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# Effect of powdered vancomycin on stopping surgical site wound infections in neurosurgery: A meta-analysis

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## Abstract

We performed a meta-analysis to evaluate the effect of powdered vancomycin on stopping surgical site wound infections in neurosurgery. A systematic literature search up to July 2022 was performed and 24 137 subjects with neurosurgery at the baseline of the studies; 10 496 of them were using the powdered vancomycin, and 13 641 were not using the powdered vancomycin as a control. Odds ratio (OR) with 95% confidence intervals (CIs) were calculated to assess the effect of powdered vancomycin on stopping surgical site wound infections in neurosurgery using dichotomous methods with a random or fixed-effect model. The powdered vancomycin had significantly lower surgical site wound infections after spinal surgery (OR, 0.53; 95% CI, 0.41-0.70, $P < .001$), deep surgical site wound infections after spinal surgery (OR, 0.45; 95% CI, 0.35-0.57, $P < .001$), superficial surgical site wound infections after spinal surgery (OR, 0.60; 95% CI, 0.43-0.83, $P = .002$), and surgical site wound infections after cranial surgery (OR, 0.37; 95% CI, 0.22-0.61, $P < .001$) compared to control in subjects with neurosurgery. The powdered vancomycin had significantly lower surgical site wound infections after spinal surgery, deep surgical site wound infections after spinal surgery, superficial surgical site wound infections after spinal surgery, and surgical site wound infections after cranial surgery compared to control in subjects with neurosurgery. The analysis of outcomes should be done with caution even though the low number of studies with low sample size, 3 out of the 42 studies, in the meta-analysis, and a low number of studies in certain comparisons.

**KEYWORDS**

cranial surgery, deep, powdered vancomycin, spinal surgery, superficial, surgical site wound infections

## Key Messages

- we performed a meta-analysis to evaluate the effect of powdered vancomycin on stopping surgical site wound infections in neurosurgery
- the powdered vancomycin had significantly lower surgical site wound infections after spinal surgery, deep surgical site wound infections after spinal surgery superficial surgical site wound infections after spinal surgery, and

surgical site wound infections after cranial surgery compared to control in subjects with neurosurgery
- the analysis of outcomes should be with caution even though the low number of studies with low sample size, 3 out of the 42 studies, in the meta-analysis, and a low number of studies in certain comparisons

## 1 | INTRODUCTION

After spinal surgeries, there is a 0.7% to 12% chance of developing an infection at the operative site.[1,2] Surgical site wound infection rates continue to be high despite careful patient selection, rigorous operating techniques, common skin preparation, and prompt administration of the necessary systemic antibiotics.[1-3] Surgical site wound infection increases the risk of morbidity and mortality, prolongs hospital stays, necessitates repeated hospital admissions, and raises healthcare expenses.[4,5] As a result, surgical site wound infections are a frequent clinical issue and a financial burden on society. Native skin flora that lives on the patient close to the wound exposure is what causes the majority of surgical site wound infections.[6] Gram-positive cocci, particularly *Staphylococcus aureus* and *Staphylococcus epidermidis* are the most frequent contaminants in spine and brain surgery.[7,8] The gold standard of care for surgical site wound infection prevention for many years has been the use of cefazolin and other broad-spectrum antibiotics.[9,10] Nevertheless, numerous investigations have demonstrated that methicillin resistance does not affect cephalosporins' effectiveness in preventing wound infections at surgical sites.[11] Research evaluating the impact of intrawound powdered vancomycin during spine surgery showed encouraging results. To further reduce the frequency of surgical site wound infections, surgeons have recently been interested in this unique preventative strategy.[12,13] However, there is conflicting evidence in the literature about the stated effectiveness of intrawound powdered vancomycin in avoiding surgical site wound infections.[14,15] Our goal was to clarify the genuine potential of local intrawound vancomycin powder for reducing surgical site wound infections in neurosurgery by qualitatively and statistically analysing the existing literature on its usage in spine and brain procedures.

## 2 | METHOD

### 2.1 | Study design

The current meta-analysis of included research studies regarding the epidemiology statement,[16] with a pre-established study protocol. Numerous search engines including, OVID, Embase, PubMed, and Google Scholar databases were used to collect and analyse data.

### 2.2 | Data pooling

Data was collected from randomised controlled trials, observational studies, and retrospective studies investigating the effect of powdered vancomycin on stopping surgical site wound infections in neurosurgery. Only human studies in any language were considered. Inclusion was not limited by study size. Publications excluded were review articles and commentary and studies that did not deliver a measure of an association. Figure 1 shows the whole study process. The articles were integrated into the meta-analysis when the following inclusion criteria were met:

1. The study was a prospective study, observation study, randomised controlled trial, or retrospective study.
2. The target population was subjects with neurosurgery.
3. The intervention program was based on powdered vancomycin.
4. The study included powdered vancomycin compared with control

The exclusion criteria were as follows:

1. Studies that did not determine the influences of powdered vancomycin on stopping surgical site wound infections in neurosurgery
2. Studies with subjects managed with other than the powdered vancomycin
3. Studies did not focus on the effect of comparative results.

### 2.3 | Identification

A protocol of search strategies was prepared according to the PICOS principle,[17] and we defined it as follows: P (population): subjects with neurosurgery; I (intervention/exposure): powdered vancomycin; C (comparison): powdered vancomycin compared with control; O (outcome):

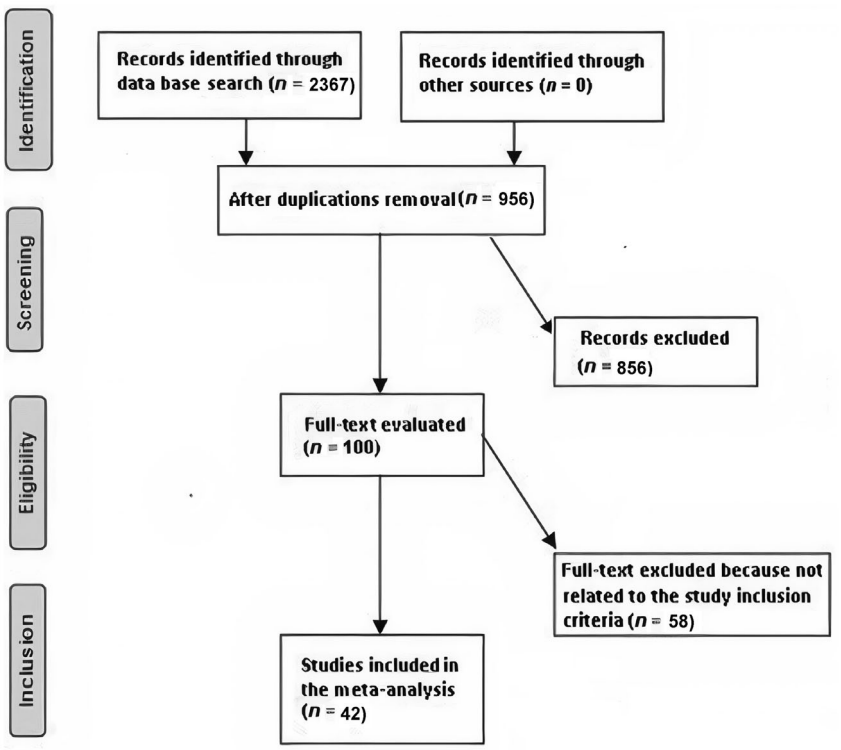


**FIGURE 1** Schematic diagram of the study procedure

**TABLE 1** Search strategy for each database

| Database | Search strategy |
|---|---|
| Pubmed | #1 'powdered vancomycin' [MeSH Terms] OR 'surgical site wound infections' [All Fields] OR 'deep and superficial' [All Fields]<br>#2 'powdered vancomycin' [All Fields] OR 'cranial surgery' [All Fields] OR 'spinal surgery' [All Fields]<br>#3 #1 AND #2 |
| Embase | 'powdered vancomycin'/exp OR 'surgical site wound infections'/exp OR 'deep and superficial'<br>#2 'cranial surgery'/exp OR 'spinal surgery'<br>#3 #1 AND #2 |
| Cochrane library | (powdered vancomycin):ti,ab,kw (surgical site wound infections):ti,ab,kw OR (deep and superficial): ti,ab,kw (Word variations have been searched)<br>#2 (cranial surgery): ti,ab,kw OR (spinal surgery): ti,ab,kw (Word variations have been searched)<br>#3 #1 AND #2 |

Surgical site wound infections after spinal surgery; deep surgical site wound infections after spinal surgery; superficial surgical site wound infections after spinal surgery, and surgical site wound infections after cranial surgery S (study design): no restriction.[18]

First, we conducted a systematic search of OVID, Embase, Cochrane Library, PubMed, and Google Scholar databases till July 2022, using a blend of keywords and similar words for powdered vancomycin, surgical site wound infections, spinal surgery, deep, superficial, and cranial surgery as shown in Table 1. All the recruited studies were compiled into an EndNote file, duplicates were removed, and the title and abstracts were checked and revised to exclude studies that have not reported an association between powdered vancomycin and control in neurosurgery subjects.

## 2.4 | Screening

Data were abridged on the following bases; study-related and subject-related characteristics in a standardised form; last name of the primary author, period of study, year of publication, country, region of the studies, and study design; population type, the total number of subjects, demographic data, clinical and treatment characteristics, categories, qualitative and quantitative method of evaluation, information source, outcome evaluation, and statistical analysis.[19] When there were different data from one study based on the assessment of the effect of powdered vancomycin on stopping surgical site wound infections in neurosurgery, we extracted them independently. The risk of bias in these studies; individual studies were evaluated using the two authors independently assessed

the methodological quality of the selected studies. The 'risk of bias tool' from the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 was used to assess methodological quality.[20] In terms of the assessment criteria, each study was rated and assigned to one of the following three risks of bias: low: if all quality criteria were met, the study was considered to have a low risk of bias; unclear: if one or more of the quality criteria were partially met or unclear, the study was considered to have a moderate risk of bias; or high: if one or more of the criteria were not met, or not included, the study was considered to have a high risk of bias. Any inconsistencies were addressed by a reevaluation of the original article.

### 2.5 | Eligibility

The main outcome focused on the assessment of the effect of powdered vancomycin on stopping surgical site wound infections in neurosurgery and an analysis of the powdered vancomycin compared with control was extracted to form a summary.

### 2.6 | Inclusion

Sensitivity analyses were limited only to studies reporting and analysing the influence of the powdered vancomycin compared with the control. Comparisons between powdered vancomycin and control were performed for subcategory and sensitivity analyses.

### 2.7 | Statistical analysis

The present meta-analysis was based on the dichotomous methods with a random- or fixed-effect model to calculate the odds ratio (OR) with a 95% confidence interval (CI). The $I^2$ index was calculated which was between 0 and 100 (%). Values of about 0%, 25%, 50%, and 75% indicated no, low, moderate, and high heterogeneity, respectively.[21] When $I^2$ was more than 50%, the random effect model was selected; while it was less than 50%, the fixed-effect model we used. A subcategory analysis was completed by stratifying the original evaluation per outcome categories as described before. A $P$-value <.05 was considered statistically significant for differences between subcategories of the current analysis. Publication bias was evaluated quantitatively using the Egger regression test (publication bias considered present if $P \geq .05$), and qualitatively, by visual examination of funnel plots of the logarithm of ORs versus their SEs.[17] All $P$-values were determined using two tailed test. The statistical analyses and graphs were presented using Reviewer Manager Version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

## 3 | RESULTS

A total of 2367 relevant studies were screened, of which 42 studies between 2011 and 2022, met the inclusion criteria and were involved in the meta-analysis.[22-63] Data obtained from these studies were shown in Table 2. The selected studies included 24 137 subjects with neurosurgery at the baseline of the studies; 10 496 of them were using the powdered vancomycin, and 13 641 were not using the powdered vancomycin as a control. The study's size ranged from 34 to 3477 subjects at the start of the study. Thirty-five studies reported data stratified to the surgical site wound infections after spinal surgery, 23 studies reported data stratified to the deep surgical site wound infections after spinal surgery, 13 studies reported data stratified to the superficial surgical site wound infections after spinal surgery, and 7 studies reported data stratified to the surgical site wound infections after cranial surgery.

The powdered vancomycin had significantly lower surgical site wound infections after spinal surgery (OR, 0.53; 95% CI, 0.41-0.70, $P < .001$) with low heterogeneity ($I^2 = 50\%$), deep surgical site wound infections after spinal surgery (OR, 0.45; 95% CI, 0.35-0.57, $P < .001$) with low heterogeneity ($I^2 = 31\%$), superficial surgical site wound infections after spinal surgery (OR, 0.60; 95% CI, 0.43-0.83, $P = .002$) with no heterogeneity ($I^2 = 1\%$), and surgical site wound infections after cranial surgery (OR, 0.37; 95% CI, 0.22-0.61, $P < .001$) with low heterogeneity ($I^2 = 35\%$) compared to control in subjects with neurosurgery as shown in Figures 2 to 5.

It was not applicable to set adjustments of individual factors such as age, gender, and ethnicity into stratified models to study their effect on the comparison results because there have been no reported data regarding these variables. Moreover, there was no evidence of publication bias ($P = .87$), according to the visual inspection of the funnel plot and quantitative measurements using the Egger regression test. However, most of the included randomised controlled trials were shown to have low methodological quality, no selective reporting bias, as well as relatively incomplete outcome data and selective reporting.

## 4 | DISCUSSION

The current meta-analysis involved 24 137 subjects with neurosurgery at the baseline of the studies; 10 496 of

**TABLE 2** Characteristics of the selected studies for the meta-analysis

| Study | Country | Total | Vancomycin | Control |
|---|---|---|---|---|
| O'Neill, 2011[22] | USA | 110 | 54 | 56 |
| Sweet, 2011[23] | USA | 1732 | 911 | 821 |
| Tubaki, 2013[24] | India | 907 | 433 | 474 |
| Caroom, 2013[25] | USA | 112 | 40 | 72 |
| Godil, 2013[26] | USA | 110 | 56 | 54 |
| Kim, 2013[27] | Korea | 74 | 34 | 40 |
| Strom 1, 2013[28] | USA | 253 | 156 | 97 |
| Strom 2, 2013[29] | USA | 171 | 79 | 92 |
| Martin, 2014[30] | USA | 306 | 156 | 150 |
| Emohare, 2014[31] | USA | 303 | 96 | 207 |
| Hill, 2014[32] | USA | 300 | 150 | 150 |
| Theologis, 2014[33] | USA | 215 | 151 | 64 |
| Suh, 2015[34] | Korea | 86 | 43 | 43 |
| Heller, 2015[35] | USA | 683 | 342 | 341 |
| Liu, 2015[36] | USA | 334 | 180 | 154 |
| Martin, 2015[37] | USA | 289 | 115 | 174 |
| Schroeder, 2016[38] | USA | 3477 | 1224 | 2253 |
| Gaviola, 2016[39] | USA | 326 | 116 | 210 |
| Lee, 2016[40] | Korea | 571 | 275 | 296 |
| Abdullah, 2016[41] | USA | 150 | 75 | 75 |
| González Ross, 2016[42] | Mexico | 210 | 70 | 140 |
| Hey, 2017[43] | Singapore | 389 | 117 | 272 |
| Van Hal, 2017[44] | USA | 1148 | 496 | 652 |
| Chotai, 2017[45] | USA | 2802 | 1215 | 1587 |
| Ravikumar, 2017[46] | USA | 350 | 125 | 225 |
| Hida, 2017[47] | Japan | 174 | 81 | 93 |
| Abode-Iyamah 1, 2018[48] | USA | 258 | 92 | 166 |
| Abode-Iyamah 2, 2018[49] | USA | 245 | 121 | 124 |
| Mallela, 2018[50] | USA | 355 | 205 | 150 |
| Kochanski, 2018[51] | USA | 419 | 260 | 159 |
| Kunakornsawat, 2019[52] | Thailand | 400 | 266 | 134 |
| Lemans, 2019[53] | Netherlands | 636 | 379 | 257 |
| Haller, 2019[54] | USA | 1287 | 252 | 1035 |
| Adhikari, 2020[55] | Turkey | 158 | 88 | 70 |
| Yatimparvar, 2020[56] | Iran | 200 | 100 | 100 |
| Qadir, 2021[57] | USA | 583 | 35 | 548 |
| Ushirozako, 2021[58] | Japan | 1261 | 623 | 638 |
| Schär, 2021[59] | Switzerland | 34 | 17 | 17 |
| Vakayil, 2021[60] | USA | 997 | 473 | 524 |
| Tafish, 2021[61] | Saudi Arabia | 456 | 81 | 375 |
| Salimi, 2022[62] | Germany | 375 | 187 | 188 |
| Wang, 2022[63] | China | 891 | 527 | 364 |
| | Total | 24 137 | 10 496 | 13 641 |

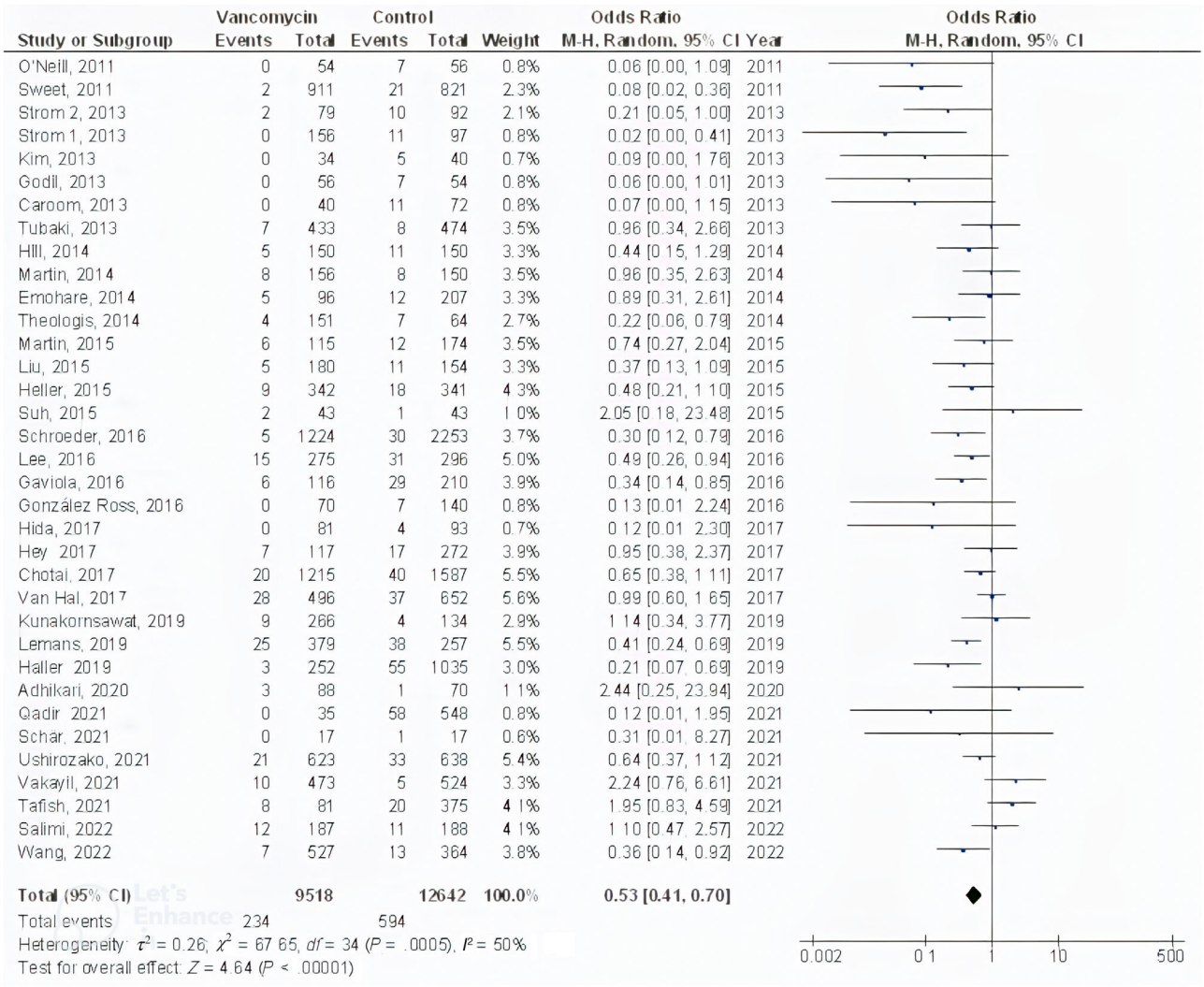


**FIGURE 2** Forest plot of the effect of vancomycin compared with control on the incidence of the surgical site wound infections after spinal surgery outcomes in subjects with neurosurgery

them were using the powdered vancomycin, and 13 641 were not using the powdered vancomycin as a control.[22-63] The powdered vancomycin had significantly lower surgical site wound infections after spinal surgery, deep surgical site wound infections after spinal surgery, superficial surgical site wound infections after spinal surgery, and surgical site wound infections after cranial surgery compared to control in subjects with neurosurgery. The analysis of outcomes should be done with caution even though the low number of studies with a low sample size, 3 out of the 42 studies, in the meta-analysis, and a low number of studies in certain comparisons.

Our findings on overall, deep, and superficial incisional surgical site wound infections following spine and cranial surgery are consistent with earlier meta-analyses on the subject, even though this meta-analysis had a patient sample that was almost five times larger.[14,15] The subfascial tissues and/or the spinal implant were both included in the definition of deep surgical site wound infections in the included studies.[32,45] Surgical debridement, intravenous antibiotics, and possibly implant removal are part of their treatment.[26,27] It is important to recognise the benefit of powdered vancomycin in this situation because deep surgical site wound infections are a significant contributor to prolonged hospital stays, repeated hospital admissions, and increased morbidity and death.[4,6] In contrast to deep surgical site wound infections, superficial surgical site wound infections have a milder clinical history. Until swab culture and antibiogram findings are obtained, superficial surgical site wound infections are typically managed with local wound care and broad-spectrum oral antibiotic treatment.[27,32] Importantly, inadvertent durotomy in cranial and spinal operations, as well as a cerebrospinal fluid leak, were relative contraindications to the use of powdered vancomycin. According to research by the National

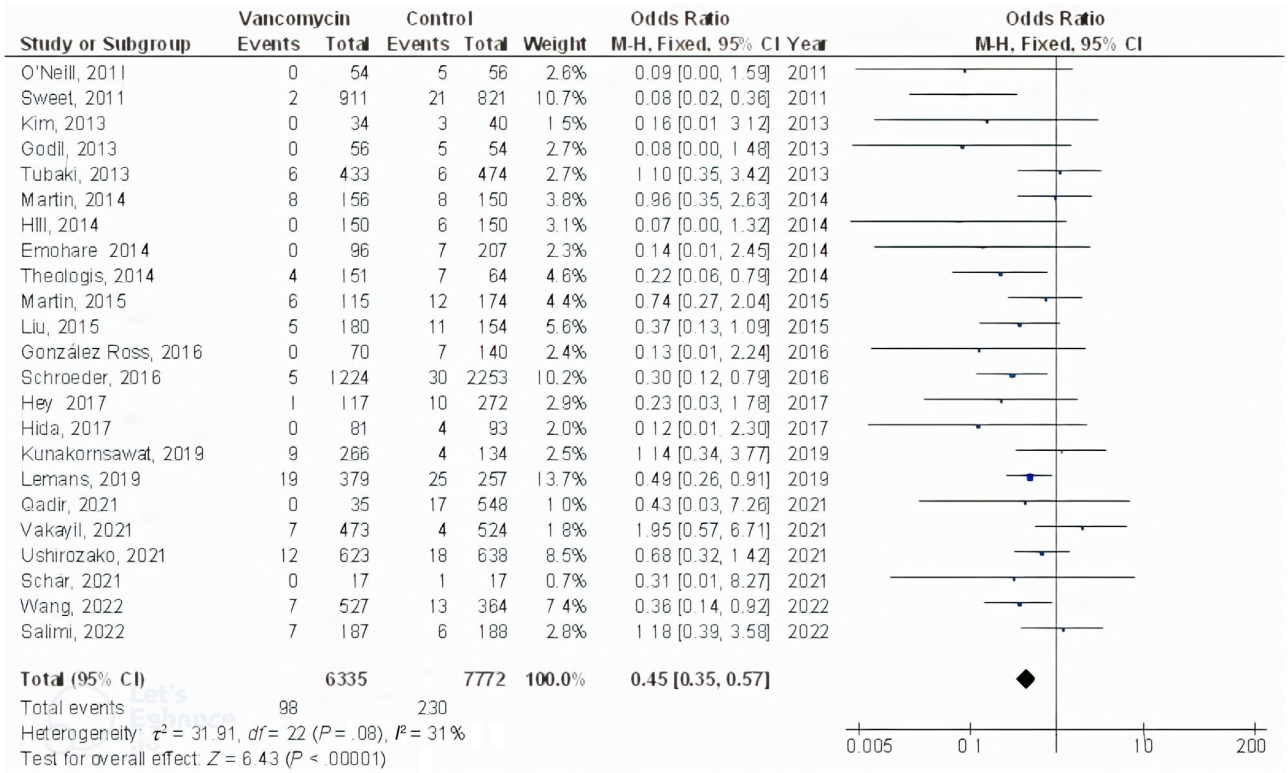


**FIGURE 3** Forest plot of the effect of vancomycin compared with control on the incidence of the deep surgical site wound infections after spinal surgery outcomes in subjects with neurosurgery

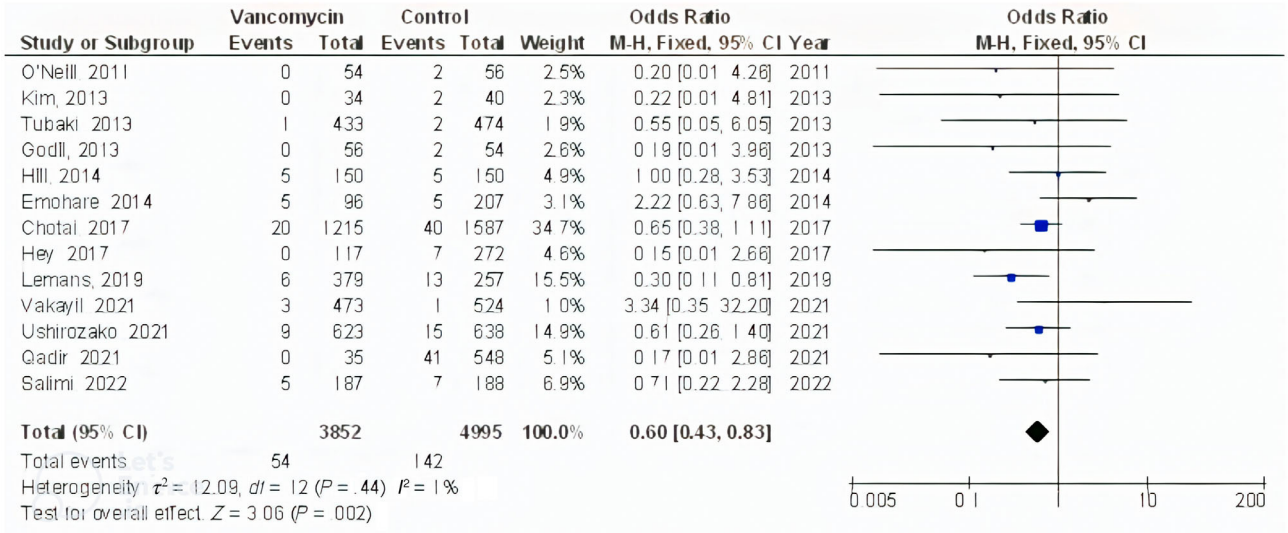


**FIGURE 4** Forest plot of the effect of vancomycin compared with control on the incidence of the superficial surgical site wound infections after spinal surgery outcomes in subjects with neurosurgery

Surgical Quality Improvement Program, surgical site wound infections happened to 2% of patients.[64] After a brain operation, several wound infections, including meningitis, epidural abscess, subdural empyema, brain abscess, and bone flap osteomyelitis, may manifest.[65] Numerous studies have demonstrated vancomycin's beneficial impact on healthcare expenses in addition to the reduction in surgical site wound infections following spine procedures. Even more so than catheter-associated urinary tract infections and central-line infections, surgical site wound infections are the most frequent hospital-acquired illnesses.[66] A single surgical site wound infection

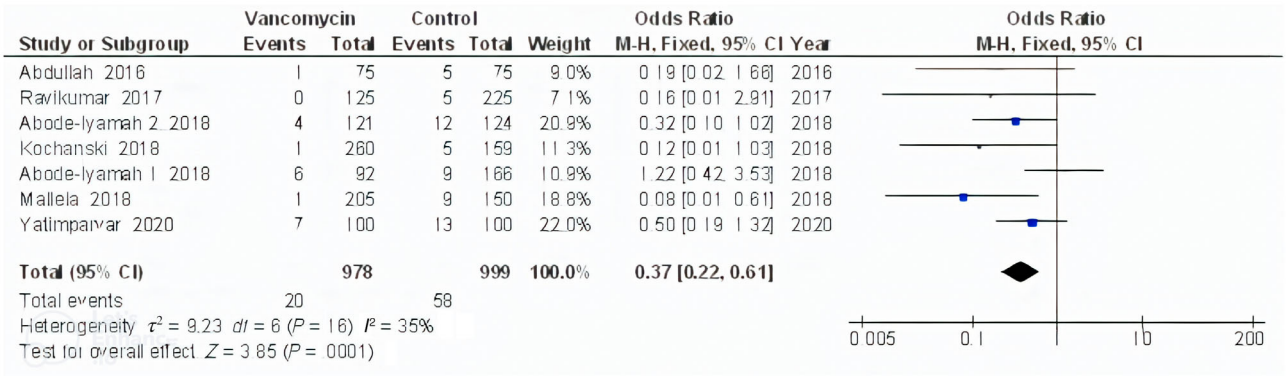


**FIGURE 5** Forest plot of the effect of vancomycin compared with control on the incidence of the surgical site wound infections after cranial surgery outcomes in subjects with neurosurgery

is thought to cost between $20 000 and $100 000 to treat.[4,26,45] According to Godil et al cost-benefits study, using vancomycin powder prevented 100 posterior spinal fusions from occurring, saving $433 765 USD. Another study that found savings of $244 402 USD for every 100 difficult spinal operations showed a similar pattern.[26] Vancomycin use was associated with a decrease in healthcare costs, though to a smaller amount when compared to spinal procedures, in one of the three studies on cranial surgeries that were included.[37] After spinal and cranial surgery, the development of surgical site wound infection has been demonstrated to be significantly related to several risk factors. Age, being a man, having previously had a wound infection, and the length of the surgery were all related to an elevated risk for surgical site wound infections, according to the analysis of 12 021 craniotomies for brain neoplasms done using the National Surgical Quality Improvement Program database.[64] Based on multivariate analysis, Lee et al demonstrated that deep surgical site wound infections following posterior lumbar surgery were significantly predicted by diabetes mellitus, length of hospital stay, and the number of spinal instrumented levels.[40] There are several known risk factors for surgical site wound infection following spinal surgery, including a higher body mass index >30, smoking, a preoperative steroid medication, posterior spinal fusion, poor nutritional status (preoperative albumin 3.5 mg/dL), postoperative radiation, and surgery length >3 hours.[67,68] It's also important to note that numerous researchers have looked into how local vancomycin affects human cells. In a human osteoblast culture, Eder et al showed that 3 mg/cm$^2$ of local vancomycin was sufficient to considerably impede cellular migration and proliferation, whereas 6 mg/cm$^2$ resulted in cellular death.[69] Another experimental in-vitro investigation also showed that local vancomycin, in a dose-dependent way, inhibits the growth of human dural fibroblasts and even results in cellular necrosis.[70] Therefore, it is probable that powdered vancomycin can impede the natural healing process, especially if the procedure involves a planned or inadvertent durotomy.[24,70] To determine a safe intrawound vancomycin bactericidal dose that would not interfere with normal dural healing, more in-vivo research is required. To shed light on the ideal application of powder vancomycin in neurosurgery, randomised studies particularly created for high-risk surgical site wound infection groups as well as the general population are required. The clinical heterogeneity that faces the current evidence on this subject has a variety of possible confounders. Inter-surgeon variations may affect ingrained practice patterns that could put patients at more risk for infection. Additionally, the type of neurosurgical intervention and related adjuncts may impact the exposure risk; for instance, extra implants or inserts used in instrumented spine surgery may need to be thoroughly sterilised. The easiest way to combat selection bias in reporting studies is to increase cohort size and stratify according to operation method. The impact of operation duration and the presence of comorbidities like diabetes, which was examined in this study, and chronic steroid-managed conditions on infection risk, will soon be the subject of research. To further strengthen the trust in vancomycin's involvement in neurosurgery; future research should make an effort to incorporate open-book controls of the aforementioned parameters.

This meta-analysis showed the influence of powdered vancomycin on stopping surgical site wound infections in neurosurgery.[71-78] However, further studies are still needed to illustrate these potential relationships as well as to compare the effect of powdered vancomycin compared with control on the outcomes studied. These studies must comprise larger more homogeneous samples. This was suggested also in a previous similar meta-analyses study which showed similar promising outcomes for improving intraoperative complications and reducing surgical site

wound infections after neurosurgery.[12,13,79-82] Well-conducted randomised controlled trials are needed to assess these factors and the combination of different ages, gender, ethnicity, and other variants of subjects; since our meta-analysis study could not answer whether different gender, ages, and ethnicity are related to the results.

In summary, the powdered vancomycin had significantly lower surgical site wound infections after spinal surgery, deep surgical site wound infections after spinal surgery, superficial surgical site wound infections after spinal surgery, and surgical site wound infections after cranial surgery compared to control in subjects with neurosurgery.

### 4.1 | Limitations

There may be selection bias in this study since so many of the studies found were excluded from the meta-analysis. However, the studies excluded did not satisfy the inclusion criteria of our meta-analysis. The sample size of 3 out of the 42 studies selected was ≤100. Also, we could not answer whether the results are related to age, gender, and ethnicity or not. The study designed to assess the effect of powdered vancomycin on stopping surgical site wound infections in neurosurgery was based on data from previous studies, which might cause bias induced by incomplete details. Possible bias-inducing factors were the variables including age, sex, and the nutritional status of subjects. Unfortunately, there might be some unpublished articles and missing data which might lead to bias in the studied effect.

## 5 | CONCLUSIONS

The powdered vancomycin had significantly lower surgical site wound infections after spinal surgery, deep surgical site wound infections after spinal surgery, superficial surgical site wound infections after spinal surgery, and surgical site wound infections after cranial surgery compared to control in subjects with neurosurgery. The analysis of outcomes should be done with caution even though the low number of studies with low sample size, 3 out of the 42 studies, in the meta-analysis, and a low number of studies in certain comparisons.

### CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

### DATA AVAILABILITY STATEMENT

The datasets analyzed during the current meta-analysis are available from the corresponding author via reasonable request.

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