Article details	
Title	Post-operative antibiotic prophylaxis in total hip and knee arthroplasty: A systematic review and meta-analysis of randomized controlled trials
Authors	Thornley, Patrick (proxy) (contact); Evaniew, Nathan; Riediger, Michael; Winemaker, Mitchell; Bhandari, Mohit; Ghert, Michelle
Abstract	Abstract: Background: Post-operative antibiotic prophylaxis is currently the standard of care for patients undergoing total hip (THA) and knee (TKA) arthroplasty. We evaluated the evidence for this practice in the reduction of surgical site infections (SSIs). Methods: We systematically searched MEDLINE, Embase, and the Cochrane Library for randomized controlled trials (RCTs) published up to August 15, 2014 using MeSH and EMTREE headings with free text combinations. We included all RCTs that compared post-operative antibiotic prophylaxis to post-operative placebo or no treatment. SSI outcomes were combined using a random effects model and heterogeneity was quantified using the chi-squared test and the I2 statistic. We assessed the overall quality of the evidence according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. Results: Across four eligible RCTs (n=4036), there were 63 SSIs in the prophylaxis group and 45 SSIs in the placebo/no treatment group. Post-operative prophylaxis did not reduce the rate of SSIs compared to placebo (risk difference 0.01, 95% CI -0.00 to 0.02, p = 0.22; I2=50%). This result was robust to sensitivity testing for losses to follow-up. According to the GRADE approach, the overall quality of evidence was 'very low'. Conclusions: The available evidence does not demonstrate efficacy for post-operative antibiotic prophylaxis for patients undergoing THA and TKA. Large multi-center RCTs are likely to have an important impact on the confidence in the effect estimate and to change the estimate itself. Further research will guide antibiotic stewardship and address the emergence of resistant organisms.
Version 1	
Reviewer 1	
Name	Pääkkönen, Markus
Position	—
Institution	—
Competing interests	—
Date review returned	23-Dec-2014

General comments	This is a well written systematic review and meta-analysis on post-operative antibiotic prophylaxis in total hip and knee arthroplasty. The article focuses on the incidence of SSI, and incidence of pneumonia or other possible sites of postoperative infection are not discussed. The systematic review highlight the lack of high-quality RCT:s and overall lack of evidence. In the meta-analysis a single study (Wymenga et al.) accounts for almost ¾ of the patients involved. Minor issues: Abstract, discussion: "The available evidence does not demonstrate efficacy for post-operative antibiotic prophylaxis for patients undergoing THA and TKA" Conclusion should be limited to the efficacy of prophylaxis of SSIs, as other infections were not reviewed in this article Intro, line 55-56. "..put forth by the English speaking orthopaedic associations." References only list New Zealand, USA, and United Kingdom. Are there no orthopaedic associations in other English speaking countries? Add more references or modify the text. Results, page 9, line 53-4. "elevated inflammatory markers" Add cutoff values for ESR and CRP Reference 23: Wymenga et al. 1991. This report has 3013 patients, but the table lists 1631 patients. Other table lists Wymenga et al. 1992, I did not find this in references. Is this reference to " Vymenga et al. Cefuroxime for prevention of postoperative coxitis. Acta Orthop Scand 1992; 63. 19-24. ?
Author response	GENERAL COMMENTS: This is a systematic review and meta-analysis on postoperative antibiotic prophylaxis in total hip and knee arthroplasty. The article focuses on the incidence of SSI, and incidence of pneumonia or other possible sites of postoperative infection are not discussed. The systematic review highlights the lack of high-quality RCT's and overall lack of evidence. In the meta-analysis a single study (Wymenga et al.) accounts for almost ¾ of the patients involved. RESPONSE: As a peri-operative management strategy, prophylactic antibiotics are directed at reducing surgical site infections. Other infections such as UTIs and pneumonia are not directly related to the surgical procedure and were therefore not examined as outcomes for SSI prophylaxis. Regarding the one larger study, statistical pooling involves weighting of the data accordingly. We have added to the Methods section: "Other infections such as urinary tract infections and pneumonia are not directly related to the surgical procedure and were therefore not examined as outcomes for SSI

	prophylaxis within our study." COMMENT: SPECIFIC COMMENTS: 1. Abstract, conclusions: "The available evidence does not demonstrate efficacy for postoperative antibiotic prophylaxis for patients undergoing THA and TKA." Conclusion should be limited to the efficacy of prophylaxis of SSIs, as other infections were not reviewed in this article. RESPONSE: We agree that the conclusion should reflect that the evidence reported in this meta-analysis should be limited to exclusively reporting a lack of efficacy of prophylaxis for prevention of SSIs. CHANGE: We have revised the abstract, conclusion section: "The available evidence does not demonstrate efficacy for post-operative antibiotic prophylaxis for prevention of SSIs in patients undergoing THA and TKA." COMMENT: 2. Intro, line 55-56. "..put forth by the English speaking orthopaedic associations." References only list New Zealand, USA, and United Kingdom. Are there no orthopaedic associations in other English speaking countries? Add more references or modify the text. RESPONSE: We agree that this sentence was ambiguous to the reader. We had intended to reflect that only three of the largest primarily English speaking orthopaedic associations globally, currently have published guidelines with respect to postoperative antibiotic prophylaxis protocols and they are all widely accepted. CHANGE: We have modified the sentence in the Introduction to reflect this: "Presently, the use of antibiotic prophylaxis (both intra-operatively and postoperatively) for primary THA and TKA is accepted as the gold standard in orthopaedic practice and is recommended by the most widely accepted consensusbased orthopaedic guidelines. (9-11)" COMMENT: 3. Results, page 9, line 53-4. "elevated inflammatory markers." Add cutoff values for ESR and CRP RESPONSE: We agree that adding the cut-off values from the study in question would be beneficial. CHANGE: We have updated the results, page 9: "...elevated inflammatory markers (erythrocyte sedimentation rate [20mm above the pre-operative value or >35mm] and c-reactive protein [an increased C-reactive protein])..." COMMENT:

	Reference 23: Wymenga et al. 1991. This report has 3013 patients, but the table lists 1631 patients. Other table lists Wymenga et al. 1992, I did not find this in references. Is this reference to " Vymenga et al. Cefuroxime for prevention of postoperative coxitis. Acta Orthop Scand 1992; 63. 19-24. ? RESPONSE: We apologize for this clerical error regarding reference year. The tables have been rechecked for accuracy. CHANGE: The reference has been referred to consistently as Wymenga 1991 throughout.
Reviewer 2	
Name	Fisher, William D
Position	—
Institution	—
Competing interests	—
Date review returned	31-Dec-2014
General comments	Unfortunately, as you observe, your source data is of low quality and not all appropriate. I am unclear why only hip data has been used in study ref 21. Table 1 also has reversed the numbers in the two groups in ref 20. You also have a mixture of studies done in clean air and, presumably, in a conventional room. I would suggest that enlarging the study to include other variables such as operating conditions may be of value.
Author response	
Reviewer 3	
Name	Vickers, David
Position	—
Institution	University of Saskatchewan, Applied Research
Competing interests	—
Date review returned	14-Jan-2015
General comments	Despite some trouble following the Methods section, the quality of the written English (for the most part) made the manuscript easy to read, and your conclusions did not extrapolate beyond the evidence you examined. However, I did find your rationale a bit strange (citing older papers—refs 9 and 10—as "standard practice", where more-recent international recommendations make no mention of post-operative antibiotic prophylaxis [1]), and your focus on RCTs a little too restrictive (RCTs produce singular, mechanical instances that can be equally as biased as other studies); it seems to me that you discovered this when you "rated down" the quality of the 4 RCTs. I am a bit surprised that you did not re-run the analysis (even as a "sanity check") to include other types of studies, such as

	the 35 observational studies. Surely, a more-extensive consensus of interpretation would've resulted. Specific Comments: I had trouble discerning what you used for a SSI case definition. Did you use NHSN definitions, or your own "clinical definition"? For example, on page 9 (3rd paragraph), it sounds like you used the latter (or something NHSN-like). If so, was there a reason why you didn't use something more standardised like NHSN definitions? With the exception of its last sentence, paragraph 3 (page 9, lines 44 to page 10 lines 3-8) could be moved to the Methods section. Figure 2: A title, caption, and legend are needed. What determined a study receiving a green "+" or a red "-"? Also, what constitutes "Other bias"? Table 2: An error must've occurred during conversion to PDF. There were four boxes in the GRADE column. Are they representative of an image or symbol? When writing 95% confidence intervals, you might want to remove the dash (e.g. 95% CI – 0.00 to 0.02) and use a colon instead (e.g. 95% CI: 0.00-0.02). It looks like your stating that the interval goes from negative zero to 0.02. Reference Cited [1] Yokoe D, et al. A compendium of strategies to prevent healthcare-associated infections in acute care hospitals: 2014 updates. Am J Infect Control, 2014; 42(8): 820-828. (doi:10.1016/j.ajic.2014.07.002)
Author response	