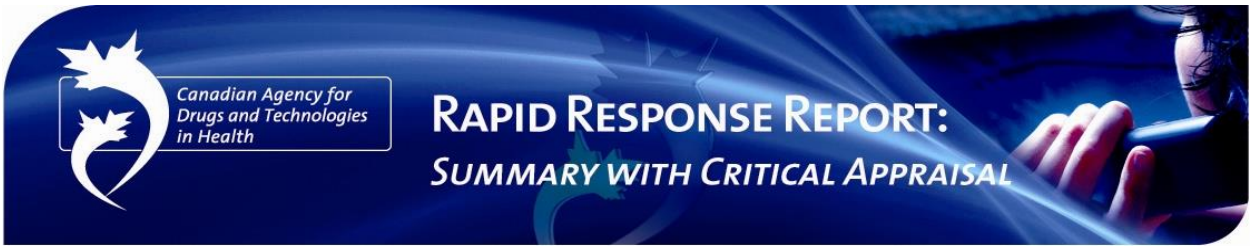

TITLE: Antibiotic Impregnated Cement for Primary Hip or Knee Arthroplasty: A Review of the Clinical and Cost-Effectiveness

DATE: 25 September 2015

CONTEXT AND POLICY ISSUES

As the population ages in North America, the rate of total joint arthroplasty (TJA) is expected to rise.[1] In tandem, associated surgical complications requiring intervention are becoming more common.[2,3] Surgical revision rates in the United States (US) are projected to increase by 66% during the period between 2005 and 2030, accompanied by forecasted annual costs of approximately 2 billion dollars.[2,3] In Canada, hip and knee arthroplasty procedures required re-hospitalization in 1.3% of cases in 2005,[4] and in 2012, approximately 20% of total knee arthroplasty (TKA) revisions were due to infection. Surgical site infections (SSIs) secondary to joint arthroplasty procedures are associated with serious complications including pain, osteomyelitis, osteoporosis, soft tissue loss, functional impairment, reduced quality of life, risk of surgical revision, prolonged hospitalization, and substantial health care costs.[5-7] In-hospital costs for joint replacement in Canada were estimated at $963 million dollars per annum in 2010.[8] With these issues on the horizon, infection control measures are of major interest.

Various infection control strategies including systemic prophylactic antibiotics, special operating room ventilation systems (e.g., laminar flow), antibiotic sutures, and antibiotic impregnated cement (AIC) are available for use alone or in combination.[9] Antibiotic impregnated cement is thought to reduce the risk of deep infection not attenuated by systemic antibiotics due to impaired circulation and thus, low local antibiotic concentrations at the surgical site.[10] Antibiotic impregnated cement is the most frequently used local antibiotic delivery system in joint replacement.[11] Historically, it has been used primarily for revision surgery in response to established infection, rather than for primary prophylaxis. The US Food and Drug Administration has approved the use of AIC in second-stage reimplantation post-revision due to infection; however, use in primary surgery is currently off-label.[12] This is in contrast to current practice in Scandinavia (e.g., Sweden and Norway) where AIC is routinely used in prophylaxis. In Alberta, Canada, AIC is recommended for all primary hip and knee arthroplasties.[13] Based on 2003 to 2008 data from the Canadian Joint Replacement Registry that captured 43% of all THAs and TKAs performed, the most commonly used cement in Canada is Simplex (79%), followed by Palacos (12%), and DePuy CMW (6%), with 46%, 53%, and 38%, respectively, containing

antibiotics though it is unclear whether the AIC formulations were pre or hand-mixed and what specific antibiotic they contained.[14]

Efficacy of AIC has been demonstrated in the context of revision surgery,[15-18] but the evidence base devoted to primary prophylaxis lacks clarity. Both long-term observational studies[16,17,19-21] and randomized controlled trials (RCTs)[22,23] have presented conflicting results. This was also apparent in two previous CADTH reports[24,25] that summarized clinical and economic evidence that reported a range of outcomes both in support of and against the use of AIC. The 2010[24] review summarized results from three systematic reviews (SRs) and several primary clinical studies on the clinical effectiveness of AIC in both primary and revision orthopedic surgery, though one SR was deemed of too poor quality to report results. Results were inconsistent, with one SR reporting no difference between AIC and systemic antibiotics in the pooled risk of wound infection, and another reporting a narrative synthesis of observational studies and RCTs with studies reporting both positive and negative results. The summary of abstracts published in 2010[25] reported on the abstract contents of three primary clinical studies and one economic study. The clinical studies reported reduced infection rates following AIC in one RCT, no differences between AIC and non-AIC in one observational study, and an increased rate of deep infection in a second observational study, adding to the variability in outcomes. The single economic evaluation reported that AIC was potentially cost effective when the outcome was revision due to infection or aseptic loosening but not revision due to infection alone.[25] Increasing age, cement costs, and surgery costs were shown to negatively influence the cost-effectiveness of AIC.[26]

Besides the disagreement in the literature regarding the efficacy of AIC, there is considerable concern about potential risks associated with the use of this technology. Risks such as antibiotic resistance, allergic reactions, kidney damage, systemic toxicity, and mechanical weakening of the cement have been put forth.[7,27,28]

Given the uncertainty surrounding efficacy and safety of AIC in primary prophylaxis, and the consequent lack of clarity with regards to resource implications, this report will review the clinical and cost-effectiveness of AIC in primary hip and knee arthroplasty patients.

RESEARCH QUESTIONS

1. What is the clinical effectiveness of antibiotic impregnated cement for patients undergoing a primary hip or knee arthroplasty?

2. What is the cost-effectiveness of antibiotic impregnated cement for patients undergoing a primary hip or knee arthroplasty?

KEY FINDINGS

Three systematic reviews with meta-analysis, one systemic review with network meta-analysis, three non-randomized studies, and two economic evaluations were identified regarding the clinical and cost-effectiveness of antibiotic impregnated cement for patients undergoing a primary hip or knee arthroplasty. The clinical evidence was of varying quality with particular concern regarding adjustment for confounders and heterogeneity. While there was limited evidence supporting lower infection rates and reduced antibiotic resistance, much of the evidence suggested no difference in effectiveness between antibiotic impregnated cement and plain cement. Antibiotic impregnated cement may provide a greater net monetary benefit over

other infection control measures in total hip arthroplasty, but given the uncertainty in the clinical evidence base the economic evidence should be interpreted with caution.

METHODS

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, and economic studies. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2010 and August 26, 2015.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients of any age undergoing primary (partial or total) hip or knee arthroplasty
Intervention	Antibiotic impregnated cement (with or without systemic antibiotics)
Comparator	Regular cement (with or without systemic antibiotics)
Outcomes	Q1: Clinical effectiveness (e.g., rate of superficial or deep surgical site infection, rate of revision, radiographic outcomes, clinical joint score); Harms (e.g., kidney damage, mortality) Q2: Cost-effectiveness outcomes
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, economic evaluations

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2010. Health technology assessment reports, SRs, MAs, and network meta-analyses (NMAs) were excluded if there was incomplete reporting of methods or if they were superseded by a more recent and/or rigorous review, or an updated review. Randomized controlled trials and non-randomized studies were excluded if they were described within an included SR. Economic studies that only reported direct costs and were not cost-effectiveness or cost-utility analyses were also excluded.

Critical Appraisal of Individual Studies

The included SRs were critically appraised using the AMSTAR checklist[29] and the methods used when conducting the literature search, study selection quality assessment, data extraction, and for summarizing the data were assessed. Network meta-analyses were critically appraised using ISPOR guidance.[30] Relevance, credibility, analysis and reporting quality, and transparency were considered. Primary clinical studies were critically appraised using the Downs and Black checklist.[31] Reporting, external validity, internal validity in terms of bias and confounding, and power were assessed. Economic evaluations were assessed using the Drummond checklist.[32] Study design, data collection, analysis, and interpretation of results were evaluated. Summary scores were not calculated for the included studies; rather, strengths and limitations of each included study were described narratively.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 250 citations were identified in the literature search. Following screening of titles and abstracts, 230 citations were excluded and 20 potentially relevant reports from the electronic search were retrieved for full-text review. One potentially relevant publication was retrieved from the grey literature search. Of these 21 potentially relevant articles, 12 publications were excluded due to irrelevant intervention(s) (n = 6),[5,33-37] irrelevant comparator(s) (n = 3),[38-40] coverage within an included SR (n = 2),[41,42] and because of publication type (n = 1, conference abstract),[43] while nine publications[5,10,41,44-49] met the inclusion criteria and were included in this report. Appendix 1 presents the PRISMA flowchart for the study selection process.

Summary of Study Characteristics

Detailed study characteristics are presented in Appendix 2.

Study Design

Four SRs,[5,10,48,49] including three with MA[10,48,49] and one with NMA[5] two economic evaluations;[45,47] and three non-randomized studies[41,44,46] were identified regarding the clinical and cost-effectiveness of AIC for patients undergoing a primary hip or knee arthroplasty.

Table A2 in Appendix 2 details overlap in included studies among the SRs.[5,10,48,49] Six primary studies were common to at least two of the four included SRs. While some differences in included studies occurred due to date ranges of the respective searches, other differences occurred due to study population (e.g., types of surgery included), and types of studies included (e.g., RCTs only versus RCTs and observational studies).

Country of Origin

The SRs were conducted by research groups in China,[10,48,49] and Australia.[5] The non-randomized studies were conducted in Canada,[41] and the US.[44,46] The economic evaluations were conducted from US,[45] and Australian[47] perspectives.

Patient Population

The SRs focused on patients populations undergoing primary TKA,[48] THA,[5] and both types of surgery.[10,49] One SR also included patients undergoing shoulder arthroplasty.[49] All SRs with MA[10,48,49] included elderly patients. The mean age of the studies of one SR[48] ranged from 65.1 to 76 years. Another SR[10] included studies with mean ages ranging from 63.7 to 75, and one study not specifying a mean but including patients ≥ 60 years. The third SR[49] included studies with a mean age ranging from 67.5 to 76. One study[49] reported various patient diagnoses including osteoarthritis, rheumatoid arthritis, posttraumatic arthritis, gouty arthritis, osteonecrosis, and cuff tear arthroplasty. The NMA[5] did not include additional patient level characteristics and did not report on the age of participants in the included primary studies.

The non-randomized studies included patients undergoing primary TKA only.[41,44,46] All studies included primarily elderly individuals[41,44,46] Less than 5% of patients in one study[41] presented with comorbidities (based on a modified Charlson score) or diabetes. One study failed to disclose additional patient characteristics.[44] Approximately one third of patients enrolled in Qadir et al.,[44] had diabetes, approximately a tenth had rheumatoid arthritis, and approximately half were obese.

The economic evaluations assessed resource implications in patients undergoing TKA[45] and THA in the hospital setting.[47] One study[45] included only patients presenting with infection following joint replacement. Most of the patients were older (mean age > 60 years) and had a median Charlson index score of 2.[45] The other study did not elaborate on specific characteristics of the hypothetical model cohort, beyond the age of the patients (65 years).[47]

Interventions and Comparators

All studies compared AIC to non-AIC, although some included additional comparators or background interventions such as systemic antibiotics,[5,10] laminar flow ventilation,[5] body exhaust suits,[5] conventional ventilation[5] and combinations of these various technologies.

Outcomes

The most frequent clinical outcome assessed was SSI and SSI leading to revision.[5,10,44,48,49] Additional outcomes included survival,[10] post-operative aseptic loosening rate,[10] clinical joint score,[10] rate of revision,[41] and antibiotic resistance patterns.[46] No studies assessed adverse kidney outcomes or systemic toxicity.

Cost outcomes included cost per infection prevented,[45] and cost per quality adjusted life year.[47]

Length of Follow-Up

Length of follow up varied. Two SRs[48,49] reported a mean follow-up between 12 and 50 months. One SR reported a follow-up range of 3 to 49 months.[10] The NMA[5] did not disclose the follow-up duration but length of follow-up was controlled for within the model. The length of follow-up for the non-randomized studies ranged from 1 year[41] up to a mean range of 53.7 to 55.7 months.[46] The time horizon for economic evaluations was the seven year duration of the before-and-after study (2000 until 2007) in one case.[45] The second model was evaluated over a time period of 30 years.[47]

Summary of Critical Appraisal

Study strengths and limitations are presented in Appendix 3.

CLINICAL EVIDENCE

Systematic Reviews with Meta-Analysis[10,48,49]

None of the SRs cited published protocols or provided details of a priori design features so it is unclear whether any post-hoc analysis/data dredging occurred. The number of reviewers involved in study selection was unclear in two cases.[10,48] In the other SR[49] one reviewer was involved in title and abstract screening, and two were involved at the full-text level. Lack of duplicate screening may have increased the possibility of missing studies of relevance. At least two authors were involved in data extraction for two reviews.[10,48] The number of reviewers involved in extraction was unclear in one study.[49] A comprehensive literature search involving multiple databases was conducted in all cases. Two reviews included limited grey literature searches[10,49] and one did not mention additional searching.[48] No studies searched clinical trial databases for ongoing studies or contacted manufacturers and authors for unpublished work. The search was limited to English and Chinese publications in one case,[48] and not limited by language in the others[10,49] though key words were limited to English and Chinese for the search of one SR.[49] Publication status was not limited in one case,[49] unclear in another,[10] and unpublished results were excluded in one case.[48] A list of included studies and study characteristics was provided in all cases. No reviews included a list of excluded studies or reasons for exclusion, limiting transparency of study selection. Quality of individual studies was assessed by all SRs and used universally in the formulation of study conclusions. Random effects models were used in all cases if statistical heterogeneity was detected. One study[48] also considered non-statistical heterogeneity when deciding on method of pooling. One study did not assess publication bias[48] whereas two did using funnel plots.[10,49] Funding was disclosed in all cases but affiliations and other conflict of interest were not discussed by one SR.[48]

Systematic Reviews with Network Meta-Analysis[5]

Relevance

Overall, there were no major issues with relevance in the single NMA.[5] The population, interventions, and outcomes were all relevant;[5] however, possibly relevant comparators such as antibiotic sutures were not considered, and neither were potential adverse events. In addition, they did not specify what type of cement and antibiotic were used in the respective primary studies so potential differences in efficacy of the various products, and current status of availability could not be accounted for. Compliance with the intervention would be expected to be similar for the trials and in the real-world setting but there might be concern over the range of publication years (1977 to 2011) as background medical care for joint arthroplasty may have changed substantially over that time.

Credibility

The search strategy for the SR portion of the work relied on searches from previously published SRs on the interventions of interest. The date ranges varied slightly and consequently, so did the portion of the search that had to be extended. It was unclear whether the quality of these foundation searches was adequate though multiple databases were searched in all cases. An

additional grey literature search was conducted but it did not consider databases of ongoing trials. Other issues with the SR methods included lack of clarity surrounding the number of reviewers involved in study selection, restriction to English language publications, and no mention of assessment of publication bias. The studies included in the NMA formed one connected network. Based on the quality assessment, some poor quality RCTs and observational studies were included. Quality concerns included lack of information on random sequence generation, blinding, and sample size calculations for several RCTs, and lack of adjustment for potential confounders. There was variability in how the included studies defined the outcome of interest. Both studies assessing deep SSI and those assessing infection requiring revision were included; however, these two outcomes are not identical. In addition, no adverse events were assessed, which may have been due to selective reporting of outcomes by the original studies. Baseline patient and study characteristics were not reported; therefore, treatment effect modifiers could potentially be different across studies and network comparisons. Factors such as age, expertise of the surgeon, other infection control measures, and comorbidities leading to higher risk for infection could have introduced confounding and would have been of interest to consider. The only confounder considered in analysis was length of follow up.

Analysis

Bayesian methods of analysis were used, which preserved randomization. Consistency was assessed using node-splitting and ultimately both direct and indirect evidence was included in the analysis. No rationale was provided for the choice of model but heterogeneity was assessed by between study variation, and ultimately a random effects model was used. Sensitivity analysis and meta-regression (to assess the influence of study type) was conducted but it was unclear whether it was pre-planned.

Reporting Quality and Transparency

Graphical representation of the evidence network including the number of studies per direct comparison was provided. Individual study results were reported, and results of direct and indirect comparisons were reported separately. Results of all pairwise contrasts were reported along with measures of uncertainty. Ranking of interventions and their uncertainty were provided. The effect of important patient characteristics on treatment effect was not reported.

Interpretation

Reporting of results was fair and balanced in the conclusion, but there was no mention of poor model fit, potential confounders and variable study quality.

Non-Randomized Studies

Reporting

All studies clearly stated a hypothesis and/or objectives.[41,44,46] Main outcomes were described for all studies in the methods or introduction section. Patient characteristics were described clearly in two cases,[41,44] and not reported in one.[46] All studies clearly described interventions of interest. The distribution of potential confounders was described in two cases.[41,44] but not mentioned by one study.[46] Main study findings were clearly described and estimates of random variability were provided in all cases. Across all studies there was general underreporting of

potential adverse events of interest, limiting ability to assess safety. No losses to follow-up were reported, though losses to follow up were likely minimized by the use of healthcare databases. Two studies excluded individuals who did not have a minimum of 12 months[44] or 24 months[46] of follow up without discussion of differences in baseline characteristics of these individuals. Actual probability values were reported by all studies.

External Validity

Two studies included patients who were representative of individuals undergoing the procedures of interest at single institutions, but may not be representative of other institutions with different peri-operative care protocols, surgical expertise, and facilities.[44,46] One study used databases that captured 43% of all procedures performed in Canadian facilities over 2003 to 2008, and this dataset likely gives a good representation of the context of joint arthroplasty across Canada. One study included all patients who had undergone the procedures of interest in analysis.[46] One study only included patients who were treated by three surgeons who adhered to the highest standard of care so the context of the treatment they received may not be representative of all scenarios.[44] One study excluded individuals at high risk of infection including individuals with rheumatoid arthritis and other inflammatory conditions so applicability of results was limited to normal risk patients such as those undergoing surgery due to degenerative arthritis.[41]

Internal Validity – Bias

As all studies were retrospective in design, no attempt was made to blind study subjects or outcome assessors, increasing the risk of information bias. In all cases, it was unclear whether the statistical analysis performed was planned in advance. None of the studies adjusted for length of follow-up.[41,44,46] Two studies used appropriate statistical tests.[41,44] One study appeared to use inappropriate tests.[46] They reported relative risk despite not discussing balance in baseline characteristics of cohort and not considering confounders. The compliance was assumed to be acceptable in all cases as it was a surgical procedure. One study used revision as a proxy outcome for infection.[50] There are other reasons for revision other than infection and this approach may have overestimated the rate of infection. The method of assessing outcomes in one study was unclear,[46] and was well described in another.[33]

Internal Validity – Confounding

Patients were recruited from the same study populations but there was concern among the two before-and-after studies[44,46] regarding the differing time period of recruitment of comparison groups. Hansen et al.,[46] compared patients recruited during the period of 2000 to 2003 who did not receive AIC to patients recruited between 2004 to 2009 who received AIC. Qadir et al.,[44] compared patients recruited during 2000 to 2005 who did not receive AIC to patients recruited between 2005 and 2010 who received AIC. None of the studies randomized patients to treatments so they were all at risk of selection bias. Further, while some studies adjusted for relevant confounders[41,44] in all cases there were several potentially relevant confounders that were not considered. One study[41] commented that the number of effect modifiers considered was limited to maintain power in analysis. It was not possible to determine losses to follow up in all cases, but one study[41] mentioned potential losses to follow-up due to relocation between provinces being balanced between groups. None of the studies reported sample size calculations or discussed power, but one study mentioned a small sample size and suggested that results be interpreted with caution.[46]

ECONOMIC EVIDENCE

Study Design

Both economic evaluations[45,47] stated a research question and discussed its economic importance. Viewpoints were explicitly stated in one case without providing justification or considering other perspectives,[47] and unclear in the other, though the viewpoint of a single institution could be assumed.[45] Neither study was conducted from the Canadian perspective and each focused on a single type of surgery so generalizability is limited. Both studies provided rationale for comparators and described them clearly. The form of economic evaluation was stated in both cases. One study[47] incorrectly identified itself as a cost-effectiveness analysis but was a cost-utility analysis – both choices were justified given the study objectives.

Data Collection

The source of effectiveness estimates were stated in both cases. The evaluation[45] that used primary single study data for effectiveness estimates provided details of the design and results. The other study[47] also provided information about the design and results of effectiveness studies and methods of synthesis. Both studies clearly describe the primary outcome measure. One evaluation did not conduct any value based assessment;[45] the other stated the methods of valuing benefits but details about the subjects from whom valuations were obtained were not provided.[47] Productivity changes were not reported by either study. One study[45] did not report quantities of resource use and unit costs. The other[47] reported them separately. The method of estimating quantities and unit costs was described well by one study.[47] The other study did not provide any discussion of method of estimating quantities and unit costs, though quantity may have been derived from the base study data.[45] One study didn't provide any information on currency data, adjustments for inflation and currency conversion.[45] Further, no formal modelling method was apparent.[45] Merollini et al., provided details of the type of model implemented as well as currency and conversion, but no adjustments were made for inflation.[47] In addition, transparency regarding modelling approach was limited as details about model development and assumptions were only available 'upon request'.[47]

Analysis and Interpretation of Results

Time horizon of benefits was stated by both studies, but for costs only one study provided information.[47] A discount rate was stated by one study though no justification was given.[47] One study did not conduct any sensitivity analysis or provide results disaggregated. The other study provided an explanation for their approach to sensitivity and scenario analysis but did not describe why specific variables were chosen.[47] Incremental analysis was reported by Merollini et al., who also reported both disaggregated and aggregated results.[47] Both studies provided an answer to the study question and conclusions which follow the data reported. However, the details behind how the final outcomes were arrived at were unclear in one case due to limited reporting.[45] Both studies provided conclusions that considered study limitations.

Summary of Findings

Detailed study findings are presented in Appendix 4.

What is the clinical effectiveness of antibiotic impregnated cement for patients undergoing a primary hip or knee arthroplasty?

The clinical effectiveness of AIC was assessed by four SRs[5,10,48,49] and three non-randomized studies.[41,44,46] The majority of evidence was for the outcome of SSI, but limited evidence from two non-randomized studies provided evidence for revision rates[41] and risk of antibiotic resistance.[46]

Surgical Site Infection

The three conventional MAs[10,48,49] all compared AIC to plain bone cement. Very little information was given about background infection control measures. Zhou et al.,[48] mentioned that systemic antibiotics and dosages differed across primary studies. Wang et al., included only studies that compared AIC to either systemic antibiotics or plain cement, not the interventions combined.[10] Yi et al.,[49] did not include any information about systemic antibiotics. Other infection control measures such as hand decontamination, skin preparation, type of dressing, type of sutures, nasal decontamination or any other general infection control procedures were not discussed. One study[48] that included both RCTs and observational evidence reported no differences in the risk of deep and superficial SSI for patients undergoing primary TKA, and reported no adverse events. Subgroup analysis of only RCTs was consistent with the main results. Another review[49] of RCT and observational evidence that included patients undergoing joint arthroplasty (including knee and hip) reported no difference in the risk of peri-prosthetic infection between AIC and plain cement groups. This observation was maintained in subgroup analysis by study type, operative site, and follow-up duration. The third review[10] of only RCTs, which included patients undergoing both hip and knee arthroplasty reported that AIC reduced the risk of deep SSI versus plain bone cement or systemic antibiotics, and increased the risk of superficial SSI. This study suggested that the benefit of AIC may be limited to deep infections. In subgroup analysis by comparator, AIC did not show a benefit over plain bone cement for the risk of superficial or deep SSI, but it increased the rate of superficial infection and decreased the rate of deep infection compared to systemic antibiotics.[10] Subgroup analysis by surgical site showed that studies focused on only hip surgeries as well as studies involving hip and knee surgery showed a reduced risk of deep SSI, whereas no difference between groups occurred in studies including only knee surgery, though there was significant heterogeneity among the two studies.[10] Subgroup analysis by type of antibiotic showed that gentamicin reduced the risk of deep SSI, but cefuroxime did not.[10]

The NMA,[5] which compared different combinations of antibiotic or plain bone cement, systemic antibiotics or no systemic antibiotics, laminar flow or conventional ventilation, and body exhaust suits as assessed by both RCTs and observational studies of THA patients, reported that five strategies including 1) systemic antibiotics + AIC + conventional ventilation (T6) 2) systemic antibiotics + plain cement + laminar airflow (T4), 3) no systemic antibiotics + plain cement + laminar airflow (T3), 4) systemic antibiotics + AIC + laminar airflow (T7), and 5) systemic antibiotic + plain cement + conventional ventilation (T2) were associated with a reduced odds of SSI versus the referent strategy of no systemic antibiotics + plain cement + conventional ventilation (T1). Model fit statistics indicated less than adequate fit. Following removal of outlier data on the interventions T2 and T5 from one study, the model fit improved, heterogeneity was reduced and the results were not substantially changed.

In addition to the evidence synthesized by the above reviews, one controlled before-and-after study[44] reported that TKA patients who received AIC versus 1) AIC only if deemed high-risk or plain cement if not, or 2) plain cement only did not have a different rate of deep SSI at 30 days, 6 months, or 1 year post surgery.

Revision Rates

One retrospective cohort study[41] in Canadian TKA patients reported that there was no difference in surgical revision rates between AIC and non-AIC groups. In adjusted analysis based on differences in age, sex, comorbidities and diabetes, and subgroup analysis of surgeons who consistently used the same type of cement, versus those that alternated, progression to revision was not different between treatment groups.

Risk of Antibiotic Resistance

One controlled before-and-after study[46] on TKA and THA patients reported that the risk of methicillin resistance *Staphylococcus aureus* (MRSA) was higher before the introduction of AIC than after. Risk of methicillin sensitive *Staphylococcus aureus*, methicillin resistant *Staphylococcus epidermidis*, and methicillin sensitive *Staphylococcus epidermidis* did not change with the introduction of AIC. No information was given on other relevant antibiotic resistant organisms (e.g., vancomycin resistant *Enterococcus*, Carbapenem-resistant *Enterobacteriaceae*).[51]

Radiographic Outcomes and Clinical Joint Score

Study results reported narratively in one SR[10] suggested no difference in aseptic loosening, stem subsidence or retroversion, and post-operative hip and knee function between AIC and non-AIC groups.

What is the cost-effectiveness of antibiotic impregnated cement for patients undergoing a primary hip or knee arthroplasty?

The resource implications of using AIC was assessed by one cost-effectiveness analysis[45] and one cost-utility analysis.[47] Overall, cost per infection prevented with the introduction of AIC in TKA was high,[45] and the combination of antibiotic prophylaxis + AIC dominated, conferring the greatest improvement in utility per cost compared to other infection prevention strategies in THA.[47]

The cost-effectiveness analysis[45] reported that in patients undergoing TKA, the cost per infection prevented based on additional costs associated with AIC versus plain cement was ~$113000. They also reported on the comparative cost-effectiveness of various alternate antibiotic cements using cost-minimization analysis, but due to inappropriate assumptions the results were not considered valid and are not presented.

The cost-utility analysis on THA patients[47] carried out from an Australian decision maker perspective, reported that antibiotic prophylaxis + AIC dominated as a prevention strategy compared with baseline antibiotic prophylaxis or antibiotic prophylaxis + laminar flow ventilation. It had the highest probability of being cost-effective and having the largest net monetary benefit at willingness-to-pay thresholds of $40 and $64 thousand Australian dollars. This outcome was persistent when baseline parameters including age, costs, rate of infection, and proportion of cemented primary THA were varied. Age did decrease the net monetary benefit (NMB) whereas higher proportion of cemented primary THA or higher baseline rate of deep SSI led to a higher NMB.

Limitations

Clinical Evidence

In addition to the important aforementioned critical appraisal points there was some concern regarding consideration of the matrix delivery of infection prevention measures, misreporting of methods, limited consideration of treatment effect modifiers, and inclusion of observational evidence in studies with pooled results.

One consideration is that in practice, infection control strategies may combine multiple technologies; therefore, studies that assess these measures in isolation versus within a matrix of care may have limited generalizability. Comparative effectiveness of strategies involving multiple measures may be more accurate to what occurs in clinical practice but this was only explored by the single NMA.[5] In the future, clinical studies should consider surgical environment, background infection control measures, and other active infection control measures when comparing interventions.

There was some misreporting with regards to study design among the included studies. Several studies identified themselves as retrospective cohort studies when they were actually controlled before-and-after studies,[44,46] which are subject to different sources of bias such as temporal differences in the context of treatment.

Overall, there was concern regarding limited evaluation of confounders and selective reporting of outcomes. Not all of the studies gave sufficient patient information beyond patient age. While a few studies mentioned comorbidities[41,44,45,49] this was not done universally. This made it difficult to determine whether comorbidities associated with an increased risk of infection such as diabetes influenced the effectiveness of AIC. In addition, only one study[44] discussed expertise of the surgeon and background infection control measures. The experience of a surgeon may have a significant impact on the outcome in surgical trials. Another issue that may have impacted the results of the MAs is confounding my indication. The possibility that care providers were more likely to provide AIC to individuals at higher risk of infection or revision could not be ruled out. The background rise in antibiotic resistant species over time is another effect modifier that was not considered. It has been reported that common antibiotic agents including gentamicin and tobramycin have reduced efficacy due to resistance-causing mutations.[52] It is unclear whether the lack of effect observed by some of the studies may be influenced in part by this factor. In addition, the risk of infection may differ based on surgical site. Knee arthroplasty has been associated with a higher rate of infection than hip arthroplasty. Regarding outcomes - none of the studies considered relevant adverse events such as duration of hospital stay, survival, kidney damage, and systemic toxicity, despite most studies having longer-term follow-up periods. It is unclear whether the data was unavailable or whether potential selective outcome reporting occurred.

Many of the SRs had possible issues with the inclusion of observational and RCT evidence. Foremost, the methodological and thus statistical heterogeneity increases simply on the basis of inherent differences in study design. While the inclusion of high-quality observational studies when RCT data is limited may increase confidence in the effect estimate, the exact study designs and limitations were often not discussed by the conventional MAs outside of generic quality assessments. Therefore, the introduction of elements of bias and heterogeneity is likely. There were also concerns regarding the inclusion of multiple study designs in the NMA, including potential differences in effect modifiers and reduced internal validity of the analysis.

The graphical display of network does not clearly identify which studies are observational and which studies are RCTs, making it difficult to determine whether the observational evidence added connectivity to the network. However, given the volume of observational evidence included it can be assumed that at least several of the network links were contributed. Unless confounding bias is minimized in the original study, introducing observational data can introduce bias to the indirect comparison. As only three of the observational studies adjusted for confounding in primary analysis and consideration of these potential treatment effect modifiers did not appear to be carried forth in analysis, it can be assumed that some bias was introduced. While meta-regression was conducted to assess the potential for influence of study type and the interaction was not significant, the level of heterogeneity and poor model fit suggests that inclusion of both study types, while increasing the amount of information available to the network, may not have been advisable. Another concern is potentially reduced transitivity. With the inclusion of observational evidence is it highly unlikely that all patients in the network would have been equally likely to receive any of the included interventions.

Economic Evidence

Both economic evaluations were potentially misclassified; one cost-effectiveness analysis was actually a cost-utility analysis, and one cost-benefit analysis was actually a cost-effectiveness analysis. The viewpoints of the included studies may be limited in their applicability to a Canadian setting. In addition, neither of the studies considered the broader societal perspective when assessing resource implications. Both studies only considered a single type of surgery (i.e., hip or knee) so results are not translatable across different surgery locations. The cost-utility model assumed a uniform response to treatment across patients, which is unlikely given that certain comorbidities may be associated with an increased risk of infection. The cost-effectiveness analysis was lacking substantially in consideration of indirect costs and confounders so the results should be interpreted with caution. In particular, the primary model did not consider potential differences in background infection control measures during the before and after time periods and relied on extrapolated increases in infection rates based on THA data to determine expected infection rates and thus, the number of infections prevented. Therefore, the number of infections prevented does not represent an actual observation and relies on the assumption that infection rates for THA and TKA would occur and increase similarly. This is contrary to the observation that knee surgery is associated with a greater rate of infection than hip surgery,[53,54], but in line with the observations of others.[55] Further, the cost-minimization analysis conducted as part of the cost-effectiveness study assumed equal efficacy across different types of cement. This assumption may have led to overestimation of the differences in cost per infection prevented between interventions. There is evidence to suggest that hand-mixed cement of lower physical integrity compared to pre-mixed cement.[56] Further, there is evidence of variable efficacy of the different antibiotics used in AIC. For instance, gentamicin but not cefuroxime loaded cement was associated with reduced deep SSI based on subgroup analysis within one of the included MAs.[10] While the efficacy of gentamicin and tobramycin (the most commonly studied antibiotics in this review) has been observed to be similar, efficacy may differ depending on the bacterial organism responsible for the infection.[57]

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

This report reviewed evidence regarding the clinical and cost-effectiveness of AIC in THA and TKA patients.

The clinical effectiveness of AIC for patients undergoing a primary hip or knee arthroplasty was addressed by four SRs[5,10,48,49] and three non-randomized studies.[41,44,46] The effectiveness of AIC for preventing surgical site infections was overall unclear, with two MAs[48,49] reporting no difference in rates of infection, and another[10] reporting reduced rates of deep and increased rates of superficial infection. The NMA, which assessed AIC in a matrix of other treatments reported that when compared to several alternate protocols, AIC + systemic antibiotics + conventional ventilation resulted in a reduced odds of SSI versus the referent strategy of no systemic antibiotics + plain cement + conventional ventilation. In the case of most of these studies, heterogeneity was unavoidable due to the inclusion of multiple study types, multiple surgery locations, and limited consideration of confounders. As such, results should be interpreted with caution. The single observational study on this outcome provided further evidence suggesting no benefit of AIC. Additional observational evidence suggested that revision rates, radiographic and functional outcomes were not affected by the introduction of AIC. Lastly, AIC did not appear to have a great impact on the risk of antibiotic resistant organisms, though the risk of MRSA appeared to decrease with its introduction in one before-and-after study.

The cost-effectiveness of AIC in the context of hip or knee arthroplasty was evaluated by two economic evaluations.[45,47] One US study[45] reported that using AIC would cost approximately $113 thousand dollars per case of infection prevented versus plain cement. An Australian cost-utility analysis reported that using AIC with antibiotic prophylaxis was a dominant strategy over antibiotic prophylaxis alone or combined with laminar flow ventilation.

Considering all of this evidence together with similarly conflicting older work by CADTH,[24,25] there is not convincing evidence in support of the clinical effectiveness of AIC for TKA and THA. Antibiotic impregnated cement may be more cost-effective than other strategies from a decision maker perspective, but these results should be interpreted with caution given the uncertainty in the evidence base for the effectiveness of this technology. Clinical benefit may depend on site of surgery, background comorbidities of the patient, and the type of infection (superficial or deep) the technology is aimed at preventing. Future studies should consider potential treatment effect modifiers and focus on more homogenous patient populations to address the threat of heterogeneity present among the included evidence syntheses. Furthermore, future studies should consider relevant safety outcomes such as survival, hospital stay, adverse events and long-term morbidity.

In conclusion, the majority of the evidence suggests that AIC may not confer any benefit over plain cement in TKA and THA. The resource implications of its use remain unclear given the uncertainty in the effectiveness evidence base.

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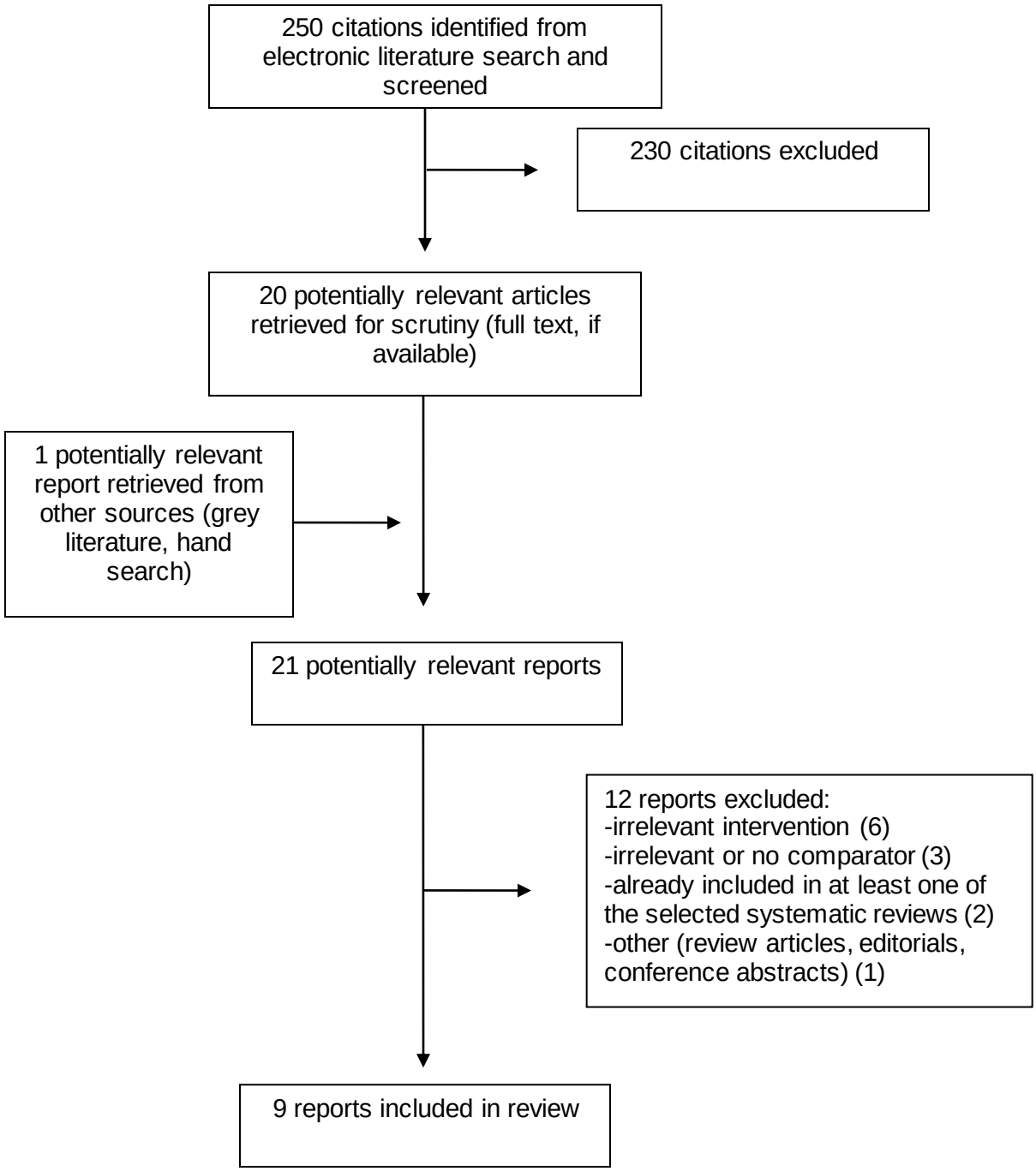
APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Publications

Table A1: Characteristics of Included Systematic Reviews, Meta-Analyses, and Network Meta-Analyses

First Author, Publication Year, Country, Study Type	Type of Review; Search Timeframe	Types and numbers of primary studies included	Population Characteristics	Intervention	Comparator(s)	Clinical Outcomes, Length of Follow-Up
Zhou, 2015[48] China	SR with MA; Search range 1966 until 2014 (months unspecified)	n = 5 comparative studies, RCTs (n = 3), retrospective comparative trials (n = 1), and prospective comparative trials (n = 1)	Patients with no history of knee infection or knee surgery undergoing primary TKA	AIC (brand of cement and type of antibiotic not specified)	Non-antibiotic loaded cement	Superficial and deep SSIs; Mean follow up = 12 to 50 months
Yi, 2014[49] China	SR with MA; Search range from 1966 to 1994 (depending on database) to August 2013	n = 6 studies, RCTs (n = 4), retrospective cohort studies (n = 2) *2 articles included results derived from 1 trial	Patients undergoing primary TJA	AIC (various but primarily Simplex P) + various antibiotics (cefuroxime, tobramycin, erythromycin and colistin, gentamicin, and vancomycin)	Plain bone cement	Infection prevention; Follow-up = 12 to 50 months
Zheng, 2014[5] Australia	SR with NMA (Single mixed treatment comparison; binomial random effects model allowing multi-arm trials); Umbrella search based on existing	n = 12 studies, RCTs (n = 6) and observational studies (n = 6)	Patients undergoing primary THA	AIC (brand and type of antibiotic unspecified) + systemic antibiotic prophylaxis (type unspecified) + laminar airflow	Any alternate combination of infection control strategies (including no systematic antibiotics, plain cement, conventional ventilation, body exhaust suit)	Total hip replacement related SSI resulting in joint revision Length of follow-up not disclosed for individual studies, duration of follow up modeled in NMA

Table A1: Characteristics of Included Systematic Reviews, Meta-Analyses, and Network Meta-Analyses						
First Author, Publication Year, Country, Study Type	**Type of Review; Search Timeframe**	**Types and numbers of primary studies included**	**Population Characteristics**	**Intervention**	**Comparator(s)**	**Clinical Outcomes, Length of Follow-Up**
	systematic reviews was used - search current until June 2011*					
Wang, 2013[10] China	SR with MA; Search current until June 2013	n = 8 RCTs	Patients undergoing primary THA or TKA	AIC (Type of cement = Palacos, Simplex P or CMW with various antibiotics = primarily gentamicin and cefuroxime, also including tobramycin, erythromycin and colistin)	Systemic antibiotics; Plain bone cement	Superficial and deep SSI; Survival; Post-operative aseptic loosening rate; Clinical joint score; Length of follow-up: range 3 months to 49 months

*Search for each intervention was based on a search from existing systematic reviews; therefore, timeframe of searches varies slightly
AIC = antibiotic impregnated cement; MA = meta-analysis; NMA = network meta-analysis; RCT = randomized controlled trial; SR = systematic review; SSI = surgical site infection; THA = total hip arthroplasty; TJA = total joint arthroplasty; TKA = total knee arthroplasty

Table A2: Systematic Reviews: Overlap Among Included Studies				
	Zhou, 2015[48]	Yi, 2014[49]	Zheng, 2014[5]	Wang, 2013[10]
Carlsson, 1977	X			
Schulitz, 1980	X			
Salvati, 1982	X			
Fitzgerald, 1992	X			
Kelly, 1996	X			
Brant, 2008	X			
Hill, 1981	X			
Espehaug, 1997	X			
Engesaeter, 2003	X			
Hooper, 2011	X			
Pfarr, 1979		X		
Wannske, 1979		X		
McQueen, 1987		X		
Namba, 2009			X	
Nowinski, 2012			X	
Gandhi, 2009				X
Zhang, 2012				X
Josefsson, 1981	**X**	**X**		
McQueen, 1990	**X**	**X**		
Bohm, 2012		**X**	**X**	
Chiu, 2002		**X**	**X**	**X**
Hinarejos, 2013		**X**	**X**	**X**
Chiu, 2001			**X**	**X**

Note: X's that are **bolded** indicate studies included in more than one systematic review

Table A3: Characteristics of Included Non-Randomized Studies

First Author, Publication Year, Country, Study Name	Study Design; Database Source(s)	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes; Length of Follow-Up
Bohm, 2014[41] Canada	Retrospective cohort study; CIHI Canadian Joint Replacement Registry and Hospital Morbidity Database, 2003 to 2008	Patients undergoing primary (initial fixation) TKA	AIC (Simplex, Palacos and CMW cement with various antibiotics [unspecified]) (n = 16665)	Plain cement (n = 20016)	Rate of revision; Length of follow up = 2 years
Hansen, 2014[46] US	Controlled before-and-after study (reported to be retrospective cohort study); Institutional database (Thomas Jefferson University Hospital, Philadelphia, Pennsylvania, US), 2000 to 2009	Patients undergoing primary TKA, n = 174 patients	AIC (Simplex P with tobramycin) (only knee arthroplasties [n = 59])	Plain cement (both hip [n = 54] and knee arthroplasties [n = 61])	Antibiotic resistance patterns (resistance to methicillin, erythromycin and tetracycline); Minimum 24 months clinical follow-up, group mean follow-up ranged from 53.7 to 55.7 months
Qadir, 2014[44] US	Controlled before-and-after study; Single institution joint registry (Oscher Health System, Jefferson, LA, US)	Patients undergoing primary TKA between 2000 and 2012	AIC (Palacos R + gentamicin, Simplex P with tobramycin, or SmartSet GMV with gentamicin) (n = 1486); Antibiotic-loaded cement in only high risk patients, otherwise plain bone cement (n = 781)	Plain bone cement (n = 1025)	Infection rate (type [deep or superficial] unclear) at 30 days, 6 months, and 1 year; Minimum 1 year follow up (analysis only up to 1 year)

AIC = antibiotic impregnated cement; CIHI = Canadian Institute for Health Information; US = United States; TKA = total knee arthroplasty

Table A4: Characteristics of Included Cost Studies

First author, Publication Year, Country	Type of Analysis; Perspective	Intervention; Comparator	Study Population; Sample Size	Time Horizon	Main Assumptions	Outcome(s)
Gutowski, 2014[45] US	Controlled before-and-after study (identified as retrospective cohort study) plus cost-effectiveness analysis + cost minimization analysis (identified as cost-benefit); US single institution	AIC (pre-mixed [Simplex P + antibiotics] or various (n = 3) hand-mixed formulations); Plain cement	TKA patients identified with infection (identified using Musculoskeletal Infection Society methodology) at a single institution (Thomas Jefferson University Hospital); n = 3048 with plain cement, n = 4830 with AIC	Intervention 2004 until 2007; Comparator 2000 until 2003	Equivalent efficacy of all interventions assessed Did not account for potential downfalls of hand mixing cement (reduced integrity and consistency of product)	Cost per infection prevented
Merrolini, 2013[47] Australia	Cost utility analysis (Markov state-transition model); Australian provider (health services, decision maker) perspective	*Intervention*: AIC (CMW1 with gentamycin or CMW2 with gentamycin or Simplex with tobramycin) + antibiotic prophylaxis; *Comparators*: Antibiotic prophylaxis; No antibiotic prophylaxis; Laminar air operating rooms + antibiotic prophylaxis	Patients undergoing THA; n = 6318 arthroplasties in intervention, n = 3101 control	"Model evaluated over 30 years, reflecting a lifetime evaluation of the patient cohort"	Patients assumed to be in 'no infection' initial health state upon entry; Treatment options include debridement, antibiotics and implant retention, 1 –stage revision, and 2 stage revision	Cost utility (cost/QALY) of strategies claiming to decrease the risk of deep SSI following THA (e.g. AIC)

AIC = antibiotic impregnated cement; QALY = quality adjusted life years; SSI = surgical site infection; THA = total hip arthroplasty; TKA = total knee arthroplasty; US = United States

APPENDIX 3: Critical Appraisal of Included Publications

Table A5: Strengths and Limitations of Systematic Reviews and Meta-Analyses using the AMSTAR checklist[29] and ISPOR questionnaire[30]

Strengths	Limitations
Zhou, 2015[48]	
• Three authors involved in data extraction • Multiple databases searched • Limited grey literature search conducted (authors of identified studies, reference lists of studies and reviews) • List of included studies provided along with study characteristics • Quality assessed independently by three reviewers • Methods used to combine findings (random effects model) considered differences in surgical technique, type of implant, and oral antibiotics • Quality considered in the formulation of conclusions • No external funding provided	• No reference to a protocol or a priori research objectives • Unclear number of reviewers involved in study selection • Unpublished research not considered in search • Search limited to English and Chinese language publications • List of excluded studies not provided • Publication bias not assessed • Appropriateness of combining different study types unclear • Affiliations and conflict of interest unclear *Other* • Limited adverse events analyzed (e.g., did not assess systemic toxicity or renal outcomes)
Yi, 2014[49]	
• Multiple databases searched; grey literature search conducted on general search engines • Search not limited by publication year, language or publication status • Two reviewers involved in study selection at full-text level • List of included studies provided along with study characteristics • Quality of studies assessed by two reviewers using the Jadad 5-point scale and the Newcastle-Ottawa quality assessment scale • Quality considered in the formulation of conclusions • Publication bias tested using funnel plots • Conflict of interest and funding sources disclosed	• No reference to a protocol or a priori research objectives • Only a single reviewer involved in initial screening of titles and abstracts • Unclear number of reviewers involved in data extraction • Keywords in search limited to English and Chinese • List of excluded studies not provided • Method of combining findings based on statistical heterogeneity (used random or fixed based on this factor)
Zheng, 2014[5]	
Relevance • Population of relevance included • All relevant interventions included and chosen based on published guidelines and expert opinion • Compliance expected to be similar in trials and real-world	*Relevance* • The primary outcome of SSIs was assessed but other adverse events (e.g., renal outcomes, systemic toxicity) were not included • Context: As study publication years ranged from 1977 to 2011 background medical care may have changed substantially during that time

Table A5: Strengths and Limitations of Systematic Reviews and Meta-Analyses using the AMSTAR checklist[29] and ISPOR questionnaire[30]

Strengths	Limitations
setting as it is a surgical procedure *Credibility* *AMSTAR[29] Items* • Multiple databases searched, grey literature search conducted (conference abstracts, hand searching of bibliographies, expert consultation) • Experts in the field consulted • Extraction completed by two independent reviewers • List of included and excluded studies along with study characteristics included • Quality of studies assessed using the National Institute for Health and Care Excellence public health • guidelines • Quality of studies considered in the formulation of conclusions *Other* • Trials (RCTs and observational studies) form one connected network • Primary outcome common to all included studies • Length of follow up controlled for in model, as no difference was observed between adjusted and unadjusted models, unadjusted was used *Analysis* • Bayesian analysis used, which preserved randomization • Node-splitting used to assess consistency: no statistically significant evidence of inconsistency between direct and indirect evidence • Both direct and indirect comparisons included in NMA • Attempt to minimize inconsistency across comparisons by controlling for length of follow up and assessing study type in meta-regression analysis • Random effects model used for all analysis • Between study variation used to	*Credibility* *AMSTAR[29] Items* • No protocol or a priori objectives mentioned • Number of authors involved in study selection unclear • Search strategy relied on the search strategies of previous SRs (that covered from 1966 to 2007 for systemic antibiotics, to 2004 for AIC, and 1970 to 2007 for operating theatre ventilation systems – searches extended to 2011) • Clinical trial databases not searched (ongoing trials may have been missed) • Search restricted to English language publications • Publication bias not discussed • Funding and conflict of interest disclosed (no concerns) *Other* • Some poor quality studies may have been included ○ Quality: RCTs lacking information on random sequence generation, blinding, sample size calculations and power were included ○ Quality: Observational studies that did not adjust for confounders and differences in baseline characteristics, did not assess withdrawals, did not have outcome measures, and were not adequately powered were included. • Outcome: Variability between studies in how the infection outcome was defined (deep SSI versus infection requiring revision) ○ Additional outcomes of interest such as systemic toxicity, renal morbidity not assessed • Baseline patient and study characteristics not reported; therefore, treatment effect modifiers may be different across studies and comparisons ○ Factors such as age, surgical expertise, infection control measures, comorbidities (immune system conditions, rheumatoid arthritis, diabetes), sex etc. should have been compared at baseline – unclear how this may have introduced confounding • No attempt to minimize inconsistency based on potential treatment effect modifiers listed above *Analysis* • No rationale provided for choice of model • Included both RCTs and observational studies in analysis ○ Reduced transitivity, consistency, and internal validity • Did not adjust for relevant confounders identified as effect modifiers at the study level for observational studies • Sensitivity analysis conducted non-systematically • Substantial heterogeneity reported • A priori nature of subgroup analyses and meta-regression unclear

Table A5: Strengths and Limitations of Systematic Reviews and Meta-Analyses using the AMSTAR checklist[29] and ISPOR questionnaire[30]

Strengths	Limitations
assess heterogeneity • Subgroup analysis and meta-regression performed to assess contributions to heterogeneity *Reporting Quality and Transparency* • Graphical representation of the evidence network with number of studies per direct comparison provided • Individual study results reported • Results of direct and indirect comparisons reported separately in supplemental issue • Results of all pairwise contrasts reported along with measures of uncertainty • Ranking of interventions as well as uncertainty provided *Interpretation* • Reporting of results fair and balanced in conclusion	*Reporting Quality and Transparency* • Reporting of relevant adverse events was absent • Effect of important patients characteristics on treatment effect not reported *Interpretation* • No mention of poor model fit, potential confounders and variable study quality in conclusions
Wang, 2013[10]	
• Multiple databases searched • Search not limited by language or date • Extraction completed by two independent reviewers • List of included studies and study characteristics provided as supplementary issue • Methodological quality graded using the Jadad scale • Quality considered in the formulation of conclusions • Publication bias assessed with funnel plots (some asymmetry detected) • Conflict of interest and funding sources disclosed	• No reference to a protocol or a priori research objectives • Number of authors involved in study selection unclear • Methods of grey literature searching unclear • Unclear whether search was limited by publication type • List of excluded studies not provided • Random effects models only used if significant statistical (i.e., >50%) heterogeneity detected, otherwise fixed effects models used *Other* • Significant verbatim text taken from other publications as published in an extensive correction document[58] – unclear whether this affected the results or presentation of the study results despite assurance from the author's to the contrary

NMA = network meta-analysis; RCT = randomized controlled trial; SSI = surgical site infection

Table A6: Strengths and Limitations of Non-Randomized Studies using Downs and Black[31]

Strengths	Limitations
Bohm, 2014[41]	
Reporting • Objectives clearly described • Outcomes described in introduction and methods sections • Characteristics of patients clearly described • Interventions clearly described • Distribution of confounders (comorbidity score, diabetes, sex, age) descried clearly • Main findings clearly described • Estimates of random variability provided • Probability values reported *External Validity* • Context of patient treatment representative of Canadian facilities during the time period of assessment *Internal Validity – Bias* • Statistical tests used for main outcomes appropriate • Compliance acceptable (surgical procedure) *Internal Validity – Confounding* • Patients in different intervention groups recruited over the same time period from the same population • Adjustment for various confounders (age, sex, comorbidities and diabetes) made in Cox regression models	*Reporting* • Adverse events (e.g., infection, systemic toxicity, renal events) underreported • Losses to follow-up not reported *External Validity* • Database source only represents 43% of hip and knee arthroplasties performed annually from 2005 to 2006 *Internal Validity – Bias* • No blinding of subjects or outcome assessors • A priori nature of analysis unclear • No adjustment for length of follow up • Used revision as a proxy outcome for infection, which may result in flawed estimation as infection is not the only factor leading to revision *Internal Validity – Confounding* • No randomization of study subjects • Several potentially relevant confounders (e.g., surgical expertise, location of surgery [hip versus knee]) not considered • No losses to follow-up reported; possibility of loss due to relocation between provinces considered to be equal between groups *Power* • Sample size calculation not disclosed; author's commented that they assessed limited confounders to maintain power of analysis *Other* • Excluded patients at high-risk of infection (e.g., rheumatoid arthritis and other inflammatory conditions • Included both hip and knee surgeries (different infection risk)
Hansen, 2014[46]	
Reporting • Aims and hypothesis clearly described • Outcomes described in introduction and methods sections • Interventions clearly described • Main findings clearly described • Estimates of random variability provided • Probability values reported *External Validity* • Participants representative of individuals receiving the treatment at the institution they	*Reporting* • Baseline characteristics of patients not provided • Distribution of confounders not described • Adverse events (e.g., infection, revision, systemic toxicity, renal events) underreported • Characteristics of patients lost to follow-up not reported • Individuals who did not have a follow-up duration of a minimum of 24 months were excluded without discussion of differences in baseline characteristics *External Validity* • Results may not be applicable to institutions with different peri-operative care protocols, level of expertise of surgeons, facilities etc. • Context of patient treatment may not be representative of smaller facilities or large trauma centers

Table A6: Strengths and Limitations of Non-Randomized Studies using Downs and Black[31]

Strengths	Limitations
attended • All patients who had undergone the relevant procedures during the specified time period were included in analysis • Context of patient treatment representative of large teaching hospitals *Internal Validity – Bias* • Patients in different intervention groups recruited from the sample study population • Compliance acceptable (surgical procedure) *Internal Validity – Confounding* • Patients all recruited from the same hospital population	*Internal Validity – Bias* • No blinding of subjects or outcome assessors • A priori nature of analysis unclear • No adjustment for length of follow up • Inappropriate statistical tests – reported relative risk despite not reporting balance in baseline characteristics of cohort and not considering confounders • Method of assessing and classifying outcomes unclear *Internal Validity – Confounding* • Unclear whether patients received different care based on date during 9 year study period • No randomization of study subjects • Inadequate adjustment for confounding • Unable to determine patients lost to follow-up *Power* • Sample size calculation not disclosed; author commented on small sample size and suggested that results be interpreted with caution *Other* • Patients who received antibiotic versus plain cement were treated during different time periods, cannot rule out differences in setting/care/level of training of surgeon • Possible measurement bias as they don't describe culturing methods, also culturing protocol may have changed (e.g., increased in sensitivity) over time • Identified study as a retrospective cohort study; however, for outcome of interest, design was controlled before-after and carried the associated limitations • Did not provide elaboration for acronyms/abbreviations; therefore, assumptions had to be made regarding what they represented • Selective reporting bias – don't report intended comparative analysis or planned statistical analysis with enough detail
Qadir, 2014[44]	
Reporting • Objectives clearly described • Outcomes described in introduction and methods sections • Characteristics of patients clearly described • Interventions clearly described • Distribution of confounders (age, diabetes, rheumatoid arthritis, obesity, sex) described clearly • Main findings clearly described • Estimates of random variability provided • Probability values reported *External Validity*	*Reporting* • Adverse events (e.g., revision rates, systemic toxicity, renal events) underreported • Individuals who did not have a follow-up duration of a minimum of 12 months were excluded without discussion of difference in baseline characteristics *External Validity* • Patients only received procedure from 3 surgeons who adhered to the highest standard of care – results not applicable to patients who received procedure from lesser trained surgeons (laminar flow, spacesuits, systematic antibiotics) • Context of patient treatment only representative of a high standard of care • Distribution of several potentially relevant confounders (e.g., surgical expertise) not presented despite discussion of

Table A6: Strengths and Limitations of Non-Randomized Studies using Downs and Black[31]

Strengths	Limitations
• Subjects representative of individuals who underwent primary TKA at a single institution • Context of patient treatment well described and consistent across procedures *Internal Validity – Bias* • Statistical tests used for main outcomes appropriate • Compliance acceptable (surgical procedure) • Method of classifying main outcome validated and clearly described (CDC criteria for deep wound infection) *Internal Validity – Confounding* • Patients all recruited from the same patient pool of three surgeons	equivalence among groups *Internal Validity – Bias* • No blinding of subjects or outcome assessors • A priori nature of analysis unclear • No adjustment for length of follow up • Influence of confounders on infection rates only examined in univariate analysis of infected individuals (not all individuals, and not within multivariate analysis) *Internal Validity – Confounding* • Groups recruited over different time periods • No randomization of study subjects • Inadequate adjustment for confounding • Unclear losses to follow up *Power* • Sample size calculation not disclosed *Other* • Infection rate (overall) consistent over the 12 year period • Only short-term follow up (compared to the other studies)

CDC = United States Centers for Disease Control and Prevention; TKA = total knee arthroplasty

Table A7: Strengths and Limitations of Economic Studies using Drummond[32]

Strengths	Limitations
Gutowski, 2014[45]	
Study design • Research question including economic importance of question stated • Rationale for comparators provided and comparators clearly described *Data collection* • Source of effectiveness estimates was primary before-and-after study at a single institution • Details of the design and results of the effectiveness study are provided • Primary outcome measures clearly stated (cost per infection prevented) *Analysis and interpretation of results* • Time horizon of benefits provided (infection up until 2 years) • Relevant alternatives are compared • An answer to the study question is provided • Conclusions consider study limitations and follow reported data	*Study design* • Patient information collected during different time periods for comparison groups • Study incorrectly self-identified as a cost-benefit analysis (was a cost-effectiveness analysis) • Viewpoint is representative of a single institution, perspective unclear *Data collection* • No value based assessment conducted • Productivity changes not reported and relevance of changes to study question not discussed • Indirect benefits not considered • Quantities of resources and unit costs not reported • Method for estimation of quantities and unit costs unclear; quantity may have been derived from # of patients who received AIC • Currency data not recorded and adjustments for inflation or conversion not provided • No modelling technique used – evaluation does not extend beyond what was directly observed by the before-and-after study; as such, no justification for choice of model and parameters provided *Analysis and interpretation of results* • Time horizon of costs unclear • No discount rate applied and no explanation as to why

Table A7: Strengths and Limitations of Economic Studies using Drummond[32]	
Strengths	**Limitations**
	not given • No details of statistical tests or confidence intervals provided for stochastic data • No sensitivity analysis • No incremental analysis • Disaggregated results not provided
Merollini, 2013[47]	
Study design • Research question including economic importance of question stated • Viewpoints of analysis clearly stated • Rationale for comparators provided and comparators described clearly (based on guidelines and clinical opinion) • Form of economic evaluation used is stated *Data collection* • Source of effectiveness estimates presented • Details of design and results of effectiveness studies and methods of synthesis provided • Primary outcome clearly stated • Method to value benefits stated • Method for estimation of quantities and unit costs well described • Quantities and costs of resources reported separately • Details of currency and conversion to USD provided • Details of decision analytic model (Markov state transition) provided *Analysis and interpretation of results* • Time horizon of costs and benefits is stated • Discount rate (3%) stated • Approach for sensitivity analysis (probabilistic sensitivity analysis) reported as well as scenario analysis methods • Relevant alternatives are compared • Incremental analysis reported • Disaggregated and aggregated results reported • Answer to the study question provided • Conclusions consider study limitations and follow reported data	*Study design* • No justification made for chosen viewpoint and decision to not assess alternative viewpoints *Data collection* • Details of subjects from whom valuations were obtained not provided • Productivity changes not reported and relevance of changes to study question not discussed • No adjustments made for inflation • Justification not provided for choice of model and key parameters *Analysis and interpretation of results* • Justification for discount rate not provided • Justification for choice of variables used in sensitivity analysis unclear *Other* • Details about model development and assumptions only available 'upon request'; limited transparency

Table A7: Strengths and Limitations of Economic Studies using Drummond[32]	
Strengths	**Limitations**
Other • Review of clinical guidelines and expert opinion used to established relevant comparators	

AIC = antibiotic impregnated cement; AUD = Australian dollar; USD = United States Dollar;

APPENDIX 4: Main Study Findings and Author's Conclusions

Table A8: Summary of Findings of Included Systematic Reviews and Meta-Analyses

Outcome; number of studies		AIC group	Non-AIC group	Effect estimate (95% CI)	Heterogeneity	Author's Conclusions
Zhou, 2015[48]						
Deep incisional SSI; n = 5 (n = 3 RCTs, n = 2 observational studies)		46/3461	60/3176	RR = 0.75 (0.43 to 1.33)	I^2 = 34%	• Antibiotic-loaded bone cement did not decrease the risk of infection in patients undergoing primary TKA • No adverse events associated with the use of AIC reported for any of the five studies (data for individual adverse events not reported)
Superficial incisional SSI; n = 3, all RCTs		27/1702	28/1664	RR = 1.40 (0.08 to 2.43)	I^2 = 0%	
Subgroup Analysis						
Study type – RCT only	Deep incisional SSI; n = 3	20/1702	30/1664	RR = 0.28 (0.04 to 1.25)	I^2 = 65%	• Antibiotic-loaded bone cement did not decrease the risk of deep incisional SSI when only RCTs were considered in analysis
Yi, 2014[49]						
Peri-prosthetic infection, n = 6		51/3982	194/22809	RR = 0.6 (0.23 to 1.56)	I^2 = 77%	• No difference in the risk of peri-prosthetic infection between antibiotic and plain cement groups

Table A8: Summary of Findings of Included Systematic Reviews and Meta-Analyses

Outcome; number of studies			AIC group	Non-AIC group	Effect estimate (95% CI)	Heterogeneity	Author's Conclusions
Subgroup Analysis							
Peri-prosthetic infection	Study type	RCTs; n = 4	NR	NR	RR = 0.43 (0.11 to 1.67)	I^2 = 60%	• When analyzed by study type, operative site, and follow-up duration the original observation of no difference in risk of peri-prosthetic infection
		Retrospective cohort studies; n = 2	NR	NR	RR = 0.62 (0.05 to 8.36)	I^2 = 84%	
	Operative site	Knee; n = 4	NR	NR	RR = 0.80 (0.32 to 2.00)	I^2 = 75%	
	Follow-up duration	Short-term follow up; n = 2	NR	NR	RR = 0.99 (0.53 to 1.83)	N/A	
		Mid-term follow up; n = 4	NR	NR	RR = 0.35 (0.06 to 2.08)	I^2 = 82%	
Wang, 2013[10]							
Superficial postoperative infection rate, n = 5 studies			129/2829	67/2788	**RR = 1.47 (1.13 to 1.91)**	I^2 = 0%	• Compared with plain bone cement or systemic antibiotics, antibiotic-impregnated bone cement use led to a reduction in deep-wound infection rate, an increase in superficial infection, and no difference in aseptic loosening rate, and postoperative joint function • Main benefit of antibiotic-impregnated cement may be in prevention of deep infection
Deep postoperative infection rate, n = 7			29/3203	54/3090	**RR = 0.41 (0.17 to 0.97)**	I^2 = 53%	
Radiographic outcomes (postoperative aseptic loosening rate)			Author's conclusions: Postoperative aseptic loosening rate was assessed by four studies and individual results of two studies suggested fewer aseptic loosening joints in the AIC group versus a control group, one study reported no significant difference, one study did not analyze differences between groups and one study reported no significant difference in stem subsidence or retroversion between groups				
Clinical joint score			Author's conclusions: Regarding clinical joint scores, two studies assessed hip and knee function, respectively, using established scales and reported no significant differences between AIC and control groups				
Subgroup Analysis							
Superficial SSI		AIC vs. SA, n = 3 studies	**100/1168**	**67/1161**	**RR = 1.48 (1.10 to 2.00)**	I^2 = 0%	Based on subgroup analysis:

Table A8: Summary of Findings of Included Systematic Reviews and Meta-Analyses

Outcome; number of studies		AIC group	Non-AIC group	Effect estimate (95% CI)	Heterogeneity	Author's Conclusions
	AIC vs. PBC, n = 2 studies	29/1661	20/1627	RR = 1.42 (0.81 to 2.50)	I^2 = 0%	• There was no difference in the rate of deep or superficial SSI between AIC and PBC, but SA use was associated with a lower rate of superficial infection than AIC and a greater rate of deep infection than AIC • Studies focused on hip surgery only and mixed studies (knee and hip) suggested a benefit for deep SSI of AIC versus no AIC, whereas studies on knee surgeries only did not • Deep SSI rate was reduced with the use of AIC versus no AIC in studies that used gentamicin but not cefuroxime
Deep SSI	AIC vs. SA, n = 3 studies	**6/1168**	**17/1161**	**RR = 0.37 (0.14 to 0.98)**	I^2 = 0%	
	AIC vs. PBC, n = 4 studies	23/2035	37/1929	RR = 0.34 (0.07 to 1.58)	I^2 = 75%	
	Hip only, n = 3 studies	**6/1195**	**25/1114**	**RR = 0.21 (0.08 to 0.50)**	I^2 = 0%	
	Knee only, n = 2 studies	20/1661	25/1627	RR = 0.42 (0.04 to 4.53)	I^2 = 65%	
	Both hip and Knee, n = 2 studies	**3/347**	**4/349**	**RR = 0.41 (0.17 to 0.97)**	I^2 = 0%	
	Gentamicin, n = 3 studies	**6/1195**	**25/1114**	**RR = 0.21 (0.08 to 0.50)**	I^2 = 0%	
	Cefuroxime, n = 3 studies	3/525	9/511	RR = 0.36 (0.11 to 1.20)	I^2 = 6%	

AIC = antibiotic impregnated cement; CI = confidence interval; NR = not reported; PBC = plain bone cement; RCT = randomized controlled trial; RR = relative risk; SA = systemic antibiotics; SSI = surgical site infection; TKA = total knee arthroplasty

Table A9: Summary of Findings of Included Network Meta-Analyses*
Odds Ratios (95% CrI) for odds of SSI resulting in revision

Zheng, 2014[5]								
T2	**OR [1,2] = 0.31 (0.12 to 0.65)**							
T3	**OR [1,3] = 0.26 (0.03 to 0.95)**	OR [2,3] = 0.92 (0.11 to 3.39						
T4	**OR [1,4] = 0.25 (0.06 to 0.66)**	OR [2,4] = 0.84 (0.28 to 1.97)	OR [3,4] = 1.93 (0.20 to 7.58)					
T5	OR [1,5] = 0.38 (0.09 to 1.12)	OR [2,5] = 1.28 (0.38 to 3.38)	OR [3,5] = 3.28 (0.27 to 14.15)	OR [4,5] = 1.96 (0.37 to 6.54)				
T6	**OR [1,6] = 0.13 (0.03 to 0.35)**	OR [2,6] = 0.44 (0.13 to 1.13)	OR [3,6] = 1.12 (0.09 to 4.62)	OR [4,6] = 0.67 (0.12 to 2.12)	OR [5,6] = 0.43 (0.09 to 1.24)			
T7	**OR [1,7] = 0.27 (0.03 to 0.93)**	OR [2,7] = 0.90 (0.13 to 3.14)	OR [3,7] = 2.47 (0.11 to 10.22)	OR [4,7] = 1.41 (0.14 to 5.35)	OR [5,7] = 0.88 (0.09 to 3.10)	OR [6,7] = 1.96 (0.52 to 5.37)		
T8	OR [1,8] = 0.52 (0.03 to 2.12)	OR [2,8] = 1.77 (0.11 to 7.20)	OR [3,8] = 5.78 (0.10 to 21.12)	OR [4,8] = 2.89 (0.12 to 11.73)	OR [5,8] = 1.71 (0.08 to 6.93)	OR [6,8] = 3.72 (0.38 to 13.75)	OR [7,8] = 2.26 (0.22 to 8.48)	
T9	OR [1,9] = 0.74 (0.05 to 2.69)	OR [2,9] = 2.49 (0.20 to 9.11)	OR [3,9] = 13.15 (0.18 to 27.4)	OR [4,9] = 4.11 (0.22 to 14.92)	OR [5,9] = 2.44 (0.15 to 8.62)	OR [6,9] = 5.00 (0.73 to 16.87)	OR [7,9] = 3.14 (0.42 to 10.41)	OR [8,9] = 2.53 (0.23 to 10.41)
	T1	T2	T3	T4	T5	T6	T7	T8

Author's Conclusions

- The strategy of systemic antibiotics + antibiotic impregnated cement + conventional ventilation resulted in a reduced odds of SSI versus the referent strategy of no systemic antibiotics + plain cement + conventional ventilation
- There was no evidence to suggest that laminar flow would be beneficial over conventional ventilation, or that antibiotic impregnated cement would be effective without systemic antibiotics

*Model fit statistics (posterior mean residual deviance) = 34.3; Model fit statistic (deviance information criteria) = 180.6; Heterogeneity (between-study deviation) = 0.63

Description of treatments:

- T1 (no systemic antibiotics + plain cement + conventional ventilation)
- T2 (systemic antibiotics + plain cement + conventional ventilation)
- T3 (no systemic antibiotics + plain cement + laminar airflow)
- T4 (systemic antibiotics + plain cement + laminar airflow)
- T5 (no systemic antibiotics + AIC + conventional ventilation)
- T6 (systemic antibiotics + AIC + conventional ventilation)
- T7 (systemic antibiotics + AIC + laminar airflow)
- T8 (systemic antibiotics + AIC + conventional ventilation + body exhaust suit)
- T9 (systemic antibiotics + AIC + laminar ventilation + body exhaust suit)

AIC = antibiotic impregnated cement; CrI = credible interval; OR = odds ratio; SSI = surgical site infection

Table A11: Summary of Findings of Included Non-Randomized Studies

Outcome	Intervention; Rate	Comparator; Rate	Rate or Effect Estimate	Author's Conclusions
Bohm, 2014[41]				
Revision rates in two years	Antibiotic-loaded cement, n = 16665; 251/16665	Non-antibiotic loaded cement, n = 20016; 281/20016	Absolute increase = 0.11% (95% CI, -0.14% to 0.35%), p = 0.41	No differences in revision rates between antibiotic-loaded cement group and non-antibiotic loaded cement group in adjusted and non-adjusted analyses
Revision rates (adjusted analysis*)	*Same as above;* NR	*Same as above;* NR	HR = 1.07 (95% CI, 0.90 to 1.27)	
Revision rates (surgeons who consistently use one type of cement), n = 375	*Same as above;* NR	*Same as above;* NR	HR = 1.04 (95% CI, 0.86 to 1.44)	There was no difference in progression to revision for surgeons who consistently used one type of cement versus those who alternated between cement types
Revision rates (surgeons who alternated between cement types), n= 36	*Same as above;* NR	*Same as above;* NR	HR = 1.19 (95% CI, 0.75 to 1.90)	
Hansen, 2014[46]				
TKA				
Risk of MRSA	Post 2003 (Simplex P infused with 1.2 g tobramycin); NR	Pre 2003 (Cement with no antibiotics); NR	RR = 2.2 (95% CI, 1.0 to 4.7, p = <0.05)	The risk of developing MRSA (but not other types of infection) infection was 2 times higher before the introduction of AIC than after
Risk of MSSA	*Same as above*	*Same as above*	RR = 0.84 (95% CI, 0.40 to 1.80)	
Risk of MRSE	*Same as above*	*Same as above*	RR = 0.81 (95% CI, 0.35 to 1.80)	
Risk of MSSE	*Same as above*	*Same as above*	RR = 0.48 (95% CI, 0.14 to 1.6)	
Qadir, 2014[44]				
30 day infection rate (deep SSI)	AIC; 0.20%	Plain cement; 0.29%	p = 0.600	No difference in the rate of deep SSI at 30 days, 6 months, and 1 year between groups;
	AIC in high risk + plain cement in regular risk; 0.13%	Plain cement; 0.29%	p = 0.298	
	AIC; 0.20%	AIC in high risk + plain cement in regular risk; 0.13%	p = 0.501	

Table A11: Summary of Findings of Included Non-Randomized Studies				
Outcome	**Intervention; Rate**	**Comparator; Rate**	**Rate or Effect Estimate**	**Author's Conclusions**
6 month infection rate (deep SSI)	AIC; 0.54%	Plain cement; 0.39%	p = 0.692	
	AIC in high risk + plain cement in regular risk; 0.38%	Plain cement; 0.39%	p = 0.727	
	AIC; 0.54%	AIC in high risk + plain cement in regular risk; 0.38%	p = 0.692	
1 year infection rate (deep SSI)	AIC; 0.61%	Plain cement; 0.78%	p = 0.550	
	AIC in high risk + plain cement in regular risk; 0.64%	Plain cement; 0.78%	p = 0564	
	AIC; 0.61%	AIC in high risk + plain cement in regular risk; 0.64%	p = 0.933	

*Adjusted for age, sex, comorbidities, and diabetes
AIC = antibiotic impregnated cement; CI = confidence interval; HR = hazard ratio; MRSA = methicillin resistant *Staphylococcus aureus*; MRSE = methicillin resistant *Staphylococcus epidermidis*; MSSA = methicillin sensitive *Staphylococcus aureus*; MSSE = methicillin sensitive *Staphylococcus epidermidis*; SSI = surgical site infection; THA = total hip arthroplasty; TKA = total knee arthroplasty

Table A12: Summary of Findings of Included Cost Studies			
Intervention	**Comparator**	**Outcome**	**Author's Conclusions**
Gutowski, 2014[45]*			
Simplex P (with tobramycin), additional $420 per procedure	Non-AIC	$112 606.67/infection prevented	Costs per infection prevented with the introduction of Simplex P AIC were high
Merollini, 2013[47]			
No antibiotic prophylaxis	Systemic antibiotic prophylaxis	ICER = spend $9308/QALY lost (dominated) NMB = -$18 million	• Compared with baseline antibiotic prophylaxis, additional use of AIC prevents 46 deep SSIs and saves $3909 for each QALY gained • Antibiotic prophylaxis plus AIC dominated antibiotic prophylaxis alone and laminar air operating rooms plus antibiotic prophylaxis as a deep surgical site infection
AIC + antibiotic prophylaxis	Systemic antibiotic prophylaxis	ICER = save $3909/QALY gained (cost saving); 46 deep SSIs prevented	

Table A12: Summary of Findings of Included Cost Studies

Intervention	Comparator	Outcome	Author's Conclusions
		NMB = $3.3 million	prevention strategy • At willingness-to-pay values of $40 and $64 thousand, AIC + antibiotic prophylaxis had the highest probability of the largest NMB = 98.6% probability of being cost-effective
Laminar flow + antibiotic prophylaxis	Systemic antibiotic prophylaxis	ICER = spend $36175/QALY lost (dominated)	
		NMB = -$18.7 million	
Scenario Analysis			
• When baseline parameters including age, costs of interventions, proportion of cemented primary total hip arthroplasties, and rate of deep SSI were varied, AIC + antibiotic prophylaxis was the optimal strategy though the incremental NMB did vary depending on these factors • Higher age decreased the NMB and increased the error probability, higher costs of AIC reduced the NMB and increased the error probability, higher proportion of cemented primary THA or higher baseline rate of deep SSI resulted in higher NMB			

*Note: the cost-minimization analysis reported by Gutowski et al., is not reported due to concern regarding inappropriate assumptions used in analysis
AIC = antibiotic impregnated cement; NMB = net monetary benefit; QALY = quality adjusted life years; SSI = surgical site infection; THA = total hip arthroplasty