact the prescribing physician.^[20] Recently, the development of Good Pharmacy Practice guidelines has united pharmaceutical care with drug information, self-care initiatives in e.g. pharmacies, clinical pharmacy, and distribution of drugs.^[21]

Safe medication use is viewed as a public health concern globally, and has resulted in reporting systems and other initiatives in many countries.^[22] In Europe, medication safety is viewed as an important system-based public health issue and “one of the fundamental areas of patient safety, since adverse drug events are the most frequent single type of adverse events”. However, it has been reported that few of the patient safety initiatives brought up by the European Union or from the World Alliance for Patient Safety has included specific initiatives concerning drug safety.^[23] The Swedish patient safety contracts, between the Swedish Association of Local Authorities and Regions and the Swedish government, acknowledge the importance of drug-related injuries in healthcare^[24] and include reference to the national drug strategy.^[25] The strategy^[26,27] was developed in 2011 and includes, for example, efforts to introduce medication reconciliation for elderly patients with many medications and in transition between caregivers. Similar interventions have been suggested to address inappropriate polypharmacy and reducing errors in countries such as the United Kingdom.^[28]

1.2 Drug safety terminology and definitions

Drug-related morbidity is thus recognised as an important drug safety issue, but previous research has identified variations in the terminology used in publications of patient safety.^[29] Below is a short description of selected terms. A complete overview is not proposed.

Adverse events and **medical errors** are terms related to the safety of any treatment (including e.g. surgery or drug therapy). An adverse event can be

described as “an injury caused by medical management rather than the underlying condition of the patient”, and a medical error is “the failure of a planned action to be completed as intended or the use of a wrong plan to achieve an aim”.^[30] A medical error resulting in harm is a preventable adverse event. However, only a small proportion of all medical errors result in adverse events and many adverse events occur without a medical error.^[30]

An adverse event resulting from drug therapy in particular is called an **ADE**, and the corresponding error term is **medication error**. ADEs are often defined as “harm resulting from the (appropriate or inappropriate) use of a drug”.^[1] However, the terminology may vary.^[31] ADE categories vary between studies, but may include e.g. **ADRs, drug dependence, drug intoxications, and STE**.^[32-34] One of several suggested definitions of medication errors is “a failure in the [drug] treatment process that leads to, or has the potential to lead to, harm to the patient”.^[35] Medication errors can be contrasted by **drug-related problems**, “an undesirable patient experience that involves drug therapy and that actually or potentially interferes with a desired patient outcome”.^[36] Medication errors comprise actual errors, while drug-related problems include also undesirable experiences resulting from rational drug therapy. ADEs are **preventable** if caused by medication errors, but not all medication errors or drug-related problems result in ADEs.

It is thus possible to distinguish between two intrinsically different medication safety issues. Medication errors are linked to the safety of the healthcare system, and ADRs are linked to the safety of the product.^[23] Garfield and colleagues have reviewed the literature to identify medication error rates during the drug use process. The authors reported that in several stages during this process, the error rates was more than 50%, and the optimal benefit of the medicines was achieved in only 4-21% of the users.^[37]

Drug-related morbidity is similar to ADE. According to Hepler and Strand, drug-related morbidity is “the phenomenon of therapeutic malfunction or miscarriage – the failure of a therapeutic agent to produce the intended therapeutic outcome” and the “manifestation of unresolved drug-related problems”. The description includes “both treatment failure (e.g. failure to cure or control a disease) and production of new medical problems (e.g. an adverse or toxic effect)”.^[17] Thus, drug-related morbidity can be divided into **new medical problems (NMP)** and **therapeutic failures (TF)**.^[38] NMPs are “effects beyond the wanted effects of the drugs and included ADRs, drug dependence and intoxications by overdose”. TFs are “insufficient effects of drugs due to erroneous therapy, such as sub-therapeutic dose, underuse, interaction or untreated indication, and sub-therapeutic effects with rational

use of drugs” (discern from the above mentioned STEs). An important distinction is that the NMPs and TFs are effects beyond or below the wanted effects (i.e. optimal drug treatment outcome) not in relation to the expected treatment outcomes. Even though it is well known that chemotherapy is likely to cause hair loss and in some cancers only delay death, to the individual hair loss is still an NMP and cancer mortality is a TF. It shall be acknowledged that regardless of the terminology used, adverse clinical outcomes resulting from drug therapy will comprise a continuum from negligible outcomes to fatal events. Drug-related morbidity can also be **preventable**.^[39,40]

The definitions used in this thesis are given on pages ix-x, and further elaborated in chapters 3.1.1 and 3.1.3.

1.3 Clinical impact of drug-related morbidity

In addition to the variation in terminology and definitions, the prevalence of drug-related morbidity varies between studies, by patient population under study, detection methods, and if the study is retrospective or prospective.^[34] It has for example been demonstrated that chart review, computer monitoring, direct care observations and prospective data collection identified more drug-related problems compared to other detection methods used in hospitals (including voluntary reports).^[41]

Studies of drug-related morbidity in ambulatory care have found a prevalence rate of 3%-35% (median: 13%).^[42] In emergency departments, the prevalence rate has been 0.2%-41% (median: 5%).^[42] ADRs have been reported to cause 0.2%-22% of all hospital admissions (median: 5%).^[43,44] According to observational studies, drug-related morbidity is associated with 0.1%-54% of hospitalisations.^[34] Among hospitalised patients, 0.2%-65% experienced drug-related morbidity.^[45,46] Moreover, for drug-related morbidity in ambulatory care the median preventability rate was 21%.^[40] Among adult patients, 52% of all outpatients’ and 45% of all inpatients’ ADRs were preventable.^[47]

Few studies have analysed the effect on drug-related morbidity prevalence by patient characteristics, but it has been suggested that some age groups and female sex may be risk factors.^[46] Previous ambulatory care studies have reported median prevalences for drug-related morbidity in prospective studies to be 3%, 9% and 23% for children, adults and the elderly, respectively.^[42] Among children, 0.5%-3% of all emergency department visits were drug-

related, and 0.2-4% of all hospital admissions were caused by drug-related morbidity.^[48]

The drugs most often associated with ambulatory care drug-related morbidity in each age group were: anti-infectives, analgesics and respiratory drugs for children; cardiovascular drugs, analgesics and central nervous system drugs among adults; and cardiovascular drugs, anti-cancer drugs and central nervous system drugs in the elderly.^[42] The four most common causes of drug-related morbidity during hospital stays in the United States of America during 2011 were steroids, antibiotics, opiates and narcotics and anticoagulants.^[49] Moreover, for these four causes of drug-related morbidity there were differences in rates by healthcare payer status of the patient, hospital teaching status, hospital ownership and region, for example. Cardiovascular drugs, analgesics and hypoglycemic agents have been reported to account for more than 80% of all preventable drug-related morbidity.^[40] A recent study found that age, number of prescription drugs and time since starting a new drug are examples of risk factors for preventable drug-related hospital admissions.^[50]

1.4 Economic impact of drug-related morbidity

In studies measuring the economic impact of drug-related morbidity large variation has also been identified in: study design and source population,^[51] lack of a standardised terminology of drug-related morbidity,^[51] causality assessment of included cases,^[52] and in varying perspective of the cost analysis.^[53]

Studies of drug-related morbidity in the general public have modelled the consequences and costs of drug-related morbidity based on experts' opinions, but most previous studies have identified drug-related morbidity in patients attending hospitals, to estimate the costs of drug-related morbidity causing hospital visits or admission, and costs of drug-related morbidity that occurs during hospitalisation.^[51] The additional cost of drug-related morbidity in patients attending hospital is USD 2300-5600 per patient.^[51] However, little is known about the actual costs to society and individuals and resources needed for prevention and monitoring of these outcomes.^[52]

This thesis work started with a literature review^[54] of methods and sources used for estimating costs of drug-related morbidity in previous research to gain knowledge of the research field. No studies were found of costs resulting from drug-related morbidity in the general public, including outside hospitals.^[54] The identified studies estimated costs from either the hospitals'

or payers' perspectives, and used a wide range of cost sources (e.g. costs from charges, billed charges or claims payments, unit costs, length of stay-based estimates using either reimbursements or daily hospital costs). The studies published after our review used costs from charges^[55] or cost-accounting data^[56,57] to measure costs and were also limited to the hospital perspective. The same limitation in the literature was found in a review of studies assessing the costs of ADRs, in particular, although that review also included more specific patient groups (e.g. only elderly patients and patients in disease-specific hospitals).^[58]

1.5 Good:harm ratio of drug therapy

The valuation of safety, effectiveness and acceptability of an intervention can be expressed as a good:harm ratio.^[59] High quality healthcare implies that the good of delivered interventions is higher (or much higher) than the harm. Under the assumption that the good:harm ratio of a specific (drug) treatment is beneficial, the decision-maker needs to decide if the treatment is affordable based on information about costs of different treatment options (including the option to sustain from any treatment). Moreover, it is possible that the healthcare professional places a lower (or higher) value on harm than the potential recipient of the intervention.^[59] Thus, treatment decisions should be based on knowledge of safety, effectiveness, acceptability, and costs of alternative treatments. Such cost estimates need to include all costs, as related to the good:harm ratio.

Although randomised controlled trials are the main pre-marketing research method for new drugs, it has been acknowledged that these studies are less adept in detecting adverse reactions to medicines.^[60] This is a result of short follow-up time and possible time-lag from starting the drug to developing an ADR, limitations of the study population to less frail and fewer patients, lack of previous knowledge of potential ADRs that can be screened for effectively, and a more controlled treatment that minimises errors, to name but a few situations. The limitations in randomised controlled trials, to calculate, for example, adequate Numbers Needed to Harm, may be solved by post-marketing surveillance based on administrative data, electronic health records and register data.^[61] Due to a suggested imbalance in comparing voluntary reports of adverse effects to effect measures from randomised controlled trials, other detection methods will be needed.^[11] Moreover, voluntary reports may be insufficient for such aspects as tracking time-trends because of underreporting.^[41] Thus, knowledge about harm of medicines is insufficient.

In Sweden, 67%^[62,63] of the population uses on average 16 prescription drugs per user annually. This use is in addition to the use of over-the-counter drugs and herbal remedies. Previous studies on the economic impact of drug-related morbidity have been divided into studies of effects occurring during hospital admission, studies of effects in the ambulatory setting that cause emergency departments visits or hospitalisation, and studies estimating the impact to the whole population based on expert opinion or extrapolations from hospital data.^[51] Thus, it appears that the adverse effects of medicines may also occur outside of emergency departments and hospital admissions, and thus have an economic impact and public health relevance that have not been included in previous research from hospital-based studies. The suggestion was further supported by a population survey from Isacson and colleagues^[64]: 6.4% of the general population reported to have experienced ADRs during a two-week period, including 10.2% of all prescription drug users, 1.0% of the population using over-the-counter drugs and 0.1% of those using herbal remedies reported ADRs as a result of these treatments.

Thus, to estimate the economic impact of drug-related morbidity in society, epidemiology and other research methods that study whole populations from public health research seems appropriate. Epidemiology is “the use of quantitative methods to study diseases in human populations so that they might be prevented and controlled”,^[65] or “the study of the distributions and determinants of diseases in populations”.^[66] In pharmacoepidemiology, “the study of the use of and effects of drugs in large number of people”,^[66] or “the use, effects, and outcomes of drug treatment are studied from an epidemiological perspective, that is, from a population perspective”.^[67]

Another aspect of public health research addresses the healthcare needs, outcomes and efficiency of healthcare services.^[68] In the World Health Report on health system financing,^[69] the WHO acknowledges the need for improved healthcare efficiency, the need to address errors in healthcare and appropriate use of drugs to avoid unnecessary expenditures, since a large proportion of resources in healthcare are reported to be wasted.

Efficiency and expenditures in healthcare are included in the scope of health economics.^[70] Health economics “analyses the economic aspects of health and healthcare, and that usually focuses on costs (input) and the consequences (outcomes) of healthcare interventions, using methods and theories from economics and medicine”.^[67] One part of the multidisciplinary speciality of health economics is pharmacoeconomics, described as “the scientific discipline that assesses the overall value of pharmaceutical healthcare products, services and programs”.^[67] According to economic

theory, resources - personnel, money, and facilities for examples - are limited, and the allocation of such resources needs to be decided.^[71] In healthcare, the choices made are critical, since patients' lives will depend on how resources are prioritised. Thus, there is a need for identifying alternative uses of resources, select from what perspective the rationing decision will be made, and estimate the magnitude of costs necessary for conducting, for example, an intervention.^[71]

1.6 Economic impact of harm

When using health economics to study public health and public goods, one important aspect is the presence of externalities - effects to other agents than the purchaser or producer of a product or service.^[72] One aspect referring to externalities can be the consequences of a rationing decision, since resources are limited and universal coverage of all needs is unfeasible. Moreover, in the international guidelines for costs of substance abuse it was argued that negative and - to the purchaser - unpredictable effects shall always be viewed as externalities, since the purchaser has not accounted for these costs in their decision.^[73] The matter is further hampered by asymmetries in knowledge between users and producers (such as trained healthcare professionals) about good:harm ratios for the suggested therapy or service, for example.^[74,75] Thus, for comprehensive knowledge on the economic impact of adverse effects of drug use, studies from a societal perspective are needed, measuring externalities occurring throughout society and unexpected costs to the drug user. Employing a societal perspective ensures that costs and resource use will be included regardless of who pays.^[76] This need is acknowledged by the Swedish Dental and Pharmaceutical Benefits Agency, in advocating a societal perspective on the costs and consequences of drugs for benefit decisions.^[77]

The combination of epidemiological knowledge and economic data to describe the economic burden for a specific disease or diseases is called an economic cost study, or cost-of-illness (COI) study.^[73] In the 1960's Rice suggested the methodological framework for estimating costs of illness, disease and death. The framework enabled comparison of illness costs to the gross national product and estimated annual costs of specific illnesses, and was presented as the first step in future economic analyses of interventions.^[78] In a COI study, the aim is to “determine the total economic impact (cost) of a disease or health condition on society, through the identification, measurement, and valuation of all direct and indirect costs”.^[67] Transfer payments, e.g. taxes, are not included to avoid double counting.^[78]

When estimating the COI, intangible costs (e.g. pain and grief) are omitted, because these do not directly involve a loss of output.

Since no comparisons to treatment outcomes or benefits are made, the COI study is not viewed as an economic evaluation study.^[71] However, the COI study can provide information about the costs to any subsequent economic evaluations.^[79] COI studies have been criticised for not measuring the marginal costs saved by preventing the disease, for not measuring the alternative costs but the occurring costs, for not being able to isolate the costs for the specific disease, and for large variations in estimated costs due to methodological differences.^[80,81] Thus, it has been suggested that such studies are of limited value to decision makers. The commonly used human capital approach, to measure indirect costs, has also been criticised for overestimating the true productivity loss,^[81] although the arguments for the friction cost method have been questioned.^[82]

The response from COI advocates has been that correctly conducted, these are still of use to decision makers, but that it is important not to confuse them with full economic evaluations such as cost-benefit analyses^[83] and not to use COI data to allocate resources due to the lack of benefit information.^[79] The aim of COI studies shall be to assess the economic burden of illness to society, identify important cost component, describe the management of the disease by identifying the distribution of costs e.g. between services, and explore cost drivers and variation in costs between settings and/or patient groups.^[83] It has also been suggested that the method for measuring and presenting the COI results will be decisive in how useful the information will be for policymakers.^[84,85] One important aspect is the presentation of costs together with resource use quantities, where the costs may enable comparison between the decision makers' different areas of responsibility and available budget, while the quantities may enable evaluation of the relevance of these costs and of used unit costs.^[76]

2 AIM

The aim of this thesis is to estimate the economic impact of drug-related morbidity in Sweden.

2.1 Specific aims

Paper I: To estimate the proportions of patients with drug-related morbidity and preventable drug-related morbidity and the COI of drug-related morbidity in Sweden based on pharmacists' expert opinions.

Paper II: To estimate the proportion of patients with drug-related morbidity and preventable drug-related morbidity and to estimate the COI of drug-related morbidity in Sweden based on physicians' expert opinions.

Paper III: To estimate the direct costs caused by ADEs, including costs for dispensed drugs, primary care, other outpatient care, and inpatient care, and to relate the direct costs caused by ADEs to the societal COI (direct and indirect costs), for patients with ADEs and for the entire study population.

Paper IV: To estimate and compare the COI of individuals with and without self-reported ADEs, from a societal perspective. A secondary aim was to estimate the direct costs resulting from two ADE-categories, ADRs and STEs.

3 METHODS

An assumption for this thesis work was that drug therapy adds value to society, and to appropriately estimate the added value of drug therapy both benefits and harm should be considered. However, it was not judged feasible to include the full good:harm ratio-calculation in the included studies, but the aim was to describe the economic impact of drug-related morbidity in society.

A combination of methods (Table 1) was deemed necessary to explore the magnitude and consequences of drug-related morbidity in society. The sub-studies were designed to identify both direct and indirect costs where possible.

Table 1. Overview of the papers included in this thesis.

Papers	Data sources	Population	Drug-related outcomes	Measured costs
I	Pharmacist practitioners experts' opinions	All patients in healthcare, in 2010	NMP and TF	Direct healthcare and drug costs for drug-related morbidity
II	Physician practitioners experts' opinions	All patients in outpatients and inpatients care, respectively, in 2010	NMP and TF	Direct healthcare and drug costs for drug-related morbidity
III	Medical records and register data	Adult population* in Östergötland County, in 2008	ADRs, drug abuse, drug dependence, drug intoxications, morbidity due to untreated indications, and STEs	Overall COI and direct healthcare and drug costs for ADEs
IV	Survey responses and register data	Adult population* in Sweden, in 2010	ADRs, drug dependence, drug intoxications, morbidity due to untreated indications, and STEs	Overall COI (including social services, transportation and informal care) and direct healthcare and drug costs for ADRs and STEs

* The studies were limited to the adult population because of limitations in register data.

The expert panel studies (papers I-II) were designed to mimic an often cited American study^[38] that had never been replicated in other settings. The studies added information about how common healthcare professionals perceive drug-related morbidity, and the costs of resources use were estimated from the expected clinical consequences of drug-related morbidity. The study of medical records (paper III) identified drug-related morbidity in patients who have made the decision to seek healthcare. The study adds knowledge about ADEs that can be identified in medical records, and the resulting resource use. In the population-based survey (paper IV), ADEs were reported and identified by the general public, i.e. the individual drug users, although hospitalised or institutionalised patients may not have received the questionnaire. The survey includes respondents' perceptions about health and medicines, experienced ADEs, healthcare and drug use. The cost analysis includes resource use and lost production reported from respondents, but also informal care and social services. Intangibles were not included in the thesis.

For the cost analyses, sensitivity analyses were conducted to analyse the impact of included cost components and clinical outcomes on the results and conclusions. The sensitivity analyses are presented in the appendix.

3.1 Methodological framework

The section includes a brief overview of some methodological choices made in the thesis, regarding drug-related morbidity and the application of the COI method to this morbidity.

3.1.1 Drug-related morbidity in the thesis

It is intended that this thesis uses coherent terminology and definitions in all studies, but due to differences in data and sources there are variations (Figure 1).

In the DRUMS project, ADE and drug-related morbidity are used as synonyms. However, in studying the resource use and costs, there appears to be advantages in having two separate terms. Thus, in this thesis it was found useful to distinguish between the injury, ADE, and the subsequent illness, drug-related morbidity (Section 3.1.3). ADE categories included were ADRs, drug abuse, drug dependence, drug intoxication from overdose, sub-therapeutic effect of medication therapy (STE), and drug-related untreated indication. The illness resulting from an ADE is referred to as drug-related morbidity. However, in some sections related to included papers, this was not

feasible and the terminology was instead adapted to the terminology in each paper.

The terms morbidity, illness and disease are used as synonyms in the thesis, based on their use in established expressions, such as drug-related *morbidity*, cost-of-*illness*, and burden of *disease*. Drug-related morbidity includes both diseases (an interruption, cessation, or disorder of body functions, systems, or organs^[86]) and experienced illness (the state of being unwell^[87]) that results from drug therapy.

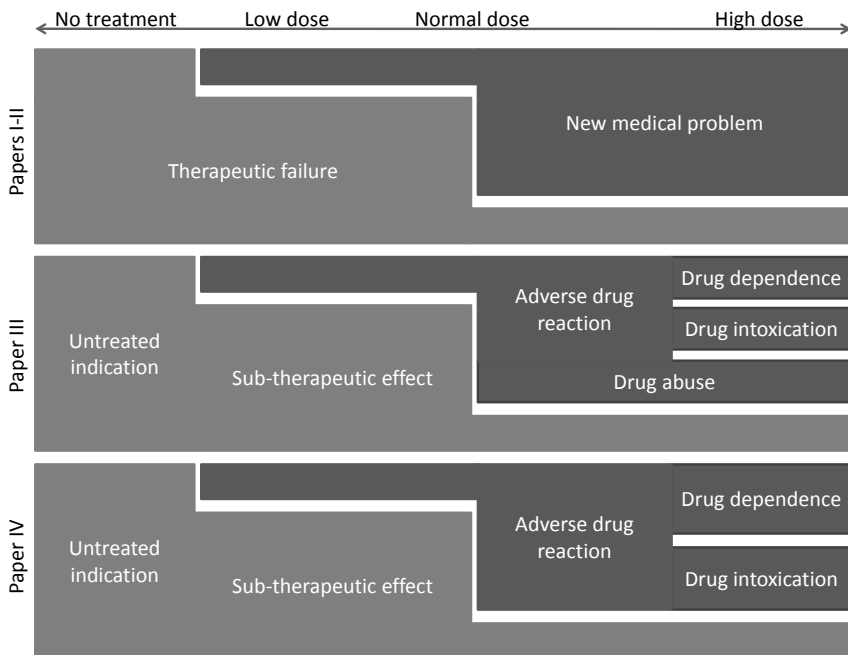


Figure 1. Conceptual overview of the drug-related outcomes in papers I-IV.

3.1.2 Economic impact in the thesis

The method used for measuring economic impact in the thesis is called COI (indicating a descriptive cost study^[73]). In such studies, several methodological decisions are required,^[79] e.g. regarding which costs to include, how costs are estimated, the time-period, and perspectives for the costs estimations.

Direct and indirect costs

Direct costs are expenditures for prevention, detection, treatment, rehabilitation, research, training, and capital investment in medical facilities.^[78] Although the theoretical price of a resource is the opportunity cost, costs are generally assigned using market prices.^[71] Indirect costs comprise the productivity loss, i.e. the loss of output to the economy, lost wages and taxes resulting from morbidity and mortality, and estimated economic loss, for example of housewives' services.^[78] According to Segel, indirect costs include mortality costs, morbidity costs due to absenteeism and presenteeism, informal care costs, and when relevant, also losses due to crime, for example.^[79] The value of resources lost due to morbidity and mortality is estimated using such methods as the human capital method, friction cost method, willingness to pay method,^[79] or Washington panel approach.^[88] In brief, the human capital approach estimates productivity loss from the lost wages multiplied by the social insurance contribution, while advocates for the friction cost method claims this will overestimate the lost productivity which needs to be adjusted based on the work compensated by the worker after returning to work, and during long-term or permanent absence for replacement by other workers after a friction period. The Washington panel approach only estimates resources lost during healthcare.^[88] Willingness to pay differs from the other methods in that it measures the amount the individual would be willing to pay to avoid the disease.

In this thesis, the direct costs resulting from drug-related morbidity were measured, based on identified resource use resulting from drug-related morbidity. When no cost could be applied (e.g. long-term outcomes in papers I-II, and interventions without a registered cost in paper III), the resource use was presented descriptively. Moreover, in papers III-IV the overall societal costs were measured, including direct and indirect costs. Indirect costs were calculated using the human capital approach. In paper IV, health-related quality of life was also measured to get an indication of the intangible effects (the results are presented in the publication).

Bottom-up or top-down

The methods used for estimating the COI are often divided into top-down and bottom-up approaches.^[79,83,84] According to the top-down approach, costs are identified at an aggregated level and assigned to each illness using information about such aspects as relative risk of the specific illness.^[79] The top-down approach can divide, for example, national healthcare expenditures by primary diagnosis disease categories using the International classification of diseases.^[83] The bottom-up approach estimates the costs using information about resource use resulting from the specific illness.^[79] The COI is calculated by multiplying the costs of specific resources by the number of resources used (from e.g. survey data).^[79,83] A third econometric approach uses the cost difference between individuals with the disease and matched controls, or regression analysis, to estimate the incremental COI.^[79]

In this thesis, bottom-up methods were used for cost assignment. However, it may be argued that several of the used costs were based on top-down estimations, e.g. weighted costs in national statistics (papers I-II, IV) and register data that included both prices based on specific resource use and standard costs (paper III).

Incidence-based or prevalence-based

COI studies can be divided into incidence-based and prevalence-based studies.^[79,83] Incidence-based estimates include all future morbidity and mortality costs due to illness initiated during the study period. Prevalence-based studies include all morbidity and mortality costs during a selected period, often a year.^[79] Moreover, it has been suggested that two types of prevalence-based studies can be distinguished: Prevalence-based COI analyses that include morbidity costs resulting from existing illness and future costs resulting from mortality and permanent disability during the study period, and burden of disease studies measuring the costs borne during a specific period.^[89] The burden of disease method is less commonly used, and includes morbidity and mortality costs during the study period and resulting from illness in previous years. For illnesses with a short duration and negligible future costs, the COI estimates are equivalent using the three methods.^[90] When illness results in future costs, the burden of disease method will result in high costs compared to the other methods, due to discounting of future morbidity and mortality costs in incidence-based estimates and of future mortality costs in prevalence-based COI analyses.^[89]

In this thesis, prevalence-based costs were measured. Previous critique of the prevalence-based COI methods has included the lack of information about possible gains achievable through prevention, although it has been argued

that prevalence-based estimates are useful for measuring aspects such as ongoing treatment costs.^[90,91]

Several layers of perspectives for cost analysis

The impact of illness can be measured on a macroeconomic or microeconomic level.^[92] Macroeconomic cost analyses are concerned with the impact of illness on society and economic welfare, and often relate costs to the gross domestic product.^[78,92] Since COI estimates are often limited to health sector spending and lost labour productivity, they provide only a partial picture of the macroeconomic impact of illness.^[92] The microeconomic impact of illness, to i.e. households, firms and government, is of interest for policy makers to identify such factors as the impact of illness on consumption.^[92] Thus, a COI study can include costs according to several different perspectives, that is costs to different decision makers: society (“societal”), healthcare providers, third-party payer, businesses, government, patients and relatives of patients.^[79] Since the organisation of healthcare differs between countries, the distribution of costs between actors will also differ. This makes international comparisons difficult, especially when only a partial picture is presented.^[93]

A postulation for a free market is that the producers and consumers are aware of and take into account all results of the resource consumption, but in healthcare there is, for example, an imbalance in knowledge between producers (healthcare professionals) and consumers (drug users). Due to imperfections in the healthcare market, the opportunity cost of healthcare resources may deviate from the market price.^[71] When studying the COI to society, costs can also be viewed as either private or external.^[73] Private costs are expenditures to the individual consumer and external costs are uncompensated expenditures to producers and other consumers, resulting from the actions of the consumer.^[72] Still, when the economic impact to the consumer is higher than the perceived cost (e.g. price of cigarettes compared to the healthcare costs from smoking), the difference can be viewed as external costs to the consumer.^[73] Since in the Nordic countries, healthcare is mainly financed collectively through taxes, neither producers nor consumers are viewed as the payers of healthcare (although the consumers will pay indirectly through taxes). The externalities (costs to others than producers or consumers) of treatment decision are likely to be high, and may not be accounted for. Thus, market prices may not be truly representative of the opportunity costs.

In this thesis, costs were measured from the societal perspective, including all costs resulting from drug-related morbidity and overall morbidity, regardless of who pays.

3.1.3 Understanding drug-related resource use

To understand the processes involved in resource use resulting from ADEs and drug-related morbidity, it was useful to adapt a framework from health disaster management. It has been suggested that the governmental view of national public health systems has shifted towards increased recognition of the need for emergency preparedness to respond to such instances as health disasters and natural catastrophes, including development of emergency management in mitigation, preparedness, response, and recovery phases.^[94] During thesis-work, these theories have influenced the view of both disease symptoms and drug-related morbidity as health disasters, albeit on a different scale. For each individual, the development of a new symptom can be viewed as a disaster for which there is ways to mitigate and improve preparedness beforehand. Likewise there are phases of response and recovery from the event.

The framework included the following phases: 1) pre-event; 2) event; 3) damage; 4) changes in function(s); 5) relief; 6) recovery; and occasionally 7) development.^[95] The framework can be explained using a fracture as an example: 1) the victim receives a blow to the leg, either because of a conducted error or randomly (potential risk or error); 2) the blow results in a fracture (injury); the consequences are 3) severe pain; and 4) inability to walk; 5) the individual needs symptomatic pain relief and instructions on how to gain the ability to walk again (treatment of illness); 6) the bone is realigned and immobilised (treatment of injury); and 7) during the treatment the individual is diagnosed with osteoporosis, and thus receives drug treatment and training to strengthen the bones further (development to improve the future “pre-event” status).

The framework enables us to think of the costs as occurring over time after the event rather than at the event; the event being the health disaster of the individual. One part of the term ADE is “event”, which is synonymous to happening or occasion, while morbidity in drug-related morbidity is related to illness or disease, an ongoing state. If studying the frequency, characteristics or preventability of these states, the results should be equal regardless of the term used and depend more on the selected definitions. However, by distinguishing the ADE and any subsequent drug-related morbidity, and using the framework, it is possible to identify distinct phases

(Figure 2): 1) the pre-event phase, i.e. an individual requiring drug therapy; 2) an ADE occurs which 3) results in damage, i.e. drug-related morbidity; and 4) changes in function. For Phase 5) relief from symptoms is achieved by treatment of drug-related morbidity and 6) after resolving the ADE, the individual recovers. With some ADEs, it is also possible to 7) develop the therapy, to lower the risk or impact of any future injuries. Even though the ADE can develop fast, such as at the first dose of a new medicine, or gradually during treatment of chronic illnesses, the phases should be the same.

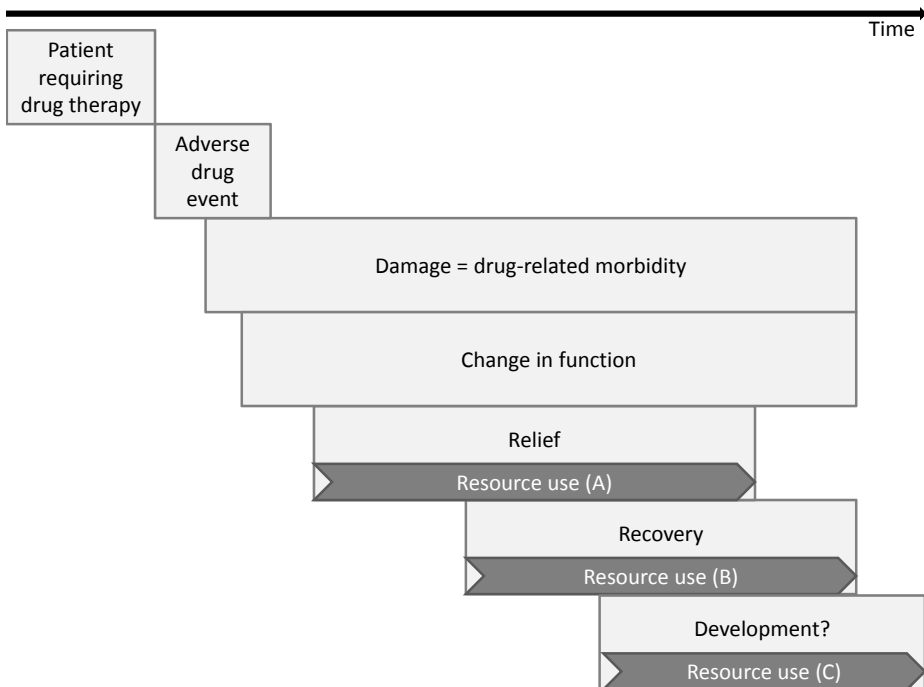


Figure 2. Using a longitudinal framework for health disaster management in describing the phases of drug-related morbidity. Resources used aims to A) alleviate or reduce the symptoms of the drug-related morbidity, B) cure the ADE, to return to the pre-event state, and C) develop and improve the drug use of the individual, to decrease the future risk, or reduce the impact of future ADE.

The terminology is arbitrary as long as it distinguishes the event from the symptomatic period following the event, but the two terms ADE and drug-related morbidity were considered useful for the purpose. Comparing this application of the terms to previous research, ADEs can still be defined as “an injury caused by medical management...” (comparable to a fractured leg). Previous applications of the term drug-related morbidity has been as “the phenomenon of therapeutic malfunction or miscarriage – the failure of a therapeutic agent to produce the intended therapeutic outcome” and a “manifestation of unresolved drug-related problems”.^[17] Also, it has been suggested that drug-related morbidity “includes outcomes by an adverse or toxic effect (direct) or failure to obtain the necessary result within a reasonable time, including occasions where an indicated therapy was either not used or was pharmaceutically ineffective (indirect)”.^[96] These definitions appear to be directed towards the clinical outcomes rather than process-oriented.^[97] Thus the suggested use of the term does not seem to contradict previous applications.

When using the framework, it appears that several types of costs can be distinguished. In this thesis, the costs for relief of the ongoing drug-related morbidity and solving the underlying ADE (resource use A and B in Figure 2) were included. In the framework, there are also costs associated with prevention of ADEs and drug-related morbidity; both resource use from primary prevention initiatives aiming to lower the risk of experiencing ADEs and from secondary prevention aiming to minimise the risk and severity of repeated events. Due to the design of the cost analyses of the DRUMS sub-studies, costs for prevention are only partially covered.

The expert panels’ estimates (papers I-II) did not distinguish ADE costs from subsequent drug-related morbidity costs. In paper III it was possible to distinguish the costs for treating ADEs from costs of the subsequent drug-related morbidity, since resource use for ADEs identified in the medical records were further divided into diagnosing, treating and monitoring drug-related morbidity. In the survey, respondents were asked to distinguish interventions used for treating the ADE, but it was not possible to separate this from other healthcare encounters resulting from ADEs.

3.2 Data collection and resource use quantities

The section describes the settings of each included sub-study and the different sources used to identify drug-related morbidity and resource use.

3.2.1 Settings

For the experts' opinions studies the setting encompassed patients within the Swedish healthcare system (paper I), and all patients in outpatient and inpatient care (paper II), respectively. In Sweden, approximately 70% of residents seek healthcare at least once annually, and 9.5% of the residents are hospitalised.^[98]

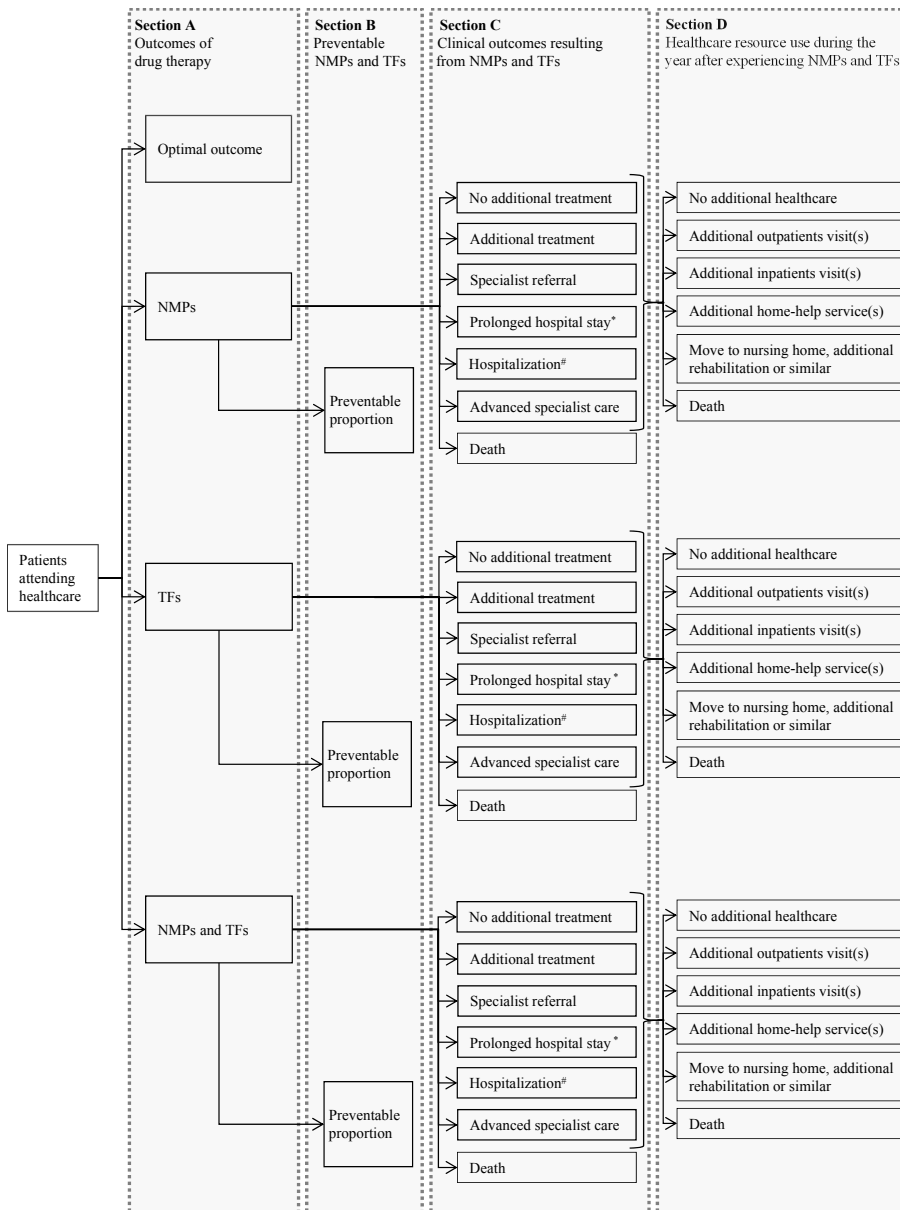
For the medical record study (paper III) the setting evaluated adults in Östergötland County, a county in the southeast of Sweden. The county was selected due to representative demographic distribution, availability of administrative healthcare use and cost data register. The random sample was identified from the population in Östergötland County, using the Population register (Statistics Sweden) that includes all Swedish residents. The county population in 2010 was 429642, 49.8% were women and 50.2% men. The age distribution was: 21.6% was 18 years or younger and 18.9% was above the official retirement age 65 years.^[99] The life expectancy at birth was 79.6 years for men and 83.2 years for women.^[100]

For the population survey (paper IV) the setting was adults in Sweden (7382226 individuals on January 1st 2010). The random sample was identified from the Swedish population, using the Population Register (Statistics Sweden) that includes all Swedish residents. The Swedish population in 2010 was 9415570; 50.2% were women and 49.8% men. The age distribution was: 20.4% was 18 years or younger and 18.5% was above the official retirement age 65 years.^[63] The life expectancy at birth was 79.5 years for men and 83.5 years for women.^[101]

3.2.2 Healthcare professionals' opinions (papers I–II)

To identify healthcare professionals' opinions of drug-related morbidity in the general public, a conceptual model of drug-related morbidity was used in two studies based on experts' opinions of strategically sampled clinically experienced pharmacists and physicians, respectively.

A published conceptual model^[38] was translated into Swedish and adjusted to the Swedish healthcare context. The model was complemented with questions on preventable drug-related morbidity, and clinical outcomes were reduced to short-term results (Figure 3).



* In section C, *Prolonged hospital stay* was excluded from the outpatient physicians' decision tree, since the outpatients physicians answered the questions based on outpatients.

In section C, *Hospitalisation* was excluded from the inpatient physicians' decision tree, since the inpatient physicians answered the questions based on inpatients.

Figure 3. The conceptual model of drug-related morbidity used in the expert panel studies (papers I-II).

In section A of the conceptual model, drug-related morbidity included three negative outcomes of drug therapy: NMPs, TFs and a combination of NMPs and TFs. In section B of the decision tree, respondents estimated if drug-related morbidity was considered preventable. Section C consisted of clinical outcomes of drug-related morbidity, and section D described additional healthcare use of patients during the following year after the drug-related morbidity. Thus our conceptual model differs from the model used in previous studies in that it is prevalence-based instead of incidence-based since it includes all prevalent drug-related morbidity, not only drug-related morbidity occurring due to prescriptions at a specific healthcare encounter. Moreover, it is not limited to estimating drug-related morbidity among those patients receiving at least one drug prescription at an incident encounter, and it divides short-term and long-term clinical outcomes into section C (short-term) and section D (long-term).

The method consisted of a two-round Delphi process. In the first round, the expert panel participants estimated the probabilities of drug-related morbidity, preventable drug-related morbidity, clinical outcomes and additional healthcare use. In the second round, each panellist received a summary (interquartile range) of other panellists' estimations and could adjust his/her own estimations accordingly.

The pharmacist expert panel (paper I) included 29 pharmacists with experience in clinical pharmacy, representing a wide range of practices and care levels. The respondents estimated probabilities of response alternatives among patients who interact with the healthcare system in general.

The physician expert panel (paper II) included eleven physicians representing outpatient and eight physicians from inpatient care. The respondents estimated probabilities of response alternatives based on patients visiting each physician's healthcare setting (outpatient or inpatient). The results were analysed separately for outpatient and inpatient care.

The conceptual model was adapted to each expert panel. The pharmacist expert panel included both *Prolonged hospital stay* and *Hospitalisation* in the clinical outcomes of drug-related morbidity. However, the inpatient physicians did not estimate the probability of being *Hospitalised*, and the outpatient physician model excluded the probability of *Prolonged hospital stay*. Cost-generating components for each branch in the decision tree were identified from published literature and decided within the research group. The cost-generating components of *Optimal outcome* and *No additional treatment* were adapted to the healthcare setting under study.

3.2.3 Medical records and register data (paper III)

To identify drug-related morbidity reported in medical records, a retrospective cohort study of healthcare professionals' records was conducted (Flow diagram: Figure 1 in paper III). A random sample of 5025 Östergötland County residents aged 18 years or older in 2008 was identified. The Regional Patient Register (Östergötland County council) was used to identify all healthcare encounters by the included patients during the selected study period. The healthcare use data from the care data warehouse^[102] includes both outpatient and inpatient care, and most private outpatient care conducted in the county. Information about dispensed drugs was retrieved from the Swedish Prescribed Drug Register (National Board of Health and Welfare).

Eligible medical records were scrutinised by expert reviewers manually in a stepwise manner, with data on prescription drug use available. First, medical records of healthcare encounters during each study period were screened manually by a pharmacist using a trigger list and information about drug-drug interactions and inappropriate drugs. Additional information about spontaneously reported ADRs from the Adverse Drug Reactions Register (Medical Products Agency), cause of death from the Cause of Death Register (National Board of Health and Welfare), and any toxicological or forensic exams from RättsBase (National Board of Forensic Medicine) and ToxBASE (National Board of Forensic Medicine), were collected from registers and used for the evaluation and analysis of drug-related morbidity.

Potential cases were then analysed and evaluated by experienced practitioners, one physician and one pharmacist, according to causality,^[103] preventability^[104] and severity.^[104] Information from the screening, final evaluation, identified ADEs, and resource use resulting from drug-related morbidity was registered in standardised data collection sheets. The ADE categories included were: ADR, drug abuse, drug dependence, drug intoxication from overdose, STE, and drug-related untreated indication.^[3]

The data in the collection sheets was complemented with register data, by record linkage using personal identity numbers. Register data encompassed information on demographic and socioeconomic variables from the Longitudinal Integration Database for Health Insurance and Labour Market Studies (Statistics Sweden), residential area (Statistics Sweden), sick-leave and disability pension from the Sickness Benefit Register (Social Insurance Agency), and administrative Cost Per Patient data (Östergötland County). In the analyses, 4970 individuals were included. Causes for Exclusion were;

deceased or migrated before the start of the allotted study period (n=25), medical records were identified but not available (n=16), the wrong quarter was reviewed (n=1), and the medical records were not reviewed by other causes (n=13).

For each healthcare encounter identified from the medical records, the association to the patients ADE was evaluated for causality using the categories dominant, partly contributing, less important or not contributing. When the ADE was judged dominant, partly contributing or less important cause for the encounter, specific resource use during the encounter for diagnosing, treating or monitoring ADEs were listed.

Data on sick-leave and disability pension was used to identify and quantify prevalent sick-leave and disability pension. During the data collection it was judged unfeasible to retain the initial aim of identifying sick-leave and disability pension caused by ADEs from the medical records.

3.2.4 Population survey and register data (paper IV)

To identify self-reported drug-related morbidity, a cross-sectional population-based survey was conducted. A postal questionnaire was sent in the first week of October 2010, to a random sample of 14000 Swedish residents aged 18 years or older. Among these, 69 individuals were excluded because they were deceased or had migrated before the questionnaire was distributed.

The questionnaire encompassed questions on demographic and socioeconomic characteristics, health-related quality of life,^[105,106] use of health and social services, beliefs about medicines^[107] and perceived sensitivity to medicines, use of prescribed and over-the-counter medicines as well as herbal remedies, experienced ADEs, perceived preventability of ADRs and STEs as well as consequences and use of healthcare due to ADRs and STEs. When possible, previously validated questionnaires were used in the survey. The questionnaire was piloted with healthcare professionals, individuals from the general public and selected patient groups, to ensure questions were covering the important aspects of the topics and were interpreted correctly by respondents. The questionnaire includes questions about five types of ADEs: ADR, drug dependence, drug intoxication from overdose, STE, and drug-related untreated indication.^[108]

Data from the questionnaire was complemented with register data, from the Social Insurance Agency and Statistics Sweden, by record linkage. Register data encompassed information on demographic and socioeconomic variables from the Longitudinal Integration Database for Health Insurance and Labour

Market Studies (Statistics Sweden), information on sick-leave and disability pension from the Sickness Benefit Register (Social Insurance Agency), dispensed drugs from the Swedish Prescribed Drug Register (National Board of Health and Welfare), and hospitalisations from the National Patient Register (National Board of Health and Welfare).

Results from pre-specified questions and from free text were categorised separately for overall healthcare use, healthcare use resulting from ADRs and healthcare use resulting from STEs. The resource use categories were:

1. Phone calls; including correspondence by mail/e-mail and contacts to book a healthcare encounter;
2. Nurse visits; including visits to district nurse, midwife, related to laboratory tests, mammography, rehabilitation and vaccinations;
3. Outpatient physician visits; including public and private outpatient physician visits, health examinations, occupational healthcare encounters, and requests for prescriptions;
4. Home healthcare; including all encounters where healthcare personnel visited the respondents home;
5. Specialist physician and emergency department visits; including surgery without hospitalisation, visits to outpatient clinics and emergency departments in hospitals, and investigations;
6. Visits to other healthcare personnel in somatic care; including visits to acupuncturists, audiologists, chiropractors, chiropody, dieticians, masseurs, naprapaths, occupational therapists, and speech pathologists;
7. Psychiatrist visits;
8. Visits to other healthcare personnel in psychiatric care; including psychologists and psychiatric care and
9. Hospitalisations, including childbirth.

In the resource use for transportation was included the healthcare encounters above, and reported dental healthcare encounters and pharmacy visits. Encounters for healthcare use of respondents' relatives, and for donations of blood or tissues, were not included in the respondents' healthcare use.

Questionnaire data was used to identify and quantify prevalent sick-leave, disability pension and informal care.

3.3 Cost sources

The section describes the application of costs to used resources, by cost components and sources.

3.3.1 Registered drug costs (papers III–IV)

The Swedish Prescribed Drug Register (National Board of Health and Welfare) was used to identify current drug use and the associated costs in the population-based survey and the medical record review. The register includes both out of pocket costs and reimbursement costs.^[109] In both papers, the drug use resulting from drug-related morbidity was the total cost (out of pocket costs and reimbursement costs), identified in the register, of a prescription medicine dispensed during the study period to treat the identified/reported ADE. For the overall COI estimate, the total prescription drug cost during the study period was estimated from the total annual prescription drug cost per individual, divided by four quarters (paper III) and 12 months (paper IV), respectively.

3.3.2 Unit costs for healthcare and drug use (papers I–II, and IV)

Unit costs for healthcare and drug use were assigned based on national statistics on costs related to healthcare and drug use. The monetary values were weighted, top-down estimations of the net prices to counties and regions.^[110] The net prices included costs financed with taxes, government subsidies and financial net income. The costs statistics excludes patient out of pocket costs, which represents 2.3% of the proceeds to the healthcare producers in Sweden.^[110]

For papers I-II the pathway costs (Table 2) used for each branch in the decision tree were estimated based on the cost-generating components and the healthcare unit costs.

In paper IV, healthcare unit costs were assigned to the resource use categories included in the questionnaire.

Table 2. Cost-generating components and pathway costs of clinical outcomes resulting from drug-related morbidity (papers I-II).

Clinical outcome	Pharmacists		Outpatient physicians		Inpatient physicians	
	Cost-generating components	Pathway cost (SEK)	Cost-generating components	Pathway cost (SEK)	Cost-generating components	Pathway cost (SEK)
No additional treatment	1 telephone call to physician*	417	1 telephone call to physician*	417	-	0
Additional treatment, e.g. drugs	1 physician visit* + 1 [additional] prescribed drug [#]	1437	1 physician visit* + 1 [additional] prescribed drug [#]	1437	1 [additional] prescribed drug [#]	186
Specialist referral	1 physician visit* + 1 specialist physician consultation*	4076	1 physician visit* + 1 specialist physician consultation*	4076	1 specialist physician consultation*	2825
Prolonged hospital stay	2 days [extra] ^[111,112] in hospital [§]	17647	NA	NA	2 days [extra] ^[111,112] in hospital [§]	17647
Hospitalisation	9 days ^[113] in hospital [§]	79411	9 days ^[113] in hospital [§]	79411	NA	NA
Advanced specialist care, e.g. intensive care	9 days in hospital [§] + 2 days ^[114] in an intensive care unit [†]	13253	9 days in hospital [§] + 2 days ^[114] in an intensive care unit [†]	13253	9 days in hospital [§] + 2 days ^[114] in an intensive care unit [†]	13253
Death	9 days in hospital [§]	79411	9 days in hospital [§]	79411	9 days in hospital [§]	79411

* The average cost of a physician (SEK 1251), nurse (SEK 434) or specialist physician (SEK 2825) visit in somatic healthcare in Sweden during 2010, and telephone calls are weighted as 1/3 of the cost of a visit.^[110]

[#] Average benefit (SEK 186) of a dispensed prescription medicine in Sweden during 2010 (T. Renberg, Apotekens Service AB/the Swedish eHealth Agency, personal communication).

[§] Average daily hospital cost in somatic healthcare in Sweden during 2009 (SEK 8676),^[115] adjusted to 2010 value using a Swedish healthcare inflation index (price index with quality-adjusted wages for the county, including medicines, 1.7 %).^[116]

[†] Average daily cost in an intensive care unit in Sweden during 2009 (SEK 26118), estimated using the assumption that personnel costs are 70% of the total costs (D. Gjestebj, Helseplan Nysam AB, personal communication), adjusted to 2010 value using a Swedish healthcare inflation index (price index with quality-adjusted wages for the county, including medicines, 1.7 %).^[116]

3.3.3 Registered healthcare costs (paper III)

The Cost Per Patient Register (Östergötland County council) was used to estimate direct healthcare costs in paper III. The register includes detailed costs in categories for all healthcare resource use conducted in public healthcare, and private healthcare financed by the county, and was used to identify all healthcare costs of the included patients during the selected study period.^[102] Costs for inpatient encounters were censored based on the proportion occurring within the study period.

For ADE-related healthcare, costs were included the total registered cost for healthcare encounters judged to be dominantly caused by ADEs. In addition, when possible to identify the costs for specific resources listed for diagnosing, treating or monitoring ADEs, the cost of such resource use was included when ADEs were partly contributing or less contributing to the encounter. For the overall COI estimate, the total registered cost for healthcare encounters were included.

For this thesis, all healthcare costs from paper III were adjusted to 2010 values using a Swedish healthcare inflation index (price index with quality-adjusted wages for the county, excluding medicines: +4.658%).^[116] Drug costs were not adjusted between years.

3.3.4 Unit costs for social services (papers I–II, and IV)

For the overall COI estimation in paper IV, average costs for home-help services and nursing homes,^[117] transportation costs for the disabled,^[118] and the average cost of a bus trip,^[119] were used as unit costs.

3.3.5 Indirect costs from wage statistics (papers III–IV)

In the overall COI estimates in papers III-IV were included productivity loss estimated by the human capital approach. For income and social insurance contributions, 2010 values were used.^[120,121]

Thus, the monetary value of lost productivity from sick-leave and disability pension was estimated based on registered (paper III) or self-reported (paper IV) sick-leave and disability pension, average income data in age-categories, and social insurance contribution. Registered sick-leave and disability pension was retrieved from the Social Insurance Agency. The lost productivity reported in the survey (paper IV) was censored to exclude

disability pension among those 65 years or older, and other long-term sick-leave among those 70 years or older. The lost productivity from informal care in paper IV was estimated based on reported informal care, average national income data, and social insurance contribution.

3.4 Analyses

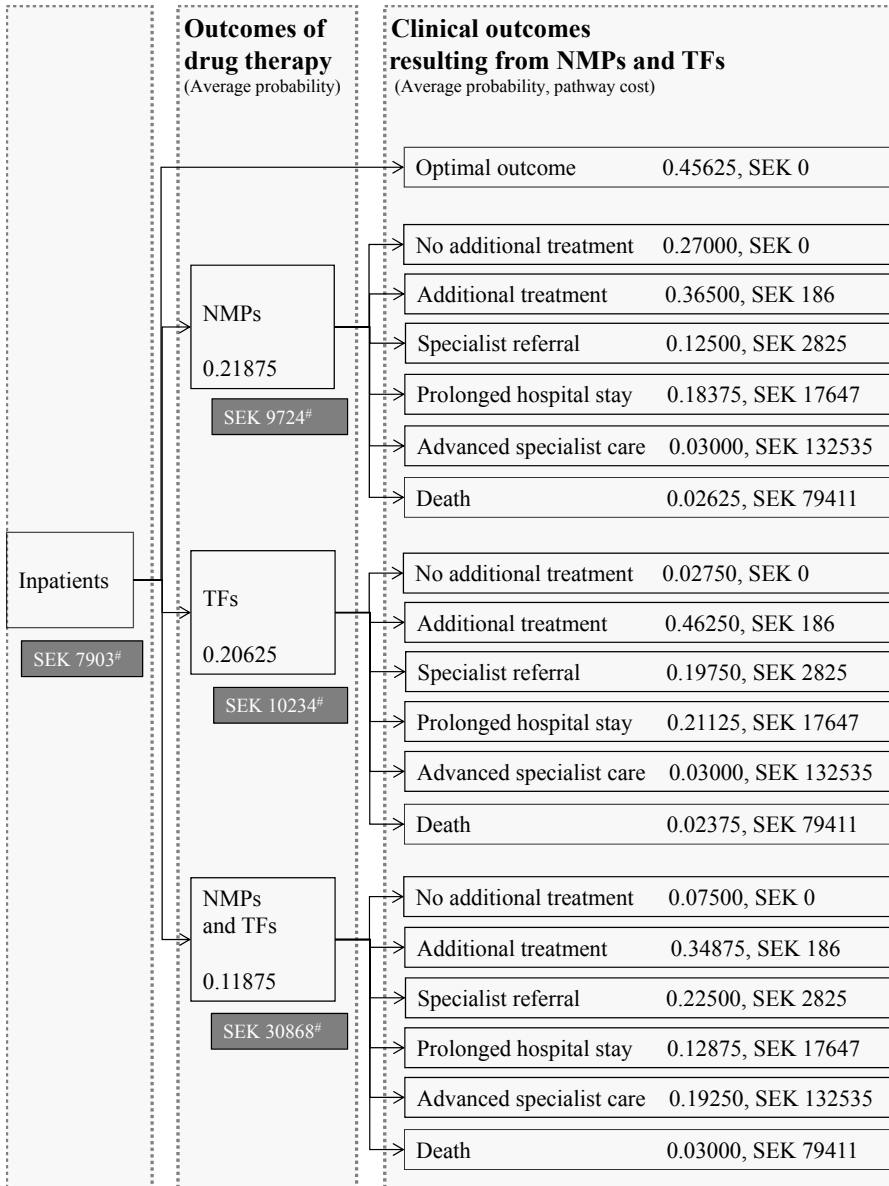
The modelling in papers I-II was made in TreeAge Pro Excel[®] 2009. Descriptive statistics and sensitivity analyses of probabilities in papers I-II, and processing of data in papers III-IV, were made using Microsoft Office Excel 2007. All statistical analyses in papers III-IV were made using STATA. In the thesis, all costs are presented in 2010 values.

3.4.1 Economic impact of drug-related morbidity (paper I-IV)

For papers I-II, the average probabilities of clinical outcomes identified from the expert panels, and pathway costs of clinical outcomes resulting from drug-related morbidity, were folded back in the decision tree (Figure 4) to calculate the COI of drug-related morbidity per patient with healthcare use. Average costs resulting from NMPs, TFs and the combination of NMPs and TFs were calculated for patients with healthcare use and the general population, respectively.

Figure 4 includes the inpatient physician panels' average probability estimates of drug-related morbidity in patients attending inpatient care, and the associated pathway costs, to illustrate the folding back of the model.

For papers III-IV average healthcare and drug use costs resulting from ADEs are presented for adults with healthcare use and the general adult population, respectively. Additional analyses based on ADE-categories were made for individuals with only one ADE identified during the study period and for preventable events separately. For paper III, the analysis of patients with one ADE included identifying individuals for which the associated resource use occurred within the study period.



Results from the modelling are rounded to the nearest SEK.

Figure 4. The decision tree used in modelling the COI of drug-related morbidity (papers I-II).

3.4.2 Overall COI with drug-related morbidity (papers I-IV)

For papers I-II, the average probabilities and conditional probabilities of clinical outcomes identified from the expert panels, during the following year after the drug-related morbidity (section D), were reported descriptively.

For papers III-IV, average direct costs, indirect costs and overall COI, and 95% confidence intervals, were calculated for the relevant study period, three months (paper III) and 30 days (paper IV), respectively. Average cost differences were tested for statistical significance (at $p < 0.05$), using a two-tailed t-test with unequal variances, for patients with/without ADEs (paper III) and for respondents with/without ADEs (paper IV). For paper IV, additional analyses were made of resource use among respondents without healthcare encounters and reporting ADEs.

3.4.3 Extrapolations to the general public (papers I-IV)

For papers I-II, probabilities of drug-related morbidity, preventable drug-related morbidity and clinical outcomes were extrapolated to the Swedish population under the assumption that 1) expected probabilities are annual probabilities; 2) 70% of residents seek and receive healthcare; 3) 9.5% of the residents are also hospitalised at least once annually:^[98] and 4) Sweden had 9.5 million residents in 2010.^[63] For preventable drug-related morbidity, extrapolations were made to minimum and maximum estimations of annual costs.

For papers III-IV, extrapolation of direct costs resulting from ADEs and overall COI were calculated for the adult Swedish population in 2010 (7382226^[63]). Moreover, the calculated percentages of costs resulting from drug-related morbidity, compared to all drug and healthcare costs in the study population, were applied to the annual prescription drug and healthcare costs in Sweden during 2010 (SEK 25534 million^[122] and SEK 197675 million,^[123] respectively). In addition, extrapolation was made of costs per month, to a population of 100000 individuals. The estimated cost was also put in perspective to the overall direct costs in the general population.

3.5 Ethical considerations

The aim of this thesis is to estimate the economic impact of drug-related morbidity in Sweden. For a full picture, the thesis includes different data

sources to identify drug-related morbidity. In the expert panel studies, professionals from different parts of healthcare were asked to participate, but all questions were associated to the professional opinion and the identity and responses of each participant was undisclosed, in accordance with the Delphi methodology. The conduct of the study should be in the interest of each healthcare professional, and participants had the possibility to withdraw from the study at all times. Thus, the ethical considerations of these sub-studies were less taxing, with added benefits from increased knowledge and no patient involvement.

The medical record review and population-based survey presented ethical challenges due to the handling of sensitive health data. The research projects were developed in accordance with the Declaration of Helsinki.^[124] This influenced the development of study protocols and ethical applications, evaluation of possible benefits and risks to study subjects, public announcement in the local papers of the medical record study and cover letter for the population survey, as well as selection and training of competent research assistants.

It is widely recognised that not all users benefit from their drug treatment. Cost-effectiveness and adverse effects of new drugs are studied before approval, sometimes even a few drug combinations, using information from randomised controlled trials. Drug use in the general public is however complex, making it difficult to randomise individuals into different drug use-groups. It would as such be unethical to administer a drug to a specific individual after identifying a high risk of developing preventable drug-related morbidity. Therefore, an observational study will be more suitable to assess drug-related morbidity and drug-use in practice.^[125] Pharmacovigilance initiatives include post-marketing surveillance of registered drugs based on national and international registration of voluntary reports of ADRs,^[66,126] but other types of ADEs are often not included. Also, it has been reported that the estimated prevalence of ADEs are higher in studies reviewing medical records, compared to studies using voluntary reports, for example.^[34]

In the study of medical records (paper III) the main issue was the amount of information collected, from both medical records and registers, without the patients' consent. The data was collected in retrospect, and presented in a way that gives no information on the identity of the patient or healthcare professionals involved. Since all data handling was retrospective there will be no effects on the healthcare of the patients. Thus the knowledge that can be gained in this unique study should outweigh the potential discomfort of patients realising they have been studied without their knowledge. After data

collection was finished the register holder replaced the personal identity numbers by a random number before we received the complemented register data, but still it may be possible to use healthcare use information to identify patients. In addition to the regulations and formal instructions in the permissions received, all researchers were encouraged to avoid handling medical records of individuals they recognised, and to ensure ethically justifiable handling of available data. The study received ethical approval from the Regional Ethical Review Board in Gothenburg in 2008 (approval reference number: 644-08). Additional permissions to handle register data have been collected from each register holder. Permission to handle medical records has also been collected from the County council in Östergötland, and all activities in the medical records were logged.

Recipients of the survey (paper IV) may not have thought about their illness in this way, and may therefore be affected negatively. Nevertheless, it may also be argued that this will benefit the individual, encourage healthcare contacts to discuss and treat the experienced symptoms. Also, the knowledge aims toward a deeper understanding of the processes causing drug-related morbidity, which should benefit future drug users. Thus, the potential anxiety or distrust in healthcare that may arise from answering the questionnaire should be justified by the added knowledge of exploring the drug users own experiences of drug-related morbidity. The study received ethical approval from the Regional Ethical Review Board in Gothenburg in 2010 (approval reference numbers: 238-10). Additional permissions to handle register data have been collected from each register holder.

4 RESULTS

The chapter includes costs resulting from drug-related morbidity, overall COI estimates, and extrapolations to the general public. Results from the sensitivity analyses are presented in the appendix.

4.1 Economic impact of drug-related morbidity

This section includes resource use and direct costs resulting from drug-related morbidity. It was not feasible to calculate indirect costs resulting from drug-related morbidity in the included studies.

4.1.1 Drug-related resource use (papers I–IV)

From the pharmacists' expert panel (paper I) it was estimated that 61% (mean \pm SD) of all patients interacting with healthcare experience drug-related morbidity, which corresponds to 42% of the Swedish population. Among these patients, 25% did not require any additional treatment but 11% were hospitalised and 8% had their hospital stay prolonged due to their drug-related morbidity.

From the outpatient physicians' expert panel (paper II) it was estimated that 51% of all outpatients experience drug-related morbidity. Among these patients, 19% did not require any additional treatment but 5% were hospitalised due to their drug-related morbidity.

From the inpatient physicians' expert panel (paper II) it was estimated that 54% of all inpatients experience drug-related morbidity. Among these patients, 15% did not require any additional treatment but 18% had their hospital stay prolonged due to their drug-related morbidity.

From the medical records (paper III) it was estimated that 23% of all adult patients visiting healthcare experienced at least one ADE during a three month period, which corresponds to 12% of the Swedish adult population. ADEs were the dominant cause of 991 healthcare encounters, including 16% of all hospitalisations and 7% of all outpatient encounters. Moreover, it resulted in resource use during 1025 additional encounters.

From the responses to the survey (paper IV) it was estimated that 22.3% of all adult patients visiting healthcare experienced at least one ADE during a 30 day period. Overall, 19.4% of the participants reported ADEs. Individuals

with ADEs reported 45% of all healthcare encounters in the study population (1106 of 2440 encounters). ADRs and STEs were reported to cause 181 healthcare encounters, 7.4% of all reported healthcare encounters. Also, in the survey (paper IV) was reported additional resource use resulting from ADRs: 600 days with informal care (n=49), 1448 days of lost leisure time (n=117), and 529 days of sick leave (n=61). For STEs, resource included: 1171 days with informal care (n=92), 2510 days of lost leisure time (n=187), and 857 days of sick leave (n=88).

4.1.2 Drug-related direct costs (papers I-IV)

According to the pharmacists' expert panel (paper I), the direct costs resulting from drug-related morbidity were SEK 9514 per patient receiving healthcare. This corresponded to an average cost of SEK 15695 per patient with drug-related morbidity.

According to the outpatient physicians' expert panel (paper II), the direct costs resulting from drug-related morbidity were SEK 3583 per outpatient. This corresponded to an average cost of SEK 6964 per outpatient with drug-related morbidity.

According to the inpatient physicians' expert panel (paper II), the direct costs resulting from drug-related morbidity were SEK 7903 per inpatient. This corresponded to an average cost of SEK 14535 per inpatient with drug-related morbidity.

According to the study of medical records (paper III), the direct costs for drugs and healthcare use resulting from ADEs, during three months, were SEK 824 per adult patient visiting healthcare. This corresponded to an average cost of SEK 3537 per patient with ADEs.

According to the responses to the survey (paper IV), the direct costs for drugs and healthcare use resulting from ADRs and STEs, during one month, were SEK 66 per adult patient receiving healthcare. This corresponded to an average cost of SEK 303 per patient with ADR or STE.

4.1.3 Distribution by care levels (papers I-IV)

According to the expert panels (papers I-II), *Hospitalisation* and *Advanced specialist care* represented the largest proportion of the COI of drug-related morbidity per patient visiting healthcare (Figure 5).

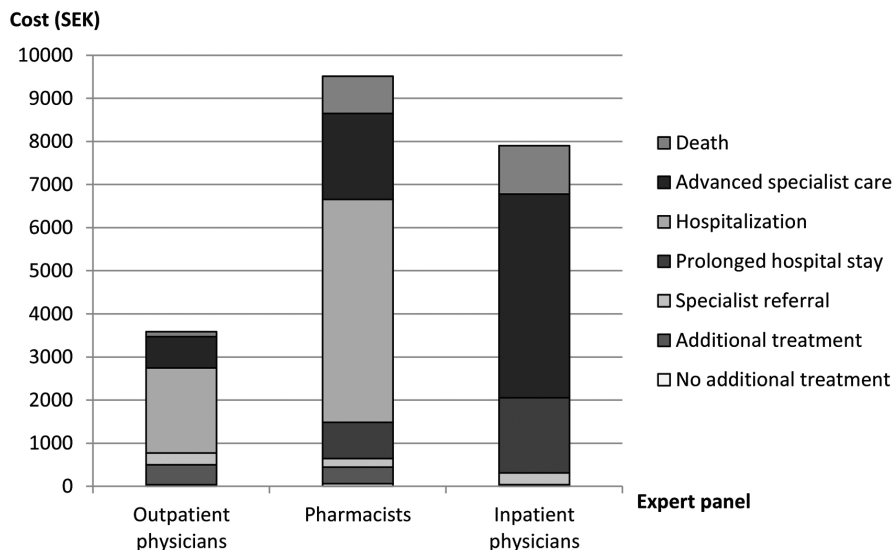


Figure 5. Distribution of costs (SEK) by clinical outcome from drug-related morbidity, according to expert panel estimates (papers I-II).

From the ADEs identified in medical records (paper III) it was estimated that inpatient care represented 54% of the costs for healthcare caused by ADEs.

From the responses in the population-based survey (paper IV) it was estimated that the largest proportion of the costs for self-reported ADRs and STEs were from specialist physician visits and psychiatric outpatient care (31% and 25%, respectively).

4.1.4 Distribution by types of drug-related morbidity (papers I-IV)

Based on the clinical outcomes reported by the pharmacist expert panel (paper I), average direct medical cost per patient with NMPs, TFs and a combination of TFs and NMPs were SEK 12489, 14865 and 23040, respectively.

Based on the clinical outcomes reported by the outpatient physician expert panel (paper II), average direct medical cost per patient with NMPs, TFs and a combination of TFs and NMPs were SEK 7164, 5722 and 8459, respectively.

Based on the clinical outcomes reported by the inpatient physician expert panel (paper II), average direct medical cost per patient with NMPs, TFs and a combination of TFs and NMPs were SEK 9724, 10234 and 30868, respectively.

Among patients with at least one ADE identified from the medical records (paper III), 255 individuals (42.8%) had only one ADE within the study period, thus enabling analysis of all costs resulting from a specific type of ADE. In this group, the average direct costs for one ADR or STE were SEK 1682 (95% confidence interval: SEK -300 to 3664, n = 117) and SEK 880 (SEK 652 to 1108, n = 121), respectively. Analyses of the resource use for the other ADE categories were not deemed feasible due to the low number of patients with only one event.

Based on the clinical outcomes reported in the survey (paper IV), the average cost for drugs and healthcare use caused by ADRs was SEK 160.5 per respondent experiencing at least one ADR. The corresponding cost for STEs was SEK 318.6. When excluding those reporting more than one ADR or STE, the average direct cost resulting from one ADR was SEK 18.8 (95% confidence interval: SEK 2.1 to 35.5, n = 210). The corresponding costs for one STE was SEK 96.8 (SEK -3.4 to 196.9, n = 191). However, these costs resulted from healthcare use among five respondents with only one ADR and average ADR-related costs of SEK 2381.0, and 11 respondents with only one STE and average STE-related costs of SEK 2486.7. In Figure 6, healthcare encounters resulting from ADRs and STEs are presented.

4.1.5 Costs for preventable drug-related morbidity (papers I–III)

Based on the proportion of patients with preventable drug-related morbidity among patients with drug-related morbidity (45%) reported by the pharmacist expert panel (paper I), the COI of preventable drug-related morbidity ranged from SEK 235, if preventable drug-related morbidity resulted in the clinical outcomes with the lowest costs, to SEK 9193, if preventable drug-related morbidity caused the clinical outcomes with the highest costs (Table 3). Thus, extrapolated to the Swedish population, the minimum annual COI of preventable drug-related morbidity was SEK 1548.5 million.

Based on the proportion of outpatients with preventable drug-related morbidity among outpatients with drug-related morbidity (24%) reported by the outpatient physician expert panel (paper II), the COI of preventable drug-related morbidity ranged from SEK 80, if preventable drug-related morbidity

resulted in the clinical outcomes with the lowest costs, to SEK 3119, if preventable drug-related morbidity caused the clinical outcomes with the highest costs (Table 3). Thus, the minimum annual COI of preventable drug-related morbidity in outpatients was SEK 529.6 million.

Based on the proportion of inpatients with preventable drug-related morbidity among inpatients with drug-related morbidity (31%) reported by the inpatient physicians' expert panel (paper II), the COI of preventable drug-related morbidity ranged from SEK 16, if preventable drug-related morbidity resulted in the clinical outcomes with the lowest costs, to SEK 7651, if preventable drug-related morbidity caused the clinical outcomes with the highest costs (Table 3). Thus, the minimum annual COI of preventable drug-related morbidity in inpatients was SEK 15.8 million.

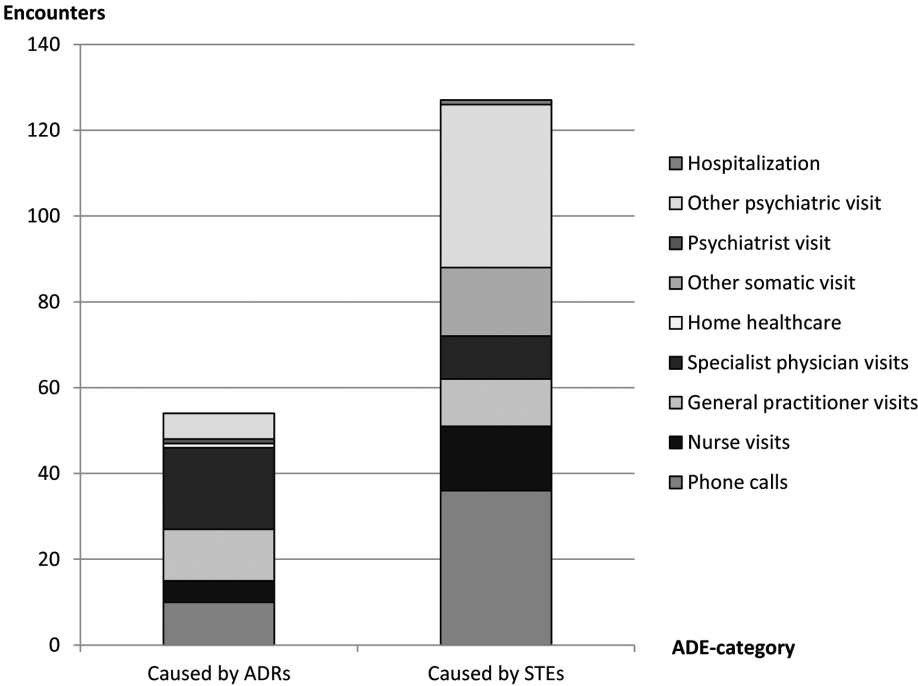


Figure 6. Resource use reported by respondents in paper IV, caused by ADRs and STEs, respectively.

Table 3. Calculated conservative and worst case estimates of the direct costs resulting from preventable drug-related morbidity (papers I-II).

Proportions among all patients visiting healthcare	Pharmacists		Outpatient physicians		Inpatient physicians	
	Conditional probability*		Conditional probability*		Conditional probability*	
	Conservative	Worst case	Conservative	Worst case	Conservative	Worst case
Preventable proportion	27.3		12.3		16.7	
No additional treatment	15.4		9.5		8.3	
Conditional probability (%)	15.4	0	9.5	0	8.3	0
Aggregate cost (SEK)	64	0	40	0	0	0
Additional treatment	26.3		32.1		21.7	
Conditional probability (%)	11.9	7.4	2.8	2.5	8.4	0
Aggregate cost (SEK)	170	121	41	36	16	0
Specialist referral	5.0		6.7		9.5	
Conditional probability (%)	0	5.0	0	6.7	0	1.8
Aggregate cost (SEK)	0	203	0	272	0	56
Prolonged hospital stay	4.8		NA		9.9	
Conditional probability (%)	0	4.8	NA	NA	0	9.9
Aggregate cost (SEK)	0	840	NA	NA	0	1748
Hospitalisation	6.5		2.5		NA	
Conditional probability (%)	0	6.5	0	2.5	NA	NA
Aggregate cost (SEK)	0	5168	0	1976	NA	NA
Advanced specialist care	1.5		0.5		3.6	
Conditional probability (%)	0	1.5	0	0.5	0	3.6
Aggregate cost (SEK)	0	1997	0	724	0	4719
Death	1.1		0.1		1.4	
Conditional probability (%)	0	1.1	0	0.1	0	1.4
Aggregate cost (SEK)	0	864	0	110	0	1128
Cost per patient (SEK)	235	9193	80	3119	16	7651
Extrapolated annual COI (million SEK)	1548.5	60670.8	529.6	20583.8	15.8	7651.0

* Conditional probabilities are estimated by multiplying the average probabilities of drug-related morbidity (NMPs, TFs, and the combination of NMPs and TFs), by the average probability of each clinical outcome. Conditional probabilities are rounded to the nearest decile, and costs are rounded to the nearest SEK.

Among the patients with at least one preventable ADE identified from the medical records (paper III), the direct costs for ADEs were SEK 3618 (SEK 1817 to 5418, n = 278). Limiting the analysis to patients with only one ADE, with resource use within the study period, the average direct costs resulting from one preventable ADE were SEK 999 (SEK 573 to 1424, n = 88). There were no statistically significant differences in costs found between patients with and without preventable ADEs.

4.1.6 Diagnosis, treatment and monitoring costs (paper III)

The 596 patients with at least one ADE identified from medical records had 991 healthcare encounters judged to be dominantly caused by ADEs, and 1025 additional encounters associated with diagnosing, treating or monitoring ADEs. Among encounters dominantly caused by the ADEs, 444 included diagnosing ADEs, 487 included interventions to treat the ADE, and 426 encounters included monitoring of ADEs. One encounter could include more than one type of intervention and was judged based on the total burden of ADEs. For other encounters associated with ADEs but not caused by the ADE, 459 were associated with diagnosing, 341 with treatment and 436 with monitoring. It was in many of these encounters not possible to identify a relevant cost for the intervention from the Cost Per Patient Register. It can be estimated that the 981 ADEs identified in the medical records were thusly associated with 903 encounters associated with diagnosing ADEs, 828 encounters including interventions to treat ADEs, and 862 encounters that included monitoring (Table 3 in paper III).

By limiting the analysis to the 255 patients with only one ADE and with the resulting resource use judged to occur during the study period, it was also possible to analyse the distribution of encounters for diagnosing treating and monitoring each ADE. Among these, there were 335 encounters associated with diagnosing ADEs, 247 encounters included interventions to treat the ADE and 181 encounters that included monitoring. Moreover, of the 234 with encounters associated with diagnosing ADEs, 168 (72%) had only one such encounter, but 66 patients had on average 2.5 encounters associated with diagnosing ADEs. Among the 170 patients with encounters associated with treating ADEs, 134 (79%) had only one encounter and the other 36 patients had on average 3.1 encounters associated with treating their ADE. For the 82 patients with encounters associated with monitoring, 41 (50%) had only one encounter and the other 41 had on average 3.4 encounters associated with monitoring.

4.2 Overall COI for individuals with drug-related morbidity

This section includes overall resource use, direct and indirect costs, for those with drug-related morbidity in the studies.

4.2.1 Resource use with drug-related morbidity (papers I–IV)

According to the pharmacist expert panel (paper I) 46% of all patients interacting with healthcare both experienced drug-related morbidity and received additional healthcare during the subsequent year (Table 4). The corresponding proportions from paper II were 44% of outpatients and 51% of inpatients. Thus, 76% of all patients, 86% of outpatients, and 94% of inpatients experiencing drug-related morbidity received additional healthcare during the subsequent year.

Healthcare was received by 239 (17.4%) of the 1377 respondents reporting ADEs in the survey (paper IV), during the one-month study period. Among the 943 reporting ADRs or STEs, 56 respondents (5.6%) received healthcare because of their ADR or STE. However, of the 1138 respondents with ADE that did not receive healthcare, 51 (4.5%) received social services.

4.2.2 COI with drug-related morbidity (papers III–IV)

According to the study of medical records (paper III), the COI of patients with ADE was (mean; 95% confidence interval) SEK 42735; SEK 37291 to 48179, during the three month study period (Figure 7). Direct costs for drugs and healthcare use corresponded to 45% (SEK 19399; SEK 15481 to 23317) of the COI, and 55% (SEK 23336; SEK 19867 to 26806) were indirect costs from lost production due to short-term sick-leave and disability pension. The average COI was higher among those with ADEs compared to other patients (COI: SEK 16682; SEK 15108 to 18256, $p < 0.0001$) receiving healthcare during the study period.

The distribution of the total COI per three months for patients with ADEs identified from medical records, and for all patients, is presented in Figure 7.

Table 4. Expert panels estimates (papers I-II) of subsequent healthcare use during the year after experiencing NMPs and TFs.

	Pharmacists	Outpatient physicians	Inpatient physicians
	Conditional probability %	Conditional probability %	Conditional probability %
NMP			
No additional healthcare	8.4	5.6	0.8
Additional outpatients visit(s)	11.4	12.5	4.0
Additional inpatients visit(s)	4.3	6.5	7.4
Additional home-help service(s)	2.0	1.0	3.7
Move to nursing home, additional rehabilitation or similar	1.7	0.8	4.0
Death	0.6	0.4	1.7
TF			
No additional healthcare	4.0	1.1	1.0
Additional outpatients visit(s)	7.5	8.6	3.3
Additional inpatients visit(s)	2.7	4.0	6.6
Additional home-help service(s)	1.4	0.7	3.5
Move to nursing home, additional rehabilitation or similar	1.1	0.5	3.4
Death	0.5	0.3	2.3
NMP and TF			
No additional healthcare	1.2	0.5	0.2
Additional outpatients visit(s)	5.9	4.9	1.5
Additional inpatients visit(s)	3.4	3.0	4.0
Additional home-help service(s)	1.5	0.6	1.8
Move to nursing home, additional rehabilitation or similar	1.3	0.5	2.4
Death	0.7	0.3	1.6
Proportion of patients[#]	46.0	44.4	51.1

* Conditional probabilities are estimated for each participant by multiplying the average probabilities of NMPs, TFs, and the combination of NMPs and TFs, by the average probability of each clinical outcome (weighted for deaths due to NMPs and TFs).

Sum the conditional probabilities for healthcare resource use, the item *No additional healthcare* is excluded from the estimate.

According to the survey responses (paper IV), the COI for individuals with ADEs was (mean; 95% confidence interval) SEK 7885.5; SEK 6953.0 to 8817.9 (Figure 8). Direct costs corresponded to 40% (SEK 3157.5; SEK 2523.5 to 3791.5) of the COI, and 60% (SEK 4727.8; SEK 4123.8 to 5332.2) were indirect costs from lost production due to short-term sick-leave and disability pension. The average COI was higher among those with ADEs compared to other respondents (COI: SEK 3075.9; SEK 2804.1 to 3347.8) during the study period ($p < 0.0001$). The distribution of the total COI per month for respondents with ADEs, and for all respondents, is presented in Figure 8.

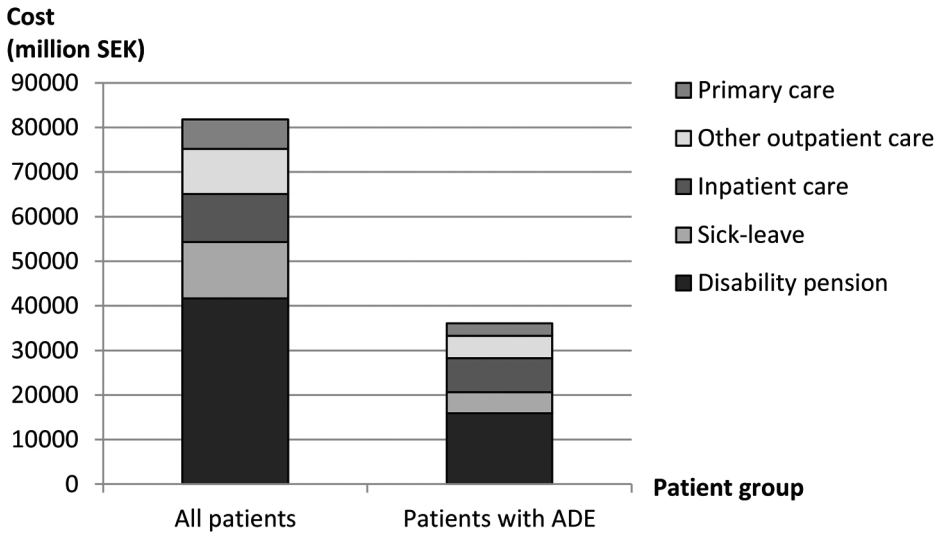


Figure 7. Distribution of the total quarterly COI for all 2560 patients, and for the 596 patients with ADE identified from medical records (paper III).

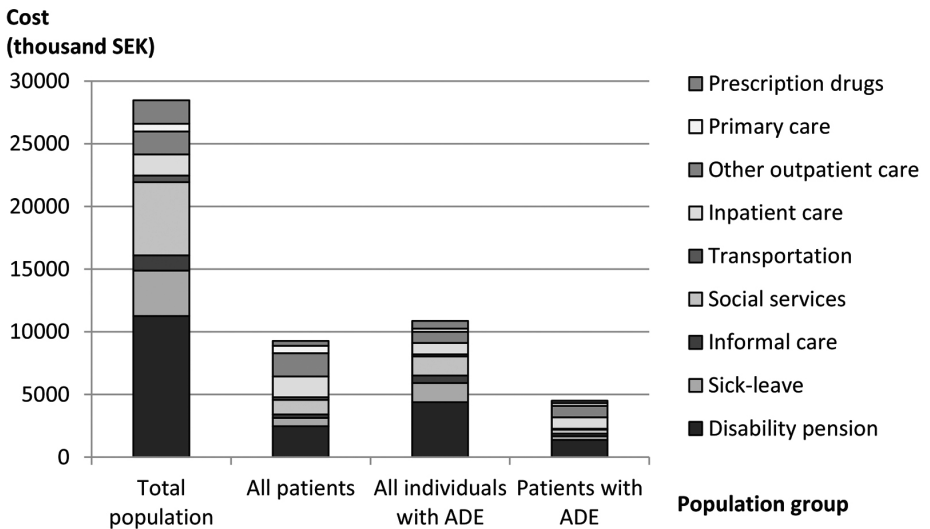


Figure 8. Distribution of the total monthly COI for all 7099 respondents, and for 1377 respondents with ADEs (paper IV).

4.3 Extrapolations to the general public

Based on the expert panel responses, the annual costs for drug-related morbidity to the Swedish healthcare system were calculated to SEK 62794 million among all patients (paper I). The corresponding figures from paper II were SEK 23651 million for outpatients and SEK 7904 million for inpatients.

The ADEs identified from medical records (paper III) were extrapolated to annual costs of SEK 3131 million using the adult Swedish population, or approximately SEK 12 million for 100000 residents each month (Table 5). This included 1.5% of all drug costs and 9.5% of healthcare costs in the population.

Self-reported ADRs and STEs (paper IV) were extrapolated to annual costs of SEK 271 million using the adult Swedish population, or approximately SEK 3.7 million for 100000 residents each month (Table 5). This included 0.5% of all drug costs, and 6.1% of all healthcare costs.

Under the assumption that the estimated proportions of drug and healthcare costs were representative to the Swedish population, these figures were applied to the annual prescription drug and healthcare costs in Sweden during 2010. ADEs (or ADRs and STEs) caused prescription drug costs of SEK 128-383 million and healthcare costs of SEK 12058-18779 million.

For example, based on the results from the medical records (paper III), 100000 Swedish residents would cause 1268 hospitalisations during one year, incurring costs of approximately SEK 48 million. Patients with ADEs caused 812 of these hospitalisations, and 70% of the costs (SEK 34 million). The costs resulting from drug-related morbidity during hospitalisations represented 14% (SEK 6.6 million) of the total hospitalisation incurred among the 100000 residents, distributed over 456 hospitalisations. Moreover, based on register data for the survey participants (paper IV), prescription drugs for 100000 Swedish residents would cost SEK 26 million. Based on the 1377 individuals reporting ADEs in the survey, it can be estimated that the prescription drug costs among 100000 resident would be SEK 8.5 million, and that 6% (SEK 520000) of these costs were for those with healthcare encounters. Moreover, ADRs and STEs would result in 732 new prescription drugs, causing 0.5% of the overall prescription drug cost in the population of 100000 residents.

Table 5. Costs per month per 100000 residents (SEK), estimated from the results in papers III-IV.

Resources used	General population	Individuals with drug-related morbidity	Patients with drug-related morbidity	Caused by drug-related morbidity
Papers	III: Medical records ^s IV: Survey	III: Medical records ^s IV: Survey	III: Medical records ^s IV: Survey	III: Medical records ^s IV: Survey
	cost, SEK (quantity)	cost, SEK (quantity)	cost, SEK (quantity)	cost, SEK (quantity)
Direct costs				
Prescription drugs	III: 24962461 (-) IV: 26456036 (-)	III: - (-) IV: 8511812 (-)	III: 7969604 (-) IV: 523791 (-)	III: 376123 (1697) IV: 132286 (732)
Over-the-counter drugs	III: - (-) IV: - (115481)	III: - (-) IV: - (31357)	III: - (-) IV: - (930)	III: - (-) IV: - (-)
Natural remedies	III: - (-) IV: - (35808)	III: - (-) IV: - (8860)	III: - (-) IV: - (268)	III: - (-) IV: - (-)
Primary care	III: 29732589 (55902) IV: 8543243 (10987)*	III: - (-) IV: - (-)	III: 12596962 (23937) IV: 3468049 (4310)*	III: 2215928 (8189†) IV: 546288 (606)*
Other outpatient care	III: 45911536 (35466) IV: 25776614 (22862)	III: - (-) IV: - (-)	III: 22838786 (15889) IV: 12592779 (10987)	III: 2931989 (4373†) IV: 2352667 (1930)
Inpatient care	III: 48450657 (1268) IV: 23695323 (521)	III: - (-) IV: - (-)	III: 34138196 (812) IV: 12808283 (282)	III: 6607264 (456†) IV: 640414 (14)
Dental care	III: - (-) IV: - (1888)	III: - (-) IV: - (817)	III: - (-) IV: - (113)	III: - (-) IV: - (70)
Pharmacy visits	III: - (-) IV: - (8889)	III: - (-) IV: - (4226)	III: - (-) IV: - (648)	III: - (-) IV: - (465)
Home-help services	III: - (-) IV: 33043978 (80107 h)	III: - (-) IV: 10753877 (26070 h)	III: - (-) IV: 199223 (483 h)	III: - (-) IV: - (-)
Nursing home stay	III: - (-) IV: 49141288 (31300 d)	III: - (-) IV: 10615580 (6762 d)	III: - (-) IV: 1326947 (843 d)	III: - (-) IV: - (-)
Transportation services for the disabled	III: - (-) IV: 5534449 (20586)	III: - (-) IV: 1590545 (5916)	III: - (-) IV: 48690 (181)	III: - (-) IV: - (-)
Other transportation	III: - (-) IV: 1995959 (86781)	III: - (-) IV: 904948 (39346)	III: - (-) IV: 149405 (5862)	III: - (-) IV: - (6170)
Indirect costs				
Sick-leave	III: 60351221 (293396 h) IV: 51015213	III: - (-) IV: 21612086	III: 21651563 (104557 h) IV: 407337 (1888 h)	III: - (-) IV: - (19516 d)

	(256050 h)	(109734 h)		
Disability pension	III: 254710197 (1209323 h) IV: 158600197 (742329 h)	III: - (-) IV: 61852712 (291557 h)	III: 71630886 (335524 h) IV: 5317078 (27271 h)	III: - (-) IV: - (-)
Informal care	III: - (-) IV: 17082772 (83801 h)	III: - (-) IV: 8244179 (40442 h)	III: - (-) IV: 760957 (3733 h)	III: - (-) IV: - (24960 d)
Lost leisure time	III: - (-) IV: - (153517 d)	III: - (-) IV: - (72132 d)	III: - (-) IV: - (5117 d)	III: - (-) IV: - (55742 d)

[§] Calculated from the three months, under the assumption that the distributions of costs and encounters are equal over time. The figures are not adjusted for monthly ADE-prevalence. The figures for primary care and other outpatient care exclude healthcare encounters not found in the Care Data Warehouse.

* Includes primary care nurse and general practitioner visits.

Includes costs resulting from ADRs and STEs, no other drug-related morbidity.

† Include encounters associated with drug-related morbidity (ADE judged to be Dominant, Partly or Less contributing).

Abbreviations: h = hours; d = days.

5 KEY FINDINGS

The opinions from the expert panels showed that healthcare professionals, both pharmacists and physicians (papers I-II), estimate drug-related morbidity to be common and cause considerable resource use for patients receiving healthcare. ADEs identified from medical records (paper III) were estimated to cause 1.5% of all drug costs and 9.5% of healthcare costs in Sweden, while self-reported ADRs and STEs (paper IV) were reported to cause 0.5% of all drug costs, and 6.1% of all healthcare costs. Moreover, self-reported ADRs and STEs (paper IV) caused informal care, lost leisure time and sick-leave.

It appears that costs of drug-related morbidity occur in all parts of the healthcare system. According to the results from the expert panels (papers I-II), a large proportion of the healthcare costs resulting from drug-related morbidity occurred in hospitals or after specialist referrals. However, based on the ADEs identified in medical records (paper III) and the resource use resulting from self-reported ADRs and STEs (paper IV), approximately half the costs occurred in primary care or other outpatient care.

Costs resulting from NMPs and TFs were similar according to the expert panels (papers I-II), although the combination of both NMPs and TFs caused more costly resource use. From the ADEs identified in medical records and self-reported ADRs and STEs (papers III-IV), STEs appear equally common and costly as ADRs.

No difference in costs could be identified based on preventability of the event, from these studies, but it was found that there is a group of patients with ADEs identified from the medical records (paper III) that had repeated encounters for diagnosis, treatment or monitoring of the symptoms. This was found even though the analysis had to be limited to the patients with relatively short duration of drug-related morbidity (within the study period), and to those with only one ADE identified during this period.

The overall COI and resource consumption for individuals experiencing drug-related morbidity was high compared to those without drug-related morbidity, including: higher costs for prescription drugs, healthcare use, transportation services, short-term productivity loss, productivity loss due to disability pension, and productivity loss for informal care.

6 DISCUSSION

This discussion starts with some methodological considerations. Thereafter the results from the sub-studies are compared to each other and to previous research. Thereafter follows a general discussion on the application of the health disaster framework to drug-related morbidity, issues related to the good:harm ratio of drug therapy, and if our results may be translated to other settings. Finally, practical implications from the presented results are suggested.

6.1 Methodological considerations

The methodological discussion focuses on the methods used for identifying drug-related morbidity and the methods used to estimate costs.

6.1.1 Drug-related morbidity detection and data sources

The main strengths of the included studies are the combined results, showing that regardless of which of these sources are used, drug-related morbidity was common and resource-intense. Moreover, the included studies were designed with the prerequisite to identify drug-related morbidity and calculate costs. Additional strengths were the availability of informed experts (papers I-II), availability of detailed register data (paper III), the population-based study designs (papers III-IV), and large number of survey responses (paper IV).

In studies of drug-related morbidity the causality of reported or retrospectively identified cases to the suspected drug has to be determined.^[66] Several methods for associating symptoms to drugs have been suggested, including expert judgment, algorithms and probabilistic methods.^[127] In this thesis, a formal causality assessment of identified ADEs was used in the medical record study (paper III). In the other sub-studies, an assessment is made by the respondents (survey respondents, pharmacists, and physicians) by “diagnosing” the drug-related morbidity.

There are some obvious limitations in using retrospective observational data.^[128,129] Such limitations were present in all of these studies, from experts’ opinions, medical records and the recall of respondents. Other important limitations were the lack of a clear time-frame (papers I-II), unidentified ADEs due to underreporting in medical records (paper III), and non-response in combination with low reported healthcare use (paper IV).

Using healthcare professionals' opinion (papers I-II)

In the expert panel studies (papers I-II), opinions of the experts were collected, but no empirical patient data was collected. The method was developed as a Delphi panel study, but because of the few rounds involved, it can be suggested to be a modified Delphi.^[130,131] Delphi methods have been criticised for being unscientific, with low reliability and sensitivity to both the used questionnaire and the expertise of the selected participants.^[132] Thus, one major limitation was the use of expert opinions for quantifying prevalence, resource use and subsequent costs. The method has however been suggested as a useful tool in economic studies when little or no empirical data is available, and for extrapolations between countries.^[133] Such lack of empirical data on the economic impact of drug-related morbidity was apparent in the literature review (paper I), e.g. on the costs occurring outside hospitals, and thus the Delphi panel studies fill a gap in the current knowledge.

Because of the limitation to two rounds, we do not claim that consensus was reached, which is an important aim in traditional Delphi studies,^[134,135] although it has been argued that a consensus does not need to imply absolute agreement between participants.^[130] However, the sensitivity analyses of the differences between rounds suggest that the changes were small, and the trend was towards low-cost treatment alternatives from no treatment or high-cost treatment alternatives. It appears that the results are relatively stable between rounds, and that the variation between respondents was small. The interpretation was that the results would not have changed much by repeated rounds, and that the presented result represents the opinion of the included experts.

In the studies, interquartile range and participants' own first-round estimates were fed back during the second round. It has been suggested that feed-back shall not include other participants' confidence in their estimates or numeric means or ranges,^[136] to avoid influence towards majority opinion and because of the deviation between confidence and expertise. It is, however, unclear how and what information should be fed back depending on the type of Delphi study being conducted, that is if participants are to select from alternatives or determine a continuous variable.^[137] Moreover, if the outcome under study is an intellectual task (deducing an existing true estimate) or judgemental forecast (has not yet occurred).^[136] Due to the low number of rounds it can be argued that these studies did not really make use of the Delphi properties, but at least enabled participants the opportunity to reassess their first-round estimates. Moreover, the changes in estimates between rounds were small.

The results from the expert panel studies are opinions, and therefore depend on the stated questions and the participating experts.^[132] This includes both the expertise of the selected experts, and their understanding of the questions. The selection of experts was designed to find those most interested and aware of drug-related morbidity, thus not representative but informative. Among the pharmacists (paper I), participation was almost complete after approach. However, among the physicians (paper II) a large proportion of those approached did not participate in the study. The main cause was time constraints. It is possible that non-participants had responded differently to the questionnaire, changing the results.

Since we could not use “common” terms like medication errors and ADRs in the study, which are not mutually exclusive (e.g. a preventable ADR should be the result of a medication error), it was possible that the experts were unable to relate to the terms and definitions used (i.e. drug-related morbidity, NMPs and TFs). To assist interpretations, researchers from the group were available for questions during the first round. The personal contact with participant may have changed the results, if respondents felt compelled to respond according to the researchers wants, due to social desirability, for example. Much work was put into ensuring a neutral approach during the presentations and responses to questions. Also, the second round should have enabled participants to reconsider their estimates.

Using medical records and register data (paper III)

In the study of medical records (paper III), some issues arose because of how and why medical information was recorded. It is previously known that medical records do not cover everything that is discussed or decided during a healthcare encounter.^[138,139] Thus the healthcare professional making an entry in the medical record will subjectively select what is being reported. The pharmacist reviewer analysed the medical record, helped by a trigger list, to identify suspected drug-related morbidity. The trigger list was developed based on previous literature.^[140-143] Trigger lists may speed up the review process, but do not evaluate the causality of the suspected event which has to be assessed afterwards.^[30] The next step was for the expert reviewers to analyse the pharmacist’s case presentation, and to reach consensus regarding the causality, helped by a checklist.^[103] Although similar processes have been used in previous research on adverse events from medications,^[111,144-146] much research is available on the subjectivity in such evaluations.^[127,147] The last step was to, based on the case presentation from the pharmacist reviewer and the case judgment from the expert reviewer, make an assumption about the relationship between the drug-related morbidity and any occurring healthcare resource use. In all of these steps, uncertainty was added. There is little

information available on how this assignment of costs has been handled in previous studies of costs resulting from drug-related morbidity.^[54] Moreover, these have focused on hospitalised patients and often only those causing admission (which should be represented by our category “dominantly caused by ADE”), which avoids some of the problem by only using relatively information-rich inpatient medical records, but instead, according to the results presented in this thesis, should underestimate the impact to society.

Using survey responses (paper IV)

In the population survey (paper IV), we limited the number of questions to improve the response rate, which was partly on the expense of detailed elaborations for the included subjects. Although the causes and patterns are debated, it is today widely recognised that response rates in surveys are declining over time.^[148] Statistics Sweden reported that among surveys distributed in the year 2000, non-response rates varied between 5.5% to 32.9%,^[149] while in 2001-2006 the average response rate was 63%.^[150] Due to non-response resulting in response bias and non-response error, it has been suggested that a minimum acceptable response rate is that at least half of the sample responds.^[151] The response rate of approximately 50%, and low reported resource use, indicates that non-respondents may account for a large proportion of the healthcare use in the population. The study may therefore have underestimated the ADE prevalence.

Today, drug users are viewed as important actors in reporting adverse events to medications,^[152] including reporting of suspected ADRs to national pharmacovigilance databases. Previous research has suggested self-reporting resulted in useful and relevant information on side-effects, albeit resulting from different drugs and reactions compared to what was reported by healthcare professionals.^[153] Although we piloted the questions with potential respondents, survey respondents may have misunderstood our questions. Moreover, respondents may wrongly assign a causal relationship or used resource to a drug. Previous research has shown deviations between ADEs reported by patients and by physicians.^[142] Therefore the responses were evaluated based on, for example, plausible connection between drug and event.^[108]

There was also the possibility that the resource use reported does not exactly match the resource use during the study period. It has previously been shown that it is difficult to answer based on a specific time period. Common events (e.g. outpatient visits compared to hospitalisations), and multiple encounters, are likely to be underreported.^[154] For healthcare resource use, recall periods over 12 months have been dissuaded,^[154] while two weeks is a common

recommendation for drug use recall.^[155] According to the sensitivity analyses presented in paper IV, there were deviations between register data and self-reported resource use. However, the interpretation of these deviations was less obvious. A large proportion was possible to explain by terminology (difference between e.g. sick-leave and disability pension, and registrations of one-day long hospitalisations), by the time-period selected for register data, or by how resource use was registered in the healthcare databases (multiple registrations per hospitalisation).

Furthermore, the free text answers may have been misunderstood, or wrongly categorised in the analyses. To avoid this, 10% of all healthcare encounters and 25% of all resource use resulting from ADRs and STEs reported in free text, were re-categorised independently by a second researcher from the DRUMS group (Katja Hakkarainen). This resulted in clarifications to the instructions for the resource use categorisation.

6.1.2 Methods used for cost analyses

In addition to the strengths related to detection and data sources, also applying to the cost estimations, one strength was the use of a method for assigning healthcare resource use and associated costs to ADEs (paper III), according to the categories dominantly, partly contributing or less important to the encounter. To my knowledge, no previous studies of costs resulting from drug-related morbidity have reported on a method for this.^[54]

There are some obvious limitations in the use of descriptive COI methods, as compared to economic evaluations which inhibits, for example, guidance on future priorities and resource use in healthcare. For the initial literature review,^[54] we identified items for assessing economic evaluation studies, including study viewpoint, costing methods, and adjustments for timing of costs. Such guidelines also contain items for assessing methods for studying consequences,^[71,156] but these were judged irrelevant for this type of descriptive cost studies. In addition to cost items, an evaluation could instead include items relevant for observational descriptive studies.^[125,157,158]

A main methodological limitation in the execution of all studies in this thesis was the lack of method to assign indirect costs, and potentially also some direct costs, to the drug-related morbidity. A limitation in the expert panel studies was the lack of time period in the chosen model, although a time-frame was suggested during the data collection. Another issue that affects the confidence in the results from the expert panel studies (paper I-II) was the method for quantifying costs, selecting pathways and extrapolating costs. The

resources used for the pathway costs were discussed and decided within the research group, and were therefore presented in the paper to enable readers own judgment of the relevance.

According to papers I-III, hospital costs were the main healthcare costs resulting from drug-related morbidity. The same was found by Chiatti et al. when reviewing consequences of ADEs in the elderly.^[159] Thus, the focus on hospitalised patients in previous research may be rational. However, the results in paper IV indicate that previous research may not give the full picture, since for example indirect costs resulting from drug-related morbidity were excluded. Moreover, there are other potential indirect costs resulting from drug-related morbidity that were not addressed in the current studies, e.g. presenteeism. It has previously been suggested that presenteeism losses represented 60% of the total costs associated with 10 selected conditions among US employees, representing a greater proportion of the costs in seasonal and temporary conditions such as allergies and migraine.^[160] Thus, the included studies enables calculating the direct healthcare and drug costs resulting from drug-related morbidity in the Swedish general public, including primary care, other outpatient care and inpatient care, but gives only an indication of the associated indirect costs and costs occurring outside the healthcare system (e.g. social services and transportation). Such costs should have been included to give the full societal perspective to the costs resulting from drug-related morbidity.

Assigning costs to drug-related morbidity

In the study of medical records (paper III), the suggested method for assigning healthcare resource use for diagnosing, treating or monitoring ADEs shall be viewed as a first step towards an assignment method. The identification of resource use other than healthcare use from medical records was challenging. Thus, to assign other resource use, more research will be needed. The cost components in the overall COI of paper IV gives an indication of what kind of costs may be relevant to measure in future studies. Moreover, the Cost Per Patient Register was not well suited for identifying costs for specific resources used. Thus, the cost analysis of ADE-related resource use was limited to healthcare costs, and for encounters not dominantly caused by the ADE also limited to costs of resources that could be specified in the Cost Per Patient Register. Due to the limitation to patients with healthcare encounters, the cost per inhabitant with drug-related morbidity should be overestimated. However, the total cost resulting from ADEs was underestimated since a large proportion of costs were not identified. The Cost Per Patient Register data can be further analysed in the future to identify incremental costs of drug-related morbidity.

Another limitation in the study of medical records (paper III) was the use of registered administrative cost data, which limits comparisons to other settings and healthcare systems. Unit costs and detailed resource use quantities were unavailable. Although the population of the selected county was representative for the Swedish population, the healthcare performance appears inferior to many other counties. Sweden often ranks high in international comparisons on population health, healthcare outcomes and quality of care, although low for technical efficiency (output, cost and access). There are however differences between counties/regions.^[161] Östergötland County had the third lowest cost per inhabitant for healthcare in an estimate based on case-mix, the lowest costs for prescription drug reimbursements in Sweden, when adjusting for age, sex and excluding some drugs aggravating the comparison, and the cost per diagnosis related group in specialised somatic care was similar to the national figure.^[162] This should avoid overestimating the costs of drug-related morbidity, due to such factors as disproportionately high healthcare costs or bad care quality.

In the survey study (paper IV), the selected unit costs and possible underreporting of ADEs resulting in healthcare use was likely to affect the final cost estimate. The selection of unit costs was preceded by a thorough search for alternative sources, including the possibilities to use list prices from counties or costs estimated from diagnosis related groups or Cost Per Patient Register data. However, the use of such prices for care encounters requires knowledge on diagnoses and interventions that were not available in the current study. The selected unit costs were the net prices reported by counties and regions^[110]: weighted prices estimated from the top-down, based on total resource use in different healthcare sectors. The costs are used to present overall costs in the Swedish counties and regions, and should therefore be well known and acknowledged among managers and decision makers in Swedish healthcare.

Out of pocket expenses for healthcare were excluded in both papers III-IV, due to limitations in the data. However, the out of pocket costs represent a small proportion of the total healthcare costs (2.3% of the proceeds to the healthcare producers^[110]), but could change the distribution of costs to some extent. Out of pocket expenses for drugs were included in the cost estimates.

Among the different methods for cost inclusion in COI studies, suggested by Akobundu and colleagues,^[84] the included studies measured total costs for individuals with ADE (papers III-IV), and attributable cost resulting from the identified ADE (papers I-IV). The costs measured represent the claims payment. The Cost Per Patient Register included administrative costs data

used for reimbursements from the county to the specific care provider, while the unit costs used for the expert panel studies and survey data were net prices calculated from the top-down based on the expenses reported by the counties and regions. Thus, the estimations should be lower than say billed charges^[163] that are used in some studies.

Measuring indirect costs

In both the study of medical records and in the survey study (papers III-IV), the human capital approach was used to estimate indirect costs for all participants. It has been argued that this method overvalues the productivity loss, that the lost productivity shall be adjusted to represent the actual lost work production.^[81] The methods used did not allow estimation of sick-leave or disability pension resulting from drug-related morbidity, and therefore estimation of future costs of incident disability pension would not add such knowledge. Results were limited to describing the overall quantity and costs of lost productivity, from sick-leave and disability pension, respectively. To understand how drug-related morbidity affects productivity and work abilities for those suffering, other research methods are needed.

6.1.3 Sensitivity of the findings

Several sensitivity analyses were conducted in the studies (appendix). Such analyses are used in economic analyses to improve understanding of circumstances that may alter the conclusions, to support judgment about the relevance of the selected cost components and clinical outcomes, and to evaluate uncertainty of the results.^[164]

The large standard deviations in papers I-II indicates difference in opinion between the experts and is the result of not reaching consensus. According to the sensitivity analyses for papers I-II, it appears that the resulting direct costs of drug-related morbidity were mainly sensitive to the high-cost clinical outcomes. Thus, the final cost estimate is dependent on representative pathway costs and attributed probabilities for *Prolonged hospital stay*, *Hospitalisation*, and *Advanced specialist care*.

The wide confidence intervals in papers III-IV will mainly be the result of skewed cost data, with a small proportion of the populations using a large proportion of all areas of healthcare. According to the analyses from the medical record study in the appendix, it appears that previous healthcare use is strongly associated with healthcare use the following month and more so among patients with ADEs. Thus, ADEs appear to be accumulated among individuals with recurrent healthcare use. Although possible to decrease the

high one-month prevalence of the survey (paper IV) to one resident in ten, based on the response rate, the results from the medical records (paper III) indicate that the survey responses were more likely to underestimate the healthcare resource use associated with drug-related morbidity. In addition, a large group reporting ADEs in the survey did not report healthcare encounters, indicating that the results in paper III may also underestimate the impact of drug-related morbidity. The effect of this accumulation will be further discussed in section 6.2.

6.2 Findings from complementing sources

In the DRUMS project studies, the aim was to provide prevalence-based estimates of drug-related morbidity. This was possible in papers III-IV, while the expert panel studies (papers I-II) were limited to all patients receiving healthcare, and thus population-based estimates could only be calculated based on external information of proportion of patients with healthcare encounters. To gain further insight into the prevalence and consequences of drug-related morbidity in society, the studies were designed to complement each other. The expert panel studies and the results from medical records (papers I-III) identify high resource use caused by drug-related morbidity among patients in healthcare, while the responses to the survey (paper IV) indicate a large proportion of the drug-related morbidity occurs in individuals outside the healthcare system. Moreover, the respondents (paper IV) reported productivity loss due to sick-leave, informal care and lost leisure time caused by drug-related morbidity, but the indirect costs were not possible to quantify in the current studies.

From papers III-IV, the estimated costs resulting from drug-related morbidity (ADRs and STEs or all ADEs, respectively) were 0.5-1.5% of all drug costs and 6.1-9.5% of all healthcare costs in Sweden. Applied to the annual prescription drug^[122] and healthcare^[123] costs in Sweden during 2010, ADEs and subsequent drug-related morbidity caused prescription drug costs in the range of SEK 130-380 million and healthcare costs in the range of SEK 12000-19000 million. The SEK 60000 million calculated based on the pharmacist expert panel responses, represented 20% of the overall costs to the Swedish healthcare system.^[123] Due to the division of responses from the physician expert panel to inpatients and outpatients, respectively, those results are less adapted to comparisons with the overall healthcare costs.

The estimated annual costs give an indication of the economic impact of drug-related morbidity in Sweden. Although the costing methods differ, these figures may be put in perspective by direct costs reported by the National

Institute of Public Health resulting from prevalent public health concerns such as alcohol, illicit drug use and tobacco in 2009; SEK 2300, 7500, and 2500 million,^[165] respectively. It appears that ADEs and subsequent drug-related morbidity shall be acknowledged as a substantial cost to society.

6.2.1 Study period and prevalence

The prevalences and estimated costs resulting from drug-related morbidity based on the expert panels (papers I-II) were high compared to the results from the other included studies. However, the expert panel studies (paper I-II) lacked information on the time period for the prevalence estimates. Decision trees are the most simple form of decision modelling techniques, and do not include a time reference.^[166] The model is therefore mainly suited for events with short duration. It is common sense that the prevalence of any outcome in the population will be affected by the time period; if we include a longer period more people will have time to develop a disease and need resource use. Our findings in the medical record study (paper III) showed that the effects of time period when limiting the study of drug-related morbidity to healthcare patients were less easy to interpret. A majority of the patients with ADE in our study had healthcare contact already the first month of the study period, and overall, a majority of all patients had healthcare encounters already the first month. Thus, when looking at encounters during the third month of the study period, 58.7% of all patients with healthcare encounters had already been prevalent patients two months previous, but as much as 75.6% of those with ADE encounters during the third month belonged to this group. This was not only affected by the accumulation of new patients over time, but by an apparent disproportional accumulation of ADE-patients, and of new ADEs affecting the same patients that had already been included in the analysis.

Comparisons between the expert panel studies (papers I-II) show a higher proportion of drug-related morbidity in the reports by pharmacists. The potentially corresponding increase in costs is less easily interpreted, since the patient population varies between the studies. The differing estimations by pharmacists and physicians may depend on their differing professional roles, resulting in higher recognition of ADEs by pharmacists. Still, it has been reported that physicians identify and report ADRs in medical records, although few reactions were coded according to the International Classifications of Diseases or reported to the pharmacovigilance system.^[167]

The study of ADEs and resource use identified from medical records (paper III), may underestimate the prevalence of drug-related morbidity to a large

extent, according to results from the survey (paper IV). According to the survey, only 17.4% of respondents reporting ADE also received healthcare during a one-month period (equalling 3.3% of the population). Moreover, the study was conducted in only one county, which although has a similar demographic distribution may differ from the general Swedish population regarding other aspects. It has previously been reported that Östergötland County is a county with favourable combination of weighted healthcare quality indicators and low costs per inhabitant.^[161] Thus, the costs for encounters identified in the study may be high compared to those few counties with lower costs, but on a national level the estimated economic impact should be viewed as a conservative estimate. This holds unless the quality of delivered care differs between drug treatment and other interventions.

The COI calculations (papers III-IV) confirm the well-known skewedness in the distribution of healthcare costs (resulting in wide confidence intervals for the estimated costs, as presented in section 6.1.3). Previous research has shown a small proportion of the population using a large proportion of healthcare resources,^[168] although it has been suggested that this has been changed during recent years due to large increases in prescription drug costs while inpatient care costs were more stagnant.^[169] The skewed distribution of ill-health is also acknowledged in the Swedish public health report, identifying inequalities in health due to socioeconomic factors and other determinants of health.^[170] This skewedness corresponds to the suggested accumulation of healthcare encounters among a small group of patients.

6.2.2 Reporting of resource use

Moreover, by comparing the proportion of respondents (paper IV) receiving healthcare to the one-month prevalence of healthcare encounters in the medical record study (paper III) it may be suggested that many residents with severe disease and high healthcare resource use did not respond to the survey (Figure 9). This became apparent also from scrutinising the distribution of costs and used resources in Table 5. The respondents with drug-related morbidity and healthcare use (paper IV) reported only a small proportion of the resource use identified from the medical records (paper III); e.g. dispensed drugs costs of SEK 0.5 million and SEK 8.0 million, respectively, and indirect costs for sick-leave being SEK 0.4 million compared to SEK 22 million.

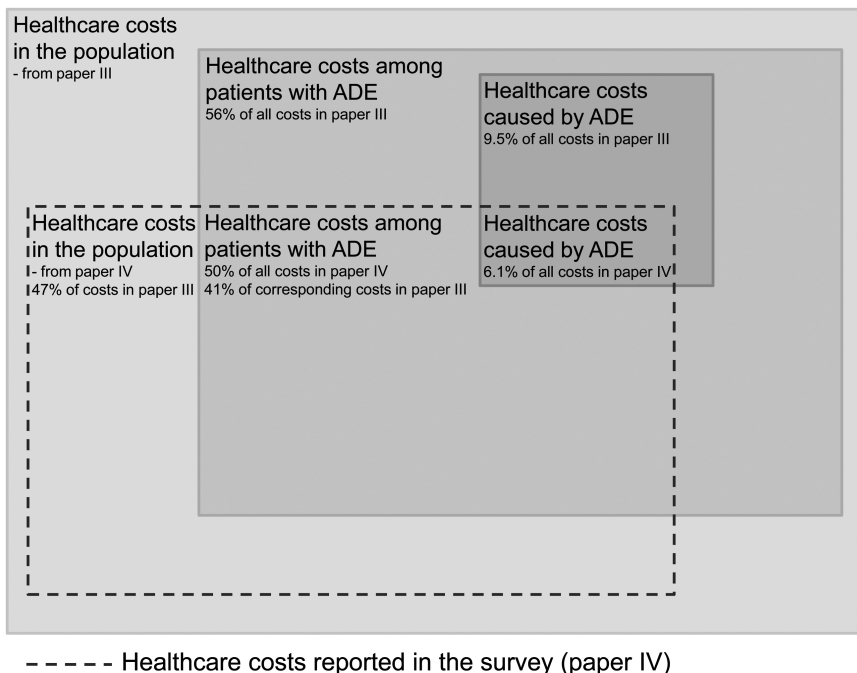


Figure 9. Monthly healthcare resource use reported by respondents in paper IV, in perspective of resource use per month identified in paper III.

For prescription drugs among the general population, the pattern was the opposite, with 6% higher prescription drug costs among all respondents compared to the sample in paper III. However, if comparing prescription drug costs among those with healthcare encounters, the prescription drug costs were 15 times higher among those with ADEs identified from medical records compared with the self-reported use in paper IV. Moreover, drug costs and quantity resulting from the ADEs were more than twice that among patients in paper III compared to paper IV. If examining indirect costs, a similar pattern emerges, with higher costs identified from the Sickness Benefit Register in paper III compared to self-reported data in paper IV. The greatest differences in costs and resource use quantities were found in patients with healthcare encounters and ADEs identified from either medical records or self-reports.

Furthermore, only resource use resulting from ADRs or STEs were included in the cost analysis from the survey, which according to results from the study of medical records represent the majority of costs, but not all, resulting from drug-related morbidity. These results strengthen the assumption that the resource use reported by the survey respondents underestimates the economic impact of overall morbidity, and drug-related morbidity in particular.

6.2.3 Population groups

According to the comparisons in papers III-IV, the direct costs resulting from drug-related morbidity for each patient did not differ significantly by age or sex, but the prevalence of drug-related morbidity may differ between population groups.^[3,108] The review of medical records resulted in an ADE-prevalence of 12% in the general public, of which more than one third were considered preventable.^[3] The ADE-prevalence was higher among the elderly population,^[3] and among women (paper III). ADEs were reported by 19% of the general public and 19% of all reported ADRs and STEs were perceived preventable.^[108] No apparent age-effect on the prevalence estimate was found, although some differences were found for specific ADE-categories.^[108] More women than men reported ADEs (paper IV). However, no association was found between several socioeconomic variables (e.g. sex, education, and disposable income) and costs resulting from ADEs, but the costs differed by age, number of medications and ADE-categories (*unpublished material*). However, the costs resulting from ADEs to each patient displaced a larger proportion of the disposable income among low income earners compared to other patients with ADEs (*unpublished material*).

The individuals with drug-related morbidity (self-reported or identified from medical records) had high COI, both in comparison to the general population and to other patients. Either individuals with drug-related morbidity will experience increased resource use due to the drug-related morbidity (more than was identified in the current studies), or individuals with large disease burden and high resource use will develop drug-related morbidity. Moreover, a large proportion of the drug-related morbidity and the associated costs were preventable. Regardless of the direction in the relationship between development of drug-related morbidity and overall disease burden, individuals suffering from drug-related morbidity appear to be a group in society that needs to be prioritised to improve equality in health.

Moreover, most ADEs in our studies were associated with commonly dispensed drugs, such as nervous system and cardiovascular treatments.^[3,108]

Thus, future research is needed to further explore the distribution of drug-related morbidity and associated costs, but due to the high prevalence in the general public (paper IV), with no clear boundaries for whom it affects, it appears that drug-related morbidity needs to be addressed by interventions in all parts of the healthcare system, in social services and in society. The suggestion is strengthened by a recent study finding that inpatient ADEs are distributed in all the medical specialities.^[171]

6.3 Comparisons to previous research

Current knowledge of the research landscape suggests that there are no previous studies measuring the economic impact of drug-related morbidity in the general public except for modelling studies based on expert panels.^[51,54] Thus, to enable comparison to previous research, analyses were also made of sub-samples from the included studies.

6.3.1 Population-based modelling studies

Our results differ from previous expert panel studies of costs resulting from drug-related morbidity (Table 6), in particular the estimated low proportion of patients with optimal outcomes. The difference may indicate an actual difference between countries, and over time, but it is not possible to draw conclusions from available data. It may be the result of how the questions were formulated, the prevalence versus incidence perspective, or the selection of experts. However, the studies complement the previous expert panel studies, with new data on probabilities, and with expert opinions derived from healthcare settings outside the United States of America.

The estimated proportion of all healthcare costs (6-10%, from papers III-IV) were similar to a recent finding that medical errors (i.e. non-safety costs, including costs for medication errors, nosocomial infections and surgical events) contributed to 6% of all healthcare costs in Spain.^[174]

Table 6. Comparison of estimated conditional probabilities* of clinical outcomes resulting from NMPs and TFs.

Paper	I: Swedish	II: Swedish	II: Swedish	Adjusted	Adjusted
	pharmacists	outpatient	inpatient	American	German
	%	%	%	data ^[172]	data ^{§ [173]}
	/prevalent	/prevalent	/prevalent	/incident	/patients with
	patients	outpatients	inpatients	visits	incident prescription
Optimal outcome	39.4	48.5	45.6	74.4	-
NMPs					
No additional treatment [†]	11.1	6.6	5.9	1.0	0.5
Physician visit	-	-	-	1.9	1.1
Additional treatment	10.4	14.3	8.0	2.8	1.9
Emergency department visit	-	-	-	0.6	0.4
Specialist referral	1.7	3.2	2.7	-	-
Prolonged hospital stay	2.0	-	4.0	-	-
Hospitalisation	2.6	1.3	-	0.3	0.3
Advanced specialist care	0.5	0.3	0.7	-	-
Long-term care admission	-	-	-	0.1	0.07
Death	0.3	0.1	0.6	0.0	0.06
TFs					
No additional treatment [†]	3.4	2.2	1.5	2.7	-
Physician visit	-	-	-	3.1	-
Additional treatment	8.8	11.1	9.5	6.6	-
Emergency department visit	-	-	-	1.5	-
Specialist referral	1.7	1.8	4.1	-	-
Prolonged hospital stay	1.2	NA	4.4	-	-
Hospitalisation	1.8	0.7	-	0.6	-
Advanced specialist care	0.4	0.1	0.6	-	-
Long-term care admission	-	-	-	0.3	-
Death	0.3	0.0	0.5	0.0	-
NMPs and TFs					
No additional treatment [†]	1.0	0.8	0.9	0.3	-
Physician visit	-	-	-	0.9	-
Additional treatment	7.1	6.7	4.1	2.0	-
Emergency department visit	-	-	-	0.5	-
Specialist referral	1.6	1.7	2.7	-	-
Prolonged hospital stay	1.6	-	1.5	-	-
Hospitalisation	2.1	0.5	-	0.4	-
Advanced specialist care	0.6	0.2	2.3	-	-
Long-term care admission	-	-	-	0.0	-
Death	0.5	0.0	0.4	0.0	-
Total	100	100	100	100	-

* Conditional probabilities are estimated by multiplying the average probabilities of drug-related morbidity (NMPs, TFs, and the combination of NMPs and TFs), by the average probability of each clinical outcome.

§ In the German study, probabilities included the combination of NMPs and TFs.

† In the American and German data, the clinical outcome was named *No treatment*. In the Swedish data, the probability of *No additional treatment* will encompass *No treatment* and *Physician visit* from the American and German data.

6.3.2 Inpatient studies

In comparing our prevalence results for hospitalisations in the study of medical records (paper III), we find that our estimates of drug-related admissions (15.8% of admissions caused by ADE,^[3] and in total 35.8% of admissions associated with ADEs) were high compared to the approximately 5% of inpatients reported in previous studies.^[34] It is possible that there is an association between our high results, and the reported low number of hospital beds^[161] in Sweden.

It has been reported that the method for data collection affects the prevalence rate; medical record review identifies more cases than computerised methods and voluntary reports.^[34] Prospective medical record review identifies more cases than retrospective review.^[42] Studies conducted to find drug-related morbidity in all inpatients find more than those limited to acute admissions.^[34] Moreover, researchers searching for ADEs find more cases than if limited to ADRs.^[34] A recent study of injuries in healthcare using the Global Trigger Tool, where medical record review in Swedish hospitals based on the trigger list identified adverse events in 13.5% of patients, and ADEs in 1.6% of patients.^[175] Except for our more comprehensive review of the records, the large difference in results may also be caused by inclusion of outpatient medical records in our study.

Since previous studies have only included hospitalised patients, the comparison of results needs to be limited to inpatient data. Our estimated average cost per admission caused by ADE (SEK 42763.4) can be compared to results from Hoonhout and colleagues, reporting an average excess cost of EUR 3105 for drug-related adverse events in 2004,^[176] and by Jha and colleagues, reporting an average total costs calculated from charges of USD 16177 in 1994-1995.^[177]

6.3.3 Outpatient studies in hospitals

From the medical records study (paper III), 206 encounters with somatic emergency departments, and 9 encounters with psychiatric emergency departments were identified. Among these, 58 (28.2%) and 3 (33.3%) were associated with ADEs, while 37 (18.0%) and 1 (11.1%) were judged dominantly caused by the ADE. Although not exactly the same, these figures are similar to the 12.2% frequency associated with ADEs reported by Hohl and colleagues,^[178] and the 28.1% frequency of visits caused by ADE reported by Tafreshi and colleagues.^[179] Both those studies included patient interviews to identify ADEs.

Previous results have been contradictory. Of 37 hospital-based studies of drug-related morbidity in ambulatory care, Taché and colleagues^[42] identified a range of ADE-estimates resulting in encounters of 0.2-41.3%. The survey respondents with ADEs (paper IV) reported 52.3% of all reported emergency department visits (79 of 151 visits), and only five of these (3.3% of all emergency department visits) were assigned to the ADR or STE. However, rereading the question in the survey, the resource use reported by the survey respondents may be interpreted as corresponding to the dominant cause category in the study of medical records, since respondents were asked to report healthcare resource use caused by the ADR or STE.

6.4 General discussion

6.4.1 Potential for prevention

In all included sub-studies, the preventability was high. The expert panels (papers I-II) reported preventability rates of 25-45% of all drug-related morbidity. The minimum estimation of annual costs for preventable morbidity was SEK 500-1500 million (for outpatients and all patients, respectively). Moreover, 47% of all patients with ADE (paper III), and 22% of all respondents with ADRs or STEs (paper IV), had at least one preventable ADE. In total, 39% of the 981 ADEs identified from medical records,^[3] and 19% of the 1592 self-reported ADRs and STEs,^[108] were judged preventable.

There was no difference in costs between patients with or without preventable ADEs (paper III), and the average cost for patients with only one (preventable) ADE within the study period was approximately SEK 1000. Under the assumption that costs were equally distributed across ADEs, it is possible to calculate an annual cost of preventable drug-related morbidity of SEK 7600 million, based on figures from the medical records study and the annual healthcare expenditures for healthcare^[123] and drug use.^[122]

The issue of preventable drug-related morbidity is problematic. It has for example been suggested that preventable events are not always possible to avoid, and that some events should be possible to prevent but are not included in current pharmacovigilance practice.^[180] Moreover, the knowledge and treatment guidelines develop over time. The time to identifying an ADEs or drug-related morbidity is likely to change based on the knowledge of the drug user and the healthcare professional, and it is therefore possible that costs for treating ADEs and drug-related morbidity are affected by the knowledge and actions of both the consumers and producers of healthcare.

Thus, the preventable cost of ADE and subsequent drug-related morbidity may need to include not only the costs resulting from preventable ADEs, but also the costs of resources used for treating drug-related morbidity after the ADE could have been identified and treated. By distinguishing the cost components it should be possible to develop a model of the economic impact of drug-related morbidity useful for future research.

In papers I-II and paper IV, costs resulting from relief of the ongoing drug-related morbidity, and costs for solving the ADE, were not distinguished. However, in paper III it was possible to distinguish resource use that may be discussed using the framework (Figure 2).

The 440 healthcare encounters dominantly caused by ADEs, that including diagnosing, may be viewed as encounters for relief of the drug-related morbidity (resource use A). These would appear to be the result of the individuals' symptoms rather than the knowledge of having developed an ADE. The 490 encounters with treatment may be more complex to assign to a specific phase in the framework, since treatment may indicate either symptomatic treatment or solving the ADE (resource use A and B, respectively). Monitoring encounters (n=426) could also be included in either resource use A or B, since these may include both monitoring if the ADE is resolved and monitoring of the ongoing drug-related morbidity to ensure e.g. symptomatic treatment is achieved. Monitoring also included resource use associated with primary prevention, but only if resulting in the diagnosing of an ADE. However, the main aim of monitoring should be to oversee the symptoms development and relieve pain and distress (resource use A). Any resources used for secondary prevention will be assigned to the development phase (resource use C), aiming to avoid recurring events.

Although not fully quantifiable, due to limitations in the register data, it appears that the resource use for relief of drug-related morbidity (resource use A) represented a large proportion of the total resource use in this study, compared to the cost for treating ADEs (resource use B). Moreover, patients often had repeated encounters resulting from diagnosis, treatment and monitoring of ADEs. This includes the costs for diagnosing ADEs, and parts of the costs for resulting from treatment and monitoring, suggesting that the potential for cost reduction is greater than the avoidable costs resulting from preventable ADEs.

Thus, medication safety interventions need to address both prevention of potential ADEs and rapid detection of emerging symptoms to avoid additional preventable resource use. If the cause is not treated, the cumulative

resource use resulting from drug-related morbidity is expected to increase over time. If the drug-related morbidity is not negligible, the resource use is likely to include both healthcare visits (for e.g. monitoring) and treatment of symptoms. The costs for treating a specific ADE should not change to a large extent based on when it is treated.

6.4.2 Harm of drug therapy

In this thesis, COI was used to measure economic impact, thus one disadvantage was the lack of positive outcomes of drug use. The economic impact of harm was estimated, but no costs of the good resulting from drug therapy. What is the health gain that puts these results for drug-related morbidity in perspective? The results must be interpreted and applied with awareness of this limitation. Thus, the results shall be viewed as one step towards understanding the resource use resulting from drug therapy, raising awareness of the resource use and costs associated with harm of drugs, i.e. drug-related morbidity. This knowledge could be put in perspective of the beneficial effects of drug therapy using for example modelling methods. Using a decision model with inpatient and outpatient data, Samp and colleagues found that the mean expected cost of one medication error was USD 89.^[181] Still, no benefits were included, and outcomes excluded non-preventable ADEs.

More conclusive information about the good:harm ratio of drug therapy may be used to guide future interventions towards better drug safety. The development of outcome-based financing of healthcare should put pressure on the healthcare system to improve safety. This could include financial incentives based on such factors as quality indicators, to direct healthcare providers towards better care quality and to optimise the healthcare resource use.^[182,183] Such interventions should be prioritised in society, since the general public appears to value interventions to address medication errors higher than interventions towards aspects such as lifestyle changes and sports injuries.^[184]

In developing new interventions to address drug-related morbidity, it is likely that the focus will be on events that are identified by care givers, with obvious causal relationship to the drug therapy, and for which there is (short-term) costs for treating the symptoms. However, the literature on costs resulting from drug-related morbidity has been limited to hospitalised patients.^[54] The same was found in a recent Dutch study^[185] that estimated the direct medical costs and lost productivity of preventable drug-related hospital admissions. The survey (paper IV) showed that those with drug-related

morbidity also have other resource use, with only a small group being hospitalised. Thus, many residents with drug-related morbidity may have been excluded in previous studies, and will therefore not be covered by potential interventions. It also appears that resource use resulting from self-reported STEs were at least as common as resource use from ADRs, which needs to be acknowledged in the development of interventions. Previous studies of specific diseases and treatments have measured the expense that drug users would be willing to pay to avoid ADRs or STEs. It appears that the individuals' willingness to pay for good treatment effect is higher than the willingness to pay on avoiding (mild) adverse effects of the treatment.^[186-188] This may be associated with the relatively resource intense consequences reported for STEs.

It has been suggested that the patient should be more involved in medical decision making^[189] in order to enable rapid identification of medication errors. Healthcare professionals may be less keen to expose their potential errors to the patients since trust in the care-giver is part of the cure.^[189] However, according to the principal-agent relationships,^[74,75] it may be argued that the large group of individuals experiencing drug-related morbidity indicated in paper IV may undermine drug users' trust in their prescriber. The potential lack of trust may result in lost confidence in the prescribers' representation of their (the drug users) interest. This could be involved in the suggested association between non-adherence and low belief/high concerns about medicines,^[190-192] in particular intentional non-adherence.^[193]

6.4.3 Implications to other settings

Since the knowledge about the economic impact of drug-related morbidity in society is scarce, the few available studies should be used by decision makers in other countries. However, there are a number of reasons why economic data is not transferable between countries and settings: variation in demography and disease patterns, access to healthcare, available treatment options and incentives to caregivers all may affect the care delivered. Moreover, price levels and expected opportunity costs may vary.^[194]

Three of the studies included in this thesis were set in Sweden, and one in the Swedish county Östergötland. The Swedish healthcare context differs from many other countries, and may therefore affect the interpretation of results. There are three independent government levels in Sweden, including the national government, the 21 county councils/regions and 290 municipalities. The counties/regions have the main responsibility of healthcare, while the

municipalities are responsible for care and housing of the elderly and disabled.^[161] Swedish healthcare is based on the equal right to care and dignity regardless of social status. In care delivery the patient with the greatest need shall take precedence, and when alternative treatments for the patient are available, a reasonable relation between costs and effects is prioritised.^[195] The foundation of the healthcare system is primary care, but there is no formal gate-keeping role. Highly specialised care is delivered in regional hospitals, organised by the six healthcare regions.^[161]

Healthcare professionals in Sweden are salaried employees. Primary care in Sweden can be either public or private but with mainly public funding through capitation combined with fee-for-service and performance-based payments. Almost all hospitals are public, financed through budgets or budgets combined with case-based and performance-based payments. Approximately 80% of health expenditures are tax based. The 17% of private expenditures are mainly user charges, for care visits and per bed-day in hospitals.^[161]

The studies in this thesis cover the years 2008-2010, when the maximum user charge for healthcare was SEK 900, and for reimbursed drugs SEK 1800 with the full cost paid by the user up to SEK 900. Healthcare expenditures in 2010 were SEK 318250 million, which equalled 9.6% of the gross domestic product.^[123] Total drug expenditures in 2010 were SEK 36026 million, of which 70.9% (SEK 25534 million) were prescription drugs and 19.1% (SEK 6875 million) were inpatient drugs paid and provided by the county councils.^[122] The out of pocket expenses represented 23.1% (SEK 6593 million) of the prescription drug costs.^[123]

Thus, the results are more likely to transfer well to other countries with global health coverage, funded mainly by taxes, with similar demography and disease patterns. Since previous studies have been conducted in settings quite different from the Swedish healthcare context, and lack population-based cost estimates,^[54] it was difficult to draw conclusions on contextual effects in the included studies. For instance, it has previously been reported that underuse of drugs due to high drug costs were more common in countries with high out of pocket expenditures.^[196] Comparative population-based studies in other Nordic countries with similar tax-funding of the systems may enable insights of the effects of different financial incentives and levels of decentralisation.^[197]

6.5 Implications to practice

The presented results have implications for individuals who take drugs, for healthcare professionals in clinical practice, for decision makers in within relevant authorities, in healthcare and social services and for researchers studying drug-related outcomes.

The survey responses show that individuals in the general public are aware of drug-related morbidity, and the associated resource use. Thus, drug users themselves are important actors in the rapid detection of occurred or potential drug-related morbidity and in seeking advice from healthcare professionals when needed. This applies also to drug-related morbidity caused by over-the-counter drugs and herbal remedies, in addition to prescription drugs.

The expert panel studies showed that both pharmacists and physicians estimate drug-related morbidity to be common and is associated with increased resource use in all parts of the healthcare system. However, there appear to be some issues regarding drug-related morbidity that could be further discussed among healthcare professionals. The expert panels judged NMPs to be the most influential drug-related morbidity, while the study of medical records showed STEs to be at least as common and costly as ADRs. Moreover, the identified group of individuals with consecutive encounters associated with drug-related morbidity indicates a potential for preventing healthcare costs and harm also among individuals with drug-related morbidity that is not initially preventable. By building an alliance with the drug users, healthcare professionals may improve treatment outcomes.

Although inappropriate to guide new interventions, COI-studies like this draw attention to important diseases. These studies show that drug-related morbidity occurs in all parts of society; also to individuals outside the healthcare system, and in all age groups. Drug-related morbidity shall thus be viewed by decision makers as an important, widespread and costly public health concern, and needs to be addressed by interventions throughout society, in the healthcare system, in social services and in the general public not receiving such services. Increased awareness of drug-related morbidity and the associated costs could bring changes to several aspects of healthcare such as the approval of new drugs, clinical guidelines and the reimbursement levels of medicines. Moreover, there is a need to initiate studies to identify how and why drug-related morbidity develops, and to find methods for prevention, rapid detection and recovery.

According to the survey responses, drug-related morbidity resulted in resource use outside the healthcare system that has not been included in previous studies. There is thus a need to broaden the range of included consequences when studying the economic impact of drug-related morbidity.

7 CONCLUSIONS

From the papers included in this thesis it can be concluded that drug-related morbidity causes resource use and harm throughout the Swedish healthcare system and the Swedish general public. Although a large group of drug users and patients with drug-related morbidity were found in the elderly population, drug-related morbidity occurred in all age groups. Moreover, there was no identified difference by age or sex in costs resulting from prevalent drug-related morbidity or overall COI.

It appears that STEs are equally as costly as ADRs, but there were also costs resulting from other categories.

According to the expert panels, a large proportion of the drug-related morbidity may be prevented by improved care. In addition to avoiding preventable ADEs, there appears to be potential for improving care and saving resources by rapid detection and treatment of ADEs in patients repeated encounters and prolonged episodes of drug-related morbidity.

Not only did drug-related morbidity cause resource use, but this group of individuals was also associated with high overall resource use and costs; from drug use, healthcare encounters, transportation, short-term sick-leave, disability pension, and informal care. It appears that a large proportion of the resource use resulting from drug-related morbidity may be unaccounted for in these studies, including both direct and indirect costs. Thus, the suggested 10% of all healthcare costs and 2% of all drug costs shall be viewed as a minimum economic impact of drug-related morbidity in Sweden.

8 FUTURE PERSPECTIVES

Based on the findings in this thesis, potential areas of future research have been identified. Firstly, additional analyses from the medical record study are planned within the DRUMS project: sensitivity analyses of our method for associating resource use to identified drug-related morbidity in paper III, calculation of attributable costs of ADEs from the overall COI in the study of medical records, using propensity score matching, and to examine the distribution of costs between payers in society from both the medical records study and the survey.

Moreover, remaining gaps in knowledge on the economic impact of drug-related morbidity after the included studies were: the associated indirect costs, the apparent association between drug-related morbidity and high overall COI and preventable costs.

According to the survey responses a large proportion of the general public experiences drug-related morbidity. However, less is known about the consequences of drug-related morbidity outside the healthcare system, which may affect individuals' adherence to therapy. There is thus a need for studies that explore the individual's own experience of drug-related morbidity and the processes involved in diagnosing, treating and monitoring such events.

The identified high overall care needs among residents with drug-related morbidity may result from resource use that cannot be captured by retrospective methods since these are limited by data availability, often to short-term outcomes, and to registered resource use and costs. It appears that there is a need for prospective studies of drug-related outcomes in the population, preferably using existing data in registers, for example. Such studies should aim to include preventable costs both from avoiding preventable ADEs and from rapid detection and treatment of non-preventable ADEs. According to the results presented in this thesis, studies need to encompass a broad range of consequences from drug-related morbidity.

Finally, this thesis excluded the benefits of drug therapy. The Swedish population-based registers could be used to monitor drug therapy over time, but the reporting of drug-related outcomes are limited and there is no national register for primary care data. Further knowledge may be gained by reporting of drug-related (preferably both positive and negative) outcomes through the Swedish quality registers, in medication summaries, or by collection of patient reported outcomes to name but a few.

ACKNOWLEDGEMENT

The financial support for the project and thesis work is gratefully acknowledged: from the National Corporation of Swedish Pharmacies (Apoteket AB); Region Västra Götaland and Östergötland County for the DRUMS project; from the Nordic School of Public Health NHV to conclude my thesis work; and from Apotekare C D Carlssons stiftelse and Forte: Swedish Research Council for Health, Working Life and Welfare for the opportunity to present my research in conferences.

I would like to express my gratitude to all that have inspired and supported me during my thesis work:

To my supervisor-trio during this thesis work: Main supervisor, Anders Carlsten, and co-supervisors, Anna K Jönsson and Clas Rehnberg. You all have very busy schedules, and I appreciate that you have always been available for discussions and good advice when I've needed them.

To the other researchers in the DRUMS project who contributed to my thesis: Daniel Alström, Johanna Gustafsson, Katja M Hakkarainen, Khedidja Hedna, Staffan Hägg, Ingela Jakobsson, Mats Klingberg, Ellinor Ottosson, Josefina Lindstén, Jennie Natanaelsson, Johnny Pettersson, Max Petzold, Karolina Andersson Sundell, Karin Tunér, Parshin Saadatarad, Staffan Svensson, Annika Yeiter, and Tatiana Zverkova Sandström. In particular my fellow doctoral student in the project, Katja M Hakkarainen, I hope we'll continue both working together and "hang out" in the future.

To my other contacts during the data collection and study design, in Östergötland County, in authorities and organisations that I have contacted for advice, and at the register holders. In particular Lars Svensson at the Cost Per Patient Register in Östergötland County.

To my colleagues at the Nordic School of Public Health NHV, in particular to my fellow doctoral students, for priceless friendship and support during these years. Also, to Johanna Andersson, Henry Ascher, Mika Gissler, Jan Johansson Hanse, Pernilla Jonsson and Ingvar Karlberg, for reviewing and commenting on my thesis during research programme seminars.

To other research colleagues, at the Section of Social Medicine in University of Gothenburg, and in my research networks within pharmacoepidemiology and health economics, respectively.

To the University of Gothenburg, for giving me the opportunity to gain a Doctoral degree from the research.

To Myriah Lesko for language editing.

Finally, to family and friends, in particular to my “drömprins”, Jörgen, for being there. Without your understanding of my overtime and recurrent focus on somewhat faraway subjects, I wouldn't have finished this thesis. Moreover, you are the best PR-manager any researcher or caregiver could ever have. Also, to my “lill-prins”, Arthur.

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9 APPENDIX: SENSITIVITY ANALYSES

Sensitivity analyses were made for selected cost estimations, to explore the sensitivity to methodological choices. The sensitivity analyses from papers I-II are also presented here, to give the results in 2010 SEK-values.

For papers I and II, sensitivity analyses for the costs resulting from drug-related morbidity included 1) varying the probabilities of drug-related morbidity and the probabilities of their clinical outcomes from the first to the third quartile of the participants' estimates, and 2) varying the pathway costs for each clinical outcome in section C. For this thesis, additional sensitivity analyses were conducted for 3) the variation in conditional probabilities and costs for each participant, and 4) changes in probabilities and costs between rounds one and two.

For paper III, analyses were made of the distribution of overall healthcare resource use and ADE-related resource use over time, based on information about when during the study period each encounter occurred. These analyses were not presented in the publication.

9.1 Results from the expert panel studies

9.1.1 Varying the probabilities (papers I-II)

Based on the pharmacists' expert opinions (paper I), the COI of drug-related morbidity per patient attending healthcare ranged from a more conservative estimate of SEK 4671 for the first quartile to SEK 12535 for the third quartile. Of the clinical outcomes of drug-related morbidity among patients attending healthcare, the costs differed the most for Advanced specialist care (cost range SEK 729-2386) and Deaths (cost range SEK 397-1151). The COI of drug-related morbidity per outpatient (paper II) ranged from SEK 922 for the first quartile to SEK 4266 for the third quartile. Of the clinical outcomes of drug-related morbidity among outpatients, the costs varied the most for *Hospitalisation* (cost range SEK 605-2456). The COI of drug-related morbidity range was SEK 1933-11128 for inpatients (paper II). Among inpatients, the cost difference was the largest for *Advanced specialist care* (cost range SEK 828-6461).

9.1.2 Varying the pathway costs (papers I–II)

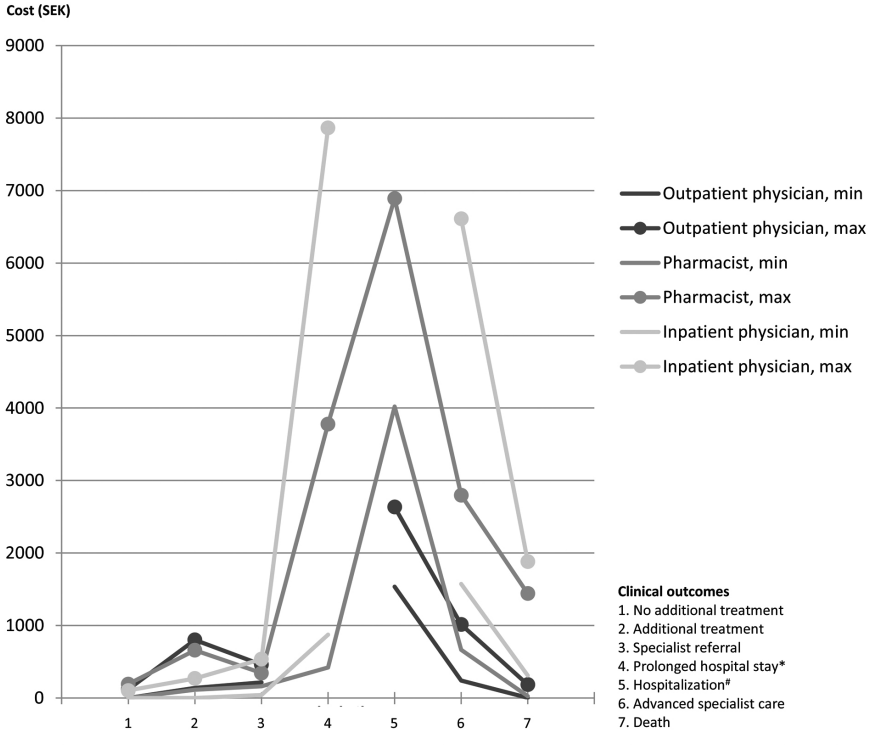
According to the pharmacists' expert panel Tornado diagram (paper I), the COI of drug-related morbidity per patient attending healthcare was primarily sensitive to costs resulting from Prolonged hospital stay. Varying from the minimum to the maximum pathway cost resulting from *Prolonged hospital stay* resulted in a cost range of SEK 420-3779 per patient attending healthcare, and varying the costs of a Hospitalisation resulted in a cost range of SEK 4019-6891.

According to the Tornado diagrams in paper II, the COI among outpatients was the most sensitive to changes in costs resulting from *Hospitalisations*, with a cost range of SEK 1537-2635. The COI among inpatients was the most sensitive to costs resulting from *Prolonged hospital stay*, resulting in a cost range of SEK 874-7866. Varying all pathway costs from the minimum to the maximum pathway costs resulted in cost ranges of SEK 5409-16105, SEK 2138-5216, and SEK 2525-17271, for the pharmacists', outpatient physicians', and inpatient physicians' estimates, respectively. Minimum and maximum cost estimates are presented in Figure 10.

9.1.3 Variation between participants (paper I–II)

According to the pharmacists' expert panel (paper I), the COI of drug-related morbidity in all patients attending healthcare was SEK 9925±5297. The COI based on physicians' individual estimates (paper II), was SEK 3311±1596 per outpatient and SEK 7732±5211 per inpatient (Table 7).

According to the participants in the pharmacists' expert panel (paper I), the proportion of patients attending healthcare and experiencing drug-related morbidity ranged from 35% to 86%, and the corresponding COI range was SEK 2247-20665 per patient. According to the outpatient physicians' individual estimates (paper II), the proportion of outpatients experiencing drug-related morbidity range from 25% to 95%, resulting in a COI range of SEK 1208-6425 per outpatient. The range was 40-85% of inpatients (paper II) experiencing drug-related morbidity, with COI per inpatient ranging from SEK 522 to SEK 13825.



* The clinical outcome *Prolonged hospital stay* was not included in the outpatient physician conceptual model.

The clinical outcome *Hospitalisation* was not included in the inpatient physician conceptual model.

Figure 10. The expert panels' minimum and maximum estimations from the Tornado diagrams (papers I-II).

Table 7. Estimated probabilities of patients experiencing NMPs and TFs, clinical outcomes of NMPs/TFs and the resulting cost (papers I-II). Average probabilities and standard deviations were estimated from each participants conditional probabilities and clinical outcome estimates.

	Pharmacists		Outpatient physicians		Inpatient physicians	
	Probability* (%±SD)	Cost# (SEK±SD)	Probability* (%±SD)	Cost# (SEK±SD)	Probability* (%±SD)	Cost# (SEK±SD)
Optimal outcome	39.4±14.1	NA	48.5±21.8	NA	45.6±17.4	NA
NMP						
No additional treatment	11.1±5.3	46±22	6.5±6.9	27±29	7.2±6.7	0
Additional treatment	10.3±4.1	148±58	11.8±6.5	170±93	6.8±2.9	13±5
Specialist referral	1.7±0.9	69±39	6.1±17.9	251±729	2.8±2.3	79±65
Prolonged hospital stay	2.1±1.6	364±286	NA	NA	4.0±3.2	708±556
Hospitalisation	2.7±1.8	2121±1425	1.0±0.7	784±549	NA	NA
Advanced specialist care	0.5±0.4	687±492	0.2±0.3	305±341	0.7±0.5	870±607
Death	0.3±0.3	258±259	0.1±0.1	64±107	0.5±0.5	392±413
TF						
No additional treatment	3.4±2.9	15±12	2.8±4.4	12±18	1.8±2.8	0
Additional treatment	8.5±2.4	122±34	9.6±4.8	138±69	9.5±4.5	18±8
Specialist referral	1.6±0.9	65±37	2.8±7.1	113±288	3.4±2.2	96±62
Prolonged hospital stay	1.2±0.7	206±125	NA	NA	4.6±4.0	811±713
Hospitalisation	1.9±2.5	1515±1192	0.7±0.7	556±558	NA	NA
Advanced specialist care	0.4±0.4	571±550	0.1±0.1	68±100	0.7±0.9	977±1200
Death	0.3±0.3	220±248	0.0±0.0	9±24	0.5±0.5	427±358
NMP and TF						
No additional treatment	1.0±1.0	4±4	0.9±1.1	4±5	1.0±1.3	0
Additional treatment	6.8±3.4	98±49	7.1±6.9	102±99	4.7±4.5	9±8
Specialist referral	1.6±1.0	65±40	1.1±1.4	43±58	1.9±1.4	55±39
Prolonged hospital stay	1.6±1.3	288±231	NA	NA	1.9±2.8	337±500
Hospitalisation	2.3±2.1	1852±1680	0.6±0.9	466±729	NA	NA
Advanced specialist care	0.6±0.5	799±660	0.1±0.2	187±308	2.0±2.6	2684±3439

Death	0.5±0.5	410±412	0.0±0.0	15±27	0.3±0.3	258±254
Among patients^S	60.6±14.1	9925±5297	51.5±21.8	3311±1596	54.4±17.4	7732±5211

* Conditional probabilities are estimated for each participant by multiplying the average probabilities of NMPs, TFs, and the combination of NMPs and TFs, by the average probability of each clinical outcome. Probabilities are rounded to the nearest decile

Costs are rounded to the nearest SEK.

\$ Due to rounding, percentages may not sum up to the proportion of the population.

A histogram of the pharmacists' expert panel estimates showed that the individual participants COI estimates were approximating a normal distribution, but a group of participants diverged from the rest by substantially higher COI estimates (Figure 11).

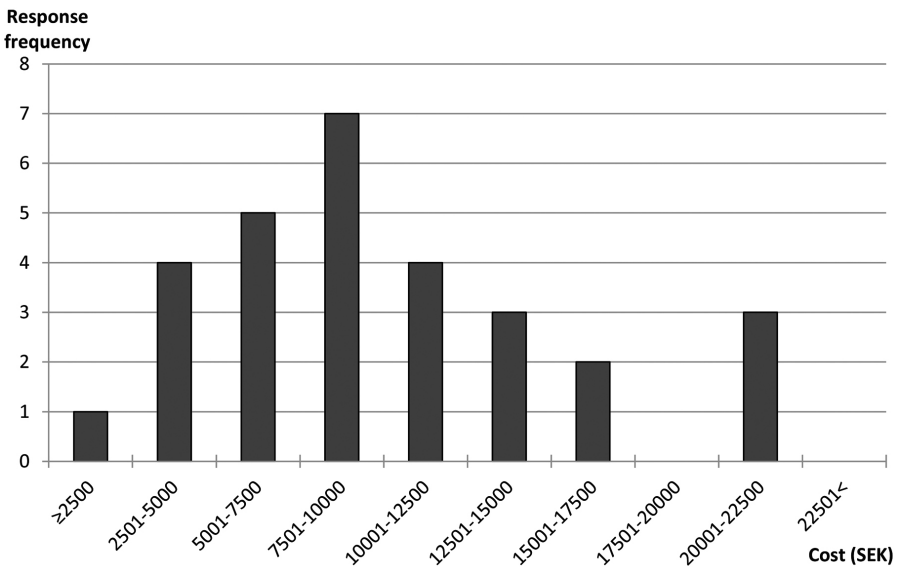
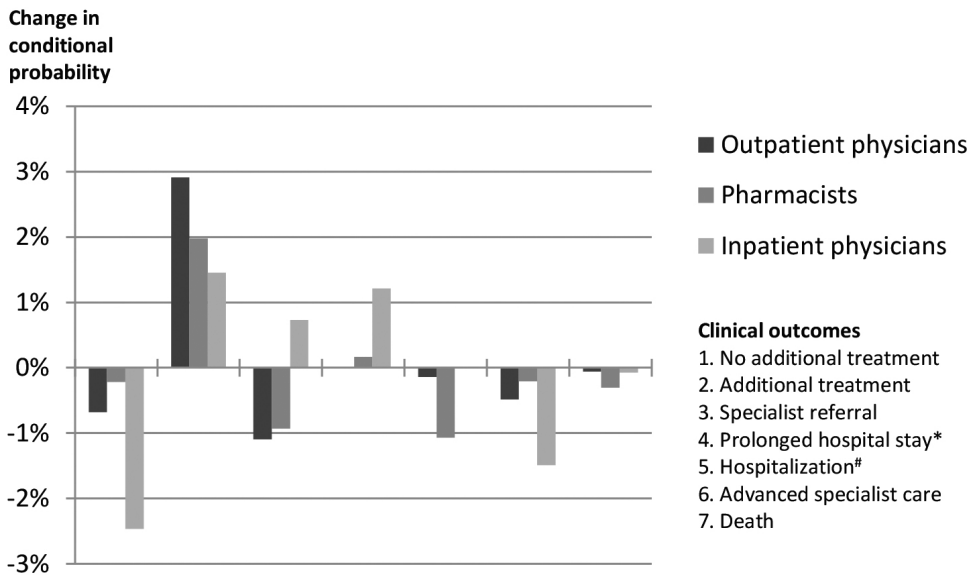


Figure 11. Distribution of cost estimates (SEK) from the pharmacists' expert panel (paper I).

Since there were fewer participants in the physician panels (paper II), the resulting histograms were difficult to interpret. It may be noted that all outpatient physicians' individual estimates were all below SEK 6425. The inpatient physicians' individual estimates were all below SEK 3237 or in the range SEK 8224-13825.

9.1.4 Changes between rounds (papers I-II)

To examine if additional rounds were likely to have changed the COI estimate, conditional probabilities of clinical outcomes resulting from drug-related morbidity were examined between the two rounds, for each group of participants. The trends were towards a larger proportion of patients' drug-related morbidity resulting in Additional treatment, and a smaller proportion resulting in No additional treatment and Advanced specialist care (Figure 12).



* The clinical outcome *Prolonged hospital stay* was not included in the outpatient physician conceptual model.

The clinical outcome *Hospitalisation* was not included in the inpatient physician conceptual model.

Figure 12. Percentage change of the expert panels conditional probabilities of clinical outcomes between rounds (papers I-II).

The variation in conditional probability was further examined for the pharmacists' estimates (paper I) of NMPs, TFs, and the combination of NMPs and TFs (Figure 13).

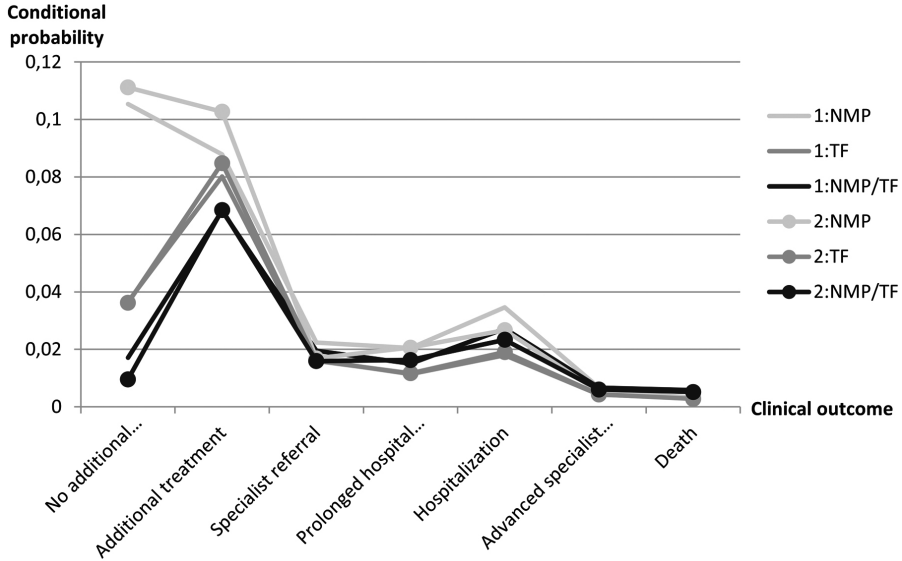


Figure 13. Variation in pharmacists average conditional probabilities for clinical outcomes of drug-related morbidity between the first and second rounds (paper I).

According to the pharmacists' estimates, the trend was primarily caused by changes in the estimates of NMPs towards more patients receiving *Additional treatment*. The same analysis of the outpatient physicians' (paper II) showed that the main difference between rounds was an increase in NMPs causing *Additional treatments* in Round Two. For the inpatients physicians, the main trend was towards the combination of NMPs and TFs causing more *Prolonged hospital stay* and less *Advanced specialist care*.

9.2 Results from the medical record study

9.2.1 Distribution of healthcare resource use over time (paper III)

The healthcare resource use and costs for all patients and for those with ADEs identified from medical records (paper III) appear evenly distributed over time (Figure 14).

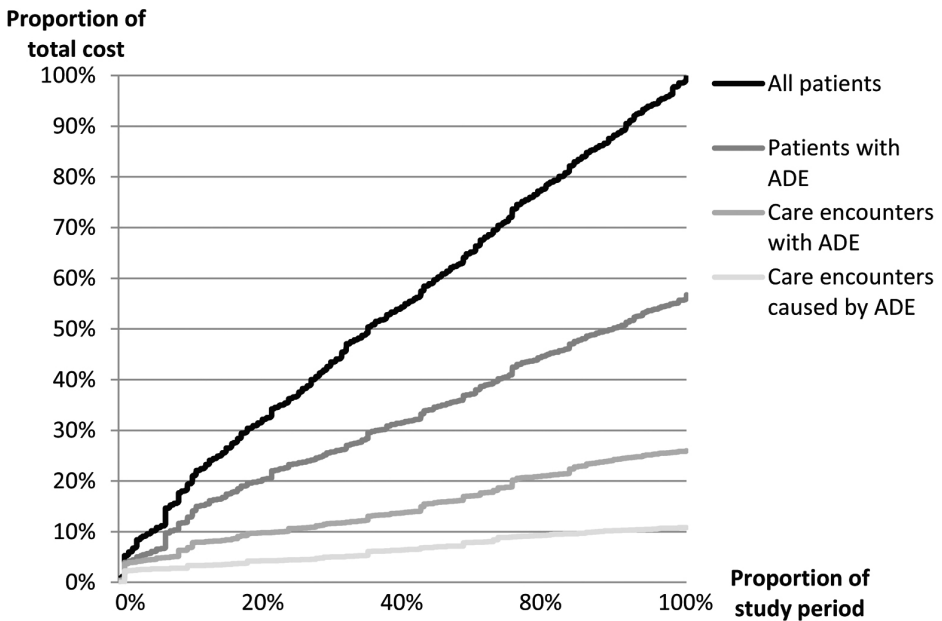


Figure 14. Accumulation of total costs and costs resulting from ADEs over time during the study period (paper III).

Although the prevalence of healthcare encounters was evenly distributed, a large group of all patients had prevalent healthcare during the first month of their study period (Table 8). Also among those with ADEs, a large proportion had healthcare already during the first month.

Table 8. Patients with care encounters during each month of the patients study period (paper III), of all patients (N=2560), and proportion of patients with encounters related to ADEs.

Group	Care encounter 1st month n (%)	Care encounter 2nd month n (%)	Care encounter 3rd month n (%)
Patients with care encounter/s the 1 st month of study period	1609 (62.9)	977 (38.2)	906 (35.3)
Of the 1609, proportion with ADE encounters during each month	276 (17.2)	250 (15.5)	233 (14.5)
Patients with first encounter 2 nd month of the study period	-	589 (23.0)	269 (10.5)
Of the 589, proportion with ADE encounters during each month	-	55 (9.3)	46 (7.8)
Patients with first encounter 3 rd month of the study period	-	-	362 (14.1)
Of the 363, proportion with ADE encounters during each month	-	-	29 (8.0)
All with care encounter during the month	1609 (62.9)	1566 (61.2)	1537 (60.0)
Proportion of all patients during the month that had ADE-related encounters	276 (17.2)	305 (19.5)	308 (20.0)

Thus, the prevalence of ADE-related healthcare among all patients during the first month of the study period was 17% (276 of 1609), corresponding to a population prevalence of 5.5%. Including the first two months, the prevalence of ADE-related care among all patients was 22% (477 of 2198), and in the population 9.5%. During the three month study period, 13 patients had no identified ADE-related healthcare (Figure 15), thus the prevalence of ADE-related healthcare among all patients was 23% (583 of 2560), and in the population 12%.

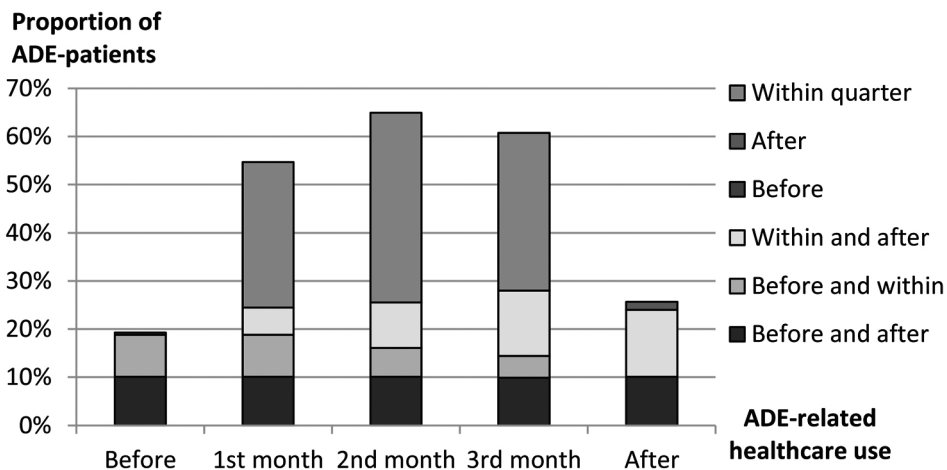


Figure 15. Proportion of patients with healthcare encounters associated with ADEs during each month of the study period (paper III), distribution based on when the ADE-related care started and stopped in relation to the patients study period.

The selected study period affects the estimated prevalence's of ADE-related healthcare use: The percentage increase in patient-based prevalence was 32.7%, while the proportion in the population was more than doubled (112.7% percentage increase).