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Research Article

Systematic Review, Meta-Analysis and Grading of Evidence on the Effectiveness of Antimicrobial Prophylaxis for Neurosurgical Site Infections

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Background: Antimicrobial prophylaxis is crucial for neurosurgical procedures, even though they are clean procedures. Observational studies have shown the effectiveness of different antibiotics in preventing neurosurgical site infections, but there remains paucity of systematic reviews and meta-analyses which have assessed their effectiveness in East Africa.

Objectives: To generate and appraise the quality of evidence that would inform antimicrobial prophylaxis in neurosurgery.

Methodology: A systematic review and meta-analysis was conducted between October 2014 and December 2015. Studies that involved the administration of systemic antibiotics for prophylaxis, use of antibiotic impregnated shunt catheters among adult patients aged over 18 years were included and subjected to abstract, title and full text screening. A meta-analysis was carried out using RevMan (Review Manager) version 5 software. The quality of evidence was evaluated using the GRADE system.

Results: One systematic review of randomized controlled trials (n=17) and 11 randomised controlled trials were included in the study. From the first meta-analysis, use of systemic antibiotics demonstrated an overall protective effect of 52% from development of surgical site infections [OR 0.48 (95% CI 0.30, 0.79)]. In the second meta-analysis, the use of antibiotic impregnated shunt catheters was associated with a higher risk of mortality compared to use of the standard shunt [(OR 1.47(95% CI 0.82, 2.62)]. Following evaluation of quality of evidence, in the antibiotics versus placebo arm, the quality of evidence was moderate, while that for antimicrobial impregnated shunts was very low.

Conclusion: Antimicrobial prophylaxis using systemic antibiotics or antimicrobial impregnated shunts is effective in preventing neurosurgical site infections. Antimicrobial impregnated shunts are too expensive for our study population.

Key words: systematic review, meta-analysis, antimicrobial prophylaxis

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1. Introduction

Surgical site infections are infections that occur after surgical procedures at and around the incision site or at distant sites. Neurosurgical procedures involve the surgical management of conditions that affect the brain, spinal cord, peripheral nerves and their surrounding tissues as well as vascular conditions of the head and neck (Chiang et al, 2014). They have a low rate of surgical site infections because they are not associated with entry into potentially contaminated fields like gastrointestinal and genitourinary tracts. However, when infections occur, they lead to high morbidity and mortality (Walcott et al, 2012).

Antimicrobial prophylaxis, in which antibiotics are given during the peri-operative period to prevent these infections, has been shown to reduce their incidence (Chiang et al, 2014). Systemic antimicrobial prophylaxis, in which antibiotics are given intravenously, intramuscularly or orally has commonly been used. In the early 2000s, antimicrobial impregnated shunts and catheters (AICs) were introduced and are commonly used, particularly in developed countries. They include ventriculo-peritoneal shunts and ventriculo-atrial shunts, which are used to drain excess cerebrospinal fluid in patients with hydrocephalous, from the ventricles of the brain to other parts of the body like the peritoneum or atrium for excretion. When impregnated with antibiotics, they have been shown to reduce the incidence of neurosurgical site infections (Ratilal, 2008).

Many studies have explored the use of systemic antibiotics and antimicrobial impregnated shunts and catheters (AICs) for prophylaxis in neurosurgery, and demonstrated differences in effectiveness, with some in favour of AICs and others reporting no difference in effectiveness (Ratilal, 2008). There is a paucity of randomised controlled trials and systematic reviews on this from developing countries. The main objective of this systematic review was to generate and appraise the quality of evidence that would inform antimicrobial prophylaxis in neurosurgery at Kenyatta National Hospital and other hospitals performing neurosurgery in low income countries.

2. Materials and Methods

2.1 Selection of Studies, PICO and Search Strategy

A systematic review and meta-analysis was conducted between October 2014 and December 2015. The research question, which incorporates the Population, Intervention, Comparison and Outcome (PICO) aspects was formulated. The population (P) of interest was "adult neurosurgical patients", while the intervention (I) was antimicrobial prophylaxis. The comparator /control (C) was "no antimicrobial prophylaxis or placebo" while the outcomes of interest (O) were all-cause mortality, development of neurosurgical site and non-surgical site infections, shunt revision and adverse effects of antibiotics. Antimicrobial prophylaxis was defined as the use of systemic antibiotics or antibiotic impregnated shunt catheters for the prevention of neurosurgical site infections. The search was done between October 2014 and December 2014.

All-cause mortality was defined as death from any cause during the course of treatment. Surgical site infections were defined as infections occurring at and around the surgical site according to the CDC classification (Mangram et al, 1999). Non-surgical site infections were defined as any other infections at distant sites, not directly related to the surgery. Shunt revision was defined as the removal or replacement of a shunt through a subsequent surgical procedure, due to development of surgical site infection (Zabramski, 2003). Adverse effects of antibiotics were defined as any untoward effects on the patient arising from use of antimicrobials (Goodman and Gillman, 2016).

The PICO question formulated was **"For adult neurosurgical patients, does antimicrobial prophylaxis compared to no antimicrobial prophylaxis, reduce the risk of development of surgical site infections?"**

The following search strategy was formulated using Medical Subject Headings (MeSH) terms and was then entered into the search databases. **"(Effectiveness OR Efficacy) AND (antibiotics OR antimicrobials OR antiinfectives) AND (Prophylaxis OR Prevention) AND (infection control) AND (neurosurgical OR neurosurgery OR neurosurgical site infections)".**

2.2 Inclusion and Exclusion Criteria for the Studies

We sought to include systematic reviews and randomised controlled trials which addressed the population, interventions, comparators and outcomes of interest. Specifically, we sought to include studies that evaluated our patient population of interest (patients over 18 years old, undergoing neurosurgical procedures, including spinal instrumentation surgery), interventions of interest (administration of systemic antibiotics for antimicrobial prophylaxis versus no antibiotics or placebo, or the use of antibiotic impregnated shunts, catheters and drains versus standard shunts), and our outcomes of interest (all-cause mortality, development of surgical site and non-surgical site infections as well as adverse effects of antibiotics). Studies that involved paediatric patients, those that compared two different antibiotics and studies involving local irrigation of wounds using antiseptics were excluded. Studies which were not in English and could not be translated were also excluded from the review. We also excluded studies that were not either systematic reviews or randomised controlled trials. No restrictions on publication date were set.

2.3 The Search

Two investigators carried out the search and study selection independently and sorted the differences by discussion and consensus building. Separate searches were done for systematic reviews and for randomized controlled trials (RCTs). For the Systematic Reviews, the search strategy was entered into MEDLINE and the Cochrane Database of Systematic Reviews (CDSR). The search was filtered as "Reviews". This yielded 16 systematic reviews. The same was repeated for the randomised controlled trials, with the search being filtered for "randomised controlled trials" into the MEDLINE database and the Cochrane Central Register for Controlled Trials (CENTRAL). This yielded 31 results.

2.4 Screening, Full Text Analysis and Data Abstraction

Title and abstract screening and full text analysis was done to select the eligible studies as illustrated in **Figure 1**.

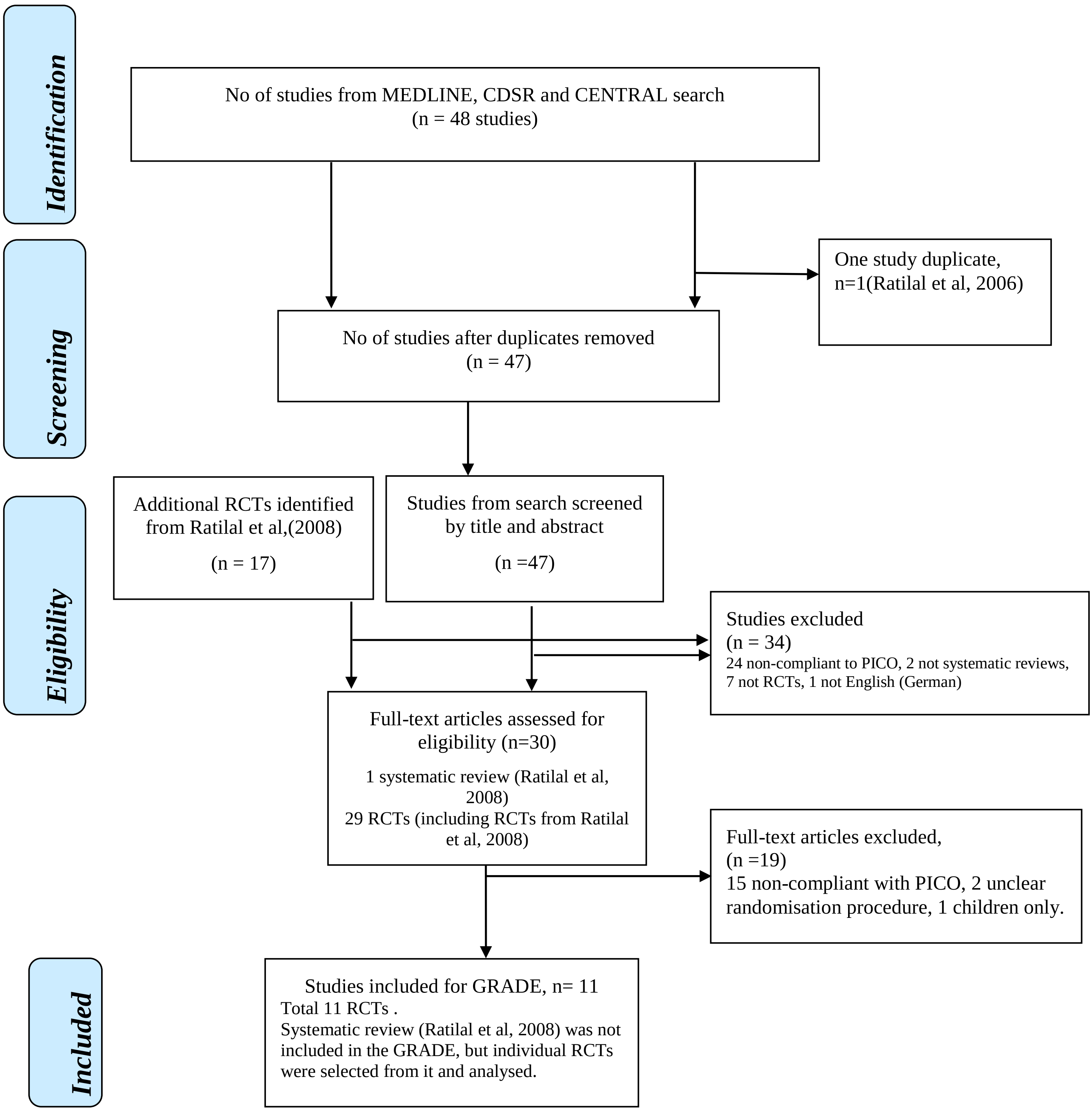

Figure 1: PRISMA Flow Diagram for the Included Studies

2.5 Evaluation of the Quality of Evidence

Two meta-analyses were performed, based on the interventions. The first intervention considered was antibiotics versus placebo; the second intervention focused on antibiotic impregnated shunt catheters versus standard shunts.

The quality of evidence was evaluated using GRADE.

3. Results

META-ANALYSIS 1: Antibiotics versus Placebo/ No Antibiotics

Development of Surgical Site Infections

From this meta-analysis, use of systemic antibiotics demonstrated an overall protective effect of 52% from development of surgical site infections [OR 0.48 (95%

CI 0.30, 0.79)]. 48 out of 100 patients are more likely to develop surgical site infections if they are not on antimicrobial prophylaxis. In six studies, use of antimicrobial prophylaxis demonstrated a protective effect (Blomstedt 1985, n=174; Bullock 1988, n=417; Djindjian 1990, n=356; Petignat 2008, n=1,237; Young 1987, n=846; and Zentner 1995, n=129). There was low observed heterogeneity across the studies as the I^2 statistic was 19%. Generally, an I^2 statistic of above 40% indicates significant heterogeneity across studies (Schunemann et al, 2013) (**Figure 2**).

Non-Surgical Site Infections (NSSIs)

Two studies, (Djindjian 1990 and Petignat 2008), which used systemic antibiotics versus no antibiotics, evaluated patients for development of non-surgical site infections. A total of 784 patients were on antibiotics while 809 patients were on no antibiotic or placebo. The average effect size of the studies for this outcome was about 1 [OR 1.04 (95% CI 0.60, 1.82)]. However, there's a slight leaning of the studies towards placebo, or no antibiotics, but this is not significant. Overall, there was no difference in development of NSSIs between patients who were on antibiotics or those who were on placebo. This means that development of non-surgical site infections is not prevented by antimicrobial prophylaxis. The I^2 statistic is zero, which suggests no heterogeneity between the effect sizes of the two studies (**Figure 3**).

There were no events reported for the following outcomes: all-cause mortality, Shunt Revision and adverse effects of antibiotics.

Grading of Evidence for Systemic Antibiotics versus No Antibiotics/Placebo

GRADE Pro GDT version 2015 software was used to evaluate the quality of evidence. The 8 RCTs were assessed for study design, risk of bias, inconsistency, indirectness and imprecision. The outcome measures were rated as critical or important depending on the impact to patients. Overall, the evidence for antimicrobial prophylaxis was of moderate quality (**Table 1**).

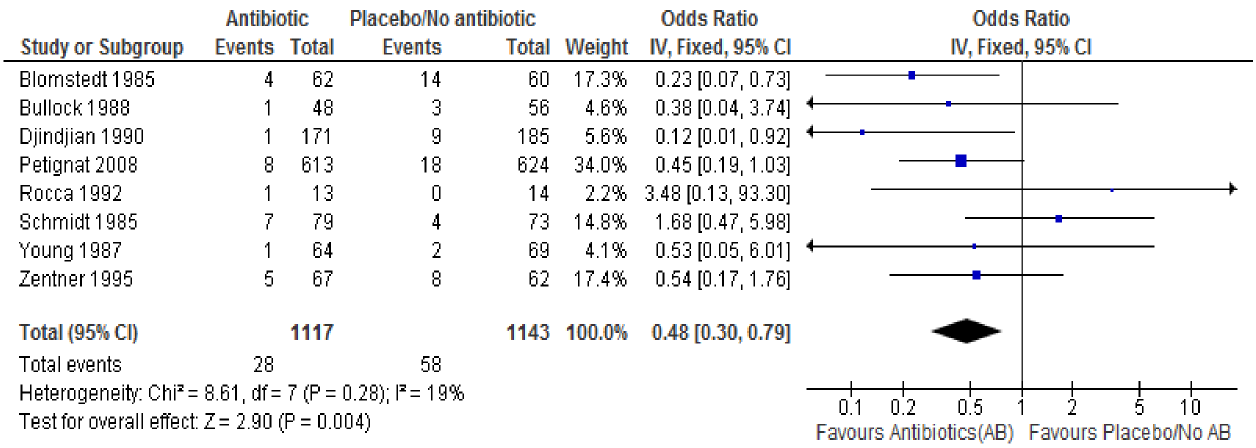

Figure 2: Forest Plot for Surgical Site Infections

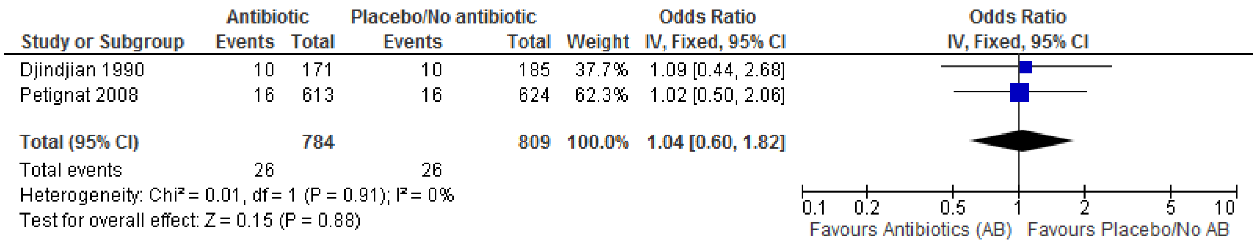

Figure 3: Forest Plot for Non-Surgical Site Infections

Table 1: GRADE Summary of Findings for Antimicrobial Prophylaxis versus Placebo

Antimicrobial prophylaxis compared to placebo or no antimicrobial prophylaxis for prevention of neurosurgical site infections

Patient or population adult neurosurgical patients

Setting low and middle income countries

Intervention antimicrobial prophylaxis

Comparison placebo or no antimicrobial prophylaxis

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Importance
	Risk with placebo or no antimicrobial prophylaxis	**Risk with antimicrobial prophylaxis**				
Development of surgical site infections (SSIs) assessed with wound infection, positive cultures, CDC classification, Malis Criteria, fever, leukocytosis, clinical signs follow up range 1 weeks to 1 years	**Study population**		**OR 0.48** (0.30 to 0.79)	2260 (8 RCTs)	⊕⊕⊕◯ MODERATE [1]	CRITICAL
	51 per 1000	**25 per 1000** (16 to 41)				
Development of non-surgical site infections (NSSIs) assessed with pneumonia, UTIs follow up range 1 weeks to 6 months	**Study population**		**OR 1.04** (0.60 to 1.82)	1593 (2 RCTs)	⊕⊕⊕◯ MODERATE [1]	CRITICAL
	32 per 1000	**33 per 1000** (20 to 57)				
Development of adverse effects of antibiotics (A/Es) assessed with Clinical signs follow up mean 6 months	**Study population**		not estimable	1366 (2 RCTs)	⊕⊕⊕◯ MODERATE [1]	IMPORTANT
	0 per 1000	**0 per 1000** (0 to 0)				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI Confidence interval; **RR** Risk ratio; **OR** Odds ratio;

GRADE Working Group grades of evidence
High quality We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality We are moderately confident in the effect estimate The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality Our confidence in the effect estimate is limited The true effect may be substantially different from the estimate of the effect
Very low quality We have very little confidence in the effect estimate The true effect is likely to be substantially different from the estimate of effect

1. unclear allocation concealment, random sequence allocation, blinding, incomplete outcome data, selective reporting for all studies

Development of Surgical Site Infections

A total of 2,260 patients were included in all the 8 studies evaluated this outcome. Patients who were on antimicrobial prophylaxis were less likely to develop surgical site infections compared to those who were on placebo or no antibiotic. 28 out of 1117 patients on antimicrobial prophylaxis developed infection while 58 out of 1143 of those without prophylaxis developed infection [OR 0.48 (95% CI 0.30. 0.79)]. The overall quality of evidence for this critical outcome was moderate.

Risk of Bias

There was a high risk of bias in the included studies as illustrated in **Figure 4.**

Indirectness

There was no indirectness with regard to population. All the studies that were included had patients with characteristics that match our patient population. It should however be noted that most of the studies were carried out in high income countries. Race and ethnicity could influence the pharmacokinetic, pharmacodynamic profiles and effectiveness of the antibiotics.

Adult patients undergoing neurosurgical procedures were given antibiotics for prophylaxis systemically. The antibiotics administered are available in our settings. Indirectness due to intervention does not therefore arise. The criteria used to evaluate this outcome measure in the systematic review are similar to the methods used in evaluating such outcomes in our study setting.

Imprecision

We applied the optimal information size (OIS) rule (Schunemann et al; 2013) to test for imprecision across this outcome and it was not noted. Additionally, the confidence interval for the estimate of effect is narrow and does not include 1. The events on the control arm are twice as many as the events in the treatment arm.

Inconsistency

Using the eye ball test, the confidence intervals were found to be overlapping. The Chi squared test yielded a p value of 0.28, which is greater than 0.05, which implies low heterogeneity across studies. The I^2 statistic was 19%, (<40%), which implies homogeneity across included studies (Schunemann et al; 2013).

Publication Bias

A comprehensive search was carried out in the accessed databases for these studies to minimise publication bias. The studies obtained were too few to generate a funnel plot, so publication bias could not be detected.

Development of Non-Surgical Site Infections

Two trials, (Djindjian 1990; and Petignat et al, 2008) considered this as a secondary outcome. Non- surgical site infections were defined as a diagnosis of pneumonia, urinary tract infections and sepsis. A meta-analysis gave the estimate of effect for this outcome as shown in **Figure 3**. The five GRADE criteria were used to evaluate the quality of evidence for this outcome.

Risk of Bias

The risk of bias for these two studies is summarized in **Figure 5**.

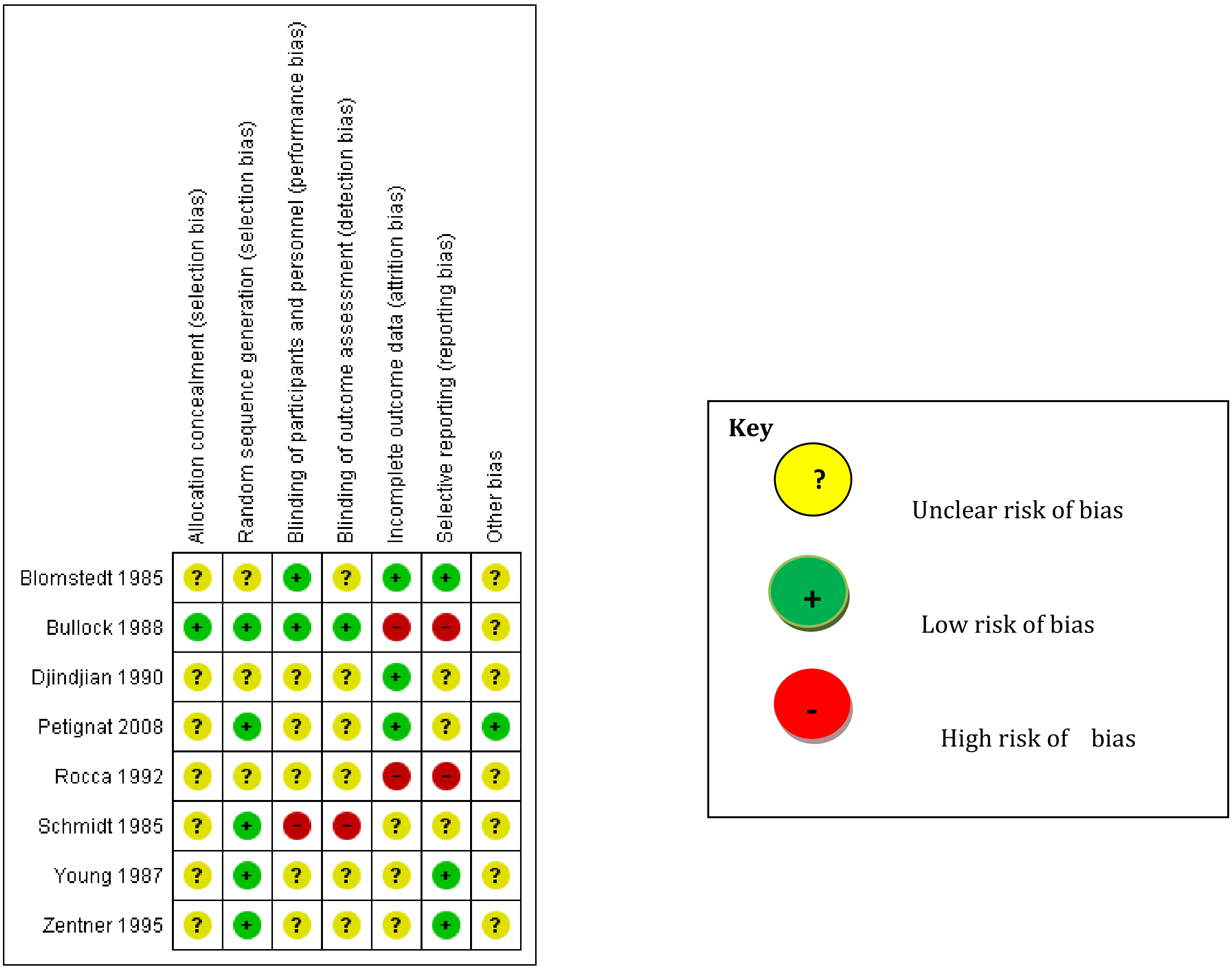

Figure 4: Risk of Bias Summary Review Authors' Judgments about Each Risk of Bias Item for Each Included Study.

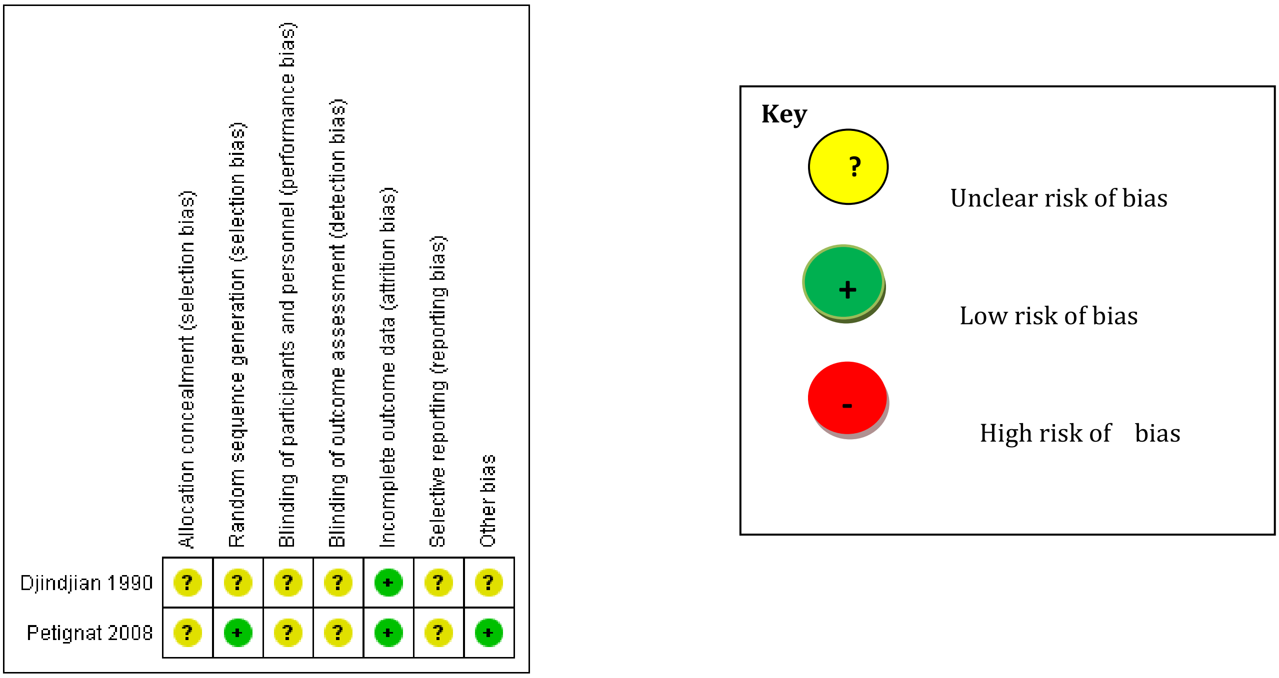

Figure 5: Risk of Bias Summary Review: Authors' Judgments about Each Risk of Bias Item for Each Included Study.

Indirectness

There was no significant indirectness with regard to population, interventions, their applicability and outcome measures to warrant downgrading the evidence for this outcome to moderate quality.

Inconsistency

The eyeball test shows overlapping confidence intervals. The p value from the Chi square test is 0.91, while the I^2 statistic for all studies form the meta-analysis was 0% less than 40%, which showed minimal heterogeneity as shown in **Figure 3.** There was therefore no inconsistency.

Imprecision

There was a wide confidence interval which included 1. The total number of events in the included studies was few. On applying the OIS rule, imprecision was detected.

Publication bias

This could not be detected because the studies generated from a comprehensive search were too few to generate a funnel plot.

Development of Adverse Effects of Antibiotics

From the meta-analysis, there were no events reported, although 2 studies (Petignat et al; 2008 and Zentner, 1995) assessed the outcome. The estimate of effect for this outcome could therefore not be obtained. High risk of bias warranted the downgrading of the quality of evidence to moderate. Since there were no events and confidence intervals, it was not possible to assess imprecision. Inconsistency of results was not detected, neither was publication bias.

META-ANALYSIS 2 Antimicrobial Impregnated Shunt Catheters versus Standard Shunts

In a second meta- analysis, the use of antibiotic impregnated shunt catheters (AICs) versus use of standard shunts was evaluated. Two studies (Govender 2003 and Zabramski 2003), were included in the meta-analysis and evaluated two outcomes: all -cause mortality and surgical site infections (**Figure 6**).

The use of antibiotic impregnated shunt catheters was associated with a higher risk of mortality compared to the use of the standard shunt [(OR 1.47(95% CI 0.82, 2.62)]. This is corroborated in the individual studies; Govender 2003 [(OR 2.11 (95% CI 0.48, 9.31)], where patients with AICs were twice as likely to die compared to those with standard shunts and Zabramski 2003 [(OR 1.38 (95% CI 0.74, 2.58)], where patients with AICs were 1.4 times more likely to die than those with standard shunts.

Risk of Bias

Govender 2003 and Zabramski 2003 had a high risk of bias as illustrated in **Figure 7.** This warranted downgrading of the evidence to moderate quality.

Indirectness

There was indirectness with respect to intervention. Antimicrobial impregnated shunts are not commonly used in our setting because they are too expensive. One

AIC costs approximately Ksh. 40,000 (US Dollars 400), which is beyond the reach of the patients who are treated at Kenyatta National Hospital. This warranted the downgrading the level of evidence from moderate to low quality.

Inconsistency

The eyeball test on the forest plot revealed overlapping confidence intervals. The p value from the Chi square test was 0.39, and the I^2 statistic was zero, hence no inconsistency for this outcome.

Imprecision

There was Imprecision because the included studies did not comply with the OIS rule. There were also wide confidence intervals. This led to the downgrading of evidence from low quality to very low quality evidence.

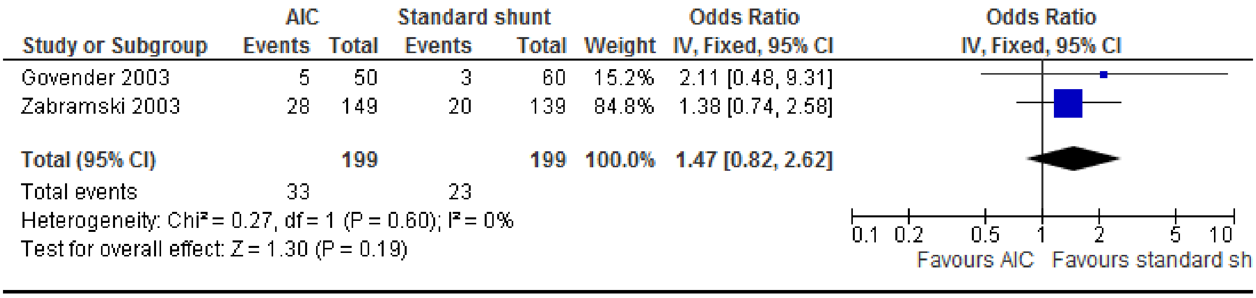

Figure 6: All-cause Mortality

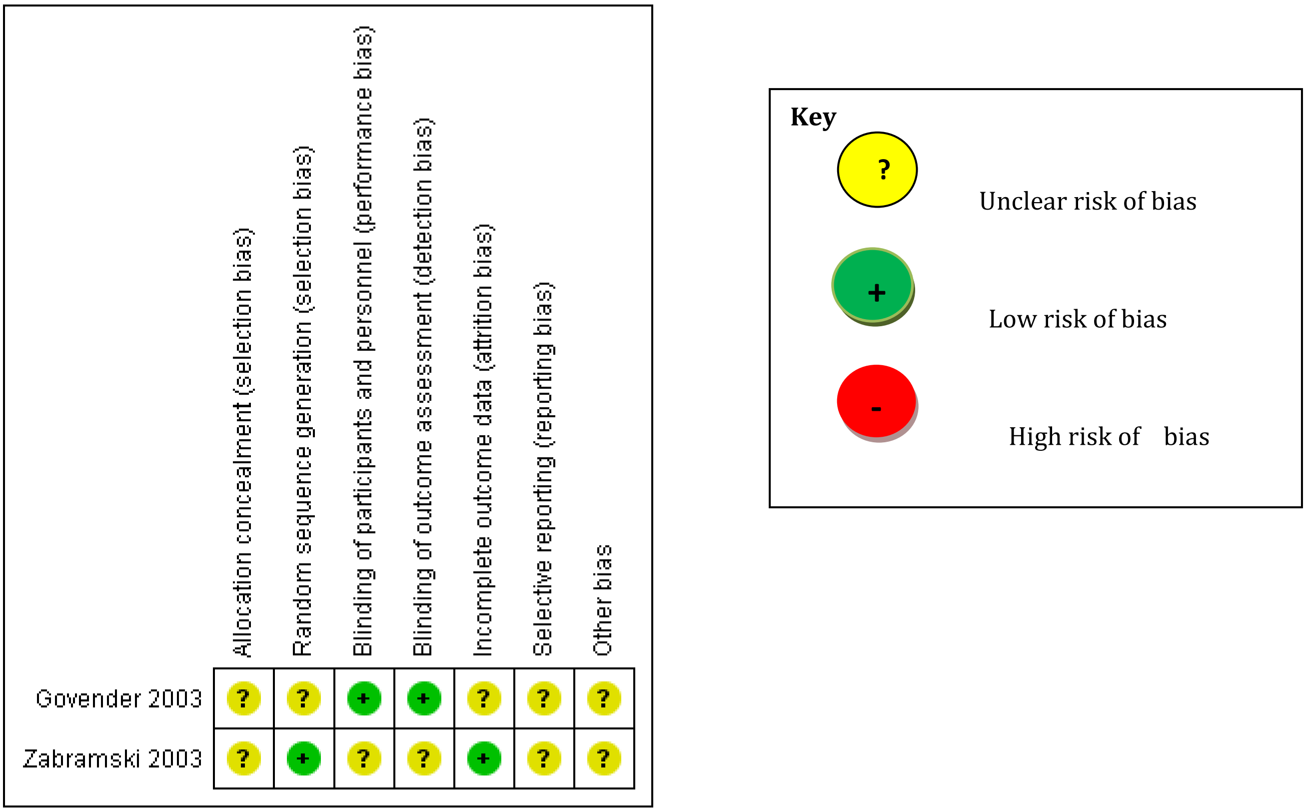

Figure 7: Risk of Bias for All-cause Mortality

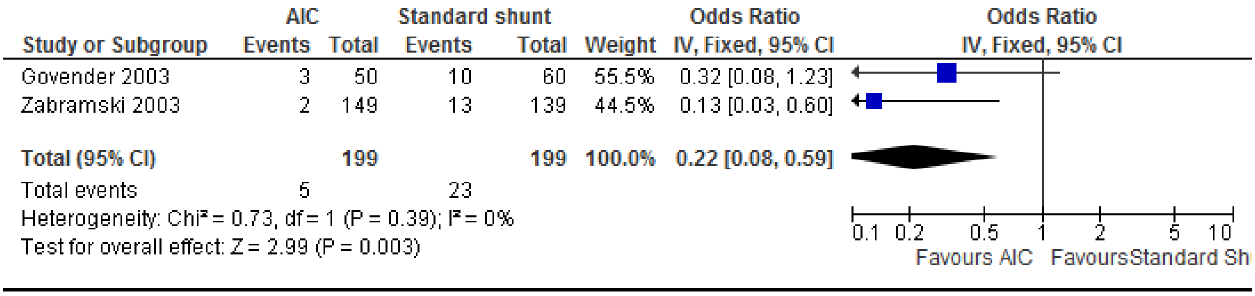

Figure 8: Surgical Site Infections

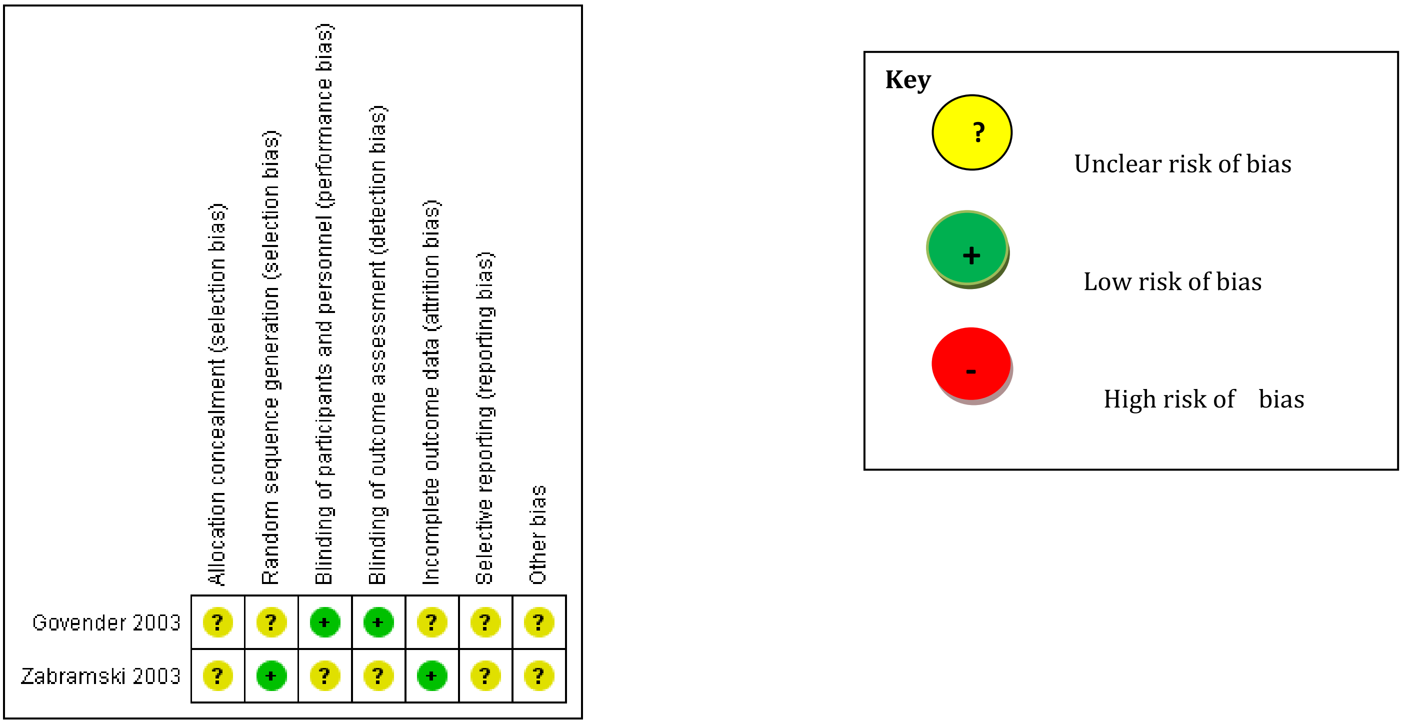

Figure 9: Risk of bias

Publication bias

The studies obtained were too few to generate funnel plots, so we were not able to detect publication bias. **Figure 8** presents the results of the meta-analysis.

The use of AICs has a strong protective effect against development of surgical site infections [OR 0.22 (95% CI 0.08, 0.59)]. The protective effect of AIC is about five times greater than that of standard shunts.

Risk of bias, Inconsistency, Imprecision and Publication bias

Govender 2003 and Zabramski 2003 were associated with a high risk of bias as shown in **Figure 9**.

Inconsistency, Imprecision and publication bias were similar to the outcome on development of surgical site infections.

Shunt Revision

One study, Govender 2003 evaluated this outcome. Patients were less likely to undergo shunt revision with AICs, compared to standard shunts [(OR 0.66 (95% CI 0.26, 1.67)].

There was a high risk of bias in this study. Therefore, the quality of evidence was downgraded from high to moderate quality. Since it was a single study, inconsistency could not be determined for this outcome. Imprecision was noted because of the wide confidence intervals and few events. This warranted downgrading of the level of evidence from moderate to low. There was indirectness with respect to intervention. Antimicrobial impregnated shunts are not commonly used in our setting because they are too expensive as described earlier. Outcomes 3 and 5 (development of non-surgical site infections and adverse effects of antibiotics) were not evaluated.

Overall Quality of Evidence for AICS versus Standard Shunts

GRADE Pro GDT Software version 2015 was used to evaluate the quality of evidence for this intervention. The quality of evidence supporting the use of AICs in our setting was very low, due to serious indirectness, risk of bias and imprecision for all the critical outcomes, as presented in **Table 2.**

Table 2: Quality of Evidence for AICs versus Standard Shunts

Antimicrobial impregnated shunts compared to standard shunts for prevention of neurosurgical site infections

Patient or population adult neurosurgical patients

Setting low and middle income countries

Intervention antimicrobial impregnated shunts

Comparison standard shunts

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with standard shunts	**Risk with antimicrobial impregnated shunts**				
Development of surgical site infections (SSIs) assessed with wound infection, positive cultures, CDC classification, Malis Criteria, fever, leukocytosis,shunt infection clinical signs follow up range 1 weeks to 20 months	**Study population** 116 per 1000	**28 per 1000** (10 to 72)	**OR 0.22** (0.08 to 0.59)	398 (2 RCTs)	⊕◯◯◯ VERY LOW [1,2,3]	CRITICAL
All cause mortality (Death) assessed with death follow up range 1 weeks to 20 months	**Study population** 116 per 1000	**161 per 1000** (97 to 255)	**OR 1.47** (0.82 to 2.62)	398 (2 RCTs)	⊕◯◯◯ VERY LOW [1,2,3]	CRITICAL
Shunt Revision (Shunt. Rev) assessed with Redo surgery follow up range 1 weeks to 20 months	**Study population** 167 per 1000	**117 per 1000** (49 to 250)	**OR 0.66** (0.26 to 1.67)	110 (2 RCTs)	⊕◯◯◯ VERY LOW [1,2,3]	CRITICAL

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI Confidence interval; **RR** Risk ratio; **OR** Odds ratio;

GRADE Working Group grades of evidence
High quality We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality We are moderately confident in the effect estimate The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality Our confidence in the effect estimate is limited The true effect may be substantially different from the estimate of the effect
Very low quality We have very little confidence in the effect estimate The true effect is likely to be substantially different from the estimate of effect

1. unclear allocation concealment, random sequence allocation, blinding, incomplete outcome data, selective reporting for all studies
2. did not comply to IOS rule for imprecision
3. Indirectness. AICs are too expensive for our study setting

4.0 Discussion

The quality of evidence for systemic antimicrobial prophylaxis was moderate while that for AICs was very low, using imprecision, indirectness, risk of bias and inconsistency. The two meta-analyses demonstrated the effectiveness of systemic antibiotics as well as antibiotic impregnated shunts in preventing surgical site infections. These findings are consistent with other studies (Ratilal et al, 2009; Bratzler et al, 2013).

Although there are many causes of mortality in surgical patients, adverse effects of antibiotics can play a role (Bratzler, 2013). In the second meta-analysis, the use of antibiotic impregnated shunt catheters was associated with a higher risk of mortality than standard shunts (Govender 2003, Zabramski 2003). There is paucity of data on the relationship between the use of intracranial ventricular shunts and all-cause mortality (Ratilal et al, 2006), although AICs have been shown to be effective in preventing surgical site infections, which in turn, reduces infection related morbidity and mortality (Parker et al, 2011).

Although there is scanty literature on the development of non-surgical site infections in neurosurgical patients, several studies have documented ventilator associated pneumonia, catheter related urinary tract infections, ventriculitis, meningitis, blood stream infections, intravascular catheter related infections, lower respiratory tract infections and gastrointestinal infections as the most common ones (Kourbeti et al, 2012; Kupronis et al, 2004).

Adverse effects of antibiotics occur commonly, but the life threatening ones are rare. Even though most studies did not evaluate this outcome, it is important to note the adverse effects as some serious and life threatening ones may occur.

Only one study evaluated shunt revision (Govender 2003) and demonstrated that use of AICs protected patients against shunt related infections. Shunt revision was done for non-infective and not infective causes. There was no evidence of infection during the procedure. This is in agreement with similar studies (Cui et al, 2015).

Overall, our systematic review is in agreement with Ratilal et al, (2008), as it shows the benefit of systemic antimicrobial prophylaxis in preventing neurosurgical site infections. In both systematic reviews, the efficacy of antimicrobial impregnated shunts could not be determined.

Our study had several limitations. The studies obtained were generated from three databases only- The CDSR, CENTRAL and MEDLINE. Other databases like EMBASE could not be accessed. There was a paucity of studies from low and middle income countries and this affected the quality of evidence, with regard to directness of evidence. Some outcomes of interest like all- cause mortality and adverse effects of antibiotics were not evaluated by most studies. Our study excluded studies that compared the use of different antibiotics in preventing surgical site infections and those that were not in English.

5.0 Conclusion

Antimicrobial prophylaxis using systemic antibiotics or antibiotic impregnated shunt catheters is effective in preventing neurosurgical site infections. Antibiotic impregnated shunts are expensive to acquire but are associated with overall reduction in treatment and hospitalisation costs.

Conflict of Interest declaration

The authors declare no conflict of interest.

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Declaration

Preliminary results contained in this article were presented at the Infectious Disease Symposium in June 2015 and published as an abstract.

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