Prevention of Severe Infectious Complications After Colorectal Surgery

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Prevention of Severe Infectious Complications After Colorectal Surgery

Het voorkomen van ernstige infectieuze complicaties na colorectale operaties

(met een samenvatting in het Nederlands)

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof. dr. H.R.B.M. Kummeling, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op dinsdag 1 oktober 2019 des middags te 2:30 uur

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No hay miel sin hiel

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Introduction

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INFECTIONS AFTER SURGERY

The human digestive tract is colonized with an unconceivable number of microorganisms that form a complex ecosystem called the gastrointestinal microbiome. These commensal microorganisms usually reside in symbiosis with the human host and serve important functions in metabolic processes, such as fermentation of undigested carbohydrates or the production of vitamins and hormones. [1] Furthermore, they play an important role in the defense against infections. They do not only lower the risk of sterile infections by dampening the host immune response to harmless microorganisms, [2] but they also form a barrier against potentially harmful bacteria by preventing invasion and overgrowth. This protective effect is also called colonization resistance. [3]
Disturbance to the gut microbiota can lead to disease. When species of the normal microbiota are eliminated or suppressed, for example after a course of broad-spectrum antibiotics, the colonization resistance is lowered which gives room for other, potentially pathogenic, microorganisms to thrive and cause infection.[4,5] This disturbance can also be caused by underlying chronic disease or increasing age, or by iatrogenic factors such as the use of immunosuppressants and surgery. [6] Also, damage to the intestinal epithelium, an inevitable consequence of surgery, can lead to leakage of microorganisms to the submucosa, the retroperitoneal cavity or even to the systemic circulation. This may cause severe complications such as urinary tract infections, intraabdominal abscesses or blood stream infections. [7]

Healthcare-acquired infections (HAIs) are infections that patients acquire while they are receiving care in a hospital or other health-care facility. [8] These infections can occur at any body site and can be associated to the treatment that patients are receiving such as urinary catheters or central lines, mechanical ventilation or operative procedures. In a prevalence survey of the World Health Organization, an episode of HAI was reported to occur in 7.0% of all hospitalized patients in developed countries at any given time, but the risk of acquiring such an infection increases when a patient undergoes surgery. [9] The development of HAIs after surgery is multifactorial. During surgery, organs that are highly colonized with microorganisms are manipulated, which increases the risk of contamination, but also the introduction of non-human implants or indwelling devices can facilitate the introduction of potentially pathogenic microorganisms to several body sites. Combined with a temporary depression of the immune response after surgery, ideal circumstances for infections are conceived. [10] One type of HAI that is specifically associated with surgery is infection of the surgical wound or surgical site infection (SSI). The diagnosis of SSIs can be complex as they share many signs and symptoms with other conditions and complications. An international definition was developed by the Centers for Disease Control and Prevention (CDC) to provide a standardized method to diagnose SSI. [11] Per this definition, SSIs are infections of the operative site that develop within 30 days of the surgical procedure, or within 90 days of the procedure when prosthetic materials are implanted. SSIs are further classified based on the depth of the infection and the anatomic layers that are affected. (Figure 1). Often, they are limited to the primary incision site and do not extend beyond the fascial layer. These are called incisional infections. However, infections may extend to anatomical structures below the fascia and these are called deep SSIs.

SSIs account for nearly a third of all HAI after surgery, which makes them the second most common HAI in Europe and the United States. [12] On average, five in every 100 patients who undergo surgery will develop an SSI. This risk, however, varies substantially between surgical procedures. With reported risks as high as twenty percent, colorectal surgery is associated with a much higher risk of SSI. [13,14] SSIs can severely impede postoperative recovery. The consequences vary depending on the severity of infection as well as on patient-related factors.

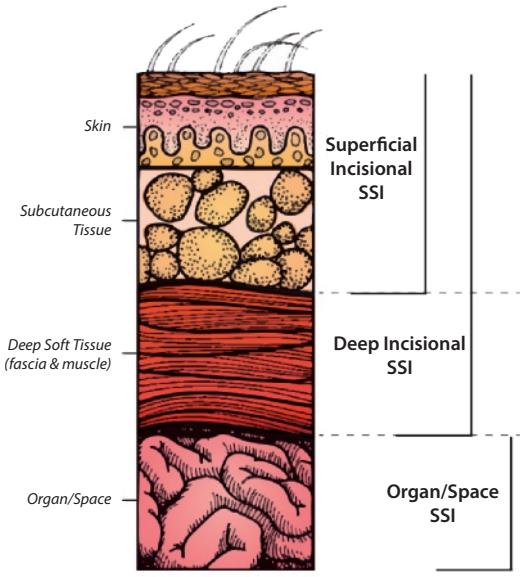

Figure 1 CDC definition of surgical site infection, adapted from Horan *et al.*, 1992 [11]

In general, they are associated with a substantial increase in morbidity [15] and mortality [16–18], a length of stay extended by nine days in the case of severe infections [19,20], and two to threefold higher healthcare costs. [21–24] Even when adjusted for factors related to the patient, the surgical procedure and the hospital, treatment of patients with a deep infection cost an extra $25,000. [25]

Measures to reduce SSIs have been explored since the 19th century. At that time, the foundations for prevention of postoperative infections were laid by Joseph Lister, a British surgeon who discovered and introduced the concept of antisepsis. [26] Implementation of antisepsis led to a drastic decline in postoperative infections. Albeit the risk is much lower today than over a century ago, SSIs persist to be common complications. The prevention of these infections remains problematic and requires integration of a range of measures before, during and after surgery. [27]

PATHOGENESIS AND RISK FACTORS OF SURGICAL SITE INFECTIONS

Infection prevention starts by understanding the pathogenesis and the factors that influence the risk of acquiring an SSI. Microbial contamination of the surgical site is a crucial precursor of SSI. [28] Microorganisms can be introduced from the environment, but more commonly SSIs are caused by microorganisms that were already residing in the body. [29] The colon and rectum are densely colonized with bacteria such as Enterobacteriaceae and facultative anaerobes. This high concentration of microorganisms does not only explain the high risk of intraoperative contamination and subsequent SSI development, but also why Enterobacteriaceae comprise more than half of the pathogens after surgery on this part of the gastrointestinal tract. [30]
Extensive research has also identified factors and conditions that affect a patient's risk of acquiring an SSI. [31–35] (Table 1). Smoking, diabetes or immune suppression have been shown to increase someone's risk. The chance of developing an SSI also depends on the wound class. This class specifies the level of contamination of the wound during the procedure which can be clean, clean-contaminated, contaminated or dirty. [36,37]

Table 1 Patient and procedure related factors that can influence surgical site infection development

Patient	Procedure
Advanced age	Preoperative
Anemia	Shaving
Diabetes mellitus	Duration of surgical scrub
Smoking	Chlorhexidine/alcohol skin antisepsis
Obesity	Perioperative
Immune suppression	Duration of surgical procedure
Malignancy	Glycemic control
Colonization with pathogenic microorganisms	Thermoregulation
Poor nutritional status	Hemostasis, blood transfusion
Infections at other body sites	Operating room ventilation
Recent surgery	Sterilization of surgical instruments
Preoperative hospitalization	Surgical drains
Severity of underlying illness	Surgical technique (open versus laparoscopic)
	Prosthetic or foreign implants
	Antibiotic prophylaxis

Identification of risk factors was a step towards a reduction of infections because infection control measures could be focused on the manipulation or the control of some of these factors. This included the management of blood glucose levels in diabetic patients or the advice to quit smoking before surgery, but also perioperative glycemic control and regulation of the body temperature.
The Institute of Healthcare Improvement suggested combining these evidence-based measures into care bundles with the aim to further improve patient outcomes. A bundle of infection control measures was shown to be extremely successful in reducing other HAIs, such as catheter-related blood stream infections [38] and ventilator-associated pneumonia. [39] A similar approach has been proposed to be used for SSI prevention, since there is a number of evidence-based interventions available.

PREVENTION OF SURGICAL SITE INFECTIONS WITH ANTIBIOTICS

Internationally accepted as a crucial component of the infection prevention bundle is the administration of systemic antibiotic prophylaxis. This can be applied in several forms, of which perioperative intravenous antibiotic prophylaxis, administered shortly before the start of the procedure, is advised in all international guidelines. [40,41] The concept of this prophylaxis is to achieve an adequate antibiotic tissue concentration at the time of the procedure to kill all microorganisms that are seeded to the surgical site. The antibiotics in the prophylaxis should cover the most common pathogens associated with SSIs at the lowest cost and the lowest toxicity for the shortest treatment duration as possible. For colorectal surgery, associated with a high risk of endogenous contamination with Enterobacteriaceae and with anaerobe species, this usually includes administration of metronidazole and cefazolin. The necessity and efficacy of this prophylaxis have been undisputed for decades. In 1981, a meta-analysis compared the risk of SSI in patients who received antibiotic prophylaxis to those randomized to placebo or no treatment. [42] An absolute risk reduction of 14% was found (from 36% in those without to 22% in those with antibiotic prophylaxis). Since then, future trials on antibiotic prophylaxis using control groups without antibiotics were deemed unethical because of the compelling evidence for systemic antibiotics. [43]

Besides systemic antibiotics, oral antibiotic prophylaxis can be another way of reducing SSI risk specifically for colorectal surgery. Although the efficacy of systemic prophylaxis is undebated and firmly established, the value of oral antibiotic prophylaxis remains controversial, even though it was introduced years earlier. The rationale behind the oral antibiotic prophylaxis is to achieve a reduction of SSIs by lowering the colonic bacterial load and thus decreasing the risk of bacterial contamination of the surgical site. The first studies used antibiotics that are poorly absorbed after oral administration which implies that the antibiotics only exert local activity with low risks of systemic side effects. [44–46] In 1973, Nichols *et al.* [47] proposed a combination of neomycin and erythromycin, covering both Gram-negative and anaerobe species, and its efficacy was confirmed in placebo controlled randomized controlled trials (RCTs). [48,49] The antibiotics were applied combined with mechanical bowel preparation (MBP), a technique that was routinely used at that time to remove feces from the lower gastrointestinal tract with osmotic agents. [50,51] It was hypothesized that the oral antibiotics could only reach optimal activity in a cleaned colon and therefore, MBP and the oral antibiotic prophylaxis (OAP) were administered simultaneously. [52] This combination of oral antibiotic prophylaxis and MBP led to SSI reduction [53–55] and was widely accepted as preoperative treatment in the late 1970s predominantly by American surgeons. Shortly thereafter, the necessity of MBP was questioned because it became increasingly apparent that its use was associated with a substantial burden to the patient because of nausea, electrolyte disturbances and abdominal pain. [56–59] More importantly, the outcomes for patients who underwent emergency procedures in an unprepared colon seemed to be similar to those of elective patients who had received MBP. One explanation for this might be that mechanical cleanse results in bacteria-laden liquid stool, which is more likely to contaminate the surgical field. [60] Several meta-analyses that followed confirmed that treatment with MBP did not result in statistically significantly different outcomes compared to no bowel preparation [61,62] which led to the abandonment of MBP as a solitary treatment. The use of the antibiotics was subsequently debated as well, because without MBP it was questioned if oral antibiotics could have a beneficial effect. [63] Furthermore, concerns were raised regarding the tolerability of the antibiotics and the risk of opportunistic infections [64] and the use of OAP declined from 86% in the 1990s [65] to 36% in 2010. [66] Most surgeons who decided to continue the practice of oral antibiotics also continued MBP. In Europe, MBP and oral antibiotics were scarcely used and most surgeons exclusively relied on intravenous antibiotic prophylaxis until the 1990s. To date, the use of oral antibiotics is still not widely accepted in Europe as standard of care. [67,68]

Besides the antibiotic regimen used in the USA, another form of oral prophylaxis can be applied with non-absorbable antibiotics that have a selective activity against certain microorganisms. This strategy, also known as selective decontamination of the digestive tract (SDD), was first introduced to prevent infections in neutropenic patients [69], but was subsequently proposed for use on the ICU [70] and as prophylaxis to prevent SSIs in colorectal surgery. [71–73] In contrast to the neomycin/erythromycin regimen that aims for complete eradication of both Gram-negative and anaerobic microorganisms residing in the colon and rectum, SDD is only directed against pathogenic aerobic bacteria, mainly the Enterobacteriaceae. The underlying hypothesis is that infections caused by endogenous, potentially pathogenic microorganisms occur due to loss of colonization resistance. The latter results from the use of systemic antibiotics disrupting (the assumed) protective anaerobic gut microbiota, which then facilitates overgrowth with Gram-negative bacilli. Maintaining colonization resistance is assumed to decrease the risk of infections with these Gram-negative bacilli. This is hypothesized to be realized by using antibiotics that have a selective activity against Gram-negatives, while sparing the anaerobes.

AIMS AND OUTLINE OF THIS THESIS

Advances in infection control have led to an impressive reduction in infection rates for most types of surgery, as was published in a recent report of the European Centers for Disease Control. [13] Despite all these efforts, the infection rates after colorectal surgery remain high, which stresses the importance of exploring additional infection control measures. The use of old measures such as oral antibiotic prophylaxis has therefore been revisited. [74] Two recent meta-analyses that pooled the results of several RCTs suggest that addition of OAP to perioperative intravenous prophylaxis may reduce the risk of SSIs substantially. [43,75] Extrapolation of these findings towards guideline recommendations, however, is hampered by the large heterogeneity between the studies and by quality issues. More importantly, MBP was used in all RCTs. Its futility without antibiotics has already been proven and combining OAP with MBP is not generalizable to European practice. To date, there is no high-level evidence for the use of OAP without simultaneous MBP administration. [27]

This thesis focusses on the detection and prevention of SSIs after colorectal surgery. Identifying patients with an SSI and monitoring SSI rates is an important part of infection control. **Chapter 2** describes the surveillance of SSIs. The current method for surveillance is through labor-intensive manual chart review. In this chapter, a novel, semi-automatd method that could improve the efficiency of surveillance is proposed. In **Chapter 3**, the concept of implementing and combining evidence-based measures into a care bundle is explained.
The following chapters focus on the use of oral antibiotic prophylaxis as a potential infection control strategy for colorectal surgery. **Chapter 4** presents the first results on the effectiveness of oral antibiotic prophylaxis to prevent SSI risk. The prophylaxis was implemented as standard of care prior to colorectal surgery in a Dutch teaching hospital. The prophylaxis consists of tobramycin and colistin; both non-absorbable antibiotics that exert a selective activity against Gram-negative bacteria. The non-absorbable nature (and thus safety) of these antibiotics as part of a comparable prophylaxis in ICU patients has been questioned recently, as in some critically ill patients, tobramycin could be detected in the blood. Whether this also occurs in patients who receive these antibiotics prior to elective colorectal surgery is discussed in **Chapter 5**. To provide an overview of all available evidence for the use of oral antibiotics before colorectal surgery, we performed a systematic review. In the absence of RCTs, the final meta-analysis included only observational studies. The results of this meta-analysis are discussed in **Chapter 6**. To confirm the effectiveness of the prophylaxis as well as to thoroughly investigate potential adverse effects associated with oral antibiotic prophylaxis, a double-blind, placebo-controlled RCT was designed. The rationale and protocol of this trial are described in **Chapter 7**. Despite many efforts, the trial was prematurely ended. The preliminary results and the lessons that were learned are presented in **Chapter 8**. A synthesis of the results and a general discussion on SSI prevention after colorectal surgery is provided in **Chapter 9**.

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2

A Diagnostic Algorithm for the Surveillance of Deep Surgical Site Infections After Colorectal Surgery

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ABSTRACT

Objective: Surveillance of surgical site infections (SSIs) is important for infection control and is usually performed through retrospective manual chart review. The aim of this study was to develop an algorithm for the surveillance of deep SSIs based on clinical variables to enhance efficiency of surveillance.

Methods: This was a retrospective cohort study (2012 – 2015) conducted in a Dutch teaching hospital. The study population comprised all consecutive patients who underwent colorectal surgery excluding those with contaminated wounds at the time of surgery. All patients were evaluated for deep SSIs through manual chart review, using the CDC criteria as the reference standard.

Analysis: We used logistic regression modelling to identify predictors that contributed to the estimation of diagnostic probability. Bootstrapping was applied to increase generalizability, followed by assessment of statistical performance and clinical implications.

Results: 1,606 patients were included, of whom 129 (8.0%) acquired a deep SSI. The final model included postoperative length of stay, wound class, readmission, reoperation, and 30-day mortality. The model achieved a 68.7% specificity and a 98.5% sensitivity and an Area Under the Receiver Operator Characteristic curve of 0.950 (95% CI 0.932 – 0.969). Positive and negative predictive values were 21.5% and 99.8%, respectively. Applying the algorithm resulted in a 63.4% reduction in the number of records requiring full manual review (from 1,606 to 590).

Conclusions: This five-parameter model identified 98.4% of patients with a deep SSI. The model can be used to develop semi-automatic surveillance of deep SSIs after colorectal surgery, which may further improve efficiency and quality of SSI surveillance.

INTRODUCTION

Surgical site infections (SSIs) are among the most common healthcare-associated infections (HAIs) in surgical patients. [1] SSIs are associated with a substantial clinical and financial burden, due to their negative impact on patient health and the increased costs associated with treatment and extended hospitalization. [2,3] On average, these infections occur in two to four per cent of surgical patients but the infection rates and severity vary across surgical procedures.[4,5] Colorectal surgery is associated with the highest risk of infection, which ranges from 15 to 30 per cent of patients. [6]

The incidence of SSIs and other HAIs are monitored in infection surveillance programs. These programs routinely collect data on HAI rates that are used as reference data for hospitals and health-care providers. [7] Data can be applied to evaluate the quality of care, to identify where improvements are needed and to support and facilitate implementation of new preventive measures. Thus, infection surveillance can be used to reduce SSI-related morbidity and costs. To ensure adequate and reliable surveillance, uniform ascertainment of infection is crucial. International definitions were therefore developed to provide a standardized approach in diagnosing and reporting SSIs. [8] SSI surveillance is traditionally performed by extensive manual review of medical records. Consequently, surveillance is labor-intensive and time-consuming. As the number of surgical procedures continues to rise, the total time spent on surveillance will likely increase as well. [9]

The objective of this study was to develop an algorithm for the surveillance of deep SSIs after colorectal surgery to reduce the number of medical records that require full manual review.

METHODS

Study design

This retrospective cohort study was conducted in the Amphia Hospital (Breda, the Netherlands), a teaching hospital that participates in the national HAI surveillance program. Medical records of all patients who underwent colorectal surgery were manually reviewed by trained infection control practitioners for the identification of a deep SSI. Deep SSIs were defined per the CDC criteria and comprised deep incisional and organ/space infections that manifested within 30 days after surgery.[8] Postoperative complications that developed after discharge were either reported when the patient was referred back to the hospital, or during a postoperative outpatient clinic visit about 30 days after surgery. For the present analysis, we used surveillance data from January 2012 through December 2015. Infection surveillance was performed by the same infection control practitioners throughout the entire study period. A multidisciplinary group of infection control practitioners, surgeons and clinical microbiologists discussed cases to reach consensus on the diagnosis when necessary. Patients who were categorized as having a dirty wound at the time of the surgical procedure (wound class 4) were excluded, because these wounds were already infected at the time of the surgical procedure. Demographic and clinical patient data and data on the surgical procedure were collected by manual chart review, except for data on postoperative use of antibiotics and diagnostic radiological procedures, which were automatically extracted.

We designed the analysis by following the TRIPOD statement for prediction modelling. [10] Candidate model predictors were selected based on literature and included known risk factors or outcomes for deep SSI. [3,11–13] One predictor was selected for every ten events. The administration of preoperative oral and perioperative intravenous antibiotic prophylaxis, ASA classification, wound class, level of emergency, blood loss during the procedure and surgical technique were selected as preoperative and operative

candidate predictors. Preoperative oral antibiotic prophylaxis comprised a three-day course of colistin and tobramycin. Perioperative intravenous prophylaxis was administered per the national infection prevention guideline. [14] Surgical technique was categorized into open, laparoscopic and robotic laparoscopic procedures. Laparoscopic procedures that were converted to open were categorized as open procedures. The postoperative predictors: length of stay, hospital readmission, reoperation, mortality, and in-hospital antibiotic use and abdominal radiologic procedures were assessed 30 days after the primary surgical procedure. Data on 30-day mortality was collected from the hospital database.

Statistical analysis

Univariable associations between baseline characteristics and candidate predictors and deep SSI were estimated using Student's T-test or Mann Whitney U test for continuous variables and Fisher's exact or Chi-square test for categorical variables. We analyzed missing data by comparing patients with complete data with patients who had one or more missing values in the outcome or in the model predictors. Missing data were subsequently imputed using multiple imputation by chained equations (MICE) and 10 datasets were created. [15] Predictive mean matching and logistic regression were used as imputation techniques for continuous and binary variables, respectively. Rubin's rule was applied to calculate pooled results. [16] We built the model using multivariable logistic regression analysis with backward selection. The Akaike Information Criterion (AIC) was used to determine if the model fit could be improved by deleting predictors. Predictors were deleted until the AIC could not be further reduced. The final model was validated internally with bootstrapping to correct for optimism (2000 samples). [17]

We determined discriminatory power and calibration to evaluate the statistical performance of the model. [18,19] Discrimination was defined as the area under the ROC curve (AUC). Calibration of the model was tested by plotting the predicted probabilities against the observed outcomes in the cohort.

The final step was to evaluate the clinical applicability of the model. A predicted probability threshold was selected corresponding to an excellent sensitivity and an acceptable specificity to ensure that the clear majority of cases will be detected. When the individually predicted probabilities exceeded the predefined threshold, the model identified the medical record as having had a high probability for a deep SSI and the medical record was kept for full manual review. The record was immediately classified as 'no deep SSI' if the threshold was not exceeded. At the threshold, the associated sensitivity, specificity, positive predictive value and negative predictive value were calculated.

As an exploratory analysis, we also assessed the diagnostic performance of the strongest predictor. $P<0.05$ (2-sided) was considered statistically significant. All statistical analyses were performed using R version 3.3.2. [20]

RESULTS

A total of 1,717 patients underwent colorectal surgery in the study period, of whom 111 (6.5%) with a dirty wound (wound class 4) were excluded. Of the 1,606 remaining patients, 129 patients acquired a deep SSI (8.0%). Baseline characteristics are presented in Table 1. The median age was 68 years and 55.7% of patients was male. When compared with patients without an SSI, those who acquired an SSI less frequently received prophylactic oral antibiotics before surgery (44.2% versus 60.3%), more frequently had ASA scores of 2 or higher (43.1% versus 28.7%), and had increased risks of reoperation (79.1% versus 6.1%), readmission (24.8% versus 8.9%) and death (8.5% versus 2.3%).

Table 1 Baseline characteristics

Variable	No SSI (n = 1,477)	No SSI (n = 146)	P value
Patient characteristics			
Age in years	68 (60 – 76)	67 (60 – 75)	0.583
Male sex	823/1,477 (55.7)	72/129 (55.8)	0.912
BMI in kg/m^2	25 (23 – 28)	25 (23 – 28)	0.076
Preoperative oral antibiotic prophylaxis	891/1,477 (60.3)	57/129 (44.2)	<0.001
ASA classification >2	400/1,395 (28.7)	53/123 (43.1)	<0.001
Wound class			
Clean contaminated (class 2)	1,355/1,477 (91.7)	112/129 (86.8)	0.082
Contaminated (class 3)	122/1,477 (8.3)	17/129 (13.2)	
Surgery characteristics			
Blood loss in ml	3 (1 – 56)	24 (1 – 60)	0.175
Normothermia	1,049/1,141 (91.9)	95/104 (91.3)	0.981
Implant of non-human tissue	4/1,477 (0.3)	1/129 (0.8)	0.871
Perioperative antibiotic prophylaxis	1,402/1,465 (95.7)	119/127 (93.7)	0.411
Colorectal malignancy	1,112/1,477 (75.3)	90/129 (69.8)	0.201
Surgery in preceding year	169/1,477 (11.4)	13/129 (10.1)	0.746
Experienced surgeon [a]	1,150/1,477 (77.9)	88/129 (68.2)	0.017
Multiple surgical procedures [b]	282/1,477 (19.1)	29/129 (22.5)	0.414
Surgical approach			
Open	729/1,470 (49.6)	80/129 (62.0)	0.022
Conventional laparoscopic	530/1,470 (36.1)	33/129 (25.6)	
Robotic laparoscopic	211/1,470 (14.4)	16/129 (12.4)	
Duration of surgery > 75th percentile [c]	358/1,477 (24.2)	35/129 (27.1)	0.531
Level of emergency			
Acute	52/1,477 (3.5)	8/129 (6.2)	0.194
Elective	1,425/1,477 (96.5)	121/129 (93.8)	
Postoperative course [d]			
Reoperation	90/1,477 (6.1)	102/129 (79.1)	<0.001
Readmission	132/1,477 (8.9)	32/129 (24.8)	<0.001
ICU admission	127/1,477 (8.6)	67/129 (51.9)	<0.001
Death	34/1,477 (2.3)	11/129 (8.5)	<0.001
Length of stay in days	7 (5 – 11)	24 (13 – 38)	<0.001
Abdominal radiological examination [e]	122/1,477 (8.3)	45/129 (34.9)	<0.001
Antibiotic use [e]	241/1,477 (16.3)	70/129 (54.3)	<0.001

Baseline characteristics before imputation. Data are presented as n/N with data (%) or median (interquartile range). P values are the estimated univariable associations between the variable and deep SSI. ASA, American Society of Anesthesiologists; ICU, intensive care unit; IQR, interquartile range; SSI, surgical site infection

a. Performed at least 25 colorectal surgical procedures in one year

b. Multiple surgical incisions during the same surgical procedure, excludes creation of ostomy

c. 75th percentiles of duration of surgery accounting for the type of resection and for the surgical approach, according to PREZIES reference values [27]

d. All postoperative variables are assessed 30 days after the index procedure

e. Starting 48 hours after the primary procedure

Table 2 Final model for the prediction of deep SSI

Predictor	Odds ratio	95% CI
Wound class		
Clean-contaminated (class 2)	*Reference*	*Reference*
Contaminated (class 3)	2.25	0.95 – 4.88
Hospital readmission	3.97	1.92 – 7.72
Reoperation	26.20	13.95 – 14.43
Postoperative length of stay, days	1.07	1.05 – 1.09
Death	3.09	1.23 – 7.57

Final logistic regression model. Intercept (alpha): -5.234. Odds ratios and confidence intervals are corrected for optimism by bootstrapping (2000 samples). Predictors not retained in the model: ASA classification, level of emergency, preoperative oral antibiotic prophylaxis, blood loss during surgery, surgical approach, administration of antibiotics and the requests for radiology of the abdomen. All patients (n= 1,616) had complete data on all five predictors. CI, confidence interval; OR, odds ratio; SSI, surgical site infection

Baseline characteristics for patients with complete data and for patients with one of more missing values are shown in Supplementary Table 1. One hundred and nine patients (6.8%) were missing data for at least one of the covariables (6.8%). Patients with complete data differed significantly from those with missing data which supported the use of multiple imputation to reduce the risk of bias due to missingness.
The final diagnostic model, including bias-corrected estimates, is shown in Table 2. The predictors retained in the model after backward selection are wound class, reoperation, readmission, length of stay and death. The prediction rule is illustrated in Supplementary figure 1. The discriminatory power of the final model was 0.950 (95% CI 0.932 – 0.969) (Figure 2A), with good calibration (Figure 2B). The calibration slope that was used to shrink the estimates was 0.978, indicating slight overprediction of the model before bootstrapping.

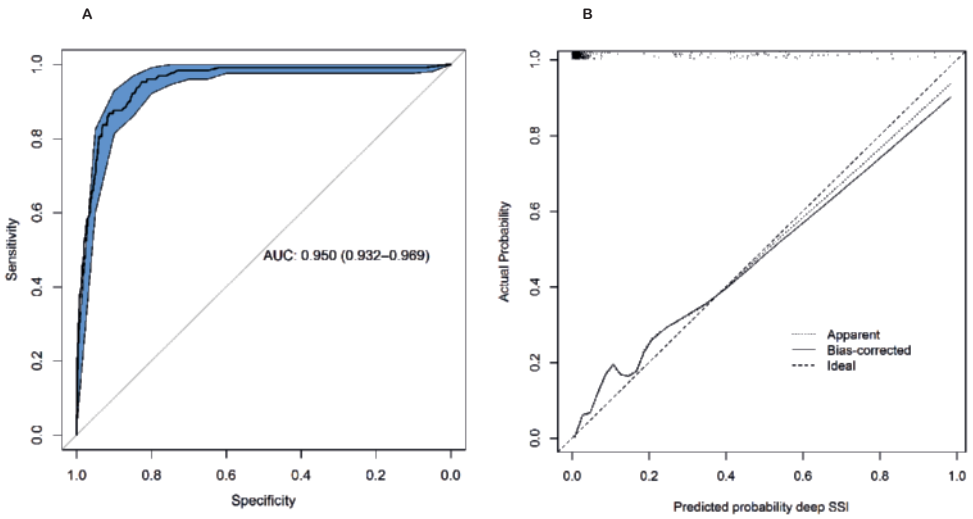

Figure 2 Statistical model performance
A. ROC curve with discriminatory power expressed as AUC (AUC 0.950, 95% CI 0.932 – 0.969). **B**. Calibration plot of the model. Calibration refers to the correspondence between the probability of SSI predicted by the model and the actual probability of infection. The diagonal line represents perfect calibration, the dotted line represents the actual calibration, and black line represents calibration after bootstrapping. Slope of the linear predictor was 0.978. AUC, area under the curve; CI, confidence interval; SSI, surgical site infection

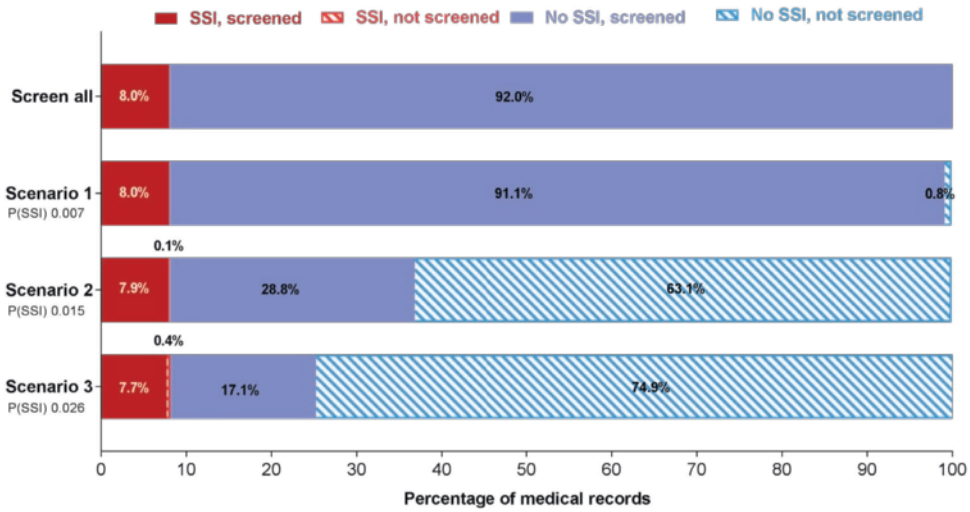

Figure 3 Clinical applicability of the prediction model. manual screening of all files is compared with screening a subset of files that are preselected by the prediction model. three scenarios with different cut offs in predicted probability for SSI are presented. When the predicted probability for a patient exceeds the cut off value, the patient file will be identified as a possible SSI and will be retained for manual review. If the threshold is not exceeded, the patient file will be discarded immediately. the solid bars represent the files that are manually screened, the striped bars represent the files that are discarded. When the predicted probability cut off increases, the number of files that need to be reviewed manually decreases. The number of missed SSI cases (i.e. false negatives) will increase. P(SSI), predicted probability for surgical site infection

To assess the clinical applicability of the model (Figure 3), we compared complete chart review with the results produced by the final model when we used three different predicted probability thresholds. At the predicted probability threshold of 0.015, the model had a 98.5% sensitivity, 68.7% specificity, 21.5% positive predictive value and 99.8% negative predictive value for predicting deep SSIs. (Table 3). The number of medical records that required manual review was reduced from 100% to 36.7% (from 1,606 to 590 records). Finally, the diagnostic performance of the strongest predictor (reoperation) was evaluated. Reoperation was strongly associated with deep SSIs and had a good discriminatory power (AUC 0.865 [95% CI 0.829 – 0.901]) at a 79.1% sensitivity, 93.7% specificity, 53.1% positive predictive value and 98.1% negative predictive value. With this single predictor, the number of charts to review manually was reduced to 11.9% (from 1,606 to 192 records).

Table 3 Contingency table for the prediction of deep SSIs

Predicted probability	Deep SSI	No deep SSI	Total	
P(SSI) ≥0.015	127	463	**590**	PPV (%): 21.5 (95% CI 20.2 – 22.9)
P(SSI) <0.015	2	1,014	**1,016**	NPV (%): 99.8 (95% CI 99.2 – 99.9)
Total	129	1,477	**1,606**	
	Sensitivity (%): 98.5 (95% CI 94.5 – 99.8)	Specificity (%): 68.7 (95% CI 66.2 – 71.0)		

CI, confidence interval; NPV, negative predictive value; P(SSI), probability of surgical site infection; PPV, positive predictive value

DISCUSSION

We developed a five-parameter diagnostic model that could identify 98.5% of all deep SSIs with a 99.8% negative predictive value. Use of the model could reduce the number of medical records that required full manual review from 1,606 (100%) to 590 (36.7%) at the cost of two missed deep infections (1.6% of deep SSIs). Increasing the predicted probability threshold would allow for further reduction of workload but would also increase the likelihood of missed SSIs. Using only reoperation to detect deep SSIs, the number of medical records for complete manual review was substantially reduced, although this method is associated with a higher false negative rate and lower discriminatory power compared to the full model. Nevertheless, we suggest that reoperation should be included as a model parameter when new algorithms are developed for colorectal SSI surveillance. We set the model threshold at an excellent sensitivity so that it could detect a high percentage of patients with an SSI. The trade-off for this high sensitivity was a relatively high rate of false positives due to a moderate specificity, which we accepted because the model would be used to identify the patients with a high probability of SSI whose records would then be reviewed. Thus, the lower specificity would not affect case finding. The moderate false positive rate decreases the efficiency of the model. However, SSI surveillance that uses the model to identify patients whose records need to be reviewed will be more efficient than reviewing every patient's record. Because this model has a high sensitivity, it could be used for quality improvement purposes and for benchmarking. Previous studies of drain-related meningitis [21], bloodstream infections [22] and SSIs after orthopedic procedures [23] found that algorithms performed well compared to manual surveillance. For the surveillance of SSIs after gastrointestinal surgery, algorithms have been developed using several approaches, such as Bayesian network modelling (AUC 0.89) [24], logistic regression modelling (AUC 0.89) [25] or machine learning (AUC 0.82). [26]
We made several efforts to secure generalizability and validity of our findings. We aimed to take an objective approach in model development by selecting predictors exclusively on theoretical grounds and by performing backward selection using the statistical model fit. Subsequently, the model was internally validated and, as such, we attempted to reduce the risk of overprediction. We obtained complete data on the outcome with the reference standard and we did not change the definition of SSI the during the study period which prevents selection bias due to partial verification.

Several limitations should be addressed. The use of routine care data as well as retrospective data collection is inevitably associated with missing information. Proper handling of missing data reduces the risk of bias and improves precision. We applied multiple imputation (MICE) to handle the missing data, which has been demonstrated previously to improve the performance of automated detection of SSIs. [26] When this model will be used in clinical practice, missing data cannot be managed using the same method, which is an issue with applying prediction models in general. In the case of missing values, the model cannot calculate a predicted probability. By using backward selection in algorithm development, the number of parameters is reduced, which also limits the amount of information that is needed for adequate diagnostic performance. As such, the clinical applicability will be enhanced because the risk of missing values is reduced. We had no missing data in any of the model covariables and thus expect that missing data will not be an important issue when the algorithm will be applied in clinical practice.
Another limitation is that the model was developed on data derived from a single hospital. The parameters in the final model should be available in most medical records. Hospitals wishing to validate the algorithm in their colorectal surgical population should therefore ensure that all parameters are available electronically. External validation will be also essential before the model can be applied in practice. Ideally, data

derived from multiple hospitals is used to confirm model performance in other settings and future studies may also investigate less data-driven methods of model development for semi-automated surveillance.

In conclusion, we developed a five-parameter diagnostic model that identified 98.5% of the patients who acquired a deep SSI and reduced the number of medical records requiring complete manual screening by 63.4%. These results can be used to develop semi-automatic surveillance of deep SSIs after colorectal surgery.

List of abbreviations:
AIC, Akaike information criterion; ASA, American Society of Anesthesiologists; AUC, area under the curve; CDC, Centers for Disease Control and Prevention; CI, confidence interval; ICU, intensive care unit; MICE, multiple imputation using chained equations; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value; SSI, surgical site infection

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SUPPLEMENTARY MATERIAL

Supplementary Table 1 Distribution of variables among patients without and with missing values

Variable	No missings n = 1,497 (93.2)	≥ 1 missing n = 109 (6.8)	P value
Age in years	68 (60 – 67)	68 (59 – 77)	0.931
Male sex	839 (56)	56 (51.4)	0.397
BMI in kg/m^2	25 (23 – 28)	25 (22 – 29)	0.976
Preoperative oral antibiotic prophylaxis	909 (60.7)	28 (25.7)	<0.001
ASA classification >2	438 (29.3)	15 (71.4)	<0.001
Wound class			
Clean contaminated	1,375 (91.9)	92 (84.4)	0.013
Contaminated	122 (8.1)	17 (15.6)	
Operative duration >75th percentile	379 (25.3)	14 (12.8)	0.005
Normothermia during surgery	1,069 (91.8)	75 (93.8)	0.675
Blood loss in ml	3 (1 – 56)	24 (1 – 60)	0.447
Implant of non-human tissue	5 (0.3)	0 (0.0)	1.000
Perioperative antibiotic prophylaxis	1,436 (95.9)	85 (89.5)	0.007
Colorectal malignancy	1,130 (75.5)	72 (66.1)	0.038
Surgery in preceding year	176 (19.2)	6 (5.5)	0.067
Experienced surgeon [a]	1,180 (78.8)	58 (53.2)	<0.001
Multiple surgical procedures [b]	287 (19.2)	24 (22.0)	0.548
Surgical approach			
Open [c]	729 (48.7)	80 (78.4)	<0.001
Conventional laparoscopic	548 (36.6)	15 (14.7)	
Robotic laparoscopic	220 (14.7)	7 (6.9)	
Level of emergency			
Acute	48 (3.2)	12 (11.0)	<0.001
Elective	1449 (96.8)	97 (89.0)	
Reoperation	119 (11.1)	73 (13.7)	0.157
Readmission	106 (9.9)	58 (10.9)	0.603
ICU admission	112 (10.4)	82 (15.4)	0.006
Death	20 (1.9)	25 (4.7)	0.002
Length of stay in days	6 (4 – 10)	7 (5 – 12)	<0.001
Abdominal radiological examination [d]	155 (14.5)	12 (2.5)	<0.001
Prescription of antibiotics [d]	290 (27.1)	21 (32.2)	0.436
Deep SSI	121 (8.1)	8 (7.3)	0.926

Comparison of complete cases to patients with one or more missing values. Complete cases were defined as absence of missing values in any of the covariables or in the outcome of the multivariable model. Data are presented as n (%) or median (interquartile range). ASA, American Society of Anesthesiologists; ICU, intensive care unit; IQR, interquartile range; SSI, surgical site infection

a. Performed at least 25 colorectal surgical procedures in one year

b. Multiple surgical incisions during the same surgical procedure, excludes creation of ostomy

c. 75th percentiles of duration of surgery accounting for the n type of resection and for the surgical approach, according to PREZIES reference values [27]

d. Starting 48 hours after the primary procedure

$$P(SSI) = \frac{1}{1 + e^{-LP}}$$

LP = LP = -5.234 + 0.890* contaminated wound (class 3) + 3.037 * reoperation + 1.489 * readmission + 0.085 * number of postoperative days admitted to the hospital + 1.127 * death

Supplementary Figure 1 Prediction rule for deep surgical site infections. LP, linear predictor; P(SSI), predicted probability of surgical site infection

3

Combining Evidence-Based Measures: Preventing Surgical Site Infections with Care Bundles

Tessa Mulder and Jan Kluytmans

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Surgical site infections (SSIs) are one of the most common hospital-acquired infections in surgical patients.[1] On average, SSI rates vary between 2 – 4%, but there is significant variation across surgical specialties and procedures. For patients undergoing colorectal surgery, the infection rates are among the highest, as 15 – 30% of the patients will develop an infection.[2] SSIs increase patient morbidity because they can have serious consequences for postoperative recovery. On average, they are associated with a two to threefold increase in costs. [3]

In the past decades, efforts have been made to reduce SSI rates. Improvements in infection control practice have led to an impressive reduction in infection rates for most surgical procedures, as was published in a recent report by the European Centers for Disease Control.[4] However, the SSI rates after colorectal procedures remain high. The number of surgical procedures continues to rise and, likewise, the number of patients at risk for an SSI increases as well. [5,6] This underlines the urgency of further improvement of infection control practice for colorectal surgery to achieve a reduction in the infection rates.

High quality studies have delivered important insights into patient-related and perioperative risk factors for the development of SSIs. Based on this knowledge, several preventative measures were developed and studied. Proven measures to lower the risk of SSIs include the administration of a perioperative intravenous antibiotic prophylaxis, chlorhexidine/alcohol skin preparation, maintenance of normothermia and normoglycemia, the use of electrical clippers instead of razors for hair removal, and preoperative bowel preparation with oral antibiotics. [7] These measures have all been shown to be effective when tested individually under well-controlled conditions [8]. Unfortunately, implementation of these measures in routine surgical practice has been difficult thus far. To improve this, the Institute of Healthcare Improvement (IHI) suggested combining the individual evidence-based measures into bundles with the aim to improve patient outcomes. A bundle of infection control measures was shown to be extremely successful in reducing catheter-related blood stream infections[9] and ventilator-associated pneumonia. [10] A similar approach has been proposed for SSI prevention, since there are several evidence-based interventions available. [11]

The retrospective study by Jaffe *et al.* [12] investigated the impact of a "bundle of care" on the SSI rate after colon surgery in Michigan State. The study was performed by 24 hospitals of the Michigan Surgical Quality Collaboration (a network of 73 hospitals) and included patients who underwent elective colon surgery from 2012 to 2015. Primary outcomes were deep or organ/space SSIs within 30 days of surgery and 30-day episodic costs. The bundle of care was comprised of six elements: prophylactic intravenous antibiotics administered within 60 minutes before surgical incision and with an appropriate selection of antimicrobial agents, minimally invasive surgery, short operative duration, maintenance of postoperative normothermia, preoperative mechanical bowel preparation with oral antibiotics and control of postoperative blood glucose levels. Risk of SSIs was adjusted for hospital-level clustering, case mix of left- and right-sided hemicolectomy and for patient risk factors including body mass index >30 m^2, history of alcohol abuse, history of corticosteroid therapy, age >70 years, wound class, ASA classification, functional status, race, diabetes, albumin and ICD9 diagnosis group. The analysis was conducted to determine the effect of the bundle compliance on SSI rate and on the value of colectomy procedures. The study reported SSI rates as low as 0.9% (95% CI 0 – 3.0%) when there was compliance with all six bundle components. On the contrary, a rate of 17.9% (95% CI 10.8 – 27.0%) was found when bundle adherence was lowest (1 or none of the components). Surgeons were consulted to assess their perceptions of poor compliance. As such, compliance to the bundle was stratified into low compliance (to 0 – 2 components) and high compliance (to 3 – 6 components). After stratification and adjustment, a risk-adjusted SSI rate of 8.2% (95% CI 7.2 – 9.2%) in the high compliance group and 16.0% (95% CI 12.9 – 19.1%) in the poor compliance group was found, which correlates to a relative risk reduction of 48.7%. The authors also reported that high compliance to the bundle leads to an average reduction in episodic costs of 23.8% or $4,664 ($p < 0.01$) when compared with poor compliance.

The results of this study are in line with findings of previous studies on the implementation of a bundle of care with the aim to reduce SSIs after colorectal surgery. Two recent meta-analyses reported pooled unadjusted risk ratios of 0.55 (95%CI 0.39 – 0.77, p = 0.005) [13] and 0.598 (95%CI 0.496 – 0.722, p <0.001) [14] on SSI development when a bundle was used, compared to patients in whom no bundle of care was applied. Even though Jaffe *et al.* did not use a proper control period or group for comparison, which may have resulted in a dilution of the intervention's effect, the study reported a substantial reduction in SSIs with the use of an infection prevention bundle.
A couple of remarks should be made after critical appreciation of this study. First of all, the authors did not report several basic and essential elements in their paper. These elements are essential for readers to appreciate the findings and, as such, they are included in the STROBE guidelines' checklist of items that should be included in the report of cohort studies. For example: absolute numbers of patients and events are lacking but also the distributions of patients across the different groups are not mentioned. An overview of the baseline demographics is missing, and more importantly, the distribution of patient risk factors, used for multivariable analysis, is not available. This information is crucial for the reader to understand the study design as well as to reflect on the results. Also, it is essential to report the final multivariable model to understand the analysis and its results. This includes reporting the unadjusted and adjusted effect estimates of all the co-variables that are used to correct for confounding. The reader of this paper is left guessing about the approach the authors used to correct for confounding bias. Correction for confounding is an important issue, especially in observational studies. When the correction is not performed carefully, the observed treatment effect can be severely affected by other factors and unjustified conclusions can be drawn. Although the authors discuss that their risk standardization cannot account for all the patient factors and that other factors might influence infection risk as well as bundle compliance, they do not include this limitation in their conclusions. These flaws in the report make the data unsuitable to draw conclusions about the effect of bundle adherence.

A second point to consider is the choice of the bundle elements. To create an effective bundle of care, several factors are important. Like the interventions used in the bundle of Jaffe *et al.,* the individual measures must all be evidence-based. Secondly, the number of components must be limited, as increasing the number of measures will lead to decreased motivation of the healthcare personnel involved and to a lower compliance rate. Ideally, three to five components are used. [15] A final aspect to take into consideration is to select measures that could be applied to every patient. In this study, it can be debated whether the components 'minimally invasive procedure' and 'short duration of surgery' are appropriate bundle components, reflecting on their applicability. The practice of minimally-invasive surgery and the duration of the surgical procedure both depend on patient-related factors and underlying morbidity. Modification of these bundle components in order to reduce infection rates is therefore problematic since this often lies beyond the control of the surgeon or the surgical team. It may be questioned if these bundle components are appropriate.

A different aspect that deserves some discussion is the definition of a bundle of care. Most bundles that are reported in the literature do not fullfil the definitions and underlying concepts of the IHI care bundles. [15] The IHI bundles entail much more than tying some interventions together. It is a strategy that aims to implement a culture of safety, which assumes full adherence to all bundle elements in all patients. The IHI states the following: "Successfully implementing a bundle is clear-cut: "Yes, I completed the ENTIRE bundle, or no, I did not complete the ENTIRE bundle. There is no in-between; no partial "credit" for doing some of the steps some of the time." [15] This important aspect is totally different from what is observed in the study by Jaffe *et al.,* where only a fraction of all patients had full adherence to all six bundle elements (we estimate that it is

a fraction as the infection rate was extremely low in the group with adherence to six bundle elements, but the exact numbers are not provided in the paper). High bundle compliance with a zero-tolerance approach is considered crucial to achieve a culture change. [16–18] By aiming for zero-tolerance, failure to comply with any bundle element is considered a serious mistake and thereby a culture of safety is created. [19] For the bundle to remain effective after its implementation, it is essential that long-term compliance is ensured. Teamwork, including active engagement of everyone involved in the procedure is essential to achieve and maintain compliance. A change of attitude and alteration of culture are vital in achieving this. [14] Making surgeons and their surgical teams aware of the results of their operations (for example by recording and reporting bundle compliance and SSI rates) can significantly improve motivation to adhere to the bundle. Regular communication meetings could also be encouraging and helpful in creating a united attitude towards improving infection control. [20] Unfortunately, the authors do not mention the methods used for implementation, nor if a zero-tolerance approach was applied.
Aside from a change of culture, formal testing of the bundle in relation to the outcome also precedes successful implementation of the bundle in daily practice. This is illustrated by the findings of a large randomized controlled trial that investigated the effect of a bundle of infection control measures for SSI reduction after colorectal surgery compared to a control arm. [21] Even though evidence-based components were selected for the bundle, an unexpected and strong increase in SSI rates was observed in the intervention arm. These findings suggest a cautious approach must be taken in bundling evidence-based measures without formal testing of the bundle in the target population, as a bundle does not necessarily produce the expected effect.

In line with the authors' conclusion, bundling infection control measures is a promising strategy in reducing SSI rates after colorectal surgery and could, therefore, have a serious impact on patient outcomes and costs. The unaffected high SSI rates after colorectal surgery force us to adapt our strategies. Previous studies have provided important insights into risk factors and interventions for SSIs that have not led to a reduction in postoperative infection rates so far. Bundling this knowledge by combining evidence-based interventions could be the first step in reducing SSI rates after colorectal surgery. However, a care bundle is more than just a compilation of evidence-based interventions. The full strength of a bundle is achieved when it is implemented using a zero-tolerance approach, with the aim to implement a safety culture. Finally, bundles are not magic bullets and the effects on outcome should be carefully monitored and reported using appropriate methods.

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4

Preoperative Oral Antibiotic Prophylaxis Reduces Surgical Site Infections After Elective Colorectal Surgery: Results from a Before-After Study

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ABSTRACT

Background: Surgical site infections (SSIs) are common complications after colorectal procedures and remain an important source of morbidity and costs. Preoperative oral antibiotic prophylaxis is a potential infection control strategy, but its effectiveness without simultaneous use of mechanical bowel preparation (MBP) is unclear. In this study, we aimed to determine whether preoperative oral antibiotics reduce the risk of deep SSIs in elective colorectal surgery.

Methods: We performed a before-after analysis in a teaching hospital in the Netherlands. Patients who underwent surgery between January 2012 and December 2015 were included. On January 1st, 2013, oral antibiotic prophylaxis with tobramycin and colistin was implemented as standard of care prior to colorectal surgery. The year before implementation was used as control period. The primary outcome was a composite of deep surgical site infection and/or mortality within 30 days after surgery.

Results: Of the 1,410 patients, 352 underwent colorectal surgery in the control period and 1,058 in the period after implementation of the antibiotic prophylaxis. We observed a decrease in incidence of the primary endpoint of 6.2% after prophylaxis implementation. When adjusted for confounders, the risk ratio for development of the primary outcome was 0.58 (95% CI 0.40 – 0.79). Other findings included a decreased risk of anastomotic leakage and a reduction of the length of postoperative stay.

Conclusions: Preoperative oral antibiotic prophylaxis prior to colorectal surgery is associated with a significant decrease in SSI and/or mortality in a setting without MBP. Preoperative oral antibiotics can therefore be considered without MBP for patients undergoing colorectal surgery.

BACKGROUND

Surgical site infections (SSIs) are common complications after colorectal surgery and affect 15% to 30% of patients. [1,2] SSIs often require extensive therapeutic intervention, prolong hospital stays and therefore increase health-care costs. To reduce the risk of SSIs, international infection control guidelines recommend administration of perioperative intravenous antibiotic prophylaxis. [3] Whereas implementation of care bundles and management of risk factors have led to a further decline in SSIs for many surgical procedures, the infection rates after colorectal surgery remain high. [4]

Colorectal surgery is inherently associated with a high risk of SSI due to high bacterial load in the colon. Initial attempts to reduce SSIs after colorectal surgery focused on lowering the bacterial load with oral antibiotics administered before surgery. These antibiotics were historically combined with mechanical bowel preparation (MBP), a technique that involves the administration of osmotic substances to clean the gastrointestinal tract. MBP and antibiotics were administered simultaneously because it was assumed that the antibiotics had an increased activity in a cleaned colon. [5,6] When combined, MBP and oral antibiotics were proven to reduce SSI rates after colorectal surgery. [7,8] However, routine use of MBP was recently omitted due to lack of evidence for advantageous effects that outweigh the potential risk of anastomotic leakage or dehydration following MBP. [9,10] Consequently, oral antibiotics were also abandoned even though their impact on the risk of SSI without MBP was unknown.

Whether oral antibiotic prophylaxis without MBP reduces the incidence of SSIs after colorectal surgery needs further investigation. [1] The aim of this study was to determine the effect of the implementation of preoperative oral antibiotic prophylaxis (OAP) as standard of care without MBP on the development of infectious and non-infectious complications after elective colorectal surgery.

METHODS

Study design and study population

We used a before-after study design to evaluate a change in clinical practice in a Dutch teaching hospital (Amphia Hospital, Breda). Patients who underwent colorectal surgery between January 2012 and December 2015 were included. OAP was implemented as standard of care for all elective colorectal procedures on January 1st, 2013. As such, 2012 was used as the control period. The first two months of 2013 were considered as the implementation phase and were excluded from the analysis. MBP was abandoned from the local protocol before the start of the study. However, it was applied sporadically in the study period, and patients who received MBP were excluded. Other grounds for exclusion included acute surgery or when infection control practitioners categorized wounds as dirty at the time of the surgical procedure (wound class 4). These wounds are assumed to be contaminated prior to hospital admission and do not meet the criteria for SSI, which are healthcare-acquired. [11]

Oral antibiotic prophylaxis

OAP is a solution of tobramycin (16 mg/ml) and colistin sulphate (20 mg/ml). OAP was administered four times daily in doses of 5 ml, during the three days before surgery. Patients who underwent rectal surgery received one additional enema with the antibiotic solution one day before surgery. All patients received perioperative intravenous antibiotic prophylaxis per the Dutch infection control guidelines. [12]

Outcomes

The primary outcome of the study was a composite of deep SSI and/or mortality within 30 days of surgery. A composite endpoint was used to account for mortality potentially being a competing event for the development of a deep SSI. SSIs were diagnosed through manual chart review using the CDC criteria. [13] Deep SSIs included deep incisional and organ/space infections. The components of the primary outcome were also analyzed as secondary outcomes. Other secondary outcomes included superficial SSI, anastomotic leakage, postoperative length of hospital stay, ICU stay, *Clostridium difficile* infection, relaparotomy and 6-month mortality. Data on patient characteristics, surgery and outcomes were extracted from the medical records by trained infection control practitioners.

Statistical analysis

The cohort was divided into a control period (2012) and OAP period (2013 – 2015) based on the date of surgery. Patient and operative characteristics were compared across study periods. We analyzed missing data by comparing complete cases to patients with missing values in baseline characteristics and primary outcome. Missing values were subsequently imputed using multiple imputation by chained equations (MICE). [14] A total of 10 imputed datasets was created and Rubin's rule was applied to calculate pooled results. [15]

We analyzed the effect of OAP implementation using a multivariable binomial regression model with a log link function to estimate the adjusted risk ratios for the primary outcome. [16,17] Age, sex, BMI, perioperative antibiotic prophylaxis, colorectal malignancy, operative duration above the 75th percentile, surgical approach, ASA classification, wound class and experience of the surgeon were included as covariables to adjust for confounding. Confounder selection was done based on literature.[18,19] Surgical approach was categorized as open procedure, conventional laparoscopy or robotic laparoscopy. Surgeon experience was defined as performing at least 25 colorectal procedures in one year. The 75th percentiles of duration of surgery were determined using predefined reference values, accounting for the type of resection and the surgical approach. [20] Time trends were inspected by plotting the percentage of patients who developed the primary outcome per month. Subsequently, we performed sensitivity analyses to evaluate whether a time trend affected the occurrence of the primary outcome by adding a time component to the original regression model. For each patient, the month of study, i.e. the number of months between the start of the study on January 1st of 2012 and the day of surgery, was added as covariable to the model. We fitted an additional model including an interaction term (month of study * study period). Model fit was assessed using the Akaike Information Criterion (AIC). P <0.05 (2-sided) was considered statistically significant. All statistical analyses were performed using R version 3.3.2. [21]

Ethics

All data were collected as part of a national infection surveillance program. No additional procedures were added to routine clinical care and all data were pseudonymized. As such, the study did not fall in the scope of the Medical Research Involving Human Subjects Act (WMO) and was not evaluated by the IRB.

RESULTS

Patient enrolment is shown in Figure 1. In total, 1,410 patients underwent elective colorectal surgery during the study period, of whom 352 in the control period (2012) and 1,058 in the OAP period (2013–2015).

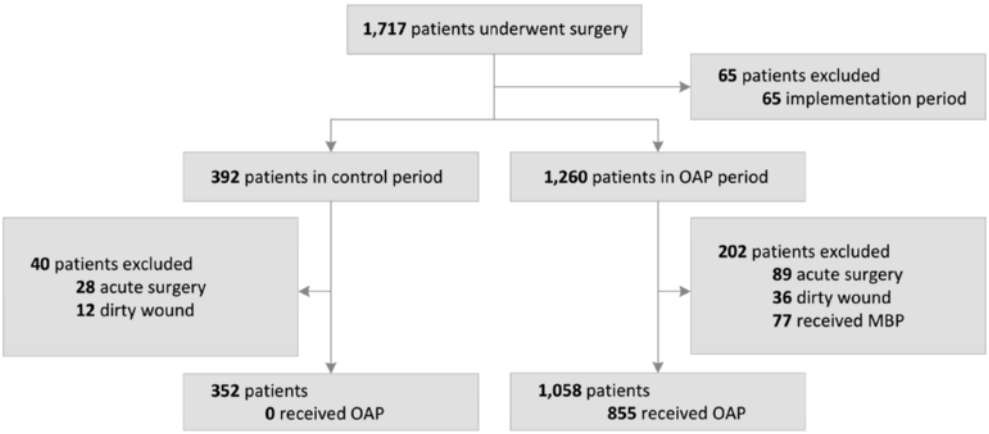

Figure 1 Enrolment of patients
Dirty wounds represent wound class 4, i.e. pre-existing infection of the wound. *203 patients did not receive OAP, of whom 159 did not receive oral antibiotic prophylaxis because of a sub-acute surgical procedure. MBP, mechanical bowel preparation; OAP, oral antibiotic prophylaxis

The baseline characteristics per study period are presented in Table 1. The median age was 68 years. In the OAP period, 79.3% of the patients underwent surgery because of an underlying colorectal malignancy, compared to 70.2% of the patients in the control period (P = 0.005). A difference in surgical techniques was found (P = 0.001), with an increase in the practice of minimally invasive surgery over time. Likewise, duration of surgery increased from a median of 107 minutes (IQR 72 – 155) in the control period to 123 minutes (IQR 83 – 185) in the OAP period (P <0.001). The percentage of patients with a clean-contaminated wound was higher in the OAP period than in the control period (93.1% versus 87.8%, P = 0.002). Baseline characteristics for complete cases and for patients with one or more missing values are shown in Supplementary Table 1. From 1,310 (92.2%) patients we had complete data, compared to 100 patients who had missing values in at least one of the model covariables (7.1%). Complete cases differed significantly from incomplete cases, which supported multiple imputation to reduce the risk of bias.

The risks of outcomes per study period (including the risk ratios) are presented in Table 2. The crude risk of a deep SSI or mortality within 30 days after surgery was statistically significantly reduced from 14.2% in the control period to 8.0% in the OAP period. (RR 0.57 [95% CI 0.41 – 0.79]). The risks of deep SSI (RR 0.54 [95% CI 0.37 – 0.78]) and anastomotic leakage (RR 0.57 [95% CI 0.35 – 0.90]) were also significantly reduced in the OAP period. Furthermore, the median length of postoperative hospital stay decreased from 8 days (IQR 6 – 14) to 7 days (IQR 5 – 11) after introduction of OAP (P <0.001). Study periods did not differ in the risk of superficial SSI, re-laparotomy, *C. difficile* infection, the number of ICU admissions and the postoperative length of ICU stay.

Table 1 Baseline characteristics

	Control period (n = 352)	OAP period (n = 1,048)	P value
Patient characteristics			
Age in years, median (IQR)	68 (60 – 76)	68 (60 – 76)	0.884
Male sex	185/352 (52.6)	602/1,058 (56.9)	0.173
BMI in kg/m^2, median (IQR)	25 (23 – 29)	26 (23 – 29)	0.464
Obese (BMI >30 kg/m^2)	57/340 (16.8)	153/1,048 (14.6)	0.223
ASA classification			
1-2	228/339 (67.3)	734/1,003 (73.2)	0.043
3-5	111/339 (32.7)	269/1,003 (26.8)	
Colorectal malignancy	247/352 (70.2)	839 (79.3)	0.005
Abdominal surgery in the preceding year	43/352 (12.2)	113/1,058 (10.7)	0.433
Operative characteristics			
Perioperative intravenous antibiotic prophyalxis	338/349 (96.8)	1,007/1,048 (96.1)	0.627
Type of resection			
Partial resection of colon	187/347 (53.9)	614/1,056 (58.1)	0.112
Total colectomy or low anterior resection	96/347 (27.7)	295/1,056 (27.9)	
Creation or removal of stoma	64/347 (18.4)	147/1,056 (13.9)	
Surgical approach			
Open surgery [a]	196/347 (56.5)	441/1,056 (41.8)	<0.001
Conventional laparoscopic surgery	112/347 (32.3)	431/1,056 (40.8)	
Robotic laparoscopic surgery	39/347 (11.2)	184/1,056 (17.4)	
Duration procedure in minutes, median (IQR)	107 (72 – 155)	123 (83 – 185)	<0.001
Duration procedure >75th percentile [b]	63/352 (17.9)	297 (28.1)	<0.001
Normothermia	222/248 (89.5)	786/848 (92.7)	0.138
Experienced surgeon [c]	280/352 (79.5)	824/1,058 (77.9)	0.561
Wound class			
Clean-contaminated (class 2)	309/352 (87.8)	985/1,058 (93.1)	0.002
Contaminated (class 3)	43/352 (12.2)	73/1,058 (6.9)	
Implants of non-human tissue	2/352 (0.6)	2/1,058 (0.2)	0.261

Data are presented as n/N with data (%), unless specified otherwise. ASA, American Society of Anesthesiologists; IQR, interquartile range

a. Includes the procedures that are converted from laparoscopic to open surgery

b. 75th percentiles of duration of surgery accounting for the type of resection and for the surgical approach, according to PREZIES reference values [20]

c. Performs at least 25 colorectal procedures in a year

Results of the multivariable analysis are presented in Table 3. The adjusted risk for the primary outcome was significantly lower in patients in the OAP period (aRR 0.58 [95% CI 0.40 – 0.79]).

Figure 2 shows the percentage of patients who developed the primary outcome per month. The intercept of the regression line fitted in the OAP period is lower, indicating that OAP implementation led to an instantaneous decrease in SSI incidence. The regression slope of the control period demonstrates that the SSI incidence was stable before OAP implementation, whereas the slightly negative slope in the OAP period indicates that other factors apart from OAP could have had a modest impact on SSI incidence as well.

Table 2 Crude associations between treatment period and outcomes

Outcomes	Control period (n = 352)	OAP period (n = 1,048)	Risk Ratio	95% CI
30 days after surgery				
Deep SSI and/or mortality	50 (14.2)	85 (8.0)	0.57	0.41 – 0.79
Deep SSI	42 (11.9)	68 (6.4)	0.54	0.37 – 0.78
Mortality	12 (3.4)	22 (2.1)	0.61	0.31 – 1.22
Superficial SSI	25 (7.1)	65 (6.1)	0.87	0.55 – 1.35
Anastomotic leakage	27 (7.6)	46 (4.3)	0.57	0.35 – 0.90
Relaparotomy	51 (14.5)	115 (10.9)	0.75	0.55 – 1.02
Clostridium difficile infection	1 (2.8)	1 (0.1)	0.33	0.02 – 5.31
6 months after surgery				
Mortality	29 (8.2)	71 (6.7)	0.81	0.53 – 1.23
ICU admission [a]	49 (13.9)	111 (10.5)	0.75	0.55 – 1.03
	Days, median (IQR)		**P value**	
Postoperative length of stay, days [b]	8 (6 – 14)	7 (5 – 11)	<0.001	
Postoperative length of ICUstay, days [b]	0 (0 – 0)	0 (0 – 1)	0.047	

Data are presented as n(%). No missing data on outcomes. ICU, intensive care unit; IQR, interquartile range; SSI, surgical site infection
a. Excluding 1 routine day of ICU admission in the case of robotic surgery.
b. Including readmissions

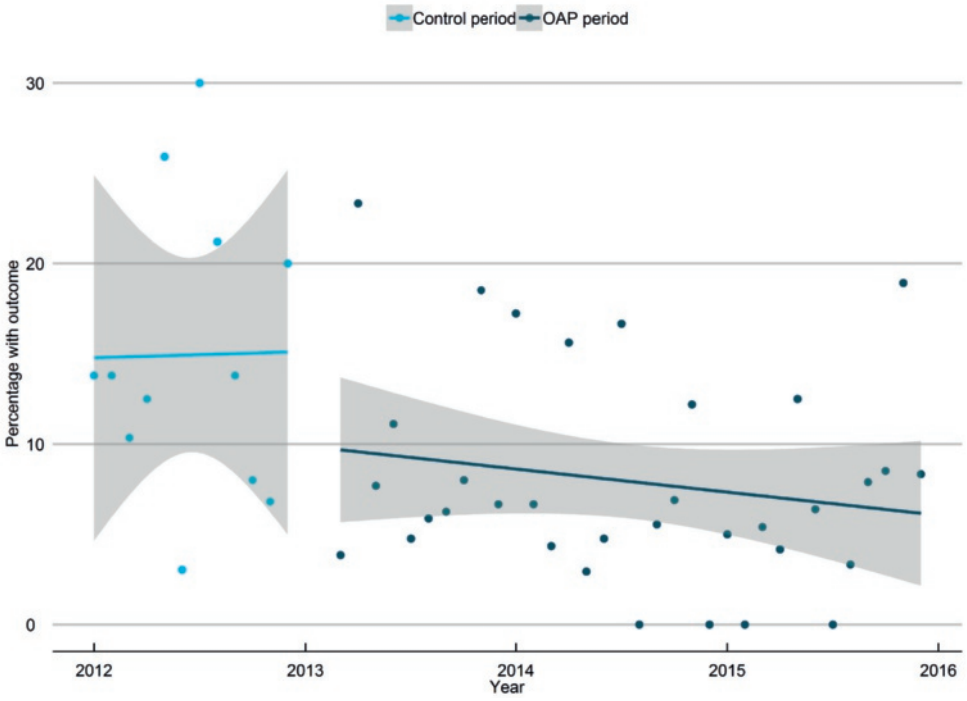

Figure 2 Percentage of patients with primary outcome per month
The percentage of patients who developed the primary outcome is shown for every month in the study period. Preoperative oral antibiotic prophylaxis was implemented on January 1st of 2013, followed by two months of implementation phase (patients are excluded). Separate regression lines are fitted for both study periods.

Table 3 Crude and adjusted risk ratios of the association between treatment period and covariables and the primary composite outcome

Covariable	Crude RR (95% CI)	Adjusted RR (95% CI)
OAP period	0.57 (0.41 – 0.79)	0.58 (0.40 – 0.79)
Male sex	0.96 (0.70 – 1.33)	1.05 (0.76 – 1.45)
Age in years	1.01 (1.00 – 1.02)	1.00 (0.98 – 1.02)
Perioperative intravenous antibiotic prophylaxis	0.62 (0.31 – 1.19)	0.76 (0.39 – 1.45)
Underlying colorectal malignancy	0.82 (0.57 – 1.18)	0.97 (0.63 – 1.48)
ASA classification		
1-2	*Reference*	*Reference*
≥ 3	1.93 (1.35 – 2.76)	1.78 (1.19 – 2.66)
Body mass index in kg/m²		
<18	1.71 (0.80 – 3.63)	2.08 (0.97 – 4.44)
18-30	*Reference*	*Reference*
≥30	0.80 (0.49 – 1.34)	0.75 (0.44 – 1.25)
Surgical approach		
Open procedure [a]	*Reference*	*Reference*
Conventional laparoscopic procedure	0.58 (0.39 – 0.83)	0.75 (0.50 – 1.12)
Robotic laparoscopic procedure	0.58 (0.34 – 0.97)	0.84 (0.46 – 1.51)
Wound class		
Clean-contaminated (class 2)	*Reference*	*Reference*
Contaminated (class 3)	1.49 (0.92 – 2.43)	1.44 (0.83 – 2.50)
Duration surgery >p75 [b]	0.87 (0.59 – 1.28)	1.16 (0.75 – 1.79)
Experienced surgeon [c]	0.59 (0.43 – 0.83)	0.69 (0.47 – 1.00)

Intercept: aRR 0.15 (95% CI 0.04 – 0.50); outcome: deep SSI and/or mortality within 30 days after surgery. ASA, American Society of Anesthesiologists; BMI, body mass index; CI, confidence interval; OAP, oral antibiotic prophylaxis; RR, risk ratio

a. Includes the laparoscopic procedures that are converted to an open procedure

b. 75th percentiles of duration of surgery per type of procedure, acoording to PREZIES reference values [20]

c. Performs at least 25 colorectal procedures per year

Sensitivity analyses (Supplementary table 2) demonstrate that adding the month of study and an interaction term to the model did not change the estimates or the model fit.

DISCUSSION

Implementation of oral antibiotic prophylaxis as standard of care prior to elective colorectal surgery was associated with a 42% relative risk reduction in deep SSIs and mortality after adjustment for several confounders. In addition, a statistically significant decrease in anastomotic leakage and a reduction in postoperative length of hospital stay was found. Because we did not restrict our analyses to a specific type of procedure or patient, we expect that our results are generalizable to all elective colorectal procedures.

A recent meta-analysis concluded that combining oral antibiotics with perioperative intravenous prophylaxis is superior in SSI reduction after colorectal surgery compared to intravenous prophylaxis alone. [22] One important shortcoming of this meta-analysis is the limited applicability of the results caused by heterogeneity with respect to antimicrobials and treatment duration. Besides, oral antibiotics were combined

with MBP in all studies. As MBP was omitted recently, the question of the effectiveness of the antibiotic bowel preparation without simultaneous practice of MBP remains.[1,23] Our study was conducted in a setting without routine MBP. Recent observational studies that investigated the impact of oral antibiotics prior to colorectal surgery in a similar setting also found a significant decrease in SSI rate. [24–26] The validity of the findings of these studies, however, is limited due to bias. Because the choice of adding oral antibiotics is usually optional and depends on physicians' preferences and on the patients' prognoses, confounding by indication can severely affect the observed outcomes. In our study, the risk of confounding by indication was substantially reduced because the administration of OAP was the standard of care and thus not dependent on physician preference. Furthermore, we used an intention-to-treat approach in analyzing the treatment effect. Patients were assigned to the treatment group based on time period and regardless of non-compliance. Nevertheless, our findings agree with the results of the previous studies, and also indicate that simultaneous mechanical cleaning might not be necessary for the antibiotics to be effective.
Previous studies on OAP did not report on the occurrence of adverse events. In this study, severe systemic side effects were not observed. We recently reported on postoperative tobramycin serum levels as a proxy for enteral absorption and systemic side effects of OAP. [27] In all patients, one-day postoperative tobramycin serum concentrations were below the detection limit, indicating a low risk of toxicity. Besides side effects, antibiotic prophylaxis might result in opportunistic infections with *Clostridium difficile* or selection of antibiotic resistance. We did not observe an increase in *C. difficile* infections after OAP implementation. The development of antibiotic resistance was not evaluated in this study. However, as studies on the use of selective decontamination of the digestive tract (SDD), an antibiotic prophylaxis comparable to OAP, have not shown any increase in antibiotic resistance during treatment with SDD in ICU patients, we do not expect that a three-day OAP regimen will be associated with an increase in antibiotic resistance. [28,29]

This study has several limitations. First, confounding bias may have been present because of the historic control group. We attempted to minimize this by adjusting for potentially time-sensitive variables in the multivariable analysis and we performed a sensitivity analysis to assess the presence of temporal trends in our data. Despite these efforts, we cannot entirely exclude residual confounding due to our observational study design. Another limitation of the historic control group, is that it is unknown if patients' prognoses in both study periods was comparable. In the OAP period, a third category was used to indicate the urgency of the procedure. From January 2013 onwards, the sub-acute category was used for procedures scheduled before the entire three-day course of OAP could be completed. Inherently, this classification was not applied in the control period and the proportion of procedures that would have been classified as sub-acute in 2012 is unknown. These procedures were most likely categorized as acute procedures, and were herewith excluded. To prevent confounding by indication, we included patients identified as 'sub-acute' in the OAP period in our (intention-to-treat) analyses. This may have resulted in an underestimation of the actual treatment effect because patients with a comparable prognosis in the control period and, thus, a higher risk of infection, were excluded. Finally, we were unable to investigate the impact of OAP on causative pathogens of SSIs. We did not present wound culture data because of an important limitation that hampers the comparison of the two study periods. Unfortunately, the reading of cultures was done for clinical purposes and was not aimed at the standardized detection of all different species present in each culture. In routine laboratory practice, the individual identification and susceptibility testing of microorganisms present in the culture will be dependent on their relative abundance. In case of fecal contamination of the wound, for example, cultures are mostly reported as 'growth of mixed/fecal microorganisms'. The use of OAP will selectively remove Gram-negatives form the gut microbiota and will therefore reduce the variety of microorganisms present in the wound after fecal contamination. For the reading and reporting

of SSI cultures, this will result in the more frequent reporting of individual microorganisms for SSI cultures from patients that used OAP that would have been reported as (part of) mixed microbiota for patients that did not use OAP. A valid comparison of different types of microorganisms present in routine cultured SSI samples is therefore not possible on our data, and would have required a standardized protocol defining the identification of all different bacteria and fungi present in the culture, independent of the number of different types of microorganisms growing. We therefore consider such a comparison to be non-informative as firm conclusions on the impact of OAP on the spectrum of causative pathogens of deep SSI cannot be drawn from our data. Well-controlled studies are necessary to provide more insights into the impact of OAP on microbiota or on culture results.

To conclude, preoperative oral antibiotic prophylaxis without MBP was associated with a significant decrease in the incidence of deep SSIs We believe our results are promising and encourage further investigation on the effectiveness as well as potential adverse effects of OAP in future well-controlled studies.

List of abbreviations:
aRR, adjusted risk ratio; ASA, American Society of Anesthesiologists; CI confidence interval, ICU, intensive care unit; IQR, interquartile range; MBP, mechanical bowel preparation; MICE, multiple imputation using chained equations; OAP, oral antibiotic prophylaxis; SSI, surgical site infection

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SUPPLEMENTARY MATERIAL

Supplementary Table 1 Distribution of variables among patients without and with missing values (100% = 1,410)

Variable	Patients, N (%)		P value
	No missings [a] (n = 1,310)	≥ 1 missing (n = 100)	
Patient characteristics			
Age in years, median (IQR)	68 (60 – 75)	68 (57 – 78)	0.842
Male sex	746 (56.2)	51 (51.0)	0.367
Body mass index in kg/m^2, median(IQR)	25 (23 – 28)	26 (23 – 29)	0.829
Obese (BMI >30 kg/m^2)	196 (15.0)	14 (17.9)	0.577
ASA classification			
1-2	949 (72.4)	13 (40.6)	<0.001
>2	361 (27.6)	19 (59.4)	
Colorectal malignancy	1018 (77.7)	68 (68.0)	0.036
Abdominal surgery in the preceding year	150 (11.5)	6 (6.0)	0.131
Operative characteristics			
Perioperative intravenous antibiotic prophyalxis	1,265 (96.6)	80 (92.0)	0.056
Type of resection			
Partial resection of colon	738 (56.3)	63 (67.7)	0.008
Total colectomy or low anterior resection	378 (28.9)	13 (14.0)	
Creation or removal of stoma	194 (14.8)	17 (18.3)	
Duration procedure >75th percentile [b]	347 (26.5)	13 (13.0)	0.004
Normothermia	941 (92.1)	67 (90.5)	0.804
Surgical approach			
Open surgery [c]	566 (43.2)	71 (76.3)	<0.001
Conventional laparoscopic surgery	526 (40.2)	17 (18.3)	
Robotic laparoscopic surgery	218 (16.6)	5 (5.4)	
Experienced surgeon [d]	1,051 (80.2)	53 (53.0)	<0.001
Wound class			
Clean-contaminated (class 2)	1,210 (92.4)	84 (84.0)	0.006
Contaminated (class 3)	100 (7.6)	16 (16.0)	
Implants of non-human tissue	4 (0.3)	0	1.000
OAP period	985 (75.2)	73 (73.0)	0.632
Primary outcome	121 (9.2)	14 (14.0)	0.155

ASA, American Society of Anesthesiologists; IQR, interquartile range; OAP, oral antibiotic prophylaxis

a. Defined as absence of missing values in any of the covariables or in the outcome of the multivariable model

b. 75th percentiles of duration of surgery accounting for the type of resection and for the surgical approach, according to PREZIES reference values [20]

c. Includes the procedures that are converted from laparoscopic to open surgery

d. Performs at least 25 colorectal procedures per year

Supplementary Table 2 Sensitivity analyses evaluating the effect of time on the primary composite outcome

Covariable	aRR (95% CI) original model	aRR (95% CI) model + time	aRR (95% CI) model + interaction time * OAP period
OAP period	0.58 (0.40 – 0.79)	0.60 (0.34 – 1.06)	0.60 (0.27 – 1.44)
Month of study [a]	-	0.99 (0.98 – 1.01)	0.99 (0.93 – 1.07)
Interaction month of study * OAP period	-	-	1.00 (0.93 – 1.07)
Male sex	1.05 (0.76 – 1.45)	0.97 (0.70 – 1.32)	0.97 (0.70 – 1.34)
Age in years	1.00 (0.98 – 1.02)	1.00 (0.99 – 1.01)	1.00 (0.99 – 1.02)
Perioperative antibiotic prophylaxis	0.76 (0.39 – 1.45)	0.69 (0.37 – 1.27)	0.70 (0.38 – 1.31)
Underlying colorectal malignancy	0.97 (0.63 – 1.48)	1.03 (0.68 – 1.58)	1.03 (0.67 – 1.57)
ASA classification			
1-2	*Reference*	*Reference*	*Reference*
3-5	1.78 (1.19 – 2.66)	1.82 (1.27 – 2.62)	1.88 (1.32 – 2.69)
Body mass index in kg/m^2			
<18	2.08 (0.97 – 4.44)	2.08 (0.97 – 4.44)	2.11 (0.99 – 4.47)
18-30	*Reference*	*Reference*	*Reference*
>30	0.75 (0.44 – 1.25)	0.82 (0.51 – 1.32)	0.81 (0.51 – 1.29)
Surgical approach			
Open procedure	*Reference*	*Reference*	*Reference*
Conventional aparoscopic procedure	0.75 (0.50 – 1.12)	0.79 (0.54 – 1.17)	0.78 (0.53 – 1.29)
Robotic laparoscopic procedure	0.84 (0.46 – 1.51)	0.87 (0.46 – 1.67)	0.87 (0.46 – 1.67)
Wound class			
Clean-contaminated (class 2)	*Reference*	*Reference*	*Reference*
Contaminated (class 3)	1.44 (0.83 – 2.50)	1.44 (0.83 – 2.51)	1.44 (0.83 – 2.57)
Duration procedure >p75	1.16 (0.75 – 1.79)	1.13 (0.74 – 1.73)	1.16 (0.71 – 1.87)
Experienced surgeon	0.69 (0.47 – 1.00)	0.68 (0.47 – 0.98)	0.67 (0.48 – 0.99)
Intercept	0.15 (0.05 – 0.49)	0.15 (0.04 – 0.51)	0.15 (0.04 – 0.55)
AIC	875.41	877.20	879.19

Outcome: deep SSI and/or mortality within 30 days after surgery. aRR, adjusted risk ratio; AIC, Akaike information criterion; ASA, American Society of Anesthesiologists; CI, confidence interval; OAP, oral antibiotic prophylaxis; SSI, surgical site infection

a. Month of study based on date of surgery, starting on January 1st, 2012

5

Evidence of the Pharmacological Safety of Oral Tobramycin Prophylaxis Prior to Colorectal Surgery

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ABSTRACT

Preoperative oral prophylaxis with non-absorbable antibiotics has been reported to reduce the risk of surgical site infections after colorectal surgery. This prospective study was conducted to evaluate the risk of toxic side effects by measuring postoperative serum tobramycin levels in patients who received a three-day prophylaxis with tobramycin and colistin prior to colorectal surgery. In all patients, serum tobramycin concentrations were below the detection limit (0.3 mg/l), implying a low risk of toxicity.

BACKGROUND

Surgical site infections (SSIs) are common complications after colorectal surgery, affecting approximately 15% of all patients. [1] SSIs are associated with substantial morbidity and often require extensive therapeutic interventions. To reduce the risk of SSIs, international infection control guidelines recommend administration of a perioperative systemic antibiotic prophylaxis. [2,3] Preoperative oral antibiotic prophylaxis (OAP) with non-absorbable antibiotics can be administered additionally to further reduce infection rates. [4–6] The non-absorbable nature of the antibiotics suggests absence of enteral absorption after oral administration. Therefore, the risk of toxic systemic side effects following OAP is presumed to be low. Findings of previous studies in critically ill patients questioned the low risk of systemic side effects. Although it was believed that non-absorbable antibiotics remain restricted to the gastrointestinal tract, increased serum concentrations of these antibiotics were found after oral administration. Antibiotic leakage from the gut [7,8] and acute renal insufficiency [9] were proposed as conditions that could lead to increased serum concentrations. It is unknown whether increased serum concentrations of non-absorbable antibiotics are also present during treatment with OAP prior to colorectal surgery. It can be hypothesized that underlying colorectal diseases or iatrogenic manipulation during surgery facilitate antibiotic leakage from the gut to the systemic circulation. Also, postoperative renal insufficiency might lead to increased serum levels of antibiotics. Therefore, the aim of this study was to investigate whether one-day postoperative tobramycin concentrations reach clinically relevant trough levels in patients who receive three-day OAP prior to colorectal surgery.

METHODS

Patients

We conducted a prospective exploratory study from October 2016 through January 2017. The study was performed in a Dutch hospital where preoperative OAP is standard of care prior to elective colorectal surgery. OAP is a solution containing tobramycin (16 mg/ml) and colistin (20 mg/ml) that is administered orally in doses of 5 ml. Patients are instructed to take the OAP four times daily during the three days prior to surgery. Patients who undergo a rectal resection receive one additional enema with the antibiotic solution when it is possible to admit the patient one day before surgery. Perioperative intravenous antibiotic prophylaxis is routinely administered according to the national infection control guideline for colorectal surgery. [3] Mechanical bowel preparation was not administered, as it is not part of routine clinical care in this hospital. All consecutive patients who underwent elective colorectal surgery in the study period and who received OAP were included.

Serum assays

Serum tobramycin was measured in blood samples that were routinely drawn on the day after surgery. Quantification of tobramycin was performed with a homogeneous enzyme immunoassay (Roche, Almere, The Netherlands). [10] The lower limit of detection was 0.3 mg/l. Serum tobramycin levels of 1 mg/l or higher were considered clinically relevant.

Ethics

The Medical Ethics Committee of the UMC Utrecht (Utrecht, The Netherlands) reviewed the study (METC number 16/490) and judged the study to be beyond the scope of the Medical Research Involving Human Subjects Act (WMO). A waiver of informed consent was granted.

RESULTS

In total, 64 patients were included in the study. Baseline characteristics are shown in Table 1. The median age was 67 years. Half of the patients had a normal renal function one day after surgery and the majority had no history of renal insufficiency. An additional enema with the antibiotic prophylaxis was administered to 32.8% of the patients. None of the patients received systemic tobramycin prior to or during surgery. The postoperative serum tobramycin levels were below 0.3 mg/l for all patients.

Table 1 Preoperative and surgical characteristics

Variable	N = 64
Male	33 (51.6%)
Age in years (median, IQR)	67.0 (58.3 – 75.0)
BMI in kg/m^2 (median, IQR)	24.9 (22.3 – 27.5)
ASA classification ≥3	21 (32.8%)
History of chronic renal insufficiency	7 (10.9%)
Chronic renal replacement therapy	0 (0.0%)
Glomerular filtration rate <90 ml/min one day after surgery	35 (54.7%)
Serum creatinine in µmol/L one day after surgery (median, IQR)	71.5 (64 – 96.8)
Antibiotic use	
Systemic use of tobramycin prior to or during surgery	0 (0.0%)
Adequate perioperative intravenous prophylaxis a	61 (95.3%)
Additional preoperative enema with OAP	21 (32.8%)
Indication for surgery	
Colorectal malignancy	49 (76.6%)
Inflammatory bowel disease	5 (7.8%)
Benign polyps	3 (4.7%)
Other	7 (10.9%)
Type of procedure	
Colon resection	33 (51.6%)
Rectum or sigmoid resection	24 (37.5%)
Creation or removal of stoma	7 (10.9%)
Surgical technique	
Open procedure	14 (21.9%)
Laparoscopic procedure	27 (42.1%)
Robot-assisted laparoscopic procedure	23 (35.9%)
Blood loss during procedure in ml (median, IQR)	50.0 (0.0 – 137.5)

All data are presented as n(%) unless specified otherwise. ASA, American Society of Anesthesiologists; BMI, body mass index; IQR, interquartile range; OAP, oral antibiotic prophylaxis.
a. Adequate perioperative intravenous prophylaxis entails the choice of appropriate antimicrobial agents as well as the appropriate timing of the prophylaxis according to the Dutch infection control guideline

DISCUSSION

In this study, the administration of OAP prior to colorectal surgery was not associated with increased serum tobramycin concentrations. These findings are in contrast to previous studies that investigated tobramycin absorption during selective decontamination of the digestive tract (SDD). Comparable to OAP, SDD is applied orally for several days. Besides tobramycin and colistin, an antifungal agent is a common component of SDD. Serum analysis demonstrated leakage of tobramycin from the gut to the serum in the majority of ICU patients treated with SDD. Leakage resulted in concentrations that were clinically relevant and in potentially toxic trough levels (>1.0 mg/l) in a few cases.[7] Tobramycin-related toxic side effects, however, were not reported.

A disrupted gut barrier, a potential consequence of critical illness, and acute renal failure were identified as risk factors for increased systemic tobramycin levels. [9,11] The absence of detectable serum tobramycin levels in our less severely ill patient population indicates that a three-day course of preoperative OAP is not associated with clinically relevant enteral absorption of tobramycin in patients undergoing colorectal surgery, even when patients have an impaired renal function. Although we were unable to perform subgroup analyses because of a limited sample size, our findings did not provide evidence for an altered risk of tobramycin leakage due to underlying colorectal disease. Serum levels of colistin, the other component of OAP, were not measured in this study. As tobramycin has a higher potential to cross the gut barrier, because of its lower molecular weight (1,425D) compared to colistin (1,748D), tobramycin levels are considered to be a more sensitive indicator for antibiotic leakage than colistin. [12] Besides pharmacological side effects, the risk of antimicrobial resistance needs to be considered as a possible complication of prophylactic antibiotics. Previous studies on ICU patients did not report a significant increase in antimicrobial resistance during SDD administration. [13–15] Because of the short treatment duration, we hypothesize that the risk of development of antibiotic resistance is negligible after OAP use as well. However, further investigation is required to monitor this.

To the best of our knowledge, this is the first study to investigate postoperative serum tobramycin concentrations in patients who receive OAP prior to colorectal surgery. Based on our findings, we consider OAP not to be associated with an increased risk of toxic side effects. Because of the short treatment duration, we expect that the risk of other complications is low as well. We therefore consider OAP to be a safe infection prevention strategy for patients undergoing elective colorectal surgery.

List of abbreviations:
ASA, American Society of Anesthesiologists; BMI, body mass index; ICU, intensive care unit; IQR, interquartile range; OAP, oral antibiotic prophylaxis, SDD, selective decontamination of the digestive tract; SSI, surgical site infection

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6

Oral Antibiotics and Mechanical Bowel Preparation Prior to Colorectal Surgery: a Systematic Review of Observational Data

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ABSTRACT

To reduce the of risk infections after colorectal surgery, oral antibiotic preparation (OAP) and mechanical bowel preparation (MBP) can be applied. Whether OAP can be used without MBP is unclear. A meta-analysis of observational studies demonstrated comparable effectiveness of OAP with and without MBP on SSI risk.

INTRODUCTION

Surgical site infections (SSIs) are common complications after colorectal surgery. To reduce the risk of SSIs, oral antibiotic preparation (OAP) or mechanical bowel preparation (MBP) can be administered before surgery. Usually, the two are combined because of their presumed synergistic effect. The combination was shown to reduce the risk of SSIs compared to no preparation, but it is unknown to what extent each of the preparations contribute to this decline. MBP was abandoned recently due to a lack of evidence for a beneficial effect compared to no preparation. [1,2] Together with the ban of MBP, OAP was also discarded, even though its efficacy without MBP was never investigated. Because SSI risk after colorectal surgery remains high, there has been a resurgence of interest in bowel preparation. A recent meta-analysis pooled all evidence from randomized controlled trials (RCTs) to conclude if no preparation, MBP, OAP, or MBP and OAP combined is the most effective in preventing postoperative complications. [3] The combination of MBP and OAP was found to result in the lowest risk of SSI. An important limitation is that it was not possible to conclude whether OAP is effective without MBP, because there have been no RCTs that only focused on OAP. In this study, we aimed to provide insight into the effectiveness of OAP without MBP on SSI risk using data from observational studies.

METHODS

We performed a systematic review and meta-analysis of observational studies that investigated OAP prior to colorectal surgery. We searched PubMed on 'oral antibiotic bowel preparation' and MeSH terms 'Colorectal surgery' and 'Surgical Wound Infection', and included all studies that investigated an OAP only strategy. Data on study design, data-analysis, and the number of SSIs per preparation strategy were collected. Because we aimed to reduce confounding bias, we extracted the adjusted odds ratios (aOR) and 95% confidence intervals (CI). Adjusted odds ratios and confidence intervals were subsequently log transformed to calculate the corresponding standard errors. We used the generic inverse variance method to calculate the pooled treatment effects for the comparisons of OAP only versus no preparation, and for OAP with MBP versus no preparation. A random effects model was applied to account for the expected clinical heterogeneity due to known variation in OAP. When studies were performed on (a subset of) the same cohort, we only included the study with the highest precision in the meta-analysis to ensure that patients were included in the meta-analysis only once. Statistical analyses were performed with Review Manager software version 5.3.

RESULTS

We found 15 studies that reported data on OAP without MBP. [4–18] (Table 1) In almost all studies, the OAP only strategy was the least often used preparation. Because thirteen studies were performed with data from the ACS-NSQIP database from 2012 through 2015, a substantial overlap in participants was suspected and only the largest study was included in the meta-analysis. The forest plots with pooled aORs are presented in Figure 1. Compared to no preparation, SSI risk was significantly reduced when patients received either only OAP (aOR 0.51 [95%CI 0.37 – 0.71]) or combined with MBP (aOR 0.42 [95%CI 0.37 – 0.49]). The largest study reported no significant difference between MBP with OAP versus OAP alone (aOR 0.78 [95% CI 0.55 – 1.08]).

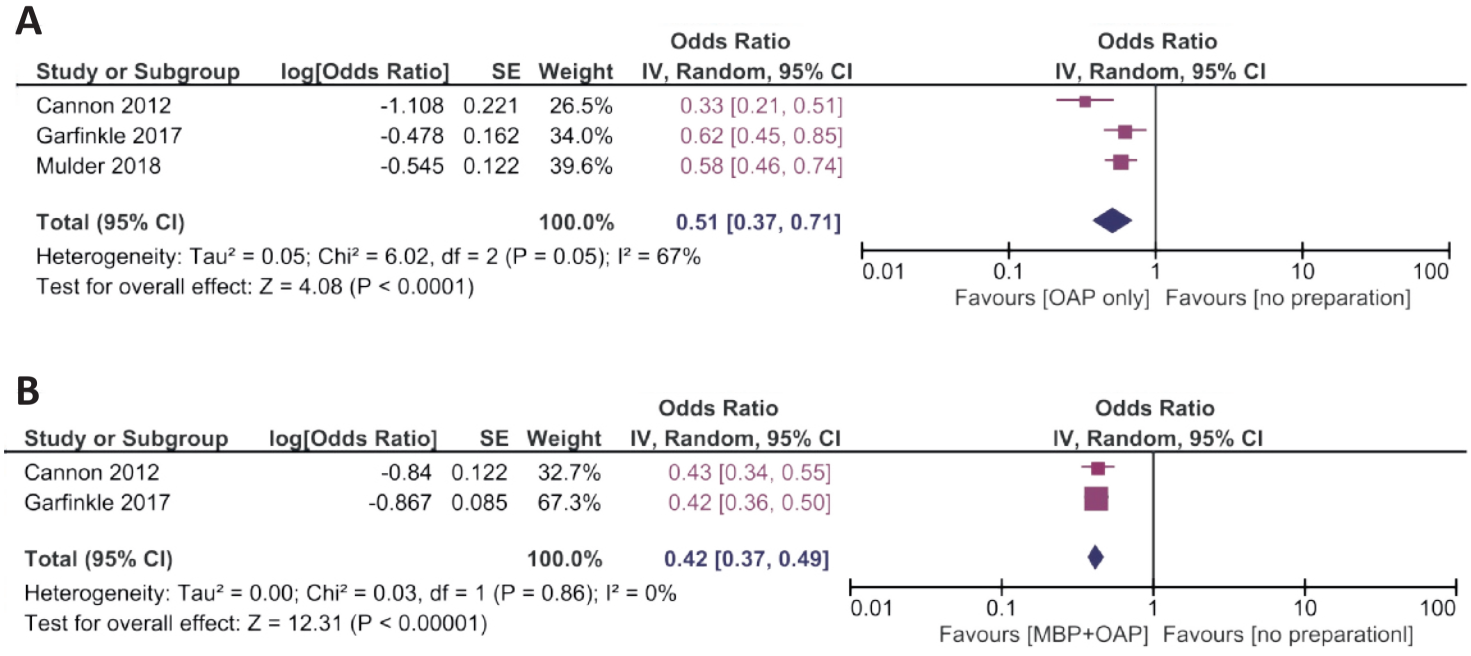

Figure 1 Forest plots of adjusted odds ratios for the outcome all SSIs **A.** OAP versus no preparation; **B.** MBP and OAP combined versus no preparation. Because of suspected overlap in participants between several studies, only the largest of the ACS-NSQIP database studies was included to calculate the pooled effect. CI, confidence interval; MBP, mechanical bowel preparation; OAP, oral antibiotic prophylaxis; SE, standard error; SSI, surgical site infection

Table 1 Observational studies on antibiotic bowel preparation

Author, year and country	Study period	Patients	Study design	Statistical methods	Confounders adjusted for	Type of SSI	Bowel preparation strategy **No. patients** No. SSI (%) No prep	MBP only	OAP only	MBP+OAP	aOR (95% confidence interval) OAP only vs no prep	OAP+MBP vs no prep	OAP+MBP vs OAP only
ACS-NSQIP database studies													
Scarbourough 2012, USA	2012	Elective colorectal	Retrospective cohort	Logistic regression analysis	BMI, diabetes, smoking, COPD, hypertension, chemotherapy, disseminated cancer, weight loss, albumin, surgical approach, wound class, operative time, total work relative units, low pelvic anastomosis	Incisional	**N=1,092** 98 (9.0)	**N=2,322** 174 (7.5)	**N=91** 4 (4.4)	**N=1,494** 48 (3.2)	0.41 (0.15–1.17)	0.33 (0.23–0.47)	
Althumairi 2016, USA	2012–2013	Elective colorectal	Retrospective cohort	Logistic regression analysis; Model 1: bowel prep Model 2: bowel prep + SSI Model 3: confounders + bowel prep Model 3: confounders, bowel prep + SSI	Age, sex, race, ASA classification, smoking status, diabetes, history of congestive heart failure, history of COPD, BMI, weight loss, indication for surgery, surgical approach, type of procedure, operative time.	All Used as independent variable, not as outcome	**N=5,060** 692 (13.7)	**N=8,020** 922 (11.5)	**N=641** 54 (8.4)	**N=5,965** 374 (6.3)	*No aOR for SSI provided*		
Atkinson 2015, USA	2012–2013	Elective colorectal	Retrospective cohort	Logistic regression analysis	Age, diabetes, smoking, operative time, blood transfusion, steroids, ASA classification, surgical approach, indication for surgery, wound class	All	**N=5,741** 786 (13.7)		**N=658** 64 (9.7)		0.66 (0.48–0.90)		
Moghdameghaneh 2015, USA	2012–2013	Elective colorectal	Retrospective cohort	Logistic regression analysis	Age, sex, race, hypertension, smoking, diabetes, COPD, CHF, weight loss, ascites, sepsis, dypnea, renal failure, use of steroids, ASA classification, functional status, bleeding disorders, type of admission, cancer stage, surgical approach, wound class	Superficial Right sided Left sided	**N=1,270** 104 (8.2)	**N=2,248** 150 (6.7)	**N=117** 3 (2.6)	**N=1,386** 31 (2.2)	 0.91 (0.89–1.00) 0.36 (0.10–1.35)	 0.14 (0.06–0.33) 0.31 (0.18–0.53)	
						Organ/space Right sided Left sided	73 (5.7)	116 (5.2)	4 (3.4)	43 (3.1)	 0.63 (0.07–5.13) 0.63 (0.17–2.26)	 0.75 (0.36–1.57) 0.44 (0.26–0.73)	

Table 1 (Continued)

Author, year and country	Study period	Patients	Study design	Statistical methods	Confounders adjusted for	Type of SSI	Bowel preparation strategy **No. patients** No. SSI (%)				aOR (95% confidence interval)		
							No prep	MBP only	OAP only	MBP+OAP	OAP only vs no prep	OAP+MBP vs no prep	OAP+MBP vs OAP only
Koller 2018, USA	2012–2014	Elective colorectal	Retrospective cohort	Propensity score adjusted logistic regression analysis with Bonferroni correction	Not specified		**N=8,658**	**N=11,862**	**N=1,232**	**N=10.363**			
						All	1,013 (11.7)	1,210 (10.2)	90 (7.3)	585 (5.5)	0.49 (0.38–0.64)	0.45 (0.40–0.50)	0.91 (0.69–1.20)
Dolejs 2017, USA	2012–2014	Elective colorectal, aged >75 yr	Retrospective cohort	Logistic regression analysis	Adjusted, but not specified for which confounders		**N=1,497**	**N=1,788**	**N=153**	**N=1,391**			
						Superficial	105 (7.0)	80 (4.5)	4 (2.5)	28 (2.0)	0.40 (0.20–1.50)	0.41 (0.27–0.62)	
						Deep	22 (1.5)	27 (1.5)	2 (1.3)	14 (1.0)	0.95 (0.15–3.0)	0.90 (0.30–2.20)	
						Organ/space	60 (4.0)	68 (3.8)	4 (2.5)	33 (2.4)	0.50 (0.20–2.10)	0.50 (0.40–0.75)	
Garfinkle 2017, USA	2012–2014	Elective colorectal	Retrospective cohort	Logistic regression analysis with Bonferroni correction	Coarsened exact matching on age, ASA classification, chemotherapy, BMI, laparoscopy and ostomy		**N=13,219**	**N=13,935**	**N=1,572**	**N=11,720**			
						All	1,903 (14.4)	1,616 (11.6)	137 (8.7)	762 (6.5)	0.62 (0.46–0.87)	0.42 (0.35–0.49)	0.78 (0.55–1.08)
Shwaartz 2016, USA	2012–2014	Elective colorectal, IBD	Retrospective cohort	Logistic regression analysis with multiple outcomes	Adjusted, but not specified for which confounders		**N=1,563**	**N=791**	**N=325**	**N=1,000**			
						Incisional	118 (7.5)	59 (7.5)	27 (8.3)	48 (4.8)	NS	0.55 (0.39–0.79)	
						Organ/space	126 (8	57 (7.2)	18 (5.5)	39 (3.9)		0.53 (0.36–0.77)	
Midura 2017, USA	2012–2015	Elective colorectomy with anastomosis	Retrospective cohort	Logistic regression analysis	Age, race, diabetes, ASA classification, smoking, disseminated cancer, steroids, renal failure, wound class, chemotherapy, indication surgery, surgical approach, location resection		**N=11,898**	**N=15,175**	**N=1,791**	**N=16,860**			
						All	797 (6.7)	895 (5.9)	82 (4.6)	489 (2.9)	0.70 (0.55–0.88)	0.47 (0.42–0.53)	
Kaslow 2018, USA	2012–2015	Elective colorectal	Retrospective cohort	Propensity score adjusted logistic regression analysis	Age, sex, race, ASA classification, BMI category, >10% weight loss in the last six months, current smoker, hypertension, COPD, dialysis, on steroid for chronic conditions, surgery indication, approach, operative time				**N=2,018**	**N=18,576**			
						All			171 (8.5)	1117 (6.0)			0.71 (0.60–0.84)
Klinger 2017, USA	2012–2015	Elective colorectal	Retrospective cohort	Propensity score adjusted logistic regression analysis	Age, sex, race, BMI, diabetes, CHF, hypertension, disseminated cancer, steroids, smoking, functional dependence, ASA classification, albumin		**N=5,471**	**N=7,617**	**N=1,374**	**N=8,855**			
						Incisional	N/A	N/A	N/A	N/A	0.63 (0.47–0.83)	0.39 (0.33–0.46)	0.62 (0.46–0.83)
						Organ/space					0.59 (0.41–0.85)	0.56 (0.47–0.68)	0.93 (0.65–1.35)

Table 1 (Continued)

Author, year and country	Study period	Patients	Study design	Statistical methods	Confounders adjusted for	Type of SSI	Bowel preparation strategy **No. patients** No. SSI (%)				aOR (95% confidence interval)		
							No prep	MBP only	OAP only	MBP+OAP	OAP only vs no prep	OAP+MBP vs no prep	OAP+MBP vs OAP only
Toh 2018, USA	2015	Left sided colorectal	Retrospective cohort	Logistic regression analysis	Indication, stoma, sex, age, BMI, ASA classification, diabetes, dyspnea, ascites, hypertension, acute renal failure, dialysis, disseminated cancer, prior wound infection, steroids, weight loss, bleeding disorder, transfusion (peri- and post-operative) systemic sepsis, *C. difficile*, albumin, WBC, Ht, operative duration, anastomotic leakage	All	**N=1,906** N/A	**N=1,713** N/A	**N=199** N/A	**N=2,721** N/A	0.50 (0.16–1.54)	0.47 (0.28–0.78)	
Ohman 2017, USA	2011–2015	Elective colorectal, matched with data from ACS-NSQIP	Single center before after study	Logistic regression analysis	Sex, wound class, ostomy, level of emergency, surgical approach Note: Bowel preparation was part of infection prevention bundle that also included hair removal, skin antisepsis, antibiotic wound irrigation and clean closure	All	**N=37** 5 (13.5)	**N=27** 5 (18.5)	**N=12** 2 (16.7)	**N=223** 6 (2.7)	1.30 (0.20–7.60)	0.20 (0.10–0.60)	
Other studies													
Cannon 2012, Canada	2005–2009	Elective colorectal	Retrospective cohort	Generalized estimated equations model	Age, diabetes, COPD wound class, type of resection	All	**N=1,978** 358 (18.1)	**N=3,839** 768 (20.0)	**N=723** 60 (8.3)	**N=3,400** 311 (9.2)	0.33 (0.21–0.50)	0.43 (0.34–0.55)	
											aRR (95% confidence interval)		
Mulder 2018, the Netherlands	2012–2015	Elective colorectal	Single center before after study	Binomial regression model with a log link function	Age, sex, BMI, perioperative antibiotic prophylaxis, colorectal malignancy, operative time >75th percentile, surgical approach, ASA classification, wound class, surgeon experience	Composite of deep incisional + organ/space SSI and mortality	**N=352** 50 (14.2)		**N=1,058** 85 (8.0)		0.58 (0.40–0.79)		

* (%)SSI and aOR were not reported and estimated from Figures 1 and 2. aOR, adjusted odds ratio; aRR, adjusted risk ratio; ASA, American Society for Anesthesiologists; BMI, body mass index; CDC, Centers for Disease Control and Prevention; CHF, chronic heart failure; CI, confidence interval; Ht, hematocrit; IBD, inflammatory bowel disease; MBP, mechanical bowel preparation; MI, myocardial infarction; N/A, not available; NS, not significant; OAP, oral antibiotic prophylaxis; PE, pulmonary embolism; RCT, randomized controlled trial; SSI, surgical site infection; WBC, white blood cell count

DISCUSSION

In our evaluation of observational studies, OAP significantly reduces the risk of SSIs after colorectal surgery by 50%. Combining OAP with MBP had a comparable effect on SSI risk. Though these findings seem conclusive, we must address several limitations.

We included only one of the studies performed on the ACS-NSQIP database because we were unable to extract the proportion of unique participants across all publications which inevitably reduced precision. Nevertheless, all studies reported a protective effect of OAP and we therefore consider the direction of the effect reliable. The magnitude of the effect, however, cannot be directly concluded because of the limitations that apply to the ACS-NSQIP database and which we believe affected all the studies performed on these data. The database contains only a limited number of variables. This likely hampered adequate adjustment for confounders and residual confounding can therefore not be excluded. Secondly, the grouping of participants may be unreliable as only MBP administered in the hospital was properly documented. This could imply the presence of misclassification bias when a part of the OAP only group did receive MBP at home. Besides, all studies excluded patients who had missing data on the determinant, which may have introduced selection bias. Another issue is that the percentage of patients in the OAP only group is very low compared to the other preparation strategies. Albeit the aORs all demonstrate a protective effect of OAP, several studies clearly lacked power to conclude on the effectiveness of OAP without MBP. More importantly, we believe these low numbers may also reflect the presence of confounding by indication. The choice of bowel preparation generally depends on surgeon's preference and on patient's prognosis. In most studies a preference for combining OAP with MBP is seen. Not adding MBP to OAP could be because patients are unable to tolerate MBP because they are less fit, or that surgery was performed sub-acutely. In both cases, SSI risk is increased. This could have led to an underestimation of the effectiveness of OAP only and it will also be impossible to disentangle the impact of MBP when comparing OAP only with OAP and MBP combined because of unknown differences in patient characteristics that influence SSI risk.

That OAP is also effective without MBP was confirmed by a study that investigated OAP in a setting where MBP is not used. In this study, the risk of confounding by indication was present but negligible as OAP was implemented as standard of care. [16] Although residual time varying confounding could not be completely excluded, a reduction in deep SSI and mortality of 42% was found. Findings from the network meta-analysis also demonstrate that OAP can be administered without MBP. Though based on indirect associations, OAP alone appeared to be a better strategy than OAP with MBP in reducing organ/space infections. In contrast, a single center RCT from Israel found no difference between OAP and OAP combined with MBP on the SSI risk, suggesting that the MBP component can be safely omitted.[19] We also demonstrated that the impact of MBP with OAP is similar to OAP alone. Considering the absence of a beneficial effect of MBP alone, the only rationale for continuation of MBP in combination with OAP is because it was hypothesized that the antibiotics were not effective in an uncleansed colon.

Based on our findings, we consider the added value of MBP to be questionable, at best. This is relevant because besides the additional costs, MBP does not only pose a risk of electrolyte disturbance, its administration is also a significant burden to the patient. There remains a need of high-level evidence to confirm the efficacy of OAP without MBP. An RCT that includes an OAP only strategy may bring us closer to closing the research gap on the use of OAP and the necessity of MBP.

List of abbreviations:
aOR, adjusted odds ratio; aRR, adjusted risk ratio; ASA, American Society for Anesthesiologists, BMI, body mass index; CDC, Centers for Disease Control and Prevention; CHF, chronic heart failure; CI, confidence interval; Ht, hematocrit; IBD, inflammatory bowel disease; MBP, mechanical bowel preparation; MI, myocardial infarction; N/A, not available; NS, not significant; OAP, oral antibiotic prophylaxis; PE, pulmonary embolism; RCT, randomized controlled trial; SSI, surgical site infection; WBC, white blood cell count

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7

Prevention of Severe Infectious Complications After Colorectal Surgery Using Oral Antibiotic Prophylaxis: Rationale and Design of the PreCaution trial

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ABSTRACT

Background: Colorectal surgery is frequently complicated by surgical site infections (SSIs). The most important consequences of SSIs are prolonged hospitalization, an increased risk of surgical re-intervention and an increase in mortality. Perioperative intravenous antibiotic prophylaxis is the standard of care to reduce the risk of SSIs. In the last decades, preoperative oral antibiotics have been suggested as additional prophylaxis to further reduce the risk of infection, but are currently not part of routine practice in most hospitals.

Objective: To evaluate the efficacy of a preoperative oral antibiotic prophylaxis (OAP) in addition to intravenous perioperative antibiotic prophylaxis to reduce the incidence of deep SSIs and/or mortality after elective colorectal surgery.

Methods: The PreCaution trial is designed as a multicenter, double-blind, randomized, placebo-controlled clinical trial that will be carried out in the Netherlands. Adult patients who are scheduled for elective colorectal surgery are eligible to participate. In total, 966 patients will be randomized to receive study medication. This will either be OAP, a solution that consists of tobramycin and colistin sulphate, or a placebo solution. The study medication will be administered four times daily during the three days prior to surgery. Perioperative intravenous antibiotic prophylaxis will be administered to all patients per the national infection control guidelines. The primary endpoint of the study is the cumulative incidence of deep SSIs and/or mortality within 30 days of surgery. Secondary endpoints include both infectious and non-infectious complications of colorectal surgery, and will be evaluated 30 days and/or six months of surgery.

Discussion: To date, conclusive evidence on the added value of preoperative oral antibiotic prophylaxis in colorectal surgery is lacking. The PreCaution trial will determine the effects of oral antibiotics in preventing infectious complications in elective colorectal surgery.

Trial registration: Netherlands Trial Register: NTR6113, registered on 11-Oct-2016, EudraCT 2015-005736-17

BACKGROUND

Surgical site infections (SSIs) are the most common hospital-acquired infections in surgical patients.[1,2] SSIs are associated with an extended hospitalization and are an important source of readmissions and surgical reintervention. [2–4] Relative to other surgical procedures, the incidence of SSIs is highest after colorectal resections, affecting up to 15% of all patients. [5] Despite extensive efforts that have been made in improving infection control practice, the incidence of SSIs after colorectal surgery remains unaffectedly high, whereas the incidence appears to decline in other surgical specialties. [6] This persisting infection rate highlights the need to explore novel measures to reduce SSIs after colorectal procedures.
To establish new infection prevention measures, it is important to understand the pathogenesis of SSIs. The development of these infections is preceded by microbial contamination of the surgical site.[7] The colon and rectum are densely colonized by microorganisms which explains the high postoperative infection rate [8,9], as well as the finding that the microorganisms that are most frequently isolated from colorectal SSIs are also the colonizing species. [10–12]

An important measure to reduce the risk of postoperative infections is to administer perioperative intravenous prophylactic antibiotics that cover these species, per the national infection control guidelines. [13] For colorectal surgery, oral antibiotics can be administered in addition to the intravenous prophylaxis. This prophylaxis contains non-absorbable antibiotics, such as neomycin combined with erythromycin or metronidazole, that are administered 1 to 2 days prior to the surgical procedure. The non-absorbable nature of these antibiotics implies almost complete absence of systemic uptake after oral intake. The antibiotics, therefore, only exert local activity in the gastrointestinal tract with low risks of side effects. The rationale of combining systemic and oral prophylaxis is that oral antibiotics reduce the colonic bacterial contamination levels directly at the surgical site, whereas systemic antibiotics are used as a safeguard by establishing effective antibiotic concentrations in the soft tissues to minimize the risk of infection and to prevent perioperative endotoxemia. Despite preventative effects of the addition of oral to intravenous prophylaxis prevents infections in individual studies, administration of oral antibiotics is currently not recommended in international infection control guidelines because of large variability in antibiotic regimens tested and limited availability of high-quality studies. [14]

The administration of oral antibiotics to reduce the colonic bacterial load became popular as surgical prophylaxis for colorectal surgery in the 1970's. [8] At that time it was believed that oral antibiotics would only be effective when the colon was simultaneously cleansed of its contents. Therefore, mechanical bowel preparation (MBP), a technique that involves the administration of osmotic substances to induce voiding of the intestinal contents, was introduced and combined with the preoperative administration of oral antibiotics [9,15] This combination became standard of care in colorectal surgery. Since then, several studies have questioned the necessity and safety of MBP. [15,16] Recent meta-analyses have concluded that the use of MBP prior to colorectal surgery could be safely omitted, as MBP alone had no overall beneficial effect on postoperative complications and caused substantial discomfort for the patient. [17–21] Furthermore, MBP has been associated with an increase in inflammatory processes, or with spillage of liquid bowel contents when bowel preparation was performed inadequately resulting in an increase in postoperative infections. [16,22] Therefore, MBP is no longer recommended in the international guidelines for colorectal surgery. The practice of MBP was also abandoned as the pre-surgical admission period has continuously decreased, precluding these preoperative preparations. The administration of oral antibiotics in an uncleansed colon was thought to be ineffective, resulting in the simultaneous disappearance of oral bowel cleansing and oral antibiotic prophylaxis. [23]

A recent Dutch single-center randomized, placebo-controlled trial (RCT) provided new insights into the use of oral antibiotics as a surgical prophylaxis prior to gastrointestinal surgery.[24] Instead of using the common regimens for oral prophylaxis consisting of tablets, the efficacy of a combination of non-absorbable antibiotics in a suspension was investigated. This suspension contained tobramycin, colistin and amphotericin B and is also used in selective decontamination of the digestive tract (SDD), an infection control measure implemented on ICUs. This study reported a 36% reduction of the incidence of infectious complications and anastomotic leakage in patients receiving the preoperative antibiotic prophylaxis. However, the study included patient who underwent all types of gastro-intestinal procedures (N = 294). Colorectal procedures were analyzed as a subgroup, resulting in limited statistical power. Furthermore, MBP was frequently administered to patients undergoing colorectal procedures. Nevertheless, the results of this study are promising and encourage further research to confirm the benefit of using oral prophylaxis.

In conclusion, the high incidence of SSIs after colorectal surgery and its associated morbidity and mortality justifies the evaluation of new preventive approaches. Preoperative oral antibiotic prophylaxis, in addition to standard perioperative intravenous prophylaxis, may reduce the incidence of SSIs after colorectal surgery. However, data on its efficacy without the concurrent practice of MBP are lacking.[25] A randomized double-blind, placebo-controlled clinical trial is, therefore, warranted.

METHODS

Study hypothesis and objectives

The objective of this trial is to determine the efficacy of preoperative oral antibiotic prophylaxis (OAP) in addition to perioperative intravenous antibiotic prophylaxis on the incidence of deep SSIs and/or mortality after elective colorectal surgery. We hypothesize that OAP will result in a relative reduction of the risk of deep SSIs and/or mortality of at least 40%.

Study design and setting

The PreCaution study is designed as a double-blind, randomized, placebo-controlled, multicenter trial. The study will be conducted in Dutch university and non-university hospitals. Study centers will be eligible to participate in the study if antibiotic prophylaxis other than the perioperative intravenous prophylaxis is not part of the standard perioperative care for colorectal surgery. Patient enrolment has started in April of 2017 and is expected to be completed within 18 months after start of the study.

Study population

Eligibility criteria

Participants will be drawn from a population of adult patients that will undergo elective colorectal surgery. Patients with an absolute contraindication for the study medication, such as pregnant women or nursing mothers, patients with a previously diagnosed allergy for the antibiotics in the study medication or patients with myasthenia gravis, are excluded from participation. Inclusion and exclusion criteria are presented in Table 1.

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Adult patients undergoing elective colorectal surgery	Age <18 years Legally incapacitated patients Patients who are unable to sign informed consent Patients who have an inability to take oral medication Patients who have undergone abdominal surgery within 30 days before randomization Patients with a documented allergy for colistin or aminoglycoside antibiotics Pregnant women or nursing mothers Patients diagnosed with myasthenia gravis Patients with a pre-existent stoma Patients who previously participated in the PreCaution trial or patients who already received study medication but for whom surgery was postponed for more than 7 days

Sample size

The sample size is calculated to be 966 patients, based on a one-sided type I error of 2.5%, a type II error of 20% and an assumed 40% reduction on the absolute risk for the primary outcome in the intervention group. The risk of the primary outcome is assumed to be 14% as is based on unpublished data from the Amphia Hospital (Breda, the Netherlands). Furthermore, one interim analysis will be conducted halfway using O'Brien-Fleming type of boundaries, with the possibility of stopping the trial for efficacy in case of overwhelming treatment effect. The 40% relative risk reduction is based on unpublished data from a four-year survey of a Dutch teaching hospital, where identical preoperative oral antibiotic prophylaxis was introduced as standard of care.

Evaluable patients

Patients who start with the three-day intervention period but for whom surgery is cancelled or postponed for more than seven days, will not be evaluable for analysis of the primary and secondary outcomes. Sample size calculations are based on evaluable patients and, herewith, assumes replacement of all non-evaluable patients. A limit of seven days is chosen as a cut-off to ensure that patients are not re-colonized at the time of surgery, since it is expected that the effects of decontamination will last for a least several days when the three-day treatment course is completed.

Assignment of interventions

Randomization

After enrolment, patients will be randomly assigned to one of two treatment arms in a 1:1 ratio. The randomization will be performed using a permuted block design with varying block sizes and stratification per study center. An independent pharmacist from Stichting Apotheek Haarlemse Ziekenhuizen, who will also be in charge of the production of the study medication, will perform the randomization. The pharmacy will provide the study medication in identical containers that will be sequentially numbered with unique medication numbers. These numbers will correspond to the treatment allocation, and will be documented on the allocation list. This list will be guarded by the hospital pharmacist of the Amphia Hospital (Breda, the Netherlands), who will coordinate the distribution of the study medication to the study centers. Members

of the local study teams will be instructed to distribute the study medication according to the allocation sequence. The unique study medication identification numbers will be linked to the subjects at enrolment on a subject identification log.

Blinding
Patients, treating physicians and individuals assessing the study outcomes, will be blinded to the treatment assignments for the duration of the study. Treatment assignments will be revealed when all patients have completed their 6-months follow-up period. Individual deblinding will be considered only when the treating physician deems knowledge of the treatment assignment essential for the safety of the patient. Any intentional or unintentional breaking of the blinding will be reported to the sponsor.

Treatment of subjects
All patients will receive study medication as part of the intervention. The intervention can either be treatment with active medication (OAP) or a placebo. OAP is a transparent solution that consists of two antibiotic components: colistin sulphate (20 mg/ml) and tobramycin (16 mg/ml). Placebos are manufactured without the active antibiotic components. The placebo solution contains flavoring additives and colorants to mimic the taste and color of OAP. All patients will receive perioperative intravenous prophylaxis according to the national infection prevention guidelines. [26] Patients are instructed to take the study medication four times daily, during the three days prior to surgery. Each dose consists of 5 ml of either OAP or placebo. In the case of OAP, this represents 100 milligrams of colistin sulphate and 80 milligrams of tobramycin.

Outcome measures
As a primary composite endpoint, we will investigate the efficacy of OAP on deep SSI and/or mortality within 30 days of surgery. The secondary endpoints including their definitions are summarized in Table 2.

Assessment and follow-up
The study procedures are listed in Table 3. The preoperative study procedures will take place during visits to the outpatient clinic. These visits will be routinely scheduled and will not be planned as study specific procedures. During the first visit, the trial will be explained and patients will receive an information letter. Informed consent will be signed during a second preoperative visit. During this visit, the study medication will be provided along with instructions for use and a study diary. Furthermore, the first rectal swab will be taken and patients will receive the first quality of life questionnaire. The study diary will be used to document the intake of study medication and to report potential side effects due to the study medication. Patients will take the study medication according to the instructions during the three days prior to surgery. The bottles with remainders of study medication will be collected at hospital admission and will be weighted to estimate treatment adherence. The study diaries will be collected at admission as well.
Patients will be followed until six months after surgery to evaluate the development of primary and secondary outcomes. The data on almost all of these outcomes, including infectious complications will be documented as part of daily practice. Thirty days after surgery, the medical records will be assessed to collect data on primary and secondary outcomes and a second rectal swab will be taken by either the patient or by a member of the local study team. Six months after surgery, the medical records will be assessed again to collect additional data on readmissions and length of hospital stay, including admissions to the ICU. Furthermore, patients will receive the second quality of life questionnaire. After the questionnaire is completed and sent back to the study team, the follow-up is completed.

Table 2 Definition of endpoints

Endpoint	Definition
Primary composite endpoint	
Cumulative incidence of deep surgical site infection and/or mortality within 30 days of surgery	Deep SSIs will be diagnosed per the CDC criteria for surgical site infections. [37] Deep SSIs include both deep incisional SSIs and organ/space SSIs
Secondary endpoints, 30 days after surgery	
Cumulative incidence of superficial SSIs	Superficial and deep SSIs will be diagnosed per the CDC criteria for surgical site infections [37]
Cumulative incidence of deep SSIs	
All-cause mortality	
Cumulative incidence of bacteremia	Blood cultures positive for microorganisms
Cumulative incidence of infection with *Clostridium difficile*	Stool sample positive for *Clostridium difficile* toxins
Cumulative incidence of infection with HRE	Clinical cultures positive for ESBL or carbapenemase-producing Enterobacteriaceae or Enterobacteriaceae resistant to quinolones and/or aminoglycosides [38]
Cumulative incidence of rectal colonization with HRE and colistin resistant species	Rectal swabs positive for HRE or colistin resistant species, measured at baseline and 30 days after surgery
Cumulative incidence of anastomotic leakage	Clinical and/or radiological evidence of leakage requiring surgical or radiological reintervention
Cumulative incidence of relaparotomy	Reoperation in the abdominal region
In-hospital use of antibiotics	Defined as 'days on therapy'
Secondary endpoints, 6 months after surgery	
All-cause mortality	
Quality of life	Measured with the RAND-36 questionnaire [39]
Length of hospital stay	In days, including all readmissions

CDC, Centers for Disease Control and Prevention; ESBL, extended-spectrum beta-lactamase; HRE, highly-resistant Enterobacteriaceae; ICU, intensive care unit; SSI, surgical site infection

Retention and withdrawal of participants

Patients are free to withdraw from the study at any time, which is in accordance with the Dutch law on medical research on humans. When patients are unwilling to undergo the rectal swab or to fill in the questionnaire, these data will be considered to be missing and will be dealt with in data analysis using the appropriate methods.

The intention-to-treat principle will be applied to our primary analysis to deal with poor or non-compliance to the study medication, as this is likely to reflect daily practice. The remainders of study medication will be weighted to estimate the compliance. To enhance the compliance, patients are informed about the bitter taste of the treatment and are advised to take the study medication together with other drinks to mask the taste. Another strategy that will be applied to enhance retention of patients, is to call the patients on the two postoperative follow-up moments to remind them about the rectal swab and questionnaire that will be sent to their home address.

Table 3 Study flow

	Study period							
			Intervention					
	Screening [a]	**Enrolment** [a]	Day			**Follow-up** [c]		
Procedure [a]	~2 wk	2wk - day-4	-3	-2	-1	Day 0 [b]	Day 30	Month 6
Patient recruitment								
Eligibility screening		●						
Informed consent		●						
Allocation		●						
Rectal swab		●					●	
Intake study medication			●	●	●			
Surgery						●		
Estimation of compliance							●	
Patient characteristics	●	●						
Surgical characteristics						●		
Primary endpoint								
Deep SSI and/or mortality							●	
Secondary endpoints								
Superficial SSI							●	
Anastomotic leakage							●	
Relaparotomy							●	
Bacteremia							●	
Rectal colonization with HRE							●	
Infection with HRE							●	
Infection with *C. difficile*							●	
In-hospital antibiotic use							●	
Length of hospital stay								●
Length of ICU stay								●
All-cause mortality							●	●
In-hospital costs								●
Quality of life		●						●
Self-report of side effects [d]			●	●	●			
Other adverse events		●	●	●	●	●	●	●
Serious adverse events			●	●	●	●	●	●
SUSARs			●	●	●	●	●	●

HRE, highly resistant Enterobacteriaceae; ICU, intensive care unit; SSI, surgical site infection; SUSAR, suspected unexpected serious adverse reaction

a. Screening and enrolment are performed during visits to the outpatient clinic. These visits are not study specific and are planned according to the local logistics

b. The day of surgery is day 0.

c. Postoperative data collection is performed by assessment of the patient registers. A phone call will be made around day 30 and month 6 to assess the status of the patient and to remind the patient to perform the rectal swab (day 30) and fill in the questionnaire (month 6)

d. Self-report by participant in medication diary during the intervention period

Microbiological methods

Clinical cultures will be performed and processed in the local microbiology laboratory of the participating centers according to the routine laboratory procedures. Date of culture, specimen, species, antimicrobial susceptibility and the production of extended-spectrum beta-lactamase or carbapenemase will be documented. Fecal samples from patients who develop nosocomial diarrhea will be tested for the presence of *Clostridium difficile* toxins, according to routine laboratory procedures and based on the indication by the attending physician.

Rectal swabs will be pre-enriched and subsequently cultured using selective media, aimed at the detection of ESBL-producing Enterobacteriaceae and carbapenem-, tobramycin- and colistin-resistant Gram-negative bacteria Species identification and antimicrobial susceptibility testing will be performed for all isolates that grow on either one of the screening agars. Phenotypic ESBL confirmation will be performed with the combination disk diffusion method according to the NVMM guideline on the laboratory detection of HRMO.

Data management

An electronic case report form (eCRF) will be used for each patient to collect all data on baseline patient characteristics and outcomes. The data management department of the Julius Center for Health Sciences and Primary care at the UMC Utrecht developed the eCRF which is hosted by ResearchOnline.

Patients will receive a unique identification number at inclusion. The list with the unique identification numbers linked to the patient will be securely stored at the study site where the patient is included. This list will be the only way to trace the identification numbers back to the individual patients. When the data are entered in the eCRF, patients will be identified with the unique identification number. No patient numbers, names, addresses or complete dates of birth will be recorded.

Statistical analysis

The primary composite endpoint will be analyzed according to the intention-to-treat principle. All patients that were randomized to receive study medication and who underwent colorectal surgery will be included in this analysis. The difference in the primary outcome between OAP and placebo will be estimated with a Z-test for proportions or by logistic regression, correcting for the stratification variable (study site). Multivariable logistic regression will be used and measured confounders will be fitted in the model as covariates. Secondary outcomes will be analyzed using the chi-square test, Fisher's exact test, logistic regression, time-to-event analysis, t-test or Mann-Whitney U-test, when appropriate. Missing data will be analyzed and handled using multiple imputation.

Exploratory subgroup analyses will be performed for study center, age, sex, BMI, ASA classification, preoperative use of immunosuppressive drugs, preoperative radiation of the surgical site, indication for surgery, wound class, surgical procedure, duration of surgery and timing of perioperative intravenous antibiotic prophylaxis. Per protocol analyses will be performed in addition to all the intention-to-treat analyses.

Interim analysis

One interim analysis will be performed when 50% of the participants completed the 30-day follow up. The Z statistic for the standardized treatment effect will be computed and compared with the 'O Brien-Fleming type of boundaries for both efficacy and futility. Recruitment will stop if the Z statistic is larger than the efficacy boundary. The futility boundaries are non-binding and thus suggestive. The unblinded results of the interim analysis will be presented to an independent Data Safety and Monitoring Board (DSMB).

Monitoring and safety

Independent Good Clinical Practice (GCP) certified monitors from the UMC Utrecht will monitor the data collection and study progress. The frequency of these visits will be on a risk-based approach according to GCP guidelines.

Data entry will be verified using internal monitoring by a member of the coordinating study team. In addition, external monitoring will be performed by the independent monitors. During the monitoring visit, data entry will be verified on a random sample of the included patients by assessment of the source documents (e.g. electronic patient files, questionnaires or diaries). In the case of discrepancies or missing data, queries will be added to the questions that need revision or additional information.

Adverse events

OAP consists of non-absorbable antibiotics. When taken orally, there is virtually no uptake of antibiotic components in the bloodstream. It is therefore expected that the occurrence of systemic side effects is negligible. More importantly, there is extensive experience with non-absorbable antibiotics applied as SDD on ICUs and severe and acute side effects that could apply to the current study have not been reported. [27–30] For this reason, we decided to refrain from an obligatory observation period after intake of the first dose of the study medication and patients can therefore take the medication at home. Nevertheless, patients will receive information about severe side effects of this study medication and are instructed to seek medical advice when they might suffer from severe acute side effects. The deblinding protocol can be freely assessed via our website, when deemed necessary. Late side effects such as the development of antibiotic resistance have not been described either. [31–35] Nevertheless, the occurrence of side effects and the development of antibiotic resistance will be monitored as secondary endpoints of this study.

All adverse events will be reported to the principle investigator. Serious adverse events (SAEs), Serious Adverse Reactions (SARs) and suspected unexpected serious adverse reactions (SUSARs) will be reported to the sponsor within 24 hours after notification of the event For the SAEs, we decided to only report life threatening infections with colistin- or tobramycin-resistant bacteria or *Clostridium difficile* colitis within 24 hours. Postoperative complications that are known to occur after colorectal surgery and are not directly related to the study medication will be reported to the ethical board in periodic line-listings and not within the 24-hour time window.

Data Safety and Monitoring Board

A Data Safety and Monitoring Board (DSMB) is established to guard patient safety during the trial. The DSMB consists of four independent experts who will have an active role during the entire study period. The board will issue recommendations to continue or stop the study, based on the unblinded results of the interim analysis and on the list of SAEs, SARs and SUSARs.

DISCUSSION

Undergoing surgery is associated with an increased risk of surgical site infections, but also mortality. To overcome the issue of mortality being a competing risk on the development of deep SSIs, our primary outcome of interest, we decided to use a composite endpoint for our primary outcome. 30-day all-cause mortality and deep SSIs will also be analyzed separately as secondary endpoints.

The rationale behind our intervention is to decontaminate the digestive tract prior to surgery, where we hypothesize that by lowering the bacterial load in the colon and rectum during the surgical procedure, the risk of postoperative infections is reduced. In a previous study, a suspension of colistin sulphate, tobramycin and amphotericin B was used to reduce anastomotic leakage and postoperative infectious complications. [24] This suspension is identical to the suspension that is used as an antibiotic prophylaxis on Dutch ICUs, often referred to as selective decontamination of the digestive tract (SDD). In contrast with SDD, the solution that will be used in our study does not contain an antifungal component (amphotericin B or nystatin). Fungi are rarely identified as the causative pathogens of SSIs after surgical procedures on the lower gastrointestinal tract and it was therefore decided to omit the antifungal component. [36] Another difference between our study and the trial from Roos *et al.,* is the timing of the treatment. In the previous trial, the intervention started two days prior to surgery and was continued during the postoperative period until normal bowel movements were observed. In our study, the intervention will only be given preoperatively and is discontinued on the night before the surgical procedure. We hypothesize that the majority of SSIs is caused by intraoperative rather than postoperative contamination of the surgical site and that the greatest reduction in SSIs will therefore be achieved by ensuring that the colonic bacterial load is at its lowermost at the time the surgical procedure takes place. The prophylaxis in our study is therefore restricted to the preoperative period. We also hypothesize that the treatment period of three days will be sufficient since we expect that the decontamination will least for several days. In our opinion, continuation of the prophylaxis in the postoperative period is not necessary as this could adversely increase the risk of developing antibiotic resistance or opportunistic infections.

To date, there is no consensus of the use of a preoperative oral antibiotic prophylaxis prior to colorectal surgery, in addition to perioperative intravenous antibiotic prophylaxis and without concurrent use of MBP. This impedes the formulation of clear-cut recommendations on its use in current infection control guidelines. This randomized, placebo-controlled, double-blind multicenter study aims to determine the efficacy of OAP in addition to perioperative intravenous antimicrobial prophylaxis on the development of SSIs and other infectious and non-infectious complications. The proposed study design offers an optimal approach to adequately minimize bias and generate generalizable results in order to guide important evidence-based recommendations regarding infection control measures in colorectal surgery.

List of abbreviations:
CDC, Centers for Disease Control and Prevention; CPE, carbapenemase-producing Enterobacteriaceae; DSMB, data safety and monitoring board; eCRF, electronic case report form; ESBL, extended-spectrum beta-lactamase; HRE, highly-resistant Enterobacteriaceae; GCP, good clinical practice; ICU, intensive care unit; MBP; mechanical bowel preparation; OAP, preoperative oral antibiotic prophylaxis; SDD, selective decontamination of the digestive tract; SAE, serious adverse event; SAR, serious adverse reaction; SSI, surgical site infection; SUSAR, suspected unexpected serious adverse reaction

Trial status: the trial has received ethical approval in September 2016. The recruitment of patients has started in April, 2017.

Ethics approval and consent to participate:
The Medical Ethics Committee of the UMC Utrecht (Utrecht, The Netherlands) has reviewed and approved the study (METC number 16/374). This trial will be conducted in agreement with the declaration of Helsinki (Version 10, Fortaleza, October 2013), in accordance with the Medical Research Involving Human Subjects Act (WMO) and with the GCP guidelines issued by the European Union. Informed consent is obtained from all participants
The PreCaution trial is registered in the Netherlands Trial Register under NTR6113 as well as in the EudraCT register under number 2015-005736-17.

Consent for publication: not applicable

Availability of supporting data: not applicable

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8

Prevention of Severe Infectious Complications After Colorectal Surgery Using Oral Antibiotic Prophylaxis: Results of the PreCaution Trial

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In preparation

ABSTRACT

Background: Surgical site infections (SSIs) are common complications after colorectal surgery. To reduce the risk of SSIs, oral antibiotic prophylaxis (OAP) can be administered preoperatively. Its efficacy without simultaneous mechanical cleaning is unknown.

Methods: This study was a double-blind, placebo-controlled randomized clinical trial conducted in six Dutch hospitals. Adult patients who underwent elective colorectal surgery were randomized to receive either a three-day course of preoperative OAP with tobramycin and colistin, or placebo. The primary composite endpoint was the incidence of deep SSIs or mortality within 30 days of surgery. Secondary endpoints included both infectious and non-infectious complications at 30 days and six months after surgery.

Results: The study was prematurely ended due to loss of clinical equipoise regarding the intervention. At that time 39 patients had been randomized to active OAP and 39 to placebo, which reflected 8.1% of the originally pursued sample size. Nine (11.5%) patients developed the primary outcome, of whom four had been randomized to OAP (4/39; 10.3%) and five to placebo (5/39; 12.8%). This corresponds to a risk ratio in the intention to treat analysis of 0.80 (95% confidence interval (CI) 0.23 – 2.78). In the per-protocol analysis, the relative risk was 0.64 (95% CI 0.12 – 3.46).

Conclusions: Observational data emerging during the course of the study provided new evidence for the effectiveness of OAP that changed both the clinical and medical ethical landscape for infection prevention in colorectal surgery. We, therefore, considered it unethical to continue randomizing patients to placebo. We recommend implementation of OAP in clinical practice and continued monitoring of infection rates and antibiotic susceptibilities

BACKGROUND

Surgical site infections (SSIs) are among the most common healthcare-associated infections and affect approximately 10 in every 100 patients who undergo colorectal surgery. [1,2] SSIs are associated with a substantial increase in morbidity [3] and mortality [4,5], prolongation of hospital stay [6,7] and higher health-care costs. [8–11] Despite the widespread adoption of infection prevention measures directed towards reducing SSIs, the risk remains high, which emphasizes the importance of exploring additional precautions. [2] In the past, preoperative oral antibiotics were applied as an infection control strategy for colorectal surgery. Because it was assumed that local antibiotics could only be effective in an "empty" colon, simultaneous cleansing was applied with osmotic fluids. [12] Routine use of this cleansing, also referred to as mechanical bowel preparation (MBP), has recently become controversial due to lack of evidence for advantageous effects that could counterbalance the risk of dehydration, anastomotic leakage or patient discomfort.[13,14] At the same time, the oral antibiotics that were often considered to be part of a package deal, were abandoned even though their efficacy without simultaneous MBP is unclear. The aim of our study was to study the efficacy of preoperative oral antibiotic prophylaxis (OAP) without the routine administration of MBP on the risk of SSIs after elective colorectal surgery.

METHODS

An in-depth description of the rationale and methods can be found in the previously published trial protocol. [15]

Trial design, participants and randomization

The study was designed as a double-blind placebo-controlled randomized trial and was conducted from April 2017 through August 2018 in six Dutch hospitals. (Supplementary table 1) Patients who were scheduled for colorectal surgery and who had no absolute contraindication for the study medication [15] were eligible to participate. Written informed consent was obtained from all participants. Eligible patients were randomly assigned in a 1:1 ratio to active OAP or placebo. The randomization was performed by an independent pharmacist, and by using a permuted block design with varying block sizes and stratification per study center. The study medication was packed in identical containers that were sequentially numbered with unique numbers. The list that linked these unique numbers to the treatment allocation was securely kept at the coordinating pharmacy (Amphia Hospital, Breda). Everyone who was involved in the study was blinded for the allocation until the end of the study.

Intervention

OAP was a solution of tobramycin (16 mg/ml) and colistin sulphate (20 mg/ml) that was taken four times daily during the three days before surgery. Each dose was 5 ml. Placebo had an identical color, smell and taste. The study medication was packed in bottles and distributed with a 5 ml syringe. The bottles were returned to the hospital after the intervention period and were weighted to estimate treatment compliance. All patients received perioperative intravenous antibiotic prophylaxis according to the national guidelines. [16]

Outcomes and safety reporting

Definitions of all outcomes are summarized in Figure 1 and are described in more detail in the trial protocol. [15] The CDC criteria were used to diagnose SSIs. [17] Rectal carriage of HRE comprised extended-spec-

trum beta-lactamase-producing Enterobacteriaceae (ESBL-E), and (non-intrinsic) carbapenem-resistant, tobramycin-resistant and (non-intrinsic) colistin-resistant Gram-negative Enterobacteriaceae. This was assessed by selective screening of rectal swabs that were obtained at inclusion and 30 days after surgery. The EUCAST clinical breakpoints were used for the interpretation of MICs. [18] Cultures with a transport interval of more than three days were excluded from analyses as the reliability and quality could not be guaranteed. Quality of life was assessed with the Rand 36 questionnaire. [19] This standardized questionnaire contains eleven questions to assess quality of life on nine different scales. The scale scores range from 0 to 100%.

Adverse events (AE) related to the study medication were self-reported in a medication diary. Other protocol related AE, Serious Adverse Events (SAE), Serious Adverse Reactions (SARs) and Suspected Unexpected Serious Adverse Reactions (SUSARs) were reported according to the Good Clinical Practice guidelines. [20]

Study procedures and data collection

An overview of the study procedures is provided in Supplementary table 2. Demographic patient data, surgery characteristics and data on the primary and secondary endpoints were collected from the medical records. Rectal carriage of HRE was assessed with one rectal swab at inclusion and one 30 days after surgery. Quality of life was assessed with one questionnaire at baseline and one six months after surgery.

Endpoints	Definitions
Primary composite endpoint	
Deep surgical site infection and/or mortality	SSIs were diagnosed per the CDC criteria
Secondary endpoints	
30 days after surgery	
Superficial surgical site infection	Superficial incisional infections
Deep surgical site infection	Deep incisional and organ/space infections
All-cause mortality	
Anastomotic leakage	Clinical or radiological evidence of leakage requiring surgical or radiological intervention
Relaparotomy	Abdominal reoperation
Bacteremia	Blood culture positive for microorganisms
Infection with *Clostridium difficile*	Stool sample positive for *Clostridium difficile* toxins
Infection with HRE	Positive culture for Enterobacteriaceae that produce ESBL or carbapenemase or that aquired quinolone or aminoglycoside resistance
Rectal colonization with HRE	Rectal swabs positive for ESBL-E or Enterobacteriaceae with non-intrinsic resistance to carbapenems, tobramycin or colistin
In-hospital use of antibiotics	Defined as days on therapy
6 months after surgery	
All-cause mortality	Evaluated by assessment of the medical record or by phone call
Quality of life	Measured with RAND-36 questionnaire
Length of hospital / ICU stay	In days, including all readmissions

Figure 1 Definitions of primary and secondary endpoints. SSIs were diagnosed with the CDC criteria. [17] CDC, Centers for Disease Control and Prevention; ESBL-E, extended spectrum beta-lactamase producing Enterobacteriaceae; HRE, highly resistant Enterobacteriaceae; ICU, intensive care unit; SSI, surgical site infection

Statistical analysis

Sample size calculation
We assumed a 14.4% baseline incidence and a 40% relative reduction in the primary endpoint to calculate the sample size. This was based on results obtained in a before-after study that was performed in a Dutch teaching hospital where OAP was introduced as standard of care prior to elective colorectal surgery. [21] With a one-sided alpha of 2.5%, power of 80% and one interim analysis, the final sample size resulted in 966 patients.

Data analysis
Data were analyzed according to the intention-to-treat principle. We calculated crude risks for every outcome and a corresponding risk ratio (RR) and 95% confidence interval (CI) to compare the risks in the intervention arm with the placebo arm. A per-protocol analysis was performed in the 100% compliant population. Continuous outcomes were analyzed using Student's T test or Mann Whitney U, as appropriate. Quality of life after six months was corrected for the baseline scores by calculating the change (delta) in scores. Negative deltas reflect worse perception of quality of life compared to baseline, whereas positive values reflect improvement. Missing questionnaire data were analyzed and imputed using single imputation using chained equations. [22]

To evaluate whether our study population was a representative sample of the patient population, average baseline characteristics were compared with surveillance data from a Dutch hospital that did not participate in the study. Statistical analyses were performed using R version 3.3.2.

RESULTS

Patient enrolment is shown in Figure 2. The number of participants and the inclusion period per hospital are presented in Supplementary table 2. The trial was ended after 18 months when 78 participants (8.1% of the sample size) had been enrolled. All patients completed the intervention period. In the six-month follow-up period, one person was lost to follow up and four discontinued active participation but gave consent to continue data collection from their medical records.

Baseline characteristics of the participants are shown in Table 1. Thirty-nine patients were included in each treatment arm. Median age was 68 years and 68% was male. Colorectal malignancies were the indication for surgery in all except one of the patients (98.7%). Even though it was not part of routine care, oral MBP was applied in 3.8% of the patients. Based on the leftovers of study medication that were returned, we estimated that 57.7% of the patients administered all twelve doses of study treatment.

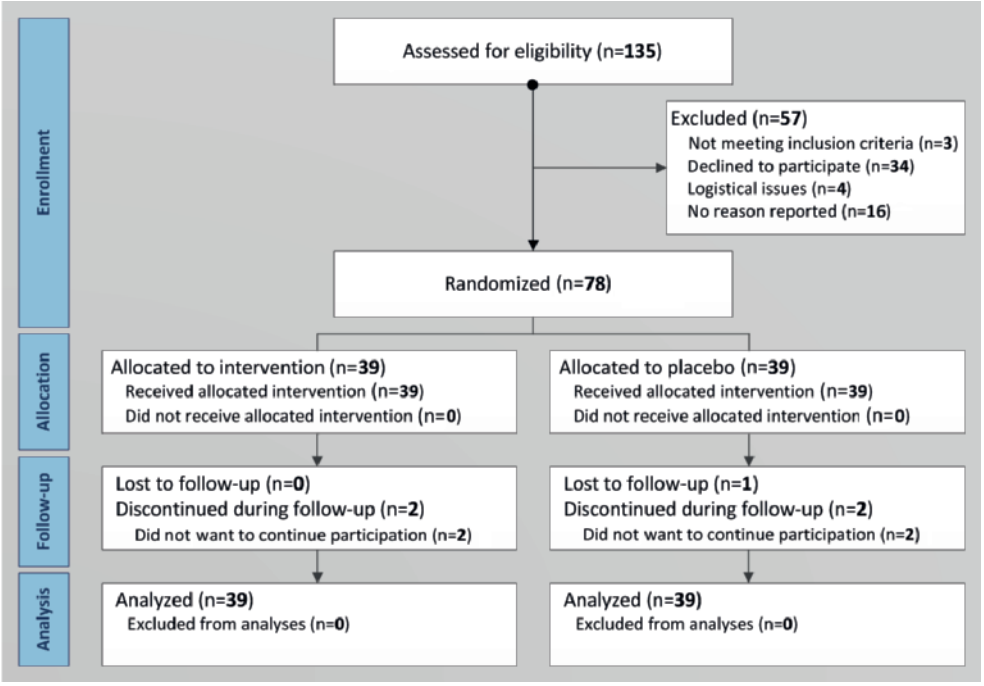

Figure 2 CONSORT flowchart of enrolment of participants.
Logistical issues were unexpected changes in the date of surgery that led to insufficient time to complete the three-day intervention period (n=1) or missed appointments for the informed consent procedure due last-minute changes in the outpatient clinic schedule (n=3).

The effect of OAP on primary and secondary outcomes is presented in Table 2. In total, nine (11.5%) patients developed the primary outcome, of whom four were patients who received OAP (3/39; 10.3%) and five who received placebo (5/39; 12.8%). This corresponds to a risk ratio in the intention to treat analysis of 0.80 (95% CI [0.23 – 2.78]). There was no statistical difference between the treatment arms for any of the outcomes, except for the difference in quality of life after six months that was improved compared to baseline on most scales in patients who had received OAP, and worsened in patients who had received placebo. In the per-protocol analysis, the risk ratio for the primary outcome was 0.64 (95% CI 0.12–3.46]). Due to insufficient power, we were unable to perform any of the preplanned subgroup analyses. [15]

We collected 66 valid baseline rectal swabs and 62 valid follow-up rectal swabs (Table 3). Of the follow-up swabs, three (4.8%) contained an ESBL-E, 25 (40.3%) contained Enterobacteriaceae resistant to tobramycin and eight Enterobacteriaceae resistant (12.9%) to colistin. This did not differ between the study arms. Of the eleven SSIs that developed, three were confirmed with a microbiological culture of which two were performed on abdominal pus collected during reoperation and one directly on the incision. (Supplementary Table 4). Pathogens that were cultured were all intestinal microorganisms. None of the pathogens were non-intrinsically resistant to antibiotics.

Table 1 Baseline characteristics

Variable	OAP (N = 39)	Placebo (N = 39)
Age in years	67 (61 – 72)	69 (61 – 73)
Male sex	28/39 (71.8)	25/39 (64.1)
ASA classification ≤ 2	26/38 (68.4)	30/36 (83.3)
Charlson Cormobidity Index		
1 – 2	22/39 (56.4)	25/39 (64.1)
3 – 4	9/39 (23.1)	2/39 (5.2)
≥5	8/39 (20.5)	12/39 (30.1)
Immunosuppressive therapy [a]	0/39 (0.0)	2/39 (5.2)
BMI in kg/m^2, median (IQR)	28 (24 – 31)	26 (23 – 29)
Abdominal surgery in the previous year	1/39 (2.3)	2/39 (5.2)
Oral mechanical bowel preparation	1/39 (2.3)	2/39 (5.2)
Indication for surgery		
Colorectal malignancy	38/39 (97.4)	39/39 (100)
Inflammatory bowel disease	1/39 (2.3)	0/39 (0.0)
Wound class		
Clean-contaminated (class 2)	37/39 (94.9)	39/39 (100)
Contaminated (class 3)	2/39 (5.1)	0/39 (0.0)
Type of resection		
Right sided hemicolectomy	13/39 (33.3)	9/39 (23.1)
Left sided hemicolectomy	2/39 (5.2)	4/39 (10.3)
Sigmoid resection	10/39 (25.6)	8/39 (20.5)
Low anterior resection or rectum amputation	10/39 (25.6)	15/39 (38.5)
(Sub)total colectomy	2/39 (5.2)	0/39 (0.0)
Surgical approach		
Laparotomy	4/39 (10.3)	4/39 (10.3)
Laparoscopy [b]	28/39 (72.0)	26/39 (66.7)
Robotic laparoscopy	7/39 (17.8)	9/39 (23.1)
Duration of surgery >75th percentile	8/38 (21.1)	13/37 (35.1)
Normothermia after procedure	22/28 (78.6)	25/31 (80.1)
Stoma	6/38 (15.8)	14/39 (35.9)
Perioperative intravenous antibiotic prophylaxis	37/39 (94.9)	37/38 (97.3)
Complete compliance to study medication (all 12 doses)	23/33 (69.7)	22/33 (66.7)
Quality of life scale scores, mean (sd) [c]		
Physical functioning	79.4 (18.2)	82.7 (20.9)
Social role functioning	84.3 (18.5)	82.1 (22.4)
Physical role functioning	64.1 (41.7)	71.2 (38.3)
Emotional role functioning	79.5 (30.2)	73.5 (37.6)
Mental health	78.7 (14.6)	77.3 (17.7)
Vitality	64.1 (21.3)	72.3 (18.5)
Pain	80.9 (21.3)	80.7 (19.8)
General health perception	59.9 (19.5)	62.8 (17.5)
Change in health	41.0 (20.3)	80.9 (19.0)

Data are presented as n/N with data (%), unless specified otherwise. ASA, American Society of Anesthesiologists; BMI, body mass index; IQR, interquartile range; OAP, oral antibiotic prophylaxis; sd, standard deviation

a. Because of chemotherapy

b. Of which 6 (15.4%) were converted to open procedures in OAP arm and 1 (2.3%) in placebo arm

c. Number of complete questionnaires: 34 (87.2%) OAP, 32 (82.1%) placebo. Missing scale scores were imputed

Table 2 Intention-to-treat analysis of OAP on the risk on primary and secondary outcomes

	OAP	Placebo	
	Patients, n/N (%)		**RR (95% CI)**
Deep SSI and/or mortality	4/39 (10.3)	5/39 (12.8)	0.80 (0.23 – 2.78)
Deep SSI	4/39 (10.3)	5/39 (12.8)	0.80 (0.23 – 2.78)
30-day mortality	0/39 (0.0)	0/39 (0.0)	N/A
Superficial SSI	1/39 (2.6)	1/39 (2.6)	1.00 (0.06 – 15.40)
Anastomotic leakage	1/39 (2.6)	2/39 (5.2)	0.50 (0.05 – 5.29)
Relaparotomy	3/39 (7.9)	2/39 (5.3)	1.50 (0.27 – 8.49)
Bacteremia	0/39 (0.0)	0/39 (0.0)	N/A
Infection with HRE	0/39 (0.0)	0/39 (0.0)	N/A
Infection with *Clostridium difficile*	0/39 (0.0)	0/39 (0.0)	N/A
6-month mortality	0/39 (0.0)	0/39 (0.0)	N/A
	Median (IQR)		**P value**
In-hospital use of antibiotics, DOT [a]	0.0 (0.0 – 0.0)	0.0 (0.0 – 4.0)	1.000
Length of stay, days [b]	7.0 (5.0 – 13.0)	6.0 (5.0 – 12.0)	0.497
Length of ICU stay, days [b]	4.0 c	0	N/A
	Mean delta (sd)		**P value**
Quality of life [d]			
Physical functioning	-5.1 (16.5)	-11.5 (17.9)	0.104
Social role functioning	2.6 (23.1)	-8.7 (20.9)	0.028
Physical role functioning	-0.6 (57.7)	-25.6 (52.7)	0.040
Emotional role functioning	15.4 (38.1)	-6.0 (43.8)	0.024
Mental health	6.9 (14.6)	2.1 (13.8)	0.138
Vitality	1.7 (18.8)	-11.5 (17.1)	0.002
Pain	1.9 (19.9)	-8.3 (22.6)	0.036
General health perception	1.2 (20.0)	-2.3 (19.2)	0.438
Change in health	10.9 (39.2)	0.6 (34.2)	0.222

Length of (ICU) stay, quality of life and 6-month mortality were assessed 6 months after surgery, all other outcomes were evaluated 30 days after surgery. DOT, days on therapy; HRE, highly resistant Enterobacteriaceae; ICU, intensive care unit; IQR, interquartile range; N/A, not available; OAP, oral antibiotic prophylaxis; RR, risk ratio; sd, standard deviation; SSI, surgical site infection

a. 9 patients in the OAP arm and 10 patients in the placebo arm were treated with antibiotics

b. Including all readmissions within 6 months of surgery

c. Only 1 patient was admitted to the ICU

d. Delta was calculated by subtracting baseline scores from scores at 6-month follow-up. Negative delta's reflect worse perception of quality of life on compared to baseline. Number of completed follow-up questionnaires: 27 (69.2%) OAP, 32 (82.1%) placebo. Scale scores in missing questionnaires were imputed

Adverse events during the intervention period are presented in Table 4. Out of the 65 (83.3%) patients who returned their medication diary, 33 (50.1%) did not report any side effects. The majority of adverse events were gastro-intestinal side effects. Patients who received OAP more often reported diarrhea compared to those who received placebo (43.8% versus 18.2%) as well as nausea (15.7% versus none). During the study, there was one SAE, which was a transient ischemic attack that occurred before the start of the intervention phase. No other adverse events related to either study medication or other study procedures were reported.

Table 3 Rectal carriage of (non-intrinsic) antibiotic resistant microorganisms

	Patients, n/N (%)		
	OAP	**Placebo**	**P value**
Baseline			
Number of valid rectal cultures	35/39 (89.7)	31/39 (79.5)	
ESBL-E	2/35 (5.7)	2/31 (6.5)	1.000
Carbapenem resistant Gram-negative bacteria	1/35 (2.9)	2/31 (6.5)	0.597
Tobramycin resistant Gram-negative bacteria	12/35 (34.3)	14/31 (45.2)	0.452
Colistin resistant Gram-negative bacteria	7/35 (20.0)	6/31 (19.4)	1.000
30 days after surgery			
Number of valid rectal cultures	34/36 (94.4)	28/35 (80.0)	
ESBL-E	2/34 (5.9)	1/28 (3.6)	1.000
Carbapenem resistant Gram-negative bacteria	0/34 (0.0)	1/28 (3.6)	0.452
Tobramycin resistant Gram-negative bacteria	15/34 (44.1)	10/28 (35.7)	0.606
Colistin resistant Gram-negative bacteria	4/34 (11.9)	4/28 (14.3)	0.320

Data are presented as n/N (%). P values are estimated using Fisher's exact test. ESBL-E, Extended-Spectrum Beta Lactamase-producing Enterobacteriaceae; OAP, oral antibiotic prophylaxis

Table 4 Adverse events

	Patients, n/N (%)	
	OAP	**Placebo**
Adverse events related to study medication		
Self-reported side effects during intervention period [a]		
No side effects	13/32 (40.6)	19/33 (57.8)
Gastro-intestinal side effects		
Diarrhea	14/32 (43.8)	6/33 (18.2)
Nausea	5/32 (15.7)	0/33 (0.0)
Stomach ache	7/32 (21.8)	6/33 (18.2)
Loss of appetite	1/32 (3.1)	0/33 (0.0)
Flatulence	1/32 (3.1)	3/33 (9.1)
Other side effects	5/32 (15.6)	4/33 (12.1)
Serious adverse reaction (SAR)	0/39 (0.0)	0/39 (0.0)
Serious unexpected suspected adverse reaction (SUSAR)	0/39 (0.0)	0/39 (0.0)
Adverse events related to other study procedures	0/39 (0.0)	0/39 (0.0)
Serious adverse event (SAE)	1/39 (2.6)	0/39 (0.0)

Data are presented as n/N with data. Denominators for the self-reported side effects are based on the number of medication diaries that were returned: OAP 32/39 (82.1%), placebo 33/39 (84.6%). OAP, oral antibiotic prophylaxis
a. Self-reported in medication diary during the three days of administration of study medication

To estimate whether our cohort was a representative sample of the patient population, we compared the baseline characteristics with a comparison cohort of 1,597 patients. (Supplementary table 5) Compared to the comparison cohort, it appears that the trial cohort consists of a higher percentage of men, (67.9% versus 55.5%), colorectal malignancies (98.7% versus 74.5%) and a lower percentage abdominal surgery in the preceding year (3.8% versus 12.0%) Also, the percentage of minimally invasive procedures seems higher in the PreCaution trial.

DISCUSSION

Due to premature study termination we were unable to determine efficacy of OAP on SSI risk and other postoperative complications after colorectal surgery in this multicenter, double-blind, placebo-controlled randomized clinical trial.

The use of oral antibiotic prophylaxis in colorectal surgery remains a controversial topic. Several studies demonstrated a reduced risk of SSIs when OAP is administered before surgery [24,25], but the question whether the oral antibiotics are effective without MBP remains unanswered as all RCTs published to date combined OAP with MBP. The best available evidence on OAP efficacy is provided by a recent network meta-analysis that aimed to study the best strategy for bowel preparation. This study also emphasized the knowledge gap on OAP without MBP as the absence of RCTs that included this strategy as a treatment arm forced the authors to estimate the efficacy of OAP based on indirect comparisons only. Though based on indirect comparisons, a significant reduction in organ/space SSIs was found compared to no preparation (OR 0.13 [95% CrI 0.02 – 0.55]), that was superior to combining OAP with MBP.
Limited data on applying OAP without MBP is also provided by several observational studies that retrospectively compared the effect of all bowel preparation strategies that reported conflicting results on the effectiveness. [26–37] Suspected confounding by indication and very low numbers of patients treated with only OAP hamper concluding on the effectiveness of OAP in the absence of MBP. This illustrates the need for well controlled and adequately powered studies.

We consider the design as one of the major strengths of our study which facilitated studying the efficacy of OAP and allowed for an objective evaluation of potential drug-related side effects. Although the quality of our design is high, selective participation could not have been prevented completely. The screening was partly based on the clinical condition of the patient, as patients suffering from multiple or more severe comorbidities were not always considered for participation even though they were eligible. Also, there were multiple other studies being conducted within this patient population which not only competed with our inclusions, but also could have led to a selective inclusion of participants. Comparison of the baseline characteristics of our cohort showed potentially relevant differences with data obtained from infection surveillance on a comparable group of patients. It could be that the patients we included were in a better clinical condition, as the percentage of patients with colorectal malignancy is higher. A recently implemented national screening program for colorectal cancer led to the detection of malignancies in an earlier stage. In general, patients are in a better clinical condition and surgery is less radical, which lowers the risk of SSIs. The lower percentage of contaminated wounds and the higher rate of minimally invasive surgical procedures could also reduce the SSI risk, though it must be noted thatv time periods are different and that some of this increase might be partly explained by advances in surgical techniques over time. If we indeed faced selective inclusion it could have affected the generalizability of our findings.

In the evaluation of quality of life, treatment with OAP was associated with a significant improvement of the perception of quality of life after six months compared to placebo on several scales. In the absence of an effect of OAP on any of the clinical outcomes that could have been a possible explanation for this improvement, we suggest further investigation to study whether and how OAP might impact quality of life. Because of the small sample size were unable to thoroughly study the safety of OAP. We did find that several patients who received OAP reported mild gastrointestinal side effects and an unappealing taste. When OAP is considered for implementation in the future, patients should be informed about these potential side effects and the necessity of completing the entire three-day course of OAP. Another im-

portant safety concern is the risk of developing antibiotic resistance. We found the prevalence of colistin and tobramycin resistance at baseline to be 16.7% and 39.4%, respectively. The prevalence of carriage of tobramycin resistant species after 30 days remained substantial though did not increase in both treatment arms. The prevalence of colistin resistance after 30 days did not differ between the study arms, either. Data on the prevalence of rectal carriage of tobramycin or colistin resistant species in this patient population is not yet available. We compared our findings with the results obtained with the implementation of selective decontamination of the digestive tract (SDD), a comparable antibiotic prophylaxis containing tobramycin, colistin and nystatin that is used in several Dutch ICUs. One study performed a post hoc analysis of two multicenter trials on SDD in ICU patients and demonstrate a baseline prevalence of colistin resistance of 2.8%. [38] During SDD, the rectal carriage of colistin ranged from 1.7% to 2.8%. The prevalence of tobramycin resistance was 12% at baseline and ranged from 6.2% to 8.0% in SDD period. Other studies on SDD found a comparable prevalence. [39–41] We used a more sensitive method to screen for colistin resistance which could explain the higher prevalence compared to the ICU studies. Due to the small numbers of patients we were unable to adequately evaluate whether OAP increases the risk of development of antibiotic resistance but other Dutch studies did not find an elevated risk of resistance following SDD administration. [40,42]

Ethical considerations

At the time this trial was initiated, there was no consensus within the Dutch surgical community on whether OAP should be used prior to colorectal surgery and, as a result, it was not part of clinical care in the vast majority of hospitals. Because of this, there was clinical equipoise regarding the use of OAP, as there was true uncertainty regarding the efficacy of the intervention. [43] A shift started when the findings of a single-center observational study were published. This study was performed in the same setting without routine MBP administration. [21] In contrast to previous observational studies, the risk of confounding by indication was minimized because OAP was implemented as the standard of care and prescribed to all patients who underwent elective colorectal surgery. After implementation, a 42% reduction was observed in the risk of SSI and mortality within 30 days after surgery (aRR 0.58 [95% CI 0.40 – 0.79)]. Due to the single-center aspect of the study and the risk of residual confounding a well-controlled study was deemed necessary to confirm the treatment effect.

We faced multiple problems recruiting participants throughout the entire study period despite our efforts to improve the inclusion rate. The unexpectedly low recruitment rate was communicated with the participating hospitals. Supported by the effectiveness found in the observational study, several investigators decided to implement OAP because of persisting high SSI rates and considered awaiting the trial results. unacceptable. The assumption of clinical equipoise regarding the administration of OAP, therefore, was no longer valid and we decided to prematurely end the trial because the use of a placebo was no longer ethically justifiable.

To conclude, we could not evaluate efficacy of OAP on SSI risk and other postoperative complications after colorectal surgery due to premature termination of this double-blind, placebo-controlled, randomized clinical trial. Because of loss of clinical equipoise we no longer consider it ethical to pursue to confirm the efficacy of OAP with placebo-controlled clinical trials. We recommend implementation of OAP in clinical practice and continued monitoring of infection rates and antibiotic susceptibilities.

List of abbreviations:
ASA, American Society of Anesthesiologists; BMI, body mass index; CDC, Centers for Disease Control and Prevention; CI, confidence interval; DOT, days on therapy; DSMB, data safety and monitoring board; eCRF, electronic case report form; ESBL, extended-spectrum beta-lactamase; HRE, highly-resistant Enterobacteriaceae; IQR, interquartile range; GCP, good clinical practice; ICU, intensive care unit; MBP; mechanical bowel preparation; OAP, preoperative oral antibiotic prophylaxis; RCT, randomized controlled trial; RR, risk ratio; SAE, serious adverse event; SAR, serious adverse reaction; SDD, selective decontamination of the digestive tract; SSI, surgical site infection; SUSAR, suspected unexpected serious adverse reaction

Ethical approval: the Medical Ethics Committee of the UMC Utrecht (Utrecht, The Netherlands) has reviewed and approved the study (METC number 16/374). This trial was conducted in agreement with the declaration of Helsinki (Version 10, Fortaleza, October 2013), in accordance with the Medical Research Involving Human Subjects Act (WMO) and with the GCP guidelines issued by the European Union. The PreCaution trial is registered in the Netherlands Trial Register under NL5932 (previous number: NTR6113) as well as in the EudraCT register under number 2015-005736-17.

Conflicts of interest: the authors declare that they have no competing interests

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SUPPLEMENTARY MATERIAL

Supplementary Table 1 Participating hospitals

Hospital	Role
UMC Utrecht, Utrecht	Study coordination
Amphia Hospital, Breda	Distribution study medication Analysis of rectal swabs
UMCG, Groningen	Inclusion of participants
Reinier de Graaf Gasthuis, Delft	Inclusion of participants
Meander Medical Center, Amersfoort	Inclusion of participants
St. Antonius Hospital, Nieuwegein	Inclusion of participants
Erasmus MC, Rotterdam	Inclusion of participants
Admiraal de Ruyter Ziekenhuis, Goes	Inclusion of participants

Supplementary Table 2 Overview of study procedures and follow-up

	Study phase					
Study procedures	**Screening**	**Enrollment**	**Intervention**	**Surgery**	**30 days after surgery**	**6 months after surgery**
Recruitment	•					
Eligibility screening		•				
Informed consent		•				
Allocation		•				
Rectal swab		•			•	
Quality of life questionnaire		•				•
Intake study medication			•			
Self-report of side effects			•			
Report protocol related AE		•	•	•	•	•
Report of SAE		•	•	•	•	•
Report of SUSAR, SAR			•	•	•	•
Evaluation primary outcome					•	
Evaluation of secondary outcomes					•	•

• Procedures performed by or with the participant • Safety reporting • Outcome assessment
AE, Adverse Events; SAE, Serious Adverse Events; SAR, Serious Adverse Reaction; SUSAR, Suspected Unexpected Serious Adverse Reaction

Supplementary Table 3 Overview of progress per study site

Hospital description			Study period					
Hospital	Category	Estimated No. eligible patients / yr	Study initiation	First recruitment	Last recruitment	Inclusion period, months	No. patients screened	No. patients included
A	University	60	Mar 2017	Apr 2017	May 2018	14	28	13
B	General	150	Jun 2017	Jul 2017	Aug 2018	14	34	16
C	General	200	Jul 2017	Sept 2017	May 2018	9	8	6
D	General	250	Aug 2017	Sept 2017	Aug 2018	12	54	33
E	University	130	Dec 2017	Jan 2018	Mar 2018	3	4	3
F	General	150	Dec 2017	Apr 2018	Jun 2018	3	7	7

Supplementary Table 4 Microorganisms cultured from SSI

Type of SSI	Intervention	Tissue	Microorganisms cultured
Deep incisional	OAP	Wound	*Pseudomonas aeruginosa*
			Enterococcus faecium
			Enterococcus faecalis
			Citrobacter freudii
Organ/space	OAP	Abdominal pus	*Proteus mirabilis*
			Enterococcus faecium
Organ/space	OAP	Abdominal pus	*Bacteroides ovatus*
			Actinomyces neuii

OAP, oral antibiotic prophylaxis; SSI, surgical site infection

Supplementary Table 5 Comparison of characteristics with data from an observational cohort of elective colorectal surgery patients

Variable	PreCaution cohort N = 78	Comparison cohort N = 1,597
Age in years, median (IQR)	68 (61 – 73)	68 (60 – 76)
Male sex	53/78 (67.9)	887/1,597 (55.5)
ASA classification		
≤2	56/74 (75.7)	1,068/1,508 (70.8)
BMI in kg/m^2, median (IQR)	27 (23 – 29)	25 (22 – 28)
Obese	14/77 (18.2)	240/1,570 (15.2)
Abdominal surgery in the previous year	3/78 (3.8)	192/1,597 (12.0)
Colorectal malignancy	77/78 (98.7)	1,190/1,597 (74.5)
Wound class		
Clean contaminated (class 2)	76/78 (97.4)	1,422/1,597 (89.0)
Contaminated (class 3)	2/78 (2.6)	124/1,597 (7.8)
Dirty (class 4)	0/78 (0.0)	51/1,597 (3.2)
Type of resection		
Right sided hemicolectomy	22/78 (28.2)	437/1,590 (27.5)
Left sided hemicolectomy	6/78 (7.7)	162/1,590 (10.2)
Sigmoid and rectum resection	43/78 (55.1)	675/1,590 (42.5)
Other	7/78 (9.0)	287/1,590 (18.1)
Surgical approach [a]		
Open	15/78 (19.2)	797/1,590 (50.1)
Laparoscopic	47/78 (60.3)	565/1,590 (37.4)
Robotic laparoscopic	16/78 (20.5)	228/1,590 (14.3)
Perioperative intravenous antibiotic prophylaxis	74/77 (96.1)	1,513/1,582 (95.6)

Data are presented as n/N with data (%), or median (interquartile range). The comparison cohort consists of all patients who underwent elective colorectal surgery between 2012 and 2015 in the Amphia Hospital (Breda, the Netherlands). ASA, American Association of Anesthesiologists; BMI, body mass index; IQR, interquartile range

a. Laparoscopic procedures that were converted are classified as open procedures

9

Summary and General Discussion

Tessa Mulder

INTRODUCTION

In the Netherlands, one in ten patients who undergo colorectal surgery will develop a surgical site infection (SSI). [1] SSIs have important consequences for the postoperative recovery: they cause pain and suffering, extend the length of the hospital stay by more than a week on average, but also increase the risk of death. Extensive treatment is often required and SSIs are therefore also associated with substantial additional costs. [2,3] Because of these severe consequences and the high incidence of infections, extensive efforts have been made to improve infection prevention. Multiple measures have been explored and employed, of which some have a strong scientific basis, whereas others are driven exclusively by expert opinion. [4] Despite the widespread adoption of infection prevention measures, the risk is still considerable. [5] At the same time, rapid advances in surgical techniques facilitate performing surgery in higher-risk patients and combined with an aging population and with recent implementation of population-based screening for colorectal cancer, this leads to an increase in the number of colorectal procedures. [6] Consequently, the number of patients at risk of an SSI will increase and, when the risk of SSIs remains stable, the number of infections will also increase. This prognosis and the substantial burden associated with SSIs stress the need for interventions that reduce the risk of infection.

This thesis aimed to provide evidence to improve infection control for colorectal surgery using two approaches. First, it was investigated whether the efficiency of **infection surveillance** could be enhanced. The second approach was to study if **infection prevention** could be improved with preoperative oral antibiotic prophylaxis. The proposed prophylaxis, containing tobramycin and colistin, has not been studied before to reduce SSIs after colorectal surgery and an important part of this thesis was dedicated to provide evidence for its efficacy and safety.

This final chapter synthesizes the evidence from literature and from the work described in this thesis to provide an answer on the following questions:

- Can the **efficiency of SSI surveillance** for colorectal surgery be improved?
- Is a **mechanically-cleaned colon imperative** for oral antibiotics to be effective?
- Is oral antibiotic prophylaxis with tobramycin and colistin **effective** in reducing SSI risk?
- Is oral antibiotic prophylaxis with tobramycin and colistin **safe**?
- Do we need **more research** on oral antibiotic prophylaxis?

IMPROVEMENT OF INFECTION SURVEILLANCE

An essential feature in the strategy to prevent SSIs is to have an effective surveillance program. Such a program routinely collects data on SSI rates that are used as reference data for hospitals and healthcare providers. [7] These data can be applied to evaluate the quality of care, to identify where improvements are needed and to support and facilitate implementation of new preventative measures. As a result, infection surveillance can be used to reduce SSI-related morbidity and costs.[4]

The definition of SSI comprises multiple criteria and as the traditional method for the ascertainment of SSIs is through extensive manual chart review, surveillance is time-consuming and labor-intensive. In **Chapter 2**, we demonstrated that a relatively straightforward five-parameter algorithm can be used to screen the medical records and to select those that need complete manual review. The algorithm found

98.5% of all deep SSIs. Only a very small proportion of deep SSIs was missed, but the payoff was a workload reduction of approximately 63%. This method has the potential to replace manual chart review for infection surveillance. Once this model is externally validated, it would be interesting to explore the use of semi-automated data extraction as this might reduce the workload even further, as manual extraction of the algorithm data can be foregone.

It must be noted that this model was developed to detect deep incisional and organ/space SSIs, specifically. Because of the severity of these infections, signs and symptoms are not easily overseen and thus more likely to be properly documented, and treatment is often initiated rapidly. Patients who develop a deep SSI after discharge are almost always readmitted to be treated. The algorithm predicts SSIs primarily by using data on these postoperative events. We presume that the clinical course and management of SSIs is comparable between hospitals and that nearly all variables will be easy to extract from the medical records. We therefore expect that the model will perform similarly when it is externally validated.
We need to stress that this algorithm cannot be applied for the surveillance of superficial incisional SSIs. These infections have a different clinical presentation and a milder clinical course. One might consider developing an algorithm to detect superficial infections, though this might be difficult because the heterogeneous clinical presentation may force searching the medical record for specific signs and symptoms through text mining. This will reduce the applicability of the algorithm and may also pose a potential problem when considering semi-automated data extraction. Complete replacement of manual screening for infection surveillance is therefore not yet possible.

> *To conclude: can the efficiency of SSI surveillance for colorectal surgery be improved?*
> Yes, we demonstrated that the five-parameter algorithm is a reliable method to detect deep infections with the highest clinical and economic burden. Close monitoring of the incidence of these complications may help to identify flaws in infection prevention in an early stage and the time saved may be invested to improve infection prevention.

IMPROVEMENT OF INFECTION PREVENTION

While the use of perioperative intravenous antibiotic prophylaxis has been widely accepted as standard of care to prevent SSI after colorectal surgery, there is ongoing debate on the best preoperative bowel preparation or whether the bowel should be prepared at all. This is also reflected by the different recommendations in infection prevention guidelines across the world (Table 1). American and Asian guidelines recommend a combination of mechanical bowel preparation (MBP) and oral antibiotic prophylaxis (OAP) with non-absorbable antibiotics, whereas in European guidelines, these methods of preparations are not advised. One point on which most guidelines agree is that MBP alone should not be used. Though proven not to be effective in reducing SSI risk [8,9], MBP still continues to be used combined with OAP because it is hypothesized that it is necessary to clean the colon to ensure optimal activity of OAP. [10,11] This assumption is based on expert opinion and whether OAP indeed needs MBP to be effective remains to be investigated due to lack of randomized controlled trials (RCTs) performed that included an OAP only arm. Due to this absence of evidence, there are no guidelines that advise to use OAP without MBP.

Table 1 Guideline recommendation on bowel preparation before colorectal surgery

Guideline	Advised bowel preparation	Suggested antimicrobials
USA [12]	MBP with OAP recommended MBP alone discouraged OAP alone not recommended	Neomycin and erythromycin Neomycin and metronidazole
WHO [13]	MBP with OAP recommended MBP alone discouraged	Erythromycin, metronidazole and an aminoglycoside
Asia [14]	MBP with OAP recommended	Not specified
Japan	MBP with OAP recommended	Kanamycin and metronidazole
Spain [15]	MBP alone discouraged	-
The Netherlands [16], UK [17], and Ireland [18]	No advice given	-

Necessity of combining oral antibiotics and MBP

We studied evidence from observational studies and indirect evidence from RCTs and found several reasons to question the necessity of adding MBP to oral antibiotics. First, we reviewed observational studies on bowel preparation in **Chapter 6**. All observational studies that reported data on OAP without being combined with MBP were included. Compared to no preparation, the reduction in SSI risk with OAP ranged from 32% to 57%. [19–22] When combined with MBP, this reduction ranged from 53% to 67% [19,21–25], with one study reporting a reduction as strong as 80%. [26] Several studies also directly compared the two strategies and, whereas two demonstrated a lower SSI risk when OAP was combined with MBP [27,28], most did not find a difference. [21,22,29,30] The vast majority of these studies was performed in the USA which explains the overall preference of combining OAP and MBP and why only a small percentage of patients who only received OAP. It must be noted that these observational studies are affected by confounding by indication and misclassification bias. Because of these biases, a suspected overlap in study participants, and due to potentially underpowered subgroups, the validity of the reported treatment effects may be questioned. However, the absence of a difference between OAP alone and OAP with MBP was also found by one RCT [31] and by a recent network analysis that aimed to conclude on the best bowel preparation strategy by pooling the results of 38 RCTs. [32] This meta-analysis demonstrated that the combination of OAP and MBP did not differ from OAP alone in terms of reduction in total SSI (OR 0.95 [95% CrI 0.56 – 1.62]) or on incisional infections (OR 0.84 [95% CrI 0.48 – 1.49]), which suggests comparable efficacy of the two strategies. Finally, our hypothesis that MBP is not strictly necessary is supported by our own findings that are presented in **Chapter 4**. In this before-after study, we investigated the effectiveness of OAP in a setting were MBP is not used and found that OAP reduced SSI risk by 42%, which is comparable to the reduction found by the other observational studies. These data suggest that the added value of MBP is questionable, at best. This is relevant because, besides the additional costs, MBP does not only pose a risk of electrolyte disturbance but its administration is also a significant burden to the patient. [33,34]

> *To conclude: Is a mechanically cleaned colon imperative for antibiotics to be effective?*
> No, oral antibiotics are also effective when the colon is not mechanically cleaned. We demonstrated in our before-after analysis that SSI risk can be significantly reduced in the absence of MBP. In addition, several other studies did not find a difference between OAP alone and OAP combined with MBP on SSI rates. We, thus, conclude that MBP is not strictly necessary, which is in contradiction to the prevailing belief of many (American) surgeons that MBP is imperative for OAP to be effective.

Impact of OAP with tobramycin and colistin on SSI risk

In the observational study presented in **Chapter 4**, the OAP used comprised a solution of tobramycin and colistin. In contrast to the regimen that is recommended in most guidelines, this OAP regimen was administered as a solution instead of tablets, and during the three days before surgery instead of only one day. Another difference is that colistin and tobramycin selectively target the Gram-negative bacterial species, whereas classical OAP also kills the anaerobic bacteria in the gut. As the Gram-negatives are generally thought to be the predominant pathogens of SSIs, we hypothesize that the anaerobic bacteria do not play an important role in the development of SSIs. By sparing these species the colonization resistance is kept intact and the risk of opportunistic infections is reduced. Colistin and tobramycin have been used as part of antibiotic prophylaxis called selective decontamination of the digestive tract (SDD) on Dutch ICUs for several years. Combined with nystatin, they have been studied as preoperative OAP for gastrointestinal surgery. [35–37]

Preoperative OAP is not standard of care in most Dutch hospitals, but the Amphia Hospital (Breda, the Netherlands) implemented preoperative OAP composed of colistin and tobramycin in 2012 for colorectal surgery. This gave us the unique opportunity to study effectiveness of OAP in a setting where OAP without concomitant MBP was the standard of care for every patient that was scheduled for colorectal surgery. As such, the risk of confounding by indication, which we considered a major limitation of all preceding observational studies, was minimized. We demonstrated that OAP reduced the risk of deep SSIs and mortality by 42% (aRR 0.58 [95% CI 0.40 – 0.79]). The risk of anastomotic leakage was also significantly lower compared to patients who had not received OAP, as was the length of hospital stay. A similar impact on SSI risk was reported by the previously mentioned network meta-analysis. The authors reported that OAP, though composed of different antimicrobials, resulted in a reduction of total SSI of nearly 40% (OR 0.62 [95% CrI 0.34 – 1.14]) compared to no preparation.[32] It is noteworthy that an even stronger reduction in organ/space infections was found (OR 0.13 [0.02 – 0.55]). An important remark is that, in the absence of trials that included an intervention arm where patients only received OAP, the efficacy of OAP is based on estimates resulting from indirect comparisons.

It must be noted that our study was a single center before-after study and residual time-varying confounding could not be completely excluded due to the study design. Also, this study did not allow for an evaluation of potential side effects and adverse events, or of more subjective outcomes of OAP. All these limitations reduced the level of evidence of our findings and due to the lack of evidence for safety and side effects, it was decided at that time that more research was required before guideline recommendations could be made. We therefore aimed to study the efficacy of OAP under the lowest risks of bias and designed a placebo-controlled, double blind randomized multicenter clinical trial. (PreCaution trial) The protocol is described in detail in **Chapter 7**.

Confirming the efficacy of OAP with tobramycin and colistin

The results of the PreCaution trial are presented in **Chapter 8**. The primary aim of the trial was to study the efficacy of OAP on the incidence of a composite endpoint of deep SSI and mortality within 30 days of surgery. All adults who were scheduled for colorectal surgery and who did not have an absolute contraindication for the antibiotic prophylaxis were eligible for inclusion. The sample size was calculated to be 966 patients. The trial was prematurely ended when 78 patients had been enrolled (8.1% of the sample size). At that time, nine patients developed the primary outcome of whom four had been randomized to receive OAP and five to receive placebo (RR 0.80 [95% CI 0.23 – 2.78]). Except for quality of life, there was no significant difference in clinical outcomes between the treatment arms.

To conclude: Is the proposed oral antibiotic prophylaxis effective in reducing SSI risk?
Yes, we assume that OAP is effective in reducing the risk of SSIs after colorectal surgery because we demonstrated a significant reduction in the risk of deep SSIs and mortality in our before-after study. Besides, the impact is comparable to the estimated effect of OAP with other antimicrobials estimated based on indirect comparisons of RCTs, which strengthens our confidence regarding the validity and strength of the treatment effect. This prophylaxis, containing tobramycin and colistin, is therefore considered a promising candidate to add to the current infection prevention measures, but a well-controlled study was deemed necessary to confirm the efficacy and to objectively evaluate the risk of adverse events. We designed and initiated such an RCT, but the trial was ended prematurely and we were unable to confirm the efficacy of OAP.

Safety of oral antibiotic prophylaxis

Besides confirming the efficacy, information on the risk of adverse events is important when deciding if a treatment should be used. In the PreCaution trial, there appeared to be a difference between the intervention and control group in mild adverse events related to the active study medication as nausea and diarrhea were more often reported by the participants. Serious side effects were not reported. Even though it's assumed that the antibiotics are non-absorbable, studies on SDD in ICU patients have shown that tobramycin can leak to the bloodstream which, in rare cases, can even result in concentrations that are associated with toxic side effects. [38,39] In **Chapter 5**, we demonstrated that this does not occur when OAP is administered before colorectal surgery and we consider the risk of severe systemic pharmacological side effects to be negligible.

In addition to pharmacological side effects, the risk of antimicrobial resistance should also be considered as a possible complication of prophylactic antibiotics. Previous studies on ICU patients did not report a significant increase in antimicrobial resistance during SDD administration. [40,41] Remarkably, we found a substantial proportion of patients already carrying non-intrinsic colistin- or tobramycin-resistant species in the rectum already before the intervention phase. Due to the small number of patients, we were unable to adequately evaluate whether OAP increases the risk of carriage of antibiotic resistant microorganisms. Though the prevalence of carriage of these resistant microorganisms in the Dutch community is unknown, it exceeds the prevalence of colistin and tobramycin resistance that was measured in a post hoc analysis of two SDD trials. [42] A final concern of antibiotic prophylaxis is the risk of opportunistic infections. One study on OAP reported an increase in *Clostridium difficile* infections, [43] whereas others found no increased risk. [44–47] With our prophylaixs, we consider this risk to be minimized because the colonization resistance should have been preserved. We also found no *C. difficile* infections during the RCT and three cases (0.3%) in the before after study.

To conclude: Is the proposed oral antibiotic prophylaxis with tobramycin and colistin safe?
Likely, yes. We did not find evidence for pharmacological side effects or the occurrence of antimicrobial resistance or opportunistic infections following OAP. The RCT lacked power to thoroughly study side effects. However, studies on SDD, a comparable prophylaxis, in ICU patients and other studies on OAP for colorectal surgery did not report increased risks of side effects, either. We therefore consider OAP containing tobramycin and colistin to be safe.

Ethical and practical considerations of the randomized controlled trial

Practical issues

During the RCT, we closely monitored inclusion rate and potential solutions to enhance recruitment were discussed. We identified several reasons for the slow recruitment that were, in our opinion, associated with issues on different levels. (Figure 1). An important and unanticipated problem was the absence of research infrastructure on most sites. This implied that there were no research nurses or other experienced personnel available who could take care of the study logistics. Consequently, surgeons and nurses had to screen and include patients during their routine outpatient clinics. Lack of time and infrastructure resulted in a very low and inefficient screening. Because this was unforeseen, we did not have sufficient budget to resolve this issue by recruiting and training research personnel on all sites. Another problem was that, in most hospitals, other studies were conducted within the same patient population, which competed with inclusions for our trial. This did not only lead to fewer patients being approached for the trial; we also could not prevent selective screening of participants as the screening was partly based on the clinical condition of the patients. Thus, patients suffering from more (severe) comorbidities were often not considered for the study even though they would have been eligible for participation. This selective screening likely affected the external validity of our trial. Lastly, some patients refrained from participation because of a fear of side effects of OAP.

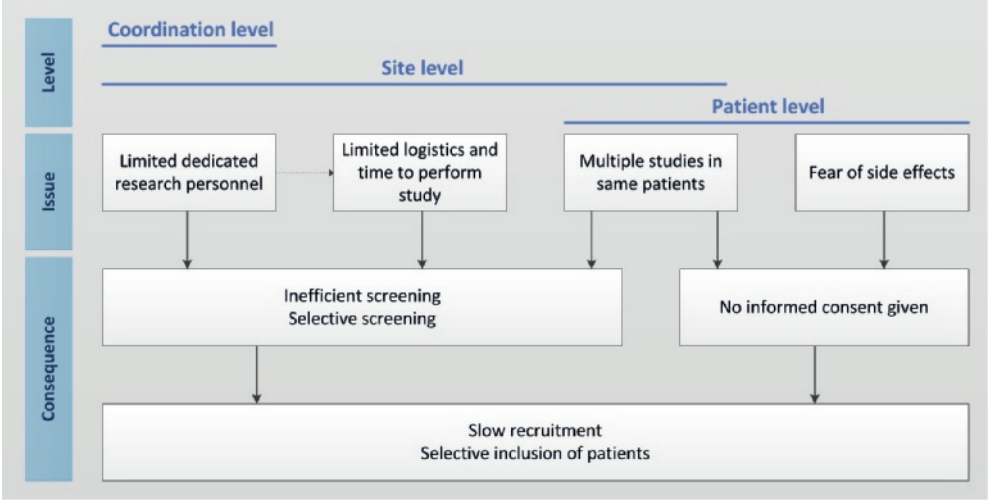

Figure 1 Issues and potential consequences encountered during the PreCaution trial

Ethical (re)considerations

Double-blind placebo-controlled randomized clinical trials are considered the most optimal and most rigorous method to study the efficacy of a treatment or prevention measure, yielding the highest level of evidence and the most reliable results. RCTs pose an ethical dilemma as in clinical practice, doctors are responsible for deciding what the best treatment is for their patient, which is in contrast with randomly assigning a treatment when patients participate in a trial. [48] To ethically justify randomization, it is critical to ensure that there is clinical equipoise or genuine uncertainty about the efficacy of that treatment among groups of experts. [49] Usually, this is reflected by differences in clinical practice, treatments that are based on expert opinion and honest disagreement between doctors about the best treatment. [50]

Already prior to the start of the trial, it was questioned whether another study following the before-after analysis was necessary. Our aim was to provide robust evidence for the use of OAP and, when proven effective, to ensure that the results could lead to increased safety for as many patients as possible. Such a high impact can be achieved when the findings are used to change or update the recommendations in the national guidelines to reach many healthcare professionals at once. The results of the before-after study are promising, but they probably do not meet the quality criteria that are required to change the guidelines.
The limitations of this study illustrate why these results were not directly translated into guideline recommendations and why we thus deemed another study to be necessary at that time. First, it was a single center study and, especially when comparing SSIs as outcomes, hospital-specific factors (such as the success of infection prevention and the level of experience of the surgeons) need to be considered in the interpretation of the results. These factors can reduce the external validity and thus applicability of the results in other settings. Furthermore, the before-after design is also vulnerable to unmeasured time-varying factors that could have affected the internal validity as well. A well-controlled multicenter study was therefore considered to be necessary to overcome these issues and the PreCaution trial was initiated.
Even though the preliminary results obtained in the Amphia Hospital demonstrated that OAP could be beneficial, we felt that it was ethically justified to initiate this trial. At the time of initiation, OAP was not part of clinical care for colorectal surgery in the majority of Dutch hospitals. The uncertainty about the optimal bowel preparation in the surgical community was (and still is) also perfectly illustrated by the different recommendations in international guidelines. We studied OAP in addition to standard of care and patients who received the placebo therefore received the same treatment as they would have received had they not participated in the trial. We therefore have no doubts that the trial was ethically justified at the start of the recruitment. The shift in equipoise started when we communicated issues with the recruitment of participants and the final results of the before-after study, in which we corrected for time-varying confounders and time trends. Several investigators indicated that they were willing to implement OAP in their local practice considering the persisting and high SSI rates. It was concluded that awaiting the trial to be completed before any actions could be taken to lower these SSI rates would be unacceptable. The assumption of clinical equipoise regarding OAP was no longer valid and we therefore decided to prematurely end the trial as the use of a placebo was no longer ethically justifiable.

Future perspectives
With the shift in clinical equipoise, it is unlikely that another placebo-controlled and individually-randomized clinical trial can be performed in the Netherlands to study the efficacy of OAP. At the same time, it is also unlikely that one single-center before-after study will change the (inter)national infection prevention guidelines. To generate more (and higher-level) evidence, alternative and more pragmatic study designs can be considered. When multiple hospitals are willing to implement OAP in clinical care, one option is to study the effect of the implementation in a unidirectional cluster-randomized cross over trial. This resembles our before-after analysis, apart from including uncertainty due to center-specific factors. All hospitals (clusters) will start with a control period and subsequently they all switch (cross over) to the intervention period (unidirectional). Like using a placebo in an individually randomized study, a control period might seem controversial when there is doubt about clinical equipoise. However, the use of this control period may be justified because implementation of new interventions in clinical practice often takes years. Hospitals that participate in the study will be offered coordination and guidance of the implementation of OAP. We therefore think that participation not only increases the feasibility, the efficiency and the likelihood of adequate OAP implementation, but also reduces the time spent on fully implementing this infection control measure as standard of care. It may be considered to randomize the cross over moment which can reduce confounding bias, mainly due to cluster-specific and time-varying factors. This design also has the potential to overcome the logistical issues we encountered during the RCT as well as the selective inclusion, as all eligible patients within the cluster are automatically considered for participation. This will only be

possible, though, when a waiver for individual informed consent can be obtained.

At the time PreCaution was initiated, other trials also started enrolling patients to study OAP for reducing SSI risk after colorectal surgery (Table 2).

Table 2 Ongoing studies on antibiotic bowel preparation

Country	Started	# sites	Blinding	Population	Intervention	Control	Antibiotics
Russia [55]	2017	SC	No	Rectal cancer	OAP + MBP	MBP	Metronidazole + erythromycine
Canada [52]	2018	SC	No	Colon	OAP	None	Metronidazole + neomycin
France [56]	2018	SC	Yes	Colon cancer	OAP + MBP	MBP	Gentamycin + ornidazole
USA [53]	2016	SC	No	Colorectal	OAP + MBP	OAP	Metronidazole + neomycin
China [57]	2019	SC	No	Laparoscopic colorectal	OAP + MBP	MBP	Metronidazole + neomycin
Greece [58]	2018	SC	Yes	Colorectal cancer	OAP + MBP	MBP	Rifaximin + metronidazole
Spain [51]	2015	MC	Yes	Colorectal	OAP	None	Cefuroxim + metronidazole
Finland [59]	2016	MC	Yes	Colon	OAP + MBP	None	Neomycin + metronidazole
France [54]	2016	SC	Yes	Colorectal	OAP + MBP	Placebo + MBP	Ordinazole
Germany [60]	DNS	Case control		Colorectal	OAP + MBP	MBP	Paromomycin + metronidazole

DNS, did not start; MBP, mechanical bowel preparation; MC, multi center; OAP: oral antibiotic prophylaxis, SC, single center

It is remarkable that there are still multiple trials ongoing that compare MBP with OAP with an MBP only arm, even though MBP only has been proven not to be of any benefit to the patient and even discouraged by many guidelines. To the best of our knowledge, there are currently only two other trials that study OAP without MBP. [51,52] The only other studies that will provide data on an OAP only arm are an American trial comparing OAP only with OAP with MBP [53] and a French trial that compares OAP with placebo and that will perform a subgroup analyses stratified on MBP. [54]

To conclude: do we need more research on oral antibiotic prophylaxis?

To change clinical practice for as many patients in the Netherlands as possible, the national infection prevention guidelines should be updated to include a recommendation for the use of OAP. In our before-after study, OAP was associated with a relevant SSI reduction. At that time, we considered a controlled study necessary to confirm the efficacy of OAP to provide high quality evidence to change the guidelines. Due to loss of clinical equipoise, albeit on the results of a non-randomized study, we consider it unethical to continue research on confirming the efficacy of OAP with new RCTs. As we also consider OAP to be safe, we suggest direct implementation of OAP in clinical practice and continuation of monitoring of infection rates and antibiotic susceptibilities. If more evidence beyond the before-after study is required to update the current guidelines, it can be considered to evaluate and quantify the effect of the implementation of OAP.

HIGHLIGHTS OF THIS THESIS

1. A five-parameter algorithm that uses data on reoperation, mortality, wound class, length of stay and readmission can be used as a reliable and time-saving method for SSI surveillance. (**Chapter 2**)

2. Implementation of OAP as standard of care prior to colorectal surgery resulted in a 42% reduction of deep SSIs and mortality. (**Chapter 4**)

3. OAP administration is not associated with systemic uptake of tobramycin and the risk of systemic side effects is therefore considered to be negligible. (**Chapter 5**)

4. High-level evidence advises against the use of MBP. However, MBP continues to be used combined with OAP because of the presumed synergistic effect. Based on data from observational studies, the impact of OAP alone on SSI risk was demonstrated to be comparable to combining OAP with MBP. (**Chapter 6**) We question whether MBP is indeed necessary and proposed a well-controlled study that investigated OAP without MBP to conclude on this ongoing controversy to finally end the practice of MBP. (**Chapter 7**)

5. Conducting a clinical trial depends on practical and ethical aspects. Patients' interest should always be the most important factor. New insights during the course of the study that could affect this deserve careful consideration; not only increased risk of harm, but also evidence for benefit, can make continuation of a trial unethical. (**Chapter 8**)

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Appendices

DUTCH SUMMARY

NEDERLANDSE SAMENVATTING

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Postoperatieve wondinfecties (POWI) zijn veelvoorkomende complicaties na colorectale operaties. Deze infecties kunnen het herstel na operatie ernstig belemmeren. POWI vereisen vaak een behandeling middels antibiotica, radiogeleide drainage of een heroperatie en zijn daarom niet alleen geassocieerd met een langere opnameduur, maar ook met aanzienlijke kosten.
Verscheidene maatregelen kunnen worden genomen om het risico op POWI te verminderen, zoals het toepassen van adequate handenhygiëne of het toedienen van intraveneuze antibioticaprofylaxe tijdens de operatie. Ondanks deze beschikbare maatregelen en de recente ontwikkelingen op het technologisch vlak waarmee het risico op veel complicaties is afgenomen, blijft het risico op POWI na colorectale operaties ongeveer 10 procent. Tegelijkertijd hebben de technologische ontwikkelingen tot gevolg gehad dat er meer operaties worden uitgevoerd bij patiënten waar dat voorheen te risicovol werd geacht. Daarnaast heeft de vergrijzing en de invoering van het bevolkingsonderzoek ter opsporing van darmkanker tot gevolg dat het aantal patiënten dat een colorectale operatie zal moeten ondergaan zal stijgen in de komende jaren. Wanneer het risico op een POWI stabiel blijft betekent een toename in het aantal operaties ook een toename in het aantal patiënten dat een POWI zal ontwikkelen. Deze prognose en de gevolgen van wondinfecties onderstrepen het belang van nieuwe interventies die het risico op infectie verlagen.

Het doel van dit proefschrift was om alle beschikbare kennis en inzichten te verzamelen waarmee de infectiepreventie verbeterd zou kunnen worden. Dit is vanuit twee verschillende invalshoeken onderzocht. Ten eerste is bekeken of de **surveillance** van POWI efficiënter kan worden uitgevoerd. Ten tweede is onderzocht of de **infectiepreventie** verbeterd kan worden en het risico op wondinfecties verlaagd kan worden met preoperatieve orale antibioticaprofylaxe. Deze antibioticaprofylaxe, bestaande uit tobramycine en colistine, was nog niet eerder uitgebreid bestudeerd als een mogelijke interventie om het risico op POWI na colorectale operaties te verlagen. Een belangrijk onderdeel van het promotieonderzoek dat is beschreven in dit proefschrift is gewijd aan het leveren van bewijs voor de werkzaamheid en veiligheid van deze profylaxe.

HET VERBETEREN VAN DE SURVEILLANCE VAN POSTOPERATIEVE WONDINFECTIES

Een belangrijke pijler in de infectiepreventie is een effectieve en adequate surveillance van infecties. Dit houdt in dat er routinematig en op betrouwbare wijze gegevens worden verzameld over het optreden van POWI. Deze gegevens worden als ijkpunt gebruikt zodat het aantal infecties over de tijd op een afdeling kan worden gevolgd en dus ook kan worden geëvalueerd of de infectiepreventie toereikend is of dat extra maatregelen getroffen moeten worden. Ook worden deze gegevens gebruikt om de prestatie van verschillende ziekenhuizen met elkaar te vergelijken. Een goede infectiesurveillance is dus van belang om de infectiepreventie te evalueren en waar nodig te verbeteren, hiermee het risico op POWI te verlagen en uiteindelijk POWI gerelateerde kosten en morbiditeit te reduceren.
Voor het vaststellen van een POWI wordt gebruik gemaakt van een definitie die bestaat uit een aantal criteria. Dit geschiedt middels handmatige controle en registratie en wordt doorgaans door een infectiepreventiedeskundige uitgevoerd die hiervoor het patiëntendossier raadpleegt van alle patiënten die een colorectale operatie hebben ondergaan. In **Hoofdstuk 2** wordt een methode beschreven om de efficiëntie van de infectiesurveillance te verbeteren. Met een relatief simpel algoritme dat bestaat uit vijf verschillende parameters kan op betrouwbare wijze het patiëntendossier worden gescreend op diepe

POWI. Het algoritme berekent een kans op POWI. Is deze kans boven een bepaalde drempel, dan moet het patiëntendossier volgens de gebruikelijke weg handmatig worden gecontroleerd om de diagnose te bevestigen. Anderzijds worden de dossiers met een lage kans meteen uitgesloten van POWI, deze hebben de handmatige controle niet meer nodig. Het algoritme bleek in staat om 98.5% van de diepe POWI op te sporen. Een zeer klein percentage POWI werd gemist, maar daartegenover stond een reductie van 63% in het aantal dossiers dat volledige handmatige controle nodig had. Dit algoritme heeft de potentie om een deel van de handmatige controle van alle dossiers te kunnen vervangen. Het is echter nog wel noodzakelijk om de betrouwbaarheid van dit algoritme te bevestigen door het op een andere dataset te testen. Als blijkt dat de werkzaamheid van het algoritme op deze dataset vergelijkbaar is, zou kunnen worden onderzocht of het algoritme toegepast kan worden in semi-geautomatiseerde surveillance. Op deze manier zou de werklast van de surveillance nog verder gereduceerd kunnen worden.
Het algoritme is specifiek ontwikkeld voor het vaststellen van diepe POWI. De ernst van deze infecties maakt dat de klachten en symptomen vaak duidelijk aanwezig zijn en dat er vrijwel altijd diagnostiek en behandeling wordt ingezet. Het algoritme gebruikt met name variabelen die hiermee geassocieerd zijn. Omdat het niet aannemekelijk is dat de presentatie en behandeling van diepe POWI sterk afwijkt tussen ziekenhuizen, wordt verwacht dat het algoritme een vergelijkbare prestatie heeft in andere ziekenhuizen dan het ziekenhuis waar het ontwikkeld is.
Dit algoritme kan niet gebruikt worden voor de surveillance van oppervlakkige wondinfecties. Deze, vaak mildere, infecties presenteren zich anders en zullen daarom niet worden opgepikt met de variabelen die in dit algoritme worden gebruik. Het kan worden overwogen om een tweede algoritme te ontwikkelen voor het opsporen van dit type infecties. Dit zal echter lastig zijn door de heterogene klinische presentatie van deze infecties. Het is niet ondenkbaar dat naar specifieke klachten en symptomen moet worden gezocht in de decursus van het patiëntendossier. Om dit te bewerkstelligen zou gebruik gemaakt moeten worden van *text mining*. Een nadeel hiervan is dat het algoritme dan minder of (nog) niet toepasbaar is in de dagelijkse klinische praktijk. Het volledig schrappen van surveillance middels handmatige controle van patiëntendossiers is daarom op dit moment nog niet mogelijk.

HET VERBETEREN VAN INFECTIEPREVENTIE

Waar het toedienen van intraveneuze antibioticaprofylaxe wereldwijd is geaccepteerd en geïmplementeerd om het risico op POWI na colorectale operaties te verlagen, is er controverse over het toepassen van preoperatieve darmvoorbereiding. Deze darmvoorbereiding kan bestaan uit mechanische darmvoorbereiding (*mechanical bowel preparation*, vanaf hier afgekort als MBP) waarbij oraal een laxerende drank wordt ingenomen om zoveel mogelijk ontlasting uit het maagdarmkanaal te spoelen. Ook kan antibiotische darmvoorbereiding worden toegepast, ook wel aangeduid als orale antibioticaprofylaxe (OAP). Er is geen consensus over de beste vorm van darmvoorbereiding voorafgaand aan colorectale operaties, wat duidelijk wordt uit de verschillende aanbevelingen in (inter)nationale richtlijnen. In de Verenigde Staten (VS) wordt geadviseerd om OAP te combineren met MBP. In Europa daarentegen, wordt in de meeste richtlijnen geen enkele vorm van darmvoorbereiding geadviseerd. Uit meerdere meta-analyses is gebleken dat alleen het toepassen van MBP niet leidt tot vermindering in POWI. Ondanks deze bevindingen blijven veel chirurgen MBP gebruiken, al dan niet in combinatie met OAP in de veronderstelling dat de orale antibiotica alleen optimaal werkzaam zijn wanneer er geen ontlasting meer aanwezig is in het colon en rectum. Dit is echter uitsluitend gebaseerd op *expert opinion.* Er is namelijk geen wetenschappelijk bewijs dat orale antibiotica inderdaad alleen effectief zijn in een schoon colon: tot op heden is nog geen gerandomiseerde studie uitgevoerd met een behandelarm waarin proefpersonen alleen met orale antibiotica

zijn behandeld voorafgaand aan operatie. Het gebrek aan wetenschappelijk bewijs verklaart ook waarom geen enkele richtlijn het gebruik van OAP zonder gelijktijdige MBP adviseert.

Is het combineren van orale antibioticaprofylaxe en mechanische darmvoorbereiding nodig?

We hebben gegevens van meerdere studies verzameld om te beoordelen of het noodzakelijk is om OAP te combineren met MBP. **Hoofdstuk 6** beschrijft de resultaten van de meta-analyse die is uitgevoerd om deze vraag te beantwoorden. Gezien het gebrek aan gerandomiseerde klinische trials (RCT's) hebben we gegevens van observationele studies gebruikt. Voor de meta-analyse zijn alle studies gebruikt waarin patiënten waren geïncludeerd die OAP hadden ontvangen zonder MBP. In vergelijking met patiënten die helemaal geen darmvoorbereiding hadden ontvangen bleek het risico op POWI 32% tot 57% lager wanneer er alleen OAP werd gegeven voorafgaand aan de operatie. Werd OAP gecombineerd met MBP, dan was de reductie in het risico op POWI tussen de 53% en 67%, waarbij één studie een reductie van 80% aantoonde. Een aantal studies heeft ook het risico op POWI vergeleken tussen OAP en OAP gecombineerd met MBP. Twee studies lieten zien dat het risico op POWI lager was met de gecombineerde darmvoorbereiding, maar de meeste studies vonden geen significant verschil tussen beide strategieën. Bijna alle observationele studies waren uitgevoerd in de VS, wat ook verklaart waarom een zeer groot percentage van alle patiënten de combinatie van OAP en MBP heeft ontvangen: dit is immers in lijn met het advies in de Amerikaanse richtlijnen. Slechts een zeer klein deel van de patiënten had alleen OAP ontvangen. We vermoeden dat de resultaten uit deze studies niet geheel betrouwbaar zijn vanwege misclassificatie bias, *confounding by indication* en door een grote overlap aan patiënten waar geen rekening mee is gehouden in de statistische analyses. Daarnaast was de groep patiënten die alleen OAP had ontvangen vele malen kleiner dan de groep die met zowel MBP als OAP was behandeld, wat kan leiden tot onvoldoende power. voor de statistische analyses Het valt daarom te betwijfelen of de gevonden behandeleffecten betrouwbaar zijn. Een RCT uit 2003 vond opmerkelijk genoeg ook geen verschil in de POWI incidentie tussen OAP en OAP gecombineerd met MBP. Dit wordt ondersteund door een recente netwerk meta-analyse die 38 RCT's heeft samengevat. De meta-analyse toonde aan dat de effectiviteit van OAP met MBP niet significant verschilt van OAP zonder MBP in het voorkomen van POWI. Dit suggereert een vergelijkbaar behandeleffect voor beide strategieën en zou kunnen betekenen dat MBP van beperkte toegevoegde waarde is. Ook uit onze eigen observationele studie, beschreven in **Hoofdstuk 4**, blijkt dat OAP zonder MBP een reductie in diepe POWI en mortaliteit geeft van 42%. Deze orde van grootte werd ook gevonden in de andere observationele studies. Alle data tezamen suggereren dat de toevoegde waarde van MBP te betwisten is. Dit is belangrijke informatie, omdat het toepassen van MBP met extra kosten is verbonden, maar ook een aanzienlijke last is voor de patiënt.

De effectiviteit van orale antibioticaprofylaxe met colistine en tobramycine op het verminderen van POWI

In de observationele studie beschreven in **Hoofstuk 4** betrof OAP een combinatie van colistine en tobramycine. In tegenstelling tot de orale profylaxe die in de VS wordt gebruikt betrof het een oplossing in plaats van tabletten en werd OAP gedurende de laatste drie dagen voorafgaand aan operatie toegediend in plaats van slechts op de laatste dag. Een ander belangrijk verschil is de werkzaamheid van de antibiotica. Kenmerkend voor tobramycine en colistine is dat zij selectief de bacteriën doden die worden gezien als potentiele verwekkers van wondinfecties. Dit zijn met name Gram negatieven behorend tot de

Enterobacteriaceae familie. De onschuldige anaerobe microbiota blijft hierbij intact. De klassieke OAP die wordt gebruikt in de VS doodt ook de anaerobe bacteriën. Door de anaerobe bacteriën te sparen wordt aangenomen dat de kolonisatieresistentie in de darm intact blijft. Dit houdt in dat er geen ruimte wordt geboden voor opportunistische pathogenen en dat het risico op dit soort infecties gering blijft. Colistine en tobramycine worden al langere tijd als onderdeel van selectieve darmdecontaminatie (SDD) gebruikt op de Nederlandse intensive care units. (IC's). Gecombineerd met het antimycoticum nystatine is deze profylaxe in Nederlandse setting in het verleden onderzocht als perioperatieve profylaxe ter preventie van naadlekkage en infectieuze complicaties na gastrointestinale operaties.
Preoperatieve OAP wordt in Nederland niet routinematig toegepast, met uitzondering van enkele ziekenhuizen waaronder het Amphia Ziekenhuis in Breda. In het Amphia Ziekenhuis is deze strategie in 2012 geïmplementeerd voor alle patiënten die electief een colorectale operatie ondergaan. Dit bood de mogelijkheid om de werkzaamheid van OAP te onderzoeken door de POWI incidentie vanaf 2012 te vergelijken met het jaar voorafgaand aan implementatie. Daarnaast is dit een setting waar geen MBP wordt gebruikt. Doordat OAP aan alle patiënten werd gegeven wordt het risico op *confounding by indication* minimaal geacht, in tegenstelling tot alle voorgaande observationele studies uit de VS. Implementatie van OAP resulteerde in een reductie van diepe POWI en mortaliteit binnen 30 dagen van 42% (aRR 0,58 [95% CI 0,40 – 0,79]). Ook het risico op naadlekkage en de duur van de ziekenhuisopname waren significant lager in vergelijking met de periode waarin OAP nog niet werd voorgeschreven. Een vergelijkbare impact van OAP werd gerapporteerd in de eerdergenoemde netwerk meta-analyse. Hier werd wellicht een OAP met andere antibiotica gebruikt, maar de reductie in POWI was vergelijkbaar: bijna 40% (OR 0,62 [95% CrI 0,34 – 1,14]) in vergelijking met geen darmvoorbereiding. Opmerkelijk is dat de reductie in organ/space infecties significant lager was werd met OAP (OR 0,13 [95% CrI 0,02 – 0,55]). Deze reductie kon echter alleen op basis van indirecte vergelijkingen tussen RCT's worden berekend omdat er geen RCT's zijn die deze vergelijking (OAP versus geen darmvoorbereiding) hebben onderzocht.
Beperkingen van onze observationele studie in het Amphia Ziekenhuis waren toe te schrijven aan de studieopzet: het was een monocenter studie met een historische controle periode en ondanks dat we hadden gecorrigeerd voor *confounding bias* kon *residual confounding* niet worden uitgesloten. Het was daarnaast niet mogelijk om bijwerkingen of meer subjectieve eindpunten van OAP te bestuderen. Al deze beperkingen reduceerden helaas de betrouwbaarheid en toepasbaarheid van onze bevindingen. Doordat we daarnaast nog geen bewijs hadden voor de veiligheid van OAP werd meer onderzoek noodzakelijk geacht voordat er aanbevelingen gedaan konden worden voor het aanpassen van de nationale richtlijnen. We ontwierpen en initieerden daarom een vervolgstudie om de effectiviteit van OAP op een zo betrouwbaar mogelijke wijze te onderzoeken middels een multicenter, dubbelblinde, placebogecontroleerde en gerandomiseerde studie. Het protocol voor deze studie (PreCaution) is uitvoerig beschreven in **Hoofdstuk 7**.

Het bevestigen van de effectiviteit van OAP met colistine en tobramycine

De resultaten van de PreCaution studie zijn beschreven in **Hoofdstuk 8**. Het primaire doel van de studie was het onderzoeken van de effectiviteit van OAP op de incidentie van diepe POWI en mortaliteit binnen 30 dagen na operatie. Alle volwassenen die werden gepland voor een colorectale ingreep en die geen absolute contra-indicatie hadden voor de antibiotica konden in aanmerking komen voor deelname aan de studie. De initieel berekende sample size was 966 proefpersonen. De studie werd echter voortijdig beëindigd toen 78 (8,1%) patiënten waren geïncludeerd. Op dat moment hadden negen patiënten het primaire eindpunt ontwikkeld, waarvan vijf patiënten placebo hadden ontvangen en vier OAP (RR 0,80 [95% CI 0,23 – 2,78]). Afgezien van het eindpunt kwaliteit van leven waren er geen significante verschillen in klinische eindpunten tussen beide behandelarmen.

Afgaand op de bevindingen uit onze observationele studie lijkt er enig bewijs te zijn voor de werkzaamheid van OAP met tobramycine en colistine. Omdat onze bevindingen overeenkomen met het effect dat andere observationele studies rapporteerden, denken we dat de door ons gevonden behandeleffect (40% reductie) een reële inschatting zou kunnen zijn. We denken daarom dat OAP met tobramycine en colistine geschikt zou kunnen zijn om als preventieve interventie in te zetten ter vermindering van POWI na colorectale operaties. De RCT was helaas niet in staat om de werkzaamheid te bevestigen vanwege vroegtijdige beëindiging en hiermee konden we geen gedegen onderzoek verrichten naar de veiligheid van OAP.

De veiligheid van OAP

Wanneer wordt overwogen om een interventie te gebruiken in de klinische praktijk is het naast het onderzoeken van de werkzaamheid ook van groot belang dat er onderzoek wordt gedaan naar de veiligheid van de interventie. In de PreCaution studie leken er meer milde bijwerkingen op te treden in de groep die werd behandeld met OAP: er werd vaker diarree en misselijkheid gerapporteerd dan in de placebogroep. Ernstige bijwerkingen traden niet op tijdens de studie. Kenmerkend voor deze antibiotica is dat zij, wanneer ze oraal worden ingenomen, niet worden opgenomen door het maagdarmkanaal. Er wordt daarom ook aangenomen dat de kans op ernstige systemische bijwerkingen gering is. Echter, werd in een aantal studies naar SDD bij IC patiënten aangetoond dat tobramycine na orale toediening toch in het bloed terecht kan komen. Dit kan gebeuren onder omstandigheden die zorgen dat de bloed-darm barrière tijdelijk verstoord is zoals shock of ileus, waardoor stoffen van het darmlumen naar het bloed kunnen lekken. Wanneer daarnaast ook de nierfunctie verminderd is, kan de concentratie van tobramycine in het bloed oplopen. In zeldzame gevallen kan de concentratie in het bloed zo hoog worden dat er mogelijk toxische schade kan optreden. In **Hoofdstuk 5** laten we zien dat dit niet gebeurt wanneer OAP voorafgaand aan operatie wordt ingenomen en we nemen dan ook aan dat het risico op ernstige systemische bijwerkingen verwaarloosbaar is.

Naast farmacologische bijwerkingen moet ook het risico op antibioticaresistentie worden overwogen als mogelijke bijwerking van profylactische antibiotica. Studies naar SDD hebben geen significante toename van antibioticaresistentie gevonden. Opmerkelijk is dat een substantieel aantal proefpersonen in de PreCaution studie al voorafgaand aan de interventie drager was van een non-intrinsieke colistine of tobramycine resistentie bacterie. Door het kleine aantal patiënten waren we niet in staat om goed te evalueren of OAP ervoor zorgt dat er een significante toename van dragerschap van resistente bacteriën optreedt als gevolg van de interventie. Ondanks dat de exacte prevalentie van deze resistentie bacteriën in Nederland onbekend is, lijkt de prevalentie van colistine en tobramycine resistentie in deze studie hoger te zijn dan de prevalentie beschreven in twee Nederlandse SDD studies. Een andere mogelijke bijwerking van deze orale antibioticaprofylaxe is het optreden van opportunistische infecties. Eén studie liet een toename in *Clostridium difficil*e infecties zien, maar de meeste studies naar OAP vonden deze toename niet. Wij nemen aan dat het risico op *C. difficil*e infecties nog lager is met de OAP die wij onderzocht hebben omdat we aannemen dat de selectieve darmdecontaminatie de colonisatieresistentie intact laat. Daarnaast vonden we geen *C. difficil*e infecties in de PreCaution studie en slechts 3 gevallen (0,3%) in de observationele studie.

Afgaand op onze bevindingen lijken er dus geen ernstige farmacologische bijwerkingen op te treden en lijkt er ook geen toename te zijn van antibioticaresistentie of van opportunistische infecties. De RCT had

helaas niet voldoende power om de veiligheid van OAP uitvoerig te onderzoeken, maar studies naar de effectiviteit van SDD op IC ondersteunen onze bevindingen. We denken daarom dat OAP met tobramycine en colistine veilig is.

Ethische en praktische overwegingen van de gerandomiseerde studie.

Praktische problemen
Gedurende de PreCaution studie hebben we de inclusiesnelheid nauwgezet gemonitord en mogelijkheden om deze te stimuleren geëvalueerd. We hebben verschillende oorzaken geïdentificeerd die (mogelijk) een aandeel hebben gehad in de trage inclusie van proefpersonen. Een belangrijk onvoorzien probleem bleek dat de meeste chirurgische afdelingen nog geen infrastructuur hadden voor het uitvoeren van klinisch onderzoek. Vaak waren er geen onderzoeksverpleegkundigen aanwezig die het onderzoek konden begeleiden. Dit had tot gevolg dat verpleegkundigen en chirurgen onderzoekstaken moesten uitvoeren tijdens hun reguliere poliklinische werkzaamheden. Gebrek aan tijd en infrastructuur leidde tot een matige en inefficiënte screening van proefpersonen. Omdat we dit niet hadden voorzien was op voorhand geen budget ingecalculeerd voor het aanstellen van toegewijd personeel in elk ziekenhuis. Een ander probleem was dat er meerdere studies binnen dezelfde patiëntenpopulatie werden uitgevoerd. Er werden hierdoor niet alleen minder patiënten dan verwacht geïncludeerd, maar we vermoeden dat er ook selectieve inclusie is opgetreden omdat de patiënten die in een relatief betere conditie verkeerden werden gevraagd voor deelname aan de klinische trial omdat zij het meest belastbaar werden geacht. Patiënten met meerdere (chronische) aandoeningen daarentegen werden regelmatig niet geïnformeerd over de trial, ondanks dat de aandoeningen geen exclusiecriterium voor deelname betroffen. Deze selectieve inclusie heeft waarschijnlijk een beperkte generaliseerbaarheid van onze bevindingen tot gevolg gehad.

Ethische overwegingen
Dubbelblinde placebogecontroleerde RCT's worden beschouwd als de meest grondige en betrouwbare methode om de effectiviteit van een interventie te onderzoeken. Het risico op bias wordt hiermee immers geminimaliseerd, wat de betrouwbaarheid van de bevindingen ten goede komt. RCT's brengen echter wel een ethisch conflict met zich mee. Normaal gesproken bepalen artsen in de klinische praktijk voor elke individuele patiënt bepalen wat de beste behandeling is, hetgeen haaks staat op randomiseren en het dus aan het lot overlaten welke behandeling de patiënt ontvangt. Om ethisch te kunnen rechtvaardigen dat er randomisatie wordt toegepast is het van belang dat er zogenaamde klinische equipoise is. Dit betekent dat er geen consensus is over de beste behandeling en dat het dus ook niet zou moeten maken welke interventie de patiënt ontvangt. Dat er geen consensus is, is meestal terug te zien in verschillende aanbevelingen in lokale protocollen, verschillen in klinische praktijk en behandelingen die enkel worden uitgevoerd op basis van expert opinion.

Al voorafgaand aan de trial werd afgevraagd of na onze observationele studie nog een extra studie noodzakelijk was. Ons doel was om robuust bewijs te leveren voor het gebruik van OAP dat, als we konden aantonen dat OAP inderdaad effectief en veilig was, zou kunnen worden gebruikt om de richtlijnen voor colorectale chirurgie aan te passen en zo de patiëntveiligheid voor zo veel mogelijk patiënten te verbeteren. Een dergelijk grote impact kan alleen worden bereikt als de resultaten leiden tot het aanpassen van richtlijnen op nationaal niveau. We achtten de resultaten van de observationele studie veelbelovend, maar niet van voldoende kwaliteit om aan de eisen te voldoen om de nationale richtlijnen te kunnen veranderen. Ten eerste was de studie slechts in één centrum uitgevoerd. Zeker bij een uitkomst als POWI

spelen centrum specifieke factoren zoals de kwaliteit van de infectiepreventie en de bekwaamheid van de lokale chirurgen een grote rol. Deze factoren kunnen de externe validiteit en dus de toepasbaarheid van de resultaten in andere (Nederlandse) ziekenhuizen verminderen. Daarnaast is het aannemelijk dat er ondanks de zorgvuldige correctie nog steeds *confounding* aanwezig is dat een deel van het gevonden behandeleffect verklaart. Vooral tijdsafhankelijke factoren die we niet hebben kunnen meten zouden een effect kunnen hebben gehad. Door al deze limitaties werd besloten dat een RCT nodig was zodat de effectiviteit van OAP zo objectief mogelijk kon worden onderzocht.
Ondanks dat de, toen nog voortijdige, resultaten van de observationele studie lieten zien dat OAP waarschijnlijk een gunstig effect had, achtten we het ethisch gerechtvaardigd om de trial uit te voeren. Ten tijde van de initiatie was OAP in bijna geen enkel Nederlands ziekenhuis onderdeel van de routine zorg voorafgaand aan colorectale operaties. Daarnaast bleek (en blijkt nog steeds) geen consensus over darmvoorbereiding te bestaan in de chirurgische gemeenschap wat naar onze mening aangaf dat er klinische equipoise was. We hebben OAP onderzocht als een aanvulling op de zorg die patiënten ook zouden hebben ontvangen als ze niet deel zouden nemen aan de trial. De patiënten in de placebogroep zijn dus ook niet onthouden van zorg. We twijfelen er daarom niet aan of de trial ethisch gerechtvaardigd was ten tijde van de initiatie.

Het verbreken van de klinische equipoise werd duidelijk toen we de problemen met de inclusie en de definitieve resultaten van de observationele studie, waarin we de analyses hadden uitgebreid met een correctie voor een tijdstrend en voor tijdsafhankelijke confounders, communiceerden naar de deelnemende centra. Een aantal onderzoekers gaf aan dat zij nu bereid waren om OAP direct te implementeren met het oog op de persisterend hoge de POWI incidentie. Het werd als onacceptabel gezien om te wachten tot de trial volledig was afgerond met het ondernemen van actie om de POWI incidentie te reduceren. Op dat moment was er geen sprake meer van klinische equipoise betreffende OAP en we besloten de trial voortijdig te beëindigen omdat we het gebruik van een placebo niet langer ethisch konden rechtvaardigen.

Toekomstperspectieven

Met het verdwijnen van klinische equipoise is het onwaarschijnlijk dat er ooit nog een placebogecontroleerde en op patiënt niveau gerandomiseerde studie zal worden geïnitieerd in Nederland. Tegelijkertijd is het ook onwaarschijnlijk dat onze observationele studie de (inter)nationale richtlijnen zal veranderen. Om meer bewijs te vergaren voor de werkzaamheid van OAP zouden een alternatieve en meer pragmatische studie overwogen kunnen worden. Wanneer meer ziekenhuizen geïnteresseerd zijn om OAP te implementeren zou het een mogelijkheid kunnen zijn om het effect van de implementatie in een uni-directionele cluster gerandomiseerde cross-over studie te onderzoeken. Dit komt overeen met hoe we de effectiviteit van OAP hebben onderzocht in de observationele studie, maar een deel van de onzekerheid over het effect dat toe te schrijven is aan centrum specifieke factoren wordt hiermee weggenomen. Alle ziekenhuizen, of clusters, starten met een controle periode en uiteindelijk zullen ze allemaal overgaan (cross-over) naar de interventie periode. Zoals met het gebruik van een placebo kan worden bediscussieerd of toepassen van een controleperiode uit ethisch oogpunt wenselijk is. Echter, deze controleperiode kan worden gerechtvaardigd gezien het implementeren van nieuwe interventies in de klinische praktijk soms erg traag gaat en jaren in beslag kan nemen. In studieverband kan deze implementatie gecoördineerd en begeleid worden waardoor dit vele malen sneller gaat dan wanneer het ziekenhuis niet zou deelnemen aan de studie. Het zou kunnen worden overwogen om het moment van cross-over te randomiseren waardoor ook *confounding bias* door centrum specifieke maar ook tijdsafhankelijke factoren

verminderd zou kunnen worden. Een ander mogelijk voordeel van dit design is dat in tegenstelling tot de PreCaution studie er nauwelijks sprake zal zijn van selectieve inclusie omdat alle patiënten in het cluster automatisch deelnemen aan de studie. Dit is overigens alleen mogelijk als er geen individueel informed consent aan elke patiënt gevraagd zou hoeven worden.

Op het moment dat PreCaution geïnitieerd werd waren enkele andere trials naar OAP gaande. Het is opmerkelijk dat de meeste studies nog steeds OAP met MBP combineren, ondanks dat bewezen is dat MBP op zichzelf niet effectief is in het verminderen van POWI. Voor zover wij weten zijn er op dit moment twee andere trials gaande die OAP zonder MBP bestuderen en het effect van OAP vergelijken met een behandelarm waarin geen darmvoorbereiding wordt gegeven.

Conclusie

Afgaand op onze evaluatie van het effect van implementatie van OAP in het Amphia Ziekenhuis lijkt het dat OAP de incidentie van diepe POWI en mortaliteit na colorectale operaties reduceert. Andere observationele studies laten een vergelijkbaar behandeleffect zien wat ons vermoeden in de werkzaamheid van OAP versterkt. Alvorens aanbevelingen geformuleerd kunnen worden voor de implementatie van OAP in de klinische praktijk, moet naast het bevestigen van de effectiviteit ook meer bewijs worden geleverd over de veiligheid van de interventie. In onze postoperatieve analyse van serum van patiënten die preoperatief behandeld werden met OAP troffen we geen tobramycine aan, wat ons doet vermoeden dat er geen absorptie en geen lekkage vanuit de darm van tobramycine optreedt. We achtten het risico op systemische bijwerkingen van OAP daarom verwaarloosbaar.
Om de veronderstelde effectiviteit en veiligheid van OAP te bevestigen werd een RCT ontworpen om dit op een zo objectief mogelijke wijze te onderzoeken. De trial werd voortijdig gestopt en hierdoor kon geen definitieve uitspraak gedaan worden over de werkzaamheid en veiligheid van OAP. Gezien de trial op ethische gronden werd beëindigd, betwijfelen we of een nieuwe RCT zal kunnen worden uitgevoerd die het verlossende antwoord zal geven. Omdat we voldoende aanwijzingen hebben voor de veiligheid van OAP stellen we voor om OAP in de dagelijkse klinische praktijk te implementeren in een aantal ziekenhuizen. Het effect van de implementatie zou dan gekwantificeerd kunnen worden om alsnog de werkzaamheid van OAP te kunnen evalueren.

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1. *(plantkunde)* bevruchting van een bloem met het stuifmeel van een andere bloem van dezelfde soort
2. *(figuurlijk)* beïnvloeding door anderen dan leden van de eigen groep

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Tessa

CURRICULUM VITAE

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Tessa Mulder was born on May 3rd 1989 in Utrecht and grew up in Vianen. She followed secondary education at the Cals College in Nieuwegein from which she graduated in 2007. Subsequently, she obtained a bachelor's degree in Biology from the University of Utrecht in 2010. During her bachelor, she developed an interest in neuroscience and behavioral biology and enrolled in the Neuroscience and Cognition master from the Graduate School of Life Sciences in Utrecht. Here, she had her first encounter with research during her research project on the neurobiological mechanisms of play behavior in young rats, as well as by being a member of the animal ethics committee. After one year, she decided to change her career path and enrolled in SUMMA, a four year master's program in Utrecht to obtain a medical degree. During her study she developed an interest in infectious diseases and acquired experience in epidemiological research at the Department of Internal Medicine and Infectious Diseases of the UMC Utrecht.

After obtaining her medical degree in 2015, Tessa took up a PhD position in the field of infectious diseases at the Julius Center for Health Science and Primary care under supervision of Prof dr. Jan Kluytmans, Prof. dr. Marc Bonten and dr. Marjolein Kluytmans-van den Bergh, which resulted in this thesis. During her PhD, she completed the postgraduate Epidemiology master, specializing in clinical epidemiology. Besides her work as a PhD candidate, she was a member of the visitation committee of the Vereniging voor Epidemiologie and contributed to the visitation of several Dutch and Flemish epidemiology programs. In August 2019, she started working as a resident (ANIOS) in internal medicine in the Diakonessenhuis in Utrecht.

LIST OF PUBLICATIONS

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