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PROPHYLACTIC ANTIBIOTIC USE IN ORTHOPAEDIC SURGERY-IS IT WORTH IT?

Bhavini Vinay Patel, Hana Morrissey and *Ayesha Rahman

School of Pharmacy, University of Wolverhampton, United Kingdom.

***Corresponding Author: Ayesha Rahman**
School of Pharmacy, University of Wolverhampton, United Kingdom.

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ABSTRACT

Introduction: The administration of pre-operative prophylactic antibiotic is widely accepted in decreasing the risk of developing surgical site infections in orthopaedic surgery. The choice of antibiotic, duration, dosage and use of antibiotic laden bone cement varies substantially in clinical practice. **Aims:** This meta-analysis was conducted to assess the association of antibiotic choice, duration and dosage on the prevalence of surgical site infections in different types of orthopaedic surgery (hip replacements, knee arthroplasty, spinal surgery, ankle and foot surgery, shoulder surgery) and the identification of causative microorganisms. **Methods:** A literature search was performed in MEDLINE databases, Cochrane Controlled Trials Register published in the Cochrane Library, and Science Direct from January 2000-February 2018. Outcomes of interest included presence of post-operative surgical site infections. The Critical Appraisal Skills Programme tool was used to assess the risk of bias, extract outcomes of interest and to identify studies for inclusion in the meta-analysis. **Results:** The literature search revealed 169 studies out of which 18 studies were analysed and ultimately six studies in total were included in this meta-analysis. The pooled data investigating the post-operative deep surgical site infections rates favouring the use of prophylactic antibiotics (p=0.03). Only one study showed statistical significance (p=0.041) favouring the usage of high dosage antibiotic loaded bone cement in hemiarthroplasty procedures. **Conclusion:** This systematic review and meta-analysis recommends the use of high-dose antibiotic loaded bone cement and prophylactic oral antibiotics concurrently and as indicated, to prevent surgical site infections in hemiarthroplasties. The duration of prophylactic antibiotic use should be restricted to 24 hours commenced preoperatively or within 1-2 hours from incision. This systematic review also highlights the urgent need for more double blind RCT to validate the prophylactic use of antibiotics.

KEYWORDS: Antibiotic resistance; antibiotic prophylaxis; surgical site infection; *Clostridium difficile*-associated infections; Orthopaedic surgeries.

INTRODUCTION

In the United Kingdom the first case of methicillin resistant *Staphylococcus aureus* (MRSA) was identified in 1961 followed by the United States in 1968 (Sengupta, Chattopadhyay and Grossart, 2013). The problem has since escalated and has become one of the biggest threats to global health (World Health Organization, 2017a). Antibiotic resistance may occur irrespective of demographics and clinical settings. Misuse of antibiotics in humans and animals is one of the main causes of the critically emerging antibiotic resistance (WHO, 2017a). Data from Public Health England (PHE), December 2015 revealed antibiotic consumption increased by 6.5% from 2011 to 2015 (Public Health England, 2015). The daily drug dose (DDD), used to indicate drug utilisation is defined as "the assumed average maintenance dose per day for a drug used for its main indication in adults" (WHO, 2017b). The number of antibiotics prescribed increased from 21.6 per 1,000 in 2011 to 23 DDD per 1,000 per day in 2014 (PHE, 2015). Failure to address this crisis may result in 10 million deaths every year globally by 2050, costing £66 trillion in lost productivity to the global economy (PHE, 2015), thus, necessitating the need for more prudent prescribing.

The administration of the prophylactic use of antibiotics in certain orthopaedic surgeries is now widely accepted to reduce the risk of development of surgical site infections (SSIs) as well as other hospital acquired postoperative infections, namely respiratory tract and urinary infections (Southwell-Keely *et al.*, 2004; Slobogean *et al.*, 2008; Gillespie and Walenkamp, 2010). However, it is also known that antimicrobial therapy has the potential to promote *Clostridium difficile*-associated infections (CDI) (Donskey, 2004) by disrupting the indigenous intestinal microflora which promotes *Clostridium difficile* growth and production of toxins (Owens, *et al.*, 2008). The primary treatment options for CDI are vancomycin for moderate to severe disease and metronidazole for mild cases (Anderson, Bernatz and

Safdar, 2017). The WHO and the American College of Surgeons guidelines recommend that "single-dose of prophylactic antibiotics is usually sufficient" and "the duration of prophylactic antibiotics for all procedures should not exceed 24 hours (Bratzler *et al.*, 2013; Allegranzi *et al.*, 2016).

Surgical Site Infection

Surgical site infection (SSI) is a term used to describe the microbial contamination of the surgical wounds, bones, meninges, joints, body cavity and other tissues during the insertion of implants or prosthetic devices (Scottish Intercollegiate Guidelines Network, 2014). In the majority of cases the natural flora present on the patients' skin or microorganisms present in the hospital environment are the causative agents (Whitehouse *et al.*, 2002). SSI acquired at the time of surgery is classified as hospital-acquired infection, however SSIs can manifest within 30 days following an operation or within one year following a surgical implant procedure (Uçkay *et al.*, 2013; Al-Mulhim *et al.*, 2014; Anderson *et al.*, 2014). In the United Kingdom, SSIs cause an increase between 5.8 and 17 extra days of hospital stay and the surplus charge per SSI is approximately € 2500 (Al-Mulhim *et al.*, 2014). During surgery, the number of bacteria can increase by a factor of 27, due to the interposition of surgical staff between the vertical laminar flow and the patient (Taylor and Bannister, 1993). The classification of SSIs is determined by the depth of invasion of microorganisms as superficial incisional or deep incisional (Elgohari et al., 2014). Depending on the time of onset of infection after surgery, prosthetic joint infections are classified into: early (0-3 months), delayed (3-12 months) and late (>12 months) (Zimmerli, Trampuz and Ochsner, 2004). Treatment options for a prosthetic infection include one-stage revision or a two-stage revision (Strange et al., 2016). Untreated infections can cause the development of bacteraemia, systemic sepsis syndrome and chronic sinuses (Moran, Byren and Atkins, 2010). More than 40% of the infecting agents in SSIs were found to be coagulase negative Staphylococci (*Staphylococcus epidermidis* and *Staphylococcus aureus*) (Fletcher et al., 2007; Saadatian-Elahi, Teyssou and Vanhems, 2008).

The Timing of Antibiotic Prophylaxis

It is crucial that the therapeutic tissue concentration of the antibiotic is maintained during the decisive interval (the first two hours following incision) to wound closure. Optimal practice indicates antibiotics should be administered within an hour of the incision, although there are discrepancies amongst surgeons and some argue administration within two hours is equally acceptable (Bratzler and Houck, 2005). If administration does not occur within the two-hour window, there is a two to six fold increase in the rate of SSIs (Burke, 2001). Additionally, use of a tourniquet reduces the timing of administration of antibiotics significantly, a ten-minute interval is required between inflation of the tourniquet and the administration of the antibiotic (Bryson et al., 2016). Long procedures, multiple transfusions or rapid clearing of the antibiotic may justify the need for repeat doses of antibiotics (American Journal of Health-System Pharmacy, 1999). However, multiple doses of antibiotics and prolonged usage ignite concern amongst surgeons regarding the risk of emergence antimicrobial resistance (Bratzler and Houck, 2005; Dhammi, Ul Haq and Kumar, 2015). Irrespective of usage of drains or catheters, the American Academy of Orthopaedic Surgeons (AAOS) recommend that in clean elective procedures, the administration of prophylactic antibiotics (Table 1) should not surpass 24 hours (Meehan, Jamali and Nguyen, 2009). A randomised controlled trial (RCT) discovered that there was no difference in SSI rates amongst patients administered with prophylaxis, of either nafcillin or cefazolin for 24 hours compared to patients who were administered with prophylaxis for seven days post-operatively after both total hip replacements (THR) and total knee arthroplasties (TKA). Following this, in a second group of patients a single preoperative dose was compared to a 48 hour regimen and yet again there was no difference in SSI prevalence (Nelson et al., 1983). Williams and Gustilo (1984) carried out a retrospective review assessing 1341 patients undergoing TKA and THR and identified no difference in deep-infection rate amongst those who received prophylaxis for three days (0.6%) and those who received a one-day course of prophylactic antibiotics (0.67%) using a dose of 2g of cefazolin.

Table 1: Summary of Antibiotics used for prophylaxis in orthopaedic procedures.

Type of Surgery	Recommended Antibiotic			Duration	References
	1st Line	Penicillin allergy	MRSA positive		
Emergency supply involving implants	Flucloxacillin 1g IV plus Gentamicin 5mg/kg IV	Teicoplanin 400mg IV		In most cases a single dose IV at induction (less than 60 minutes before operation to achieve maximum tissue concentrations at the time of surgery.	(Aujla *et al.*, 2013) (Joint Formulary Committee, 2017a)
Elective joint replacement surgery	Cefuroxime 1.5g IV on induction	Teicoplanin 400mg IV			(Prokuski, 2008)
Other elective orthopaedic surgery involving implants	Cefuroxime 1.5g IV on induction single dose	Teicoplanin 400mg IV			(Bryson *et al.*, 2016) (Joint Formulary Committee, 2017b)
Shoulder surgery	Co-amoxiclav 1.2g IV	Teicoplanin 400mg IV			(Nanchahal *et al.*, 2009)

Primary Aim

This systematic review has been conducted to assess the association of antibiotic choice, duration, and dosage on the prevalence of surgical site infection in different types of orthopaedic surgery.

Search Strategy

A literature search was performed to identify all published randomised clinical trials or randomised control trials. This search includes published works from January 2000-February 2018 in MEDLINE databases, Cochrane Controlled Trials Register published in the Cochrane Library, and Science Direct.

Databases were searched using the following key words: prophylactic antibiotics, orthopaedic surgery, double blind, randomised control trial, total hip replacement, hemiarthroplasty (HA), knee replacement, shoulder, ankle, foot, spinal procedures/ surgeries. Eligibility criteria for articles selected to conduct this review is in table 2.

Table 2: Inclusion and Exclusion Criteria.

Inclusion Criteria:	Exclusion criteria:
– Published works – From 2000-2018 – Reports on the prophylactic use of antibiotics in orthopaedic surgery – Randomized, double blinded controlled trials – Trials involving adults ≥18 years of age – Orthopaedic surgeries including: - Total Hip Replacement - Hemiarthroplasty - Knee arthroplasty - Spinal surgery - Ankle and Foot surgery - Shoulder surgery – Where randomized, double blinded trials were not available randomized trials alone, randomized clinical trials, prospective or retrospective trials were considered.	– Unpublished studies – Studies only available in abstract form – Grey material – Dissertations – Book chapters

The search strategy revealed 169 studies, from which 89 were duplicates and 62 were rejected due to the title and abstract being irrelevant. The remaining 18 studies were retrieved for full papers and analysed using the Critical Appraisal Skills Programme (CASP) tool. Out of these, 12 studies were rejected on the basis that they did not meet our inclusion and exclusion criteria, leaving 6 studies which were included in the meta-analysis. Figure 1 displays a flow chart detailing the study selection process.

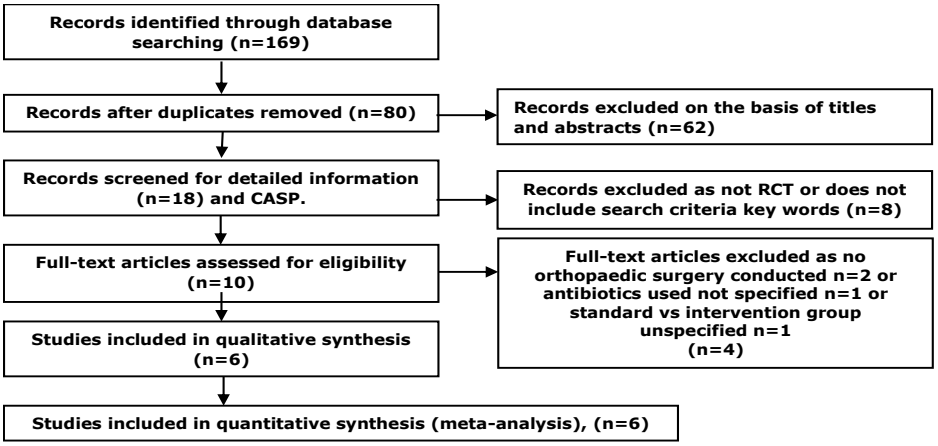

Figure 1: Flow diagram of the selection of studies included in the Meta-analysis.

Quality Assessment

Qualitative data was assessed and extracted using the CASP tool (Critical Appraisal Skills Programme, 2018) which was also used to assess the risk of bias (Appendix 1).

Outcome Measures and Statistical Analysis

Data was pooled using REVMAN 5.0 software. The relative risk (RR) with 95% confidence intervals (CIs) for dichotomous data (data with two mutually exclusive groups, i.e. presence or absence of SSI) was calculated

for each study to quantitatively measure the probability of an event occurring (Higgins and Green, 2011). Where appropriate, the results of comparable groups of trials were pooled and combined using REVMAN 5.0 software using the fixed-effect model. A random-effect model was used when significant heterogeneity was identified ($P<0.10$; $I^2>50\%$). Where possible, based on the reviewed study design, the numbers needed to treat (NNT) were calculated to measure the number of patients who need to be treated to prevent one additional adverse outcome.

FINDINGS AND DISCUSSION

Orthopaedic Surgery and Antibiotic Loaded Bone Cement

In orthopaedic surgeries requiring cement, antibiotic-laden cement inserted into the surgical site may be a useful way of maintaining high concentration of the drug, which would not be reached by intravenous administration without causing toxicity and general complications (Belt et al., 2001). However, effectiveness of this strategy is currently under debate and there are discrepancies amongst surgeons regarding the method of preparation, mechanical properties of antibiotic loaded cement, choice of antibiotic, effective release and diffusion of antibiotic in surrounding tissues (Belt *et al.*, 2001). Bulchoz and Engelbrecht (2004) introduced erythromycin; gentamicin and penicillin into cement used to stabilize the hip, and discovered a more prolonged concentration of the antibiotic (Elson *et al.*, 1977). However, a Norwegian study analysed 22,170 THRs and reported a lower rate of THR revision surgeries conducted in the patient population which received both systematic antibiotics and antibiotic loaded bone cement. The authors identified a 1.8% higher risk of revision caused by infection in patients only treated with systemic prophylaxis (Engesæter *et al.*, 2003). Furthermore, the same research group later identified antibiotic loaded bone cement prosthesis had a non-dissimilar outcome than uncemented protheses. Data collected on 56,275 identified a 0.7% and 0.6% revision rate for infection, respectively for uncemented THRs compared to cemented THRs with antibiotic loaded cement (Engesæter *et al.*, 2006).

Evidence shows certain bacteria grow favourably on specific biomaterials; *Staphylococcus aureus* has displayed preferential adhesion to metallic biomaterials whereas coagulase negative *Staphylococci* prefer adhesion to bone cement (Schildhauer *et al.*, 2006). A report of 97,344 THRs identified an increase in rate of revisions due to deep infections in THRs in un-cemented prostheses and plain cement prosthesis compared to antibiotic-loaded cement THRs. This validates the usages of antibiotic-loaded bone cement in THRs (Dale *et al.*, 2009). However, another possible explanation for the unexpected increase in deep infections is the emergence of pathogenic strains with increased virulence and resistance to systemic prophylaxis. Therefore, wide clinical use of antibiotic laden bone cement must be carefully considered.

Hip Replacements and Antibiotic Prophylaxis

In the England and Wales in 2017 the NHS carried out a total of 138,364 hip procedures and a further 37,993 were carried out independently (National Joint Registry, 2016). THR are carried out to relieve joint pain, stiffness and deformities caused by arthropathy of the hip, namely rheumatoid arthritis and osteoarthritis (Glenny and Song, 1999) and can be primary or revision in nature. Revision surgeries of THRs occur when a replacement fails due to loosening or breaking of the prothesis, or when the prothesis becomes infected, justifying the re-assessment of antibiotic prophylaxis and the impact it may have on fuelling antibiotic resistance (Glenny and Song, 1999). The risk of developing an SSI in THR is 2.23% (3.68% require revision) and 4.97% in HA (7.6% require revision) procedures (Glenny and Song, 1999). Additionally, HAs are associated with loosening of the joint and pain (Parker and Gurusamy, 2005). Over 50% of SSIs in hip arthroplasties identified *Staphylococcus aureus* as the infection causing pathogen, 59% of these isolates were MRSA, justifying the need for reassessment of the prophylactic use of antibiotics in orthopaedic surgery (Saadatian-Elahi, Teyssou and Vanhems, 2008). Ridgeway et al. (2005) conducted a multivariate analysis which proposed that the differences in incidences of SSIs are explained by the underlying characteristics of the patients undergoing the procedures as opposed to the type of procedure.

Knee Arthroplasty and Antibiotic Prophylaxis

The National Joint Registry (NJR) for England and Wales reported that 102,252 knee procedures were performed in 2017. Post-operative infections following TKA are responsible for approximately 23% of revision surgeries (Vanhegan et al., 2012). Although there have been several advances in infection control practises and surgical techniques, SSIs following TKA remain a catastrophic complication. Specifically, deep-implant SSIs are associated with functional disability, long-term knee pain and mortality, necessitating the need for the removal of the prosthesis followed by stage revision surgeries (Wu et al., 2016). The incidence of infection in TKA ranges from 0.5%- 1.8%, however the incidence may increase significantly in high-risk groups (Kurtz, 2007). The rising rates of SSIs following total joint arthroplasty validates more stringent controls of known risk factors, in particular the timing, dose, and type of prophylactic antibiotics administered (van Kasteren et al., 2007).

Spinal Surgery and Antibiotic Prophylaxis

The optimal choice for treatment of spinal trauma and degenerative spinal diseases is spinal surgery with instrument fixation. However, postoperative complications, particularly rate of SSIs in spinal surgery was reported between 1-9% (Anderson *et al.*, 2017). Rubinstein et al. (1994) performed another study

comparing a single dose of 1g cephazolin against a placebo. The authors concluded that in patients undergoing lumbar spinal surgery, a single dose of preoperative cephazolin is recommended (Rubinstein et al., 1994). However, both studies were prospective, single-centre studies, which are limited due to data collection bias and incomplete medical records. Silver-plated poly axial screws have recently been used as an antimicrobial, however, there are few experimental and clinical studies validating their usage (Oksuz et al., 2016).

Ankle and Foot Surgery and Antibiotic Prophylaxis

Infection risk following ankle and foot surgery range from 0.5% to 6.5% causing great concern compared to other orthopaedic surgical sites (Zgonis, Jolly and Garbalosa, 2004). Furthermore, there is a greater risk of infection in diabetic patients with infections rates as high as 19% (SooHoo et al., 2009). The NJR reported that 863 ankle procedures were performed in 2017 (NJR, 2016). Severity of SSIs following ankle and foot procedures range from minor to catastrophic (Wukich et al., 2010). Zgonis et al. (2004) reported that there were no significant differences in post-operative SSI rates in primary or elective outpatient surgeries performed on the ankle or foot. Paiement et al. (1994) investigated the post-operative prophylactic use of antibiotics in 122 closed ankle fractures. Similarly to Zgonis et al. (2004), there were no significant differences in the prevalence of SSIs in patients who did and did not receive postoperative prophylactic antibiotics. However, both authors acknowledged that the studies were underpowered due to small sample sizes, hence further research is required.

Shoulder Surgery and Antibiotic Prophylaxis

The NJR reported 7204 shoulder procedures were performed in 2017 (National Joint Registry, 2016). Although SSIs are rare in shoulder surgery they can have detrimental effects, often resulting in extensive revision surgery (Bents et al., 2017). *Propionibacterium acnes* is a non-spore forming, anaerobic, Gram-positive bacillus commonly found on the skin of the upper body and is known to have a high propensity for the shoulder (Kadler, Mehta and Funk, 2015), accounting for 56% of shoulder infections involving orthopaedic implants (Levy et al., 2008).

Post-operative Superficial and Deep SSI Rate

Six trials were included which assessed the post-operative infection rate (both deep and superficial) in patients as displayed in the forest plot in Figure 2. The line of null effect represents the vertical line in which there is no difference between the two interventions and the length of the horizontal lines represents the confidence intervals (CI) (Page, 2014). The Backes et al., (2017) study had the smallest CI, indicating this study is more reliable compared to others. Whereas, the Kato et al., (2006) Study showed the highest CI thus reducing the reliability of the study. Therefore, despite the Kato et al., (2006) study having a point estimate to the left of null effect, favouring the experimental outcome, the study's reliability is reduced due to its large CI. Similarly to Kato et al., (2006), Marwa et al., (2015) had the second largest CI and furthermore, similarly to Kato et al., (2006) despite having a point estimate left to the line of null effect the large CI diminishes the validity of the favourable outcome.

The Backes et al., (2017) study has the largest weighting of 37.4%, this is represented by the size of the box indicating the study had the largest weighting compared to the others. The weighting of the studies on uncertainty of estimates and risk of bias assessment are adjusted by Revman™ 5.0 (Higgins and Green, 2011). Sprowson et al., (2016) had the second largest weighting suggesting it has a small uncertainty estimate and a smaller risk of bias compared to other studies. Although Takemoto et al., (2015) had the third largest weighting of 24%, the point estimate of the study crossed the line of null effect signifying there was no statistical significance in both arms of the trial.

All CIs representing the studies crossed the line of null effect, indicating there are no statistically significant findings, aside from Sprowson et al., (2016) which had its CI left of the line of null effect favouring the intervention i.e. the use of prophylactic antibiotics. This also implied the experimental group is statistically significant and thus favourable compared to the control arm of the trial.

The diamond represents the point estimate and confidence intervals of the combined studies investigating the SSIs (both deep and superficial) of all six studies included in the meta-analysis. The horizontal points of the diamond represent the 95% CIs of the pooled data and coincide with the line of null effect indicating the combined results are not potentially statistically significant. The vertical points (the centre of) of the diamond represent the point estimate of the pooled data which lies to the left of the line of null effect and the relative risk (RR) of 0.83 suggesting a large proportion of the data favours the experimental outcome. Heterogeneity was I^2=41% indicates there is little researcher bias or issues with the data collected across the studies.

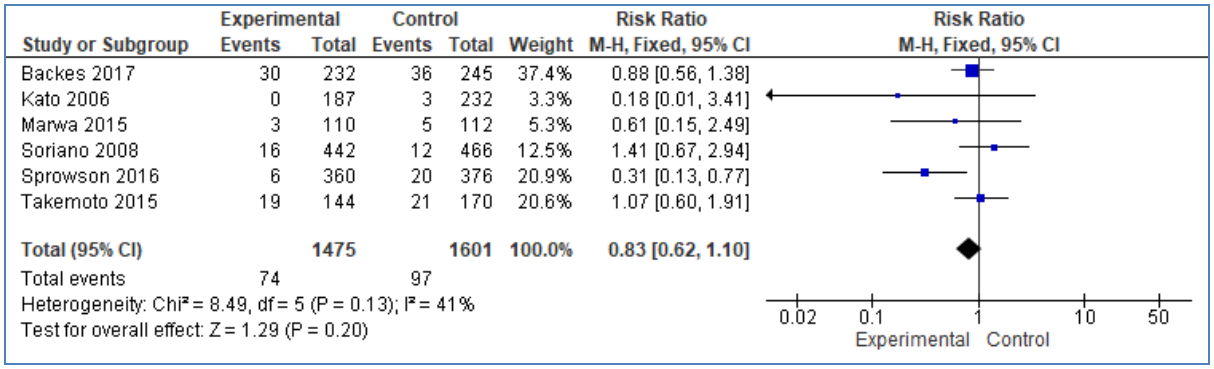

Figure 2: Forest plot showing the RR and 95% CIs for the incidence of post-operative surgical site infections among patients treated in the experimental group vs. control group.

Post-operative Deep SSI Rate

Four trials investigated the presence of deep incisional SSIs as displayed in figure 3 forest plot. The CI of Backes et al., (2017), Kato et al., (2006), and Takemoto et al., (2015) studies crossed the line of null effect indicating there were no statistically significant findings. However, the CI in Sprowson et al., (2016) did not cross the line of null effect indicating findings were statistically significant (P=0.041) (CI: 0.11, 0.98). Furthermore, Sprowson et al., (2016) had the largest weighting of 43.7% suggesting it has a small uncertainty estimate and a smaller risk of bias compared to other studies. The combined results were statistically significant (Total (95% CI): 0.26, 0.92) with a RR of 0.49 favouring antibiotic use. Thus, the overall outcome rate in the intervention group is significantly different to the control group. Despite the P-value being 0.03 which suggests the results of pooled data and are potentially statistically significant, the I^2= 52% indicating some heterogeneity. However, this is expected and is due to different experimental and control variables compared in the studies. The calculation of numbers needed to treat (NNTs) was 66, therefore to prevent post-operative deep surgical site infection in one patient, 66 patients will have to be administered prophylactic antibiotics as implicated in the studies.

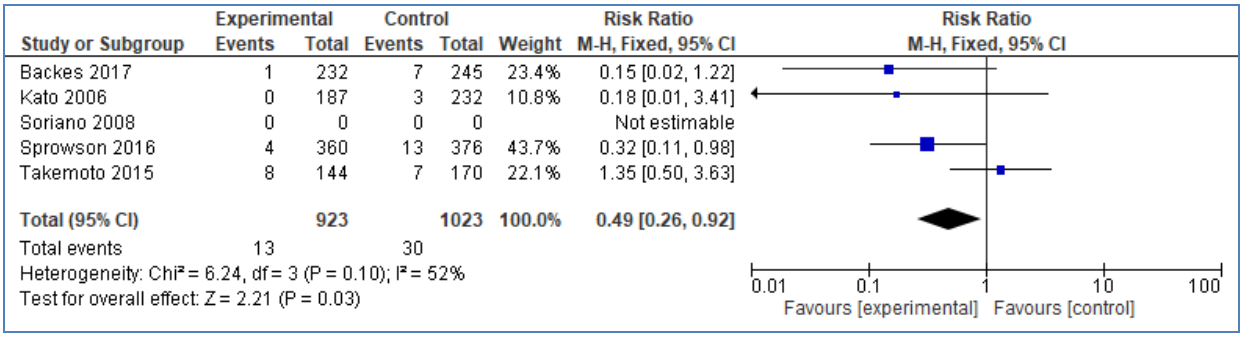

Figure 3: Forest plot showing the RR and 95% CIs for the incidence of post-operative deep surgical site infection amongst patients treated in the experimental group vs. control group.

Post-operative Superficial SSI Rate

These are represented in Figure 4 forest plot which includes data from three studies. The CI of all the three studies crossed the line of null effect, indicating no statistically significant outcome. Interestingly, the confidence interval of the Backes et al., (2017) study appeared almost evenly distributed across the experimental and control groups. This is due to the same number of events occurring in both the experimental control group. Kato et al., (2006) with the largest CI was the least reliable of the studies analysed. Compared to Backes et al., (2017) and Kato et al., (2006), the Sprowson et al., (2016) point estimate sat left to the line of null effect suggesting the experimental arm was favoured in this trial. The combined results of the studies were not statistically significant, however the vertical lines of the diamond which represents the point estimate lies slightly to the left of null effect, suggesting the pooled data favours the experimental arms of the studies. The heterogeneity is I^2= 33% indicating there is little researcher bias or issues with the data collected across the pooled studies.

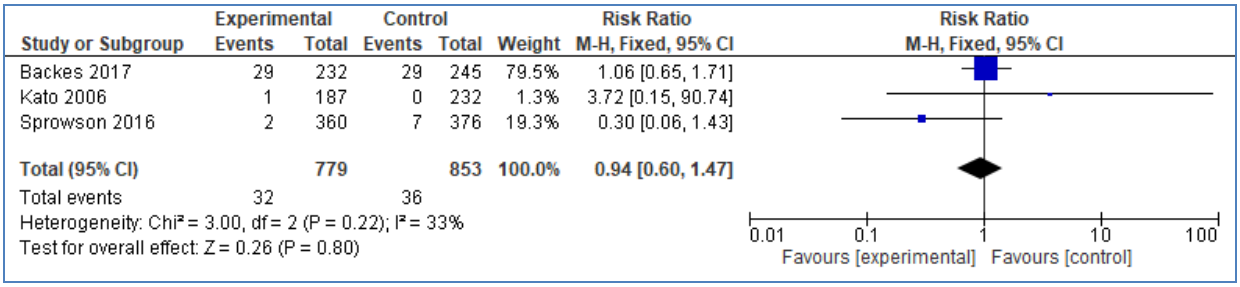

Figure 4: Forest plot showing the RR and 95% CIs for the incidence of post-operative superficial surgical site infection amongst patients treated in the experimental group vs. control group.

Post-operative SSIs Caused by MRSA

Both the Kato et al., (2006) and Soriano et al., (2008) studies have their point estimates left to the line of null effect with the point estimate of the Kato et al., (2006) study lies further to the left compared to Soriano et al., (2008), in which the point estimate was closer to the line of null effect. This suggests experimental outcomes are highly favoured in the Kato et al., (2006) study compared to the Soriano et al., (2008) study. The point estimate of the pooled data lies to the left of the line of null effect and the relative risk (RR) of 0.37 suggesting a large proportion of the data favours the experimental outcome. Kato et al., (2006) had a weighting of 75.3%, represented graphically by the larger size of the box suggesting it has a small uncertainty estimate and a smaller risk of bias compared to Soriano et al., (2008). However studies evaluating the post-operative SSIs caused by MRSA had large CIs which diminished reliability of these studies.

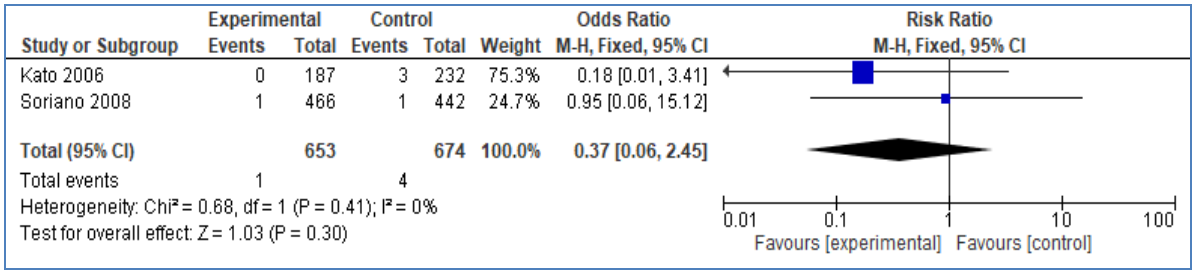

Figure 5: Forest plot showing the RR and 95% CIs for the incidence surgical site infections caused by MRSA amongst patients treated in the experimental group vs. control group.

Post-operative SSIs Caused by MSSA

These are represented in Figure 6 forest plot in which the CI representing Kato et al., (2006) is longer than Soriano et al., (2008). This indicates the Soriano et al., (2008) study is more reliable due to having smaller CIs compared to Kato et al., (2006). Both the point estimates were left of the line of null effect and were located in similar positions, thus both studies favour the experimental outcome. The weighting of the Soriano et al., (2008) trial is 82.1% compared to Kato et al., (2006) which had a weighting of 17.9%. This suggests that Soriano et al., (2008) trial has small uncertainty estimate and a smaller risk of bias compared to Kato et al., (2006). The horizontal points of the diamond cross the null effect indicating no statistical significance in the pooled data (p=0.23) whereas the vertical points are toward the left of line of null effect favouring experimental outcomes with a RR of 0.46 for the pooled data.

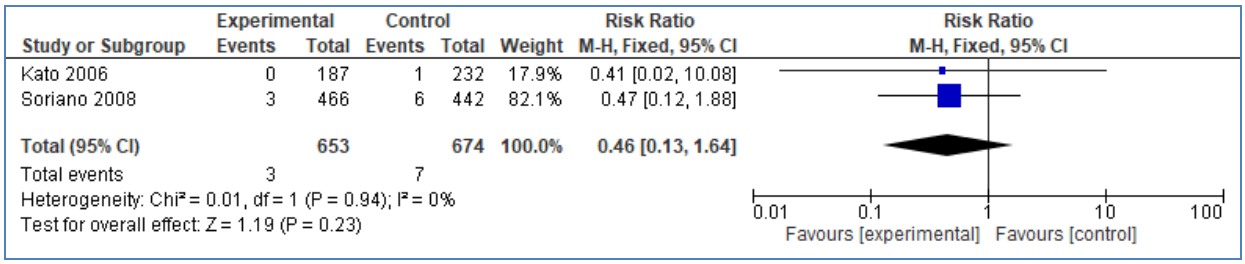

Figure 6: Forest plot showing the RR and 95% CIs for the incidence surgical site infections caused by MSSA amongst patients treated in the experimental group vs. control group.

Post-operative SSIs Caused by *Escherichia coli*

These are represented in Figure 7 forest plot in which the CIs representing both studies are of similar length and both the point estimates are left of the line of null effect. However, the point estimate lies further to the left in the Kato et al., (2006) study compared to Soriano et al., (2008), in which the point estimate was closer to the line of null effect. This suggests outcomes are highly

favoured in the Kato et al., (2006) study compared to the Soriano et al., (2008) study. Both studies displayed similar weightings, visually represented by similar size boxes. The horizontal points of the diamond cross the null effect indicating no statistical significance in the pooled data (p=0.68) are wide apart indicating large confidence intervals.

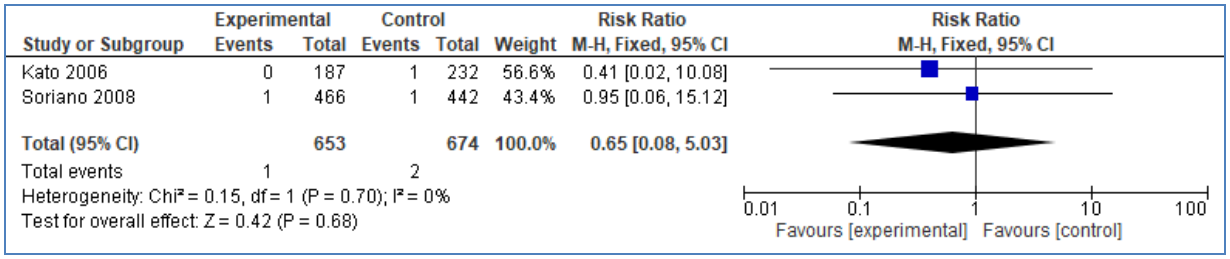

Figure 7: Forest plot showing the RR and 95% CIs for the incidence surgical site infections caused by Escherichia coli amongst patients treated in the experimental group vs. control group.

Post-operative SSIs Caused by *Pseudomonas aeruginosa*

The forest plot in Figure 8 represents the post-operative SSIs caused by *Pseudomonas aeruginosa*. This forest plot indicates that the Soriano et al., (2008) study is more reliable than Marwa et al., (2015) as it has smaller CIs, hence the true value in the population is expected to fall within a smaller range compared to Marwa et al., (2015). The point estimate of Marwa et al., (2015) lies to the right of the line of null effect favouring the control arm of the study whereas, the point estimate of the Soriano et al., (2008) study lies to the left of the line of null effect favouring the experimental arm of the study. The weighting of the Soriano et al., (2008) study is 89.2% compared to Marwa et al., (2015) which had a weighting of 10.8% suggesting the former trial had a small uncertainty estimate and a smaller risk of bias compared to the latter. The horizontal points of the diamond cross the null effect and are wide apart indicating no statistical significance in the pooled data (p=0.31) and large CIs respectively.

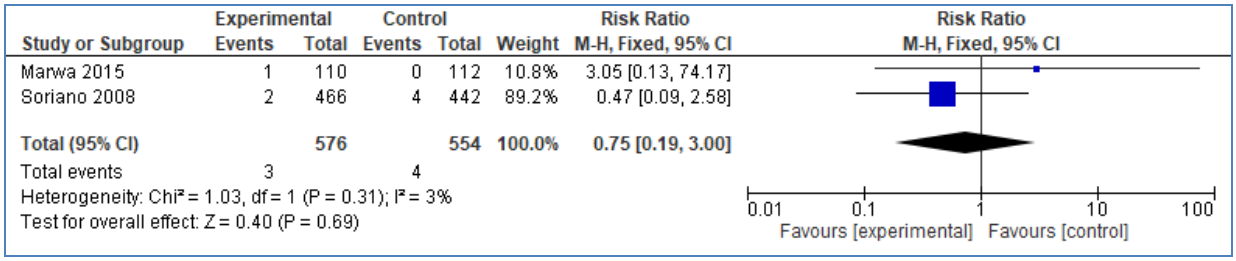

Figure 8: Forest plot showing the RR and 95% CIs for the incidence surgical site infections caused by Pseudomonas aeruginosa amongst patients treated in the experimental group vs. control group.

In general the point estimates of studies included in the forest plots displayed by figures 2-8, were displayed left of the line of null effect. The vertical points of the diamonds represent the point estimates of pooled data, which favour experimental outcomes i.e. use of prophylactic antibiotics.

Publication Bias

Publication bias was assessed using with a funnel plot, this demonstrates the relationship between the precision in estimating treatment effect and the study sample size. Each dot in the funnel plot represents a single study. The y-axis represents the standard error of the effect estimate. Larger studies with higher power are located towards the top of the plot and lower powered studies are located further down (Higgins and Green, 2011). As displayed in Figure 9, 5 studies are located towards the top of the graph with 1 located further down. The x-axis represents mean results for the study in the form of a risk ratio. In Figure 9, the post-operative deep and superficial SSI was measured. Through visual analysis of both deep and superficial infection rate, graphically suggests mild asymmetry suggesting minimal evidence of publication bias. This is due to four dots located on the left of the line of symmetry and two dots located on the right. However, all the dots on the plots are displayed as open circles which suggest study sizes are small, without statistically significant effects. This is because all the studies included in the meta-analysis are smaller and do not show statistically significant effects except studies included to estimate post-operative deep SSI rate.

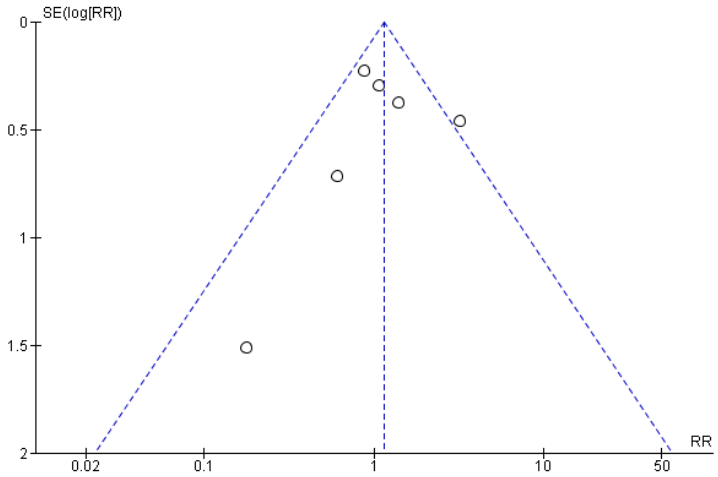

Figure 9: Funnel plot to assess publication bias in the studies used in the meta-analysis.

Limitations

There is paucity in the eligibility of RCTs which evaluate antibiotic prophylaxis in different types of orthopaedic surgery, thus a less stringent search criterion was imposed. This lead to different experimental and control variables being compared to evaluate SSIs in the meta-analysis. The usage of antibiotic prophylaxis in orthopaedic surgery is necessary due to the detrimental effects of SSIs. Accordingly, it was difficult to identify placebo-controlled trials. The small sample size in the used studies produced results which appear more or less significant than they actually are, thus introducing bias. Furthermore, the studies were conducted in different type of patient and different countries, which may have influenced the outcomes. Different types of bacteria (MRSA, MSSA, *Escherichia coli*, and *Pseudomonas aeruginosa*) were identified; therefore the antibiotics used were also different. Studies included in this review included the investigation of THR, HA, TKA, spinal Surgery, fractures below the knee, however, the majority of result outcomes did not state which type of surgery had SSIs.

Appendix 1: Critical appraisal skills programme (CASP).

Sprowson et al., 2016	
1. Did the trial address a clearly focused question?	Yes No Can't tell - Incidence of SSI in patients who received low single-antibiotic impregnated cement (control group) with patients who received high dose dual-antibiotic impregnated cement (intervention group). - Population- 848 patients, 448 patients received low dose single antibiotic impregnated cement (control group), 400 patients - Intervention- high dose (1g Clindamycin and 1g of Gentamicin (Copal G+C) - low dose antibiotic-laden cement (Palacos R + G, 0.5g of Gentamicin) - Comparator- high dose, low dose antibiotic 1g Clindamycin and 1g of Gentamicin (Copal G+C) - Outcomes- deep SSI one year after surgery
2. Was the assignment of patients to treatments randomised?	Yes No Can't tell - quasi randomised trial - not practical or feasible to attempt randomisation due to concerns about impact on credibility and fidelity, lack of specific local support - treatment was allocated depending on the month surgery was undertaken increases selection bias
3. Were all of the patients who entered the trial properly accounted for at its conclusion?	Yes No Can't tell - Primary endpoint of trial- loss to follow-up was less than 6% in both groups - All patients accounted for - low dose antibiotic cement (n=448) - n=6 -did not receive allocated intervention- received alternate intervention - Lost to follow up (n=26, 5.8%) - Death within 30 days (n=46) - High dose antibiotic cement (n=400) - n=22 did not receive allocated intervention- received alternate intervention - lost to follow-up (n=5) - Death within 30 days (n=35)

4. Were patients, health workers and study personnel 'blind' to treatment?	Yes <u>No</u> Can't tell - Patients- blinded - Study personnel- blinded - Participating surgeons were not blinded to treatment- however; all staff involved in assessment of outcomes was blinded.
5. Were the groups similar at the start of the trial?	- Age- all participants >18 years - Medically fit for operation - Suitable for cemented hemiarthroplasty - To explore generalisability data was anonymised data regarding age and gender was recorded for all patients
6. Aside from the experimental intervention, were the groups treated equally?	- Both groups received standard hemiarthroplasty implants - Analysis in this trial was performed on an intention to treat basis
7. How large was the treatment effect?	- Combined data (deep/superficial SSIs counted) rates were: ▪ Control group 5.3% (95% CI 3.4% to 8.2%) ▪ Intervention group 1.7% (95% CI 3.4% to 8.2%) ▪ P values from analogous analysis- 0.009 (Control group) and 0.010 (intervention group) ▪ Total number of infections both deep and superficial differed significantly between groups ▪ No evidence of difference in length of stay in hospital - 80% power - Use of high dose dual-antibiotic impregnated cement significantly reduced the rate of SSI when compared to standard low dose single antibiotic loaded bone cement
8. How precise was the estimate of the treatment effect?	- Authors concluded high dose dual antibiotic impregnated cement in these patients significantly reduces the rate of SSI (both deep or superficial) compared with standard low dose single antibiotic loaded bone cement - P values 0.009
9. Can the results be applied in your context?	- The study shows the use of dual -antibiotic impregnated cement in hemiarthroplasties does reduce the risk of SSI development, however - Reject the null hypothesis- rate of SSI at one year after hemiarthroplasty does not differ between patients undergoing surgery using standard low dose antibiotic impregnated cement and those in whom high dose dual-antibiotic impregnated cement is used
10. Were all clinically important outcomes considered?	- Limitation include the use of quasi randomisation - differences in target population, local environment, procedures at each of the sites - Although quasi-randomization was used- study of 540,000 patients with hip fracture concluded that the risk of mortality in these patients were associated with to the fracture itself, and further post-operative complications
Marwa et al., 2015	
1. Did the trial address a clearly focused question?	<u>Yes</u> No Can't tell - Yes, the trial evaluated the safety of cefepime and ceftriaxone as peri-operative systemic antimicrobial prophylaxis in elective orthopaedic surgery in our centre. - There was no control group in this study. Criticism can be levelled at the authors for not including a control group; however, antimicrobial prophylaxis has to be administered to reduce the incidence of postoperative wound infections. - 230 participants were subjected to final analysis. - The trial's hypothesis is a null hypothesis, the authors assume the treatment difference on the proportion of elective orthopaedic surgery SSI in the two arms should be less or equal to +/- 5%. The differing treatments were due to a dearth of information on the clinical effectiveness spectrum limitations on third and fourth generation cephalosporins. SSIs were the primary end point investigated after day 3 and 30
2. Was the assignment of patients to treatments randomised?	<u>Yes</u> No Can't tell - Yes, both treatment groups were designated as 'A' (ceftriaxone) and 'B' (cefepime) using four digits from randomly generated computer numbers. Randomization helps ensure findings are truly because of the treatment and reduces selection bias.
3. Were all of the patients who entered the trial properly accounted for at its conclusion?	<u>Yes</u> No Can't tell - Out of the total 248 patients, patients lost to follow up were defined as treatment failure, therefore no bias was introduced.
4. Were patients, health workers and study personnel 'blind' to treatment?	Yes <u>No</u> Can't tell - No, both the patients and study personnel were not blinded to treatment. However, the study aimed to reduce bias by alienating two members of the orthopaedic team whom

	provided surveillance and clinical diagnosis of surgical site infection in the ward or surgical outpatient department.
5. Were the groups similar at the start of the trial?	- Yes, there were a similar proportion of patients recruited to group 'A' as 'B', 117 versus 113. - The study states that 'there was an even distribution of the participants with respect to the demographic and baseline characteristics.' - Criticism can be levelled at the authors because the patient groups were not very well identified making it difficult to confirm the similarity between the groups clinically.
6. Aside from the experimental intervention, were the groups treated equally?	- Yes, all patients were treated equally. The analysis in the trial was performed following intent to treat basis.
7. How large was the treatment effect?	- The treatment with cefepime compared to ceftriaxone in preventing SSIs following clean elective orthopaedic surgery was not statistically significant. - Superficial SSI occurred in 5 out of 117 patients receiving cefepime compared to 3 out of 113 patients receiving ceftriaxone. Although ceftriaxone did demonstrate a lower cumulative incidence compared to cefepime arm used for prophylaxis, the difference was not statistically significant.
8. How precise was the estimate of the treatment effect?	- The authors had hypothesised the treatment with both ceftriaxone or cefepime would be equally effective as one another in the trial. This was proved correct in trial.
9. Can the results be applied in your context?	- It is difficult to estimate if the results of this trial can be applied in a global context.
10. Were all clinically important outcomes considered?	- Yes, all major clinical outcomes were considered.
Takemoto et al., 2015	
1. Did the trial address a clearly focused question?	Yes No Can't tell - Trial investigates infection rates between those treated with antibiotics for 24 hours and those who received antibiotics for the duration for which the drain was placed - 314 patients underwent thoracolumbar spinal surgery followed by the use of a postoperative drain - Operations were for multilevel thoracolumbar spine arthrodesis for deformity and degenerative conditions
2. Was the assignment of patients to treatments randomised?	Yes No Can't tell - Randomization was conducted using a computer randomization programme. - Operating surgeons blinded for the duration antibiotic prophylaxis was administered
3. Were all of the patients who entered the trial properly accounted for at its conclusion?	Yes No Can't tell - All patients were followed for a minimum of 1 year - All patients were analysed in the groups, no patients were lost to follow up.
4. Were patients, health workers and study personnel 'blind' to treatment?	Yes No Can't tell - Randomization was conducted using a computer randomization programme. - Operating surgeons were blinded to the duration for which antibiotic prophylaxis was to be used
5. Were the groups similar at the start of the trial?	- Baseline characteristics for both groups displayed no statistical significant differences at the start of the trial
6. Aside from the experimental intervention, were the groups treated equally?	- Both arms of the trial treated the same- all drains placed below fascia and exited through the skin adjacent to the incision, drain was removed when output was <30ml in eight hours, dressings were changed daily on post- operative day 3 or on the day of discharge.
7. How large was the treatment effect?	- SSI infection ▪ 21/170 24-hour group (Control) ▪ 19/144 drain duration group - Deep infection ▪ 7/170 24-hour group (Control) ▪ 8/144 drain duration group - SSI in primary surgery ▪ 10/119 24-hour group ▪ 10/97 Drain-duration group - SSI in revision surgery ▪ 11/80 24-hour group ▪ 9/70 Drain- duration group
8. How precise was the estimate of	- No significant differences were identified between the g24-hour group and the drain

the treatment effect?	group. (p=0.48, 95% CIs).
9. Can the results be applied in your context?	- Because no statistical significance was identified between the groups, the usage of drains should only be inserted for 24 hours post operatively following spinal.
10. Were all clinically important outcomes considered?	- The usage of drains should only be kept inserted post-operatively for 24-hours. The usage of drains for any longer, has no additional advantage in the surgical site infection.
Kato et al., 2006	
1. Did the trial address a clearly focused question?	Yes No <u>Can't tell</u> - Study compares the usage of Cefazolin compared to Sulbactam/ampicillin - Cefazolin- first generation cephalosporin- had been previously used- control from the study - Control prevalence of MRSA in the ward and to reduce SSI caused by MRSA - Shorter duration of prophylaxis than was previously used - Results of SSIs caused by any organism not just MRSA was also attributed for
2. Was the assignment of patients to treatments randomised?	Yes No Can't <u>tell</u>
3. Were all of the patients who entered the trial properly accounted for at its conclusion?	<u>Yes</u> No Can't tell - 419 out of 441 patients prospectively evaluated ▪ 22 patients excluded because they were administered with antibiotics preoperatively ▪ All were accounted for in the methods ▪ No patient excluded- reliable
4. Were patients, health workers and study personnel 'blind' to treatment?	Yes <u>No</u> Can't tell - Patients and health workers were not blinded, this allows for the introduction of bias into the study.
5. Were the groups similar at the start of the trial?	- Baseline characteristics for both groups displayed no statistical significant differences at the start of the trial - Both arms of the trial had similar baseline characteristics- no significant difference between the groups despite having more patients in the SA group compared to the C group (187 vs 232) ▪ Mean age of the S/A group 46.14 years ▪ Mean age of the C group 47.34 years ▪ Numbers of inpatients with MRSA including colonization 10 in the S/A group and 8 in the C group ▪ Mean duration of post-operative closed-suction drainage was 1.79 days (0-14 days) in S/A group and 1.69 days (0-7 days) in the C group ▪ Mean duration of surgery was 137.8 minutes in S/A group and 124.0 minutes in the C group
6. Aside from the experimental intervention, were the groups treated equally?	- 419 out of 441 patients prospectively evaluated ▪ 22 patients excluded because they were administered with antibiotics preoperatively ▪ All were accounted for in the methods ▪ No patient excluded- reliable - Both groups were treated equally - Both S/A group and the C group were infused over the same time period- 15 minutes IV immediately after the induction of anaesthesia, 3 h after initial administration and 3 h after the second administration on the day of surgery ▪ However, the medical situations, hospital environments differ ▪ Duration of prophylaxis varies depending on each surgeon
7. How large was the treatment effect?	- SSIs caused by MRSA ▪ 0/187 in S/A group ▪ 3/232 in the C group - Deep incisional SSIs caused by MRSA ▪ 0/187 in S/A group ▪ 2/232 in the C group - Organ/space SSI caused by MRSA ▪ 0/187 in S/A group ▪ 1/232 in the C group - Spinal surgery SSI caused by MRSA ▪ 0/187 in S/A group ▪ 2/232 in C group - Closed fracture SSI caused by MRSA

	▪ 0/187 in S/A group ▪ 1/232 in C group - No significant differences in frequencies for spinal surgery or closed fracture surgery (P=0.4586 and P=0.2737) - Superficial SSI caused by *Enterococcus faecium* ▪ 1/187 in S/A group ▪ 0/232 in C group - Deep incisional SSI caused by MSSA ▪ 0/187 in S/A group ▪ 1/232 in C group - Deep incisional SSI caused by *Escherichia Coli* ▪ 0/187 in S/A group ▪ 1/232 in C group - Total number of SSIs (including SSIs caused by other organisms)- difference is not statistically significant ▪ 1/187 in S/A group ▪ 5/232 in C group
8. How precise was the estimate of the treatment effect?	- No significant differences were identified between the two arms of the trial (p>0.05) with 95% CIs.
9. Can the results be applied in your context?	- Difference in SSIs rates not statistically significant (P=0.17) - Study compares the usage of Cefazolin compared to Sulbactam/ampicillin - There is no difference between the two groups.
10. Were all clinically important outcomes considered?	- Yes, however SSIs were not specified for types of surgery. Thus, necessitating the need for further research.
Soriano et al., 2008	
1. Did the trial address a clearly focused question?	Yes No Can't tell - Trial assesses the optimal timing to infuse an antibiotic during knee arthroplasty performed during ischemia - Standard arm- 1.5g cefuroxime 10-30 minutes before inflation and placebo 10 minutes before release of tourniquet - Experiment arm- placebo 10-30 minutes before tourniquet inflation and 1.5g cefuroxime 10 minutes before release of tourniquet - Standard arm- 1.5g cefuroxime 10-30 minutes before inflation and placebo 10 minutes before release of tourniquet
2. Was the assignment of patients to treatments randomised?	Yes No Can't tell - This trial is a randomised trial - Single centre, randomized, double blind, placebo-controlled trial
3. Were all of the patients who entered the trial properly accounted for at its conclusion?	Yes No Can't tell - Yes, all patients were attributed for in the trials conclusion, all patients were analysed in the groups they were assigned too. - Patients were treated in an intent-to-treat basis
4. Were patients, health workers and study personnel 'blind' to treatment?	Yes No Can't tell - Yes, this trial is double-blinded reducing the introduction of bias with both assessors and patients blind to treatment.
5. Were the groups similar at the start of the trial?	- Baseline characteristics for both groups displayed no statistical significant differences at the start of the trial.
6. Aside from the experimental intervention, were the groups treated equally?	- Both arms treated the same- postoperative dose of 1.5g of cefuroxime administered at 6h after the end point of surgical procedure - 7 surgeons performed the procedure- ensure similar surgical technique, avoids bias and reduces SSIs.
7. How large was the treatment effect?	- Difference in SSIs rates not statistically significant (p>0.05) with 95% CIs.
8. How precise was the estimate of the treatment effect?	- There were no significant differences in the two arms of the trial (p=0.21) at 3 months, with 95% CI.
9. Can the results be applied in your context?	- The administration of prophylactic antibiotics just before tourniquet release was not inferior to standard antibiotic prophylaxis.
10. Were all clinically important outcomes considered?	- The administration of prophylactic antibiotics just before tourniquet release was not inferior to standard antibiotic prophylaxis. However, this is the first trial analysing the best moment to infuse an antibiotic during knee arthroplasty, thus further research is necessary

	before it can be applied to practise.
Backes et al., 2017	
1. Did the trial address a clearly focused question?	Yes No Can't tell - Trial investigates the effect of a single dose of preoperative antibiotic prophylaxis on the incidence of SSIs following removal of orthopaedic implants used for treatment of fractures below the knee.
2. Was the assignment of patients to treatments randomised?	Yes No Can't tell - Multicentre, double blind, randomized clinical trial - Randomization was performed using a randomization sequence generated by dedicated computer randomization software program - Randomization was conducted using a 1:1 ratio
3. Were all of the patients who entered the trial properly accounted for at its conclusion?	Yes No Can't tell - 500 patients included and accounted for in trial results. - 232 patients in Cefazolin treatment group - 245 patients in Saline group (control group) - 7 patients were lost to follow up
4. Were patients, health workers and study personnel 'blind' to treatment?	- Cefazolin group received 10000mg in a bolus of sodium chloride (0.9%) IV - Control group: received a bolus of sodium chloride (0.9%) IV (saline group) preoperatively - Bolus prepared was identical in appearance
5. Were the groups similar at the start of the trial?	- Baseline characteristics for both groups displayed no statistical significant differences at the start of the trial.
6. Aside from the experimental intervention, were the groups treated equally?	- All patients were treated equally, there were no discrepancies between treatments. - All patients were treated on an intention- to treat basis.
7. How large was the treatment effect?	- 232 patients in Cefazolin treatment group - 245 patients in Saline group (control group)7 patients were lost to follow up - SSI ▪ 30/232 Cefazolin group ▪ 36/245 Saline Group (control group) - Superficial SSI ▪ 29/232 Cefazolin group ▪ 29/245 Saline Group - Deep SSI ▪ 1/232 Cefazolin group ▪ 7/245 Saline Group
8. How precise was the estimate of the treatment effect?	- Difference in SSI of primary outcomes was not statistically significant. ($p>0.05$) with 95% CIs.
9. Can the results be applied in your context?	- A single preoperative dose of IV Cefazolin compared with saline did not reduce the risk of SSI within 30 days following implant removal.
10. Were all clinically important outcomes considered?	- A single preoperative dose of IV Cefazolin compared with saline did not reduce the risk of SSI within 30 days after implant removal. - The effect of a single dose of preoperative antibiotic prophylaxis on the incidence of SSIs following removal of orthopaedic implants used for treatment of fractures below the knee is not favourable.

Appendix 2: Summary of reviewed papers.

Clinical Condition	• Dose	• Comparator	• Duration of treatment	• Patients Number	• Clinical endpoints	• Outcome	• Comments	• Reference
Clean orthopaedic surgery	Unasyn-S (1.5g/vial, containing 1.0g ampicillin and 0.5g sulbactam) Cefamezin- a (alpha) (1.0g/vial containing 1.0g cefazolin)	Sulbactam/ampicillin vs cefazolin	Immediately after induction of anaesthesia, 3h after initial administration, 3 hours after second administration, postoperatively twice daily for up to 3 days.	419	Presence/ absence SSIs	SSIs caused by MRSA found in 3 patients S/A group- 1/187 patients (0.53%) C group- 5/232 (2.16%)	Difference in SSIs rates not statistically significant (P=0.17)	(Kato et al., 2006)
Safety of cefepime and ceftriaxone as peri-operative systemic antimicrobial prophylaxis in elective orthopaedic surgery	50mg/kg up to 2g single dose perioperative intravenous infusion at least 30 minutes before incision	Ceftriaxone (group A) vs Cefepime	Each patient received 50mg/kg (maximum 2g) IV administered 30 min before surgery. If surgery lasted longer than 4h or blood loss surpassed 1500ml dose was repeated.	230	Surgical site infection between day 3 and 30 following surgery.	Incidence of SSI in elective surgery Total 8 patients (3.47%) developed SSI. Ceftriaxone group was 2.7% 3/113 (95% CI 0.3-5.6) compared to 4.3% 5/117 (95% CI 0.6-7.9) in Cefepime group (P=0.380) Efficacy of cefepime over ceftriaxone Ceftriaxone 0.9 and Cefepime 1.45 per 1000 person (p=0.380)	Difference in SSIs not statistically significant	(Marwa et al., 2015)
Hemiarthroplasty for treatment of an intracapsular fracture of the femur.	Low dose antibiotic-laden cement (Palacos R + G, 0.5g of Gentamicin) vs high dose, low dose antibiotic 1g Clindamycin and 1g of Gentamicin (Copal G+C)	Low dose vs high dose of antibiotic-laden cement.	Ongoing- dual antibiotic laden cement was used in surgery.	848	Presence/ absence SSIs one year after surgery	Primary outcome: Deep SSI 13/376 control group vs 4/360 intervention group Death 60/390 control group vs 56/347 intervention group Deep or superficial SSI 20/376 vs 6/360	Difference in SSI of primary outcomes was statistically significant (P=0.041) Difference in SSI in secondary outcomes was also statistically significant (deep or superficial SSIs) p=0.009 providing strong evidence total number of infections both deep and superficial differed significantly between groups.	(Sprowson et al., 2016)
Single dose of preoperative antibiotic prophylaxis on the incidence of SSIs following removal of orthopaedic	Cefazolin group received 10000mg in a bolus of sodium chloride (0.9%) IV Control group: received a bolus of sodium chloride (0.9%) IV (saline group) preoperatively	Cefazolin group received 10000mg in a bolus of sodium chloride (0.9%) IV	Administered 15 to 60 minutes prior to incision by the anaesthesiologist or nurse anaesthetist in absence of surgeon	500	SSI within 30 days after removal of orthopaedic implants- defined by the CDC	232 patients in Cefazolin treatment group 245 patients in Saline group (control group)7 patients were lost to follow up Primary outcome SSI	Difference in SSI of primary outcomes was not statistically significant.	(Backes et al., 2017)

implants used for treatment of fractures below the knee					SSI is classified as superficial or deep	30/232 Cefazolin group 36/245 Saline Group (control group) Superficial SSI 29/232 Cefazolin group 29/245 Saline Group Deep SSI 1/232 Cefazolin group 7/245 Saline Group		
Thoracolumbar spinal surgery	170 patients- 24-hour group 144 patients randomized to drain duration group- received antibiotics for the duration of time for which the drain was placed	24-hour group vs drain duration group	24-hour group vs drain duration group	314	Presence/ absence SSIs	SSI infection -21/170 24-hour group (Control) -19/144 drain duration group Deep infection -7/170 24-hour group (Control) -8/144 drain duration group SSI in primary surgery -10/119 24-hour group -10/97 Drain-duration group SSI in revision surgery -11/80 24-hour group -9/70 Drain- duration group	Difference in SSI infection rates not statistically significant	(Takemoto et al., 2015)
Knee arthroplasty performed during ischemia	Experiment arm- placebo 10-30 minutes before tourniquet inflation and 1.5g cefuroxime 10 minutes before release of tourniquet Standard arm- 1.5g cefuroxime 10-30 minutes before inflation and placebo 10 minutes before release of tourniquet	placebo 10-30 minutes before tourniquet inflation and 1.5g cefuroxime 10 minutes before release of tourniquet	Post operatively patients regularly monitored 15 days, 3 ,6 and 12 months after discharge	908 patients	Presence/ absence SSIs	SSIs 3 months 15/442 standard arm 9/466 experimental SSIs 12 months 16/442 standard arm 12/ 466 experimental SSI MRSA 1/442 standard arm (1/16) 1/466 experimental (1/12) SSI MSSA 6/442 standard arm (6/16) 3/466 experimental arm (3/16) SSI Pseudomonas aeruginosa 4/442 standard arm (4/16) 2/466 experimental arm (2/12) SSI Escherichia Coli 1/442 standard arm (1/16) 1/466 experimental arm (1/12)	Difference in SSIs rates not statistically significant	(Soriano et al., 2008)

CONCLUSION

Although the usage of antibiotic prophylaxis is widely accepted in orthopaedic surgery, there is considerable debate over: choice of antibiotic, Duration of antibiotic administered and the optimal timing of antibiotic administration across different types of orthopaedic surgery. Data extracted from the six studies included in this meta-analysis is presented in appendix 2.

The principal discovery of the analysis highlighted that the use of high dose dual-antibiotic impregnated cement in HA does significantly reduces the rate of SSI development when compared to a standard low dose single antibiotic loaded bone cement (p=0.041) (Sprowson et al., 2016). However other studies demonstrated that the addition of any substance to bone cement has the potential to have an effect on its mechanical properties (Wang et al., 2013). Furthermore, clinical studies have illustrated low-dose (<2g of antibiotic powder per 40g cement) of antibiotic laden bone cement should not lead to an increase of the mechanical loosening rate (Jiranek, Hanssen and Greenwald, 2006) and high-dose (>4.5g of gentamicin powder per 40g cement) may decrease the mechanical strength of the antibiotic cement (Lautenschlager et al., 1976). However, patients included in Sprowson et al., (2016) did not display rates of mechanical loosening in either arms of the study even after being monitored for 1 year post-operatively.

Compared to the Sprowson et al., (2016) study, the Backes et al., (2017) study results were not statistically significant even though the trial was multicentre and double-blinded decreasing selection bias. Backes et al., (2017) investigated the effect of single dose of preoperative antibiotic prophylaxis on the incidence of SSIs following removal of orthopaedic implants (OI). A study measuring the SSI rate following OI removal identified 11.6% SSI rate, with the highest incidence occurring in the lower leg region (Backes et al., 2015). Higher than anticipated SSI rates following removal of OIs have been reported, justifying the investigation of the potential benefits of antibiotic prophylaxis in removal of OIs (Vos, Hanson and Verhofstad, 2012). In spite of more deep SSIs being present in the saline group than Cefazolin group (1 patient vs. 7) the difference was not statistically significant. This may be due to the number of patients in participating centres not being available, which may introduce selection bias. Cefazolin was the antibiotic used in the intervention group in the Backes et al., (2017) trial, and although cephalosporins exhibit a strong safety profile they remain ineffective against 90% coagulase-negative Staphylococci, which explains why they are no longer the first-line prophylactic antibiotic of choice in many hospitals (Aujla et al., 2013). Furthermore, single dose cephalosporins have been identified to promote colonisation with *Clostridium difficile*, thus limiting their usage in orthopaedic surgery (Privitera et al., 1991).

As opposed to Sprowson et al., (2016) and Backes et al., (2017) the study conducted by Kato et al., (2006) was a randomised prospective study. Due to the lack of literature found investigating the incidence of SSI caused my MRSA, the Kato et al. (2006) trial has been included in this review, this emphasises the necessity for more research to be conducted in the field. Both arms of the study had similar baseline characteristics, with no significant different amongst either of the groups. The study investigated the prophylactic use of Cefazolin (1.0g/vial containing 1.0g Cefazolin) as the control compared to ampicillin and sulbactam (1.5g/vial containing 1.0 g ampicillin and 0.5g sulbactam). However, results from the retrospective review conducted by Williams and Gustilo (1984) found no difference in deep-infection rate amongst those who received prophylaxis for three days compared to those received a one-day course of prophylactic antibiotics, thus reinforcing prophylactic antibiotic coverage should be restricted to 24-hours postoperatively. Takemoto et al., (2015) also investigated the timing of 24-hour antibiotic prophylaxis after spinal surgery in which a drain was utilized. Although use of a drain was not investigated in the Williams and Gustilo trial, results from Takemoto et al., (2015) study also showed no statistical significance in SSI outcomes when timing of postoperative antibiotic prophylaxis was investigated. The common practice to prevent infection in spinal surgery includes the postoperative use of prophylactic antibiotics for the duration the drain is in place. Although, this raises concerns amongst prescribers regarding prolonged antibiotic administration, bacterial resistance, cost and development of opportunistic infections.

Data pooled from Soriano et al., (2008) similarly to Kato et al., (2006) investigated the relative risk and 95% CIs for the incidence of SSIs caused by MRSA, MSSA, *Escherichia coli* and found no statistical significance. Soriano et al., (2008) investigated the rate of SSIs on timing of administration of used antibiotic prophylaxis for primary TKA performed during ischaemia. Unlike other trials discussed this is a single-centre trial, which may allow the introduction of bias. However, similarly to Sprowson et al., (2016) and Backes et al., (2017) the study design was randomized and double-blind restricting the introduction of performance and selection bias. Though the SSI prevalence was consistence across both trial arms the lack of available literature substantiates the need for further studies to be conducted.

Implications for practice

This systematic review and meta-analysis recommends the use of high-dose antibiotic loaded bone cement and prophylactic oral antibiotics concurrently and as indicated, to prevent SSIs in hemiarthroplasties. No evidence was found in the studies analysed to support prolonged use of prophylactic antibiotic post-operatively in preventing SSIs, instead it could lead to antibiotic resistance. However this systematic review also

highlights the urgent need for more double blind RCT to validate further the prophylactic use of antibiotics.

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