SPINE An International Journal for the study of the spine Publish Ahead of Print
DOI : 10.1097/BRS.0000000000001371

Intrawound Vancomycin Decreases the Risk of Surgical Site Infection after Posterior Spine Surgery– A Multicenter Analysis

Clinton J. Devin, MD[1], Silky Chotai MD[1], Matthew J. McGirt, MD[3], Alexander R. Vaccaro, MD, PhD[2], Jim A. Youssef, MD[4], Douglas G. Orndorff, MD[5], Paul M. Arnold, MD[6], Anthony K. Frempong-Boadu, MD[7], Isador H. Lieberman, MD, FRCSC, MBA[8], Charles Branch, MD[9], Hirad S. Hedayat, MD[9], Ann Liu, BS[9], Jeffrey C. Wang, MD[10], Robert E. Isaacs, MD[11], Kris E. Radcliff, MD[12], Joshua C. Patt, MD[3], Kristin R. Archer, PhD, DPT[1,13]

[1]Department of Orthopedics and Neurosurgery, Vanderbilt University Medical Center, Nashville, TN, USA,

[2]Department of Orthopedics, Thomas Jefferson University and Rothman Institute, Philadelphia, PA, USA

[3]Department of Neurological Surgery, Carolina Neurosurgery and Spine Associates, Charlotte, North Carolina, USA,

[4,5]Spine Colorado, Durango, CO, USA,

[6]Department of Neurosurgery, University of Kansas Med Center, Kansas City, KS, USA,

[7]Department of Neurosurgery, New York University Langone Medical Center, New York, NY, USA

[8]Scoliosis and Spine Tumor Center, Texas Back Institute, Texas Health Presbyterian Hospital Plano, Plano, TX, USA

[9]Department of Neurosurgery, Wake Forest Baptist Medical Center, Winston Salem, NC, USA,

[10]Department of Orthopedic Surgery, Keck School of Medicine, University of Southern California, Los Angeles, California, U.S.A.

[11] Division of Neurological Surgery, Department of Surgery, Duke University Medical Center, Durham, NC, USA

[12]Department of Orthopedics, Rothman Institute, Thomas Jefferson University, Egg Harbor Township, NJ, USA,

[13]Department of Physical Medicine and Rehabilitation, Vanderbilt University Medical Center, Nashville, TN, US

Corresponding author:
Dr. Clinton J. Devin, MD
Department of Orthopedics Surgery,
Vanderbilt Spine Institute,
Vanderbilt University School of Medicine,
Medical Center East, South Tower,
Suite 4200, Nashville,
TN 37232-8774, USA.
Tel.: (615) 479-6034
Email- clintondevin@gmail.com

Acknowledgement: August 26, 2015
1st Revise: October 1, 2015
2nd Revise: October 30, 2015
Accept: November 3, 2015

The drug that is the subject of this manuscript is not FDA-approved for this indication and is commercially available in the United States.

No funds were received in support of this work.
Relevant financial activities outside the submitted work: grants, consultancy, expert testimony, royalties, stocks, grants, stocks, travel/accommodations/meeting expenses.

Abstract:

Study-Design:
Secondary analysis of data from a prospective multicenter observational study

Objective:
To evaluate the occurrence of surgical site infection (SSI) in patients with and without intrawound vancomycin application controlling for confounding factors associated with higher SSI after elective spine surgery.

Summary of Background Data:
SSI is a morbid and expensive complication associated with spine surgery. The application of intrawound vancomycin is rapidly emerging as a solution to reduce SSI following spine surgery. The impact of intrawound vancomycin has not been systematically studied in a well-designed multicenter study.

Methods:
Patients undergoing elective spine surgery over a period of four-years at seven spine surgery centers across the United States were included in the study. Patients were dichotomized based on whether intrawound vancomycin was applied. Outcomes were occurrence of SSI within postoperative 30-days and SSI that required return to the operating room (OR). Multivariable random effect log-binomial regression analyses were conducted to determine the relative risk of having a SSI and a SSI with return to OR.

Results:
A total of 2056 were included in the analysis. Intrawound vancomycin was utilized in 47% (n=966) of patients. The prevalence of SSI was higher in patients with no vancomycin use (5.1%) compared to those with use of intrawound vancomycin (2.2%). The risk of SSI was higher in patients in whom intrawound vancomycin was not used (RR-2.5,$p<0.001$), increased number of levels exposed (RR-1.1,$p=0.01$), and those admitted postoperatively to intensive care unit (ICU) (RR-2.1,$p=0.005$). Patients in

whom intrawound vancomycin was not used (RR-5.9,p<0.001), increased number of levels were exposed (RR-1.1,p=0.001) and postoperative ICU admission (RR-3.3,p<0.001) were significant risk factors for SSI requiring a return to the OR

Conclusion:

The intrawound application of vancomycin after posterior approach spine surgery was associated with reduced risk of SSI and return to OR associated with SSI.

Key Words: Surgical site infection, SSI, Vancomycin, Multicenter, Return to OR

Level of Evidence: 2

Introduction:

There are an estimated 500,000 surgical site infections (SSI) annually in the United States (U.S.) accounting for up to $1.8 billion additional health-care costs annually.[1,2] SSI is associated with increased length of hospital stay by a median of 2-weeks, higher readmission, repeat operations, and a two-fold increase in mortality.[2-4] The rate of spine related SSI ranges between 2 to 13%, depending upon the procedure and pathology being treated.[4-12] SSI has profound impact on patients` life and healthcare utilization. Patients may require extended rehabilitation, prolonged antibiotic therapy, multiple surgical procedures for wound debridement and implant revision, revision for pseudoarthrosis and instrumentation failure; with conservative cumulative costs of $100,000 per patient.[4,8,12]

SSI is being viewed as a “never event” and key metric by which a provider and facility are judged as to the quality of care provided. Reducing the SSI rates is vital for demonstrating safety and containment of health care resource utilization. To mitigate the risk of infection various techniques have been utilized including: preliminary surgical site preparation with alcohol foam, appropriate timing of IV antibiotics, identification and prophylactic measures for MRSA carriers, utilization of providine or bacitracin in the irrigant, and timely drain removal [3,13-16] One additional technique is the use of local intrawound antibiotic placed at the time of wound closure. The rationale of using local

antibiotic is to achieve a local high antibiotic concentration, high bacterial killing rates and to minimize the systemic toxicity. Buchholz HW et al first described the use of local antibiotics in 1970[17], since then the local application of antibiotic has been investigated in orthopedics, cardiothoracic, vascular, and spine surgeries.[9,18-21] The most common organisms associated with SSI are gram-positive *Staphylococcus aureus and Staphylococcus epidermidis*[22]. Therefore, the application of intrawound vancomycin is rapidly emerging as a solution to reduce the SSI following spine surgery specifically associated with these bacteria.

There is insufficient and contradicting evidence on use of vancomycin and its effectiveness at mitigating infection. Several studies have demonstrated that application of local intrawound vancomycin powder significantly reduces infection rates.[4,11,23-30] The addition of prophylactic intrawound vancomycin to standard systemic prophylaxis in elective spine surgery was shown to reduce infection rates from 2.6% to 0.2%[29] In contrast, others have reported no impact of using intrawound vancomycin on SSI. [12,31] The aim of this multicenter study was to evaluate the risk of SSI in patients with and without intrawound vancomycin application and determine the factors associated with higher SSI after elective spine surgery. The hypothesis of the present study was that intrawound vancomycin decreases the risk of SSI. Outcomes were occurrence of SSI within postoperative 30-days and occurrence of SSI that requires return to the operating room (OR).

Methods:

A secondary analysis, of data from a prospective multicenter observational study, was conducted after obtaining approval from the institutional review board of the participating centers. Patients undergoing spine surgery via a posterior approach for degenerative spine pathology, between November 2010 and July 2014, at seven academic medical centers sites across the U.S. were included in the study. These sites consisted of both community and academic medical centers. Patients from all sites were dichotomized based on whether intrawound vancomycin was applied. The application of

intrawound vancomycin was up to the treating physician. The treatment group was defined as patient receiving local vancomycin powder spread throughout the surgical wound in addition to standard IV systemic prophylaxis. Patients with any of the following associated conditions were not eligible to receive intrawound vancomycin: 1) known allergy to vancomycin, 2) previous spine surgery at the operated level within 6 months, 3) pregnancy, 4) history of Stevens - Johnson syndrome, 5) history of infection at the surgical site, or 6) radiation treatment at the operated level. The control group received standard systemic prophylaxis only.

Patients underwent a posterior spinal surgery with and without fusion for degenerative pathologies, spinal trauma, or tumor. All patients had identical preoperative surgical site preparation specific to each site. Patients received standard antibiotic prophylaxis consisting of 1-gram of intravenous (IV) cefazolin within 1-hour of surgical incision followed by 1-gram of IV cefazolin every 8-hours for one day postoperative. In patients allergic to penicillin, 900 mg of IV clindamycin was used. Subfascial drains were used and connected to suction canisters. Dressings and drains were kept in place until daily drain output was less than 80 ml per 24 hours. The drains were not clamped, as based on our experience and previously published studies[29,32] the supratherapeutic levels of local vancomycin are achieved for 2 days without clamping, which is considered enough time to allow for epithelialization to occur. Based on the surgeon's preference, the vancomycin group received an additional 1-gram vancomycin powder (Hospira, Inc.) for every 10 cm of longitudinal wound length spread throughout the surgical wound upon closure. The powder was placed directly on the muscle, fascia, and subcutaneous tissues taking care not to expose bone graft or dura mater.

Patient demographics were collected including: age, sex, race, height and weight, smoking status, and presence of diabetes, chronic steroid use, and chronic renal insufficiency. Furthermore, the diagnosis, spinal level operated upon, revision versus primary surgery, use of instrumentation, arthrodesis, need for postoperative admission to intensive care unit (ICU), number of spinal levels exposed, and length of hospital stay

were obtained from the medical record. The presence of SSI was determined by visual wound inspection and contrast-enhanced MRI, which was used in all cases when superficial or deep SSI was suspected. Superficial infections were treated with a spectrum of oral antibiotics directed at the most common offending organisms. Deep infections, in which cultures were obtained, underwent treatment with IV antibiotics based on culture sensitivities and under the direction of an infectious disease consultant. A deep SSI was treated with excision and debridement of the wound with removal and or exchange of the hardware as deemed necessary. The attending surgeon at each center recorded the incidence of superficial or deep SSI as well as whether the SSI required a return to the OR.

Statistical analysis:

Descriptive statistics examined the mean, standard deviation (SD), and frequency of all demographic and clinical characteristics of the study population as well as the distribution of SSI by site and use of vancomycin. Student's t-tests and Chi-square or Fisher exact tests examined differences in patient characteristics by vancomycin group. Outcomes of SSI and SSI requiring a return to the OR were compared across treatment groups using Chi-square tests. Multivariable random effect log-binomial regression analyses were conducted to determine the relative risk of having a SSI and a SSI with return to OR. Covariates that were significant at $p < 0.05$ in bivariate log-binomial regression analyses were entered into the multivariable model. Site was included as a random effect *a priori* to account for clustering of patients within site. Analyses were performed using stata statistical software, (Version 11.0; Stata Corp, College Station, TX, USA). The stata GLLAMM macro produced estimates of the variance of the random effects for site. The fraction of the variance attributable to differences between sites was calculated by dividing the variance of the site random effect by the total variance in the model (site + participants). The variance for participants was considered to be $\pi^2/3$ for calculation purposes. The stability of the final model was test by adding back in each excluded variable one at a time. Missing data were less than 5% and handled using regression models that imputed the missing values as a function of the other covariates. A p-value <0.05 was considered statistically significant.

Results:

Patient demographic and clinical characteristics

A total of 2056 patients underwent elective spine surgery for degenerative spine pathologies across seven sites, and were included in the analysis. The mean number of levels exposed was 3.6 ± 2.8, 82% (n=1695) underwent fusion and 79% (n=1628) of patients underwent instrumentation. Intrawound vancomycin was utilized in 47% (n=966) of patients.

The mean length of hospital stay was 5.0 ± 4.7 and 21.1% (n=434) of patients were admitted to the ICU after surgery. The vancomycin group had significantly higher number of patients with diabetes (21.5% vs. 17.7%, p=0.03), steroid use (6.7% vs. 4.5%, p=0.03) and fusion rates (84.5% vs. 80.6%, p=0.02) compared to the no vancomycin group. Patients with chronic renal failure (4.4% vs. 3.4%, p=0.22) and obese (37.2% vs. 33.9%, P=0.26), were higher in vancomycin group, but this did not reach statistical significance. Table 1 summarizes the patient characteristics in the vancomycin and no vancomycin groups.

SSI by site and use of vancomycin

The site-to-site variation in occurrence of SSI ranged from 1.4% to 5.8% (Table 2). The prevalence of SSI across all sites was 3.8% (n=77) (Table 3). A significantly higher rate of SSI was found in patients with no vancomycin use 5.1% (n=56) compared to those with use of intrawound vancomycin 2.2% (n=21) (P<0.001). There was a significantly higher rate of SSI requiring return to OR in the no vancomycin group 3.9% (n=42) compared to those with use of intrawound vancomycin 0.7% (n=7) (P<0.001).

Log-binomial regression analyses

Multivariable random effect log-binomial regression analysis found that no vancomycin use was a statistically significant risk factor for SSI (RR-2.5, CI-1.5-4.1, p<0.001) and SSI requiring return to the OR (RR-5.9, CI 2.6-13.2, p<0.001) (Table 4). Additional risk factors for SSI were increased number of levels exposed (RR-1.1, CI 1.0-1.2, p=0.01) and postoperative ICU stay (RR-2.1, CI-1.3-3.6, p=0.005). Increased number of levels

exposed (RR-1.1, CI- 1.0-1.2, p=0.001) and postoperative ICU stay (RR-3.3, CI-1.8-6.2, p<0.001) were also significantly associated with SSI that required a return to the OR. Site contributed significantly to the model and accounted for 3% of the variance in SSI and 20% of the variance in SSI that required return to the OR.

Discussion:

In this analysis, utilizing multicenter observational data on contemporaneous patients, we demonstrated that the intrawound application of vancomycin after posterior spine surgery is associated with reduced overall SSI and SSI requiring a return to the OR. Multivariable analyses also found that increasing number of operated levels and post-operative ICU stay were independent risk factors for SSI.

Previous studies have reported conflicting results on impact of intrawound vancomycin application on SSI rates.[5,9,33] Analogous to our findings, several retrospective, single-center, observational studies have advocated the use of intrawound vancomycin to prevent SSI. [4,7,11,23,25-27,29,30,34] In our analysis, across all the sites included in the study, the risk of SSI (5.1% vs. 2.2%) and SSI requiring return to OR (3.9% vs. 0.7%) was higher in patients that did not have application of intrawound vancomycin. A meta-analysis performed by Khan NR et al[9] reported 2.99 times higher likelihood of SSI when intrawound vancomycin power was not used in spine surgery. The protective benefit of intrawound vancomycin is demonstrated in both instrumented and non-instrumented spine surgeries.[23] In contrast, a study by Tubaki et al demonstrated that intrawound vancomycin had a minimal impact on reducing SSI. . [12], Based on their prospective randomized control trial of 907 patients, they reported no significant difference (1.61% vs. 1.68%) in the rates of SSI among the patients in treatment group (intrawound vancomycin) and control group (no vancomycin). There are several flaws in the Tubaki study, no a priori sample size calculation was performed and the rate of SSI was too low (n=8, 1.68% in each group) making it difficult to derive any statistical significance. Furthermore, the authors did not evaluate confounding risk factors known to increase the risk of SSI. In addition Martin et al[31], in their retrospective single-center study of 306 patients, reported that the use of intrawound vancomycin was not protective for deep SSI

in patients undergoing thoracolumbar fusion for spinal deformity. In our analysis, the rate of SSIs were significantly lower in the intrawound vancomycin cohort, despite having a higher number of patients with known risk factors for SSI, such as diabetes and older age. Furthermore, there was a higher number of patients with obesity, chronic renal failure, and post-operative ICU stay in the vancomycin cohort as compared to the control group, but this did not reach statistical significance.

Intrawound vancomycin powder is an appealing intervention given minimal to no local or systemic adverse events attributable to intrawound vancomycin application. Reported or potential side effects include tissue irritation resulting in neuritis or seroma formation, development of vancomycin resistant organisms, selection of gram-negative organisms, inhibition of osteoblasts with resultant pseudoarthrosis, renal toxicity, and anaphylactic reaction. Ghobrial et al[35] reported a 1.4% (n=14) rate of post-operative sterile seroma in patients that had intrawound vancomycin. The authors postulated that fat necrosis or an occult infection at undetectable levels due to a high local vancomycin concentration might attribute to the seroma occurrence. The local concentration of vancomycin, based on levels obtained from surgical drains, has been shown to range between 263 to 2938 µg/ml on day of surgery with a trend down to undetectable levels by postoperative day 4.[29] This creates a concentration that is nearly a thousand fold higher than the minimum inhibitory concentration for MRSA and coagulase negative staphylococcus making the development of resistant organisms low.[29,32] Intrawound application of vancomycin powder may, however, select out gram-negative spine infections.[25] Therefore, to further reduce the risk of SSI one may consider adding to add another antibiotic with gram-negative or broad polymicorbial coverage, which can achieve minimal systemic absorption, high local concentration, and minimal local adverse events.

The impact of intrawound vancomycin on osteogenesis and fusion rates following spine surgery is not well reported. In vitro studies have demonstrated that a high local concentration up to 10,000 µg/ml or 3-6mg/cm2 is needed to inhibit osteogenesis.[5,36,37] As demonstrated by drain concentrations, the doses are well below these concentrations. However, no well-done clinical studies have evaluated the effect of intrawound vancomycin on pseudoarthrosis rates.[38] Systemic renal toxicity is unlikely due to the low serum levels noted in multiple studies.[29,32]Anaphylactic reaction is a possibility and was

reported by Mariappan et al[39] describing a case of circulatory collapse about 30 minutes after application of 1 gram of vancomycin over the dura and exposed vertebrae. The currently used dose of 1-2 gram is empirical, therefore further pharmacokinetic studies are needed to determine effective and safe dose for spine surgery.[36] For this study we utilized 1 g per 10cm of longitudinal incision length. With the current empiric dose regimen, a single local application of vancomycin costs between $12 and $40. This makes it an extremely cost effective intervention given a SSI requires on average $3000 - $25,446 more for their care.[2,40] Previous studies reported cost savings of using intrawound vancomycin in spine surgery ranging from $220,000 to $500,000 per 100 patients.[5,7,30]

Several limitations need to be considered when interpreting results. The differences in pre and peri-operative measures to prevent infection at each site were not analyzed in this study, which might have confounded the overall SSI rates. Given the multi-center nature of this study and the diverse patient population undergoing posterior spine surgery, the rate of SSI can be somewhat generalized. We analyzed the prevalence of SSI and return to OR rates at 30-day after the index spine surgery. The impact of intrawound vancomycin on 90-day or 1-year SSI was not analyzed. The rate of SSI is high within 30-days post-operatively and decreases subsequently; therefore this time point was chosen *a priori.* However, due to lack of high-level evidence on local and systemic adverse effects it is unclear if the intrawound vancomycin should be a standard of care or to be used only for high-risk patients. Finally, there are limitations inherent to a non-randomized intervention study. However, this study can be considered a "natural experiment" study-design. Although, the natural experiments are more prone to bias compared to a randomized control trial; they are utilized when the randomized control trial is unethical or impractical, as in most surgical intervention research. The natural experiments have some strength that randomized control trial does not have, the results of this study design reflects, what happens when the results of a randomized control trial are implemented[41].

Nonetheless, in the present analysis, using multicenter data of patients undergoing elective spine surgery with and without intrawound vancomycin application, at seven sites across the U.S., we demonstrated that the use of intrawound vancomycin

significantly reduced the risk of overall SSI and SSI returning return to OR. The relatively large number of patients in each treatment group allowed a robust statistical analysis to derive a meaningful difference in the risk of SSI in patients without intrawound vancomycin application.

Conclusion:-

The intrawound application of vancomycin after spine surgery decreased: i) the risk of SSI; ii) return to OR due to SSI and iii) SSI in patients previously shown to be high-risk for SSI. An increased risk of returning to OR due to SSI was found in patients in whom intrawound vancomycin was not used, higher number of operated levels and post-operative ICU stay. The application of local intrawound vancomycin is safe and has the potential to reduce health care-resource utilization.

Acknowledgement: The authors would like to acknowledge the Association for Collaborative Spine Research (ACSR) for coordinating this research.

References:

1. Awad SS. Adherence to surgical care improvement project measures and post-operative surgical site infections. *Surgical infections* 2012;13:234-7.
2. Kirkland KB, Briggs JP, Trivette SL, et al. The impact of surgical-site infections in the 1990s: attributable mortality, excess length of hospitalization, and extra costs. *Infection control and hospital epidemiology* 1999;20:725-30.
3. McGirt MJ, Godil SS. Reduction of surgical site infection in spine surgery: an opportunity for quality improvement and cost reduction. *The spine journal : official journal of the North American Spine Society* 2013;13:1030-1.
4. O'Neill KR, Smith JG, Abtahi AM, et al. Reduced surgical site infections in patients undergoing posterior spinal stabilization of traumatic injuries using vancomycin powder. *The spine journal : official journal of the North American Spine Society* 2011;11:641-6.
5. Bakhsheshian J, Dahdaleh NS, Lam SK, et al. The use of vancomycin powder in modern spine surgery: systematic review and meta-analysis of the clinical evidence. *World neurosurgery* 2015;83:816-23.
6. Glassman SD, Dimar JR, Puno RM, et al. Salvage of instrumental lumbar fusions complicated by surgical wound infection. *Spine* 1996;21:2163-9.
7. Godil SS, Parker SL, O'Neill KR, et al. Comparative effectiveness and cost-benefit analysis of local application of vancomycin powder in posterior spinal fusion for spine trauma: clinical article. *Journal of neurosurgery. Spine* 2013;19:331-5.
8. Hedequist D, Haugen A, Hresko T, et al. Failure of attempted implant retention in spinal deformity delayed surgical site infections. *Spine* 2009;34:60-4.
9. Khan NR, Thompson CJ, DeCuypere M, et al. A meta-analysis of spinal surgical site infection and vancomycin powder. *Journal of neurosurgery. Spine* 2014;21:974-83.
10. Levi AD, Dickman CA, Sonntag VK. Management of postoperative infections after spinal instrumentation. *Journal of neurosurgery* 1997;86:975-80.
11. Pahys JM, Pahys JR, Cho SK, et al. Methods to decrease postoperative infections following posterior cervical spine surgery. *The Journal of bone and joint surgery. American volume* 2013;95:549-54.

12. Tubaki VR, Rajasekaran S, Shetty AP. Effects of using intravenous antibiotic only versus local intrawound vancomycin antibiotic powder application in addition to intravenous antibiotics on postoperative infection in spine surgery in 907 patients. *Spine* 2013;38:2149-55.
13. Olsen MA, Mayfield J, Lauryssen C, et al. Risk factors for surgical site infection in spinal surgery. *Journal of neurosurgery* 2003;98:149-55.
14. Olsen MA, Nepple JJ, Riew KD, et al. Risk factors for surgical site infection following orthopaedic spinal operations. *The Journal of bone and joint surgery. American volume* 2008;90:62-9.
15. Parker MJ, Livingstone V, Clifton R, et al. Closed suction surgical wound drainage after orthopaedic surgery. *The Cochrane database of systematic reviews* 2007:Cd001825.
16. Savage JW, Anderson PA. An update on modifiable factors to reduce the risk of surgical site infections. *The Spine Journal*;13:1017-29.
17. Buchholz HW, Engelbrecht H. [Depot effects of various antibiotics mixed with Palacos resins]. *Der Chirurg; Zeitschrift fur alle Gebiete der operativen Medizen* 1970;41:511-5.
18. Bibbo C, Patel DV. The effect of demineralized bone matrix-calcium sulfate with vancomycin on calcaneal fracture healing and infection rates: a prospective study. *Foot & ankle international* 2006;27:487-93.
19. Kanj WW, Flynn JM, Spiegel DA, et al. Vancomycin prophylaxis of surgical site infection in clean orthopedic surgery. *Orthopedics* 2013;36:138-46.
20. Mohammed S, Pisimisis GT, Daram SP, et al. Impact of intraoperative administration of local vancomycin on inguinal wound complications. *Journal of vascular surgery* 2013;57:1079-83.
21. Vander Salm TJ, Okike ON, Pasque MK, et al. Reduction of sternal infection by application of topical vancomycin. *The Journal of thoracic and cardiovascular surgery* 1989;98:618-22.
22. Anderson DJ, Kaye KS. Staphylococcal surgical site infections. *Infectious disease clinics of North America* 2009;23:53-72.

23. Caroom C, Tullar JM, Benton EG, Jr., et al. Intrawound vancomycin powder reduces surgical site infections in posterior cervical fusion. *Spine* 2013;38:1183-7.
24. Emohare O, Ledonio CG, Hill BW, et al. Cost savings analysis of intrawound vancomycin powder in posterior spinal surgery. *The Spine Journal*;14:2710-5.
25. Heller A, McIff TE, Lai SM, et al. Intrawound Vancomycin Powder Decreases Staphylococcal Surgical Site Infections Following Posterior Instrumented Spinal Arthrodesis. *Journal of spinal disorders & techniques* 2013.
26. Hill BW, Emohare O, Song B, et al. The use of vancomycin powder reduces surgical reoperation in posterior instrumented and noninstrumented spinal surgery. *Acta neurochirurgica* 2014;156:749-54.
27. Molinari RW, Khera OA, Molinari WJ, 3rd. Prophylactic intraoperative powdered vancomycin and postoperative deep spinal wound infection: 1,512 consecutive surgical cases over a 6-year period. *European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society* 2012;21 Suppl 4:S476-82.
28. Strom RG, Pacione D, Kalhorn SP, et al. Lumbar laminectomy and fusion with routine local application of vancomycin powder: decreased infection rate in instrumented and non-instrumented cases. *Clinical neurology and neurosurgery* 2013;115:1766-9.
29. Sweet FA, Roh M, Sliva C. Intrawound application of vancomycin for prophylaxis in instrumented thoracolumbar fusions: efficacy, drug levels, and patient outcomes. *Spine* 2011;36:2084-8.
30. Theologis AA, Demirkiran G, Callahan M, et al. Local intrawound vancomycin powder decreases the risk of surgical site infections in complex adult deformity reconstruction: a cost analysis. *Spine* 2014;39:1875-80.
31. Martin JR, Adogwa O, Brown CR, et al. Experience with intrawound vancomycin powder for spinal deformity surgery. *Spine* 2014;39:177-84.
32. Armaghani SJ, Menge TJ, Lovejoy SA, et al. Safety of topical vancomycin for pediatric spinal deformity: nontoxic serum levels with supratherapeutic drain levels. *Spine* 2014;39:1683-7.

33. Chiang HY, Herwaldt LA, Blevins AE, et al. Effectiveness of local vancomycin powder to decrease surgical site infections: a meta-analysis. *The spine journal : official journal of the North American Spine Society* 2014;14:397-407.
34. Tomov M, Mitsunaga L, Durbin-Johnson B, et al. Reducing surgical site infection in spinal surgery with betadine irrigation and intrawound vancomycin powder. *Spine* 2015;40:491-9.
35. Ghobrial GM, Thakkar V, Andrews E, et al. Intraoperative vancomycin use in spinal surgery: single institution experience and microbial trends. *Spine* 2014;39:550-5.
36. Eder C, Schenk S, Trifinopoulos J, et al. Does intrawound application of vancomycin influence bone healing in spinal surgery? *European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society* 2015.
37. Zebala LP, Chuntarapas T, Kelly MP, et al. Intrawound vancomycin powder eradicates surgical wound contamination: an in vivo rabbit study. *The Journal of bone and joint surgery. American volume* 2014;96:46-51.
38. Strom RG, Pacione D, Kalhorn SP, et al. Decreased risk of wound infection after posterior cervical fusion with routine local application of vancomycin powder. *Spine* 2013;38:991-4.
39. Mariappan R, Manninen P, Massicotte EM, et al. Circulatory collapse after topical application of vancomycin powder during spine surgery. *Journal of neurosurgery. Spine* 2013;19:381-3.
40. Adogwa O, Parker SL, Shau DN, et al. Cost per quality-adjusted life year gained of revision neural decompression and instrumented fusion for same-level recurrent lumbar stenosis: defining the value of surgical intervention. *Journal of neurosurgery. Spine* 2012;16:135-40.
41. Craig P, Cooper C, Gunnell D, et al. Using natural experiments to evaluate population health interventions: new Medical Research Council guidance. *Journal of epidemiology and community health* 2012;66:1182-6.

Table 1 Demographic and Clinical Characteristics of Study Participants (N=2056)

Characteristic	Total	Vancomycin (N=966)	No Vancomycin (N=1090)	P Value
Demographic Characteristics				
Age in years, Mean ± SD	58.8 ± 14.8	60.5 ± 13.6	59.5 ± 13.9	.09
Sex, N (%)				
Female	1042 (50.7)	489 (50.6)	553 (50.7)	.96
Male	1014 (49.3)	477 (49.4)	537 (49.3)	
Race, N (%)				
White	1801 (87.3)	850 (88.0)	951 (87.3)	.61
Non White	255 (12.7)	116 (12.0)	139 (12.7)	
BMI Category, N (%)				
Normal	504 (24.5)	236 (24.4)	268 (24.6)	.26
Overweight	9823 (40.0)	371 (38.4)	452 (41.5)	
Obese	729 (35.5)	359 (37.2)	370 (33.9)	
Current Smoker, N (%)	504 (24.5)	228 (23.6)	276 (25.3)	.37
Diabetes, N (%)	401 (19.5)	208 (21.5)	193 (17.7)	.03
Steroid Use, N (%)	114 (5.5)	65 (6.7)	49 (4.5)	.03
Chronic Renal Insufficiency	80 (3.9)	43 (4.4)	37 (3.4)	.22
Clinical Characteristics				
Location, N (%)				
Lumbar-Sacral	1409 (68.5)	685 (70.9)	724 (6.4)	< .001
Cervical	525 (25.5)	212 (22.0)	312 (28.7)	
Thoracic	122 (5.9)	69 (7.1)	53 (4.9)	
Revision Surgery, N (%)	642 (31.2)	314 (32.5)	328 (30.1)	0.24
Instrumentation, N (%)	1628 (79.2)	755 (78.2)	873 (80.1)	0.28
Arthrodesis, N (%)	1695 (82.4)	816 (84.5)	879 (80.6)	0.02
ICU Stay, N (%)	434 (21.1)	206 (21.3)	228 (20.9)	0.82
Number of spine levels exposed	3.6 (2.8)	3.6 (2.9)	3.6 (2.7)	0.67
Length of Stay in days, Mean ± SD	5.0 ± 4.7	5.2 ± 4.4	4.9 ± 4.9	0.17

BMI = body mass index; ICU = intensive care unit

Table 2 Distribution of SSI by Site and Use of Vancomycin (N=2056)

Site	*Total SSI* *N (%)*	*Vancomycin* *N (%)*	*No Vancomycin* *N (%)*
A.	5 (2.4%)	2 (2.3%)	3 (2.4%)
B.	14 (4.3%)	4 (2.5%)	10 (6.1%)
C.	16 (3.9%)	6 (3.1%)	10 (4.7%)
D.	19 (5.0%)	1 (.5%)	18 (11.1%)
E.	14 (5.8%)	4 (4.0%)	10 (7.1%)
F.	5 (1.4%)	3 (1.7%)	2 (1.2%)
G.	4 (2.7%)	1 (2.8%)	3 (2.7%)

SSI = surgical site infection

Table 3 Prevalence of SSI by Use of Vancomycin (N=2056)

Characteristic N (%)	Total	Vancomycin (N=966)	No Vancomycin (N=1090)	P Value
Total SSI	77 (3.8%)	21 (2.2%)	56 (5.1%)	<0.001
SSI that required return to OR	49 (2.4 %)	7 (0.7%)	42 (3.9%)	<0.001
SSI that did not require return to OR	28 (1.4 %)	14 (1.5%)	14 (1.3%)	0.75

SSI = surgical site infection; OR = operating room

Table 4 Multivariable Random Effect Log-binomial Regression Model of SSI and SSI with Return to OR (N=2056)

	Total SSI		SSI OR	
	RR (95% CI)	P value	RR (95% CI)	P value
Vancomycin: No vs. Yes (ref)	2.5 (1.5, 4.1)	< 0.001	5.9 (2.6, 13.2)	< 0.001
Overweight BMI vs. Normal	0.99 (0.5, 1.8)	0.97	0.97 (0.47, 2.0)	0.95
Obese BMI vs. Normal	1.7 (0.9, 3.0)	0.08	1.2 (0.56, 2.6)	0.64
Number of levels exposed	1.1 (1.01, 1.2)	0.01	1.1 (1.0, 1.2)	0.001
ICU Stay: Yes vs. No (ref)	2.1 (1.3, 3.6)	0.005	3.3 (1.8, 6.2)	<0.001
Diabetes: Yes vs. No (ref)	0.64 (0.34, 1.2)	0.17	0.81 (0.37, 1.8)	0.60
Site Variance	*0.10 (0.09)*		*0.82 (0.37)*	

Model included a random effect to account for clustering of patients within site.

SSI = surgical site infection; OR = operating room; RR = relative risk; CI = confidence interval; ref = reference; BMI = body mass index; ICU = intensive care unit