ECONOMIC ANALYSIS OF SURGICAL SITE INFECTIONS AFTER CEASARIAN SECTION IN NORWAY

Martin Jack Mwamba

University of Oslo, Faculty of Medicine

Department of Health Management and Health Economic

Supervised by:

Professor Ivar Sømbø Kristiansen - UiO

Associate Professor Tron Anders Moger - UiO

Senior advisor: Hanne Merete Eriksen - NIPH

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Martin Jack Mwamba

http://www.duo.uio.no/

University of Oslo

ABSTRACT

Background: Surgical site infection is a common complication after caesarian section. Correct identification of risk factors for SSI is key to the design and implementation of effective preventive strategies. Preventive strategies are costly, however, and should be implemented up to the point where the costs per surgical site infection avoided are less than the benefits gained per surgical site infection. This means that only cost effective strategies should be embarked on.

Objectives: To identify risk factors of surgical site infections and the associated costs and to perform a cost-effectiveness analysis on extending antibiotic prophylaxis to all women undergoing caesarian section in Norway.

Study Group: Women who under-went caesarian section in Norway and were captured by the Norwegian surveillance system for hospital-acquired infections (NOIS) between September 2012 and December 2014.

Methods: Three analyses (risk analysis, cost analysis and cost-effectiveness analysis) were conducted from a hospital perspective. Logistic regression was used for the risk analysis, micro-costing for the cost analysis and decision analytical model for the cost-effectiveness analysis. Surgical site infection avoided was the measure of effect in cost effectiveness analysis. All costs were in Norwegian kroner (NOK, 2015).

Results: A total of 19,796 women who underwent caesarian section were included in the study. The mean age was 31± 4. The rate of surgical site infections was 4.4% or 868 out of 19,796 caesarian sections. Data on 10 variables were analyzed and three of these were identified as independent risk factors of surgical site infections: (i) ASA score greater than III (OR 11.49; p-value 0.05; 95% CI 1.02 – 129.46), (ii) hospitals with bed capacity 250 – 500 (OR 1.44; p-value 0.04; 95% CI 1.01–2.06) and (iii) secondary level hospitals (OR 2.30; p-value 0.00; 95% CI 1.36 – 3.89).

The average cost of caesarian section not complicated with SSI was NOK 52,117. For caesarian section complicated with SSI, it was NOK 124,321. The costs of SSI increased with the depth of infection. For superficial SSI, the costs were NOK 97,301, for deep SSI there were NOK 189,329 and for organ/space infections there were NOK 196,754. Prolonged length of stay accounted for 78% of all the costs and the least costs were for laboratory tests.

The average cost per patient with the current antibiotic guidelines was NOK 55,634 while it was NOK 55,231 if the antibiotic prophylaxis is given to all women undergoing caesarian section. The proportion of women with SSI was 5% and 4% for the current and extended guidelines respectively, representing a cost saving of NOK 40,300 per avoided SSI. The difference in costs and effects between the extended guidelines and the current guidelines was NOK 403, (95% CI: NOK -900 to NOK150) and 0.01, (95% CI: 0.0025 to 0.012).

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Martin Jack Mwamba

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ACRONYMS AND ABBREVIATIONS

ASA	American Association of Anesthesiologists
CDC	Center for Disease Control
CS	Caesarian section
CSR	Caesarian Section Rate
HAI	Health-care Associated Infections
ICER	Incremental Cost Effectiveness Ratio
LOS	Length of Stay
MRSA	Methicillin Resistant Staphylococcus Aureus
NHB	Net Health Benefit
NIPH	Norwegian Institute of Public Health
NMB	Net Monetary Benefit
NNIS	National Nosocomial Infection Surveillance System
NOIS	Norwegian Surveillance System for Health-care Associated Infections
NSB	Net Social benefit
OECD	Organization for Economic Co-operation and Development
PDS	Post Discharge Surveillance
RHT	Regional Health Trust
SG	Standard Gamble
SSI	Surgical Site Infection
STI	Sexually Transmitted Infections
VRE	Vancomycin Resistant Enterococcus
WHO	World Health Organization
WTP	Willingness To Pay

1. Introduction

In Norway as in many other countries, the caesarian section rate (CSR) has been rising from 2.5% in 1972 to 17 % in 2012[1] (Figure 1). A high CSR, defined as the number of caesarean deliveries over the total number of live births[2] has resource implications for the health care sector. For example, the WHO report (2010) estimated that the Norwegian CSR of 17 % translates into 928 unnecessary caesarian sections (CS) with an estimated cost of $ 1,915 956[1].The rising CSR are also associated with a high risk of maternal complications such as surgical site infections (SSI)[2]. According to Mangram et al[3] a patient with an SSI has a postoperative surgical infection localized to the part of the body where the surgery took place. Such a patient is likely to suffer from the cost of human suffering and pain and lose out on productivity. On the health care sector, SSI imposes considerable economic burden in terms of extended hospital stay (LOS), nursing care costs, extra diagnostics and medical/surgical interventions costs[4].

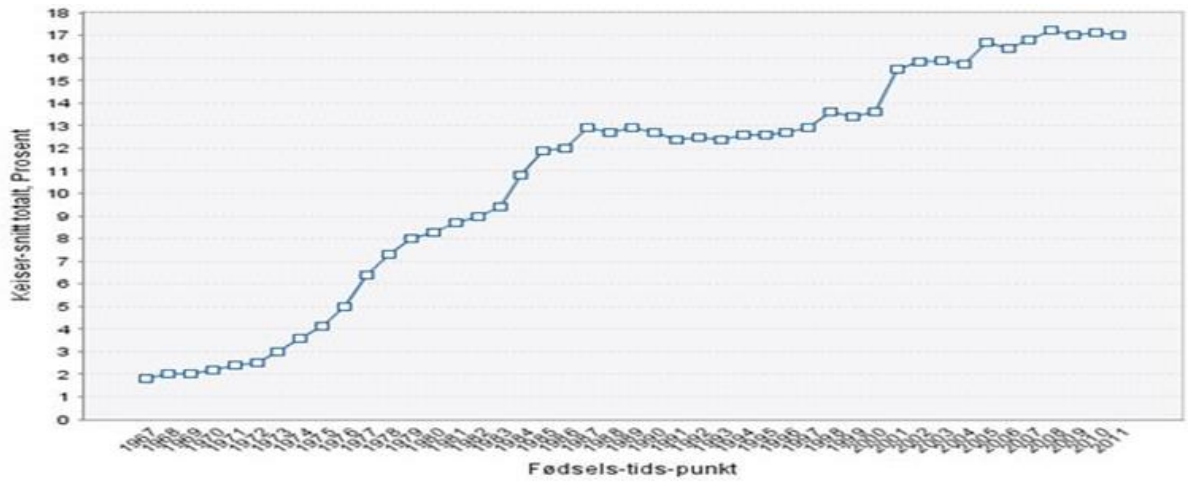


Figure 1: Increase in proportion of caesarian sections in Norway: 1967 – 2011

(Source: Folkehelseinstituttet, http://www.fhi.no/artikler/?id=52705)

Understanding the risk factors for SSI and the costs associated with it is fundamental to the development of effective preventive strategies. One such strategy is the use of antibiotic prophylaxis in caesarian section. However, since there are economic consequences to the implementation of such preventive strategies', conducting cost-effective analysis helps health care decision-makers to choose cost-effective programs.

[1] Source: *World Health Report (2010) Background Paper, No 30*

From the Norwegian Health care perspective, the exact extent of the economic burden of SSI after CS on the nation's health care system is unclear. What seems clear though is that SSI following CS imposes significant costs on the Norwegian health care system. In order to ascertain the exact extent of the economic burden these infections impose on the health care system, a comprehensive analysis of costs associated with SSI after CS needs to be conducted. By conducting a cost analysis, this study will generate cost estimates that might ultimately influence health care policy decisions such as guideline formulation and infection prevention strategies in Norway. Secondly, even though this study may not be considered comprehensive enough owing to its limitations in perspective, costs inclusion and method of cost estimation, it will add to the knowledge of cost analysis of SSI that follows CS in Norway and continue as a foundation on which future studies on costs associated with SSI can build upon.

This study will focus mainly on health care related costs of SSI after CS. Societal and patient related costs are beyond the scope of the study though factors (societal and patient related) that are pertinent to the study will be brought forward and discussed whenever necessary.

The study is divided into three parts – risk analysis, cost analysis and cost effectiveness analysis. It is outlined as follows: Chapter 2 discusses the theoretical background of the study. Chapter 3 presents the data and methods used in the study. The findings of the study are then presented in the chapter on results (chapter 4). Chapter 5 discusses these findings and the study ends with reiterating the importance of identifying the risk factors of SSI after CS, estimating the costs associated with SSI after CS and performing a cost-effectiveness analysis for preventive strategies.

2. Theoretical Background

In this chapter I present the theoretical foundations of the study. The basics of CS such as the rate, indications and complications of CS are discussed first. Followed thereafter is a discussion on SSI as one of the post-operative complication. Then the cost consequences of SSI after CS are deliberated before the chapter ends with a discussion on methods of economic evaluation.

2.1 Caesarian section

Cesarean delivery is defined as the delivery of a fetus through a surgical incision made through the abdominal wall (laparotomy) and the uterine wall (hysterotomy)[5]. This definition ignores the status of the fetus, whether alive or dead and only considers the location of the fetus. From an anatomical point of view, the surgeon has to cut through three major layers of the abdomen before reaching the baby (Figure 2).

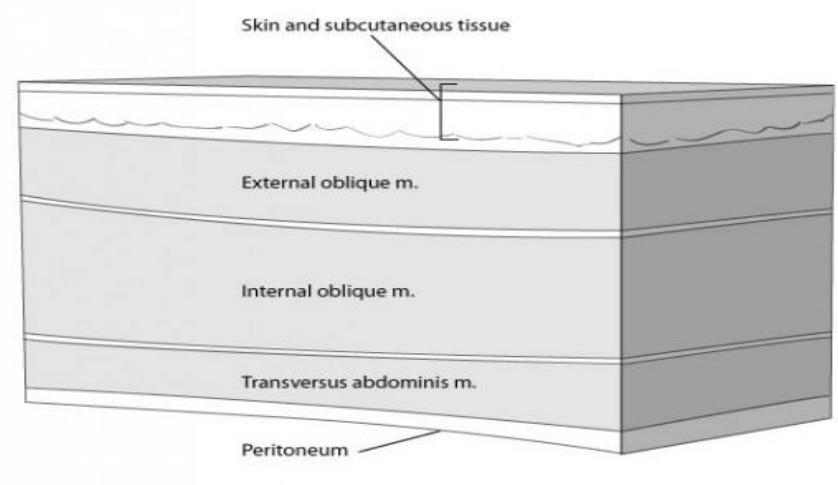


Figure 2. Anatomical outline of the layers of the abdominal wall

(Source:http://stefanwirawan1.hubpages.com/hub/Instant-anatomy-Anatomy-lecture-made-easy-Anterior-abdominal-wall#slide6380902)

The first layer to be incised is the skin with the subcutaneous tissue and fascia underneath it. The second is a layer of muscles and then the lining of the abdominal cavity, called the peritoneum, which encloses the abdominal organs. The uterus lies right below the peritoneum. It is a muscular sac enclosing the baby and the surgeon makes either a transverse or vertical incision through it to deliver the baby[6].

Cesarean sections are generally defined as elective when they were performed at least 8 hours after the decision to operate is made[7]. Usually this is made before the onset of labor and with intact membranes. Conversely cesarean sections are defined as emergency when not planned[6-9]. Often this happens during labor or with ruptured membranes.

2.1.1 Caesarian section rate

Over the years the global rate of CS has been steadily increasing and this increase has generated a number of controversies, among them is the issue of what the optimum rate of CS is. Many explanations have been put forward in an attempt to explain the CS inflation: Improved surgical practice, increasing maternal age, more multiples babies, maternal request, the hostile obstetric medical-legal environment and physician convenience and economic benefit of care givers[1, 10].

Global concerns over the steady increase in the rate of CS are mainly derived from the fact that higher CS rates do not seem to provide additional health gains but may increase maternal risks, have implications for future pregnancies and have resource implications for health services[2]. For this reason, the WHO set an upper threshold of 15% CSR. Although the global CSR are estimated around 1.8% – 42%, the rates are unevenly distributed and follow the health care inequity pattern of the world with low rates in low income settings, and moderate or high rates in middle and high income settings[2]. In Norway, a similar trend is seen with the CSR varying widely (6% to 20%) between different obstetric departments[7]. The variations are explained by the fact that larger hospitals are often referral hospitals, which receive many mothers with increased risk of complications and thus increased need for cesarean delivery[2]. On a global scale, comparable studies with other countries reveal that the Norwegian CSR lies in the lower segments[2].

2.1.2 Indications for caesarian section

Indications for caesarean delivery vary depending on the clinical situation, resource availability and individual surgical management techniques[5]. Initially CS was clinically indicated as a lifesaving procedure for the mother and the baby. However, non-medical indications centered mostly on legal and socio-economic motives have in the recent past been recognized as acceptable indications for performing CS[1, 11]. Considering that there are risks and benefits involved, these new indications have stirred an ongoing debate among medical

[2] Adopted from http://www.fhi.no/artikler/?id=52705. Last viewed 18.02.2015

professionals and women themselves. Caesarian delivery on maternal request (CS – MR) for instance raises a lot of emotive, contemptuous and economic questions to health care policy makers, medical professionals and the women groups[1, 11]. Whereas medical professionals are obliged to perform CS when medically indicated and women have the right to choose the method of delivery, health care policy makers consider the cost effectiveness of performing an extra CS.

Even though indications for CS have evolved tremendously, the two most frequent indications for emergency cesarean deliveries in Norway are fetal stress and failure to progress, while the most frequent indications for elective CS are previous cesarean delivery and maternal request[1] (Table 1).

Table 1 Distribution of First Choice indications for caesarian section in Norway (N=2778)

	Type of sections (n = 2747)		*Parity (n = 2692)*	
Indication	*Emergency (%)*	*Elective (%)*	*Para 0 (%)*	*Para 1+ (%)*
Fetal stress	98.2	1.8	63.5	36.5
Failure to progress	87.8	12.2	66.2	33.8
Previous cesarean delivery	12.4	87.6	0	100
Breech ≥34 wk (guidelines for vaginal birth not complied with)	42.4	57.6	67.8	32.2
Maternal request	10.1	89.9	29.4	70.6
Preeclampsia	78.1	21.9	65.0	35.0
Failed induction	75.7	24.3	71.3	28.7
Abruptio placentae	100	0	42.0	58
Previous complicated delivery	14.0	86.0	0	100
Placenta previa	61.8	38.2	28.3	71.7
Transverse lie	52.8	47.2	24.5	75.5
Intrauterine growth restriction	35.7	64.3	48.8	51.2
Preterm breech <34 wk	84.8	15.2	43.8	56.2
Macrosomia (estimated weight ≥4500 g)	21.4	78.6	25.9	74.1
Previous operation on uterus	12.0	88.0	37.5	62.5
Chorioamnionitis	95.5	4.5	54.5	45.5
Previous rupture of anal sphincter (3-4 degrees)	5.0	95.0	0	100
Previous perinatal death/morbidity	5.6	94.4	0	100
Cord prolapse	100	0	26.3	73.7
Bleeding of other reasons	78.6	21.4	42.9	57.1
Eclampsia	100	0	60.0	40.0
Rhesus immunization	40	60	0	100
Diabetes mellitus	20	80	80.0	20.0
Other indications	33.6	66.4	52.2	47.8
No indication choice	26.7	73.3	62.5	37.5

(Source: Volume 188, Number 4 Kolås et al. 865 Am J Obstet Gynecol.)

2.1.3 Surgical site infection as a complications of Caesarian Section

Despite CS being viewed as a lifesaving procedure for both mother and baby, the study by Håger et al[7] revealed that cesarean delivery is associated with complications in one of five women in Norway. Complications of CS can be maternal or fetal or affect both. Maternal complications are divided into intraoperative complications and postoperative complications. In the postoperative period, CS can complicate in many ways but the predominant complications are hemorrhage, thrombo-embolic complications and infections.

Post-operative infections can further be divided into Surgical Patient Infections (SPI) and SSI. According to Horan et al[12], SPI are systemic and remote complicating infections that follow an operative procedure, and for this reason they are not classified among SSI. On the other hand, SSIs are defined as infections involving areas that were incised, opened or manipulated during an operative procedure[12].

2.2 Surgical Site Infections

Surgical site infections are a heterogeneous group of complications that follow surgical interventions. The heterogeneity can be shown by the many ways SSIs are classified. The first is the ASEPSIS score system, which is based on the clinical signs of infected wounds. It is an acronym for Additional treatment, Serous discharge, Erythema, Purulent exudate, Separation of deep tissues, Isolation of bacteria and Stay as inpatient prolonged over 14 days[13]. The Altemeier classification system is another classification system based on the level of risk of infection and classifies surgical wounds as clean, clean- contaminated and contaminated or dirty. The CDC classification is based on anatomical location and pathophysiological changes and is endorsed by the various National Nosocomial Infections Surveillance systems (NNIS) including the Norwegian Surveillance System for Healthcare-Associated Infections (NOIS) [12, 14-17].

Surgery specific classification of SSI considers independent surgical procedures such as SSI after caesarian section, cholecystectomy, hip replacement, cardiac surgery etc. The study focus is on SSI after CS. SSIs are also defined with a time frame in mind, during initial admission (often 2-3 days post-op), at 30 days post-operative period or at one year if an implant is in place. Further classification considers the type of bacteria involved with gram positive cocci (Staphylococcus aureus and Streptococcus pyogenes) and gram negative bacilli (Enterobacteriaceae) being particularly classified as the most common and virulent strains[18].

Adopting a reliable and consistent classification for SSI is crucial for three reasons: (i) It defines a common language and provides a standardized assessment tool for physicians or infection control practitioners to assess and classify SSI, (ii) It enables the surgical team to provide the appropriate surgical care and (iii) it enables accurate estimation of SSI associated costs since costs are directly related to the type of infection. Based on these reasons, SSI after CS will be discussed under the CDC classification[3].

2.2.1 The CDC classification of SSI

The CDC (1992) classification of SSI distinguishes incisional SSI from organ/space SSI (Figure 3). Incisional SSI are further divided into superficial incisional SSI, comprising only the skin and subcutaneous tissue and deep incisional SSI, involving deep soft tissues of the incision (fascia and muscle layers)[12].For superficial incisional SSI, the infection, in addition to involving only the skin and subcutaneous tissues must occur within 30 days after the operation. Additional criteria for deep incisional SSI include infections occurring 30 days into the post-operative period without implants or within one year if implants are in place.

The term Organ/space SSI encompass infections in any anatomical organs or spaces besides the incision that were either opened or manipulated during the operation[12]. With regards CS, endometritis and intra-abdominal abscesses are typical examples of an organ/space SSI. These are site-specific SSI with the same additional time criteria as deep incisional SSI[12] Whilst the CDC classification of SSI was done for surveillance purposes the study will in addition use it for the purpose of analyzing cost estimates of SSI following CS.

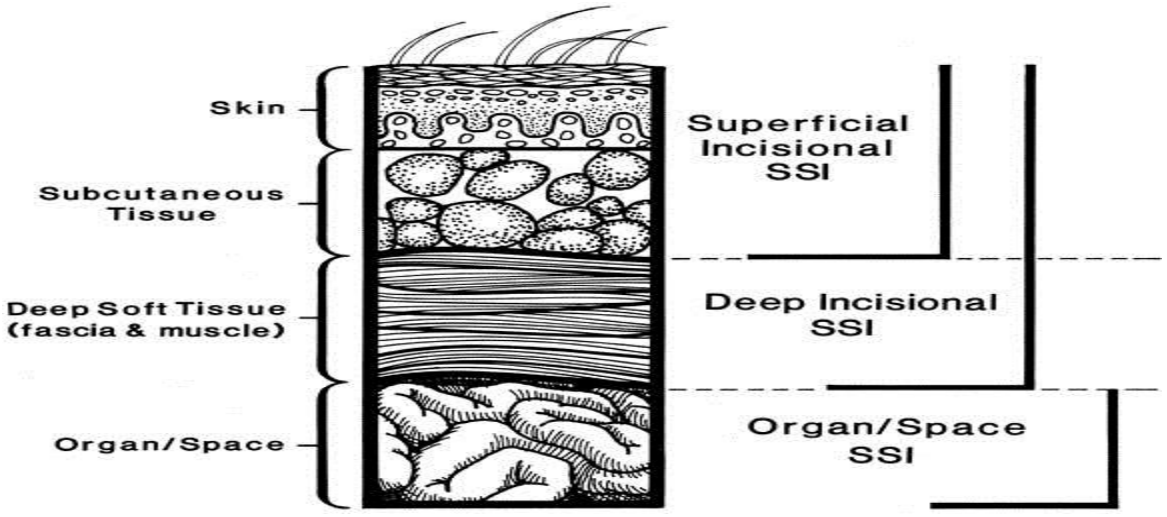


Figure 3 Schematic of SSI anatomy and appropriate classification

(Source: Infection Control and Hospital Epidemiology, Vol. 13, No. 10 (Oct., 1992), pp. 606-608)

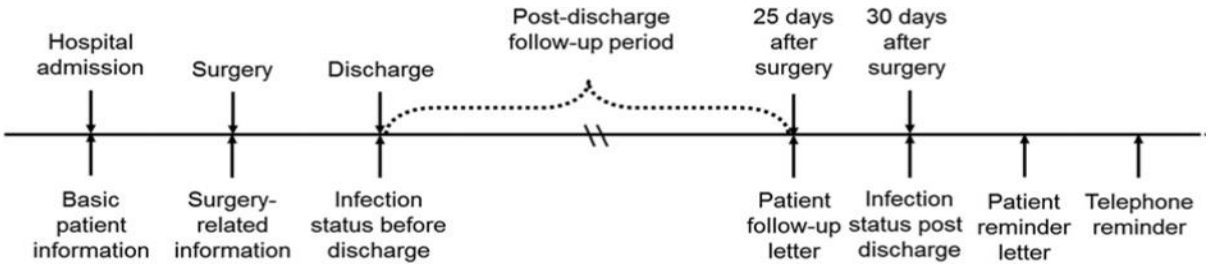
2.2.2 Norwegian Surveillance System for Healthcare-Associated Infections (NOIS- SSI)

The NOIS register is a mandatory surveillance system for HAI in Norway. The NOIS system aims to conduct a systematic collection, analysis, interpretation, and dissemination of data about the occurrence of SSI after CS in the hospitals[19]. In additional to CS, the NOIS-SSI register has the following infections under its surveillance: coronary bypass, hip arthroplasty,

cholecystectomy and colon surgery.

It is founded on the CDC's NNIS system and became set up in Norway as a regulatory system in 2005. By NOIS regulation, all Norwegian hospitals participate in the surveillance system and govern the collection, collation, storage and use of data, and the submission of data to the Norwegian Institute of Public Health (NIPH)[20]. The three key features of NOIS are (i) It is national and mandatory, and therefore provides a broader and better overview of the country's infection status, (ii) utilizes highly automated data collection and harvesting systems and (iii) the NOIS has an active post discharge surveillance (PDS) for 30 days (1year for implants) after surgery[20]. Data are collected before, during, and 30 days after CS (Figure 4). The importance of this timing is twofold. To begin with, most SSI appears after discharge from hospital. Urban et al[21] estimates these post discharge infections to range from 47% to 84 %. Secondly, SSI diagnosed after discharge were more costly to treat than SSI diagnosed during the initial admission period[22].

Geographically, Norway is divided into four Regional Health Trusts (RHT) or Regionalt helseforetak (RHF) (Appendix 1). All the four RHT fall directly under the Ministry of Health and Care Services. The Helse Sør-Øst RHF is the largest of the four RHT and others include Helse Nord RHF, Helse Vest RHF and Helse Midt-Norge RHF.



(Source: American Journal of Infection Control xxx (2013) 1-6)

Figure 4 Points in time for collection of information during 30-day follow-up in NOIS-SSI.

All hospitals in Norway have electronic Patient Administration Systems (PAS) and Computerized Infection control Modules (ICM) that harvest data from the hospitals' existing systems or the surgery scheduling systems. Even though these systems harvest almost all the background and explanatory variables, the outcome variable - infection status, is manually entered by the health staff[20]. To ensure compliance, the NOIS register is a regulatory instrument and all hospitals in Norway are by law required to submit data to NIPH. The NOIS-SSI has around 162 variables but not all are relevant to the study, therefore only 10

independent variables will be used.

Studies show that surveillance of SSI after CS with feedback to the surgeon results in reduced infection rates (20%-30%), aids in identifying and evaluating preventive measures and is the basis for evidenced based strategies in infection control[3, 19, 20, 23, 24]. Therefore the NOIS report on SSI after CS is fed back to the hospitals after undergoing a quality assurance at NIPH. The hospitals in turn are expected to convey their own data back to the departments, surgeons, and hospital administrators.

2.2.3 Risk factors for SSI after CS

In the strictest terms, a risk factor refers to a variable that has a significant, independent association with the development of SSI after a specific operation[3]. Risk factors are therefore identified using multivariate analysis. In general terms, the use of the term risk factor has been extended to include both patient and operational features which are not necessarily independent predictors but are associated with the development of SSI in bivariate analysis.

Knowledge of risk factors is fundamental to the prevention of SSI and the development of cost saving strategies in health care systems. Risk factors for post-CS SSIs can be classified as intrinsic or extrinsic. Intrinsic risk factors are patient related while extrinsic risk factors are related to the obstetric and operational factors[9]. A review of past studies on risk of SSIs after CS reveals that a multitude of factors predispose women to developing post-CS SSI[6, 8, 24, 25]. Intrinsic risk factors include, among others, age, race, body mass index (BMI), American Society of Anesthesiology (ASA) score, gestational diabetes, Sexually Transmitted Infections (STI) and use of alcohol and tobacco. Extrinsic factors are even more numerous and include obstetric related: previous CS, number of vaginal examinations before operation, duration of labor, gestational age at delivery and presence of vaginal discharge or bleeding, Operational related: urgency of operation (elective or emergency), type of skin and uterine incisional (vertical or lower segment), type of skin closure (staples or sutures), receipt of antibiotic prophylaxis, type of anesthetic technique (General or regional anesthesia), volume of blood loss and level of surgeon and type of hospital.

Another way of assessing the risk status of women undergoing caesarian deliveries is the use of the NNIS risk index. The CDC's NNIS risk index is an internationally recognized system of stratifying the risk of post-CS SSI. It is based on three major factors: (i) the American Society of Anesthesiologists' (ASA) classification of the patient's physical status >2 (ii) the

duration of the surgical procedure > 75th percentile (1 hour for CS) and (iii) the wound classification system that reflects the degree of contamination >2 (contaminated or dirty). The risk of SSI increases with increasing risk index score[9]. For CS, modified wound classifications are used that take into consideration membrane rupture and presence of labor. According to Tran[26] "Cesareans are classified class I if there is no rupture of membranes or labor, class II if there is less than 2 hours of rupture of membranes without labor or labor of any length with no rupture of membranes, class III for rupture of membranes greater than 2 hours, and class IV for purulent amniotic fluid". Rupture of membranes duration is the interval, in hours, between recorded timing of rupture of membranes and surgical incision[26].

2.2.4 Prevention and treatment of SSI after CS

The possibility of developing a post-CS SSI is represented by the proportion of caesarian deliveries that result in infection and conventionally this is expressed in percentage[27]. In Norway, Eriksen et al[24] found that the incidence rate of SSI after CS in Norway was 8.3 % in 2007. Estimating the rate of SSI after CS is important for assessment of merits and demerits of adopting caesarean section as a delivery method, and for evaluating the choice of preventive measures[24].

There exist several preventives strategies against SSI after CS and the provision of antibiotic prophylaxis is one of them. However, not every patient due for CS receives antibiotic prophylaxis in Norway and studies show that around 25% of CSs are not given antibiotic prophylaxis[28]. The general practice in most Norwegian hospitals is that antibiotic prophylaxis is not given in elective CS. The Norwegian guidelines in clinical obstetrics recommend the use of antibiotic prophylaxis in the form of a single dose of ampicillin or first generation cephalosporin in emergency CS or special situations such as prolonged operation or excessive hemorrhage. This is contrary to the Cochrane guidelines which recommend antibiotics prophylaxis to all CS regardless of urgency, risk or duration of surgery.

The management of SSI after CS depends on the depth of the infection. Because superficial incisional post-CS SSI involve only the skin and subcutaneous tissues, the common interventions needed are the removal of sutures and drainage of the infected area, with or without antibiotics[29]. The prime cost drivers are relatively few and include costs for GP visit, wound dressings and occasionally cost for antibiotics and analgesics. Superficial incisional post CS SSIs are by far the most common type encountered in clinical practice[9, 14].

Deep incisional post-CS SSI affect the facial and muscles and because of the depth of the infections, these SSI require repeated debridements and sometimes extensive wound reconstruction surgeries[29]. Likewise, deep incisional post-CS SSI attracts more costs than superficial incisional SSI. Additional costs arise from extended re-hospitalization, increased diagnostic tests and repeated surgical interventions[29].

The organ/space post-CS SSI are by far the most severe and attract more costs[29]. These infections require prolonged hospitalization and often multiple re-operations[29].

2.3 Economic burden of SSI after CS

There exists a uniform recognition that SSI presents a major economic cost and high price of human suffering[29]. Indeed studies have demonstrated a clear relationship between SSI on one hand and the amount of medical interventions and associated health-care costs on the other[15, 30-32].

2.3.1 Cost implications of SSI after CS

The health care costs attributed to SSI following CS are significant. In England a study by Jenks et al[33] reveal that a total of 4,694 hospital bed days, equivalent to 6.4 bed days per day were lost due to SSI during the period April 2010 and March 2012. Of these 142 days were attributed to post CS SSI. During the same period, a total of £2, 491 424 was aggregately attributed to SSI with £97, 021 attributed to post-CS SSI[33]. In the United Kingdom (UK) Mugfold et al[34] estimated that costs per day and for each patient were, respectively, £56 and £716 higher for women with infection than for those without infection. In the United States, costs of SSI following CS are estimated at $3400 - $3700[31].

The trend is likely to be the same throughout the Scandinavia. For instance a report from Denmark, shows that the cost of care for all SSIs in general consumes 0.5% of the annual hospital budget[29]. In Norway, the exact cost of these SSI are not yet fully known, at least to my knowledge, though with the CSR approaching 17%, they are likely to be substantial.

SSI adds to hospital costs in several other ways. For example, the prolonged use of antibiotics as part of the management of some SSI exposes women to the risk of developing antibiotic resistant SSI that cannot be treated by the commonly used antibiotics. This may occur because prolonged antibiotic use causes bacteria to metamorphose into drug – resistance strains such as Methicillin Resistant Staphylococcus Aureus (MRSA) and

Vancomycin Resistant Enterococcus (or VRE). The treatment of these drug resistance strains demands that women stay even longer in the hospital and undergo more repeated diagnostics and therapeutic interventions.

2.3.2 Methods for estimating costs associated with SSI after CS

There are two common methods of estimating costs associated with SSI after CS. The first is the top down method like the DRG system, which provide cost estimates for an average patient. The second is the bottom up method or micro costing. With this method, each procedure is identified, quantified and valuated to represent total health care resource usage. In the study, both methods are used.

Fry et al[29] states that using hospital charges is a common but flawed method of estimating those additional supplies and personnel required for care of the SSI. Besides the use of hospital charges, most studies use the mean costs per bed day instead of the marginal cost[29]. While the former is easy to calculate, the later provides more accurate way of estimating that additional costs of SSI after CS. Despite the shortcomings, most studies still use hospital charges to liberally estimate costs[21, 29, 35, 36]. Sources of cost information include hospital finance departments, financial databases or the accounting systems and previous studies. Other sources use clinical pathways that reveal and itemize resources consumed by women as they transit through the health care system. Market prices and national guidelines are often applied to these cost estimates.

2.4 Economic Evaluation of Costs of SSI after CS

Decision making in health care involves both costs and consequences. Drummond et al[37] thus define economic evaluation as "the comparative analysis of alternative courses of action in terms of both their costs and consequences". Implicitly economic evaluation is a tool for identifying, measuring, valuing and comparing costs and consequences of alternative actions[37].

2.4.1 Economic Evaluation

The term economic evaluation is rightly used when the study compares at least 2 alternatives and includes both costs and consequences of the alternative courses of action[37]. Table 2 illustrates the difference between partial economic evaluations, outcome description, cost

description, cost – outcome description, effectiveness evaluation, cost analysis and full economic evaluation: cost effectiveness, cost benefit and cost utility analyses.

Table 2. Distinguishing characteristics of health care evaluation

	Are both costs and consequences of the alternatives examined?		
	NO		YES
Is there comparison of two or more alternatives?	Examines only consequences	Examines only costs	Examines both consequences and costs
NO	PARTIAL ECONOMIC EVALUATION		
	1 A. Outcome description	1B.Cost description	2. Cost- Outcome description
	PARTIAL ECONOMIC EVALUATION		FULL ECONOMIC EVALUATION
YES	3 A. Efficacy or Effectiveness evaluation	3B.Cost Analysis	4. Cost effectiveness Analysis Cost Benefit Analysis Cost Utility Analysis

(Adopted from Drummond et al[37]: Methods for Economic Evaluation of Health Care Guidelines.)

Regarding the question of antibiotic prophylaxis in CS, economic evaluation enables decision makers to weigh the costs and consequences of extending the provision of antibiotic prophylaxis to all women undergoing caesarian section regardless of their risk status. Decision makers can then use the empirical evidence provided by economic evaluation to decide whether it is cost effective or not to include all women in the guidelines given the data.

Results from a study can differ depending on the perspective adopted. For example, one guideline may be considered cost effective when viewed from a health care perspective and not cost effective when considered from a societal perspective. For this reason Drummond et al[37] recognize five main perspectives of economic evaluation: the individual patient, the specific institution, the target group for specific services , the government in general and the societal perspective[37].

2.4.2 Cost Analysis

Costs can be divided into direct and indirect costs. According to Urban et al.[21], direct costs are those costs that are measured and quantified easily. They include costs for prolonged

hospitalization, readmission, GP visits, additional surgery, prolonged antibiotic therapy, extra radiology and laboratory services etc. Indirect costs on the other hand are difficulty to quantify and include loss of productivity for the patient, relatives (care givers), cost of human suffering and pain, reduction of the quality of life etc.

By definition, cost analysis is the analysis of comparative costs of alternative treatments or health care guidelines[37]. Since cost analysis is a comparative analysis, the comparator in this study is the baseline case of CS without a post-operative complication of SSI. According to Drummond et al[37] costing has two elements: the measurement of the quantities of resource use (q) and the assignment of unit costs or prices (p), and the below equation depicts this relation:

$$\boldsymbol{Costs\ of\ SSI\ after\ CS} = \sum_{i=1}^{n}(\boldsymbol{P_i} \times \boldsymbol{Q_i}) \qquad [1]$$

Where P = price of resources and Q = quantity of resources used, and N = number of cost drivers.

2.4.3 Cost Effective Analysis (CEA)

Full economic evaluation is performed using one or a combination of any of the three types: Cost Effective Analysis (CEA), Cost Benefit Analysis (CBA) and Cost Utility Analysis (CUA). From the cost side, all three are similar. However, the difference stems from the way consequences are valued. The study will only employ CEA since the consequences are measured in a natural unit, which is SSI avoided. Secondly, the options (antibiotic prophylaxis for all CS and antibiotic prophylaxis for high risk CS) have a common effect or consequence (SSI) and lastly the options are independent guidelines of action whose effects do not interfere with each other. CEA is mostly used in budget constrained health care systems with limited range of available options. The results of CEA may be stated either as cost per unit of effect or as effect per unit of cost[37].

Cost-effectiveness is expressed as an incremental cost-effectiveness ratio (ICER), which is the ratio of change in costs to the change in effects. The numerator of the ICER is the marginal difference of the mean cost of each treatment option and the denominator is the marginal mean difference of the effectiveness of each treatment option[37].

$$\boldsymbol{ICER} = \frac{\Delta \boldsymbol{C}}{\Delta \boldsymbol{E}}\ \boldsymbol{or}\ \frac{\boldsymbol{C_{new} - C_{comp}}}{\boldsymbol{E_{new} - E_{comp}}} \qquad [2]$$

In the above expression, ΔC is the change in costs, ΔE is the change in effect, C_{new} are the cost for the new guideline and C_{comp} are the costs of the comparator. E_{new} is the effect of the new guideline whilst E_{comp} is the effect of the comparator.

Incremental costs effectiveness ratios state the additional costs per additional unit of effectiveness and this way, they compare the incremental costs of the new alternative to the best-known alternative or comparator. For decision making in CEA, the ICER is compared to the maximum cost effectiveness ratio or the threshold ratio (R_T). The threshold ratio represents the maximum willingness to pay (WTP) for one unit of effect. The best decision therefore is when the ICER is less than the threshold ratio or WTP, represented algebraically as:

$$\frac{\Delta \boldsymbol{C}}{\Delta \boldsymbol{E}} < \boldsymbol{R_T} \qquad [3]$$

An alternative method to ICER is the Net Monetary Benefit (NMB) of a guideline, expressed as $R_T \Delta E - \Delta C$. The NMB is the increase in effectiveness (ΔE) multiplied by the amount the decision maker is willing to pay per unit of increased effectiveness (R_T), minus the increase in costs (ΔC)[37]. The decision rule with this method is that the best competing guideline should have a positive NMB, thus:

$$\boldsymbol{NMB = R_T \Delta E - \Delta C > 0} \qquad [4]$$

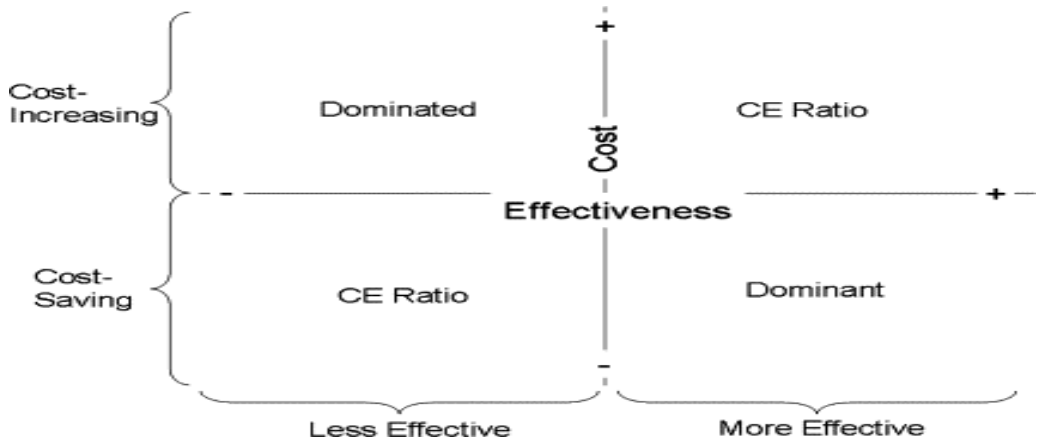
Certainly, if R_T is estimated from individual's actual willing to pay, then the NMB would be equivalent to calculations based on cost benefit analysis[37].

Another method to decision making in CEA is the use of Net Health Benefit (NHB). Using the NHB approach, a guideline is deemed cost effective if:

$$\boldsymbol{NHB = \Delta E - \left(\frac{\Delta C}{R_T}\right) > 0} \qquad [5]$$

This implies that for NHB to be positive, the health gains (ΔE) should be greater than those from investing the same resources in an alternative, marginally cost- effective guideline, with the cost effectiveness ratio R_T.

Finally, the ICER can also be presented graphically as in cost effectiveness plane, with cost difference on the vertical-axis and effect difference on the horizontal-axis. As shown in Figure 5 below:



(Adopted from: David J. Cohen, Interpreting the Results of Cost-Effectiveness Studies. Volume 52, Issue 25,)

Figure 5. The cost effectiveness plane

Depending on the ICER results, the guideline of interest can fall in any of the quadrants. The northeast and southwest quadrants represents situations where the decision depends on the maximum cost effectiveness ratio the decision maker is willing to pay. Represented as a slope between competing guidelines, the maximum willingness to pay has to be compared to the ICER. For the northwest and southeast quadrants, the decision is quite straightforward. The southeast quadrant is the best choice since it represents situations where the intervention of interest is more effective and less costly whilst the northwest quadrant is where the intervention of interest is dominated and therefore not optimal.

Results from studies on the cost effectiveness of antibiotic prophylaxis in caesarian section vary. On one hand, some studies have found antibiotic prophylaxis to be cost effective. For instance, Mugford et al[34] found that the odds of wound infection were likely to reduce by 50% - 70% when antibiotic prophylaxis is given. On the other hand, studies in Norway show that antibiotic prophylaxis was not correlated with the risk of SSI and thus not cost effective[24]. Another study by Eriksen et al[28] showed marginal effects of antibiotic prophylaxis in preventing SSI. They found that antibiotic prophylaxis reduced the odds of developing an infection only in women with superficial infections.

2.5 Study aims and research questions

The aim of this study was to explore risk factors for and estimate costs of SSI following CS in Norway. Since SSI after CS require hospital resources, there is need to estimate how much of the hospital resources are used to treat women with SSIs. Only after estimating these costs are we able to estimate the cost effectiveness of infection prevention strategies. The main

hypothesis was therefore that SSI after CS impose significant economic burden on hospitals. Furthermore, the study will explore the possible significance of antibiotic use in elective CS.

The study addresses the following questions:

1. What are the risk factors SSI after caesarian section in Norwegian hospitals?

2. What are the hospital costs related to SSI after caesarian section in Norway?

3. What are the costs and effects of antibiotic prophylaxis for high versus low risk CS?

3. Materials and Methods

This chapter outlines the data and methods used to identify the risk factors of developing SSI after caesarian section, estimate the costs associated with SSI after caesarian section and analyze the cost effectiveness of extending antibiotic prophylaxis to all women undergoing caesarian section in Norway. All costs were presented in Norwegian Kroner (NOK) (USD 1.00 ≈ NOK 8.00).

3.1 Study Design

The study was a retrospective register study based on the Norwegian Surveillance System for Healthcare-Associated Infections (NOIS) register and questionnaire from clinicians to identify the clinical management (pathway) for caesarian section with and without SSI. The NOIS –SSI register was the main source of data. It was chosen because it provided a sample that essentially included all women who underwent CS and those who developed SSI during the period September 2012 through December 2014. The study period (September 2012 – December 2014) corresponds to the time the NOIS register started recording data for the whole year. Earlier, data were captured only for a three months period each year. In addition, the period constitutes a complete 28 months study period and seasonal variations are likely to be captured. Comparing the NOIS register with the National Patient Register (NPR), which in essence captures all CS done in Norway, shows that the completeness of the NOIS register is rising and was 96.1 % in 2010[20].

3.2 Risk analysis

All SSI reported were physician diagnosed and composed of all the three type: superficial, deep and organ/space infections. For the purpose of identifying the risk factors of SSI after CS, the primary dependent variable was the infection status, dichotomized as SSI or no SSI. The predictor variables were selected based on their clinical and economical relevance to the study. Data from the NOIS register and past studies on the risk of SSI after CS were also considered when selecting the predictor variables. Table 3 summarizes the variables used in the risk analysis.

Table 3. Description and coding of the variables in NOIS register used in the study to identify potential risk factors of SSI after CS.

Variable name	Code	Description of variables
Infection status	SSI No SSI	An ordinal variable with four ordinal points: no SSI, superficial SSI, deep SSI and organ/space SSI. For risk identification this variable was dichotomised into SSI and no SSI.
Age	Number of years	A continuous variable with a range in data set of 14 – 54 years.
ASA score	ASA I ASA II – III ASA IV - V	An ordinal variable that indicates the patient's physical health. Categorized as health = ASA I, Mild systemic disease = ASA II, severe disease but not incapacitating = ASA III, Incapacitating disease =ASA IV and moribund patient = ASA V
Wound contamination	1 = Clean (1 - 2) 2 = Contaminated /Dirty (3 - 4)	A nominal variable representing the degree of contamination with 1 = no rupture of membranes and no labor, 2 = less than 2 hours of rupture of membranes and labor, 3 = rupture of membranes greater than 2 hours and 4 = purulent amniotic fluid.
Pre-operative hospitalization	Number of days	A continuous variable that refers to the number of days a patient stays in hospital before operation.
Urgency of operation	1= Elective 2 = Emergency	A binary variable coded 1 for elective and 2 emergency
Duration of Surgery	1 = < 30 minutes 2 = 31 – 60 minute 3 = > 61 minutes	An ordinal variable measuring the time of the operation and is divided into 3 categories: < 30 minutes, 31 - 60 minutes, 60+ minutes or greater than the 75th percentile (60 minutes).
Antibiotic Prophylaxis	Yes No	Binary variable which is considered as given or not.
Regional Health Trust	Helse Nord RHF Helse Vest RHF Helse Sør-Øst RHF Helse Midt-Norge RHF	Nominal variables that refers to the four health regions of Norway
Hospital size	1 = < 200 beds 2 = 201 – 500 beds 3 = > 500 beds	An ordinal variable referring to the size of the hospital in terms of bed capacity.
Hospital type	1 = Primary 2 = Secondary 3 = Tertiary	A nominal variable for the type of hospital coded 1 (primary), 2 (secondary) and 3(tertiary),

SSI – Surgical Site Infection ; ASA - American Society of Anaestheologists ; NNIS - National Nosocomial Infections Surveillance systems ; NOIS - Norwegian Surveillance System for Healthcare-Associated Infections ; Helse Midt-Norge RHF – Central Norway Regional Health Trust ; Helse Nord RHF - North Norway Regional Health Trust; Helse Sør-Øst RHF – South – east Norway Regional Health Trust ; Helse Vest RHF – West Norway Regional Health Trust.

3.2.1 Statistical Methods for risk analysis

Statistical analyses were carried out using Statistical Software (StataSE 13). The two continuous variables (age and preoperative hospitalization) were tested for normality using the SKtest and graphical methods – histograms and Q-Q plots. A two-sample t-test was carried out to test the mean age differences between those who developed SSI and those that did not. A Mann Whitney test was performed for the median difference in pre-operative hospitalization between those that had SSI and those that did not. For the rest of the nominal and ordinal variables, the Pearson's Chi Square test was used to test for the differences in proportions across the two groups. A binary logistic regression model was used to identify the risk factors for SSI .A goodness of fit test was carried out using the Hosmer and Lemeshow's method. All tests were analyzed as two tailed. Throughout the study, a P-value of < 0.05 was considered significant.

The model: Equation [**6**]

$$\boldsymbol{logit\,(SSI) = \beta_0 + \beta_1 \mathrm{Age} + \beta_2 ASA_{II-III} + \beta_2 ASA_{IV-V} + \beta_3 WC_{\mathrm{clean}} + \beta_4 \mathrm{PH} + \beta_5 UoS_{\mathrm{elective}} + \beta_6 DoS_{31-60} + \beta_6 DoS_{>60} + \beta_7 ABp_{\mathrm{Yes}} + \beta_8 RHA_{vest} + \beta_8 RHA_{\mathrm{nord}} + \beta_8 RHA_{midt} + \beta_9 Hsize_{201-500} + \beta_9 Hsize_{>500} + \beta_{10} Htype_{\mathrm{secondary}} + \beta_{10} Htype_{tertiary}}$$

Where SSI was the binary indicator of infection status, WC was wound contamination, PH was preoperative hospitalization, UoS was urgency of surgery, DoS was duration of surgery, ABp was antibiotic prophylaxis, RHA was regional health authorities, Hsize was hospital size and Htype was hospital type.

The logistic regression model estimated the log odds that a patient develops an SSI as a linear function of explanatory variables. The logit transformation was defined as the logged odds and refers to the ratio of the probability of SSI over the probability of no SSI, thus:

$$\boldsymbol{Odds = \frac{p}{1-p} = \frac{Probability\ of\ SSI}{probability\ of\ no\ SSI} = logit\,(SSI = 1) = ln\frac{p(SSI)}{1-p(SSI)}} \qquad [7]$$

Odds ratios with 95% confidential interval can be calculated by taking the exponential of both sides of the regression equation. From the equation, when predictor variables increase by one unit, the odds increase by a factor of e^{β} all else kept constant. The factor e^{β} is the odds ratio (OR) for the corresponding predictor variables and refers to the relative amount by which the odds of an outcome increase (OR >1) or decrease (OR <1) when the value of the predictor variable increase by one unit.

3.3 Cost analysis

For the cost analysis, the variable infection status was categorized into four (no SSI, superficial SSI, deep SSI and organ/space SSI). This was done in order to estimate and compared costs across these four types of infections. The assumption behind categorizing infection status into four was that costs differed according to the depth of infection while risk was the same for all types of SSI.

To capture direct medical costs associated with SSI after CS, we quantified the use of additional hospital resources by women with SSI during the two periods; the initial period of admission and the readmission period. Costs associated with the initial period were the cost of the initial surgery (NOK 52,117), estimated from the DRG 371 at unit cost of NOK 41,462 and cost weight of 1.257, (DRG price list 2015). This cost was used as a baseline cost and applied to all women regardless of their infection status (no SSI, superficial SSI, deep SSI and organ/space SSI). Mean estimates for length of stay and reoperations were obtained from the NOIS register.

Cost components for the readmission period were obtained from a questionnaire and used to quantify the additional physician time, drugs, laboratory and imaging services consumed by women with SSI in hospitals. A conceptual framework (clinical pathway) that depicted the women' trajectory through the hospital from the day of readmission till the end of the 30-day surveillance period was adopted (Appendix 2). This was designed with guidance from my supervisors at Norwegian Institute of Public Health (NIPH) and the Department of Health Management and Health Economics at University of Oslo. It was then sent to four representative obstetricians/gynecologists in each of the four regional health trusts. The obstetricians/gynecologists were representing the different regions in the NOIS reference group. Since there was considerable variation in the estimates from the gynecologists, the median point estimates were used (Appendix 3).

Unit cost for physician time was estimated from the fee schedule for physician services while the cost per additional day in hospital was obtained from SAMDATA report of 2013. Unit costs for drugs and laboratory/imaging services were obtained from the Norwegian Medicines Agency and lovdata.no respectively. Costs for surgical interventions were estimated per DRG using the 2015 DRG price list (Table 4).

Table 4 Unit cost estimates (2015 Norwegian Kroner (NOK)) for cost drivers for surgical site infections after caesarian section. (September 2012 – December 2014). Norway

Type of cost	Type of unit Cost	Cost (NOK)	Fee/DRG number	Reference
Physician visit	Cost/Visit	340		Fee schedule for physician services
Additional length of stay per day	Cost/episode of care	15,008		SAMDATA 2013 report
Antibiotics*				
Diclocil 500mg	Cost/Pack of 30	171.92		Norwegians Medicines Agency
Gentamicine 80mg	Cost/Pack of 5	193.76		Norwegians Medicines Agency
Metronidazole 500mg	Cost/Pack of 20	800.56		Norwegians Medicines Agency
Analgesic*				
Paracetamol 500mg	Cost/Pack of 20	21.52		Norwegians Medicines Agency
Ketorax 2.5mg	Cost/5 packs of 5	170.60		Norwegians Medicines Agency
Voltaren 50mg	Cost/Pack of 50	127.20		Norwegians Medicines Agency
Pinex forte 30/500mg	Cost/Pack of 20	87.50		Norwegians Medicines Agency
Laboratory				
Blood test (Leucocyte count & CRP)	Cost/test	54.00		Lovdata.no
Culture from infection site	Cost/test	50.00	Fee 704a	Lovdata.no
Image diagnostics				
Ultrasound examinations	Cost/ultrasound	362.00	UL2	Lovdata.no
CT scan	Cost/CT scan	952.00	CT2	Lovdata.no
Surgical Interventions for SSI				
Conservative treatment at policlinic	DRG weight 0.026	1,078	DRG 9140	DRG price list 2015
Readmissions with conservative treatment with Vaccum Assisted Closure (VAC)	DRG weight 0.645	26,742	DRG 376	DRG price list 2015
Readmissions with day surgery	DRG weight - 0,195	8,085	DRG 3770	DRG price list 2015
Readmissions with surgical intervention in hospital care	DRG weight – 0.630	26,121	DRG 377N	DRG price list 2015

SSI = Surgical site infections; DRG = Diagnostic related Groups; * Antibiotics and analgesics were adjusted by the tax rate of 25%.

3.3.1 Statistical methods for cost analysis

The cost model included 6 cost drivers for the four types of SSIs (no SSI, superficial, deep and organ/space SSI).

The Model:

$$\boldsymbol{Costs\ of\ SSI\ after\ CS\ per\ patient} = \sum \boldsymbol{Cost\ for\ initial\ CS} + (\boldsymbol{LOS} * \boldsymbol{Price/day} + \boldsymbol{GP\ visit} * \boldsymbol{hours/day} + \boldsymbol{D.tests} * \boldsymbol{cost/test} + \boldsymbol{Drugs} * \boldsymbol{cost/dose} + \boldsymbol{Surgery} * \boldsymbol{DRG})$$

[**8**]

In the model above, the cost of one additional day in hospital (LOS) was computed on the basis of the mean cost of a day in Norwegian somatic hospitals, physician time (GP visit) was computed with the median number of physicians visits reported by the gynecologists, diagnostic tests including both laboratory tests and image diagnostics (D.tests) were computed on the basis of the reimbursement schedule per test, drugs were priced per dose at market prices after deducting 25% value added tax and costs for additional surgery were based on DRG cost weights.

An independent sample t-test was performed to test the significance of the difference in costs between those with and without infections using cost data based on LOS. The cost data were not normally distributed and the Mann Whitney test would have been appropriate. However, due to the large sample size in the groups (18,928 for those with no SSI and 868 for those with SSI), t-tests were used. A one- way analysis of variance was used to compare and test whether the mean costs for the three types of SSI were significantly different (NOK 45,184 for superficial SSI, NOK 137,122 for deep SSI and NOK 144,637 for organ/space infections). A non-parametric alternative to one-way ANOVA (Kruskal Wallis test) was also conducted to reaffirm the findings of the ANOVA test.

3.4 Cost effectiveness analysis

The 2008 revised Norwegian Society of Obstetrics and Gynecology guidelines recommend that only women considered to be at high risk of developing SSI should receive antibiotic prophylaxis. The high-risk category includes: emergency caesarian sections, long duration of surgery and severe hemorrhage. The current guidelines are compared to extended guidelines where all women undergoing CS receive antibiotic prophylaxis, regardless of their risk status.

The antibiotic of choice for prophylaxis is either ampicillin or a second-generation cephalosporin[38]. In the analysis, ampicillin was used. The acquisition cost for a single dose of 2 grams of ampicillin was NOK 54.80[50]. The type of antibiotic, dose and price were similar for the two groups. The only difference was in the proportion of women receiving the antibiotic prophylaxis. The cost for the initial surgery was NOK 52,117 (DRG 370). The

additional costs for specific types of SSI were obtained from the cost analysis. For superficial SSI, the extra cost was NOK 45,184 whilst for deep SSI it was NOK 137,122. The additional cost for organ/space infection was NOK 144,637 (Table 14).

The measure of health benefit is one SSI avoided represented as 1 = SSI and 0 = no SSI. Transition probabilities were calculated from the proportions in Table 5. For the current guidelines, 63% (12,468 vs. 19,796) were high risk and received antibiotic prophylaxis whilst 18% (3,629 vs 19,796) were low risk and did not receive antibiotic prophylaxis. A total of 3,699 (19%) were lost to follow-up and thus not included in the model. For the high risk, 95% had no SSI (11,811 vs. 12,468), 3.7% had superficial SSI (467 vs 12,468), 0.6% had deep SSI (85 vs 12,468) and 0.8% had organ/space SSI (106 vs 12,468). For the low risk group, 96% had no SSI (3,473 vs 3,629), 3.3% had superficial SSI (121 vs 3,629), 0.4% had deep SSI (17 vs 3629) and 4% had organ/space SSI (18 vs 3629).

For the extended guidelines, the proportions for the high-risk group were similar to those from the current guidelines. The proportions for the low risk groups were adjusted by 40%[3]. Lamont et al[39] estimates that routine use of antibiotic prophylaxis in caesarian section reduces the risk of SSI by 40 – 60%[39]. Estimates for the effects of routine use of antibiotics in caesarian sections were obtained from the literature. Data from the NOIS register was unsuitable for estimating the effects of antibiotic prophylaxis because antibiotic prophylaxis was provided to high-risk patients only. The NOIS data is not randomized hence the use of estimates from literature for the CEA model. With 40% reduction in the proportions for the low risk group with the extended guidelines, the likelihood of no SSI was 97.4% (3,535 vs 3,629) and for superficial SSI it was 2% (73 vs 3,629). The likelihood of developing deep and organ/space infections was 0.3% for each type of SSI (11 vs 3629).

[3] Routine use of antibiotic prophylaxis in caesarian section is estimated to reduce the risk of SSI by 40 – 60% (Lamont et al, 2011).

Table 5 Proportion of women with surgical site infection among the high and low risk groups in Norway September 2012 – December 2014 (N= 19,796).

Antibiotic prophylaxis	No SSI (N= 18,928)	Superficial SSI (N= 629)	Deep SSI (N= 106)	Organ/space SSI (N= 133)	Total (N= 19,796)
Yes (%) (High risk)	11,811 (94.73)	467 (3.75)	85 (0.68)	105 (0.84)	12,468 (100)
No (%) (Low risk)	3,473 (95.70)	121 (3.33)	17 (0.47)	18 (0.50)	3,629 (100)
Missing	3,644 (98.44)	41 (1.16)	4 (0.11)	10 (0.28)	3,699 (100)
Total	18,928 (95.58)	629 (3.21)	106 (0.54)	133 (0.68)	19,796 (100)

3.4.1 Statistical Methods for CEA of antibiotic prophylaxis

Using TreeAge Pro 2015, a decision analytic model was developed (Figure 6). The model looked at the cost effectiveness of antibiotic prophylaxis against SSI in caesarian sections for both high risk and low risk groups. In this cost effectiveness analysis the probability of developing SSI imposed by other risk factors such age, ASA class, urgency of operation and wound contamination were not factored in. Inclusion of all these variables would require a more complicated model than the decision tree employed here. In order to make simple, the CEA considered only the costs and effects of antibiotic prophylaxis with all other variables kept constant. Because of the short time horizon no discounting of costs was done in this study.

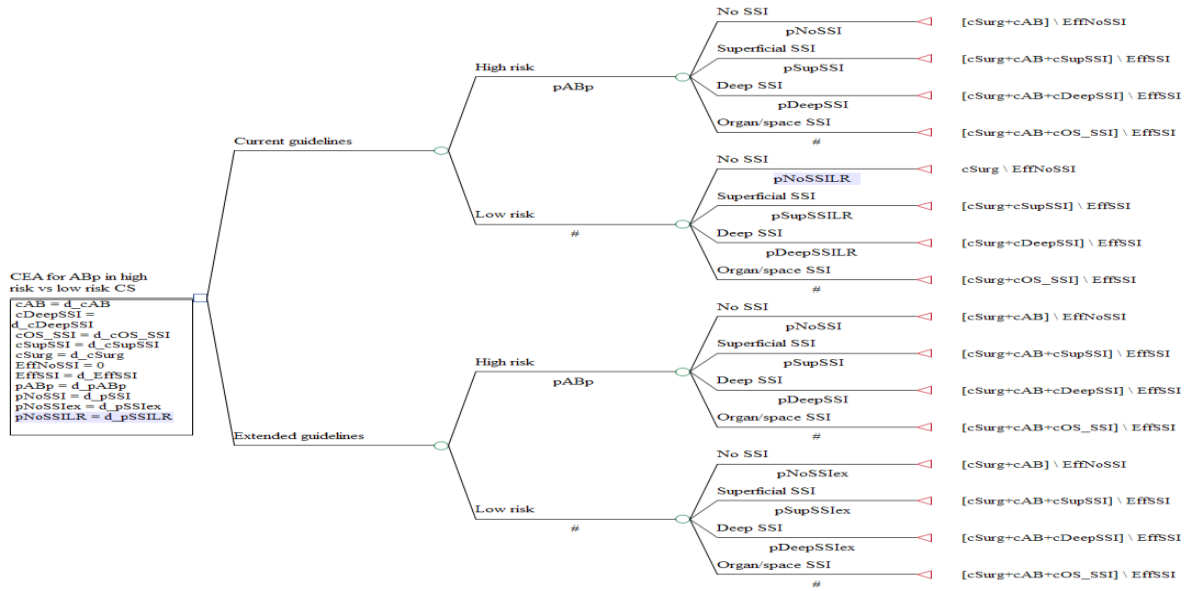


Figure 6 Decision analytic model for CEA of antibiotic prophylaxis in caesarian section.

The costs for women who received antibiotic prophylaxis and developed SSI were calculated as:

$$\boldsymbol{Cost\ of\ SSI = C_{initial\ Surg} + C_{AB} + (P_{sup} \times C_{sup} + P_{deep} \times C_{deep} + P_{o/s} \times C_{o/s})}$$

[9]

Where $C_{\text{initial Surg}} = \text{cost of initial surgery}$, $C_{AB} = \text{cost of antibiotic prophylaxis}$, P_{sup}= the probability of superficial SSI, C_{sup} = Additional cost of superficial SSI, P_{deep} = probability of deep SSI, C_{deep} = Additional cost for deep SSI, $P_{o/s}$ = probability of organ/space SSI and $C_{o/s}$ = Additional cost for organ/space SSI. The cost for women who did not receive antibiotic prophylaxis and did not develop SSI was for the initial surgery only (NOK 52,117), whilst those that received antibiotic prophylaxis had the cost of antibiotic included (NOK 52,117 + NOK 54.8). Table 6 shows the parameters included in the model.

Table 6. Descriptions and valuations of Parameters used in the model (Costs, Effects and probabilities)

Costs	**Value**	**Description**
cAB	54.8	Acquisition cost for antibiotic
cSurg	52,117	Cost for initial surgery
CSupSSI	45,184	Additional costs for superficial SSI
cDeepSSI	137,122	Additional costs for deep SSI
cO/S_SSI	144,637	Additional costs for organ/space SSI
Effects	**Values**	**Descriptions**
SSI present	1	Women with SSI
SSI not present	0	Women with no SSI
Transition probabilities	**Values**	**Descriptions**
pABp	0.63	Probability of receiving antibiotic
$pNoSSI_{HR}$	0.95	Probability of no SSI for the high risk groups
$pNoSSI_{LR}$	0.96	Probability of no SSI for low risk group with current guidelines
$pNoSSI_{LR}$	0.97	Probability of no SSI for low risk group with extended guidelines
$pSupSSI_{HR}$	0.04	Probability of developing superficial SSI for the high risk groups
$pSupSSI_{LR}$	0.03	Probability of developing superficial SSI for low risk group with current guidelines
$pSupSSI_{LR}$	0.02	Probability of developing superficial SSI for low risk group with extended guidelines
$pDeepSSI_{HR}$	0.007	Probability of developing deep SSI for high risk groups
$pDeepSSI_{LR}$	0.005	Probability of developing deep SSI for low risk group with current guidelines
$pDeepSSI_{LR}$	0.003	Probability of developing deep SSI for low risk group with extended guidelines
pOS_SSI_{HR}	0.008	Probability of developing organ/space infections for high risk groups
pOS_SSI_{LR}	0.005	Probability of developing organ/space infection for low risk groups with the current guidelines
pOS_SSI_{LR}	0.003	Probability of developing organ/space infection for low risk groups with the extended guidelines

Uncertainty in cost effectiveness analysis was analyzed by performing probabilistic sensitivity analysis (PSA). Sensitivity analysis examines both structural and parameter inputs in the model to see how they affect the model output. Implicitly, this affects the conclusion of the study. In probabilistic sensitivity analysis, a Monte Carlo simulation with 10,000 simulations was performed using all the distributions in the model for all the 19,796 women. The societal willingness to pay for one SSI avoided was not estimated when performing Monte Carlo simulations. However, reference was made to a study done at Baerum hospital in Norway where the stated willingness to pay for one SSI avoided was NOK 18, 833[4].

The cost of antibiotic prophylaxis and the cost of initial surgery were fixed at NOK 54.8 and NOK 52,117 respectively. The number of women who underwent caesarian section (19,796) and those that received antibiotic prophylaxis (12,468) was large enough to allow their costs to be approximated to a normal distribution. The central limit theorem states that the sampling distribution of the mean will be normally distributed irrespective of the underlying distribution of the data with sufficient sample size[40]. Therefore a normal distribution was assumed for these two parameters. For both the cost of antibiotic and cost of initial surgery, a 20% standard deviation[5] was applied and the resulting inputs were a mean cost of NOK 54.8 and standard deviation of 10.9 for the cost of antibiotic prophylaxis and NOK 52,117 as mean and a standard deviation of 10,423 for the cost of initial surgery (Figure 7 shows an example for the cost of antibiotic).

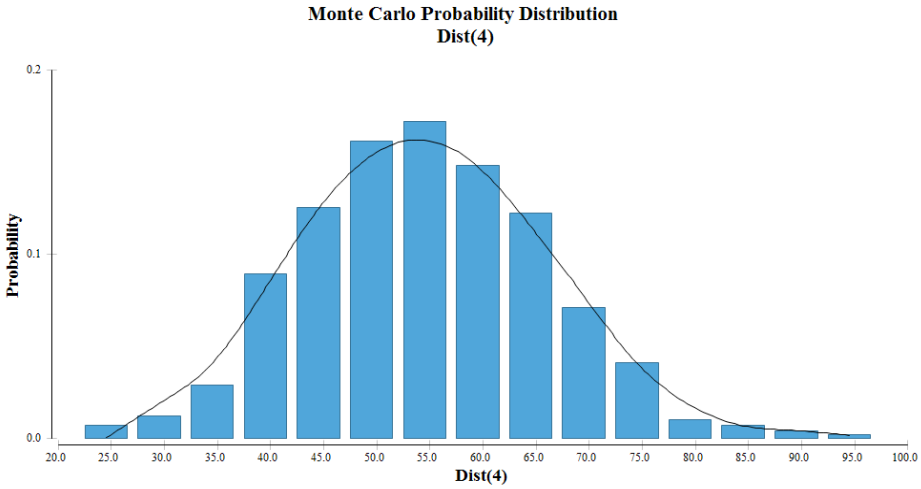


Figure 7 Normal distribution for the cost of antibiotic prophylaxis (NOK 54.8).

[4] https://www.duo.uio.no/handle/10852/30295. Permanent link http://urn.nb.no/URN:NBN:no-32288

[5] Approximation of Standard deviation, Briggs et al, 2011, page 89

The gamma distribution is constrained over the interval 0 to positive infinity and was used to estimate uncertainty for the cost of the three types of SSI (Figure 8 shows an example for cost of deep SSI). The mean cost and standard deviation for each of the three types of SSI was obtained from the ANOVA results that compared the costs of the three types of SSI and used to analyze the cost difference between the three types of SSI (Table 14).

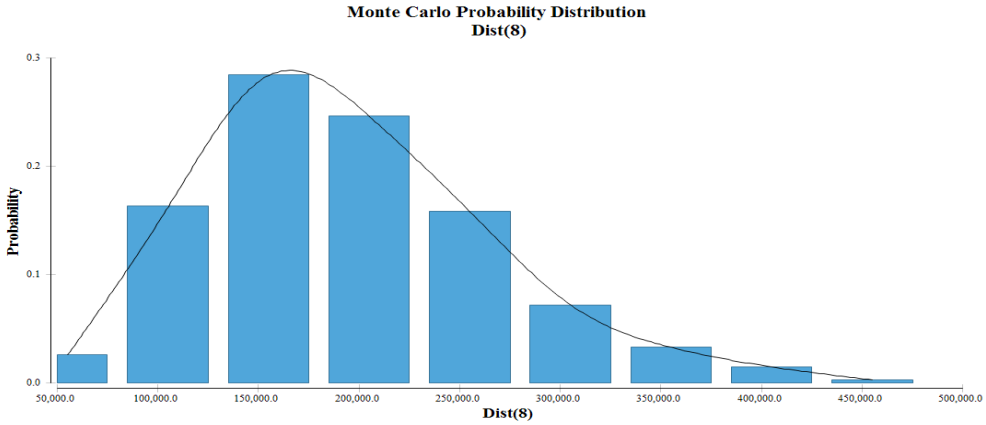


Figure 8 Gamma distributions for the costs of deep surgical site infections (Mean cost = NOK 197,601, Std.dev = NOK 124,343).

In TreeAge, gamma distribution is parameterized with the reciprocal of beta, ($\beta' = 1/\beta$) and to fit a gamma distribution the mean and variance of the distribution can be represented by the alpha and beta (α, β) [40]. The mean and variance of the gamma distribution can be expressed as functions of the alpha and beta parameters and calculated as follows[40]:

$$\boldsymbol{\alpha = \frac{\mu^2}{s^2}}, \quad \boldsymbol{\beta = \frac{s^2}{\mu}} \qquad [\mathbf{10}]$$

The lognormal distribution was used to fit the data for effectiveness since effectiveness is bound by two states, the state of perfect health on one hand and the infinity state of worst possible health on the other. In the model this was represented as 0 for no SSI present and 1 for SSI present. Women with SSI present were assigned a score of 1 regardless of the type of SSI (superficial, deep or organ/space). The mean and standard error of the lognormal distribution were calculated from the relative risk of developing SSI using data from Table 5. Since the relative risk (RR) is calculated from ratios, the natural log scale can be used[40]. The calculated mean and standard error of the lognormal distribution were 0.078 and 0.010 respectively (Table 7).

$$\ln(RR) = \ln(a) - \ln(a+c) + \ln(b+d) - \ln(b) \qquad [11]$$

$$se[\ln(RR)] = \sqrt{\frac{1}{a} - \frac{1}{a+c} + \frac{1}{b} - \frac{1}{b+d}} \qquad [12]$$

Where a = the proportion of women in the high-risk group with the current guidelines; b = the proportion of women in the high-risk group with the extended guidelines; a+c = the sum of women in the current guidelines and b+d = the sum of women in the extended guidelines.

The beta distribution was used to fit the distribution for the probabilities of binomial data since it is constrained between 0 and 1[40]. In the study, it was used to fit the distribution for the probability of receiving antibiotic prophylaxis. Since the sample size (n) and the number of women receiving antibiotics (r) were known, the integer form is suitable for use to represent the beta distribution (α, β). With α set to r and β set to n- r, the distribution for the probability of receiving antibiotics and developing SSI was fit into the model. For both the current and extended guidelines, the beta distribution for the probability of receiving antibiotics was (12,468; 7,328), where α = 12,468 and represent the number of women who received antibiotic prophylaxis and β = 3,629 for those who did not receive antibiotic prophylaxis (Table 7). Equation 13 expresses the integer form of the Beta distribution:

$$f(x) = \frac{(n-1)!}{(r-1)!\,(n-r-1)!}\, x^{r-1}(1-x)^{n-r-1} \qquad [13]$$

Where x = probability of receiving antibiotic prophylaxis; $r = \alpha$; $n - r = \beta$

A Dirichlet distribution was used to represent multinomial data on the terminal nodes. A Dirichlet distribution is a multivariate generalization of the beta distribution with parameters equal to the number of categories in the multinomial distribution[40]. In TreeAge, these distributions are represented as the number of women developing specific types of SSI. For the high risk group, the Dirichlet distribution for the probabilities of SSI was (11,811; 467; 87; 106), where 11,811 represents the proportion with no SSI, 467 represents those who developed superficial SSI, 87 represents those who developed deep SSI and 106 represents those who developed organ/space infections (Table 7). For the low risk group, the Dirichlet distribution for the probabilities of developing SSI was (3,473; 121; 17; 18). With the extended guideline, the Dirichlet distribution for the probabilities of developing SSI for the low risk group was (3535; 73; 11; 11).

Table 7 Description and valuation of distributions used to analyze uncertainty in the model for cost effectiveness analysis of antibiotic use in caesarian section.

Normal distribution	**Value**	**Mean**	**Std.dev**	**Description**		
d_cSurg	**52,117**	**52,117**	**10,423**	**Normal distribution for cost of initial surgery**		
D_cAB	**54.8**	**54.8**	**10.9**	**Normal distribution for cost of antibiotic**		
Gamma distribution	**Value**	**Mean**	**Std. dev**	**Alpha (α)**	**Beta (β)**	**Description**
d_cSupSSI	133,750	133,750	42,835	$((133,750)^2)/(42,835)^2)$	$(133,750)/((42,835)^2)$	Gamma distribution for cost of superficial SSI
d_cDeepSSI	197,601	197,601	124,343	$((197,601)^2)/((124,343)^2)$	$(197,601)/((124,343)^2)$	Gamma distribution for cost of deep SSI
d_cOS_SSI	211,095	211,095	108,784	$((211,095)^2)/((108,784)^2)$	$(211,095)/((108,784))^2$	Gamma distribution for cost of organ space SSI
Lognormal distribution	**Value**	**Mean**	**Std. dev**	**Description**		
d_RRSSI	1	0.078	0.010	Lognormal distribution for the relative risk of developing SSI		
Beta distributions	**Value**	**Alpha (α)**	**Beta (β)**	**Description**		
d_pABCP	12,468	12,468	7,328	Beta distribution for the probability of receiving antibiotic prophylaxis for high risk groups		

Dirichlet distributions	**Value**	**Dirichlet**	**Description**
d_pSSI$_{HR}$	11,811	(11,811;467;87;106)	Dirichlet distribution for probability of superficial, deep and organ/space SSI in high risk groups
d_pSSI$_{LR}$	3,473	(3,473; 121; 17; 18)	Dirichlet distribution for probability of superficial, deep and organ/space SSI in low risk group with current guidelines
d_pSSI$_{LR}$	3,535	(3,535; 73; 11; 11)	Dirichlet distribution for probability of superficial, deep and organ/space SSI in low risk group with extended guidelines

d_cSupSSI = distribution for costs of superficial SSI; d_cDeepSSI = distribution for costs of deep SSI; d_cO/S_SSI = distribution for costs of organ/space SSI.Std.dev = standard deviation

3.5 Ethical Considerations

This study was a joint guideline between the University of Oslo (UiO) and the NIPH. On the part of UiO, this study was part of the master thesis and therefore permission to carry out the study was granted by the thesis committee. All university regulations pertaining to thesis writing were adhered to. At NIPH, the Norwegian Social Science Data Services (NSD) was notified about the thesis proposal and permission to access the data was granted by the Data Protection Officer for research.

4. Results

Section 4.1 is devoted to the risk analysis of SSI after CS in Norway. Section 4.2 contains the results from the cost analysis and section 4.3 summarizes the results of the CEA of extending the provision of antibiotic prophylaxis to all women who underwent CS in Norway.

4.1 Risk Analysis

Of all caesarian sections (19,796) performed from September 2012 through December 2014, 18,928 (95%) women had no SSI, 629 (3.17%) women developed superficial SSI, 106 (0.53%) developed deep SSI and 133 (0.67%) developed organ/space infections. In total 868 (4.4%) women satisfied the CDC definition of SSI and were matched against those that did not develop SSI (18 928). Of the 868 women who developed SSI, 72% were superficial, 12% deep and 15% organ/space infections.

The mean number of days of hospitalization for women without SSI was 4.2 days and for women with SSI it was 5.1. When estimated against each type of SSI, the mean number of hospital days for women with superficial SSI was 4.5. For women with deep and organ/space SSI, it was 6.3 and 6.8 days respectively. A total of 170 (19.3%) women with SSI were re-admitted based on their SSI status. Women with superficial SSI accounted for the majority of the re-admission 71(42.0%) and those with organ/space SSI were the second highest with 56 (33.0%) re-admissions .43 (25%) of all readmissions were for deep SSI (Table 8).

Table 8 Descriptive statistics for Women with Surgical Site Infections (N= 868)

Variable name	Superficial infection N= 629	Deep infection N= 106	Organ/space infection N=133	Total N= 868
Number of SSI (% of total)	629 (72)	106 (12)	133 (15)	868
Mean length of stay (s.d)	4.5 (2.9)	6.3 (4.6)	6.8 (5.1)	5.1 (2.6)
Re-admissions (% of total)	71 (42.0)	43 (25.0)	56 (33.0)	170 (100)
Re-operations (% total)	35 (33.0)	35 (33.0)	36 (34.0)	106 (100)

SSI – Surgical Site Infection; SD – standard deviation

Among the 170 re-admitted women, 62.0% (106) had re-operations. Most of the re-operations were for organ/space infections (34.0%). Superficial and deep SSI each had a 33.0% proportion of re-operations. In comparison to re-admissions, 50.0% of all re-admitted

superficial SSI were re-operated and 64.0% of all re-admitted organ/space SSI were re-operated. Deep SSI had the highest rate of re-operations after re-admission (81.0%).

4.1.1 Patient Characteristics

Table 9 Patient Characteristics (Caesarian Section) (N= 19 796)

Patient Characteristics	No infection (N = 18 928)	Infection (N= 868)	Total (N = 19 796)	P-value
Age (years)				**0.94§**
Mean (s.d)	31.3 (5.4)	30.9 (5.5)	31 (0.2)	
Median	31	31	31	
Range	14 -54	18 - 48	14 -54	
ASA				**0.54ϕ**
ASA I (%)	4 210 (95.3)	207 (4.7)	4 417 (100)	
ASA II-III (%)	13 771 (95.5)	648 (4.5)	14 419 (100)	
ASA IV-V (%)	21 (91.3)	2 (8.7)	23 (100)	
Missing (%)	910 (97.1)	27 (2.9)	937 (100)	
Total (%)	18 928 (95.3)	868 (4.7)	19 796 (100)	
Wound contamination				**<0.05ϕ***
Clean (%)	12 458 (95.9)	534 (4.1)	12 992 (100)	
Contaminated/dirty (%)	5 450 (94.5)	319 (5.5)	5 769 (100)	
Missing (%)	1 004 (97)	31(3.0)	1 035 (100)	
Total (%)	18 928 (95.3)	868 (4.7)	19 796 (100)	

* = Significant results; § = t-test; ϕ = Pearson's Chi Square test; ASA = American Society of anesthesiologists; NNIS= National Nosocomial Infections Surveillance systems;

The mean and median age of women who underwent CS in Norway during the study period (September 2012 – December 2014) was 31. The age range was from14 to 54 years. The majority of the women (73.0%) were classified as ASA I and II and only a few (less than 0.01) were women with the least chance of surviving the surgical procedure (ASA IV-V). In terms of wound contamination, 60.0% of women had intact membranes and were not in labor (Class I) when the operation was done. Only 36.0% of those who developed an infection were in active labor or had membranes ruptured (Table 9).

Table 10 Operational Characteristics of Caesarian Section (N= 19 796)

Operational Characteristics	No infection (N = 18 928)	Infection (N= 868)	Total (N = 19 796)	P-value
Time in hospital before surgery (days)				**<0.05ϖ***
Mean (s.d)	1.1 (2.9)	1.2 (2.5)	1.1 (2.8)	
Median	0.0	1.0	0.0	
Min (Max)	0 (93)	0 (39)	0 (93)	
Urgency of operation				**<0.05ϕ***
Elective (%)	6 991 (96.5)	253 (3.5)	7 244 (100)	
Non elective (%)	11 920 (95.0)	631 (5.0)	12 551 (100)	
Total (%)	18 928 (95.5)	868 (4.5)	19 795 (100)	
Duration of operation				**<0.05ϕ***
< 30 minutes (%)	5 326 (96.1)	217 (3.9)	5 543 (100)	
31 – 60 minutes (%)	13 135 (95.3)	645 (4.7)	13 780 (100)	
> 60 minutes (%)	241 (92.7)	19 (7.3)	260 (100)	
Total (%)	18 702 (95.5)	881 (4.5)	19 583 (100)	
Antibiotic Prophylaxis				**< 0.05ϕ***
Yes (%)	11 811 (94.7)	657 (5.3)	12 468 (100)	
No (%)	3 473 (95.7)	156 (4.3)	3 629 (100)	
Missing (%)	3 628 (98.0)	71(1.9)	3 699 (100)	
Total (%)	18 928 (94.9)	868 (5.0)	19 796 (100)	
Length of stay				< 0.05ϖ
Mean (s.d)	4.2 (4.8)	5.1 (4.8)	4.2 (4.8)	
Median	4	4	4	
Min (Max)	0 (338)	0 (49)	0 (338)	

* = Significant results; ϖ = Wilcoxon Mann Whitney test; ϕ = Pearson's Chi Square test

4.1.2 Operational Characteristics (Caesarian section)

The average time from admission to operation was 1.1 days. For those who had an SSI, the average time was 1.2 days (std. dev 2.5). The majority of CSs were non-elective (63.4%). Of all the non-elective CS, 5.0% developed an SSI whilst 3.0% of the elective CS developed an SSI (p-value <0.05). The average duration of surgery was 74 minutes for those without SSI and 78 minutes for those with SSI (p-value <0.05). Antibiotic prophylaxis was given to 63.0% (12,468 vs 19,796) of all CS and out of these 5.3% (657 vs 12,468) developed SSI. 18.0% (3,629 vs 19.796), did not receive antibiotic prophylaxis and out of these 4.3% (156) developed SSI (p-value <0.05). There were missing observations on antibiotic prophylaxis (3,699) representing 19.0% of all CS. All operational characteristics were significantly associated with SSI as can be seen from Table 10.

Table 11 Regional and Hospital Characteristics (Caesarian Section) (N= 19 796). Norway.

Regional/Hospital characteristics	No infection (N = 18 928)	Infection (N= 868)	Total (N = 19 796)	P-value
Regional Health Trust				$< 0.05^{\Phi *}$
Helse Midt-Norge RHF (%)	3 009 (95.5)	142 (4.5)	3 151 (100)	
Helse Nord RHF (%)	1 607 (93.7)	109 (6.4)	1 716 (100)	
Helse Sør-Øst RHF (%)	10 611 (95.7)	481 (4.3)	11 092 (100)	
Helse Vest RHF (%)	3 685 (96.0)	152 (3.9)	3 837 (100)	
Total (%)	18 928 (95.5)	868 (4.5)	19 796 (100)	
Hospital size				0.22^{Φ}
< 200 beds capacity (%)	4 684 (95.3)	229 (4.7)	4 913 (100)	
201 – 500 beds capacity (%)	7 051 (94.9)	374 (5.0)	7 425 (100)	
> 500 beds capacity (%)	7 177 (96.2)	281 (3.8)	7 458 (100)	
Total	18 928 (95.5)	868 (4.5)	19 796 (100)	
Hospital type				0.77^{Φ}
Primary (%)	4 372 (95.5)	204 (4.5)	4 576 (100)	
Secondary (%)	5 199 (95.7)	234 (4.3)	5 433 (100)	
Tertiary (%)	9 341 (95.5)	446 (4.5)	9 787 (100)	
Total (%)	18 928 (95.5)	868 (4.5)	19 796 (100)	

4.1.3 Hospital characteristics

Table 11 shows that hospitals in the Helse Sør-Øst RHF performed most of the CS (56.0%) and those in the Helse Nord RHF performed the least (8.6%). The overall infection proportion was 4.5% with the least (3.9%) in the Helse Vest RHF and the highest (6.3%) in the Helse Nord RHF. Hospitals with bed capacity of less than 200 performed fewer CSs (2.4%) compared to those with higher bed capacity. Fewer SSI (3.7%) were reported in hospitals with bed capacity greater than 500 while hospitals with bed capacity of 201 to 500 recorded the highest percentage of SSI (5.0%). Of all the SSIs, 26.0% were reported in hospitals with a bed capacity of less than 200 and 42% and 32% of all SSI were reported in hospitals with bed capacity of 201 – 500 and greater than 500 respectively. Tertiary hospitals performed most of the CSs (49%) and primary hospitals performed the least (23%). Secondary hospitals had the lowest incidence of SSI (4.3%) while tertiary hospitals had the highest (4.5%). In terms of the overall SSI, tertiary hospitals accounted for 50.4%, secondary hospitals 26.5% and primary hospitals 23.0%. Only RHT showed a significance difference in proportion between those with SSI and those without.

4.1.4 Bivariate and multivariate logistic regression

In the bivariate logistic regression analysis described in Table 12, six variables were identified to be significantly associated with SSI (p-value < 0.05): Wound contamination (score 2+), Elective surgery, CS lasting 31 – 60 minutes and > 60 minutes, antibiotic prophylaxis, women residing in Helse Nord RHF. Women with wound contamination score greater than 2 were more likely to develop SSI (OR 1.37; 95% 1.18 – 1.57; p-value <0.05) than those with wound contamination score of less than 2. Elective caesarian sections posed a lesser risk of SSI than non-elective (OR 0.68; 95% CI 0.59 -0.79; p-value <0.05). Operations lasting > 60 minutes implied a 1.93 times higher odds than the base line operations lasting <30 minutes. Women receiving antibiotics were more likely to develop SSI compared to those that did not receive antibiotic prophylaxis (OR 1.23; 95% CI 1.03 – 1.48; p-value 0.01). Women residing in Helse Nord RHF had a 1.44 times higher odds of developing SSI than those in Helse Midt-Norge RHF.

In the multivariate logistic regression, three independent risk factors for SSI after CS were identified as significant and these included ASA class IV & V, hospitals with bed capacity 201 – 500 and secondary hospitals (Table 12).

Table 12 Bivariate and multivariate logistic regression output from Stata. (N = 868)

	Bivariate Logistic Regression			Multivariate Logistic Regression		
Patient characteristic	Odds ratio	95 % CI	p-value	Odds ratio	95% CI	p-value
Mean Age	0.99	0.98 - 1.00	0.13	1.00	0.98 - 1.03	0.90
ASA						
ASA I	1			1		
ASA II and III	0.96	0.82 - 1.12	0.59	0.87	0.65 - 1.17	0.36
ASA IV and V	1.94	0.45 - 8.32	0.37	11.49	1.02 - 129.46	0.05
Wound contamination						
Contaminated (score 2+)	1.37	1.18 - 1.57	< 0.05	1.03	0.75 - 1.41	0.86
Pre-operative hospitalization	1.01	0.99 - 1.03	0.26	1.00	0.96 - 1.06	0.73
Urgency of surgery						
Elective	0.68	0.59 - 0.79	< 0.05	1.22	0.89 - 1.67	0.22
Duration of Surgery						
< 30 minutes	1					
31 -60 minutes	1.21	1.03 - 1.41	0.02	1.27	0.91 - 1.78	0.15
> 60 minutes	1.93	1.19 - 3.15	< 0.05	2.41	0.82 - 7.04	0.11
Antibiotic prophylaxis						
Yes	1.23	1.03 – 1.48	0.01	1.01	0.69 - 1.48	0.92
Regional Health Authorities						
Helse Midt-Norge RHF	1					
Helse Nord RHF	1.44	1.11 - 1.85	< 0.05	1.30	0.80 - 2.12	0.28
Helse Sør-Øst RHF	0.96	0.79 - 1.16	0.68	1.19	0.78 - 1.80	0.41
Helse Vest RHF	0.87	0.69 - 1.10	0.25	1.46	0.85 - 2.52	0.17
Hospital size						
< 200 beds capacity	1			1		
201 – 500 beds capacity	1.26	0.96 - 1.64	0.96	1.44	1.01 - 2.06	0.04
> 500 beds capacity*	1			1		
Hospital type						
Primary	1					
Secondary	0.96	0.79 - 1.17	0.71	2.30	1.36 - 3.89	< 0.05
Tertiary	1.02	0.86 - 1.21	0.79			

*Stata dropped the observations for these variables. ASA = American Society of Anesthesiologists; CI = confidence interval; Helse Midt-Norge RHF = Central Norway Regional Health Trust; Helse Nord RHF = North Norway Regional Health Trust; Helse Sør-Øst RHF = South –east Norway Regional Health Trust; Helse Vest RHF = West Norway regional Health Trust.

There was a marginal association between women classified as ASA IV and V with the risk of SSI (p-value <0.05). Keeping all other variables constant, women with ASA class IV and V had 11.49 times higher odds of developing SSI than women in the baseline line ASA class 1.

After adjusting for other variables, women operated in hospitals with bed capacity of 201 – 500 were 1.44 times more likely to develop SSI compared to women operated in hospitals with bed capacity of less than 200. Of all the three significant variables in multivariate regression, secondary hospitals were the most significant (p-value <0.05). Women operated in secondary hospitals were 2.30 times more likely to develop SSI than those operated in primary hospitals (OR 2.30; 95% CI 1.36 -3.89).

The model was tested for how well it fits the data using Hosmer Lemeshow method. The Hosmer Lemeshow measures how well the model is calibrated between the predicted and observed frequencies. An insignificant test result with a large P-value (0.42) was obtained, indicating a good fit.

4.2. Cost Analysis

The average cost of caesarian section for women without SSI was NOK 52,117 (DRG 371) and for women with SSI the average cost was NOK 124,321. The mean cost of SSI per patient was NOK 72,204 more than those without SSI (124,321 vs. 52,117). The cost per SSI for women with superficial SSI was NOK 97,301. For those with deep and organ/space SSI, the cost per SSI was NOK 189,329 and NOK 196,754 respectively (Table 13).

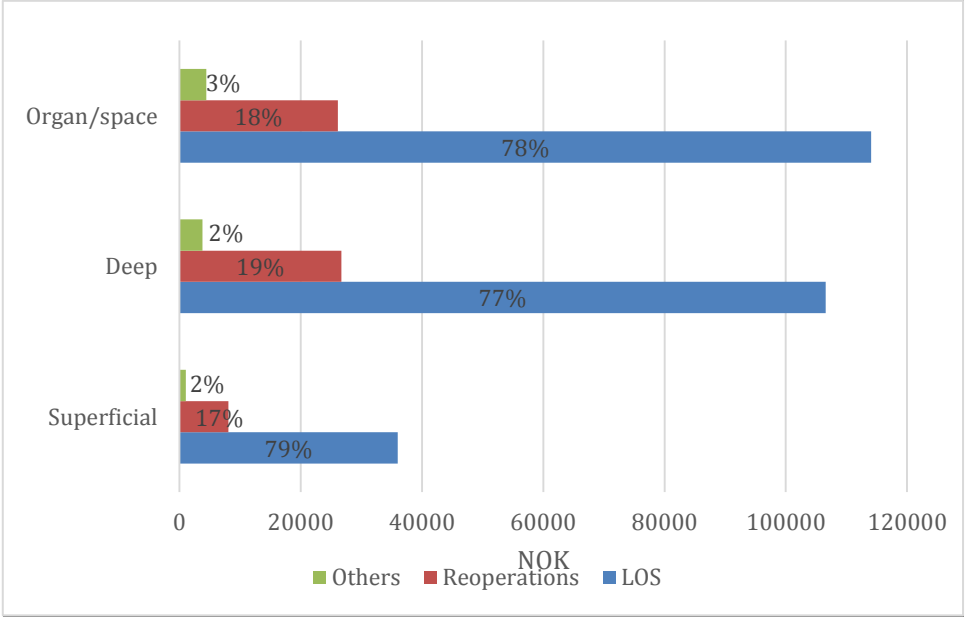
The overall added cost for treating 642 superficial SSIs after caesarian section during the study period (September 2012 to December 2014) was NOK 29 008,128. During the same period, NOK 14 534,932 was used to treat deep SSI. Hospitals in Norway spent NOK 19 670,632 in treating organ/space infections after caesarian section during the same period. In total NOK 63 213,692 was spent on treating all SSI during the study period.

Table 13 Estimates of additional costs per patient for the three types of SSI (N= 868)

COSTS FOR SUPERFICIAL SSI (N=642)				
Cost driver	**Unit of care**	**Unit estimate**	**Unit Cost**	**Total cost**
Initial Surgery	DRG 371	1	52,117	52,117
Length of stay	Days	2.3*	15,008	36,019
Reoperations	DRG 3770	1	8,085	8,085
Physician visit	GP visit	1	340	340
Laboratory tests	Leucocyte count & CRP	2.5	54	135
	Culture from infection site	1	50	50
Diagnostic Imaging	Ultra sound	1	362	362
	CT scan	0	952	0
Drugs	Analgesics	3 days	21,52	21.52
	Antibiotics	3-5 days	171,92	171.92
		Total extra costs		**45,184**
		Total costs with initial surgery		**97,301**
COSTS FOR DEEP SSI (N=106)				
Initial Surgery	DRG 371	1	52,117	52,117
Length of stay	Days	7.1*	15,008	106,556
Reoperation	DRG 376	1	26,742	26,742
Physician visit	GP visit	2	340	680
Laboratory tests	Leucocyte count & CRP	5	54	270
	Culture from infection site	2	50	100
Diagnostic Imaging	Ultra sound	2	362	724
	CT scan	1	952	952
Drugs	Analgesics	> 3 days	127	127
	Antibiotics	> 5 days	971	971
		Total extra costs		**137,122**
		Total costs with initial surgery		**189,239**
COSTS FOR ORGAN/SPACE SSI (N= 136)				
Initial Surgery	DRG 371	1	52,117	52,117
Length of stay	Days	7.6*	15,008	114,060
Reoperation	DRG 377N	1	26,121	26,121
Physician visit	GP visits	3	340	1,020
Laboratory tests	Leucocyte count & CRP	6	54	324
	Culture from infection site	2	50	100
Diagnostic Imaging	Ultra sound	2	362	724
	CT scan	1	952	952
Drugs	Analgesics	> 7 days	170	170
	Antibiotics	> 7 days	1,166	1,166
		Total extra costs		**144,637**
		Total costs with initial surgery		**196,754**

SSI = Surgical site infections; NOK = Norwegian kroner; DRG = Diagnosis Related Groupings; C-RP= C-reactive protein; DRG 3770, weight = 0.195; DRG 376, weight = 0.645; DRG 377N, weight = 0.630;*Sum of estimates from the initial period and the readmission period

After dividing these costs into their component cost drivers, the most costly was the cost for staying in hospital (LOS), which accounted for an average of 78% of the total costs for all the three types of SSI (Figure 9). This was followed by cost for surgical interventions (18%) and the rest (2%). The costs per SSI associated with LOS were highest during the readmission period compared to the initial period. For superficial SSI, the costs per SSI for LOS were NOK 6,003 for the initial period compared to NOK 30,016 for the readmission period. For deep infections the costs per SSI associated with LOS was NOK 31,516 for the initial period compared to NOK 75,040 for the readmission period. A similar trend was observed for organ/space infection with the cost per SSI associated with LOS of NOK 39,020 for the initial period and NOK 75,040 for the readmission period.



LOS = Cost for length of stay; SI = Cost for surgical interventions; others = Physician costs, laboratory costs, Costs for diagnostic tests and drugs.

Figure 9 Distribution of Costs for SSI according to cost drivers

4.2.1 Comparing costs for women with and without SSI

The results from the independent sample t-test indicate that there was a significant difference in costs between those with and without SSI (p-value < 0.05; 95% CI 62,013 – 64,086). The results are summarized in Table 14. The mean cost of LOS for women with SSI was higher (NOK 76,500) compared to the mean cost of LOS for women without SSI (NOK 63,050). The ANOVA results showed that the costs for the three types of SSI were significantly different from each other except for deep and organ/space infections. ANOVA results showed that organ/space infection had the highest costs compared to the baseline cost of superficial SSI.

Table 14 Independent sample t-test for the difference in costs between women with SSI and without SSI and ANOVA test for the difference in cost between the three types of infections (N = 19,784).

Results for Independent sample t-test					
Group	**Obs.**	**Mean**		**Std.Err.**	**95% Conf. Interval**
No SSI	18,900	63,050.28		528.87	62,013 – 64,086
SSI	884	76,500.05		2,062.05	72,452 – 80,547
Combined	19,784	63,651.25		513.94	62,643 – 64,658
Diff		-13,449.78		2,485.79	-18,322.14 - -8,577.41
Pr (T) > (t) = < 0.05					
Results for ANOVA test					
Cost	**Mean cost**	**Std dev.**	**t**	**P > (t)**	**95% Conf. Interval**
Superficial	133,750	42,835	8.02	0.000	100,681 – 166,819
Deep	197,601	124,343	2.71	0.008	17,084 – 210,617
Organ/space	211,095	108,784	3.30	0.001	30,905 – 123,786
Bartlett's test for equal variance					
Between groups	P value = 0.0029				
Within groups	P value = < 0.05				
Pairwise comparison of means with equal variance					
	Contrast	**Std.Err.**	**t**	**P > |*t*|**	**95% Conf. Interval**
Deep SSI vs Superficial	61,448	23,580	2.61	0.028	5,372 – 117,524
Organ/space SSI vs Superficial SSI	76,203	23,416	3.25	0.004	20,518 – 131,888
Organ/space SSI vs Deep SSI	14,755	23,416	0.63	0.804	-40,929 – 70,440

SSI = Surgical Site infections

4.3 Cost Effectiveness Analysis

The TreeAge output (Figure 10) shows that the expected probability of SSI was higher with the current guidelines (0.05) compared to the extended guidelines (0.04). This translates into 5 out of 100 caesarian sections ending up with a SSI in the current guidelines and 4 out of 100 caesarian sections ending up with SSI in the extended guidelines. The health benefit was 0.01 or 1 SSI per 100 caesarian sections. The expected cost per patient in the current guidelines (NOK 55,634) was higher compared to the extended guidelines (NOK 55,231). The extended guidelines were more effective (lower probability of SSI) and less costly compared to the current guidelines.

Table 15 The incremental cost –effectiveness ratio (ICER) for the current and extended guidelines of antibiotic prophylaxis (NOK 2015).

Guideline	Cost	Effectiveness	Cost - effectiveness	Change in cost	Change in effectiveness	ICER
Current Guideline	55,634	0.05	1 112,680	-	-	
Extended Guideline	55,231	0.04	1 380,775	403	0.01	40,300

ICER = incremental cost effectiveness ratio

The incremental cost-effectiveness ratio (ICER) was NOK 40,300 per SSI avoided. This means that if we choose to adopt the extended guidelines, we could save NOK 40,300 per avoided SSI (Table 15).

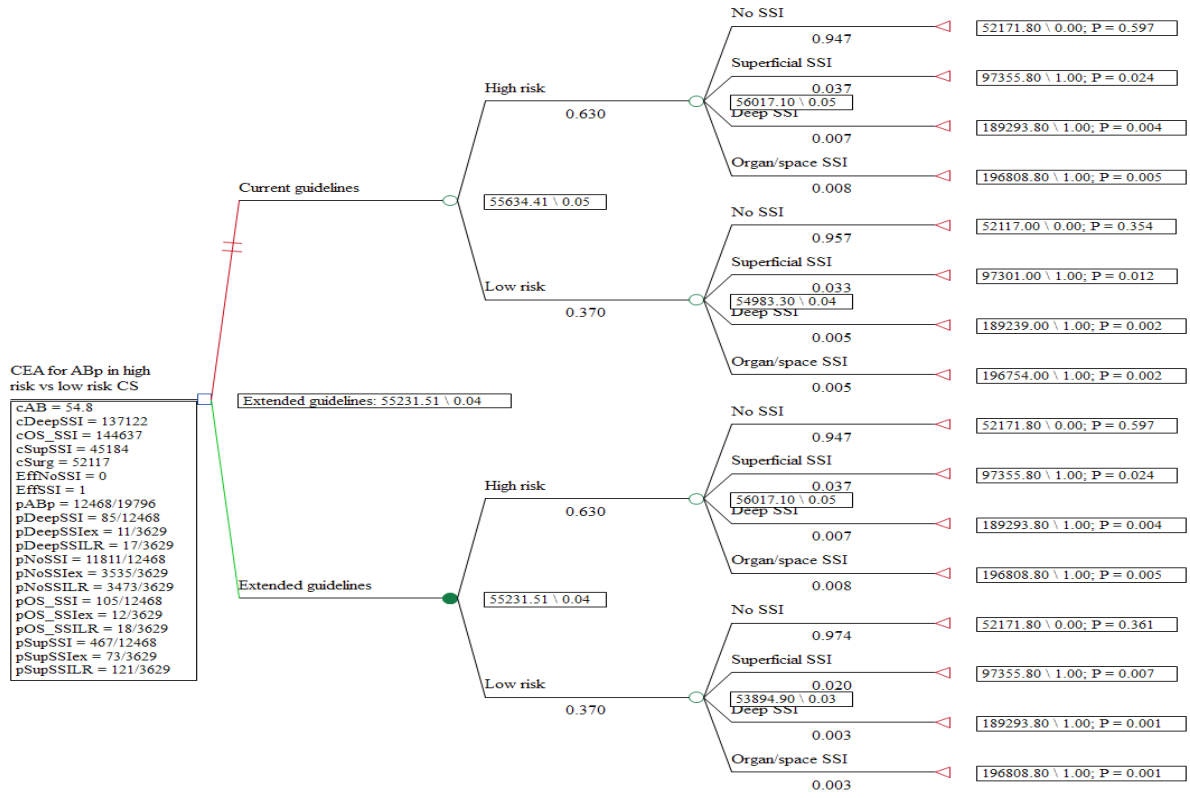


Figure 10 Decision Analytic model for CEA of antibiotic prophylaxis in caesarian section

4.3.2 Probabilistic Sensitivity Analysis

Probabilistic sensitivity analysis was performed to analyze the uncertainty surrounding the estimates of the expected incremental costs and expected incremental effects of the extended guidelines compared to the current guidelines of antibiotic prophylaxis in caesarian section. The incremental cost-effectiveness scatterplot (Figure 13) shows the spread of pairs of incremental costs and incremental effectiveness values (ICERs) from running 10,000 Monte

Carlo simulations. In the scatter plot, the differences in incremental costs and effectiveness between the two guidelines were used as base case point estimates (NOK -403; 0.01). From the scatterplot, 97.1% of the cost-effectiveness pairs fell on the southeast quadrant (II) (ICER <NOK 18,833), an indication that the extended guidelines are more effective and less costly that the current guidelines. This implies that the extended guideline dominates the current guidelines.

The location of ICER points on the scatterplot indicates that there is some uncertainty with regards to the cost savings associated with the extended guidelines compared to the current guidelines. The uncertainty surrounding the cost savings range from NOK -900 to NOK150 for the costs and 0.0025 to 0.012 for the effectiveness. This indicates a significant difference in costs and non-significant difference in effectiveness between the two guidelines.

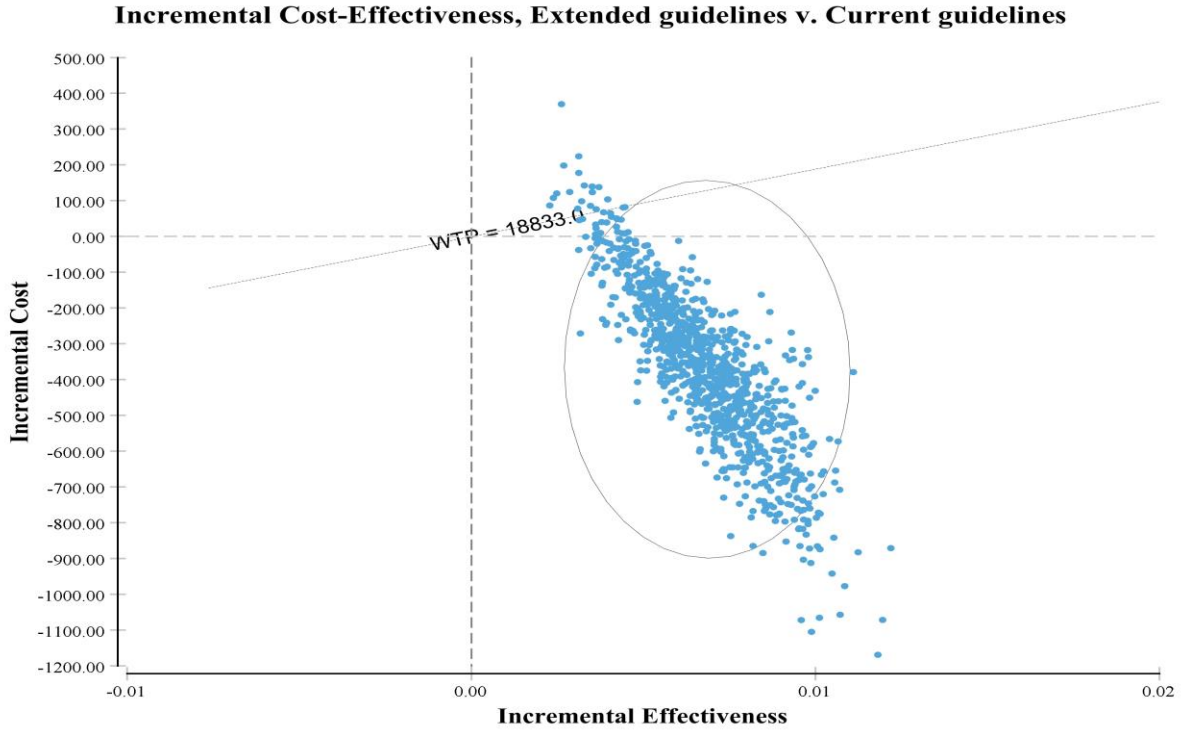


Figure 13. Incremental cost effectiveness scatterplot for the extended guidelines vs the current guidelines

The CEAC (Figure 14) indicates the probability (on the y-axis) that the extended guidelines are cost-effective compared to the current guidelines given a range of willingness to pay (on the x-axis). The results are consistent with the findings from the incremental cost-effectiveness scatterplot. At a willingness to pay of NOK 0 per SSI avoided, a total of 9,652 cost-effectiveness points fell below the y-axis, indicating that the probability of the extended guidelines being cost-effective compared to the current guidelines was 0.96. When the stated

willingness to pay increased to NOK18, 833, a total of 9,712 cost-effectiveness points fall below the slope of the NOK 18,833 line. This implies that given the maximum willingness to pay of NOK 18,833 per SSI avoided, the probability that the extended guidelines are cost-effective compared to the current guidelines increase to 0.97.

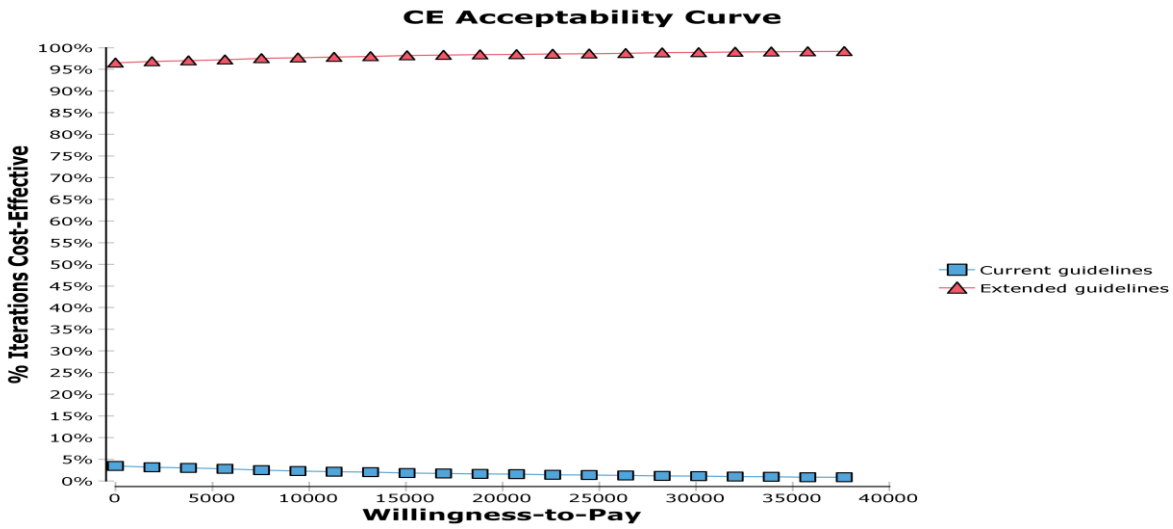


Figure 14 Cost-effectiveness acceptability curves for the two guidelines.

The results of the cost-effectiveness analysis show that the extended guidelines significantly reduce SSI after ceasarian section compared to the current guidelines (0.01, CI: 0.0025 to 0.012). The extended guidelines were also less costly than the current guidelines (NOK -403, CI: NOK -900 to NOK150).

5. Discussion

In this chapter, I discuss three pertinent questions: What are the risk factors for SSI after caesarian section in Norwegian women? What are the hospital costs associated with SSI after caesarian section in Norway? How cost effective is it to extend antibiotic prophylaxis to all women undergoing caesarian section in Norway?

5.1 Main findings and implications for risk analysis

During the 28-month study period (September 2012 – December 2014), there were 868 SSI among 19,796 caesarian sections, representing a SSI rate of 4.4%. This translates into one in every 22 women who undergo caesarian section ending up with SSI. Compared to the SSI rate of 8.3% observed in 2007[24], this represents a 3.7% reduction in SSI after caesarian section**.**

Three independent risk factors for SSI after caesarian section were identified by multiple logistic regressions: ASA score greater than III, Hospitals with bed capacity of 201 – 500 and secondary care hospitals. These risk factors could be the target when designing and implementing preventive strategies for SSI after caesarian section in Norway. The study findings show that women with ASA score greater than III were 11.5 times more likely to develop SSI than those with ASA score of 1. The ASA score accesses the physical health status of patients before surgery and a score greater than III indicates the presence of an incapacitating disease that is a constant threat to life. ASA score greater than III is associated with other factors that increase the risk of SSI such as increased duration of surgery, increased intra-operative blood loss and prolonged post-operative stay. This study finding was consistent with studies by Tran et al[26] who showed that women with ASA score greater than III were 5.3 times more likely to develop SSI than those with ASA score of 1. However, a study done in England by Graham et al[42] did not find any association between ASA score greater than III and SSI, neither did the study done in Norway by Eriksen et al[24].

The study findings show that women having caesarian sections in hospitals with bed capacity 201–500 were 1.44 times more likely to develop SSI than those from hospitals with bed capacity of less than 200. We did not find any other studies done both in Norway and elsewhere that found hospital size to be significantly associated with SSI. However, our findings could be a result of hospitals with higher bed capacities having higher caesarian section rates and hence higher risk for SSI. Another probable explanation is that hospitals

with higher bed capacities receive patients with severe systemic illnesses (ASA score >III) from hospitals with less bed capacities. Hospitals with bed capacity less than 200 are not likely to offer specialized health care and thus refer patients with complicated or severe systemic illnesses to hospitals with much larger bed capacities. These referred patients are already predisposed to developing SSI. During the post-operative period, patients with complicated or severe systemic illnesses are likely to stay longer in hospital further increasing their odds for developing SSI.

Secondary care hospitals had the lowest p-value in multivariate logistic regression. Having a caesarian section in a secondary care hospital was associated with an increased risk of SSI of 2.3 times more compared to primary care hospitals. Similar to hospitals with bed capacity of 201 – 500, secondary care hospitals are more likely to receive women with complicated conditions (ASA score > III) from primary care hospitals and thus perform more caesarian sections.

5.2 Main findings and implications for the cost analysis

Results from the cost analysis conducted in the study indicate a significant difference in costs between women with and without SSI. The results also show a significant difference in costs among the three types of SSIs except between deep and organ/space infections. Deep and organ/space infections both demanded longer hospital stay and required more resource intensive re-operations, hence the non-significant finding for the difference in costs. Overall SSI results in up to NOK 35 million in costs every year. The costs of caesarian section for one patient with SSI were 2.4 times that of a patient without SSI.

The finding of a significant difference in costs between those with and without SSI was consistent with the findings of several other studies[31, 36, 43]. As there was limited data on costs of surgical site infections after caesarian section in Norway to compare with, we looked at a cost-effectiveness analysis that was done at Bærum hospital (Norway) where the costs of SSI per patient were reduced by NOK 727.64 after implementing a quality improvement guideline[44]. In line with our study findings, the Bærum study indicated that SSI causes a significant economic burden on Norwegian health hospitals.

In the study, the average cost per SSI was NOK 72,204. After comparing our study findings to that from other countries, we found similar costs of $ 3,500 (NOK 27,134) per SSI from a study done in the US by Olsen et al[36]. Costs associated with SSI increased with depth of

infection. The estimated extra costs per SSI ranged from NOK 45,184 for superficial SSI to NOK 137,122 for organ/space infection. This finding was in accordance with the findings from Urban et al[21] and Olsen et al[45]. Urban et al[21] found that the cost per SSI varied widely from $400 (NOK 3,235) for superficial SSI to $30,000 (NOK 242,677) for organ/space infections. The costs of superficial SSI after caesarian section were lowest (NOK 45,184) and this was not surprising considering that most women with superficial infections required few or no interventions at all (Appendix 3). However the costs of organ/space infections were 3 times higher than the costs of superficial SSI. The reason would be that organ/space infections demanded longer hospital stay (2.3 vs 7.6) and required more resource intensive procedures than superficial SSI (Table 14).

The major cost driver in all the three types of infections was the cost of hospital stay (78%) and the least costly was the cost for laboratory tests (2%). Olsen et al[45] found comparable results with 76% of the costs due to prolonged hospital stay. This finding is in line with the findings from risk analysis where women with ASA score > III were 11.5 times more likely to develop SSI. In terms of costs, such women are more likely to stay longer in hospital and consume more hospital resources than women with ASA score of 1.

5.3 Main findings and implications for the cost-effectiveness analysis.

The results of the cost effectiveness analysis show that the extended guideline was cost effective compared to the current guideline. With regards to the effectiveness, the probability of SSI was 5% with the current guidelines and 4% with the extended guidelines. In terms of costs, the current guidelines had higher costs per SSI avoided (NOK 55,632) compared to the extended guidelines (NOK 55,231). With the extended guidelines, NOK 40,300 was spared for each SSI avoided compared to the current guidelines.

The results of the probabilistic sensitivity analysis as summarized in the incremental cost-effectiveness scatter plot (Figure 13) indicate that 97.1% of the ICER points fell on the south-east quadrant below a stated willingness to pay of NOK 18,833. The CEAC indicated similar results with the probability of 0.97 that the extended guidelines were cost-effective compared to the current guidelines at all range of willingness to pay.

The results of the cost-effectiveness analysis ought to be interpreted with caution considering that we adjusted the effects for the comparator using literature data external to the study. A randomization of patients receiving antibiotic prophylaxis would have produced more

reliable results that could have been used in the model. In this case we could not use the results from the study to incorporate the effects of antibiotic prophylaxis because the selection of patients was biased. Secondly, other factors such as the emergency of antibiotic resistant bacteria were not taken into consideration in the model. Providing routine antibiotic prophylaxis to all caesarian sections would increase the risk of developing resistant bacteria that are difficulty and costly to treat.

5.4 Strength and limitations of the study

The study has some strengths and limitations. First, the study used data from a regulatory surveillance register with 96% completeness. The completeness of the register provided a rich source of data for the study. For instance, from the register, we were able to get close approximations for hospital stay and re-operations.

Secondly, the sample size was sufficiently big (19,769) to permit generalizability of the results to other settings within and outside Norway.

The study had limitations with regards to the identification of the risk factors of SSI in caesarian section. The retrospective nature of the study makes it susceptible to the effects of biases and confounding. Even though we controlled for confounding in the multivariate regression, we still cannot infer causality of the identified risk factors in the study to SSI as other confounding factors maybe at play. We can therefore only correlate the risks identified to the outcome variable (SSI). There were missing observations in most of the variables and of particular concern was the number of missing observations on the antibiotic prophylaxis (18% or 3,699). It is likely that the loss to follow-up on the antibiotic prophylaxis had an influence on the significance of antibiotic prophylaxis in the analysis. In additional, the NOIS data proved unsuitable for analyzing the effects of antibiotic prophylaxis in caesarian section due to patient and treatment selection biases. NOIS data is not randomized and only high risk women receive antibiotic prophylaxis. Therefore the finding that antibiotic prophylaxis increases the odds of getting SSI was not unusual.

The study also had a number of limitations in the cost analysis and notable among them was the hospital perspective adopted. Even-though we attempted to capture the costs of SSI after caesarian section in Norway, the hospital perspective provided a limited view as patient related costs and costs from other sectors were disregarded. A societal perspective would have provided a broader view of the costs of SSI after caesarian section. For instance, one of

the gynecologists who helped fill out the questionnaire noted that women with SSI demand a lot of emotional attention whose costs were unfortunately not captured in the study.

Inclusion of DRG estimates for re-operations in the micro-cost analysis added certain limitations to the study results. Considering that the DRG approach is based on reimbursing the gross average costs and has the potential to omit other relevant costs involved in the treatment of SSI after caesarian section, our results could have been underestimated. Since, to our knowledge, there have not been similar studies on costs of SSI after caesarian section in Norway, we had little data to compare our results with locally. For this reason, the results of this study should be interpreted with some degree of caution.

Furthermore, the three gynecologists who responded to the questionnaire on the clinical pathway were not representative enough. Their estimates varied widely and this rendered them to be less reliable. From the challenges we faced in interpreting their responses, we concluded that they (Gynecologists) too had difficulties in understanding the questionnaire. The example in point is where one gynecologist indicated the number of reoperations as a percentage of all the reoperations and the other gynecologist estimated it as the number of reoperations per patient per SSI. In this case, interviews with the gynecologists would have been helpful. However, since the NOIS register captures no cost estimates, we had to make use of the clinical pathway and accept its inherent flaws.

There were some limitations in the cost-effectiveness analysis. Firstly, we had limited time to complete our study and this time constraint was compounded by the delayed access to the data. Data for the cost-effectiveness analysis was based on the prior results of the risk and cost analyses conducted in the same study. This meant that the cost-analysis was done towards the end of the study period when time was of real essence. Secondly, we did not translate the intermediate outcome measure (SSI avoided) to a final measure such as quality adjusted life years (QALYs). The QALY would have represented the utility measure better than the intermediate outcome used.

The study, through its limitations has opened up more opportunities for further research on the risk, cost and cost effectiveness analyses of SSI after caesarian section. There is need for further studies that will take on a societal perspective on the costs associated with SSI in Norway. And as data quality in the NOIS register continues to improve, there is need to incorporate cost data into the register. Future studies in CEA that go beyond simple decision

trees and can include all the other variables that we were not able to include would provide better and in-depth understanding of the costs and effectiveness of SSI interventions.

5.5 Conclusion

The study aimed at identifying risk factors for SSI after caesarian section, estimating the costs of these SSI and analyzing the cost-effectiveness of providing antibiotic prophylaxis to all women undergoing caesarian sections. For the risk factors, the multivariate logistic regression identified three risk factors for SSI after caesarian section. These are ASA score > III, hospitals with bed capacity between 200 – 500 and secondary care hospitals. These three risk factors could effectively be targets for prevention strategies for SSI after caesarian section. For the cost part, the study has provided a primary impression of the costs associated with SSI. The cost per caesarian section complicated with SSI was 2.4 times higher than uncomplicated caesarian section. For the cost effectiveness part, the study has indicated a 97% chance of the extended guidelines being more cost effective compared to the current guidelines at the stated willingness to pay of NOK 18,833.

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APPENDICES

APPENDIX 1 Map of Norway showing the location of regional health authorities

APPENDIX 2 Clinical pathway questionnaire used in estimating costs of SSI after CS. Please include information on patient interventions AFTER the caesarean section.

Management Strategy	**Name of intervention**	**Unit range Min –Max**	**Patient Categories**			
			No infection	**Superficial SSI**	**Deep SSI**	**Organ/space SSI**
Laboratory	Blood test	Min-max (number)				
	Culture for infected site	Min-max (number)				
	Other tests……	Min-max (number)				
Image diagnostics	X-rays	Min-max (number)				
	Ultrasound	Min-max (number)				
	Others ……CT scan……	Min-max (number)				
Treatment of surgical site infection	Number of dressing changes	Min-max (number)				
	Need for (yes/no):					
	1. Advanced dressings	Type % needing				
	2. Debridement					
	3. Re-operation	DRG code % needing				
	4. Others					
		DRG code % needing				
		% needing				
Medications (write down the names/dosage/days of administration)	Analgesics type/ dose …Paracetamol &Diklofenak	Dose & Days 1 g x 4 50 mg x 3				

	…Opiates….	Dose & days				
	Antibiotics type/dose …Stable penicillin…….. …Sepsis regimen	Mean Dose & Days Mean Dose & days				
Gynaecologist care		Mean hours/day				
Re-hospitalization	Length of stay for readmitted women	Min-max (days)				
Policlinic visits	Number of policlinic visit	Min-max (number)				
Any other cost driver not mentioned						
Any other cost driver not mentioned						

APPENDIX 3. Calculated median values of the estimates from the gynecologists

Additional Intervention	**Superficial SSI**				**Deep SSI**				**Organ /space SSI**			
	Gyn1	**Gyn2**	**Gyn3**	**Median estimate**	**Gyn 1**	**Gyn 2**	**Gyn3**	**Median estimate**	**Gyn 1**	**Gyn 2**	**Gyn3**	**Median estimate**
LOS for re-admitted women (days)	3 - 4	0 -1	0 - 3	2	3 - 4	3 - 10	0 - 5	5	3 - 4	3 - 10	0 - 5	5
Physician care (number of visits)	1	2	0 - 1	1	4	3	0 - 3	2	4	5	0 - 2	3
Nursing care	3 - 4	not included	Not included	Not included	3 - 4	not included	Not included	Not included	3 - 4	Not included	Not included	Not included
Laboratory												
Blood test (CRP & Leucocyte count)	1- 5	0 - 2	1 - 5	2.5	5 - 10	1 - 3	2 - 10	5	5 - 10	2 - 4	2 - 10	6
Culture from infection site	1	1	1 -2	1	2	1 - 3	1 -3	2	1	2 - 4	1 - 3	2
Image diagnostics												
Ultrasound	1 - 2	1	0-1	1	2	1 - 3	1-2	2	2 - 5	3	1 - 3	2
CT scan	0	0		0	1 - 2	0 - 2		1	0 - 1	1 - 2		1
Medications	Usual dose				Higher dose				Higher dose			
Analgesics												
Paracetamol 500mg *3*7	1 - 7 days	0	3 – 15 days	Paracetamol for 3 days	1 -7 days		3 – 15 days		1 - 7 days	3 – 15 days		
Ketorax	1- 3 days	0			1 - 7 days				1 - 7 days			Ketorax for 3 days
Voltaren	1 -3 days	0	0 – 5day		1 - 3 days	0 – 10days		Voltaren for 3 days	1 - 7 days	0 - 10		
Pinex Forte	1 - 3 days	0			1 - 3 days							
Antibiotics	Triple Antibiotics	Mono antibiotic	Mono antibiotic	Mono antibiotic	Triple Antibiotics	Double antibiotics		Double antibiotics	Triple Antibiotics	Double antibiotics	Triple antibiotics	Triple antibiotic
Surgical Interventions for SSI												
Number of usual dressing	3 - 7	0	1 - 15	7.5	3 - 7	3	1 - 15	9	0 - 2	1 -2	0	1
Advanced dressing – VAC (Yes/No)	Yes	No	No	Yes	Yes	Spriking i sårel (0-1)	Maybe	YES	NO	NO	Maybe	NO

Re-operation	2 - 4	0	-	3	2 - 4	0	2-4	3	1 - 2	1	2-4	3
Policlinic follow up	3 - 4	1	0 - 7	4	3 - 4	3	0	2	0 - 4	2	0	2
Mental health												

Gyn = Gynecologist; CRP = C- reactive protein; LOS = length of stay; VAC = Vacuum Assisted Closure; Triple antibiotics include a penicillin. Aminoglycoside and flagyl; double antibiotics include a penicillin or cephalosporin with flagyl; Mono antibiotic included Diclocil only.