Systematic Review and Meta-analysis of Randomized Controlled Trials of Antibiotics and Antiseptics for Preventing Infection in People Receiving Primary Total Hip and Knee Prostheses

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Infection rates in primary (first-time) major joint arthroplasty continue to be a significant issue. The effect of antibiotic and antiseptic prophylaxis on outcomes for this type of surgery has not been adequately reviewed. A systematic search of the main databases for randomized controlled trials (RCTs) evaluating antibiotics and antiseptics was conducted to evaluate the predetermined endpoints of infection, adverse events, costs, quality of life, and concentration levels of antibiotics. A meta-analysis using pooled effect estimates and fixed-effect and random-effect models of risk ratios (RR), calculated with 95% confidence intervals (CI), was utilized. Thirty (30) RCTs examined the effects of antibiotic and antiseptic prophylaxis on infections after primary total hip arthroplasty (THA) (total of 11,597 participants) and total knee arthroplasty (TKA) (total of 6,141 participants). For THA, preoperative systemic intravenous (i.v.) antibiotic prophylaxis may be effective in reducing the incidence of infection after THA from 6 months to ≥5 years. For TKA, there is no RCT evidence that antibiotics and/or antiseptics have any effect on infection rate. Preoperative systemic antibiotic prophylaxis in primary THA may be effective at reducing infection rate. There is no evidence that timing, route of administration, or concentration levels have an effect on reducing infections, adverse events, or costs in THA or TKA. Many of the trials included in this study were published in the 1980s and 1990s. Thus, it would be important to replicate a number of them based on current patient demographics and incidence of bacterial resistance.

Over 1.5 million primary total hip (THA) and knee (TKA) replacements (arthroplasties) are implanted annually worldwide (1). Additionally close to 1 million are performed in the United States annually (320,000 THA and 630,000 TKA) (2). Additionally, over 10 million people in the United States live with a total hip or knee replacement (3).

The incidences of infection associated with these types of replacements have been estimated to be anywhere from 0.39% to 2.5% for primary TKA (4–7) and 1% to 2% for primary THA (4, 5, 8, 9). In developed countries such as the United States, there has been a close to 2-fold increase in the incidence of infection in THA and TKA between 1990 and 2004 (10). This increase is due to patient and surgery-related factors (e.g., tobacco abuse, obesity, immunosuppression, diabetes, and longer operative times) (11, 12). This infection burden is expected to increase due to the number of primary and revision procedures, which is expected to increase dramatically over the next 20 years (10).

Prosthetic infections also have an overall mortality rate of 1% to 2.7% for patients around 65 years of age, increasing to 7% for patients who are >85 years old (13). These infections require three to four times the hospital and surgical resources required for (uninfected) primary replacement surgery (14), and costs to treat them stand at or exceed US$50,000 per replacement for infection (15–17).

Antiseptics and antibiotics are antimicrobial substances that are able to kill or inhibit the growth of microorganisms. Antiseptics are applied to the skin and nostrils prior to surgery to reduce the possibility of infection. Antibiotics can be delivered either locally or systemically (to the whole body). When delivered locally, during these types of surgery, antibiotics are commonly mixed with the cement used to fix the implant to the bone. If delivered systemically, the antibiotics are administered intravenously prior to the surgery. Furthermore, surgical antibiotic prophylaxis should be administered in sufficient doses (amount and duration) so as not to overwhelm the host's defenses or permit the emergence of microbial resistance, while ensuring that the antibiotic is present in the blood serum and tissues during the entire time the wound is open and at risk for infection (18). Studies have examined commonly used antiseptics for surgical site antisepsis and have found that chlorhexidine-alcohol is superior to povidone-iodine (19).

Protocols and guidelines have been developed for antibiotic and antiseptic prophylaxis for many different types of surgical procedures (20, 21), but to date, none relate to primary total joint replacements. Such guidelines generally advocate antibiotic administration 1 h prior to initiation of the surgical procedure and discontinuation 24 to 48 h postoperatively (20). It is also impor-

tant to separate out primary THA procedures from primary TKA procedures and not to evaluate and report on a combined rate of infections (TKA plus THA), as there are differences in infection rates between the two types of implants (10). Only two meta-analyses of the results (THA and TKA) have been published to date. The first systematic review examined primary THA (22) but ended up also evaluating studies where THA and TKA were performed but were not considered separately. Furthermore, this meta-analysis is now out of date, as there have been advances in antibiotic agents and joint replacements since its publication. It focused primarily on a comparison of different types of antibiotics in order to evaluate the superiority of certain antibiotics, and it did not use the accepted criteria for defining a surgical site infection (SSI) (23). The second systematic review included English-language publications only (24), with a restricted definition of infection based on the presence of visible purulent exudate at the surgical site. Additionally, this review only examined primary or revision THA or TKA and limited the analysis of local antibiotic administration solely to antibiotic-impregnated cement.

Another reason why it is important to undertake this study is the risk posed by nosocomial (hospital-acquired) bacterial infections that are resistant to the antibiotics commonly used prophylactically in orthopedic procedures, such as THA and TKA (25). These resistant bacteria include *Clostridium difficile* and methicillin-resistant *Staphylococcus aureus* (MRSA). Cefuroxime, a second-generation cephalosporin, is an example of a prophylactic antibiotic commonly used in THA and TKA to which *C. difficile* (26) and MRSA (27) can be resistant. Patients undergoing THA or TKA can have an increased risk of developing *C. difficile* infections due to their more advanced age and the length of their hospital stay (28). While incidence of hospital-acquired MRSA seems to be declining (29), infections caused by MRSA can be 1.19 times more expensive to treat than infections caused by methicillin-sensitive *Staphylococcus aureus* (30).

An additional reason to perform this study is that there is a statistically significant difference in infection rates between THA and TKA (10), which is likely due to the higher prevalence of obesity (i.e., a body mass index [BMI] of more than 30) and diabetes in TKA patients than that in THA patients (31). It has also been noted that infection after a total joint implant is markedly higher in obese patients (32) and that obesity and diabetes have been noted to be independent predictors of infection in patients receiving a TKA (33, 34).

MATERIALS AND METHODS

A systematic review and meta-analysis of randomized controlled trials (RCTs) was undertaken that investigated the effect of perioperative antibiotic prophylaxis, with or without antiseptics, on outcomes related to surgical site infections (SSIs) during primary THA or TKA replacement. For definition purposes, in this analysis we are defining a primary THA as first-time replacement of the femoral head of the femoral bone and the acetabulum (socket) of the pelvic bone. Similarly, primary TKA is defined as first-time replacement of the top/upper portion of the tibial bone and the bottom portion of the femoral bone (or femoral condyles) and/or the replacement of the patella. Implants that did not meet the definition of THA and TKA were excluded. The years in which antibiotics and antiseptics were first introduced up to the present were considered. All languages were considered, and preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines were followed.

The search methodology, criteria, and databases searched are as follows.

Electronic searches. The following electronic databases were searched: the Cochrane Wounds Group Specialized Register (searched 31 March 2015), the Cochrane Central Register of Controlled Trials (CENTRAL, 2015, issue 3), the Database of Abstracts of Reviews of Effects (DARE, 2015, issue 1), the NHS Economic Evaluation Database (NHS EED, 2014, issue 1), Ovid MEDLINE (1948 to week 15, March 2015), Ovid MEDLINE (in-process and other nonindexed citations, 31 March 2015); Ovid EMBASE (1980 to week 15, 2015), EBSCO CINAHL (1982 to 31 March 2015), and the Network Digital Library of Theses and Dissertations (NDLTD).

Searching other resources. We attempted to contact the corresponding authors of included trials (where updated contact information existed) in addition to the manufacturers and distributors of antibiotics (linezolid, quinupristin-dalfopristin, daptomycin, tigecycline, telavancin, and other antistaphylococcal agents and antiseptics). U.S. Food and Drug Administration (FDA) briefing documents used in the licensing of antistaphylococcal agents were also searched. The citation lists of the papers identified by the above strategies were also checked for further reports of eligible studies. The following journals were also hand searched: the Journal of Bone and Joint Surgery (American volume) (most recent 6 months up to 3 April 2015; searched on 3 April 2015), the Journal of Bone and Joint Surgery (British volume) (most recent 6 months up to 3 April 2015; searched on 3 April 2015), Clinical Orthopedics & Related Research (most recent 6 months up to 3 April 2015; searched on 3 April 2015), and the Journal of Antimicrobial Agents and Chemotherapy (most recent 6 months up to 3 April 2015; searched on 3 April 2015).

Hand searching the journals above was undertaken because of the time lag between their publication and their availability on electronic indexes.

In addition, ClinicalTrials.gov was searched on 10 March 2015 to identify any trials in process or recently completed. Google was searched on 12 March 2015 using the search terms mupirocin, prophylaxis, and orthopedic. The first 8 pages of results were evaluated.

Medical subject headings (MeSH) search terms can be found in Appendix S1 in the supplemental material. Two of us independently screened the titles and abstracts of all studies identified by the search. Upon verbal agreement of these two, full text versions of all studies identified as potentially relevant were obtained, and two of us independently assessed them against the inclusion criteria. Any disagreements between these two were resolved by discussion or adjudicated by the third author.

Data collection and analysis. (i) Selection of studies. Two of us independently screened the titles and abstracts of all studies identified by the search. Upon agreement of these two, full text versions of all studies identified as potentially relevant were obtained, and two of us independently assessed them against the inclusion criteria. Any disagreements between these two were resolved by discussion or adjudicated by the third author. Only full text versions of studies were considered (published or unpublished). Abstracts and conference proceedings were not considered unless a full-length manuscript existed.

(ii) Data extraction and management. A data extraction form was developed (see Appendix S1 in the supplemental material). One of us extracted the data, and a second validated the extracted data (performed via written comments and verbally). If a study had more than one publication, all versions were considered in order to maximize data extraction, and the primary publication was identified along with the secondary references.

Assessment of risk of bias in included studies. Two of us independently assessed each included study using the Cochrane collaboration tool for assessing risk of bias (35). This tool addresses six specific domains, namely, sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other issues (e.g., extreme baseline imbalance) (see Appendix S1 in the supplemental material for details of the criteria on which judgements were based). Blinding and completeness of outcome data were assessed for each outcome separately. A risk of bias table was completed for each eligible study. Any disagreements among us were discussed to achieve a consensus.

Assessment of risk of bias was evaluated using a risk of bias summary figure that presents all of the judgements in a cross-tabulation of study by entry. This display of internal validity indicates the weight the reader may give the results of each study.

Funnel plots were used to help in the assessment of selection bias, and the plots were examined for evidence of potential publication/location bias (high versus low impact journals and country publication bias). If asymmetry existed in the funnel plots, selection bias was examined further. In addition, a separate examination of the results was reported according to journal of publication and country to determine whether results differed according to the impact of the journal (high versus low [36]) and country (location bias [37]).

We also assessed studies other than RCTs (i.e., quasi-RCTs) using the same criteria. However, no quasi-RCTs were included due to the identification of RCTs. We incorporated the results of the risk of bias assessment into the study through systematic narrative description and commentary about each of the domains, leading to an overall assessment of the risk of bias of the included studies and a judgement about the internal validity of the results.

Measures of treatment effect. Results of binary outcomes were summarized descriptively (e.g., infection) as percentages, and presented treatment comparisons were summarized as risk ratios (RR) with corresponding 95% confidence intervals (CI). For continuous data (e.g., costs, length of stay, quality of life), we used the mean difference (MD) when trials measured outcomes in the same way, and we used the standardized mean difference (SMD or Hedges' adjusted g) when trials used different methods to measure the same outcomes (38).

Unit of analysis issues. If clustering existed and study comparisons did not account for clustering during analysis, the goal was to reanalyze these data, where possible, by calculating an effective sample size. In the event that the intraclass correlation coefficient (ICC) for clustering was reported, it was used to estimate the effective sample size. Otherwise, an attempt was made to estimate the ICC using external sources. If reanalyzed, we annotated the resulting P value as "reanalyzed." Additionally, since primary THA and TKA are major surgeries, it was highly unlikely that a patient would undergo surgery on 2 legs at the same time.

If trials included multiple intervention groups (e.g., different antibiotics), the goal was to split the shared control group into two or more groups with smaller sample sizes, depending upon the number of interventions and to include two or more comparisons.

Dealing with missing data. Missing data for primary binary outcome variables were assessed as follows. (i) Where possible, the original investigators were contacted to request the missing data. (ii) If it was not possible to obtain the missing data from the original investigators, it was assumed that the data were missing at random or not missing at random. For this study, the work of Yuan and Little (39) was used to estimate the impact of the missing at random assumption. If the analysis determined that the impact of the missing data was low, the assumption was made that the data were missing at random. In such a case, it was considered acceptable to ignore the missing data. (iii) If, according to the methodology of Yuan and Little (39), the data were not missing at random, the plan was to impute the missing data with replacement values and treat these as if observed. A sensitivity analysis would then be performed to assess how sensitive the results were to inclusion and exclusion of the imputed values. (iv) Lastly, if the data were not missing at random, a discussion of the potential impact of missing data on the findings of the study was included in Discussion.

It was possible that information about study design characteristics needed for subgroup analyses would not be provided in the original trial reports as well as data relating to secondary outcomes such as cost. In such cases, attempts were made to contact authors. The impact of missing data is also addressed in Discussion.

Authors of papers that we identified only as abstracts were contacted
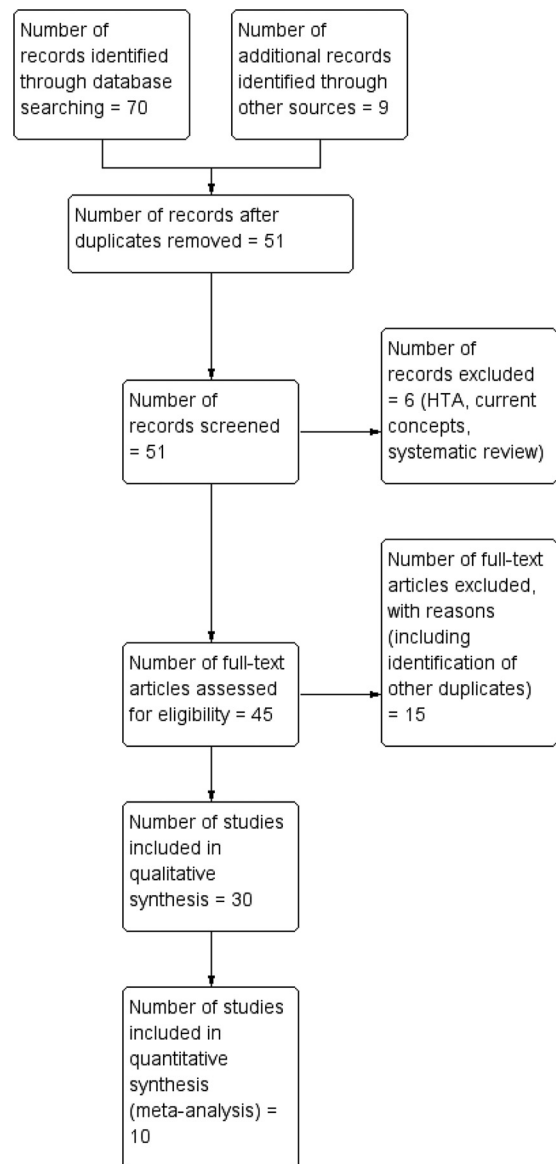
FIG 1 PRISMA flow diagram.

to see whether the full paper had been published in a peer-reviewed journal or was available from the author as an unpublished draft.

Assessment of heterogeneity. The I^2 statistic was used to determine statistical heterogeneity and the appropriateness of meta-analysis. The heterogeneity thresholds described in the Cochrane Handbook for Systematic Reviews of Interventions were used to identify the levels of heterogeneity in the trials. These thresholds are 0% to 40% (might not be important), 30% to 60% (may represent moderate heterogeneity), 50% to 90% (may represent substantial heterogeneity), and 75% to 100% (considerable heterogeneity) (35). If the I^2 value was greater than 60%, a sensitivity analyses was undertake in an attempt to identify those studies that were most likely to be causing the problem. If there were only a few such studies and they could be identified, the reasons for their differences were explored and the appropriateness of removing them was determined. Where appropriate, meta-analysis excluding these studies was performed. Likely variables that might represent important clinical differences included type of implant (cemented versus noncemented), timing of antibiotic administration, route of antibiotic administration, dosing of antibiotics, and type/spectrum of antibiotic.

TABLE 1 Studies included in analysis broken out by outcome, primary THA or TKA

Comparison	Primary total hip arthroplasty (n = 11,597)	Primary total knee arthroplasty (n = 6,141)
Preoperative systemic i.v. antibiotic versus placebo (total of 4 studies identified)	Ericson 1973 (51), Gunst 1984 (69), Hill 1981 (49), Schulitz 1980 (44)	None
One preoperative systemic i.v. antibiotic vs another (total of 9 studies identified)	Davis 1987 (47), DeBenedictis 1984 (66), Evard 1988 (67), Mauerhan 1994 (53), Pollard 1979 (48), Soave 1986 (45), Suter 1994 (54), Scaglione 1997 (55), Tyllianakis 2010 (59)	Chareancholvanich 2012 (60), Davis 1987 (47), DeBenedictis 1984 (66), Mauerhan 1994 (53), Soave 1986 (45), Tyllianakis 2010 (59)
Systemic i.v. antibiotic ± local antibiotic (total of 1 study identified)	None	Hinarejos 2013 (62)
Timing and route of administration (total of 3 studies identified)	Josefsson 1981 (42), McQueen 1990 (70)	McQueen 1990 (70), Soriano 2008 (58)
Dosing regimens (total of 2 studies identified)	Wymenga 1992 (71), Ritter 1989 (43)	Ritter 1989 (43)
Concentration levels of antibiotics in surrounding tissues (total of 5 studies identified)	Vainionpää 1988 (46)	De Lalla 1993 (65), Friedman 1990 (68), Johnson 1987 (72), Richardson 1993 (52), Vainionpää 1988 (46)
Nasal antiseptic versus placebo (total of 1 study identified)	Kalmeijer 2002 (56)	Kalmeijer 2002 (56)
Nasal and antiseptic soap versus placebo (total of 1 study identified)	van Rijen 2012 (61)	van Rijen 2012 (61)
One preoperative antiseptic versus another (total of 2 studies identified)	Jacobson 2005 (57), Phillips 2014 (64)	Jacobson 2005 (57), Phillips 2014 (64)
Additional antiseptic application versus traditional antiseptic application (total of 1 study identified)	Morrison 2014 (63)	Morrison 2014 (63)

Lastly, as part of the assessment of heterogeneity, in those studies that could be combined for meta-analytic purposes, a qualitative assessment of the clinical heterogeneity (differences associated with the participants and interventions) and methodological heterogeneity (differences in study design or risk of biases) was also undertaken—especially where substantial statistical heterogeneity existed (I^2 value of >50%).

Assessment of reporting biases. Funnel plots were used to assess reporting bias. Each primary outcome was reported separately. Furthermore, an assessment of publication bias (including a review of unpublished studies), location bias (types of journals), and language bias was performed. The results of trials were examined as favorable or not, with the assumption that favorable results demonstrated a positive effect of antibiotic prophylaxis in lowering the infection rate and, thus, were published (versus not published) (40). Location bias refers to more significant results being published in less-respected/low-impact-factor journals (36). Lastly, an analysis was performed of the reporting of outcomes (reporting bias) as identified below in the risk of bias tables.

Data synthesis. Where possible, studies that were similar were grouped together. A fixed-effect meta-analysis was used first. In the absence of heterogeneity (I^2 statistic of 0%) or in the presence of low heterogeneity (I^2 statistic of <40%) in the initial fixed-effect model, it was assumed that the observed difference was solely due to chance and used only a fixed-effect model. If heterogeneity was moderate in the fixed-effect model (I^2 statistic of >40% and ≤60%), a random-effects model was used when heterogeneity could not be readily explained, otherwise a fixed-effect model was employed (35). In situations of high heterogeneity, a sensitivity analysis was undertaken as described below to identify the studies that were causing the problem and to determine the appropriateness of removing them (35).

Subgroup analysis and investigation of heterogeneity. We planned to perform subgroup analyses, if needed, by grouping studies on the basis of characteristics to be investigated for heterogeneity, including type of implant (e.g., cemented versus noncemented), route of administration (systemic versus local), and timing of perioperative administration. However, these characteristics could not be investigated in subgroup analysis, as the relevant data were not reported in the studies included in this work.

Sensitivity analysis. A sensitivity analysis was performed to determine the effect of risk of bias on the results. We classified studies as being at low risk of bias if the randomization sequence was generated appropriately,

the allocation was concealed, bias due to nonblinding was unlikely (with blinding of the outcome assessor evaluated only), and if incompleteness of outcome data had been addressed. Lastly Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) assessments were performed for the major findings.

RESULTS

Results of the search. The electronic searches identified a total of 70 potentially relevant reports. We obtained abstracts for all 70 for further review and evaluation (see PRISMA flow diagram in Fig. 1 for included and excluded studies).

Bibliographic reference checking of a Health Technology Assessment article (22), other systematic review articles (24), and of current concept review articles (15, 41) identified six additional articles (42–47). Hand searching of journals for RCTs also identified three articles (48–50). Thus, a total of nine studies were identified through hand searches.

After duplicates were removed, a total of 51 study reports were retrieved for full text screening.

Included studies. Thirty RCTs met the inclusion criteria for the study (42–49, 51–72). Table 1 identifies how the studies were broken down according to numbers of participants for THA and TKA and comparisons made in each study. Six study authors were contacted to clarify questions on the number of infections, blinding, and/or the randomization scheme, and five of these answered satisfactorily (Hinarejos et al. [62], Morrison et al. [63], Phillips et al. [64], Tyllianakis et al. [59], and van Rijen et al. [61]). On 26 March 2014 and 31 March 2014, we attempted to contact the lead author and coauthors of reference 56; eventually, on 2 April 2014, one of the coauthors stated that the data were not available regarding the breakdown of the number of infections by treatment group. Therefore, we used the data on infections, as they were presented in the Kalmeijer et al. (56) study. The majority of the studies were performed in Europe (20/30 or 67%). Eight studies were performed in the United States (8/30 or 27%). One study was

performed in Thailand. Twenty studies were single-centered, and 10 studies were multicentered.

For the included studies, the comparisons by type of implant along with summary data regarding trial design/methodology, sample size, setting, outcomes, and important differences among trials were as follows (see also the Characteristics of Included Studies section in Appendix S2 in the supplemental material for more details).

Excluded studies. Six of the 51 full-text copies of studies that were retrieved for assessment were excluded because they were technology assessments or systemic reviews/current concept papers (15, 22, 24, 41, 73, 74). Three quasi-RCTs were excluded because we identified RCTs that examined dosing regimens and so did not need to include quasi-RCTs (75–77). A number of RCTs were excluded where infections were not broken down according to the type of primary implant received (78–85) (the 1987 study by Jones et al. [50] referred to the same trial as the 1988 study by Jones et al. [79] and was thus counted as one excluded trial). Studies by Wall et al. (85) and Winter et al. (86) were excluded because the implant used was an endoprosthesis (i.e., only one part of the joint was replaced, such as the upper femur, and not the acetabulum in a hip). The Gilliam and Nelson study (87) was excluded, as it was not determined whether the total joint surgeries were of a primary or revision nature or whether they were TKA or THA. The Zde-blick et al. study (88) was excluded because it excluded total joint arthroplasty (TJA) patients. Thus, a total of 20 studies were excluded. For further detail on excluded studies, see the Characteristics of Excluded Studies in Appendix S2 in the supplemental material.

Risk of bias in included studies. (i) Generation of the randomization sequence. In the majority of the trials (16/30), the type of randomization scheme employed to allocate participants to one group or the other was not clear. In the other 14 trials, the randomization scheme employed was defined.

(ii) Allocation concealment. In the vast majority of the studies (26/30), it was not clear whether concealment of allocation occurred.

(iii) Blinding (performance bias and detection bias). In the majority of the trials (21/30), the clinicians performing the procedures knew the treatment group to which each patient was allocated (performance bias). Furthermore, in the majority of the trials (21/30), it was not clear whether outcome assessors were aware of the treatment group to which each patient had been allocated (detection bias). In one study in particular, that by Hill et al. (49), which was a very large multicenter RCT with over 2,100 participants, allocation concealment was broken for 169 patients after 5 days due to signs of infection (99 in the placebo group and 70 in the cefazolin group) to allow for modification of treatment if necessary. Thus, clinicians who were previously blinded to the treatment arm became aware of the treatment arm to which the patients were allocated.

(iv) Incomplete outcome data (attrition bias). In the majority of the trials (26/30), participants who entered the trial were followed up for the endpoint of infection— especially over the short-term (up to 1 year). As the follow-up period lengthened, there was a loss of participants, mainly due to death. Other reasons for attrition included lack of follow-up on living participants over time (45, 49), protocol violations (53), and reasons that were not stated (42). In the Hill et al. (49) study, one of the 10 trial sites was excluded for not sending in follow-up report forms; however, it

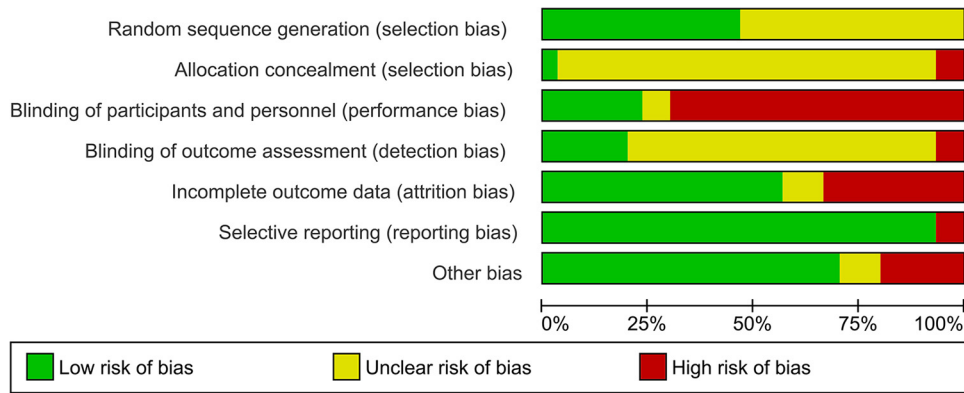| Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Chareancholvanich 2012	+	?	?	?	+	+	−
Davis 1987	?	?	+	?	−	+	?
DeBenedictis 1984	?	?	+	?	−	−	−
De Lalla 1993	?	?	−	?	+	+	+
Ericson 1973	?	?	+	?	?	+	+
Evard 1988	+	?	+	+	+	+	+
Friedman 1990	?	?	−	?	+	+	+
Gunst 1984	?	?	?	?	+	+	+
Hill 1981	+	?	−	?	?	+	+
Hinarejos 2013	+	?	−	+	+	+	+
Jacobson 2005	+	?	−	?	+	+	−
Johnson 1987	?	?	−	−	+	+	+
Josefsson 1981	?	?	−	?	−	+	+
Kalmeijer 2002	+	+	+	?	?	+	+
Mauerhan 1994	+	?	+	?	−	+	+
McQueen 1990	?	?	−	−	+	+	−
Morrison 2014	+	−	−	+	−	+	?
Phillips 2014	?	?	−	+	+	−	−
Pollard 1979	?	?	−	?	+	+	+
Richardson 1993	+	?	−	?	+	+	+
Ritter 1989	?	?	−	?	+	+	?
Scaglione 1997	?	?	−	?	+	+	+
Schultiz 1980	?	?	−	?	−	+	+
Soave 1986	?	?	−	?	−	+	+
Soriano 2008	+	?	−	+	+	+	+
Suter 1994	+	?	−	?	−	+	+
Tyllianakis 2010	+	?	−	+	+	+	+
Vainionpää 1988	?	?	−	?	+	+	−
van Rijen 2012	+	?	+	?	+	+	+
Wymenga 1992	+	−	−	?	−	+	+

FIG 2 Risk of bias summary.

FIG 3 Risk of bias graph.

was not clear how many participants were excluded because of this. Lastly, in the study by Ericson et al. (51), 59 out of 230 patients (26%) were excluded for reasons that did not include death. Most of these exclusions (44/59; 20 in the placebo group and 24 in the cloxacillin group) were due to the side effects of the procedure (nausea and vomiting, gastrointestinal symptoms, skin reaction). Again, it was unclear from the data how many of these participants were excluded in the THA group. In the Schulitz et al. study (44), 47 out of 259 patients (18%) were excluded for reasons other than death, including 12 in the control group who received antibiotics postsurgery, 16 who received another antibiotic during the 2-year follow-up, 7 who required additional surgery for reasons other than infection, and 10 who received a bilateral implant less than 6 months after the first surgery. The loss across all studies ranged from 0% to 50% (with the study by Hill et al. [49] at 50%). The Yuan and Little (39) methodology did not permit detection of a discernible pattern indicative of a relationship between the attrition rate and size of the effect in those studies included in the meta-analysis. The correlation that was found of -0.12714 between the attrition rate and effect size was not statistically different from zero. Accordingly, it was concluded that the attrition rate was not related to the size effect and that the "missingness" in the studies may be ignored—which in turn supports the missing-at-random assumption made in this section.

(v) Selective reporting (reporting bias). Most of the trials (28/30) reported on the outcomes described in their methods sections in their results sections. It should be noted, however, that the complete trial protocol was obtained for only one trial (63). There were several studies that listed infection as an endpoint in the methods section but did not define clearly what infection meant (Davis and Kane [47], Jacobson et al. [57], McQueen et al. [70], Ritter et al. (43), and Tyllianakis et al. [59]). For the study by

Phillips et al. (64), the endpoints of superficial infections and the length of hospital stay, which were listed in its summary protocol (NCT 01313182), were not reported on in the paper.

(vi) Other potential sources of bias. Most of the trials (29/30) were published in English in orthopedic or infectious disease journals. One trial was published in French (Gunst et al. [69]) and was translated by one of us (J. Voigt). No unpublished RCTs were identified. Five studies received funding/financial assistance from drug firms whose antibiotics were being evaluated (Charean-cholvanich et al. [60], DeBenedictis et al. [66], McQueen et al. [70], Vainionpää et al. [46], and Morrison et al. [63]). However, in the Morrison et al. (63) trial, the author stated that 3M (who provided funding) had no say in the trial development, execution, or writing and publication of the study, so the study was considered to be at unclear risk of bias, but the other four studies that received funding/financial assistance were deemed to be at high risk of bias.

The included studies were also examined for selection/location bias using funnel plot analyses; all funnel plots were symmetrical. All of the included studies were performed in developed countries—specifically in the United States and Europe. We identified no studies that were performed outside these regions. Four of the eight United States trials examined the effect of one antibiotic versus another on infection rate (Davis and Kane [47], DeBene-dictis et al. [66], Mauerhan et al. [53], and Soave et al. [45]). Two United States trials examined the dosing and concentrations of antibiotics (Friedman et al. [68] and Ritter et al. [43]). The first positive findings of the effectiveness of antibiotics for reducing the incidence of infection versus placebo were published in high-impact journals, namely, the Journal of Bone and Joint Surgery and The Lancet (Ericson et al. [51] and Hill et al. [49]). Statistically nonsignificant findings were published in low- and high-impact
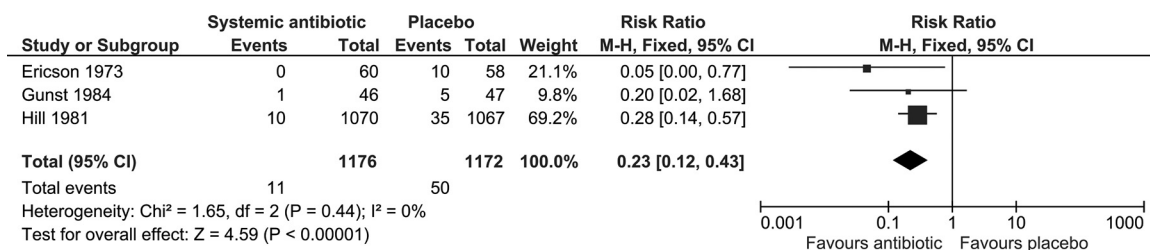

FIG 4 Forest plot THA. Infection at 6 months.

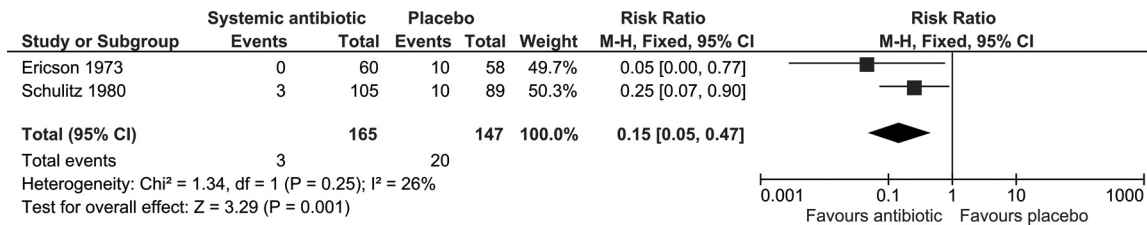| Study or Subgroup	Systemic antibiotic Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ericson 1973	0	60	10	58	49.7%	0.05 [0.00, 0.77]
Schulitz 1980	3	105	10	89	50.3%	0.25 [0.07, 0.90]
Total (95% CI)		**165**		**147**	**100.0%**	**0.15 [0.05, 0.47]**
Total events	3		20			
Heterogeneity: Chi² = 1.34, df = 1 (P = 0.25); I² = 26%						
Test for overall effect: Z = 3.29 (P = 0.001)						

FIG 5 Forest plot THA. Infection at 2.5 years.

medical journals, and thus we could draw no conclusions regarding location bias. Furthermore, we could draw no conclusions regarding location bias related to country-specific publication bias (37).

Risk of bias is found in Fig. 2 (risk of bias summary) and Fig. 3 (risk of bias graph) (see also Appendix S2 in the supplemental material).

The results of the search identified the following studies, which are broken out by outcomes (Table 1).

Effects of interventions (main outcomes). The effects of interventions by major findings are found in Appendix S3 in the supplemental material. As can be seen from these findings, the use of preoperative systemic intravenous (i.v.) antibiotics appears to have an effect on reducing infection rates for the short and longer term in primary THA (Fig. 4 to 6). These findings and the GRADE assessment can be found in Appendix S4 in the supplemental material. Further, it was found that the use of preoperative antibiotics versus that of intraoperative antibiotic-impregnated cement demonstrated no statistical difference in reducing the superficial and deep infection rates (Fig. 7). Again, this GRADE assessment can be found in Appendix S4 in the supplemental material. In all other findings examining the effect of antibiotics and/or antiseptics on the outcome of surgical site/systemic infection, there was no statistical difference in the comparisons made in their use in either primary TKA or THA. These comparisons included one antibiotic versus another (Fig. 8 and 9), dosing of antibiotics and antiseptics (preoperatively, intraoperatively, or postoperatively), and the timing of antibiotics (preoperatively, intraoperatively, and postoperatively) and antiseptics (preoperatively). Lastly, adverse events defined as repeat or revision surgery due to infection (Fig. 10) show no statistically significant difference when comparing preoperative systemic antibiotic prophylaxis to placebo.

Additional outcomes that were evaluated but not included were the concentration levels of the antibiotics (where this was the sole endpoint). One primary TKA study evaluated the concentration levels (in milligrams per liter) of systemic antibiotics delivered preoperatively in the blood and synovial fluid at 16 to 30 min, 31 to 45 min, and 46 to 60 min after the operation had begun (46).

It found high concentrations of the two antibiotics evaluated (cefamandole versus cloxacillin) in the blood and high concentrations of cefamandole in the synovial fluid at 16 to 30 min versus much lower concentrations of cloxacillin at that time point (33.2 ± 17.8 mg/liter versus 8.0 mg/liter, respectively; no statistical analysis was undertaken). Four small studies evaluated the concentration levels in milligrams per liter of various systemic or regional antibiotics delivered preoperatively in the surrounding tissue, bone, and serum (in milligrams per liter or micrograms per gram) after tourniquet inflation during and after the primary TKA procedure (52, 65, 68, 72). All of these trials administered a different systemic antibiotic preoperatively for prophylaxis and evaluated the concentrations at different times during surgery and in different tissues (e.g., bone, subcutaneous tissue, blood). The purpose of this evaluation was to determine whether the concentration of antibiotic was adequate (i.e., a sufficient dose to inhibit bacterial growth—known as the MIC). As a result of all of these differences, the trials were not pooled for meta-analysis. The largest trial in this group was that of Richardson et al. (52), which evaluated 36 participants. The Johnson (72) trial found that systemic antibiotics should be administered 10 min or more prior to tourniquet inflation in order to provide an adequate MIC. This concentration was significantly different (when evaluated in the surrounding subcutaneous fat) and an adequate MIC was reached when systemic i.v. antibiotics were administered at 10, 15, and 20 min prior to tourniquet inflation but not when administered 5 min prior to tourniquet inflation. However, this trial had a small sample size of 22 participants, did not evaluate the longer-term infection rate, and evaluated antibiotic concentrations in bone and the surrounding subcutaneous fat only (not in serum).

DISCUSSION

This is the first time RCTs have been evaluated, in a systematic manner (along with meta-analysis), for the effects of antibiotics and antiseptics in primary THA and TKA. The data from the trials included in this study suggest that systemic antibiotic prophylaxis delivered preoperatively in primary THA procedures significantly reduces the incidence of infection in the short term and longer

Study or Subgroup	Systemic antibiotic Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ericson 1973	2	60	14	58	22.5%	0.14 [0.03, 0.58]
Hill 1981	10	1070	49	1067	77.5%	0.20 [0.10, 0.40]
Total (95% CI)		**1130**		**1125**	**100.0%**	**0.19 [0.10, 0.35]**
Total events	12		63			
Heterogeneity: Chi² = 0.23, df = 1 (P = 0.63); I² = 0%						
Test for overall effect: Z = 5.36 (P < 0.00001)						
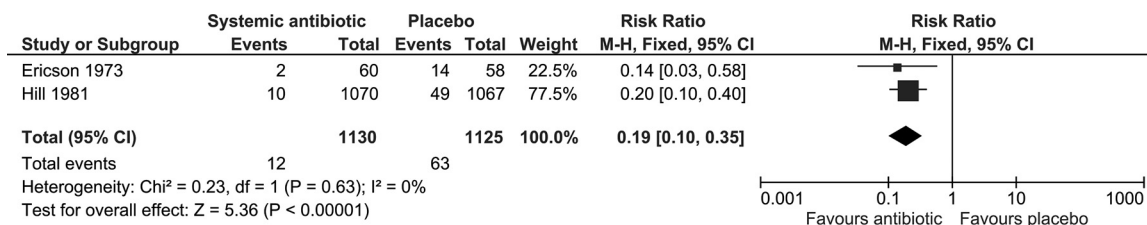
FIG 6 Forest plot THA. Infection at ≥5 years.

Study or Subgroup	Systemic antibiotic (SA)		Antibiotic cement (AC)		Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total			
McQueen 1990	9	190	16	190	17.9%	0.56 [0.25, 1.24]	
Josefsson 1981	62	835	74	853	82.1%	0.86 [0.62, 1.18]	
Total (95% CI)		1025		1043	100.0%	0.80 [0.60, 1.08]	
Total events	71		90				
Heterogeneity: Chi² = 0.93, df = 1 (P = 0.34); I² = 0%							
Test for overall effect: Z = 1.44 (P = 0.15)							

0.001   0.1   1   10   1000
Favours SA   Favours AC
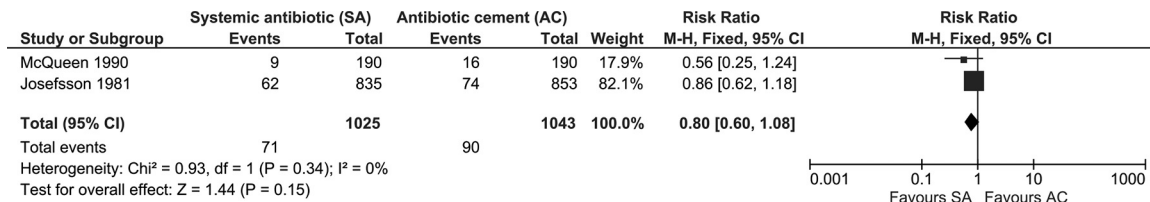
FIG 7 Forest plot THA: systemic antibiotic versus antibiotic cement. Infection at 2 years.

term (Fig. 4 to 6; see also Appendix S3 in the supplemental material). For all other outcomes, there were no differences found in any other comparisons made (see Appendix S3). Additionally, no studies were found that examined the use of antibiotics versus the use of placebo in primary TKA. GRADE assessment (see Appendix S4 in the supplemental material) of the two systemic i.v. antibiotics used in primary TKA and in comparing systemic i.v. versus antibiotic cement in TKA demonstrated a moderate quality of evidence finding—meaning that further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. The overall quality of the data in the vast majority of the studies was evaluated as having an unclear or a high risk of bias. Therefore, the overall quality of the data can be regarded as poor. Further, given that the age of the majority (20 out of 30) of these studies is >20 years and that patient characteristics have changed during this time (i.e., increased obesity and diabetes), it would be beneficial to replicate some of these trials—most especially in primary TKA.

Further, only 9 of the 30 RCTs included were performed after the year 2000 (56–64). Thus, there may be an issue in interpreting the applicability of their findings, as antibiotic-resistant bacteria, such as MRSA and *C. difficile*, have only recently become prevalent in the hospital environment. Additionally, there is a comparative dearth of high-quality published studies from the United States; only 9 of the 30 included studies were conducted in the United States (43, 45, 47, 53, 57, 63, 64, 66, 68), with six of them being at least 20 years old (43, 45, 47, 53, 66, 68). Further, patients today are 20% heavier and are more physically active, there are twice as many TKAs performed than THAs, and patients live more than 25% longer than they did when these trials were completed (89). Furthermore, diabetes in the United States is close to four times more prevalent than it was in 1990 (90), and obesity and diabetes are known risk factors for infection (10, 11). The implications of these findings are that there is a need for more up-to-date studies in the United States.

None of the 30 studies included in this study identified antimicrobial resistance to antibiotics. With the exception of those noted above, 21 out of the 30 studies are at least 15 years old (i.e., published prior to 2000). It has been noted that the greater the exposure of participants to cephalosporins (e.g., cefazolin and cefo-

nicid), the greater their risk for the development of MRSA infection (91). *S. aureus* is also one of the more common pathogens associated with orthopedic implant SSIs (18). Once MRSA is present, it forms a biofilm on foreign objects such as hip and knee implants, increasing the difficulty of eradicating it. In a study published in 2004 (92), it was found that there was a significant increase in the proportion of hospital-based MRSA infections from 22% in 1995 to 57% in 2001 (P value of <0.001 for trend). While there appears to be a recent decrease in hospital-based MRSA infections (93), mortality for these types of infections exceeds 20% (92), so they need to be closely monitored, and programs should be put in place to ensure appropriate interventions for infection control (94, 95). Finally, and unfortunately, based on the recent increase in incidence of *C. difficile* cases (a bacteria resistant to antibiotics), none of the more recent studies identified *C. difficile* as one of the microorganisms causing infection.

As it relates to the two other systematic reviews noted in the introduction, one published systematic review of antibiotic prophylaxis for wound infections in total joint arthroplasty (TJA) found that antibiotic prophylaxis is effective in reducing wound infections in TJA (24). Additionally, the AlBuhairan et al. (24) review found, as this study found, no difference in one antibiotic versus another. AlBuhairan et al. (24), however, include in their analysis studies that were excluded from this study because the number of infections could not be broken down by type of implant (78, 79, 81, 82) and lack of randomization (75–77).

This study goes further than that of AlBuhairan et al. (24) in performing meta-analyses on the studies identified, including an evaluation of antiseptics and including nine additional studies 44, 56, 58–64. This study agrees with that of AlBuhairan et al. (24) in that antibiotic prophylaxis is effective at reducing infections in primary THA. The current analysis further states that antibiotic cement with or without systemic i.v. antibiotic prophylaxis compared to systemic i.v. antibiotic prophylaxis alone does not reduce the infection rate in either THA or TKA.

Another meta-analysis of studies that investigated prophylactic antibiotic-impregnated cement versus a comparator group (which lumped systemic i.v. antibiotics, no antibiotics, and systemic i.v. antibiotics plus antibiotic cement together) in primary THA analyzed over 15,000 THAs for deep infection (74). It eval-
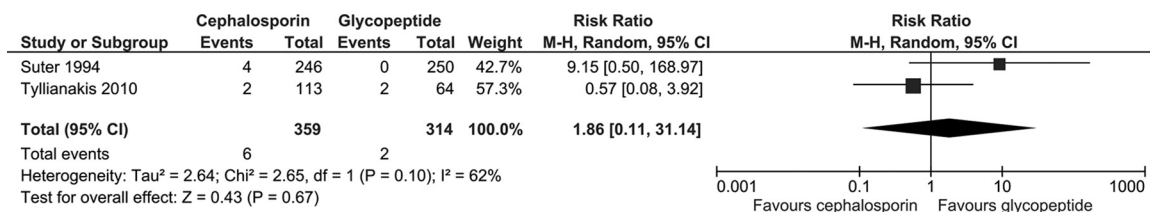
Study or Subgroup	Cephalosporin		Glycopeptide		Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
	Events	Total	Events	Total			
Suter 1994	4	246	0	250	42.7%	9.15 [0.50, 168.97]	
Tyllianakis 2010	2	113	2	64	57.3%	0.57 [0.08, 3.92]	
Total (95% CI)		359		314	100.0%	1.86 [0.11, 31.14]	
Total events	6		2				
Heterogeneity: Tau² = 2.64; Chi² = 2.65, df = 1 (P = 0.10); I² = 62%							
Test for overall effect: Z = 0.43 (P = 0.67)							

0.001   0.1   1   10   1000
Favours cephalosporin   Favours glycopeptide

FIG 8 Forest plot THA: i.v. systemic cephalosporin versus glycopeptide. Infection at 2 years.

Study or Subgroup	Antibiotic 1 Events	Total	Antibiotic 2 Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chareancholvanich 2012	0	56	1	56	12.4%	0.33 [0.01, 8.01]
Davis 1987	0	17	0	22		Not estimable
DeBenedictis 1984	0	21	0	23		Not estimable
Mauerhan 1994	7	178	7	207	53.7%	1.16 [0.42, 3.25]
Soave 1986	0	18	0	22		Not estimable
Tyllianakis 2010	4	75	3	35	33.9%	0.62 [0.15, 2.63]
Total (95% CI)		**365**		**365**	**100.0%**	**0.88 [0.40, 1.94]**
Total events	11		11			

Heterogeneity: Chi² = 0.86, df = 2 (P = 0.65); I² = 0%
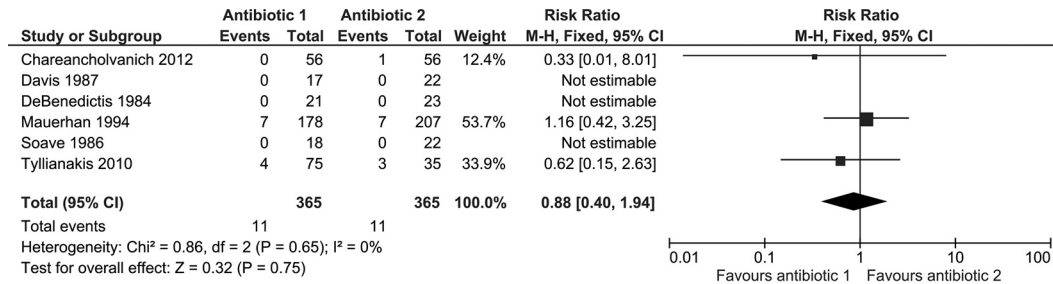Test for overall effect: Z = 0.32 (P = 0.75)

FIG 9 Forest plot TKA. Infection rate for one antibiotic versus that of another.

uated revision rates due to infection and showed a reduction in the rate of infection when antibiotic bone cement was used versus when it was not (1.2% versus 2.3%; RR, 0.51; 95% CI, 0.34 to 0.75; *P* value, 0.001). The main differences between the study of Parvizi et al. (74) and this study were that the Parvizi et al. (74) intervention group was given antibiotic cement and the comparator group included subjects given a combination of systemic antibiotics, no antibiotics, or systemic antibiotics plus antibiotic cement. Further, follow-ups at 2 and 4 years were also combined in the study of Parvizi et al. (74) to form the comparator group versus the antibiotic cement group. This study did not combine comparator groups nor did it combine durations of analysis for outcome assessment. The Parvizi et al. (74) analysis evaluated only deep infection (with a variety of definitions of deep infection accepted for inclusion), whereas the current analysis compared all infections (superficial and deep). The Parvizi et al. (74) analysis also included two RCTs included in the current study (42, 70) and included three retrospective reviews: Espehaug et al. (10,905 patients) (96), Lieberman et al. (35 patients) (97), and Lynch et al. (98) (1,542 implants). According to the definitions for quality assessment in observational studies established by Higgins and Green (35), these retrospective studies were of low quality, as there was no large treatment effect in any of these trials. Double counting of infection events was likely in the study by Parvizi et al. (74), as their study included participants in two later follow-up reports of Josefsson et al. (99) and Josefsson and Kolmert (100). A confounding point in the study by Parvizi et al. (74) was the use of systemic antibiotics in combination with antibiotic cement, which made it difficult to determine which of these had an effect on the infection rate. Consequently, the Parvizi et al. (74) finding that antibiotic cement produced a reduction in the infection rate is somewhat suspect because of the poor quality of the data used in the meta-analysis.

Limitations of this analysis include the following: meta-analyses could not be performed on a number of the endpoints due to a lack of multiple RCTs examining that endpoint and even though the search methodology was comprehensive, we were not 100% confident that all trials were identified. Further, we were unable to

separate out THA and TKA results from a number of older studies (which combined them) where the information may have been useful. These studies have been excluded and are identified in Appendix S2 in the supplemental material. The endpoints where meta-analysis could not be performed are included in Appendix S3 in the supplemental material for comprehensiveness sake and to identify areas of further research.

Lastly, based on the above analysis, additional research in the following areas would be helpful using a standard definition for infection (101) (the issue of disparate definitions of infection identified in this analysis can be found in Table 2). (i) Because a randomized controlled trial (RCT)—especially versus a placebo—to investigate antibiotic prophylaxis in primary total knee arthroplasty (TKA) is likely to be difficult to undertake as antibiotic prophylaxis is considered the standard of care in TKA, new analyses based on clinical registries and other types of observational data may be a more practical approach to gather data on therapies such as preoperative versus intraoperative antibiotic prophylaxis (i.e., antibiotic-impregnated cement). (ii) RCTs may be used to investigate preoperative antibiotics versus intraoperative antibiotics (antibiotic-impregnated cement) with or without preoperative antibiotics for primary THA and TKA that use antibiotics that are more commonly used with cement, such as tobramycin or gentamicin. (iii) Investigations of what constitutes adequate infusion of antibiotics prior to tourniquet inflation in TKA, including the types of tissue(s) to monitor and the accompanying rates of infection may be performed. (iv) Cost-effectiveness studies may be used to examine routes, type, and timing of antibiotic prophylaxis or antiseptics or both. Cost-effectiveness outcomes should be included in the methods section of the studies and appropriate statistical analysis should be used to evaluate the differences between study groups. (v) Routine collection of quality of life data may be done. (vi) Use of systemic i.v. antibiotic plus antibiotic-impregnated cement versus use of systemic i.v. antibiotic alone in patients at high risk for infection (i.e., people with diabetes, obese patients, older patients, and those who are immunocompromised) may be investigated. (vii) Longer-term follow-up (over 12
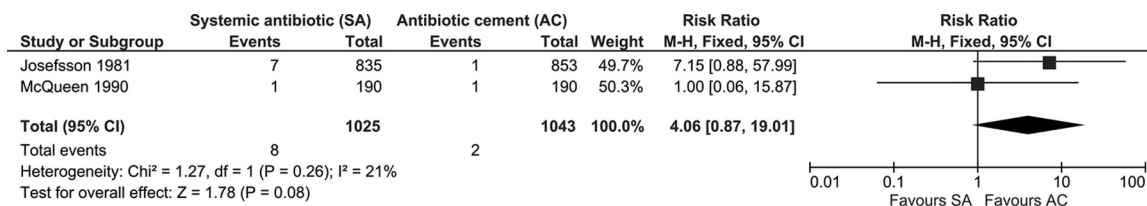

Study or Subgroup	Systemic antibiotic (SA) Events	Total	Antibiotic cement (AC) Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Josefsson 1981	7	835	1	853	49.7%	7.15 [0.88, 57.99]
McQueen 1990	1	190	1	190	50.3%	1.00 [0.06, 15.87]
Total (95% CI)		**1025**		**1043**	**100.0%**	**4.06 [0.87, 19.01]**
Total events	8		2			

Heterogeneity: Chi² = 1.27, df = 1 (P = 0.26); I² = 21%
Test for overall effect: Z = 1.78 (P = 0.08)

FIG 10 Forest plot THA. Adverse events: repeat or revision surgery.

TABLE 2 Definition of infection

Definition	Reference(s)
Deep tissue infection as defined by the CDC	Hinarejos 2013 (62), Kalmeijer 2002 (56), Morrison 2014 (63), Phillips 2014 (64), Soriano 2008 (58), van Rijen 2012 (61)
Abscess, septicemia, lethal infection	Hill 1981 (49)
Superficial: abnormal redness of wound, presence of secretion and firm diagnosis. Deep: pain, elevated ESR,[a] progressive radiographic resorption of bone stock	Chareancholvanich 2012 (60), Josefsson 1981 (42), McQueen 1990 (70), Schulitz 1980 (44), Suter 1994 (54)
Superficial: purulent discharge, with or without fever. Deep: pain, fever, redness with discharge containing pathogenic organism, elevated ESR, progressive radiographic resorption of bone stock	Evard 1988 (67), Pollard 1979 (48), Tyllianakis 2010 (59)
Clinical signs and positive culture	Ericson 1973 (51), Gunst 1984 (69), Soave 1986 (45)
Positive culture, evidence of sepsis, erythema	Wymenga 1992 (71)
Deep infection with positive culture of purulent drainage from inflamed wound	Mauerhan 1994 (53)
Sepsis	DeBenedictis 1984 (66)
No clear definition provided	Davis 1987 (47) (infection defined as clinical), Ritter 1989 (43) (latent deep wound infection), Jacobson 2005 (57), De Lalla 1993 (65)

[a] ESR, erythrocyte sedimentation rate.

months) after systemic i.v. antibiotic plus antibiotic-impregnated cement versus systemic i.v. antibiotics alone using commonly used antibiotics may be performed. (viii) Trials on antibiotic prophylaxis for THA and TKA conducted in parts of the world other than the United States and Europe, including Asia, Australia, South America, and Africa may be undertaken. (ix) Use of better extraction methods for obtaining tissue samples for the diagnosis of latent/late infection, such as sonication, may be investigated. (x) Larger trials investigating the use of various antiseptic techniques may be performed. (xi) Use of antibiotics indicated for resistant bacteria (e.g., vancomycin and teicoplanin for MRSA and *C. difficile*) in large clinical trials should be considered carefully. Increased use of these types of antibiotics in large clinical trials may produce resistance to them.

In conclusion and as it specifically relates to implications for practice, the available data suggested that preoperative systemic antibiotic prophylaxis should be employed in primary total hip arthroplasty (THA). The use of preoperative systemic antibiotics or antibiotic-impregnated cement may be sufficient for antibiotic prophylaxis in THA. We recommend that judicious use of antibiotics that are indicated for resistant bacteria (e.g., vancomycin and teicoplanin for methicillin-resistant *Staphylococcus aureus* [MRSA] and *Clostridium difficile*) be carefully considered, as increased use of these antibiotics may create resistance to them.

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