Surgical site infection prevention in a local hospital setting

A cost-effectiveness analysis of a multi-modal intervention to prevent surgical site infection after hemi arthroplasty in hip fracture patients

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Abstract

Background: Surgical site infections (SSI) are associated with incremental hospital costs, cause diverse clinical consequences and are detrimental to quality of life. The aim of this study was to identify risk factors of SSI, identify clinical consequences and estimate the cost-effectiveness of a multi-modal intervention strategy to prevent SSI in a local hospital setting. The strategy included use of antibiotic cement, antibiotic prophylaxis and minimum two surgeons for hemi arthroplasty treatment of hip fracture.

Methods: Patient level data from Bærum hospital (Norway) was analyzed to identify risk factors, clinical consequences and to estimate hospital costs. Decision analytical modeling was employed to estimate the cost-effectiveness of the intervention strategy. The analyses results and available evidence informed the input parameters of the economic model. Second order uncertainty was explored using probabilistic sensitivity analysis.

Results: No risk factors of statistical significance were identified. Clinical consequences distributed unevenly between those with deep infection and those without infection were new primary hemi arthroplasties (HA), reoperations, numbers of out-patient controls and surgeries for hip infection. Mean total one year hospital costs of those with deep infection were NOK414,975, NOK275,466 for those with superficial infection and NOK228,879 for those without infection. Mean total hospital days were 25 in the deep infection group and 13 in the no infection group. These differences were significant. The economic model results indicated dominance of the multi-modal intervention strategy over the standard practice.

Acknowledgements

I would like to thank Ivar Sønbø Krisitiansen for his sound academic advice and for allowing me to discuss and disagree with him before finally realizing he was right all along. I would also like to thank him for his sense of humor. I want to thank Hanne-Merete Eriksen for always being available, offering counseling and perspectives only her level of expertise and experience can accommodate. I want to thank all the people at Bærum hospital, including Mette Walberg, Ellen Brustad, Wender Figved, Pål Gundersen, Tom Lian and Henriette Henriksen, for their interest in this project and for setting aside time to contribute to its progression through answering questions and providing data. Hege-Line Løwer has been invaluable to me through her constant optimism, knowledge of statistical software and the field itself. Sandre Svatun Lirhus, Martin Jack Mwamba and Mengyuan Cheng and many other friends at Harald Scheldrups Hus have provided comic relief and have been excellent academic and Backgammon sparring partners. My mom, my dad and my aunt have proof read and told me how impressed they were of the scope of the thesis (excluding giving me a lifetime of love and support). It is nice to impress. Nicoline, you have been amazing through the last two years. I want to thank you for making it possible for me to retain a sense of direction and coherence, and for not letting me get away with being a douche.

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Abbreviations and acronyms

AB	Antibiotics
AHA	American Hospital Association
APIC	Association for Professionals in Infection Control and Epidemiology
ASA	American Society of Anaestesiologists
AUD	Australian Dollars
BMI	Body Mass Index
CBA	Cost-Benefit Analysis
CDC	The Centers for Disease Control and Prevention
CEA	Cost-Effectiveness Analysis
CEAC	Cost-Effectiveness Acceptability Curve
CEAF	Cost-Effectiveness Acceptability Frontier
CT	Computer Tomography
DRG	Diagnosis Related Groups
EQ-5D	Test of quality of life
EVPI	Expected Value of Perfect Information
FCF	Fracture of the neck of femur
HA	Hemi Arthroplasty
HAI	Hospital Aquired Infection
HCAI	Health Care Associated Infection
HELICS	Hospitals in Europe Link for Infection Control through Surveillance
HF	Health Enterprise
HOD	Ministry of Health and Care Services
HRQoL	Health Related Quality of Life
ICD-10	International Classification of Diseases
ICER	Incremental Cost/Effectiveness Ratio
IDSA	Infectious Diseases Society of America
ISF	Norwegian system of performance based financing
LPM	Linear Probabilistic Model
NCMP	Classification system for medical procedures
NCSP	Classification system for surgical procedures
NDH	Norwegian Directorate of Health
NHBR	Norwegian Hip Fracture Register
NIPH	Norwegian Institute of Public Health
NNIS	The National Nosocomial Infection Surveillance System
NOIS	The Norwegian surveillance system for antibiotic consumption and healthcare associated infections
NOK	Norwegian Kroner
OLS	Ordinary Least Squares
OR	Odds Ratio
OpR	Operating Room
QALY	Quality Adjusted Life Years
SHEA	Society for Healthcare Epidemiology of America
SSI	Surgical Site Infection
THA	Total Hip Arthroplasty

THR	Total Hip Replacement
UK	United Kingdom
USD	United States Dollars
VVS	Vestre Viken Hospital
WLS	Weighted Least Squares
WTP	Willingness-to-Pay

1. Introduction

There seem to be a wide consensus that surgical site infections (SSI) account for a significant increase in mortality, morbidity and health care costs (Merollini, Crawford, Whitehouse, & Graves, 2013; Miletic, Taylor, Martin, Vaidya, & Kaye, 2014; Plowman et al., 2001; Scott, 2009; Shepard et al., 2013). Since 2000, the Norwegian efforts to monitor SSI and other health care associated infections (HCAI) have been guided by several overlapping governmental agency action plans, and monitoring efforts are presently the responsibility of the Norwegian Institute of Public Health, through the Norwegian surveillance system for antibiotic consumption and healthcare associated infections (NOIS). Among those surgical procedures subject to surveillance are total and hemi hip arthroplasty (THA and HA).

Although SSI incidence rates are readily available and agreement about the severity of these infections seem to have been established, agreement on concrete estimates of the economic impact of HCAI's and SSI, and the cost-effectiveness of various preventive measures seem to be elusive.

Norwegian incidence rates are available through NOIS (Kacelnik, 2014). There are large unexplained variations in Norwegian SSI incidence rates between the health enterprises and regions presented in the NOIS report of 2013 (Kacelnik, 2014). It was our view that this represented potential for improvement in prevention.

According to the Norwegian National Hip Fracture Register (NHBR 2014) 21.420 hip fractures have been treated with HA since the registry started surveillance. SSI is one of the primary complications to these procedures. It was our ambition to identify predictors and consequences of SSI among the HA treated hip fractures.

Predictors and consequences of SSI in hemi arthroplasty treated hip fractures

Previous research have indicated causality in the relationships between SSI and extended duration of surgery, patient obesity (BMI>30), patients being younger than 60 years and surgery waiting time. One of our goals was to identify new possible predictors. We wanted to explore to potentially verify or contradict the predictors already identified in previous

research, in order to contribute to the ongoing efforts to understand any factors important in facilitating SSI, and further to reduce SSI incidence.

As already mentioned, there seem to be a wide consensus that SSI has vast clinical and economic consequences. Others have indicated that deep and organ space infection are the reason for reoperation of HA in 12% of the cases in Norway in 2013 (NHBR, 2013). Others indicate SSI as causing increased incidence of revision surgery, more hospital days to be consumed and higher health sector costs. SSI also directly or indirectly cause increased mortality and morbidity (Merollini et al., 2013; Miletic et al., 2014; Plowman et al., 2001; Scott, 2009; Shepard et al., 2013). We wanted to add to this research and further identify clinical consequences of SSI. In addition we wanted to make an estimate of SSI attributable hospital costs in the current patient population in a Norwegian setting, which - to our knowledge – was not available at the time of this study.

Prevention and cost-effectiveness

Several studies have investigated the effectiveness of practical SSI prevention measures, and several strategies have been indicated effective. We would like to refer the reader to a meta-analysis of such studies for a thorough introduction to the available strategies (Anderson et al., 2014). Aside from these practical measures, surveillance systems are featured as a cornerstone in efforts to reduce HCAI's, and surveillance with feedback to surgeons are said to possibly reduce rates of SSI's by an estimated 20% (Sparling et al., 2007; A. P. Wilson et al., 2006).

However, whether or not implementation of such preventive measures is economically desirable for the society, the health care sector or health care providers themselves is at this time an open discussion, and its conclusion depend on the costs of the strategies, the effectiveness of the strategies, the perspective of the researcher, and the systems under which the health care sector is financed (Jenks, Laurent, McQuarry, & Watkins, 2014) (Drummond, Sculpher, Torrance, O'Brien, & Stoddart, 2005). We wanted to, and were given the opportunity to assess the cost/effectiveness of a multi-modal SSI prevention intervention in the setting of a local hospital in Bærum municipality in Norway.

Materials and methods

The hospital management at Bærum hospital provided a data file by means of the Nimes system (Nirvaco AS) for quality assurance, medical coding, procedure and diagnosis registry and analysis of activity data. We included patients admitted to Bærum hospital for hip fracture (ICD-10 code: S72.0/.1/.2) and subsequently treatment with a hemi prosthesis (NCMP/NCSP code: NFB.02/-.12, cemented and non-cemented) from September 2010 through January 2014 that had completed at least one year follow up by December 2014. Admission for hip fracture treated with hemi arthroplasty as described by the ICD-10 and NCMP/NCSP codes above would define the index event.

Statistical analysis and data cleaning was performed using Microsoft Excel 2010 and Stata13. Economic decision analytical modeling was performed using TreeAgePro.

Thesis structure

This introduction included a brief presentation of the problem area and its context, the objectives of the present study and a short description of the material and methods utilized. In chapter 2 a deep tour of the theoretical background is provided, moving from a broad perspective on hip fractures, towards hip fracture treatment and complications related to this the most common treatment methods. We move on, still in chapter 2, to discussing nosocomial (=hospital acquired infections, health care associated infections) and SSI and related prevention strategies. Chapter 3 include a presentation of the study site at Bærum hospital and the multi-modal intervention strategy to be evaluated. In chapter 4 we present and clearly define the study objectives. We further move on to present and discuss our data material and the methods used in analysis and evaluation, in chapter 5, before we move on to presenting our results in chapter 6. The paper concludes with a discussion followed by our conclusion, in chapters 7 and 8.

2. Theoretical Background

We examined selections of the scientific literature about hip fractures and the treatment of such. The information we found was on costs, incidence and complications and consequences of some of the treatment options available and also hip fracture as a standalone event. We discussed arthroplasty and surgical site infection and other health care associated infections thoroughly in relation to each other and to hip fracture.

We began elaborating on hip fracture, before we moved on to its treatment and further moved to discuss surgical site infection as a complication, and finally prevention of such infections, with a brief discussion on the cost-effectiveness of prevention efforts and the potential for perverse incentives in preventing infection.

Hip Fractures

Most patients with hip fractures are characterized by older age (>70 years), frailty, and functional deterioration, and their long-term outcomes are poor with increased costs (Prestmo et al., 2015). Hip fracture was in this thesis defined as fracture of the femoral neck and fracture in the area of the small and large femoral knot, the definition including ICD-10 diagnostic codes S72.0, S72.1 and S72.2. Liv Faksvåg Hektoen of Oslo and Akershus University College writes in her 2014 report on the costs of hip fracture in the elderly in Norway:

> *"Norway is on the world top when it comes to hip fractures. This is resource intensive seen in an economic perspective and very challenging for the elderly themselves. According to the Norwegian Patient Register (NPR) approximately 9,000 people incur hip fractures in Norway every year. In other words, a hip fracture happens every hour. Oslo has the highest reported hip fractures incidence in the world (Osnes et al., 2004). Incidence of hip fracture increases with age. Advancing age increases risk of low bone density that increases the risk of fragility fracture (SBU, 2003). Seven out of ten hip fractures affects women. During one year, 1 in 1,000 55 year old men and women break their hip, while among 90 year olds, 60 of 1,000 women and 50 men in 1000 get a hip fracture (Lofthus et al., 2001; Osnes et al., 2004)."*
>
> (Hektoen, 2014) pp. 8-9. Own translation)

Incidence and risk factors

Hip fractures regularly occur in relation to falling(NIPH, 2015a). In Norway the annual number of hip fracture procedures was reported between 7000 and 10000 during the period 2005 through 2013 and has been slightly declining the last two years(NHBR, 2014). Although the age specific risk of hip fracture, measured as new fractures per age group (figure 2), has been decreasing in Norway in the latter years (NHBR, 2013; NIPH, 2015b) the number of hip fractures will likely increase as the population of Norway is aging (Hektoen, 2014; NIPH, 2015b). Figure 1 (NIPH, 2015b) shows the strong increase in the risk of fracture at 70 years of age, while figure 2 shows the decreasing age specific hip fracture risk.

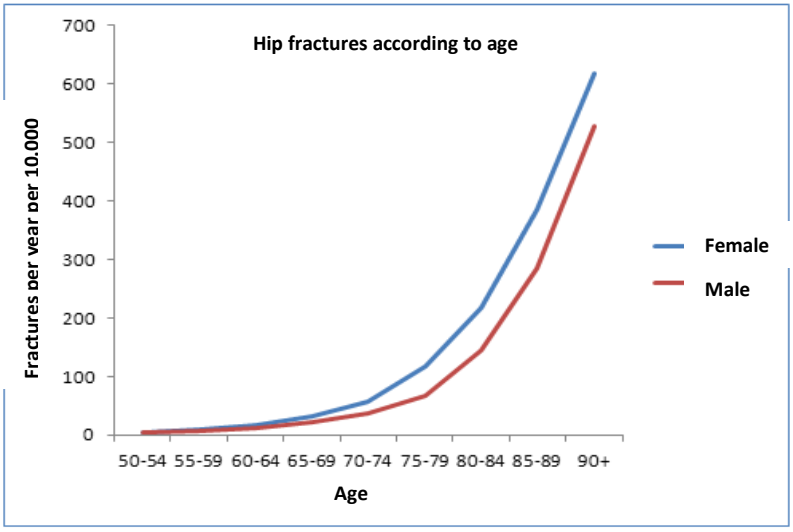

Figure 1 (NIPH, 2015b): The risk of hip fracture (per 10.000 population per year) by age and sex in Norway.

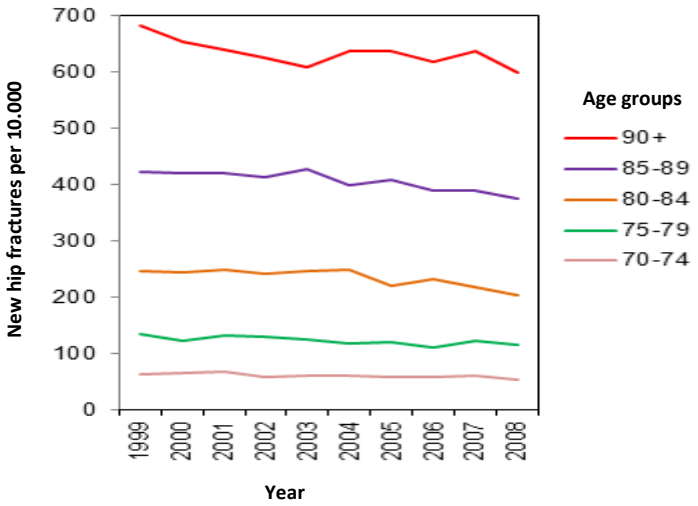

Figure 2 (NIPH, 2015b): Age specific hip fracture risk (per 10.000 popuplation per year) according to year.

Consequences

Elderly patients with fracture constitute a large patient group which to a large extent requires municipal welfare services after their hospital stay. Many patients experience considerable pain and become dependent on help in their everyday activities (Hektoen, 2014). Hip fractures require a lengthy rehabilitation phase, in which regeneration of function and health related quality of life (figure 3) in many instances is not possible (Lofthus et al., 2001; Osnes et al., 2004).

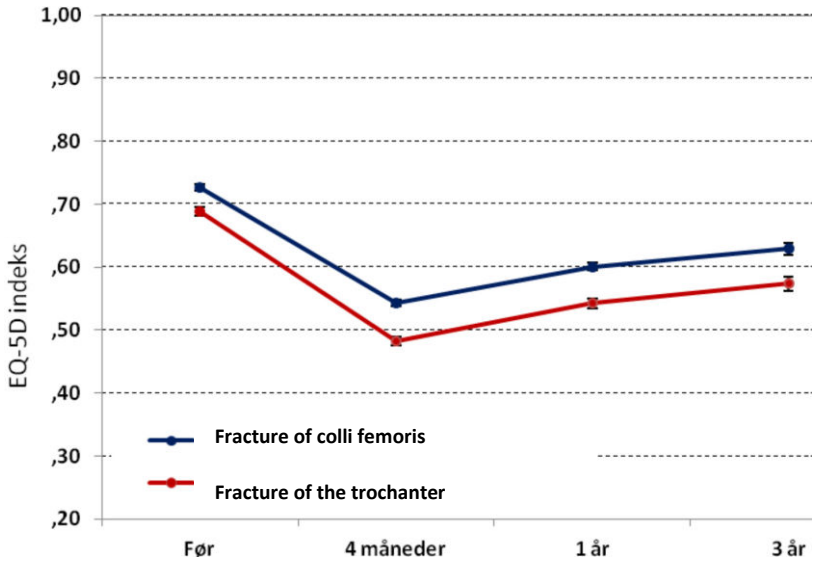

Figure 3 (NHBR, 2013): EQ-5D indeks (as measure of HRQoL) by time (before, 4 months, 1 year, 2 years) after fracture.

Survival

The survival for patients having suffered hip fracture is significantly lower than for hip and knee prosthesis surgery in general which is also reflected in a significantly higher comorbidity as measured by the ASA classification (American Society of Anestesiologists) at time of surgery (NHBR, 2014).

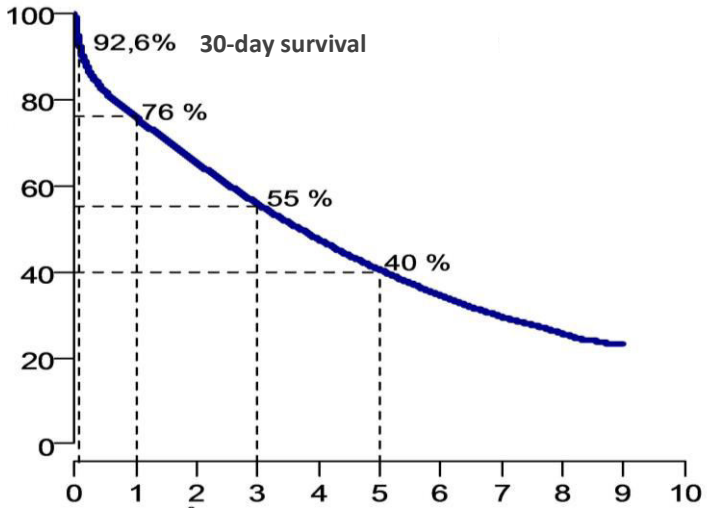

Figure 4 (NHBR, 2014): Survival (%, y-axis) by years after operation (years, x-axis) in Norway. Notice the 92,6% 30-day survival rate.

Costs

The latest estimation of the societal costs (excluding the cost of family members' time) of hip fractures in Norway has been estimated by Hektoen (Hektoen, 2014). In her report on the costs of hip fracture in the elderly she has used three typical patient pathways to make estimates of an annual monetary resource use one year following the fracture for a population of 396 >70 years old patients. The pathways are based on the place to which the patient is discharged. These include (annual estimated costs) home (NOK 322.000), nursing home (NOK 953.000) and rehabilitation institution (NOK 469.000) (see table 5 in (Hektoen, 2014). She reports an average total cost of all pathways including those who died during the index stay of NOK 542.000. Excluding those who died during the index stay results in an annual estimate of NOK 562.000. This is an increase in costs of about NOK 500.000 from an annual average health care and personal assistance resource use valued at NOK 30.000 the year before fracture. Assuming equivalent monthly costs for the next year as in the last months of year one, Hektoen get a minimum estimate of the health care and personal assistance costs related to one hip fracture in a person living at home and still alive of NOK 800.000 – 1.000.000 (Hektoen, 2014). With 9000 hip fractures annually, the societal costs are clearly substantial.

Hip fracture treatment - Arthroplasty

"Arthroplasty for an intracapsular hip fracture entails replacing the femoral head, which has fractured from the femur with an artificial hip joint. The type of arthroplasty may be either a hemi arthroplasty (partial hip replacement) or a total hip replacement (THR). Hemi arthroplasty (HA) involves replacing the femoral head with a prosthesis whilst retaining the natural acetabulum and acetabular cartilage (...) The metal femoral stems used for an arthroplasty may be either held in place with cement or inserted as a 'press fit', without cement (...) Total hip replacement involves the replacement of the acetabulum in addition to the femoral head."

(Parker & Gurusamy, 2006)

We used total hip arthroplasty (THA) synonymously with total hip replacement (THR).

Incidence

In Norway, around 8000 primary hip arthroplasties are performed every year. In addition to this, nearly 1300 revision surgeries are done. The most complete (97% degree of coverage for the years 2008-2011) record of performed primary hip arthroplasties, both HA and THA, with common causes of primary operation, revision and complications can be found in the reports of the National Registry for Joint Prostheis and hip fractures (NHBR) report of 2014 (NHBR, 2014).

Complications to hip arthroplasty and complication risk factors

The NHBR reports that the risk of early revision surgery is increasing and that an increase in deep infections make up the main portion of reported causes for revision, in addition to luxation and fracture close to the prosthesis (NHBR, 2014). Håvard Dale et al, having done substantial research into the risk factors of early revision due to infection in Norway, have found that the use of uncemented total hip arthroplasties (THA) is related to a 5 times increase in relative risk of early revision due to deep infection from 1987-1992 to 2007-2009 although the results are complicated due to changes in confounding factors (Dale et al., 2009). NHBR (NHBR, 2014) data show that the use of uncemented THA's has been increasing

in the latter years, for older patients (>80) as well. The reason for using uncemented prosthesis in the elderly is that especially in ill elderly patients with hip fractures, cementing the femur prosthesis can increase the risk of embolization during cementing. It is unclear how big an impact this has on mortality associated with elective arthroplasty and whether possible reduced perioperative mortality with uncemented femur is offset after some months by increased mortality due to reoperations for fracture, luxation or infection(NHBR, 2013).

However, Dale (Dale et al., 2012) further finds an increased risk of revision due to infection after primary THA in Denmark, Finland, Norway and Sweden in recent years. Also, he finds the cumulative rate of revision due to infection after THA increased and he concluded that there seems to be a true increase in incidence of prosthetic joint infections. He finds support for his findings in two other publications (Kurtz et al., 2008; Pedersen, Svendsson, Johnsen, Riis, & Overgaard, 2010). Finally, the risk patterns for revision due to infection appear to be different for HA and THA (Dale et al., 2011).

To summarize, the primary complication to hip arthroplasty is revision surgery, whereof luxation, fracture close to the prosthesis and deep infections constitute the main causes. Additionally, the effects on morbidity and mortality of using uncemented prosthesis in old, ill patients are unclear. The risk of revision due to infection after THA seems to be increasing in all the Nordic countries. Also, risk patterns for revision due to infection may differ between HA and THA.

Hemi Arthroplasty (HA)

Hemi arthroplasty was in this thesis defined by the NCMP/NCSP codes NFB.02/-.12.

Incidence

The use of HA for hip fracture treatment is steadily increasing in Norway. Today 90 % of all dislocated hip fractures are treated with insertion of hemi arthroplasty (HA), which is a change from 2005 when the equivalent number was only 50 % (NHBR, 2014). Also, an

increase in the portion of primary hip fracture operations constituted by HA for all fractures of the hip from 18,9 to 37,4% is reported by the NHBR (NHBR, 2013).

Complications

Complications to HA include revision surgery and surgical site infection, whereof deep and organ space infections might be among the more severe in itself, and certainly through its impact on the reoperation rate. Deep and organ space infection is given as the reason of reoperation of HA in 12,3% of the cases in 2013 (NHBR, 2013). According to Dale, the incidence of revision due to infection in Norway was 1.5% after primary HA during 2005-2009 and the incidence of surgical site infection in Norway was 7.3% after primary HA during 2005-2009 (Dale et al., 2011). The Norwegian surveillance system for antibiotic consumption and healthcare associated infections (NOIS) (Kacelnik, 2014), using national data, report an incidence of deep and organ space infections after HA of 2,5%, with variation between hospitals from less than 1 up to 9%. Westberg (Westberg, Snorrason, & Frihagen, 2013) found an incidence of deep infection post HA after hip fracture of 9%.

As infection in and around the prosthetic joint seem to be an important complication of this procedure, not only in its own right but also through influencing the rate of revision surgery, the next paragraph will examine some of the predictors of infection in hip fracture patients by previous research. Infection of the prosthetic joint and of the surgery wound will be discussed thoroughly in the section on nosocomial and surgical site infections.

Risk factors of SSI in the HA group

Few studies have examined risk factors of surgical site infections in this group. Dale identified age <60, insertion after fracture and short duration of surgery as risk factors of revision due to infection (Dale et al., 2011). Furthermore, he finds that there may be differences in risk pattern between SSI and revision due to infection after arthroplasty (Dale et al., 2011). Westberg (Westberg et al., 2013) found that a preoperative waiting time of 72 and 96 hours gave a statistically significant increase in risk of prosthetic joint infection (p=0,01 and 0,04), and a stay of more than 24-36 hours was associated with an "unacceptable" risk of infection (p=0,06 and 0,08). Obesity (=BMI>30) was also found

statistically significant (p=0,04), so was having one or more and two or more of the considered risk factors (p=0,01 and 0,02).

It seems that knowledge can influence practice, and that changing practice in line with new research does influence complication rates. The change in hip fracture treatment practice (mentioned in the paragraph about HA incidence) is believed to be related to the risk of reoperation after hip fracture being higher when using internal fixation than when using hemi prosthesis. A reduction in the reoperations as a portion of all post hip fracture surgeries has in fact been observed over the period of practice change, from 17% in 2005 to 10 % in 2013 (NHBR, 2014; Parker & Gurusamy, 2006).

In summary, predictors of revision and infection after HA treated hip fractures indicated in the research presented here are age<60, short duration of surgery, preoperative waiting time above 24 hours and having a BMI>30. In addition, knowledge of best practice and understanding the risk factors of infection may influence practice and in turn reduce the incidence of infection. Infection prevention strategies, HCAI and SSI will be discussed thoroughly in the following chapter.

Nosocomial, or Hospital and Health Care Associated Infections (HAI/HCAI) and Surgical Site Infections (SSI)

Nosocomial infections, also known as Hospital/Health Care Associated Infections (HAI/HCAI), are a cause of a significant increase in morbidity, mortality, direct hospital costs and national healthcare system costs (Merollini et al., 2013; Miletic et al., 2014; Plowman et al., 2001; Scott, 2009; Shepard et al., 2013). This chapter will provide a scope of the problem of these types of infections nationally and internationally and will further go on to present methods of prevention, including both national systematic surveillance systems and more practical measures. The Norwegian surveillance system for antibiotic consumption and healthcare associated infections (NOIS) will be presented briefly as an example of a surveillance system. Finally a brief review and discussion of cost-effectiveness analysis literature in the context of infection prevention strategies will be presented. This last section will show that the

presence of perverse incentives and narrow perspectives might complicate the decision on whether or not to invest in infection prevention strategies.

Costs

Numbers from the United States on annual direct hospital costs of HAI's range from USD 28,4 billion to USD 45 billion using various consumer price indexes and adjusting to 2007 dollars (Scott, 2009). A UK study indicated that infected patients on average incurred costs almost three times higher than those not infected, and remained in hospital 2,5 times longer (Plowman et al., 2001). An Australian cost-effectiveness analysis of a basic SSI prevention strategy related to total hip arthroplasty (THA) surgery indicated that AUD 3909 could be saved per QALY gained (Merollini et al., 2013). P.J. Jenks (Jenks et al., 2014) also report in a UK study on the clinical and economic burden of SSI's that median additional cost attributable to SSI was £5,239.

Distribution

As far as nosocomial infections go, surgical site infections (SSI) comprise a substantial part of these. In the United States, an estimated 20% of annual 2 million nosocomial infections are SSI's (Shepard et al., 2013). According to the British Health Protection Agency, in 2011 SSI's were the third most frequently occurring healthcare-associated infection (HCAI), causing 15.7% of reported infections (HPA, 2012).

In Norway, the prevalence of nosocomial infections has been estimated, including four common types of these infections, at 5,1 to 5,4 %, (n=12257 and 12736). SSI prevalence in this study was estimated at 5,3% to 6,1% of those operated (Eriksen, Iversen, & Aavitsland, 2005). In 2013 the incidence proportion of SSI after five given surgical procedures (including THA and HA) was estimated at 4,6 % for deep and organ space infection (Kacelnik, 2014).

Surgical site infection (SSI)

According to the Norwegian Institute of Public Health (NIPH) and the Norwegian surveillance system for antibiotic consumption and healthcare associated infections module for SSI (NOIS-SSI), all SSI with the exception of superficial wound infections occurring after

discharge need to be diagnosed by a physician as in accordance to the CDC (Centers for Disease Control, USA) criteria. This requirement do not need to be met by patient diagnosed superficial infections (H. L. Lower, Eriksen, Aavitsland, & Skjeldestad, 2013).

The CDC definition of SSI include three levels (figure 5) which each have specific criteria that need to be met for the status SSI to be given (CDC, 2015) :

Superficial incisional SSI

- Infection occurs within 30 days after any operative procedure (where day 1 = the procedure date)
- involves only skin and subcutaneous tissue of the incision
- patient has at least ***one*** of the following:
    - purulent drainage from the superficial incision.
    - organisms isolated from an aseptically-obtained culture from the superficial incision or subcutaneous tissue.
    - superficial incision that is deliberately opened by a surgeon, attending physician or other designee and is culture positive or not cultured
- patient has at least ***one*** of the following signs or symptoms (a culture negative finding does not meet this criterion)
    - pain or tenderness
    - localized swelling
    - erythema
    - heat
- diagnosis of a superficial incisional SSI by the surgeon or attending physician or other designee.

Deep incisional SSI

- Infection occurs within 30 or 90 days after the operative procedure (where day 1 = the procedure date)
- involves deep soft tissues of the incision (e.g., fascial and muscle layers)
- patient has at least ***one*** of the following:
    - purulent drainage from the deep incision.
    - a deep incision that spontaneously dehisces, or is deliberately opened or aspirated by a surgeon, attending physician or other designee and is culture positive or not cultured
- patient has at least ***one*** of the following signs or symptoms (a culture negative finding does not meet this criterion)
    - fever (>38°C)
    - localized pain
    - tenderness
- an abscess or other evidence of infection involving the deep incision that is detected on gross anatomical or histopathologic exam, or imaging test.

Organ/Space SSI

- Infection occurs within 30 or 90 days after the operative procedure (where day 1 = the procedure date)
- infection involves any part of the body deeper than the fascial/muscle layers, that is opened or manipulated during the operative procedure
- patient has at least ***one*** of the following:
    - purulent drainage from a drain that is placed into the organ/space (e.g., closed suction drainage system, open drain, T-tube drain, CT guided drainage)
    - organisms isolated from an aseptically-obtained culture of fluid or tissue in the organ/space
    - an abscess or other evidence of infection involving the organ/space that is detected on gross anatomical or histopathologic exam, or imaging test

The term attending physician for the purposes of application of the criteria may be interpreted to mean the surgeon(s), other physician on the case, emergency physician or physician's designee (nurse practitioner or physician's assistant) (CDC, 2015). For the purposes of this thesis, in accordance with reporting in other studies (Dale et al., 2011; Hege Line Lower, Dale, Eriksen, Aavitsland, & Skjeldestad, 2015) and the NOIS (Kacelnik, 2014; H. L. Lower et al., 2013) deep and organ space infections have been combined in a "deep infection" category.

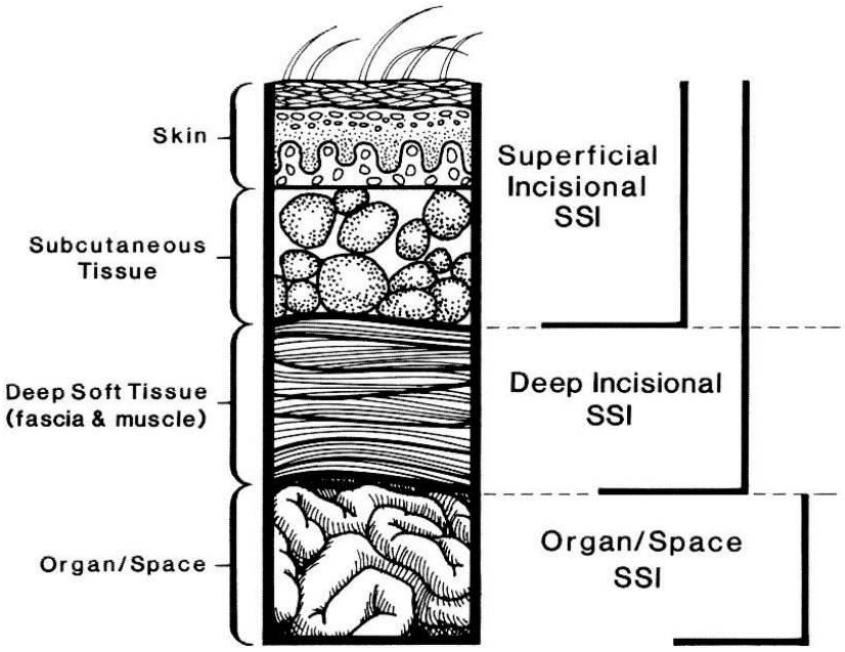

Figure 5: The Centers for Disease Control and Prevention National Healthcare Safety Network (CDC) classification for SSI. Figure in Horan et al (Horan, Gaynes, Martone, Jarvis, & Emori, 1992).

Although the additional cost associated with SSI has not been fully elucidated due to inconsistencies in study design and variation in methods of cost calculation (Beyersmann, Kneib, Schumacher, & Gastmeier, 2009; Graves, 2004; Graves et al., 2010), from the scope of the problem it is arguably easy to see why health care providers and health care financers might want to reduce the incidence of SSI's and other HCAI's. Treating these often preventable infections is both economically and manpower demanding work, occupying precious resources potentially spent towards providing high quality, life preserving services elsewhere. The next sections will discuss how to prevent HCAI, especially SSI, and whether or not it might be beneficial to the providers and financers of health care to do so.

SSI prevention

Many methods contribute to the goal of reducing incidence of SSI. This section will present the use of surveillance systems as a preventive measure, the evolution of such systems and go on to briefly present the Norwegian system of surveillance. Further, a bundle of prevention methods is introduced in the section about practical procedure related measures to be performed in relation to surgery itself.

Prevention by surveillance

Surveillance systems are a cornerstone in efforts to reduce HCAI's, and surveillance with feedback to surgeons may reduce rates of SSI's by an estimated 20% (Sparling et al., 2007; A. P. Wilson et al., 2006). The Centres for Disease Control and prevention (CDC) initiated The National Nosocomial Infection Surveillance System (NNIS) in the 1970's and the system has evolved into the NHSN as it is today. Being the foundation for most current surveillance systems for HCAI's internationally, the NHSN estimate the magnitude of the nosocomial infection problem in the United States and monitor trends in infections and risk factors. By 2003 the Hospitals in Europe Link for Infection Control through Surveillance (HELICS), based on the NNIS, was operational with 16 official European surveillance networks integrated (Emori et al., 1991; J. Wilson, Ramboer, & Suetens, 2007).

The Norwegian surveillance system for antibiotic consumption and healthcare associated infections (NOIS)

The Norwegian efforts to monitor antibiotic consumption and HCAI's has since the year 2000 been directed by "Action plan to counter antibiotic resistance 2000-2004" and "Action Plan for preventing hospital infections 2004- 2006". The latter strategies were followed by "National strategy for prevention of infections in the health service and antibiotic resistance 2008-2012". The strategy contains relevant measures in many sectors and at different levels to still preserve a favorable situation in Norway (HoD, 2008).

Following the action plans above the Norwegian surveillance system for antibiotic consumption and healthcare associated infections (NOIS) was founded in 2005. The first years a three month surveillance period for minimum one of the listed procedures was required and from the year 2012 all hospitals where, under NOIS, obligated to register and follow up for 30 days post-surgery all patients having undergone all five types of surgeries all year in order to identify and register data on the patients that go on to develop SSI's. The system follows protocols equivalent to those used in other European countries (HELICS) and in the United States (NNIS) and thus complies with international standards and contributes to the current trend toward public reporting and international comparisons (HoD, 2005; Kacelnik, 2014; H. L. Lower et al., 2013).

The surgical procedures included in NOIS are:

- Coronary artery bypass graft (CABG) surgery
- Caesarian section
- Hip arthroplasty
  - Total
  - Hemi
- Cholecystectomy
- Colon surgery

Kacelnik, O. et al (Kacelnik, 2014) report rates of hospital response and a rate of completion of 30 day follow-up averaging on 93%, varying between surgeries and hospitals. Løwer H. L. et al (H. L. Lower et al., 2013) report a 90,7% completeness of 30 day follow-up and almost complete hospital participation during the first 5 years of NOIS operation.

Table 1: *30 day follow-up portions nationally and variation between hospitals per surgery (after Kacelnik, O. et al (Kacelnik, 2014))*

Surgery	Percentage complete follow-up	Variation in follow-up between hospitals
Bypass (CABG)	91 %	83-100%
Cesarean section	89 %	63-100%
Hip arthroplasty (total)	97 %	78-100%
Hip arthroplasty (hemi)	92 %	74-100%
Colecystectomy	92 %	75-100%
Colon	96 %	66-100%

Prevention by practical measures

Anderson (Anderson et al., 2014) highlight practical recommendations in a concise format designed to assist acute care hospitals to implement and prioritize their SSI prevention efforts, and present a list of measures coupled with a grade (high to low quality = 1, 2, 3) indicating quality of evidence to support the specific measure (for definitions of levels of quality of evidence, see Anderson (Anderson et al., 2014) table 1). The practical recommendations are the product of a collaborative effort led by Society for Healthcare Epidemiology of America (SHEA), the Infectious Diseases Society of America (IDSA), the American Hospital Association (AHA), the Association for Professionals in Infection Control and Epidemiology (APIC), and The Joint Commission, with major contributions from representatives of a number of organizations and societies with content expertise. The procedure related measures discussed are the following (quality of evidence):

- Hair removal (2)
  - Do not remove unless hair will interfere with the operation. If hair removal is necessary, remove outside the OR by clipping. Do not use razor.
- Surgical scrub of surgical team members' hands and forearms (2)
  - Use appropriate antiseptic agent to perform preoperative surgical scrub. For most products, scrub the hands and forearms for 2–5 minutes.
- Skin preparation (1)
  - Wash and clean skin around incision site. Use a dual agent skin preparation containing alcohol, unless contraindications exist.
- Antimicrobial prophylaxis
  - Administer only when indicated (1)
  - Administer within 1 hour before incision to maximize tissue concentration (1)
    - Vancomycin and fluoroquinolones can be given 2 hours prior to incision
  - Select appropriate agents on the basis of surgical procedure, most common pathogens causing SSI for a specific procedure (1)
  - Stop prophylaxis within 24 hours after the procedure for all procedures (2)

- Blood Transfusion (2)
  - Blood transfusions increase the risk of SSI by decreasing macrophage function. Reduce blood loss and need for blood transfusion to the greatest extent possible.
- Surgeon skill/technique
  - Handle tissue carefully and eradicate dead space (3)
  - All members of the operative team should double glove and change gloves when perforation is noted (3)
  - Adhere to standard principles of operating room asepsis (3)
  - No formal recommendation for operating time in most recent guidelines; minimize as much as possible without sacrificing surgical technique and aseptic practice (1)
- Operating room (OR) ventilation (3)
  - Follow recommendation of American institute of architects
- OR traffic (3)
  - Minimize OR traffic
- Environmental surfaces (3)
  - Use an EPA-approved hospital disinfectant to clean visibly soiled or contaminated surfaces and equipment
- Sterilization of surgical equipment (2)
  - Sterilize all surgical equipment according to published guidelines. Minimize the use of immediate use steam sterilization

As is evident in the above, Anderson and colleges strongly recommend skin preparation and antimicrobial prophylaxis (read: pre-, peri- and postoperative antibiotics use) to prevent SSI. As will become clear in the next chapter (chapter 3) of this text, an important part of the intervention we were to examine was exactly antibiotic prophylaxis, implemented according to Norwegian national guidelines. For this reason we wanted to briefly illuminate the Norwegian national guidelines and compare them with the recommendations made by Anderson et al.

The Norwegian Directorate of Health recommendations for antibiotic prophylaxis

Norwegian national guidelines for antibiotic prophylaxis in the context of joint prosthesis surgery include a strong recommendation to administer 2 grams Cefalotin intravenously 30-60 minutes preoperatively and every 90 minutes peroperatively, with a total duration of 24 hours (4 doses). The guidelines emphasize the lack of documented effect of extending the prophylactic treatment after the procedure (Helsedirektoratet, 2013).

Anderson with colleges seemed to give the same recommendations as the Norwegian Directorate of Health (NDH) in regards to antibiotic (antimicrobial) prophylaxis. Regarding the judgment on whether or not prophylaxis is indicated required by Anderson, NDH claims that in relation to prosthesis procedures the risk of infection is high, indicating prophylaxis in all cases (Helsedirektoratet, 2013).

Further examination into prevention measures discussed in the literature is possible, as the field is littered with interesting studies of effectiveness of such measures. For now, however, the recommendations made by Anderson et al, the NDH and the risk factors of SSI presented in the sections about THA and HA will do as a backdrop for discussion and analysis on the intervention which is the focus of this thesis.

To add to the epidemiological and medical perspective presented this far, we wanted here to give a brief presentation of one economic issue arising in the context of cost-effectiveness studies of SSI prevention interventions in single center studies. A more thorough introduction to and discussion of methods of cost-effectiveness studies will be given as we progress in this paper.

Cost effectiveness of prevention - Potential prevention disincentive

"The economic rationale for preventing hospital acquired infections has been discussed, and can be summarized as follows: hospital acquired infections take up scarce health sector resources by prolonging patients' hospital stay; effective infection-control strategies release these resources for alternative uses. If these resources have a value in an alternative use, then the infection control programs can be credited with generating cost-savings; these infection control programs are costly themselves, so the expense of infection control should be compared to the savings. For many hospital infections the costs of prevention are likely to be lower than the value of the resources released (…) Under these circumstances, infection control should be pursued, since more stands to be gained than lost"

((Graves, 2004), p. 1 (561))

Many analyses of cost-effectiveness of prevention interventions indicate that infection reductions are beneficial in the sense that they save money and improve the post-operative health status of patients. An Australian cost-effectiveness analysis of a basic SSI prevention strategy related to total hip arthroplasty (THA) surgery, indicated that a combination of antibiotic prophylaxis and antibiotic impregnated cement saved AUD 3909 per QALY gained (Merollini et al., 2013). A study made in the UK into the cost-effectiveness of a hospital SSI audit system indicated that the average savings per averted case was 422 pounds (Reilly, Twaddle, McIntosh, & Kean, 2001). A US study analyzing the cost-effectiveness of a multi-faceted intervention to reduce the incidence of central line-associated bloodstream infection and ventilator-associated pneumonia in intensive care units concluded that, given a cost-effectiveness threshold of 85000 USD per QALY, the intervention was effective in all cases (Dick et al., 2015).

However, by concretizing opportunity costs (defined as "the value of the best alternative use of the funds" (Drummond, Sculpher, Torrance, O'Brien, & Stoddart, 2005)), Jenks (Jenks et al., 2014) indicate that there might be perverse incentives in not preventing at least some SSI's. The study was done at a 1200-bed university hospital in Derriford, England. The economic evaluation showed that for some procedures, eliminating all SSI's resulted in a negative overall financial impact, a financial loss. The reason for this contra intuitive and paradoxical result, Jenks and colleges explain, was that for all procedures except bile, liver, pancreatic and cardiac surgery the hospital made a loss without SSI. This would accrue a negative opportunity cost of preventing SSI as the alternative use of the freed resources from not having to treat SSI (here: beds), would be more loss-generating procedures. In addition, the hospital received income for SSI episodes, which meant that the impact of having to treat infection on profitability was less than it would have been had they not been compensated.

A similar result was found in a US study on occurrence of post-surgical complications associated with a higher contribution margin for certain patients, giving a potential for adverse financial effects of reducing post-surgical complications (Eappen et al., 2013).

To put the previous section in context with the thesis in general, the next section will briefly introduce the reader to basic theory of economic evaluation and decision analytical modeling.

Economic evaluation and decision analytical modeling

Economic evaluation in health care can be defined as the comparison of alternative options in terms of their costs and consequences (Drummond, Sculpher, Torrance, O'Brien, & Stoddart, 2005). In the context of health and health care, costs refer to the value of available resources, such as clinical and other staff time, medication and other materials, hospital beds and floor space. Consequences refer to all effects of the options of treatment but mainly focus on the changes to individuals' health, positive or negative. There are several disciplines of economic evaluation based on different normative theories of societal resource allocation, although some form of cost-effectiveness analysis (CEA) seem to be predominant in applied research within health. CEA would typically have a health related objective and be constrained by a narrow or broad health care budget. The health related objective may be disease or program specific or, as is increasingly applied, a generic measure of health. The type of CEA that use the QALY – the one of these generic measures of longevity and health related quality of life that is most widely adopted - as its effect measure is often called a cost-benefit analysis (CBA) (Briggs, Claxton, & Sculpher, 2006).

Decision analytic modeling is used increasingly in health care systems to inform decisions about which alternative of medical devices, diagnostic technologies or treatment options to fund and reimburse, and has a strong rationale as a framework for economic evaluation. This rationale is based on the ability of decision models to incorporate several required features of economic evaluation seeking to inform decision making. A central requirement of economic evaluation is to use all relevant evidence on *effectiveness of individual programs* and the *effectiveness of all relevant alternative programs*. Further, an appropriate economic evaluation requires *consideration of all costs and effects accruing within a relevant time horizon*, which for many interventions effectively means a life-time follow-up period. Decision modeling provides a framework for structuring extrapolations based on shorter term costs and effects estimates. Finally, decision modeling provides a framework for

indicating uncertainty in available evidence, translating that uncertainty into *decision uncertainty* meaning a probability of a decision being correct under its criteria (Briggs et al., 2006).

3. Study site: Vestre Viken HF, Bærum Hospital

As this study was based on data from Bærum hospital, and the SSI prevention intervention under analysis was implemented at the hospital, we wanted to briefly introduce the reader to the hospital and the setting under which it operates before we present the intervention itself.

Bærum hospital is one of four somatic hospitals in Vestre Viken HF. It is a large acute and local hospital for Asker and Bærum, one of the most dens populated areas in Norway. The hospital has highly qualified specialists in surgical, medical, orthopedic, gynecologic, anaesthesialogic, intensive care and operational disciplines, as well as a large maternity ward. Bærum hospital provides acute care for 350 people having suffered hip fractures annually. Some of these are treated with hemi arthroplasty (HA), and the hospital performs some 133 HA procedures annually whereof 94% of these where uncemented in 2013 (Figved, 2013). According to NOIS numbers from 2013 the HA treated patients at Bærum hospital had an incidence of superficial, deep and organ space SSI of 4,0 %, which is above the country wide average of 2,5 % in that year, and an incidence of 6,0 % for the years 2006-2013 (Kacelnik, 2014).

The intervention

In 2010, a surgeon at the orthopedic department of Bærum hospital, in collaboration with the Boston Consulting Group (BCG) initiated a pilot project to reduce the incidence of SSI in relation to hip fracture treatment through introducing a suggested best practice and

strengthening awareness around the practice of a bundle of infection preventing measures (Figved, 2013; Figved, Mariero, Skarsgård, & Bjørnland, 2013). The measures included:

1. Early surgery
    - Operate all hip fractures within 36 hours of admission
2. Infection prophylaxis
    - Patient transport
    - Maintaining operating room sterility
    - Correct antibiotic prophylaxis, according to Norwegian national guidelines (Helsedirektoratet, 2013)
    - Hygiene measures in the ward
3. Operation method
    - Change method for dislocated fractura colli femoris (FCF) from uncemented Corail prosthesis to Exeter prosthesis with antibiotic cement
4. Numbers of and experience level of surgeons
    - No assistant surgeon to operate HA alone
    - Consultant surgeon or assistant surgeon as second operator on all HA procedures
5. Involving a geriatrician
    - Define interaction between orthopedic dept. and geriatric dept.
6. Secondary osteoporosis profylaxis
    - Prescribe bisfosfonat to all hip fracture patients on discharge

Through these new measures, Figved estimate an annual absolute reduction in reoperations of 13 procedures, and savings to Bærum hospital of NOK 1,2 million.

Points 2 (specifically correct antibiotic profylaxis), 3 and 4 would be assumed 100% implemented when our first observed patient received their care at Bærum hospital in 2010, and these points would make up the foundation for costing of the intervention (ref. Methods section: economic model).

When compared to the recommendations of Anderson and colleges above, it seems the anti-infection measures at Bærum hospital are in accordance with these guidelines. Correct antibiotic prophylaxis according to national guidelines (Helsedirektoratet, 2013) are in line with Anderson (see discussion in prevention by practical measures section).

4. Study objectives and research questions

The numbers presented by the NOIS indicate a substantial local and regional variation in the incidence of SSI (Kacelnik, 2014). This indicates a potential for improving practice towards a standard resulting in lower incidence of SSI. The implementation and effects of the pilot project described above is still ongoing. This present an opportunity to analyze the patient level data of all patients treated with hemi arthroplasty after hip fracture from September 2010 to December 2014 at VVS Bærum hospital. The opportunity is interesting, as a similar study into the costs and effects of a local hospital intervention has not been conducted in Norway previously (to the best of our knowledge). The relationship between costs and effectiveness of the intervention might be interesting for the hospital in question in deciding whether or not to continue intervening in the same way, but also for other hospitals in relation to their decisions on how to tackle SSI.

Research question and objectives

The overall aim of this study was to examine risk factors for deep SSI and the clinical and economic consequences of such infections at VVS Bærum. Further, the study aimed to estimate the cost-effectiveness of an ongoing multi modal SSI prevention program in order to guide a decision on whether or not to maintain the multi modal infection prevention program. The study should address the following research questions:

1. Determine risk factors for SSI after hemi arthroplasty treatment of hip fracture, and analyze their impact on the risk of SSI of the study population
2. Determine clinical consequences of hemi arthroplasty treatment of hip fracture when SSI is present, and compare them with when it is not
3. Determine costs when SSI is present, and compare them with costs when it is not
4. Estimate the cost per quality adjusted life year (QALY) before and after implementation of the multi modal SSI prevention intervention at Bærum hospital

5. Material and methods

Study design

This was a retrospective cohort study including a cost effectiveness analysis, using patient level registry data and decision analytical modeling.

Material

Data source

The hospital management at Bærum hospital provided a data file by means of the Nimes system (Nirvaco AS) for quality assurance, medical coding, procedure and diagnosis registry and analysis of activity data. We included patients admitted to Bærum hospital for hip fracture (ICD-10 code: S72.0/.1/.2) and subsequent treatment with a hemi prosthesis (NCMP/NCSP code: NFB.02/-.12, cemented and non-cemented). Patients were included from September 2010 through January 2014, and they needed to have completed at least one year follow up by December 2014. Admission for hip fracture treated with hemi arthroplasty, as described by the ICD-10 and NCMP/NCSP codes above, defines the *index event*. All included patients were followed for one year, and all hospital episodes of care during this period were recorded. All patients were grouped as no SSI, superficial SSI or deep SSI, according to instructions given in NOIS, in accordance with the CDC definitions (ref. section on SSI).

Data structure

The data set contains “long data” with episode of care (in-patient, out-patient, day-care) as the unit of observation, and 877 observations were recorded. Each patient had one or more episodes of care, and observations were clustered through a patient ID variable and sorted according to date and time of care. The dataset included variables on NMCP/NCSP procedures, ICD-10 diagnoses, background information about the patient like age and gender, where the patient was admitted from and where they were discharged to, the ASA (American Association of Anesthesiologists) score (a measure of comorbidity and frailty), infection status with severity of infection and whether or not the patient was alive upon discharge (table 2).

Table 2: *Descriptive statistics of the data on all patients (n=239) having undergone the index event*

Variable	N*	Number of patients (%)	Proportion/ mean	95 % CI		Median	1st quartile	3rd quartile	Range
Type of infection									
Deep	877	6 (2,5)	0,044	0,029	0,060	0	0	0	1
Superficial	877	3 (0,0)	0,010	0,003	0,018	0	0	0	1
None	877	230 (96,2)	0,945	0,928	0,962	1	1	1	1
Gender									
Female	877	155 (64,8)	0,588	0,551	0,626	1	0	1	1
Age group									
45-66	877	16 (6,7)	0,096	0,073	0,118	0	0	0	1
67-79	877	51 (21,3)	0,239	0,207	0,272	0	0	0	1
80-89	877	115 (48,1)	0,517	0,479	0,554	1	0	1	1
90+	877	57 (23,9)	0,148	0,121	0,175	0	0	0	1
ASA score									
1	877	4 (1,7)	0,005	-0,001	0,010	0	0	0	1
2	877	97 (40,6)	0,114	0,090	0,138	0	0	0	1
3	877	99 (41,4)	0,115	0,091	0,139	0	0	0	1
4	877	15 (6,3)	0,017	0,007	0,027	0	0	0	1
Missing value	877	24 (10,0)	0,749	0,716	0,782	1	0	1	1
Number of comorbidities									
0	877	49 (20,5)	0,447	0,409	0,485	0	0	1	1
1	877	53 (22,2)	0,204	0,174	0,235	0	0	0	1
2	877	57 (23,9)	0,133	0,108	0,159	0	0	0	1
3	877	35 (14,6)	0,083	0,062	0,104	0	0	0	1
>3	877	45 (18,8)	0,132	0,107	0,158	0	0	0	1
Surgery delay (hours)* **									
Total**	239	239 (100,0)	19,960	16,295	23,625	16,483	7,283	24,600	210,820
Negative (=missing)**	9	9 (3,8)	-12,050	-13,828	-10,272	-11,916	-13,330	-11,000	7,166
Admitted from									
Home	877	237 (99,2)	0,994	0,989	1,000	1	1	1	1
Other institution	877	2 (0,8)	0,006	0,000	0,011	0	0	0	1
Discharged to									
Home	877	30 (12,6)	0,586	0,549	0,623	1	0	1	1
Nursing home	877	99 (41,4)	0,200	0,169	0,230	0	0	0	1
Other institution	877	57 (23,9)	0,114	0,090	0,138	0	0	0	1
Other	877	50 (20,9)	0,090	0,068	0,112	0	0	0	1
Missing	877	3 (1,3)	0,007	0,001	0,013	0	0	0	1
Hip fracture	877		0,295	0,261	0,330	0	0	1	1
Primary hemi prosthesis	877		0,286	0,252	0,320	0	0	1	1
Secondary hemi prosthesis	877		0,025	0,013	0,037	0	0	0	1
Reposition of luxated hip	877		0,033	0,020	0,047	0	0	0	1
Open exploration	877		0,001	-0,001	0,004	0	0	0	1
Surgery due to infection	877		0,005	-0,001	0,010	0	0	0	1

Wound revision	877		0,017	0,007	0,027	0	0	0	1
Removal of prosthesis	877		0,011	0,003	0,019	0	0	0	1
Reoperation	877		0,006	0,000	0,011	0	0	0	1
Rehabilitation in hospital	877		0,008	0,001	0,015	0	0	0	1
Out-patient control	877		0,188	0,159	0,218	0	0	0	1
Patient died	877	26 (10,9)	0,066	0,047	0,085	0	0	0	1
Hospital days**	877		3,527	3,105	3,948	0	0	0	40
DRG weight**	877		1,565	1,420	1,710	0,372	0,026	3,795	7,611
Total cost according to DRG weight (NOK)**	877		63807	57897	69716	15167	1060	154765	310386

**Observations of variable*
*** Mean value instead of proportion*
****Unit of observation is index contact*

For coding of the infection variable the patient status was monitored at discharge and at 30 days post-surgery as is in accordance with the standards of NOIS, described previously. Deep and organ space SSI was assumed equal as there are no distinction between them in the dataset, and because the practice has precedence in other studies (Dale et al., 2011; Hege Line Lower et al., 2015) and with the NOIS (Kacelnik, 2014; H. L. Lower et al., 2013).

Our dataset allows for analysis of whether prolonged surgery waiting time influences the occurrence of SSI in our sample. However, in defining a variable for the delay between admission and surgery during the index stay, due to registry errors, 9 negative numbers were produced. As this indicates surgery before admission the negative values were dropped and replaced by missing values.

We estimated cost per episode of care ("Total cost according to DRG weight") by multiplying the ISF cost weights ("DRG weight") by the unit prize per diagnosis related group (DRG) point for 2014, defined by the Directorate of Health at NOK40,772 (Helsedirektoratet, 2014) (ref. section on cost effectiveness of prevention). We used constant price weights and followed each patient for a maximum of one year, and thus did not adjust for inflation or discounting of costs or effects.

Methods

Data cleaning

Patients admitted to Bærum hospital from September 2010 who had completed one year follow up in December 2014 after experiencing a hip fracture (ICD-10 code: S72.0) and

subsequent treatment with a hemi prosthesis (NCMP/NCSP code: NFB.02/-.12) where to be included in the analysis, making no distinction between the use or no-use of cemented prosthesis. Admission after hip fracture and consequent treatment with hemi arthroplasty, as defined here, defines the index event. All included patients were sought followed for 1 year, and all hospital contacts in this period recorded. However, the data set contained information on several patients who had not had this type of index contact, including observations predating it. Additionally, some patients had recorded observations more than one year from the index contact.

The data set was examined and corrected using Microsoft Excel, as well as Stata13. All patients who had not experienced the combination of hip fracture and subsequent treatment with HA (the index contact) were excluded. Observations of hospital contacts before such an event were deleted as well as observations of contacts more than one year later than the index event. We proceeded to search for illogical findings in the dataset. Per definition (ref. data structure and limitations) there can be no more first contacts than patients in the sample, there can be more fractures than HA's and there can be more HA's than patients and therefore first contacts. Searches for illogical findings included looking for different numbers of first contacts and numbers of patients, fewer hip fractures than first contacts and patients, fewer HA's than hip fractures and so on. With such findings the data set was subjected to further scrutiny and corrections. For the variables "ASA score", "Surgery delay" and "Discharged to" there were missing information. In the work with the dataset, missing values were generally treated as no observation. While the initial dataset contained 974 observations and 251 patients, the resulting dataset contained 877 observations and 239 patients all having experienced a HA treated hip fracture (=index event), where the index event constituted the first observation for all patients.

Descriptive analysis

Variables were described by means of proportions, means, medians, standard deviations, 95% confidence intervals, ranges, 1st and 3rd quartiles and the number of observations registered where applicable. We also presented numbers of missing values (Table 2). The data was further divided into two groups. One group consisted of characteristics of the index

contact which would be the basis for our risk factors or predictors of infection analysis (Table 4). The other group consisted of accumulated consequences of the index event accruing over the year after the index stay, which would be the basis for our consequence analysis (Table 5). We further grouped the data by infection status, such that distribution of risk factors and consequences within infection status subgroups could be analyzed.

Univariate analysis

The normality distribution plays an important role in statistics and many practical procedures rely for their validity on an assumption that the data is normally distributed. We subjected the variables described in tables 4 and 5 to a test of skewness and kurtosis, using the Stata13 "sktest" (selection of results in table 6). Skewness is a measure of symmetry, and is known to be 0 for a normal distribution. Kurtosis is a measure of the weight of the tails or "peakedness" of a probability density function, and is known to be 3 in a normal distribution (Newbold, Carlson, & Thorne, 2013). For each variable "sktest" presents a test for normality of data based on skewness and another based on kurtosis and then combines the two tests into an overall test statistic by which a null hypothesis of normality can be rejected or not (stata.com, 2015c).

Bivariate analysis

Comparisons of measures of central tendency were used broadly to describe the dataset. When the data are not normaly distributed, non-parametric tests are often appropriate (Newbold et al., 2013). Dependent on the distribution of data and statistical data type we performed either Wilcoxon rank-sum test (for ordinal or interval variables) of Fischer's exact test (for categorical variables) to check for significant differences in distribution of the variables according to infection status. Wilcoxon rank-sum test tests the hypothesis that two independent samples (unmatched data) are from populations with the same distribution. The test indicates whether or not the median values of a variable are statistically different by group (stata.com, 2015b). Fischer's exact test was used as an alternative to the Chi-square test, as one or more of the cells had an expected frequency of five or less in our data (UCLA, 2015c). The dependent variable (infection status) for the risk factor analysis (characteristics of the index contact) is the same as the independent variable (also infection status) for the

analysis of consequences (events experienced in one year after the index contact), and was defined as has been described in the section on SSI. Infection status groups superficial and deep were individually and consistently tested against the no infection group.

We obtained estimates of the unadjusted odds ratios and adjusted odds ratios related to having both a deep and superficial infection. To obtain unadjusted odds ratios we used bivariate logistic regression. The results of these analyses were presented in the section on multivariate. The rationale behind the choice of logistic regression and regression theory is presented in the next section.

Multivariate analysis

We aimed to identify risk factors of SSI after the initial surgery. Multiple linear regression could enable us to determine the simultaneous effect of several independent variables on a dependent variable using the least squares principle, estimated by coefficients (Bk). In multiple linear regression these coefficients depend on what other variables are included in the model. The coefficient Bk estimates the change in Y given a unit change in Xk, while controlling for the simultaneous effect of the other independent variables. The random error term, Ei, captures all the variation in Yi not explained by the X variables (Newbold et al., 2013). A typical multiple regression equation is demonstrated below (equation 1):

$$Yi=B0+B1X1+B2X2+ \dots +BkXki+Ei \quad (1)$$

There are several standard assumptions to linear regression. Without verifying that our data had met these assumptions, the results could be misleading (UCLA, 2015a). The following paragraphs contain explanations on the nature of the assumptions and the methods we used to test whether or not they were met.

The standard assumptions for linear regression analysis exclude cases of perfect correlation between independent variables. The term collinearity implies that two variables are near perfect linear combinations of one another. When more than two variables are involved it is often called multicollinearity, although the terms are often used interchangeably. It is

discouraged to select independent variables in developing a multiple regression model that are highly correlated, as the variance of the coefficient estimates increase as the correlation moves away from zero. In addition, the point estimate of a coefficient can be quite different from the actual mean value of the coefficient. The result could be not statistically significant or misleading coefficient estimates. This phenomenon is referred to as multicollinearity (UCLA, 2015a) (Newbold et al., 2013).

There are several methods to check for the presence of multicollinearity. The Spearmans rank correlation coefficient (r subscript s or rho) is a nonparametric measure of correlation that is not susceptible to serious influence by extreme values. The factor describe correlation in terms of both direction (+/-) and strength (0 - 1) of the relationship. To reject the null hypothesis that there is no association, at the 5% level of significance, the Spearman rank correlation coefficient need to be within the range of -0,490 to 0,490 (Newbold et al., 2013). The variance inflation factor (VIF factor) and tolerance value (1/VIF) can be used to check for multicollinearity. A variable with VIF higher than 10 or tolerance lower than 0,1 can be considered a linear combination of other independent variables (UCLA, 2015a). For corrections in the case of multicollinearity, see Newbold (2013). We estimated the correlation coefficients between all the potential predictor variables to look for signs of linear relationships between individual variables. We also used the variance inflation factor and tolerance values to check for multicollinearity.

In developing the linear model we assumed a linear relationship between the predictor variables and the dependent variable (infection status), and included in the analysis all variables assumed to markedly influence the dependent variable. The joint influence of variables with a strong influence on the independent variable omitted from the model is absorbed in the models error term. When significant predictor variables are excluded from the model, the coefficient estimates included are usually biased, and the estimated model error will be large (Newbold et al., 2013).

There are several methods to control for such model specification errors. We used the link test, which is based on the idea that if a model is properly specified one should not be able to find any other significant predictor variables than the ones included in the model, except by chance. The test creates two new variables, one based on the prediction of the model

and the other is the prediction squared. If the squared prediction has explanatory power (p<=0,05), link test can reject the assumption of correct specification of the model (UCLA, 2015a). As the availability of potential predictor variables in our dataset was restricted to those presented in table X, we included all of them in the analysis.

It is assumed that the error terms are normally distributed random variables, with a mean of 0 and uniform variance (Newbold et al., 2013). We will come back to the latter in the next paragraph. Normality of error terms, although a formal assumption of statistical inference (see part on bivariate analysis), can be relaxed under the central limit theorem if the sample size is large enough (Newbold et al., 2013).However, we conducted a Shapiro-Wilk test and produced a histogram and graphed both a standardized normal probability (P-P) plot and a Q normality plot of the quantiles of a variable against the quantiles of a normal distribution to check for normality. The standardized normal probability (P-P) plots are sensitive to non-normality in the middle range of data and Q normality plots are sensitive to non-normality near the tails (UCLA, 2015a).

As mentioned, it is a standard assumption of multiple regression models that the variance of the error terms are equal. In other words, the standard multiple regression model assume homoscedasticity. We used the Breusch-Pagan/Cook-Weisberg test to test the null hypothesis that the variance of the residuals was homogenous. If the p-value was very small (<0,05), we would have to reject the null hypothesis and accept the alternative hypothesis that the variance was not homogenous, i.e. there was heteroscedasticity (UCLA, 2015a).

Another way in which error terms can de dependent on each other is through autocorrelation. This is especially a problem when working with time-series data (Newbold et al., 2013). As our predictor variables are estimated at a single point in time, we did not consider autocorrelation to be a plausible problem.

The outcome of interest of our risk factor analysis was infection status, a binary variable taking values of 0 or 1 according to infection status deep/superficial or no infection. Authors are not in agreement about how to model the relationship between an outcome and predictor variables when the outcome or dependent variable is binary. Juul and Frydenberg

(Juul & Frydenberg, 2010) claims the linear regression models are not valid in these cases, and suggest the use of a logistic model instead. UCLA suggest using logistic (Logit) or Probit regression in these cases. They agree with Jones (Jones, 2007) that using an ordinary least squares regression (as described by Newbold above), called a linear probability model (LPM) when used for predicting of a binary variable, can be used to describe conditional probabilities. However, the error terms will in this case violate the assumptions of homoscedasticity and normality of error terms, resulting in invalid standard errors and hypothesis tests (UCLA, 2015b).

Jones claims a simple way to model such binary data is to use a linear function, and that the linear probability model is relatively straightforward to estimate, using a robust estimator of standard errors and a weighted least squares regression model to counter the by design heteroscedastic error terms in a binary outcomes model:

$$E(y|x) = 0.P(y=0|x) + 1.P(y=1|x) = P(y=1|x) = F(x) \quad (2)$$

He claims that in practice the LPM may provide a reasonable approximation for binary choice models, although a major drawback of the method is that predicted values of the regression function can lie outside of the range 0 to 1. This may lead to logical inconsistencies given that the model is supposed to estimate the likelihood of an outcome E(y|x) (equation 2) (Jones, 2007).

By using non-linear functions for F(.) by choosing non-linear models using “S-curves”, naturally bounded to 0-1, this problem can be avoided. The most common choices are Logit and Probit models. Assuming that the error term in these models has a standard normal distribution gives the Probit model. Assuming a standard logistic distribution gives the Logit model. Both models are estimated by the maximum likelihood estimation method (Jones, 2007). Although there are assumptions about the distribution of error terms that differ between the models, Probit and Logit models produce similar results and the choice between them depend largely on individual preferences. In these models, the log odds of the outcome is modeled as a linear combination of the predictor variables. The coefficients give the change in log odds of the outcome for a one unit change in the predictor variable.

By exponentiating the coefficients they can be interpreted as odds-ratios. The same results can be obtained using the logistic regression command in Stata13 (UCLA, 2015b).

We wanted to find the change in the likelihood of deep and superficial infection associated with changing the values of our predictor variables. Because y (1 or 0) is inherently unobservable, unlike the probabilities regarding its outcome, the coefficients of the Probit and Logit models should only be given a qualitative interpretation, translating to an increased likelihood of infection given a positive coefficient and vise versa. To interpret the quantitative implications of the coefficients we needed to compute partial effects, using marginal effects for continuous predictor variables and average partial effects for binary predictors. These partial effects are estimates of predicted probabilities. The marginal effects method produce predicted probabilities of having deep infection for a marginal change in a variable, holding all other variables in the model at their mean. As this approach might be problematic - in that an individual possessing the average value of a dummy variable indicating for example gender does not exist - average partial effects are used for categorical predictors. Here, the effect of each observation is computed using their specific x-values, before summary statistics such as the sample mean of effects are reported (Jones, 2007).

As the literature did not provide a conclusive suggestion as to which multivariate method to use for our risk analysis, we decided to implement several models, including OLS, LPM using weighted least squares (WLS), Probit, Logit (providing relative risks) and Logistic (providing adjusted odds ratios), and compare the goodness of fit, estimated coefficients and predicted probabilities of infection for the sample.

Goodness of fit was assessed by comparing R-squared (coefficient of determination) of the LPM and pseudo R-squared of the Logit and Probit models. A high value would indicate a high degree of explanatory power (Newbold et al., 2013). Further, we performed Wald tests of the hypothesis that the squared model predicition is equal to zero. The hypothesis can be rejected given a p-value less than or equal to, which would indicate a poorly fitted model (stata.com, 2015d). We further obtained an estimate of the percentage correctly classified cases by the Probit and Logit models, using the “estat classification” command in Stata13

(stata.com, 2015a), and performed a link test on the squared prediction of our LPM as a confirmation of the Wald test result of this model. Linktest is described in more detail above.

All data cleaning and subsequent analyses were performed using Microsoft Excel and Stata13.

Economic Model

We developed a decision analytical model who would host a probabilistic cohort cost-benefit analysis of the infection prevention intervention at Bærum hospital. We constructed a decision tree (figure 6) in which the expected outcomes of the intervention and the no intervention branches would be mediated primarily through the interventions effect on SSI incidence. We assumed infection status and mortality was dependent on the index stay, making four possible health states possible after the index event. Depending on whether or not the patients received the intervention program, the groups would consequently accumulate a different amount of QALY's and costs as the infection incidence changed. Expected costs would depend on the incremental cost of the intervention itself and the discrepancy in average yearly cost between the infection groups. Additionally, QALY's and costs would accrue for those who died during the index contact. Both outcomes and costs were weighted through the model by the probabilities of acquiring infections (the incidence) or dying or neither.

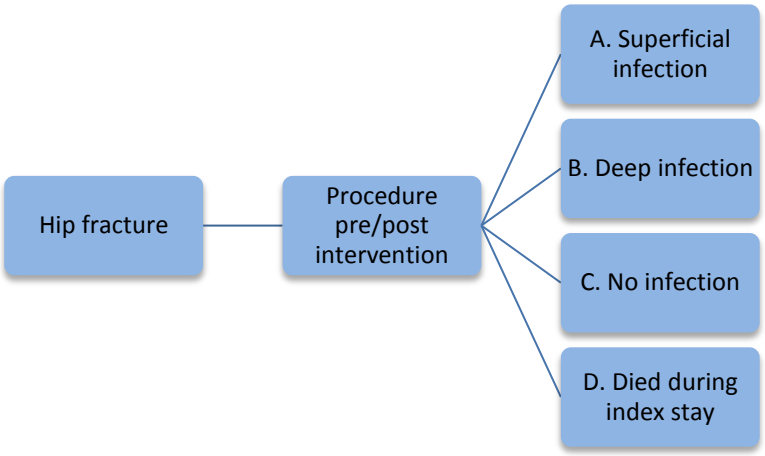

Figure 6: Decision tree illustrating possible transitions between health states.

Our parameters were (table 3): infection probabilities with or without intervention, one year QALY scores with superficial, deep or without infection, one year hospital costs for the same states in addition to the cost of an index contact for a patient dying during this period, and finally an estimate of the intervention's incremental cost per procedure.

Prior superficial and deep infection probability we found doing a search in the NOIS-database revealing 5 superficial infections and 8 deep infections in 121 procedures. The estimate does not exclude HA procedures done for other reasons than hip fracture, and incorporates procedures done in the period 1.1.2006-31.12.2009. Deep and superficial infection probabilities after intervention implementation was calculated using our data, and was estimated at 2,5% and 1,3%. Mortality probabilities among patients prior to the intervention were based on the NOIS-database (5 deaths among 121 patients). Post intervention mortality was based on our own data. One year QALY estimates for deep and no infection were assumed to be equal to the estimates used by Merollini and colleges when they investigated a similar problem in a similar population (Merollini et al., 2013), and was assumed to be 0 for patients dying during the index stay. As no empirical estimates were found, one year QALY score for patients suffering superficial infection was based on a method described by Elliot and colleges (Elliott et al., 2010) (** in table 3). One year hospital costs were estimated from our cost according to ISF variable included in the data material we received from Bærum hospital (tables 3, 11 and 12). The incremental intervention cost was calculated as the cost difference between the old practice's Corail uncemented prosthesis and the new strategy's Exeter prosthesis with antibiotic cement, plus the cost of having an extra operator attending each procedure (= one average hourly wage for specialists in training or consultant surgeon), plus the cost of antibiotic profylaxis. To account for overheads, the surgery personnel time costs where weighted by a factor of 1,4 (accumulating to NOK721). Hourly wage rates where attained from The Norwegian Medical Association, whereas the new cemented prosthesis (NOK7,625) and antibiotic profylaxis (NOK881) costs where derived through personal communication with the orthopaedic staff at Bærum hospital and from an Australian study (Merollini et al., 2013), respectively. After subtracting the cost savings of the Exeter cemented prosthesis (NOK3,952) from the additional antibiotic profylaxis and extra surgeon time costs (NOK1,602), the net cost saving

per procedure was NOK2,350 and the 20% standard deviation on this number was NOK470. All costs were expressed in 2014 Norwegian Kroner (NOK).

Table 3: *Parameters of our decision tree.*

Parameters	Mean	S.D.	Distribution
Superficial infection prob.			
*Pre intervention	0,041	0,200	Dirichlet
****Post intervention	0,013	0,112	
Deep infection probability			
*Pre intervention	0,089	0,030	Dirichlet
****Post intervention	0,025	0,157	
Probability of dying during index stay			
*Pre intervention	0,041	0,200	Dirichlet
****Post intervention	0,042	0,201	
One year QALY			
**Superficial infection	0,854	0,012	Beta
***Deep infection	0,400	0,051	
***No infection	0,858	0,012	
Hospital costs (NOK)			
****Superficial infection	275.466	89.095	Gamma
****Deep infection	414.975	198.742	
****No infection	228.879	137.725	
****Died during index stay	178.708	47.854	
Incremental intervention cost (NOK)	-2.350	470	Gamma

* NOIS data 2006-2009 including 121 HA procedures
** (days without infection*no infection HRQoL)+(mean hospital days with superficial infection*superficial infection HRQoL) = (351*0,858)+(14*0,758). SD assumed equivalent to No infection.
***(Merollini et al., 2013)
****Present study

To account for second order uncertainty (parameter uncertainty) in the parameter estimates we undertook probabilistic sensitivity analyses. Here we specified input distributions, or probability density functions, for input parameters in which random draws would be made in 1000 Monte Carlo simulations. This was done to propagate internal (=parameter) uncertainty through the model resulting in a distribution of the outcome parameters. The mean of the outcome distributions would then become the point estimates for the outcomes and costs. We followed standard procedures for distributional assumptions to enhance the quality and credibility of the analysis (Briggs et al., 2006). The distributions we chose are presented in table 3.

Assumptions

For the analysis and economic evaluation it was assumed that points 2 (specifically correct antibiotic profylaxis), 3 and 4 of the intervention regime as described in chapter 3 (section on the intervention) was fully implemented and adhered to 100% from the time the first patient was admitted in 2010. To repeat, it was assumed that all HA procedures use

cemented Exeter prosthesis, that there were two operators whereof a consultant surgeon or assistant surgeon was the second operator on all HA procedures and that the use of antibiotic prophylaxis was in accordance with the guidelines of the Norwegian Directorate of Health (ref. section on the intervention).

As we used constant price weights and a one year perspective, we did not adjust for inflation and we did not discount costs or effects (Glick, Doshi, Sonnad, & Polsky, 2007).

Decision analytical modeling was performed using the modeling software TreeAgePro.

Ethical considerations

The data protection authority at Bærum hospital was involved in the study. The data set was anonymized before we received it. To maintain patient anonymity age in years was replaced with an age variable consisting of 4 groups. The data set did not contain the 11 digit social security number, but a 10 digit generic ID number that allowed us to distinguish between patients.

6. Results

In this chapter the results obtained through implementation of the methods discussed in the previous chapter will be presented in text, tables and figures. Texts will summarize briefly the information given in the tables and figures, while the latter two will provide a full picture of the findings. We present descriptive statistics before moving on to results of the uni-, bi-, and multivariate analysis. Finally, we present the results of our economic evaluation. This chapter will contain limited or no discussions or interpretations of the results as this will be the topic of the next chapter. Conclusions of the discussion will follow suit.

Descriptive statistics

Study population and material

The study population comprised predominantly of women (65%) in the age range of 80-89(48%), admitted from their homes (99%) and discharged to another place than home (87%). 91% had an ASA score of 2 or 3. Most (96%) of the population was alive at discharge, and their index stay (first contact) accrued an average cost of NOK160,000 per patient, NOK172,589 for patients with superficial infection and NOK163,519 for patients with deep infection. Table 4 describes the distribution of variables of interest for the analysis of differences in patient characteristics and other descriptors of the index stay.

Table 4: *Characteristics of the index contact according to infection status at 30 days.*

Variable	Total (%)	Infection (%)	Superficial infection (%)	Deep infection (%)
Patients				
Male	84 (35,2)	5 (5,6)	1 (1,2)	4 (4,8)
Female	155 (64,8)	4 (2,6)	2 (1,3)	2 (1,3)
Total	239	9 (4,9)	3 (1,3)	6 (2,5)
Age				
45-66	16 (6,7)			
67-79	51 (21,3)	2 (3,9)		2 (3,9)
80-89	115 (48,1)	4 (3,5)	1 (0,9)	3 (2,6)
90+	57 (23,9)	3 (5,3)	2 (3,5)	1 (1,8)
Total	239	9 (4,9)	3 (1,3)	6 (2,5)
Length of stay (LOS)				
Mean per patient	7,7	8,6	14,0	5,8
Total	1829	77 (4,2)	42 (2,3)	35 (1,9)
ASA score				
1	4 (1,9)			
2	97 (45,1)			
3	99 (46,0)	7 (7,1)	3 (3,0)	4 (4,1)
4	15 (7,0)	1 (6,7)		1 (6,7)
Missing	24	1		1
Total	239	9 (4,9)	3 (1,3)	6 (2,5)
Number of comorbidities				
Mean per patient	2,2	2,1	1,7	2,3
Total	519	19 (3,7)	5 (2,1)	14 (5,9)
Surgery delay				
Mean per patient (n=230)	21,2	14,2	8,8	16,9
Total	4878,9	127,7 (2,6)	26,5 (0,5)	101,2 (2,1)
Admitted from				
Home	237 (99,2)	9 (3,8)	3 (1,3)	6 (2,5)
Other institution	2 (0,8)			
Total	239	9 (4,9)	3 (1,3)	6 (2,5)
Discharged to				
Home	30 (12,7)	1 (3,3)		1 (3,3)
Nursing home	99 (42,0)	6 (6,1)	2 (2,0)	4 (4,1)
Other institution	57 (24,2)	1 (1,8)		1 (1,8)
Other	50 (21,2)	1 (2,0)	1 (2,0)	
Missing	3			
Total	239	9 (4,9)	3 (1,3)	6 (2,5)
Status at discharge				
Alive	229 (95,8)	9 (3,9)	3 (1,3)	6 (2,6)
Dead	10 (4,2)			
Total	239	9 (4,9)	3 (1,3)	6 (2,5)
Cost by ISF (NOK)				
Mean per patient	160,419	166,542	172,589	163,519
Total	38,340,027	1,498,880	517,766	981,114

**standard deviation*

Further, events experienced through the year-long follow up period include (NMCP-/NCSP-code in parenthesis) new primary hip prosthesis (NFB), secondary hip prosthesis implantation (NFW), repositioning of hip luxation (NFH), removal of implant (NFU), reoperation due to deep infection (NFW), revision due to infection, open exploration of soft tissue of the hip, out-patient controls, rehabilitation in hospital and death. Numbers in table 5 are the total experienced of an event, hospital days or accrued costs according to group.

Due to discrepancies in coding practice, two surgeries for hip infection were recorded for patients not coded with infection. There was considerable variation in the events experienced by patients in the year following the index contact. Some of the events experienced were excluded from the tables describing consequences and the analysis of these, but they were included in the estimates of costs and hospital days. Such events include percutaneous puncture of the bladder, gastroscopy, excision of lesion of skin of upper limb, colonoscopy, endoscopic polypectomy of the colon, cystoscopy and dialysis.

During the first year after the index contact, 8 prosthesis were removed, 15 wound revisions were undertaken, 5 reoperations were done and 16 people died. When we included all services consumed at Bærum hospital by this patient sample, the estimated hospital costs according to the DRG weight system amounted to NOK 17,618,370, whereof NOK 1,508,735(9%) was spent treating those with deep infection and NOK 308,632(2%) was spent treating those with superficial infection. The cost of treating those without infection amounted to NOK15,501,003. Per patient mean treatment costs excluding the index stay amounted to NOK251,334 for deep infection, NOK10,877 for superficial infection and NOK71,823 for those without infection.

Table 5: *N events experienced by 229 patients during one year after the index contact. According to infection status.*

Type of event	N	No infection (%)*	Superficial infection (%)*	Deep infection (%)*
New primary hemi prosthesis	**12**	7 (58,3)	1 (8,3)	4 (33,3)
New hip fracture	**20**	18 (90,0)	1 (5,0)	1 (5,0)
Secondary hemi prosthesis	**19**	16 (84,2)	0 (0,0)	3 (15,8)
Reposition of luxated hip	**25**	22 (88,0)	0 (0,0)	3 (12,0)
Removal of prosthesis	**8**	7 (87,5)	0 (0,0)	1 (12,5)
Reoperation	**5**	3 (60,0)	0 (0,0)	2 (40,0)
Wound revision	**15**	15 (100,0)	0 (0,0)	0 (0,0)
Open exploration	**1**	1 (100,0)	0 (0,0)	0 (0,0)
Rehabilitation in hospital	**5**	5 (100,0)	0 (0,0)	0 (0,0)
Poli clinical control	**165**	147 (89,1)	3 (1,8)	15 (9,1)
Surgery for hip infection	**4**	2 (50,0)	0 (0,0)	2 (50,0)
Hospital days	**1264**	1140 (90,2)	8 (0,6)	116 (9,2)
Patient died	**16**	14 (87,5)	1 (6,25)	1 (6,25)
Total cost according to DRG weight (NOK)	**17.618.370**	15.801.003 (89,7)	308.632 (1,8)	1.508.735 (8,6)

*Percent of total. N=229.

Analysis

Univariate analysis

A skewness and kurtosis test of normality of data indicated all variables except ASA score deviated strongly from the normal distribution. The *p*-values for the individual tests of skewness and kurtosis normality below 0,05 indicated they differed significantly from the normal distribution. We saw that based on skewness alone, age was not different from normal at the 5% level, but the kurtosis was.

Table 6: *Skewness and kurtosis test of assumption of normality of data distribution.*

Variable	n	Skewness	Kurtosis	adjusted X2	Significance (p=0,05)
Gender	239	0,0002	.	.	.
Age	239	0,0037	0,3514	8,51	0,0142
LOS	239	0,0000	0,0000	.	0,0000
ASA	215	0,1138	0,2495	3,86	0,1449
Comorbidity	239	0,0000	0,0000	50,84	0,0000
Surgery delay	230	0,0000	0,0000	.	0,0000
Status in discharge	239	0,0000	0,0000	.	0,0000
Admitted from	239	0,0000	0,0000	.	0,0000
Discharged to	236	0,0000	0,0013	21,95	0,0000
Remuneration ISF	239	0,0000	0,0000	.	0,0000

**H0: distribution is normal. "." indicate an "absurdly large number" meaning the distribution is almost certainly not normal (stata.com, 2015c).*

An sktest of normality of the consequences variables (table X) was also provided strong evidence of the non-normality of all variables.

Bivariate analysis

Based on the findings in the univariate analysis and the statistical data type of the variables to be tested, we used Wilcoxon rank-sum and Fischer's exact tests for bivariate analysis of differences in central location of variables according to infection status superficial, deep or no infection.

For the risk factor analysis of superficial infection, we found that the amount of hospital days (p=0,051) and hospital costs (p=0,069) were both borderline significant at the 5% level. Although they arguably are consequences of the index event, they also describe the index stay and are included here pending further discussion (ref. Discussion). A more liberal 20% level of alpha would have given results indicating statistically significant differences between

the groups in distribution of 90+ year olds (p=0,144), ASA score (p=0,125) and surgery delay (p=0,160). Tests were done for the other three age groups, returning P values of 1.

Table 7: *Characteristics of the index contact according to infection status superficial or none.*

Variable	Superficial infection (n=3)	No infection (n=230)	Total	P-value
Gender (female=1)	2	151	153	1*
Mean	0,667	0,657		
Standard deviation	0,577	0,476		
Min	0	0		
Max	1	1		
Age 90+	2	54	56	0,144*
Mean	0,667	0,235		
Standard deviation	0,577	0,425		
Min	0	0		
Max	1	1		
ASA score				0,125**
Mean	3,000	2,304		
Standard deviation	0,000	0,986		
Min	3	0		
Max	3	4		
Comorbidites				0,799**
Mean	1,666	2,174		
Standard deviation	1,155	2,008		
Min	1	0		
Max	3	11		
Hospital days	42	1752	1794	0,051**
Mean	14,000	7,617		
Standard deviation	8,185	6,254		
Min	7	1		
Max	23	40		
Surgery delay (n=224)	(n=3)	(n=221)		0,160**
Mean	8,8	21,5		
Standard deviation	3,9	25,4		
Min	4,4	0,3		
Max	12,1	195,1		
Admitted from home				1*
Mean	1 (100%)	0,991 (99%)		
Standard deviation	0	0,093		
Min	1	0		
Max	1	1		
Costs according to DRG weight (NOK)	517.766	36.841.147	37.358.913	0,069**
Mean	172.589	160.179		
Standard deviation	0	27.674		
Min	172.589	126.666		
Max	172.589	311.038		

Wilcoxon rank-sum test(**) and Fischer's exact test(*) of the null hypothesis that two independent samples are from populations with the same distribution (stata.com, 2015b) (UCLA, 2015c). (Significance judged at the 5% level).

Of the predictors of deep infection, none demonstrated a distribution statistically significantly different from the no infection group (table 8). However, an alpha value of 20% would indicate significant differences in gender (p=0,188) and ASA score (p=0,143).

Of the age groups, the distribution of 67-79 year olds demonstrated strongest evidence (p=0,613) of not being equal between the deep and no infection groups. A Fischer's exact test of the other age groups indicated no significant difference and a P value of 1.

Table 8: *Characteristics of the index contact according to infection status deep or none.*

Variable	Deep infection (n=6)	No infection (n=230)	Total	P-value
Gender (female=1)	77	151	228	0,188*
Mean	0,333	0,657		
Standard deviation	0,516	0,476		
Min	0	0		
Max	1	1		
Age 67-79	77	49	126	0,613*
Mean	0,333	0,213		
Standard deviation	0,516	0,410		
Min	0	0		
Max	1	1		
ASA score				0,143**
Mean	2,667	2,304		
Standard deviation	1,366	0,986		
Min	0	0		
Max	4	4		
Comorbidites				0,725**
Mean	2,333	2,174		
Standard deviation	1,862	2,008		
Min	0	0		
Max	5	11		
Hospital days	1342	1752	3094	0,593**
Mean	5,833	7,617		
Standard deviation	2,858	6,254		
Min	3	1		
Max	11	40		
Surgery delay (n=227)	(n=6)	(n=221)		0,950**
Mean	16,9	21,5		
Standard deviation	8,1	25,4		
Min	1,4	0,3		
Max	24,6	195,1		
Admitted from home				1*
Mean	1 (100%)	0,9913 (99%)		
Standard deviation	0	0,09305		
Min	1	0		
Max	1	1		
Costs according to DRG weight (NOK)	981.114	36.841.170	37.822.284	0,625**
Mean	163.519	160.179		
Standard deviation	14.575	27.674		
Min	154.765	126.666		
Max	189.468	311.038		

Wilcoxon rank-sum test(**) and Fischer's exact test(*) of the null hypothesis that two independent samples are from populations with the same distribution (stata.com, 2015b) (UCLA, 2015c). (Significance judged at the 5% level).

Several of the consequence variables were indicated by the statistical tests to have significant differences in distribution according to infection status groups (tables 9 and 10). For the difference between deep and no infection these variables included (p) numbers of

new hemi prosthesis' (0,002), reoperations (0,024), out-patient controls (0,013) and surgeries for hip infection (0,015) (in spite of the coding error already mentioned). In addition, the difference in numbers of secondary hemi prosthesis' was significant at the 7% level. Had a 20% level of significance been applied, reposition of luxated hip (0,136) and hospital costs (0,192) would also have been considered significantly different.

Table 9: *Events experienced during one year after the index event according to infection status deep or no infection.*

Type of event	Deep infection	No infection	Total	P-value
New primary hemi prosthesis	4	7	11	0,002*
New hip fracture	1	18	19	1*
Secondary hemi prosthesis	3	16	19	0,071*
Reposition of luxated hip	3	22	25	0,136*
Removal of prosthesis	1	7	8	0,35*
Reoperation	2	3	5	0,024*
Wound revision	0	15	15	1*
Open exploration	0	1	1	1*
Rehabilitation in hospital	0	5	5	1*
Out patient control	15	147	162	0,013*
Surgery for hip infection	2	2	4	0,015*
Patient died	1	14	15	0,577*
Hospital days	116	1140	1256	0,436**
Mean	3,515	1,903		
Standard deviation	6,615	4,248		
Min	0	0		
Max	25	31		
Cost according to DRG weight (NOK)	1.508.735	15.801.003	17.309.738	0,192**
Mean	45.719	26.379		
Standard deviation	90.529	54.795		
Min	652	652		
Max	311.038	311.038		

Wilcoxon rank-sum test(**) and Fischer's exact test(*) of the null hypothesis that two independent samples are from populations with the same distribution (stata.com, 2015b) (UCLA, 2015c). (Significance judged at the 5% level).

For the corresponding analysis of the differences between the groups superficial and no infection, none of the variables examined were indicated statistically significant at the 5% level of confidence. However, applying a 20% level of alpha would have left us with

significant differences in the following procedures (p value): new primary hemi prosthesis (0,077), new hip fracture (0,175) out-patient controls (0,165) and patient deaths (0,140).

Table 10: *Events experienced during one year after the index event according to infection status superficial or no infection.*

Type of event	Superficial infection	No infection	Total	P-value
New primary hemi prosthesis	1	7	8	0,077*
New hip fracture	1	18	19	0,175*
Secondary hemi prosthesis	0	16	16	1*
Reposition of luxated hip	0	22	22	1*
Removal of prosthesis	0	7	7	1*
Reoperation	0	3	3	1*
Wound revision	0	15	15	1*
Open exploration	0	1	1	1*
Rehabilitation in hospital	0	5	5	1*
Out patient control	3	147	150	0,165*
Surgery for hip infection	0	2	2	1*
Patient died	1	14	15	0,140*
Hospital days	8	1140	1148	0,479**
Mean	1,333	1,903		
Standard deviation	1,506	4,248		
Min	0	0		
Max	3	31		
Cost according to DRG weight (NOK)	308.632	15.801.003	16.109.635	0,957**
Mean	51.439	26.379		
Standard deviation	69.493	54.795		
Min	693	652		
Max	154.765	311.038		

Wilcoxon rank-sum test(**) and Fischer's exact test(*) of the null hypothesis that two independent samples are from populations with the same distribution (stata.com, 2015b) (UCLA, 2015c). (Significance judged at the 5% level).

For the analysis of the difference in total number of deaths, hospital costs and hospital days according to infection status, the results for deep infection indicated a statistically significant difference both for hospital days (p=0,0371) and hospital costs (p=0,0038) (table 11). For the analysis of difference between those having had a superficial infection and those having had no infection, only total hospital costs was indicated significantly different between the groups (p=0,004) at the 5% level. Hospital days were indicated significant at the 20% level in this comparison (table X).

The estimated total hospital costs of treating the 239 patients for the whole period was approximately NOK 56 million divided by a total number of episodes of care of 877, giving an average episode of care cost of approximately NOK 63.854 and an estimated average patient cost of NOK 234.136, disregarding infection status.

The deep infection group had statistically significantly more total hospital days (p=0,04) and total hospital costs (p=0,004) than the no infection group.

Table 11: *Total hospital days, hospital costs and deaths according to infection status deep or no infection.*

Type of event	Deep infection	No infection	Total	P-value
Hospital days	151	2892	3043	0,037**
Mean	25,167	12,574		
Standard deviation	15,316	13,631		
Min	4	1		
Max	46	131		
Cost according to DRG weight (NOK)	2.489.850	52.642.170	55.132.020	0,004**
Mean	414.975	228.879		
Standard deviation	198.742	137.725		
Min	203.332	126.666		
Max	714.906	1.153.685		
Deaths	1	24	25	0,493*
Mean	0,167	0,104		
Standard deviation	0,408	0,306		
Min	0	0		
Max	1	1		

Wilcoxon rank-sum test(**) and Fischer's exact test(*) of the null hypothesis that two independent samples are from populations with the same distribution (stata.com, 2015b) (UCLA, 2015c). (Significance judged at the 5% level).

Those with superficial infection had statistically significantly higher total hospital costs than the no infection group (p=0,004).

Table 12: *Total hospital days, hospital costs and deaths according to infection status superficial or no infection.*

Type of event	Superficial infection	No infection	Total	P-value
Hospital days	50	2892	2942	0,154**
Mean	16,666	12,574		
Standard deviation	7,095	13,631		
Min	9	1		
Max	23	131		
Cost according to DRG weight (NOK)	826.397	52.642.170	53.468.567	0,004**
Mean	275.466	228.879		
Standard deviation	89.095	137.725		
Min	172.589	126.666		
Max	327.353	1.153.685		
Deaths	1	24	25	0,290*
Mean	0,333	0,104		
Standard deviation	0,577	0,306		
Min	0	0		
Max	1	1		

Wilcoxon rank-sum test(**) and Fischer's exact test(*) of the null hypothesis that two independent samples are from populations with the same distribution (stata.com, 2015b) (UCLA, 2015c). (Significance judged at the 5% level).

We conducted univariate logistic regression analysis (Logit) on deep infection, using all predictor variables, but found no significant (p>0,05) coefficients and low (<0,1) pseudo R-squared values. Gender exhibited an average of mean marginal partial effect estimate of -

0,027 with a significance level of p=0,075, which was by far the closest to a statistically significant result found across all of our predictor variables during this analysis.

Multivariate

We wanted to find the influence of each of the predictor variables on the subsequent infection status of the patient sample and attempted first to fit an ordinary least squares model.

In a correlation matrix Spearmans rank correlation coefficient estimates were all between 0,4 and -1,0 indicating presence of linear relationships between several of the predictor variables. Such relationships cannot be described as strong for most of the variables, although a perfect correlation (Spearmans rank coefficient equal to -1,0) was (expectedly) found between the dummy variables describing where a patient was admitted from. Additionally, a significant association was found between age groups 67-79 and 80-89 and between age groups 80-89 and 90+ (both coefficients equal to -0,5) (Newbold et al., 2013). For all other variable combinations correlation coefficients were less than the critical limit. The results were supported by the VIF factor and tolerance value estimates, all well outside the range to suspect multicollinearity. The by far most extreme VIF factor and tolerance value found was 6,05 and 0,17, respectively.

A link test of model specification returned a p value of 0,001 relating to the explanatory power of the squared prediction of our model. Link test thus rejected the hypothesis of correct specification of the model at a 99,9% level of confidence.

A Shapiro-Wilk test on the normality of the error terms returned a p-value of <0,000, rejecting the hypothesis of normality.

A Breusch-Pagan/Cook-Weisberg test of homogeneity of the residuals of the error terms gave a p value of 0,000, indicating the presence of heteroscedasticity at above a 99,9% level of confidence.

Based on the results from the link test, the Shapiro-Wilk test and the Breusch-Pagan/Cook-Weisberg test in addition to an R-squared of 0,020 we concluded the OLS-model was a poor choice to model our outcome variable, and moved on to the LPM, Probit and Logit regression models. However, none of these models resulted in goodness-of-fit values indicating satisfactory levels of outcome explanation. The R-squared estimate of the LPM was 0,037 and pseudo R-squares for the Logit and Probit models were 0,153 and 0,155, respectively. For the LPM a link test returned a p-value of 0,415, which served to reject the hypothesis of correct specification of this model. Furthermore, none of the models returned statistically significant coefficient estimates for any of the predictor variables (for the OR coefficient estimates of the logistic regression, see tables 13 and 14). For this reason the results of these and the OLS model are not presented.

However, we present estimates of the unadjusted odds ratios (ref. Methods section: Bivariate analysis) and adjusted odds ratios related to having a deep infection for our predictor variables. We did bivariate and multivariate logistic regression to attain point estimates and adjusted point estimates, respectively. We found that the estimates had wide 95% confidence intervals and where insignificant at the 5% level and the model had poor explanatory power (table 13). Gender would have been significant at the 20% level of significance for both estimates (OR = 0,26, adjusted OR = 0,27).

Table 13: *Predictors of deep infection by characteristics of the index stay.*

Variable	Point estimate of OR (n=239)	95% conf. int.		p	Point estimate of adjusted OR (n=125)	95% conf. int.		p
Gender (0=male, 1=female)	0,261	0,047	1,458	0,126	0,270	0,042	1,715	0,165
Age group								
45-66	1 (ref.)	.	.	.	1**			
67-79	1,878	0,334	10,552	0,474	5,039	0,373	68,133	0,224
80-89	1,080	0,214	5,464	0,926	2,208	0,204	23,913	0,515
90+	0,632	0,072	5,525	0,678	1*			
Not admitted from home (n=237)	1	.	.	.	1*,**			
ASA score								
1	1	.	.	.	1**			
2	1	.	.	.	1**			
3	2,905	0,522	16,182	0,224	0,489	0,039	6,123	0,579
4	3,129	0,342	28,633	0,313	1**			
Comorbidites	1,041	0,707	1,532	0,840	0,890	0,524	1,513	0,667
Surgery delay (hours) (n=230)	0,988	0,934	1,044	0,665	0,981	0,915	1,051	0,580
Hospital days	0,922	0,739	1,151	0,474	0,912	0,740	1,125	0,391

The Pseudo R-squared of the multivariate logistic model was 0,114.
** omitted due to collinearity*
***complete separation, 130 observations not used*

We did the same comparison of predictors according to infection status superficial or none, and found similar results (table 14). No predictors were statistically significant at the 5 % level, although several would have been so at the 20 % level. Hospital days and the comorbidity count both displayed borderline significant results after adjustment, with adjusted odds ratios of 1,8 and 0,05 and p-values of 0,056 and 0,078, respectively.

Table 14: *Predictors of superficial infection by characteristics of the index stay.*

Variable	Point estimate of OR (n=239)	95% conf. int.		p	Point estimate of adjusted OR (n=76)	95% conf. int.		p
Gender (0=male, 1=female)	1,085	0,097	12,144	0,947	771,873	0,142	4202857,0	0,130
Age group								
45-66	1 (ref.)				1*			
67-79	1	.	.	.	1*			
80-89	0,535	0,048	5,981	0,612	0,086	0,002	3,376	0,190
90+	6,582	0,586	73,970	0,127	1*			
Not admitted from home	1	.	.	.	1*			
ASA score								
1	1	.	.	.	1**			
2	1	.	.	.	1**			
3	1	.	.	.	1*			
4	1	.	.	.	1**			
Comorbidites	0,854	0,426	1,716	0,658	0,238	0,048	1,176	0,078
Surgery delay (hours) (n=230)	0,887	0,738	1,067	0,203	0,784	0,496	1,238	0,296
Hospital days	1,086	0,982	1,201	0,109	1,771	0,000	8,905	0,056

The Pseudo R-squared of the multivariate logistic model was 0,516.
** omitted due to collinearity*
***complete separation, 154 observations not used*

Economic Model

The incremental cost/effectiveness ratio (ICER) reports the trade-off between cost and effect for the therapy with the larger effect estimate in the denominator, here the SSI prevention intervention (Glick et al., 2007). The intervention was a dominant strategy with cost savings of NOK11,060 per patient and QALY gains of 0.02. The model predicted the strategies to produce the same amount of QALY's in several of the iterations. This left us with a considerable amount of zero values for incremental cost/effectiveness ratio estimates. The associated credible interval estimate had a wide range between its lower and upper limit, and did contain 0.

Table 15: Incremental cost/effectiveness ratio (ICER) of the new intervention compared to the old (no intervention) with 95% confidence interval.

Strategy	Total cost	Incremental cost	Total QALY	Incremental QALY	ICER	95 % CI	
No intervention	243,096		0.79				
Intervention	232,035	-11,060	0.81	0.02	-587,105	-2,436,478	1,346,262

In the cost-effectiveness plane (figure 7), each of the 1000 plots represent a possible combination of incremental costs and effects given the uncertainty in the economic model parameters. The red line indicates the Norwegian Directorate of Health stated willingness-to-pay (WTP) for a QALY, in 2012 equal to NOK588.000 (Helsedirektoratet, 2012). There was considerable variation across iterations of the Monte Carlo simulation with outcomes in all four quadrants of the cost-effectiveness plane, however primarily in the south-east and -west quadrants, indicating dominance of the new strategy over the old. The lines indicating the 95% confidence interval upper and lower bounds indicate that the difference in cost was not significant, and the difference in effect was significant.

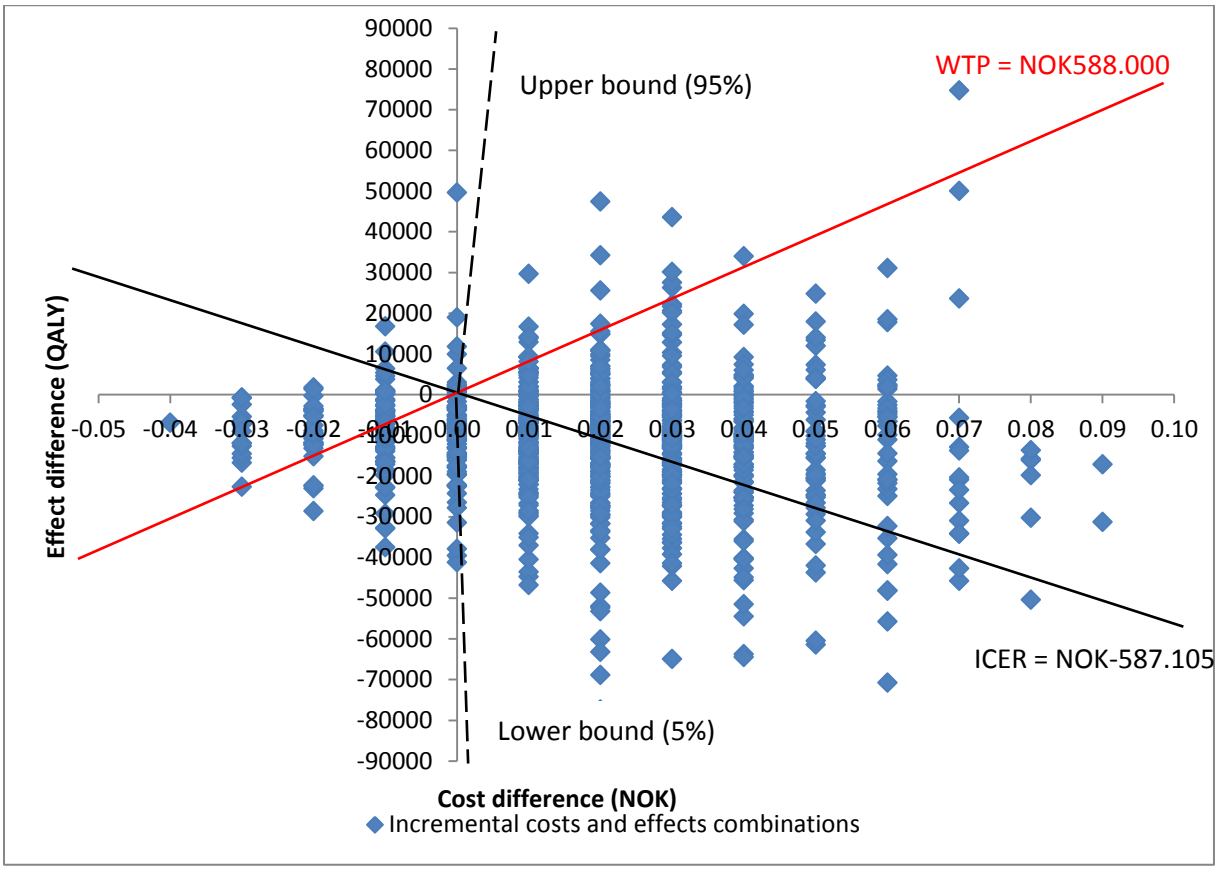

Figure 7: Cost-effectiveness plane of joint incremental cost/effectiveness points of 1000 Monte Carlo simulations, according to mode of SSI prevention with the ICER point estimate (black line), the threshold value of willingness-to-pay (WTP) at NOK588.000 (red line), and upper and lower bounds of the ICER estimate confidence interval (dashed lines).

The cost-effectiveness acceptability curve (CEAC) includes indicators of the ranges of the point estimates standard errors. As the curves of the strategies hardly differ for levels of WTP above NOK0 (table 16), only the "no intervention" strategy is visible in figure 8.

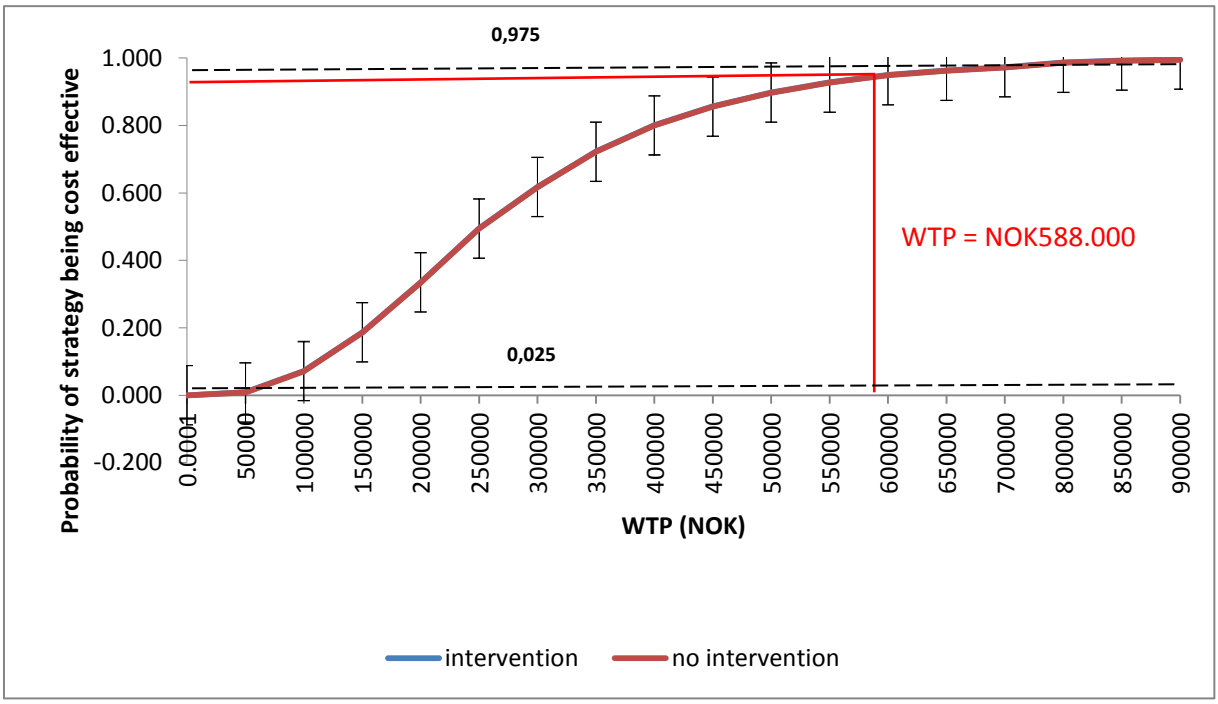

Figure 8: Cost-effectiveness acceptability curve (CEAC). Probability of each of the strategies being cost effective according to levels of willingsness-to-pay. 95% confidence interval upper(0,975) and lower(0,025) bounds in dashed lines.

Table 16: Probabilities of strategies being cost-effective according to willingness-to-pay (thousands).

Strategy	0	50	100	150	200	250	300	350	400	450	500	550	600	650	700	800	850	900
Intervention	0,000	0,009	0,072	0,187	0,335	0,495	0,618	0,723	0,801	0,857	0,898	0,928	0,950	0,963	0,973	0,987	0,993	0,996
No intervention	0,000	0,008	0,071	0,186	0,334	0,494	0,617	0,722	0,800	0,856	0,897	0,927	0,949	0,962	0,972	0,986	0,992	0,995

The cost-effectiveness acceptability frontier (CEAF) indicate that the new intervention was more likely to be cost-effective than the old strategy even at a threshold value of WTP for a QALY of NOK0, and certainly so at the Norwegian Directorate of Health defined threshold value of NOK588.000 (Helsedirektoratet, 2012) (figure 9). However, the probability increment at which it was, was small (table 16).

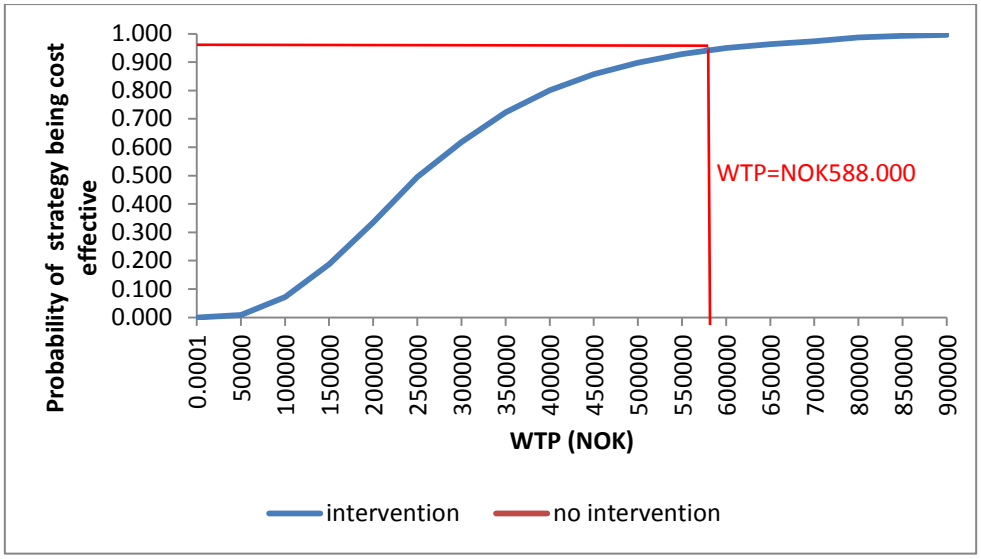

Figure 9: Cost effectiveness acceptability frontier (CEAF).

The expected value of perfect information (EVPI) can be interpreted as the expected cost of uncertainty, or expected opportunity loss, as perfect information can eliminate the possibility of making the wrong decision. The EVPI through this logic places a bound on the value of conducting further research. The EVPI curve is generally at its highest where we are most uncertain about whether to adopt or reject the intervention strategy based on current existing evidence (Briggs et al., 2006). At a threshold WTP of NOK 588.000 the incremental EVPI was NOK849.

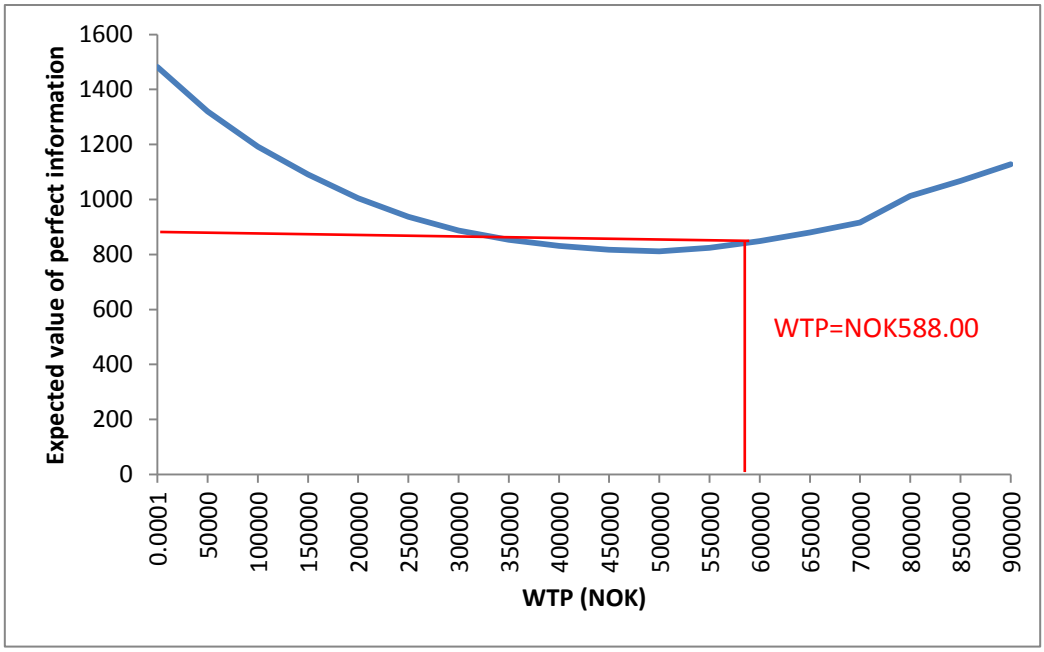

Figure 10: Incremental expected value of perfect information (EVPI) at different levels of willingness-to-pay (WTP). The Norwegian cost-effectiveness threshold of NOK588.000 is indicated with a red line.

7. Discussion

Principal findings

We found no significant differences in predictor variable distribution between the deep and superficial groups as opposed to in the no intervention group. For the comparison of the deep infection and no infection groups, the significantly differently distributed clinical events were getting a new primary HA, having a reoperation, out-patient control and having surgery for hip infection. Similar results were not found in the comparison of the clinical consequences in the superficial and no infection group. We found significant differences between the groups in total hospital costs, and between the deep and no infection group in total hospital days. In the economic model, the new intervention strategy dominated the old, although the results were not statistically significant after incorporating second order uncertainty.

Strengths of the study

In the present study, we were able to use detailed information through patient level data to assess both risk factors and clinical and economic consequences of SSI in a local hospital setting in Norway. To the (limited) extent of our knowledge this has not been done by others before us, and the study results may thus provide the foundation for future exploration into this area of SSI research in Norway.

The present study used the potential to analyze all events one year post the index stay as consequences of the index stay, as contrasted by the methodology of the NOIS (H. L. Lower et al., 2013). This allowed us to look at the various infection statuses as risk factors of future clinical and economic consequences and find that there were more of certain events in a group of infected people than in a group of none infected.

We were able to use QALY weights as an outcome measure. Although estimates were based on previous foreign research, the QALY weights gave us the opportunity to investigate cost/effectiveness within the cost-benefit analysis framework, thus facilitating comparison of our results across a number of domains and therapeutic areas, and additionally to be able to consider our results in the light of generally understood ranges of WTP for a unit of outcome, strengthening the generalizability of our results.

A probabilistic sensitivity analysis of our economic model was performed to account for second order uncertainty, and the results were presented in a cost effectiveness plane (figure 7). We also presented results in a CEAC (figure 8) and a CEAF (figure 9). The input parameter point estimates with standard deviations and choice of probability distribution functions to represent them were presented in table 3. These measures served to present uncertainty and improve transparency.

Weaknesses of the study

We used hospital costs as estimated through the DRG system for our analysis. This can be considered a weakness of the study as using financial costs to represent the costs may lead to erroneous conclusions (Graves, 2004). In Norway in 2008, main diagnosis was miscoded in 36% of the stays surveyed, against 38% in 2003. As a result of the revision, DRG payout sums for all stays totally declined by 5,24% against 5,14% in 2003. Much of the reduction in 2008 was due to regrouping of complicated to uncomplicated DRGs. A complicated DRG provide higher payments to the health providers. Weak code quality thus contribute to reduce confidence that patient statistics can be used as a basis for planning, management and evaluation of health services locally and nationally, and restricts the ability to use patient statistics for medical research (Riksrevisjonen, 2008). We did not consider and thereby did not control for coding practice in the present study. This implies that cost estimates in our results may be upward biased. Whether or not such a bias would influence the significance of differences in costs between groups is questionable, as the same bias can be assumed to have influenced all estimates.

A valid concern that could be raised in the context of the current economic model is the lack of comparison of the new intervention strategy to all potential alternative strategies, as is good practice in health economic evaluation (Glick et al., 2007). We could have adopted a third strategy, known cost/effective in other comparisons, to the comparison to contrast the findings we made during our study, and indirectly position the current strategy in relation to those in the other comparison (Glick et al., 2007). Such course of action might have improved the generalizability of our results.

When treatment benefits are large, all else equal, it is easier to demonstrate cost/effectiveness, and vice versa (Glick et al., 2007). Thus, the magnitude of the observed benefits plays a role in decision advice to be concluded upon given the economic model results. Ideally we would like all our input data to be collected from at least a country specific setting. As we were unable to find national QALY estimates for our infection statuses and as we did not have time to conduct a survey, we had to look elsewhere. Our QALY estimates where attained from studies done in what seemed like similar settings as the present study. This might have impaired the generalizability of our results.

A potential critique of our study design is the adoption and modelling of a one year follow-up of our sample. It is often presumed that because of the presumption that cost/effectiveness ratios are either always improving or worsening, life-time projections of therapies are necessary to understand the impact of medical therapies. This is, however, not necessarily the case, as by the end of a one year trial, the ratio may already be asymptotically approaching a long term cost/effectiveness ratio (Glick et al., 2007).

As there were ambiguities as to the nature of the content and levels of implication of the multimodal SSI intervention strategy over the period of data gathering and analysis, we chose to assume full implementation and adherence to the three pillars of the intervention strategy outlined in the section “The intervention”, from September 2010 until December 2014. An incremental cost of such an intervention was defined and QALY and one year hospital cost estimates attached to the endpoints (ref. Methods: Economic model). This assumption contributed towards increasing the parameter and structural uncertainties of our economic model, and is likely to have contributed to underestimation of the intervention costs.

Results in relation to other studies

From previous research (ref. section on theoretical background) we have seen that the duration of surgery might be an important predictor of SSI in the patient group in question. No variable indicating surgery duration was available in this dataset. Previous research also indicates obesity is a predictor of SSI in this patient group, but again we had no information.

Previous research indicates increased risk of SSI with age less than 60 and a surgery waiting time of above 24 hours (Dale et al., 2011; Westberg et al., 2013). We did not find any correlations between surgery waiting times and presence of infection. In fact, we found that the mean waiting times were lower in the two infection groups than overall (=21,2 hours) and in the no infection group. We further found that none of our SSI patients where below the age of 67.

We could verify the presence of more revision surgeries and reoperations in the infected patient sample than in the one without infection, as stated in previous research (NHBR, 2013).

Plowman et al (Plowman et al., 2001) claims SSI cause 2,5 times longer hospital stay as opposed to no infection. We found that for the totality of one year, those with deep infection had 2 times the hospital days of none infected, and that those with superficial infection had 2 times longer index stays than those without.

Our cost estimates should be compared to estimates found in other studies. Hektoen (Hektoen, 2014) estimated an average one year societal cost of one hip fracture in an elderly population at NOK542.000, disregarding infection status. Our estimate of hospital costs was NOK234.000. Merollini and colleges (Merollini et al., 2013) estimate AUD3.909 (=NOK24.000) in health sector costs per QALY could be saved by preventing SSI, and Jenks and colleges (Jenks et al., 2014) estimated equivalent savings over a two year period at GBP3.214 (=NOK38.000). We estimated a cost saving of NOK11,060 per patient and a gain of 0.02 QALY per patient using the intervention, equivalent to savings of NOK587.105 per QALY, although the ICER in the context of such dominance is formally irrelevant as a decision criteria (Glick et al., 2007). In any case our results indicated dominance of the intervention over the old strategy. This is similar to what Merollini and colleges discovered in their study on SSI prevention in relation to THA (Merollini et al., 2013). Plowman and colleges (Plowman et al., 2001) estimated hospital sector costs of HAI's at 3 times that of no infection. The additional costs of SSI in our estimates where far from the estimates made by Plowman and

colleges, at a 1,8 times increase in the case of deep infection, whereas the superficial infection group had a 1,2 times higher average cost than the no infection group.

Generalizability

It is the opinion of the researchers that the study sample represents the population in distribution of demographics and it can thus be argued to be a representative sample of the patient population most likely to use the therapies evaluated. However, under conditions such as differing population demographics, practice patterns and prizes of medical services and supplies, limitations as to the extent of applicability of the results might be present.

Implications for decision-makers

We estimated the expected value of perfect information (EVPI) at different thresholds of WTP for a QALY (figure 10). At the guiding threshold defined by the Norwegian Directorate of Health in 2012 of NOK588.000, the EVPI was NOK849 per patient. A conservative estimate of 100 annual cases at Bærum hospital would thus suggest an EVPI of 84.900 per year, and this value is to be interpreted as an upper bound on the value of conducting further research at this institution, given these assumptions.

We have further shown and thereby confirmed statements in previous research about the statistically significant increase in one year hospital costs and number of hospital days of patients attaining SSI. The fact that there seem to be increased costs and various clinical consequences associated with SSI, and thus an economic argument for SSI incidence reduction, should prompt decision-makers to further pursue intervention strategies to reduce the incidence of such infections.

Several tests and variables included in the regression models were indicated borderline significant and significant within a 20% level of alpha. When we reject the null hypothesis (usually that a value or difference is equal to 0) we usually conclude there is strong evidence to support our conclusion. Choosing a higher level of alpha for our significance level would increase the probability of rejecting a true null hypothesis, or committing a type 1 error, and at the same time decrease the probability of rejecting a false null hypothesis when the alternative is true, or a type 2 error. When we fail to reject the null hypothesis we know that either the null hypothesis is true or that we have committed a type 2 error. If the alternative

hypothesis is true, the probability that a test result or a regression coefficient lie in the non-rejection zone of the null hypothesis (equal to the type 2 error) is

$$B=P(z<(x-\mu)/(\frac{\sigma}{\sqrt{n}})) \quad (3)$$

and

$$\text{Power} = 1-B \quad (4)$$

When testing for the true statue of reality we usually want a small probability of type 2 error, and conversely a large power. From equations 3 and 4, three things are clear: all else being equal, the farther the true mean is from the hypothesized mean; the smaller the population variance; and the larger the sample size, the larger is the power (Newbold et al., 2013). The sample size (N=239), and the unbalanced distribution of patients in the groups (deep infection=6, superficial infection=3 and no infection=230) might have been inadequate in terms of providing a high enough power to give us results within the 5% level of alpha, and can thus be argued to be a weakness of our study. Had we employed a 20% level of alpha for our decision rule, many more predictors would have been identified given the dataset.

The economic model results fell into a category of findings characterized by the confidence interval upper and lower bounds excluding the cost-effectiveness plane Y-axis, and equivalently when the CEAC intersects horizontal lines drawn at both 0,025 and 0,975 on the CEAC Y-axis. This pattern of findings includes three ranges of WTP, each pointing towards a different conclusion about the underlying strategies. Increasing from negative infinity is the range of WTP where we can be confident the more effective therapy is not good value, decreasing from positive infinity is the range of WTP where we can be confident the more effective strategy is good value, and the range in between where we cannot be certain the two therapies differ. The boundaries of these ranges are given by the 95% confidence interval of the ICER. Thus, for any WTP above our identified upper bound, we can be confident the new strategy is good value, but for the range of WTP below it, we cannot. Had the confidence interval contained only negative values, we could be certain the strategy with the higher effect estimate dominated the other strategy. As our interval contains 0, we

cannot. Finally, had we wanted to explore other levels of confidence we would have calculated new confidence intervals. This could have been applicable in settings where decision makers where interested in other levels of confidence when making decisions (ref. discussion of power above) (Glick et al., 2007). However, as we were confident the new strategy yielded a higher QALY score and the point estimate of the incremental costs of the intervention represented a cost saving, we would still recommend the new strategy as opposed to the old.

Limitations

This study has a number of limitations that should be addressed.

Results of model based economic evaluations are based on a simplification of reality thought to represent true patient pathways. As the results are highly dependent on the structure of the model and its input variables, misspecification of the model could bias the results.

In this dataset the timing of infection detection was not registered. Thus the infection status can only be used to group patients according to those who have had an infection and those who have not, and according to severity of infection. As a consequence of this, the risk factor, consequences and economic analysis would be based on the first occurrence of hip fracture with subsequent treatment with HA the patients experienced (denominated the index event) within the period the data were extracted. This implies that although a patient might experience two primary HA procedures resulting from hip fractures within the one year follow up, and both secondary HA and reoperation during this period, all subsequent events after the index event where considered consequences of the index event, i.e. not imposing risk of SSI in themselves. It also implies that it is impossible to know whether or not length of stay (=hospital days) and hospital costs of the index stay are to be considered consequences or risk factors of infection, given this data.

Additionally, we were limited by the lack of variables informing factors indicated by future research to be significant predictors of SSI in this patient group, as discussed above.

Consequences of increased spread of antibiotic resistant organisms as a consequence of increased antibiotics use was not considered in the present study. The issue is interesting, and should be the focus of future research. With a backdrop of increasing incidences of antibiotic resistant infections internationally (ECDC, 2014), we believe risk factor targeting measures is the way to go for the future rather than an "all for one" prophylactic approach.

We did not define opportunity costs and we did not micro cost procedures in the present study. Depending on the design of the remuneration system and the profitability of the procedure performed, individual institutions may or may not be financially better off from preventing SSI in the short term. With the "Innsatsstyrt finansiering" (ISF) system of funding in Norway (activity based funding), which is based on classifying patient treatments in diagnosis related groups (DRG) - where the level of remuneration is defined as the population wide average cost of treating a certain DRG - on the institution level there will inherently be a wide span in actual resource use in either direction of the mean (Helsedirektoratet, 2014), leaving potential for both profits and losses related to specific procedures. A further discussion into the incentive structures created by the remuneration systems faced by health care institutions is beyond the scope of this thesis. It is worth noting, however, that the societal benefits of improved HAI prevention in the hospital include not only the immediate health benefits and cost reductions of infection prevention examined by this study, but also the long-term benefits of improved survival and the value of future health care expenditures (Dick et al., 2015). When adopting a narrow perspective as has been done in the present study, economic analysis may very well underestimate the social benefits of infection-control programs (Graves, 2004).

Costs of the intervention were based on expert opinion and the study was a cohort study, not a randomized controlled trial, which limits the strength of the results. Scenario analysis of cases with different cost estimates could illuminate this uncertainty but was not conducted due to time restrictions.

As the study is written as a master thesis, rather sturdy limits on duration of the work period needed to be met, limiting the depth of analysis, economic model development and

parameter specification and the ability to further explore uncertainties surrounding the coding practice and intervention content.

Future research

As the incremental EVPI indicated at a threshold WTP of NOK588.000 was NOK849 there might be considerable potential for harvesting the value of future research into this field, considering the relatively large amount of HA treated hip fractures in Norway.

An alternative approach to our poorly powered regression analyses and hypothesis testing is the case-control method. Here, infected and non-infected patients can be matched on the basis of factors thought to influence the outcome variable of interest, and attributing the difference in the outcome to infection status. The approach is attractive in light of the failure of this and other regression based cohort studies to consistently identify risk factors of SSI.

The DRG approximations to costs may be flawed (ref. discussion above). We would therefore recommend future research to attain procedure specific cost estimates based on resource use. Coupled with actual patient QALY scores for the various infection statuses, although the present study did demonstrate significant differences between the strategies in their effectiveness, this would further the accuracy of the cost and effect estimates.

Anderson with colleges seemed to give the same recommendations as the Norwegian Directorate of Health (NDH) in regards to antibiotic (antimicrobial) prophylaxis (Anderson et al., 2014; Helsedirektoratet, 2013).Regarding the judgment required by Anderson on whether or not prophylaxis is indicated, NDH claims that in relation to prosthesis procedures the risk of infection is high, indicating prophylaxis in all cases (Helsedirektoratet, 2013). As was mentioned in the theoretical background, the observed trend of transferring from cemented to uncemented THA'S was based on the assumption that this would decrease the embolization incidence (NHBR, 2013). As the intervention at Bærum hospital turned the other way in their HA procedures, towards using cemented HA's only, an analysis into the effects in terms of changes in embolization incidence would have been interesting. We did not have such information available, neither did we have time to pursue such adverse effects measures of the intervention. Further examination into costs, effectiveness and

adverse events for prevention measures discussed in the literature is possible, as the field is littered with interesting studies of effectiveness of such measures. An overview of the present status of the field is provided by Anderson and colleges (Anderson et al., 2014).

A major drawback of the present study was the fact that at the time of analysis and during the time of data gathering, a varying degree of the intervention measures (previously discussed and presented) had already been implemented. Some were being implemented and some were not implemented. The assumption of full compliance with all the measures discussed in the "The intervention" section, starting September 2010 is thus questionable. Future research would benefit from attaining a clearly defined list of intervention measures implemented and at what time, in order to strengthen the accuracy and applicability of the results.

8. Conclusion

This study is to our knowledge the first study to use patient level data to investigate the cost-effectiveness of an SSI intervention strategy in a local hospital setting in Norway. Through this study we added more weight to the claim that SSI's accumulate more hospital costs than infection free patient pathways, and that SSI's may lead to adverse clinical consequences. An intervention strategy to prevent SSI in this patient population does not have to be costly to be effective. We found that a cost saving intervention generated more QALY's than the alternative. Therefore it would be our perception that Bærum hospital, and other local hospitals like it, will be better off financially and will provide better quality services if their HA procedures include an intervention strategy like the one discussed in the present study. With a backdrop of increasing incidence of antibiotic resistant organisms and antibiotics use, however, more work into illuminating risk factors of SSI is warranted as the facilitating mechanisms of such infections can only be said to be poorly understood today.

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