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Surgical site infection prophylaxis strategies for cardiothoracic surgery: a decision-analytic model

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Abstract

Background—Methicillin-resistant *Staphylococcus aureus* (MRSA) is a common cause of invasive surgical site infection (SSI) in the USA. Antimicrobial prophylaxis for SSI typically includes a cephalosporin. Vancomycin is used to provide MRSA coverage, but administration timing is challenging. Linezolid is an attractive agent for SSI prophylaxis, particularly for the prevention of SSI due to MRSA.

Methods—We developed a decision-analytic model to evaluate linezolid use for cardiothoracic SSI prophylaxis. A theoretical cohort of 10,000 cardiothoracic surgery patients was followed through 2 stages: 1) occurrence of SSI, and 2) mortality after SSI. All patients were administered cefuroxime, vancomycin, or linezolid between 1–180 minutes prior to surgical incision. SSIs were categorized into three pathogen categories: 1) methicillin-susceptible Gram-positive, 2) methicillin-resistant Gram-positive, and 3) other organisms. The most effective strategy resulted in the fewest SSIs. Assumptions for antibiotic effectiveness, impact of administration time, and pathogens were based on the published literature.

Results—Compared with cefuroxime, there was a 1% increase in the total number of SSIs in the linezolid group (mean SSI increase = 7), while there was a 12% increase in the vancomycin group (mean SSI increase = 86). Linezolid prophylaxis resulted in fewer SSIs due to methicillin-resistant Gram-positive infections ($n=108$) compared with cefuroxime ($n=200$, 46% reduction in the linezolid group) and vancomycin ($n=119$, 9% reduction in the linezolid group).

Conclusions—This simulation indicates that linezolid may offer benefits for SSI prophylaxis over existing prophylactic agents, particularly for the prevention of SSI due to Gram-positive methicillin-resistant pathogens.

Keywords

Surgical site infection; prophylaxis; decision-analytic model; linezolid; vancomycin

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Introduction

Surgical site infection (SSI) is a common hospital-acquired infection, complicating 1–5% of cardiovascular surgeries performed in the USA annually [1]. SSI is associated with increases in mortality, duration of hospitalization, and hospital cost [2]. Methicillin-resistant Gram-positive organisms, particularly methicillin-resistant *Staphylococcus aureus* (MRSA), are common causes of SSI in the USA and, according to some reports, MRSA is the single most common cause of invasive SSI [2–4].

Pre-operative antimicrobial prophylaxis is an effective method for preventing SSI, especially if administered within 60 minutes prior to surgical incision [5,6]. Published guidelines and quality improvement collaborations identified interventions, including antimicrobial prophylaxis, that reduce the incidence of SSI. Cephalosporins (e.g. cefazolin or cefuroxime) are the most commonly used agents for pre-operative antimicrobial prophylaxis [7]. They should be administered within 60 minutes prior to surgical incision; however, they do not provide protection against infections due to methicillin-resistant Gram-positive organisms.

Although not recommended for routine use, vancomycin is often administered as prophylaxis when SSI due to MRSA is a concern. Vancomycin demonstrates *in vitro* activity against a variety of Gram-positive organisms including methicillin-resistant strains [8]. Vancomycin possesses a complex pharmacokinetic profile and is infused over at least 1 hour to minimize adverse events [9]. This long infusion requirement may result in suboptimal timing with regards to initial surgical incision, thus resulting in inadequate prophylactic activity [5,10]. Alternative agents with favorable pharmacokinetics and MRSA activity should also be considered for pre-operative surgical prophylaxis.

Linezolid demonstrates microbiologic activity against a broad range of Gram-positive bacteria including *S. aureus* (both methicillin-resistant and susceptible strains) [11]. After oral administration linezolid is rapidly absorbed and reaches peak concentrations within 1–2 hours with an absolute bioavailability of 100% [12]. Linezolid is typically administered over 30 minutes, achieves peak plasma concentrations at the end of infusion [12], and penetrates well into perfused body spaces including pulmonary tissues [13] and skin blister fluid [14].

Linezolid's antimicrobial activity, pharmacokinetic profile, tissue penetration, and relatively short infusion time lend itself to investigation for the prevention of SSI due to methicillin-resistant Gram-positive organisms. Although data describing the use of linezolid for prophylaxis are lacking, pharmacokinetic and tissue penetration of linezolid in patients undergoing surgery, including coronary artery bypass graft and hip replacement surgery, are available [15,16].

We hypothesized that linezolid would be associated with a decreased risk for SSI due to methicillin-resistant Gram-positive organisms compared with cefuroxime or vancomycin. The objective of this study was to compare prophylaxis treatment strategies prior to cardiothoracic surgery on the risk for SSI involving the chest wall or mediastinum due to methicillin-resistant Gram-positive pathogens using Monte Carlo simulation techniques.

Materials and methods

Decision-analytic model

We developed a decision-analytic model (Figure 1) that simulates alternative strategies for prevention of SSIs in cardiothoracic surgery patients through Monte Carlo simulation. The model begins with a cohort of 10,000 cardiothoracic surgery patients and follows them through 2 stages: 1) occurrence of SSI and 2) the outcomes following those SSIs. Each

patient was assigned a baseline risk of a SSI based on published rates of SSI for cardiothoracic procedures [1]. Baseline risk could be influenced by when the antimicrobial agent was administered in relation to the first surgical incision and the antimicrobial's activity and efficacy in reducing SSIs.

All patients were administered standard doses of 1 of the 3 prophylactic regimens: 1) cefuroxime, 2) vancomycin, or 3) linezolid. SSIs of the chest wall were caused by 3 general categories of pathogens: 1) methicillin-susceptible Gram-positive organisms, 2) methicillin-resistant Gram-positive organisms, and 3) all other organisms (e.g. Gram-negative bacilli). Once a simulation established the infection, the organism causing the infection influenced the probability of recovery or death. The model tracked the number of chest SSIs, SSIs by pathogen and SSI deaths.

The model allowed the use of distributions in each stage, creating dependence on earlier stages for subsequent transitions, and discrete event counts for each stage. The Monte Carlo simulation allowed each individual in the population to be simulated separately by sampling probabilities from multiple *a priori* distributions. This use of a Monte Carlo simulation approach allowed for 10,000-second order samplings of each of the distributions described in Table I. This approach allowed for the incorporation of uncertainty into each model variable. The model produced outputs that represented the mean number of events across all simulations of the cohort and was designed and analyzed using TreeAge Pro 2009 [TreeAge Software, Williamstown, MA, USA].

Clinical data

To populate the model we conducted a PubMed search of relevant clinical studies published between 1990 and 2009. Table I summarizes all model parameters and describes the range of values drawn upon during each simulation. We assumed that all patients were given an appropriately dosed prophylactic antibiotic prior to surgical incision. Baseline risk of SSI involving the chest wall or mediastinum was based on published SSI rates following inpatient coronary artery bypass graft procedures performed during 2006 and 2007 [1]. We used baseline proportions of causative organisms for SSIs from Finkelstein et al [17]. The probabilities of all-cause hospital death occurring following no SSI and susceptible and resistant Gram-positive organisms was based upon Kaye et al [3]. The probability of death due to organisms categorized as "other" was set to equal the probability of death associated with methicillin-susceptible Gram-positive pathogens. Estimates of the efficacy of each agent were based upon timing of the antimicrobial's administration in relation to surgical incision time and its activity and efficacy against SSI pathogens.

The effect of administration time for cefuroxime was based on Weber et al [6]. They determined that the optimal administration time for 1.5 g of cefuroxime (infused over 2–5 minutes) was between 45 and 59 minutes prior to incision. Estimates of the administration time effect for vancomycin was based upon Garey et al [5] who established adjusted risk-ratios for SSIs as a function of the timing of administration of 1 g of vancomycin pre-operatively and two post-operative 1 g doses. Optimal administration time for vancomycin was determined to be between 16 and 60 minutes prior to incision.

The effect of administration time for linezolid was based upon the work of Lovering et al [15]. In this study, linezolid was infused over a 20-minute period prior to surgical incision. Other investigators have demonstrated peak serum and tissue levels of linezolid approximately 30 minutes after intravenous infusion [12]. Given these infusion and pharmacokinetic properties, the authors assumed an optimal infusion time for a 600 mg intravenous dose of linezolid to be 45–59 minutes prior to incision.

The antimicrobial effects of cefuroxime and vancomycin are based upon the meta-analysis of SSI prophylaxis conducted by Bolon et al [18]. While both agents were equally effective in preventing SSIs due to all pathogens at 30 days post surgery, β -lactams were associated with a lower risk of SSIs due to methicillin-susceptible pathogens (RR = 1.36), glycopeptides were associated with a lower risk of SSI due to methicillin-resistant Gram-positive pathogens (RR = 0.54). The antimicrobial activity of linezolid was assumed to be the same as that of vancomycin. Linezolid has a broad spectrum of activity against Gram-positive pathogens and no appreciable activity against aerobic Gram-negative pathogens [11,19,20].

Evaluation of pre-operative antimicrobial prophylaxis strategies

The most effective strategy was defined as the strategy that resulted in the lowest overall probability of SSI. Exact counts of SSIs are not reported during the Monte Carlo simulations; only mean values are reported. In addition to SSIs, the model tracks the number of pathogen-specific SSIs and deaths. Variability was built into each of these scenarios through the use of Dirichlet distributions for the probability of each organism type. Dirichlet distributions allow variability in each of the component probabilities while forcing the total probability to equal 100%. As with deaths, this approach does not report actual numbers of SSIs, but rather the average number of SSIs resulting from each strategy.

Sensitivity analyses

As this model uses a Monte Carlo simulation approach, probabilistic sensitivity analyses are incorporated into the primary outputs of the model. We performed several sensitivity analyses around the role of the baseline SSI risk, the number of patients with resistant Gram-positive infections, and the pattern of antimicrobial prophylaxis administration timing. The 3.9% baseline overall risk of SSI was varied using a triangular distribution (minimum = 2%, maximum = 6%). Though no specific variables were included in the model to account for individual patient-risk variability (e.g., obesity, diabetes, cigarette smoking), these variations allow interpretation of the model using patients with different baseline risks. In addition, we created low-, medium- and high-risk scenarios by altering the 27% baseline proportion of SSIs due to resistant Gram-positive infections. We decreased the baseline risk of resistant Gram-positive SSIs by 5%, and increased the risk by 5% and 10% for the low-, medium- and high-risk categories, respectively.

The pattern of prophylaxis timing presented challenges in producing appropriate variability; thus several approaches were explored. Since administration times were used to determine the relative risk reduction of SSI for the first stage of the model, we were not able to create distributions of antimicrobial administration times incorporating variability similar to other types of variables in the simulation. To overcome this limitation, we created additional distributions of antimicrobial prophylaxis administration times that were considered “best-case” and “worst-case” scenarios. In the best-case scenario, we subtracted 10% of the administration time from each of the non-reference time periods and added them to the reference time period. This resulted in more patients receiving prophylaxis at the optimal administration time. In the worst-case scenario, we subtracted 10% of the administration time from each of the time periods, but added them to the time period that had the highest overall risk in our baseline scenario. This resulted in more patients receiving prophylaxis at the least favorable administration time.

Results

Analysis utilizing base-case risk for SSI

Table II presents the results of our analysis prophylaxis strategies administered to 10,000 patients undergoing cardiothoracic surgery using a 3.9% baseline risk of SSI. Values reported are the mean of the number of outcomes from within the 10,000 first order trials of the model. There were 739, 828, and 746 total SSIs in the cefuroxime, vancomycin, and linezolid prophylaxis groups, respectively (SSI rates of 7.4%, 8.3%, and 7.5%, respectively). Linezolid prophylaxis resulted in fewer SSIs due to methicillin-resistant Gram-positive infections ($n = 108$) compared with cefuroxime ($n = 200$, 46% reduction in the linezolid group) and vancomycin ($n = 119$, 9% reduction in the linezolid group). Cefuroxime was more effective than either vancomycin or linezolid for the prevention of methicillin-susceptible Gram-positive infections. Compared with cefuroxime, linezolid and vancomycin resulted in 72 (36%) and 101 (51%) additional SSIs, respectively, due to methicillin-susceptible pathogens. All-cause mortality was similar among all three groups.

Sensitivity analyses

To determine the sensitivity to fundamental changes in key model parameters, analyses were conducted using alternate assumptions. Table III presents the results of the sensitivity analyses. Total infections for each agent were most sensitive to changes in the baseline risk for SSI, although changes were similar among the 3 prophylaxis groups. A low baseline risk of SSI of 2% resulted in an overall reduction of total SSI of 48% compared with baseline risk, while a high baseline risk of 6% resulted in a 53% increase. Adjusting for the baseline risk of SSI due to resistant organisms had minimal effect on the overall results. However, as the risk of SSI due to methicillin-resistant organisms increased, the number of SSIs prevented increased for both the vancomycin and linezolid strategies and remained unchanged for the cefuroxime strategy.

Changing the distribution of administration times from “best-case” to “worst-case” scenarios had the largest impact on vancomycin, with a 34% difference in the number of SSIs between the two scenarios. Linezolid and cefuroxime each showed a difference in the number of SSIs of approximately 13% from best- to worst-case scenarios.

Discussion

Our model demonstrates that cefuroxime was the most effective agent for the prevention of SSIs overall, although vancomycin and linezolid compared favorably when the baseline patient risk for SSI due to MRSA was increased. Compared with cefuroxime, linezolid prophylaxis resulted in a 1% increase in total SSIs (mean increase = 7 SSIs), while vancomycin resulted in a 12% increase (mean increase = 86 SSIs). However, for SSIs due to methicillin-resistant Gram-positive pathogens, linezolid prevented more SSIs than either cefuroxime or vancomycin. As the risk of SSI due to methicillin-resistant Gram-positive organisms increased, prophylaxis with linezolid (and, to a lesser degree, vancomycin) prevented more SSIs than cefuroxime.

Our model was robust to the performed sensitivity analyses. The overall SSI rates were most sensitive to changes in the baseline risk for SSI which resulted in predictable changes in total SSI occurrence regardless of the agent selected. Changing the distribution of administration times had differing impacts on the efficacy of agents. These ranges in numbers of SSI have important implications on the impact of prophylaxis strategies using different agents, as there is likely to be tremendous variability in SSI prophylaxis administration times in different hospitals and between surgical teams.

A major limitation of our model is the lack of any direct information on the efficacy and timing effects of linezolid in the prevention of SSIs. However, the assumptions regarding linezolid are supported by existing literature. The efficacy profile of linezolid against the Gram-positive pathogens known to cause the majority of SSIs is well established [21,22]. In a randomized, comparator-controlled, open-label, multi-center study, linezolid was shown to be as effective as vancomycin for the treatment of complicated skin and soft tissue infections including in patients with a SSI [23]. In a subset analysis of patients with a SSI, the clinical cure rates were similar between groups and microbiologic cure rates for SSIs due to MRSA were 87% for linezolid and 48% for vancomycin [24]. The pharmacokinetic profile and tissue penetration of linezolid are consistent with that of an agent that penetrates tissues in time to limit bacterial growth [12-14]. These factors coupled with a short infusion time suggest that linezolid should have the timing benefits of a drug administered close to the time of surgical incision. While these assumptions may be consistent with the known characteristics of linezolid, additional research regarding its use in the operative setting and optimal administration timing would be helpful to further inform prophylaxis modeling and decision-making.

This study had additional limitations. First, the rate of SSIs of the chest wall was 7.4% for the cefuroxime group, which is higher than most published benchmarks [1]. This high rate of baseline SSI was a function of how the “baseline” risk of SSI was set for the model and this risk does not impact on the relative preventive efficacy among the agents. It is important to note that in all of the model scenarios SSI risk was increased over “baseline” because of the combined impact of baseline risk, antimicrobial efficacy, and most importantly, administration timing. As the model does not assume optimal administration timing for all individuals, the efficacy in reducing the baseline risk is attenuated resulting in an increase in the baseline risk of infection. Second, this study did not analyze the impact of different prophylaxis regimens on the risk for emergence of multi-drug resistant organisms due to “selective antibiotic pressure”. Third, specific patient-risk parameters, such as age and presence of specific underlying diseases were not factored into the model. However, these patient risk parameters were factored into the baseline risk sensitivity analysis. Fourth, this study assumes that only a single pre-operative dose of prophylactic antibiotics was administered. Since the pre-operative dose has the major impact on SSI prophylaxis, this final limitation was not deemed to be important in the construction of study models. Finally, this study did not differentiate between superficial, deep, and organ/space SSI. Fifth, the study used best available literature to determine values for model inputs and when the literature was conflicting with regards to the value for a particular input, the authors adjudicated which model inputs were most appropriate. It was beyond the scope of this study to build multiple models to account for a variety of different input values. However, sensitivity analyses across ranges for any given variable were conducted to improve generalizability of the study results.

Linezolid is often reserved for the treatment of serious infections due to Gram-positive bacteria. Therefore, its use for the prophylaxis of SSIs may be controversial given its cost and concerns for the development of resistance. However, given the increasing prevalence of MRSA-caused SSIs and the limitations of currently available agents we felt that there was a need to evaluate linezolid in this setting.

Due to the difficulty in conducting randomized controlled trials for SSI prophylaxis, decision models like this are one of the best sources of information pertaining to the relative strengths and weakness of different prophylaxis regimens. It would be beneficial to have additional pharmacokinetic information on the tissue penetration of linezolid at the site of surgical incision. These data would allow further, and potentially more powerful, estimations of timing benefits. Long-term observational follow-up of linezolid’s use and

efficacy in reducing SSI prevention would also facilitate the design of better studies and models. Ultimately, a randomized controlled trial analyzing the efficacy of linezolid in preventing SSIs is needed to inform best clinical practice for clinicians on how to prevent SSIs due to resistant Gram-positive pathogens such as MRSA.

The advantages of linezolid over vancomycin for SSI prevention related mostly to more appropriate timing of antimicrobial infusion in the linezolid group. These advantages relating to time of infusion are important and relevant considering that in 2012 the Center for Medicare and Medicaid Services will implement a value-based purchasing program for hospitals based upon quality performance, which ties financial reimbursement to appropriate administration of antimicrobial prophylaxis following surgery, including cardiothoracic surgery [25]. In areas with high rates of SSIs due to methicillin-resistant Gram-positive pathogens such as MRSA, linezolid may be an alternative to vancomycin in a comprehensive SSI prevention policy.

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Fig. 1.
 Decision-analytic model of antimicrobial prophylaxis for the prevention of SSIs in
 cardiothoracic surgery patients.
 Decision analysis tree
 SSI = surgical site infection; p = probability

Table I

Model variables for decision-analytic model of antimicrobial prophylaxis for the prevention of SSIs in cardiothoracic surgery patients

Variables	Base case	Range/ distribution	References
Baseline SSI risk	0.039	0.02 – 0.06	[1]
Causative organisms (proportion of total SSIs)			
Susceptible Gram-positive	0.270	Dirichlet	[14]
Resistant Gram-positive	0.270	Dirichlet	[14]
Other organisms	0.460	Dirichlet	[14]
Causative organisms – low resistance risk (proportion of total SSIs)			
Susceptible Gram-positive	0.295	Dirichlet	
Resistant Gram-positive	0.220	Dirichlet	
Other organisms	0.485	Dirichlet	
Causative organisms – medium resistance risk (proportion of total SSIs)			
Susceptible Gram-positive	0.245	Dirichlet	
Resistant Gram-positive	0.320	Dirichlet	
Other organisms	0.435	Dirichlet	
Causative organisms – high resistance risk (proportion of total SSI)			
Susceptible Gram-positive	0.220	Dirichlet	
Resistant Gram-positive	0.370	Dirichlet	
Other organisms	0.410	Dirichlet	
Probability of hospital death			
Susceptible Gram-positive	0.067	+/- 25%/Triangular	[3]
Resistant Gram-positive	0.207	+/- 25%/Triangular	[3]
Other organisms	0.050	+/- 25%/Triangular	
No infection	0.021	+/- 25%/Triangular	[3]
Relative risk of SSI based upon prophylaxis administration times prior to incision			
Cefuroxime			
0–14 minutes	RR = 1.75	0.9–3.4/Gamma	[5]
15–29 minutes	RR = 2.82	1.5–5.3/Gamma	[5]
30–44 minutes	RR = 1.37	0.7–2.6/Gamma	[5]
45–59 minutes	RR = 1.00	Reference group	[5]
60–74 minutes	RR = 1.40	0.6–3.3/Gamma	[5]
>75 minutes	RR = 3.16	1.4–7.0/Gamma	[5]
Linezolid			
0–14 minutes	RR = 1.75	0.9–3.4/Gamma	
15–29 minutes	RR = 2.82	1.5–5.3/Gamma	
30–44 minutes	RR = 1.37	0.7–2.6/Gamma	
45–59 minutes	RR = 1.00	Reference group	

Variables	Base case	Range/ distribution	References
60–74 minutes	RR = 1.40	0.6–3.3/Gamma	
>75 minutes	RR = 3.16	1.4–7.0/Gamma	
Vancomycin			
0–14 minutes	RR = 7.82	2.5–24.7/Gamma	[4]
15–59 minutes	RR = 1.00	Reference group	[4]
60–119 minutes	RR = 2.25	0.99–5.09/Gamma	[4]
120–179 minutes	RR = 2.01	0.87–4.62/Gamma	[4]
>180 minutes	RR = 2.29	0.94–5.56/Gamma	[4]
Relative risk of SSI due to specific organisms based upon choice of prophylactic agent			
Cefuroxime			
Susceptible Gram-positive	RR = 1.00	Reference group	[17]
Resistant Gram-positive	RR = 1.00	Reference group	[17]
Other organisms	RR = 1.00	Reference group	[17]
Vancomycin			
Susceptible Gram-positive	RR = 1.36	0.98–1.91/Gamma	[17]
Resistant Gram-positive	RR = 0.54	0.33–0.90/Gamma	[17]
Other organisms	RR = 1.08	0.75–1.55/Gamma	[17]
Linezolid			
Susceptible Gram-positive	RR = 1.36	0.90–1.7/Gamma	
Resistant Gram-positive	RR = 0.54	0.33–0.90/Gamma	
Other organisms	RR = 1.08	0.75–1.55/Gamma	
Percentage of antibiotic administrations in relation to time to incision			
Cefuroxime			
0–14 minutes	0.217	0.1953	[5]
15–29 minutes	0.275	0.2475	[5]
30–44 minutes	0.258	0.2322	[5]
44–59 minutes ^a	0.129	0.2161, 0.1161	[5]
60–74 minutes	0.069	0.0621	[5]
>75 minutes ^b	0.052	0.0468, 0.1468	[5]
Linezolid			
0–14 minutes	0.217	0.1953	
15–29 minutes	0.275	0.2475	
30–44 minutes	0.258	0.2322	
44–59 minutes ^a	0.129	0.2161, 0.1161	
60–74 minutes	0.069	0.0621	
>75 minutes ^b	0.052	0.0468, 0.1468	
Vancomycin			
0–14 minutes ^b	0.007	0.0063, 0.1063	[4]

Variables	Base case	Range/ distribution	References
15–59 minutes ^a	0.086	0.1774, 0.0774	[4]
60–119 minutes	0.434	0.3906	[4]
120–179 minutes	0.342	0.3078	[4]
>180 minutes	0.131	0.1179	[4]

SSI = surgical site infection;

^a best-case scenario;

^b worst-case scenario

Number of outcomes from 10,000 microsimulations on a cohort of 10,000 patients undergoing coronary artery bypass graft surgery using base-case assumptions

Table II

	Cefuroxime		Vancomycin		Linezolid	
	Mean	95% CI	Mean	95% CI	Mean	95% CI
SSIs	742	(747–736)	828	(833–823)	749	(755–743)
Due to MR organisms	200	(202–198)	119	(121–118)	108	(109–106)
Due to MS organisms	200	(202–199)	301	(303–299)	272	(275–270)
Due to other organisms	342	(344–339)	407	(410–405)	369	(372–366)
Deaths from all causes	267	(267–266)	258	(259–258)	254	(254–253)

SSI = surgical site infection; MR = methicillin-resistant; MS = methicillin-susceptible

Table III

Sensitivity analysis results: percentage change in total SSIs versus baseline total number of infections

	Cefuroxime (Baseline = 742)	Vancomycin (Baseline = 828)	Linezolid (Baseline = 749)
	Mean (%Δ)	Mean (%Δ)	Mean (%Δ)
Change in baseline risk of SSI			
2%	381 (−48.6%)	427 (−48.4%)	386 (−48.4%)
6%	1138 (53.3%)	1271 (53.5%)	1147 (53.2%)
Change in risk of resistant Gram-positive organisms			
Low risk (−5%)	742 (0.0%)	860 (3.8%)	775 (3.4%)
Medium risk (+5%)	739 (−0.4%)	798 (−3.6%)	720 (−3.8%)
High risk (+10%)	743 (0.2%)	774 (−6.5%)	700 (−6.5%)
Change in administration timing			
Best-case scenario	706 (−4.8%)	781 (−5.7%)	713 (−4.8%)
Worst-case scenario	794 (7.1%)	1062 (28.3%)	801 (6.9%)

SSI = surgical site infection