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Control strategies to prevent total hip replacement-related infections: a systematic review and mixed treatment comparison

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ABSTRACT

Objective: To synthesise the available evidence and estimate the comparative efficacy of control strategies to prevent total hip replacement (THR)-related surgical site infections (SSIs) using a mixed treatment comparison.

Design: Systematic review and mixed treatment comparison.

Setting: Hospital and other healthcare settings.

Participants: Patients undergoing THR.

Primary and secondary outcome measures: The number of THR-related SSIs occurring following the surgical operation.

Results: 12 studies involving 123 788 THRs and 9 infection control strategies were identified. The strategy of 'systemic antibiotics+antibiotic-impregnated cement +conventional ventilation' significantly reduced the risk of THR-related SSI compared with the referent strategy (no systemic antibiotics+plain cement+conventional ventilation), OR 0.13 (95% credible interval (CrI) 0.03–0.35), and had the highest probability (47–64%) and highest median rank of being the most effective strategy. There was some evidence to suggest that 'systemic antibiotics+antibiotic-impregnated cement +laminar airflow' could potentially increase infection risk compared with 'systemic antibiotics+antibiotic-impregnated cement+conventional ventilation', 1.96 (95% CrI 0.52–5.37). There was no high-quality evidence that antibiotic-impregnated cement without systemic antibiotic prophylaxis was effective in reducing infection compared with plain cement with systemic antibiotics, 1.28 (95% CrI 0.38–3.38).

Conclusions: We found no convincing evidence in favour of the use of laminar airflow over conventional ventilation for prevention of THR-related SSIs, yet laminar airflow is costly and widely used. Antibiotic-impregnated cement without systemic antibiotics may not be effective in reducing THR-related SSIs. The combination with the highest confidence for reducing SSIs was 'systemic antibiotics+antibiotic-impregnated cement+conventional ventilation'. Our evidence synthesis underscores the need to review current guidelines based on the available evidence, and to conduct further high-quality double-blind randomised controlled trials to better inform the current clinical guidelines and practice for prevention of THR-related SSIs.

Strengths and limitations of this study

- This study is the first to examine the comparative effectiveness of various infection control strategies involving multiple infection control measures in preventing THR-related SSIs. Multiple sensitivity analyses contributed to the methodological rigour of the study.
- The small number of studies available for evidence synthesis reduced the statistical power and resulted in wide credible intervals for some comparisons.
- Owing to limited data available, the MTC model was unable to adjust for potential confounders such as casemix, different types of laminar airflow systems and temporal changes in clinical practices and infection control technology which may have taken place over the past several decades.

INTRODUCTION

Despite numerous advances in hip arthroplasty, surgical site infection (SSI) following total hip replacement (THR) remains a serious threat. Infection causes functional impairment, reduces quality of life and creates large costs for patients and the healthcare system. Identifying evidence based and effective infection control strategies to prevent THR-related SSI is critically important.

Evidence for the effectiveness of infection control measures in reducing THR-related SSI has been inconsistent.[1–3] Previous evidence syntheses focused on single infection control measures such as systemic antibiotic prophylaxis,[4 5] antibiotic-impregnated cement[6 7] or ventilation systems alone[8] without examining the combined effect of multiple control measures. In practice, infection control strategies combine multiple infection control measures, yet no good evidence is available on the combined comparative effectiveness of strategies involving multiple measures.

Previous evidence syntheses relied on narrative systematic reviews or conventional pairwise meta-analysis. These do not compare the effectiveness of all trialled control measures when the evidence base of published studies does not include all possible comparisons.[9] The remedy is to define a connected network of the evidence base and combine all the available data in a single mixed treatment comparison (MTC) model.[9 10] This enables comparisons of all available infection control strategies to better inform decision making.

We conducted a MTC, also known as network meta-analysis, to synthesise the available evidence and determine the combined comparative effectiveness of infection control strategies in preventing THR-related SSI in patients undergoing THR.

METHODS

We applied the Patient, Intervention, Comparison and Outcome (PICO) framework. The population of interest was patients undergoing THR. The interventions were infection control strategies to prevent THR-related SSI. The comparison was an intervention strategy that was compared with the other intervention strategies in the MTC network. The outcome of interest was the number of THR-related SSIs. The PICO framework was specified in box 1.

Study identification

We chose antibiotic prophylaxis, antibiotic-impregnated cement and laminar airflow based on published guidelines and a survey of expert opinion.[11] We followed the systematic review guidelines in the PRISMA statement.[12] We used a two-stage search strategy. First, we used systematic reviews by Glenny and Song[4] and AlBuhairan *et al*[5] to locate studies on the efficacy of systemic antibiotic prophylaxis in preventing THR-related infection. Together, these covered the years from 1966 to 2007. Systematic reviews by Parvizi *et al*[6] and Block and Stubbs[7] were used to locate trials on the effect of antibiotic-impregnated cement in preventing THR-related SSI. These reviews covered the years from 1966 to 2004. We used the recent systematic review by Whitehead *et al*[8] to locate studies on the efficacy of operating theatre ventilation systems in preventing THR-related SSI, which covered the years from 1970 to 2007.

Box 1 Patient, Intervention, Comparison and Outcome framework

Population: Patients undergoing total hip replacement.
Intervention: Infection control strategies to prevent total hip replacement (THR)-related surgical site infection (SSI).
Comparison: An infection control strategy compared with other control strategies in the mixed treatment comparison network.
Outcome: The number of THR-related SSIs.

Second, we updated these systematic reviews by extending the search periods to June 2011. The electronic databases searched were MEDLINE, EMBASE, CINAHL and the Cochrane Central Register of Controlled Trials. Relevant journals, conference proceedings and bibliographies of retrieved papers were searched. Eleven orthopaedic surgeons and infection control experts from six hospitals were consulted. The search was limited to English-language papers (the search details are in online supplementary appendix 1).

Studies were included if they reported THR-related deep SSI or infection requiring a joint revision procedure as an outcome. While the precise definitions varied, they encompassed signs of infection involving the joint and/or fascial tissue at the site of the joint. Owing to the limited number of studies available, we included observational studies as well as randomised controlled trials (RCTs).

Studies were excluded if THR-related SSIs were not separated from knee or other joint replacement-related infections. Studies that only compared different types, doses or durations of antibiotic regimens were treated as one-arm trials and excluded from the network meta-analysis as MTC relies on there being at least two arms that can become part of the network.[10] The antibiotics were combined because there is little evidence of different efficacies in preventing THR-related SSI between antibiotics according to their type, dose or duration.[4] The two-stage search process is in the flow chart (figure 1; reasons for exclusion are shown in online supplementary appendix 2).

Data extraction

Data were extracted by two independent reviewers and discrepancies were resolved by consensus. The key data were the number of THRs performed and THR-related deep SSIs; use of antibiotic prophylaxis and its delivery mode; and operating theatre ventilation system.

Quality assessment

The quality of the included studies and their level of evidence were assessed based on the National Institute for Health and Care Excellence (NICE) public health guidelines[13] (see online supplementary appendix 3), and quality scoring systems for RCTs by the Joanna Briggs Institute[14] and observational longitudinal studies by Tooth *et al*[15] (see online supplementary appendix 4).

Statistical methods

MTC models produce estimates of the relative effects of each infection control strategy compared with every other strategy in a network, thus allowing coherent judgements to be made on which strategy is the most effective.[9] It enables simultaneous comparisons of multiple infection control strategies from trials that did not necessarily directly compare all strategies.[9 10] Bayesian methods have been developed for MTC models (see online supplementary appendix 5).[16]

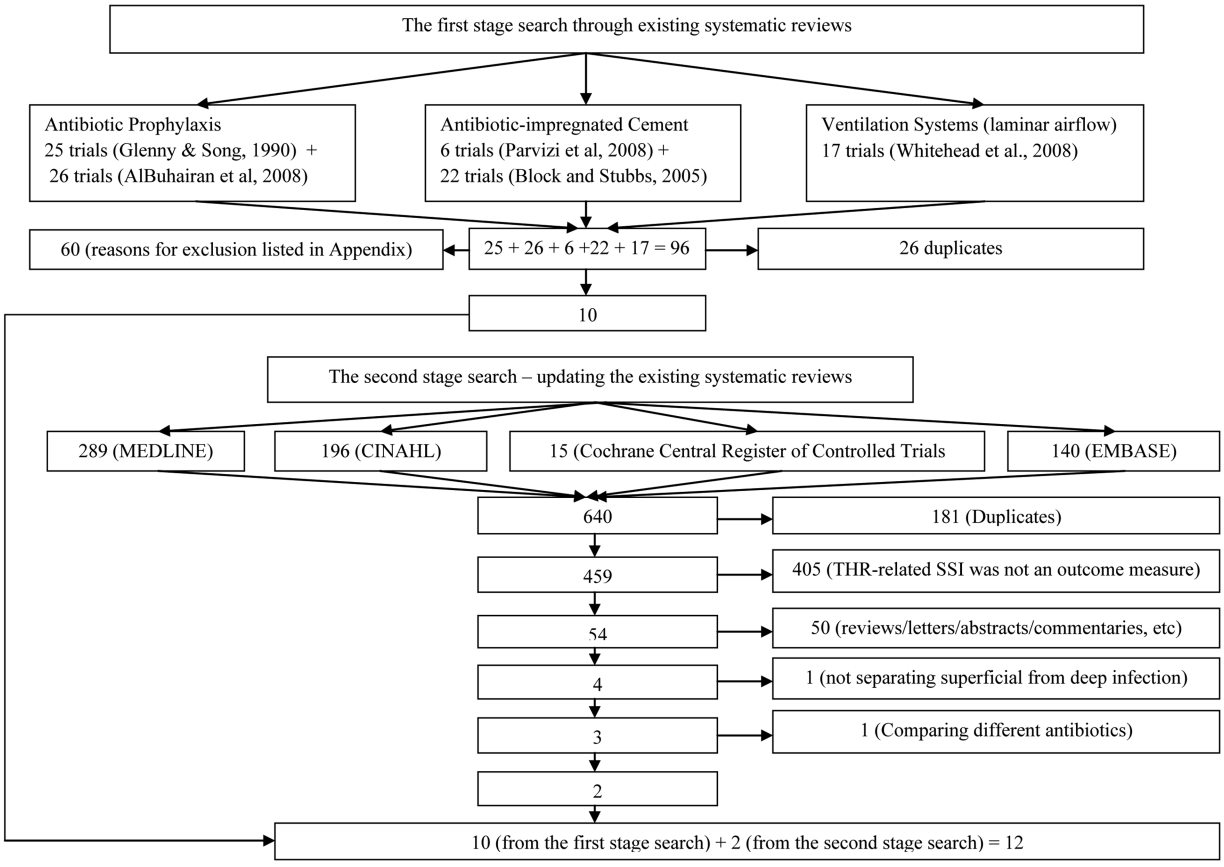


Figure 1 Two-stage literature search flow chart.

The MTC analysis was performed using a binomial random effect model allowing multiarm trials.[17] The key summary statistics were the relative infection control effects using ORs, and the probability and median rank of being the most effective strategy. Studies with longer follow-up periods were likely to find more infections; hence, we accounted for this by modelling the duration of follow-up (see online supplementary appendix 6). The models were fitted in a Bayesian framework using the WinBUGS program and code by Dias *et al*.[17]

Evaluation of model fit and evidence consistency

We assessed the models' goodness of fit (see online supplementary appendix 7). Where the model fit was poor, we explored the influence of each study on the model fit (see online supplementary appendix 8).

An assumption of MTC models is that direct and indirect sources of evidence estimate the same true treatment effect across the network. We checked this assumption by conventional pairwise meta-analyses and by removing the constraint that direct and indirect evidence estimate the same effect.[18] The latter is also known as node-splitting (see online supplementary appendix 9).

Heterogeneity and sensitivity analysis

Heterogeneity of the MTC network was quantified by using the between-study SD. We performed sensitivity analyses by removing outliers as identified through diagnostic assessment.

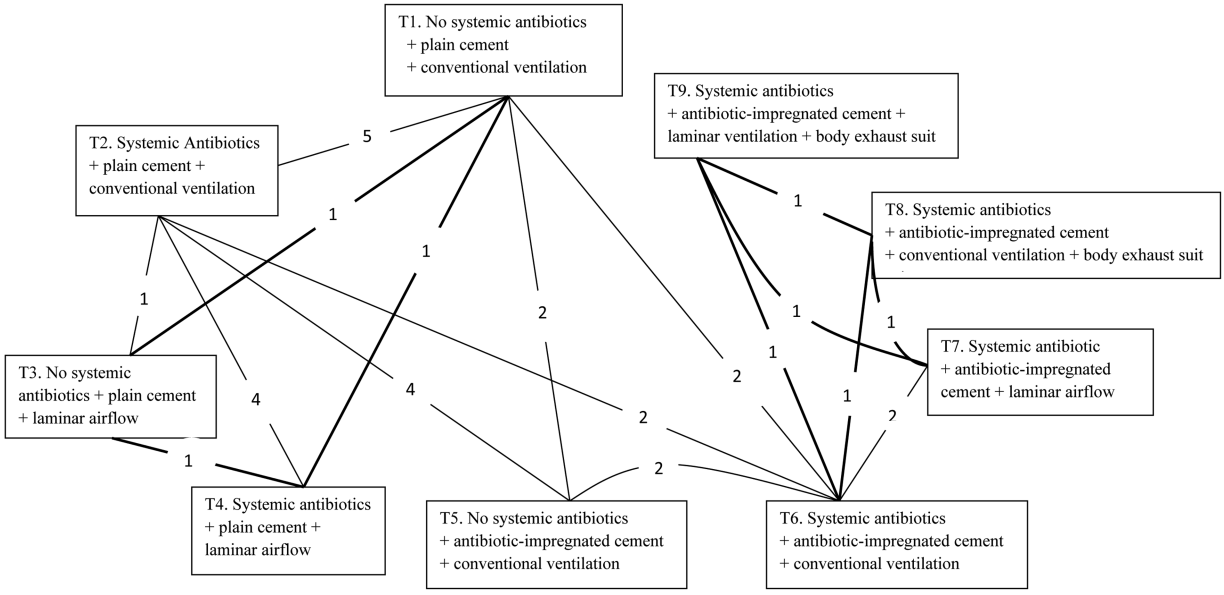
There may have been a difference in evidence between RCTs and observational studies. To examine this, we performed a meta-regression with study type as an interaction (see online supplementary appendix 10).[19] In further sensitivity analyses, we excluded the RCT by Hill *et al*[20] due to its reported violation of the RCT trial code, and included the RCT by Lidwell *et al*[1] which was initially excluded because it did not separate THRs from knee replacements.

RESULTS

The two-stage search strategy yielded 529 studies, of which 12 met our inclusion criteria. Six were RCTs[20–25] and six were observational studies.[2 3 26–29] The studies included 123 788 THRs and 9 infection control strategies as mapped in the MTC network (figure 2). The raw data are in the Summary of Evidence (table 1).

The quality of evidence was mixed with the level of evidence ranging from 1 to 2 (table 1).

Five of six studies[21–25] provided no information on random sequence generation; four[22–25] provided no information on blinding assessors; and only one reported prior calculation of the sample size.[20] The statistical power for most RCTs was generally low. Only one



Note: The lines represent direct evidence comparisons; boxes represent infection control strategies involving multiple infection control measures; the numbers on the lines represent the numbers of comparisons. The three-way loops in bold lines represent loops only formed by a multi-arm trial

Figure 2 The mixed treatment comparison network consisting of 12 studies with 9 infection control strategies.

RCT reported primary analysis based on all randomised cases[20] while the rest did not report intention to treat.

Of the six observational studies, three[3 28 29] identified and adjusted for confounding variables. One[26] reported that cases and control groups were comparable on diagnostic confounding factors, and two[28 29] described and included in the analysis the outcomes of the patients who withdrew. Four studies[2 3 28 29] used objective measures to assess the outcomes, and were adequately powered with large sample size ranging from 10 905 to 51 485.

For every infection control strategy in the connected network, a relative effect was estimated against another infection control strategy using the OR. We chose 'no systemic antibiotics, plain cement and conventional ventilation' as the referent strategy, as it was compared with the greatest number of other strategies.

Thirty-six relative effects involving nine infection control strategies were estimated in the MTC network using models that did and did not adjust for duration of follow-up (see online supplementary appendix 11 and table 2). The results from both models were almost identical, as were estimates of the model fit. Hence, the differences in follow-up duration had little effect on the effectiveness of the infection strategies. We therefore report the results of the model without adjustment for follow-up from now on (table 2). The 36 ORs for all pairwise comparisons are in the Forest Plot (figure 3).

The five infection control strategies associated with a statistically significant reduction in THR-related SSI compared with the referent strategy T1 were: T6 (systemic antibiotics+antibiotic-impregnated cement+conventional ventilation), OR 0.13 (95% credible interval (CrI) 0.03–0.35); T2 (systemic antibiotics+plain cement+conventional ventilation), 0.31 (0.12–0.65); T3 (no systemic antibiotics +plain cement+laminar airflow), 0.26 (0.03–0.95); T4 (systemic antibiotics+plain cement+laminar airflow), 0.25 (0.06–0.66); and T7 (systemic antibiotics+antibiotic-impregnated cement+laminar airflow), 0.27 (0.03–0.93; table 3).

Statistically non-significant reductions in THR-related SSIs as compared with the referent were T5 (no systemic antibiotics+antibiotic-impregnated cement+conventional ventilation), OR 0.38 (95% CrI 0.09–1.12); T8 (systemic antibiotics+antibiotic-impregnated cement+conventional ventilation+body exhaust suit), 0.52 (0.03–2.12) and T9 (systemic antibiotics+antibiotic-impregnated cement+ laminar ventilation+body exhaust suit), 0.74 (0.05–2.69).

The OR for T7 (systemic antibiotics+ antibiotic-impregnated cement+laminar airflow) compared with T6 (systemic antibiotics+antibiotic-impregnated cement +conventional ventilation) was 1.96 (95% CrI 0.52–5.37), suggesting that laminar airflow could potentially increase infection risk.

There was no high-quality evidence that antibiotic-impregnated cement without systemic antibiotics was effective in reducing infection compared with plain cement with systemic antibiotics (T2 vs T5), 1.28 (95% CrI 0.38–3.38).

Strategy T6 had the highest probability and highest median rank of being the best strategy in reducing THR-related SSI (see online supplementary appendix 12).

Model fit and evidence consistency

The model fit statistics indicated that the fit was less than adequate (table 2). This was confirmed by diagnostic plots, which showed that infection control strategies

Table 1 Summary of evidence: comparisons of nine control strategies across the MTC network

Author/year/study design/country	Comparison of infection control strategies	Infection control strategy	Number of THR-related SSIs	Number of THRs	Evidence level and quality assessment	Study number
Carlsson *et al* (1977)[21] RCT, Sweden Schulitz *et al* (1980)[22] RCT, Germany	The referent strategy T1 (no systemic antibiotics +plain cement+conventional ventilation) vs T2 (systemic antibiotics+plain cement+conventional ventilation)	T1 T2	7 0	58 60	Evidence level: 1^{-} C1 C2 C3 C4 C5 C6 C7 C8 1 2 2 1 1 1 3 3	1
		T1 T2	8 1	89 105	Evidence level: 1^{-} C1 C2 C3 C4 C5 C6 C7 C8 1 1 1 1 2 2 3 2	2
Salvati *et al* (1982)[26] Observational study, Italy Fitzgerald (1992)[23] RCT, USA	T2 (systemic antibiotics+plain cement +conventional ventilation) vs T4 (systemic antibiotics+plain cement+laminar airflow)	T2 T4	11 13	761 1518	Evidence level: 2^{-} C1 C2 C3 C4 C5 C6 C7 C8 1 2 3 2 1 2 1 3	5
Kelly *et al* (1996)[27] Observational Study, UK		T2 T4	4 1	1739 1682	Evidence level: 1^{-} C1 C2 C3 C4 C5 C6 C7 C8 1 2 1 1 1 1 1 2	7
		T2 T4	0 3	236 207	Evidence level: 2^{-} C1 C2 C3 C4 C5 C6 C7 C8 1 1 1 1 1 3 1 2	8
Josefsson *et al* (1981)[24] RCT, Sweden McQueen *et al* (1990)[25] RCT, UK	T2 (systemic antibiotics+plain cement +conventional ventilation) vs T5 (no systemic antibiotics+antibiotic-impregnated cement +conventional ventilation)	T2 T5	10 2	812 821	Evidence level: 1^{-} C1 C2 C3 C4 C5 C6 C7 C8 1 2 1 1 1 1 3 3	4
		T2 T5	1 2	190 190	Evidence level: 1^{-} C1 C2 C3 C4 C5 C6 C7 C8 1 2 1 1 1 2 3 3	6
Brandt *et al* (2008)[3] Observational study, Germany	T6 (systemic antibiotics+antibiotic-impregnated cement+conventional ventilation) vs T7 (systemic antibiotics+antibiotic-impregnated cement+laminar airflow)	T6 T7	99 242	10 966 17 657	Evidence level: 2^{+} C1 C2 C3 C4 C5 C6 C7 C8 2 3 1 3 2 2 2 3	11
Hill *et al* (1981)[20] RCT, France	The referent strategy T1 (no systemic antibiotics +plain cement+conventional ventilation) vs T2 (systemic antibiotics+plain cement+conventional ventilation) vs T3 (no systemic antibiotics+plain cement+laminar airflow) vs T4 (systemic antibiotics+plain cement+laminar airflow)	T1 T2 T3 T4	31 4 4 6	596 590 471 480	Evidence level: 1^{-} C1 C2 C3 C4 C5 C6 C7 C8 **2 2 2 2 2 3 2 3**	3

Continued

Table 1 Continued

Author/year/study design/country	Comparison of infection control strategies	Infection control strategy	Number of THR-related SSIs	Number of THRs	Evidence level and quality assessment	Study number
Espehaug *et al* (1997)[28] Observational study, Norway	The referent strategy T1 (no systemic antibiotics +plain cement+conventional ventilation) vs T2 (systemic antibiotics+plain cement+conventional ventilation) vs T5 (no systemic antibiotics +antibiotic-impregnated cement+conventional ventilation) vs T6 (systemic antibiotics +antibiotic-impregnated cement+conventional ventilation)	T1 T2 T5 T6	3 25 3 8	276 4586 239 5804	Evidence level: 2+ C1 C2 C3 C4 C5 C6 C7 C8 2 3 2 3 2 3 3 3	9
Engesaeter *et al* (2003)[29] Observational study, Norway		T1 T2 T5 T6	3 46 3 50	280 5960 254 15 676	Evidence level: 2+ C1 C2 C3 C4 C5 C6 C7 C8 2 3 2 3 2 3 3 3	10
Hooper *et al* (2011)[2] Observational study, New Zealand	T6 (systemic antibiotics+antibiotic-impregnated cement+conventional ventilation) vs T7 (systemic antibiotics+antibiotic-impregnated cement+laminar airflow) vs T8 (systemic antibiotics+antibiotic-impregnated cement +conventional ventilation+body exhaust suit) vs T9 (systemic antibiotics+antibiotic-impregnated cement+laminar ventilation+body exhaust suit)	T6 T7 T8 T9	17 9 4 16	31 939 8772 2696 8078	Evidence level: 2+ C1 C2 C3 C4 C5 C6 C7 C8 2 2 2 3 1 3 2 3	12

Note: 'C' denotes the quality assessment criterion as specified in online supplementary appendix 4.
RCT, randomised controlled trial; SSI, surgical site infection; THR, total hip replacement.

Table 2 ORs with 95% credible intervals of all nine infection control strategies based on the logit link random effect MTC model

Comparison of infection control strategies			OR and 95% credible interval				
OR (1,2)							
0.31 (0.12–0.65)							
OR (1,3)	OR (2,3)						
0.26 (0.03–0.95)	0.92 (0.11–3.39)						
OR (1,4)	OR (2,4)	OR (3,4)					
0.25 (0.06–0.66)	0.84 (0.28–1.97)	1.93 (0.20–7.58)					
OR (1,5)	OR (2,5)	OR (3,5)	OR (4,5)				
0.38 (0.09–1.12)	1.28 (0.38–3.38)	3.28 (0.27–14.15)	1.96 (0.37–6.54)				
OR (1,6)	OR (2,6)	OR (3,6)	OR (4,6)	OR (5,6)			
0.13 (0.03–0.35)	0.44 (0.13–1.13)	1.12 (0.09–4.62)	0.67 (0.12–2.12)	0.43 (0.09–1.24)			
OR (1,7)	OR (2,7)	OR (3,7)	OR (4,7)	OR (5,7)	OR (6,7)		
0.27 (0.03 to 0.93)	0.90 (0.13–3.14)	2.47 (0.11–10.22)	1.41 (0.14–5.35)	0.88 (0.09–3.10)	1.96 (0.52–5.37)		
OR (1,8)	OR (2,8)	OR (3,8)	OR (4,8)	OR (5,8)	OR(6,8)	OR (7,8)	
0.52 (0.03–2.12)	1.77 (0.11–7.20)	5.78 (0.10–21.12)	2.89 (0.12–11.73)	1.71 (0.08–6.93)	3.72 (0.38–13.75)	2.26 (0.22–8.48)	
OR (1,9)	OR (2,9)	OR(3,9)	OR(4,9)	OR (5,9)	OR(6,9)	OR (7,9)	OR (8,9)
0.74 (0.05–2.69)	2.49 (0.20–9.11)	13.15 (0.18–27.4)	4.11 (0.22–14.92)	2.44 (0.15–8.62)	5.00 (0.73–16.87)	3.14 (0.42–10.41)	2.53 (0.23–10.41)
Model fit statistic (posterior mean residual deviance) 34.3*			Model fit statistic (DIC) 180.6		Heterogeneity (between-study deviation) 0.63		

*Compared with 32 data points (model fit is considered to be adequate if the posterior mean residual deviance is approximately equal to the number of total data points; see online supplementary appendix 6 for reference).
DIC, deviance information criterion; MTC, mixed treatment comparison.

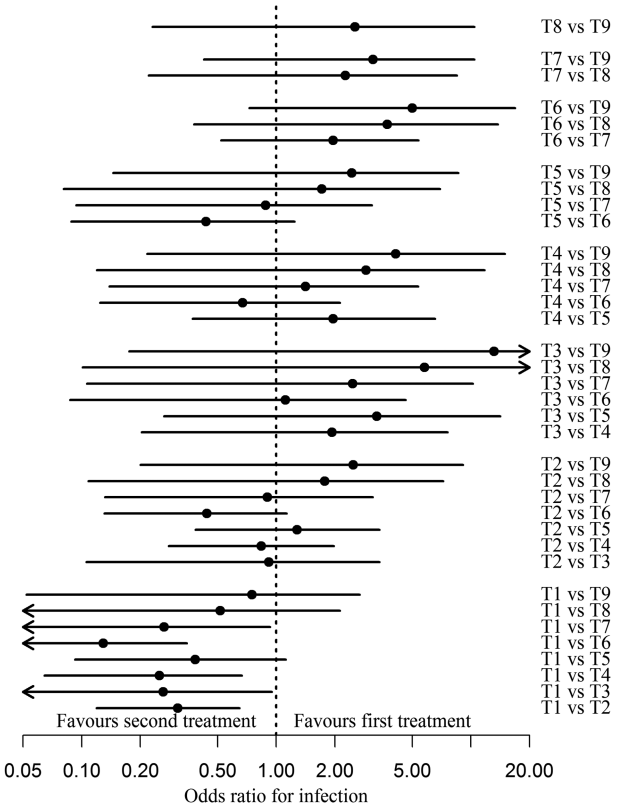


Figure 3 The forest plot of ORs of infection control strategies (random effect model).

T2 and T5 of study 4 and the referent strategy of study 10 were outliers contributing to the inadequate model fit (see online supplementary appendix 13). After exclusion of these two studies, the model fitted the data well, as indicated by model fit statistics, and the heterogeneity was significantly reduced, but the results were little changed (see online supplementary appendix 14). Infection control strategy T6 remained dominant with the highest probability (64%) and highest median rank of being the most effective strategy (see online supplementary appendix 15), and OR 0.09 (95% CrI 0.02–0.25; see online supplementary appendix 14).

The direct evidence from all conventional pairwise meta-analyses was presented in online supplementary appendix 16. There was broad agreement among the direct evidence from: conventional pairwise meta-analyses, the direct and indirect evidence from node splitting, and the evidence from the MTC model (see online supplementary appendix 16). Tests for inconsistency between direct and indirect evidence from node splitting suggested that there was no statistically significant evidence of inconsistency. The model fit statistics for the node-splitting and the MTC models were similar, implying that there was no conflict between the direct and indirect evidence (see online supplementary appendix 16). It is worth noting that the 95% CrIs for some pairwise comparisons widened greatly following node splitting. This is explained by the node splitting reducing the evidence available to inform the variance.

A test of interaction between RCTs and observational studies was not statistically significant, suggesting that combining these study types was not inappropriate (see online supplementary appendix 17).

The results were little changed by excluding the RCT by Hill *et al*[20] or including the RCT by Lidwell[1] *et al*. Strategy T6 remained dominant with the highest probability (63% and 83%, respectively) and highest median rank of being the most effective strategy (the details of the sensitivity analyses are shown in online supplementary appendix 18).

DISCUSSION

Laminar airflow has been widely used as an important infection control measure in many countries around the world. In the UK, for instance, around 98% of all hip arthroplasties are carried out in operating theatres equipped with laminar airflow systems.[30] The current infection control guidelines in the UK[31] and the USA[32] recommend the use of laminar airflow to reduce THR-related SSIs. It is an expensive technology, costing US$60 000–US$90 000 for construction and installation for each operating room.[33] However, our study showed that conventional ventilation together with systemic antibiotics and antibiotic-impregnated cement was most likely to provide the best protection against THR-related SSIs. We found no convincing evidence in favour of the use of laminar airflow over conventional ventilation for prevention of THR-related SSIs.

Although the point estimate for the infection control strategy T3 (no systemic antibiotics+plain cement +laminar airflow) compared with the referent was statistically significant, caution needs to be taken in its interpretation because it had only one RCT conducted between 1975 and 1978 by Hills and colleagues, and the study reported that about 8% of the patients (99 in the placebo group and 70 in the antibiotic group) did not follow the RCT trial protocol with unreported use of antibiotics. We therefore conducted a sensitivity analysis by excluding this RCT from the MTC network and the results for other strategies changed little, with T6 remaining the most effective.

A recent systematic review concluded that laminar airflow tended to lower infection rates as opposed to conventional ventilation, but the authors emphasised that it was difficult to draw a definite conclusion due to confounding.[8] The systematic review was descriptive, involving no statistical analysis. It cited, among others, the RCT by Lidwell *et al*[1] as the key evidence for reducing wound infection using laminar airflow. However, this RCT did not control for antibiotics as a significant confounder. Our sensitivity analysis found that the overall results changed little with the inclusion of this RCT, so it had little influence on our conclusions.

Contrary to the key early evidence in the late 1960s to early 1980s that laminar airflow and body exhaust suit reduced wound contamination and SSIs,[1 34] a number

Table 3 Odds ratios with 95% credible intervals of infection control strategies based on the random effect MTC model

	No systemic antibiotics	Plain cement	Conventional ventilation	Systemic antibiotics	Antibiotic-impregnated cement	Laminar airflow	Body exhaust suit	OR	95% Credible interval
T1	✓	✓	✓	×	×	×	×	Referent	
T6	×	×	✓	✓	✓	×	×	0.13	0.03–0.35
T2	×	✓	✓	✓	×	×	×	0.31	0.12–0.65
T3	✓	✓	×	×	×	✓	×	0.26	0.03–0.95
T4	×	✓	×	✓	×	✓	×	0.25	0.06–0.66
T7	×	×	×	✓	✓	✓	×	0.27	0.03–0.93
T5	✓	×	✓	×	✓	×	×	0.38	0.09–1.12
T8	×	×	✓	✓	✓	×	✓	0.52	0.03–2.12
T9	×	×	×	✓	✓	✓	✓	0.74	0.05–2.69
T2 vs T5	–	–	–	–	–	–	–	1.28	0.38–3.38
T6 vs T7	–	–	–	–	–	–	–	1.96	0.52–5.37
Model fit statistic (posterior mean residual deviance) 34.3*			Model fit statistic (DIC) 180.6			Heterogeneity (between-study SD 0.63			

*Compared with 32 data points (model fit is considered to be adequate if the posterior mean residual deviance is approximately equal to the number of total data points; see online supplementary appendix 7).
Note: T1–T9: nine infection control strategies. Refer to table 1 for details.
✓: The strategy contains the infection control measure as indicated by the column heading.
×: The strategy does not contain the infection control measure as indicated by the column heading.
DIC, deviance information criterion; MTC, mixed treatment comparison.

of subsequent studies in the 1980s and 1990s found no convincing evidence that laminar airflow was effective in reducing SSIs compared with conventional ventilation.[23 26 27] Four recent large-scale observational studies of 113 183 THRs suggested that laminar airflow and body exhaust suit conferred no protective benefit against SSI and might increase the risk of SSI.[2 3 28 29]

A hypothesis of the early studies by Charnley[34] and Lidwell *et al*[1] on laminar airflow and body exhaust suits was that one of the main routes of wound contamination and infection was the air in the operating room, and laminar airflow and body exhaust suits could reduce airborne bacteria load and therefore wound contamination and infection. The studies demonstrated that laminar airflow ventilation reduced airborne organisms or colony forming units (cfu) to 10 cfu/m^3 between 150 and 300 cfu/m^3 in conventional operating theatres. To be most effective, key operating theatre staff should wear body exhaust suits while working in the ultraclean environment.[1 34] However, standard culture techniques by air sampling or landing 'mode' as a method to assess potential wound contamination do not directly correlate with wound contamination, and they are at best surrogate measures representing the degree of air contamination at the point of sampling, which might be some distance away from the implant zone.[35] There was also evidence that wound contamination was greater at the end of surgery than at the beginning.[35]

The surgeons' heads position above the surgical site and directly in the laminar airstream might facilitate pathogen-contaminating particles falling directly into the wound.[36] Laminar airflow could also result in lower intraoperative tissue temperatures in the surgical wound,[3] and systemic hypothermia is a known risk factor for SSI.[37]

Our study found no high-quality evidence that antibiotic-impregnated cement without systemic antibiotic prophylaxis was effective in reducing THR-related SSI compared with plain cement with systemic antibiotic prophylaxis. Contrary to our findings, a recent meta-analysis showed that the use of antibiotic-impregnated cement lowered the infection rate by approximately 50% compared with plain cement.[6] However, the meta-analysis failed to stratify the infection control arms according to antibiotic regimens and pool on a comparable basis. We reanalysed the data from this meta-analysis by stratifying infection control arms based on antibiotic regimens and pooling the rest of the studies on a comparable basis for summary estimation (see online supplementary appendix 19). The pooled relative risk of antibiotic-impregnated cement compared with plain cement was 0.76 (95% CI 0.46 to 1.28). So there was no high-quality evidence that antibiotic-impregnated cement without systemic antibiotic prophylaxis was effective in reducing THR-related infection compared with plain cement with systemic antibiotic prophylaxis.

A RCT showed that antibiotic-impregnated cement together with systemic antibiotic prophylaxis was

effective in reducing knee replacement-related infection compared with plain cement with systemic antibiotic prophylaxis.[38] All the procedures were performed in a standard operating room without laminar airflow or body-exhaust suit. The authors stressed that while they did not believe that antibiotic-impregnated cement alone would prevent deep infection, it could aid in prevention of early or intermediate infection in conjunction with systemic antibiotic prophylaxis. This might be explained by the capacity of antibiotic-impregnated cement as a drug-delivery vehicle. It was suggested that the polymeric nature of polymethylmethacrylate allowed ingress of physiological fluids, which permitted elution of incorporated antibiotic, but the relative hydrophobicity of bone cement allowed only 10% of the antibiotic to elute effectively.[39]

Our evidence synthesis has limitations. The small number of studies available for evidence synthesis reduced the statistical power and resulted in wide CrIs for some comparisons. MTC can only synthesise evidence in a connected network. Consequently, one study[40] meeting our inclusion criteria could not be included as it could not be connected to the network. However, the exclusion of this study should not change our results, as the study concluded that there was no statistical difference in THR-related SSIs between plain cement and antibiotic-impregnated cement, which accorded with our findings.

Owing to the limited data available, the MTC model was unable to adjust for potential confounders such as case-mix, particularly patient comorbidity in different hospital settings, different types of laminar airflow systems used (eg, horizontal vs vertical laminar airflow systems), and temporal changes in clinical practices, infection control technology (eg, the use of ultra-high flows in modern conventional operating theatres and forced air blankets) and patient profiles which may have taken place over the past several decades.

The evidence in our study covered a period from 1966 up to June 2011 when the literature search was performed. The evidence needs to be updated when new studies become available.

CONCLUSIONS

This is the first study to examine the comparative effectiveness of various infection control strategies involving multiple infection control measures in preventing THR-related SSI. We found no convincing evidence in favour of the use of laminar airflow over conventional ventilation for prevention of THR-related SSI. Systemic antibiotic prophylaxis in conjunction with antibiotic-impregnated cement and conventional ventilation was likely to be the most effective infection control strategy for preventing THR-related SSI based on the available evidence. There was no high-quality evidence that antibiotic-impregnated cement alone without systemic antibiotic prophylaxis was effective in reducing THR-related SSI compared with plain cement with systemic antibiotics. Our evidence synthesis underscores the need to review current guidelines based on the available evidence, and to conduct further high-quality double-blind RCTs to better inform the current clinical guidelines and practice for prevention of THR-related SSI.

Contributors NG, AGB, HZ, KM, AS, NC, TB and JW were involved in the inception and design of the study. NG and AGB oversaw the implementation of the study. HZ and KM were involved in study identification and data acquisition. JW advised on interpretation of the literature. HZ performed the statistical analysis with help from AGB. HZ, AGB, NG, AS, NC,TB and JW interpreted the data. HZ wrote the first draft of the paper with input from AGB and NG. AGS, NC, TB and JW critically reviewed and revised the draft. All authors approved the final version of the manuscript for publication.

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Appendices

Appendix 1

The search terms and search strategies used for updating existing evidence

Medline

1. MH “arthroplasty, replacement, hip’ (12088)
2. MH “Hip prosthesis” (16064)
3. or/1-2 (23923)
4. MH “Surgical wound infection” (24907)
5. MH “prosthesis-related infections” (5875)
6.MH “sepsis+” (78337)
7. MH “bacterial infections+” (651285)
8. or/4-7 (718898)
9. MH “infection control+’ (44638)
10. infection prevent*/ (33276)
11. MH “antibiotic prophylaxis” (6889)
12. MH “anti-infective agents+” (427375)
13. MH “Anti-Bacterial Agents+” (226839)
14. intravenous antibiotics/ (3008)
15. systemic antibiotics/ (2001)
16. or/9-15 (489991)
17. MH “bone cements” (7563)
18. Antibiotic cement / (448)
19.antibiotic bone cement (smart text searching) / (7715)
20. Antibiotic-impregnated cement (smart text searching)/(733)
21. Antibiotic-impregnated cement (smart text searching)/(1001)
22. Antibiotic-loaded cement (smart text searching)/ (1129)
23.Antibiotic-loaded bone cement (smart text s) / (7969)
24.or/17-23 (11656)
25. MH "Environment, Controlled+" (218646)
26.MH “ventilation” (4202)
27.MH “Air conditioning” (2075)
28.MH “operating rooms” (9370)
29.Operating theatre/ (1937)
30.laminar air flow (smart text searching) / (3374)
31. laminar airflow (smart text searching)/ (244)
32. laminar air flow system (smart text searching) (4345)
33. ultra-clean air (smart text searching) /(2527)
34. ultra clean air (smart text searching) /(2527)
35. ultra-clean air system (smart text searching) (4496)
36. conventional operating room (smart text searching)/ (22235)
37. conventional operating theatre (smart text searching) / (2777)
38. Turbulent air flow (smart text searching)/ (2613)
39.or/25-38 (256457)
40. 3 and 8 and 16 (697)
41.3 and 8 and 24 (292)
42.3 and 8 and 39 (87)
43.40 or 41 or 42 (834)
44. Limit 43 to 2004-2011 (01/01/2004-01/06/2011) (343)
45. Limit 44 to English (289)

CINAHL

1. MH “arthroplasty, replacement, hip’ (4105)
2. MH“joint prosthesis” (2008)
3. Hip prosthesis (smart text searching) (1894)
4. or/1-3 (5474)
5. MH “Surgical wound infection” (3410)
6. MH “prosthesis-related infections” (529)
7.MH “sepsis+” (7640)
8. MH “bacterial infections+” (39831)
9. or/5-8 (48616)
10. MH “infection control+’ (31116)
11. infection prevent*/ (10134)
12. MH “antibiotic prophylaxis” (2227)
13. MH “anti-infective agents+” (45136)
14. Anti-Bacterial Agents (smart text searching) /(2578)
15. intravenous antibiotics (smart text searching)/ (1301)
16. systemic antibiotics (smart text searching)/ (665)
17. or/10-16 (79414)
18. MH “bone cements” (804)
19. Antibiotic cement (smart text searching) (96)
20.antibiotic bone cement (smart text searching) / (610)
21. Antibiotic-impregnated cement (smart text searching)/(107)
22. Antibiotic-impregnated cement (smart text searching)/ (126)
23. Antibiotic-loaded cement (smart text searching)/ (144)
24.Antibiotic-loaded bone cement (smart text s) / (638)
25.or/18-24 (1140)
26. MH "Environment, Controlled+" (4265)
27.MH “ventilation+” (747)
28.MH “Air conditioning” (118)
29.MH “operating rooms” (4319)
30.Operating theatre (smart text searching) (663)
31.laminar air flow (smart text searching) (126)
32. laminar airflow (smart text searching)/ (38)
33. laminar air flow system (smart text searching) ((137)
34. ultra-clean air (smart text searching) / (40)
35. ultra clean air (smart text searching) /(40)
36. ultra-clean air system (smart text searching) (126)
37. conventional operating room (smart text searching)/ (359)
38. conventional operating theatre (smart text searching) / (664)
39. Turbulent air flow (smart text searching)/ (52)
40.or/26-39 (9280)
41. 4 and 9 and 17 (216)
42.4 and 9 and 25 (59)
43.4 and 9 and 40 (24)
44.41 or 42 or 43 (233)
45. Limit 44 to 2004-2011 (01/01/2004-01/06/2011) (196)
46. Limit 45 to English (196)

The Cochrane Central Register of Controlled Trials

1. MH “arthroplasty, replacement, hip +”/exp (1254)
2. MH”Hip prosthesis” / exp (942)
3.or/1-2 (1949)
4. MH “Surgical wound infection” / exp (2470)
5.MH “prosthesis-related infections” /exp (127)
6. MH “sepsis ”/exp (2684)
7. MH “bacterial infections” /exp (13168)
8.or/4-7 (17095)
9. MH “infection control”/ exp (1116)
10.infection prevent*/ (16554)
11. MH “antibiotic prophylaxis” / exp (1040)
12.MH “anti-infective agents” / exp (44153)
13.MH “Anti-Bacterial Agents” / exp (18759)
14.intravenous antibiotics/ (2375)
15. systemic antibiotics/ (1220)
16. or/9-15 / (55871)
17. MH “bone cements” / exp (579)
18.Antibiotic cement / (39)
19.antibiotic bone cement/ (32)
20. Antibiotic-impregnated cement /(7)
21. Antibiotic-impregnated bone cement /(7)
22. Antibiotic-loaded cement /(3)
23. Antibiotic-loaded bone cement / (3)
24.or/17-23 (601)
25. MH "Environment, Controlled" /exp (1948)
26.MH “ventilation” /exp (52)
27.MH “Air conditioning” /exp (25)
28.MH “operating rooms” / exp (230)
29. Operating theatre/ (402)
30. laminar air flow / (39)
31. laminar airflow / (11)
32. laminar air flow system / (7)
33. ultra-clean air / (5)
34. ultra clean air / (6)
35. ultra-clean air system / (2)
36. conventional operating room / (184)
37. conventional operating theatre / (59)
38. Turbulent air flow / (5)
39.or/25-38 (2697)
40. 3 and 8 and 16 / (58)
41.3 and 8 and 24 / (9)
42.3 and 8 and 39 / (11)
43.40 or 41 or 42 / (59)
44. Limit 43 to 2004-2011 (15)
45. Limit 44 to English (15)

Embase

1. 'hiparthroplasty'/exp (32,814)
2. 'hip prosthesis'/exp (26,568)
3. OR / 1-2 (32,814)
4. 'surgical infection'/exp (18,425)
5. 'prosthesis infection'/exp (2,624)
6. 'sepsis'/exp (129,060)
7. 'bacterial infection'/exp (667,479)
8. OR / 4-7 (767,273)
9. 'infection control'/exp (55,345)
10. 'infection prevention'/exp (31,360)
11. 'antibiotic prophylaxis'/exp (16,495)
12. 'anti-infective agent'/exp (1,827,014)
13. 'antibiotic agent'/exp (833,849)
14. 'intravenous'/exp AND 'antibiotics'/exp (57,368)
15. systemic AND 'antibiotics'/exp (70,947)
16. OR / 9-15 (1,886,128)
17. 'bone cement'/exp (9,336)
18. 'antibiotic'/exp AND 'cement'/exp (1,532)
19. 'antibiotic'/exp AND 'bone'/exp AND 'cement'/exp (340)
20. 'antibiotic'/exp AND impregnated (1,038)
21. 'gentamicin bone cement'/exp (343)
22. 'antibiotic loaded' AND 'cement'/exp (204)
23. 'antibiotic loaded' AND 'bone'/exp AND 'cement'/exp (31)
24. OR / 17-23 (10,339)
25. 'microclimate'/exp (30,703)
26. 'air conditioning'/exp (10,256)
27. 'operating room'/exp (15,854)
28. 'laminar airflow'/exp (566)
29. laminar AND 'air'/exp AND 'flow'/exp AND system (29)
30. 'ultra clean' AND 'air'/exp (15)
31. ultra AND clean AND 'air'/exp (16)
32. 'ultra clean' AND 'air'/exp AND system (2)
33. conventional AND operating AND room (886)
34. conventional AND operating AND theatre (135)
35. 'turbulent flow'/exp (2,813)
36. OR / 25 - 35 (49,434)
37. 3 AND 8 AND 16 (828)
38. 3 AND 8 AND 24 (226)
39. 3 AND 8 AND 36 (37)
40. 37 OR 38 OR 39 (915)
41. 7 OR 38 OR 39 AND (English)/lim AND (20004-2011)/py (529)
42. 37 OR 38 OR 39 AND (English)/lim AND (Embase)/lim NOT (Medline)/lim AND (2004-2011)/py (140)

Appendix 2

a. Studies excluded and reasons for exclusion (antibiotic prophylaxis)

Studies excluded from MTC	Reasons for exclusion
Bryan et al.,1988 [1]	Without separating total hip replacements (THRs) from total knee replacements (TKRs)
Chiu et al.,2001 [2]	Outcome measure was TKR-related infection
Chiu et al.,2002 [3]	Outcome measure was TKR-related infection
Davies et al.,1986 [4]	Only compared different types of antibiotic agents
Davis et al.,1987 [5]	Only compared different types of antibiotic agents
DeBenedictis et al.,1984 [6]	Only compared different types of antibiotic agents
Doyon et al.,1987 [7]	We included the study by Hill et al., (1981) instead of Doyon et al., (1987) as the latter was a long-term follow-up study (both studies have the same patient population)
Gunsts et al.,1984 [8]	In French
Heydemann and Nelson,1983, 1986 [9] (2 studies published)	Without separating THRs from TKRs
Jones et al., 1987, 1987, 1988 [10-12] (3 trials)	Without separating THRs from other joint replacements. The studies covered gastrointestinal, obstetrics and gynaecology, orthopaedic and other procedures with limited data for joint replacements.
Mauerhan et al.,1994 [13]	Only compared 2 different types of antibiotic agents
Mollan al.,1992 [14]	Without separating TKRs from THRs
Periti et al.,1992 [15]	Without separating THRs from TKRs
Periti et al.,1999 [16]	Without separating THRs from TKRs
Ritter et al.,[17] 1989	Without separating THRs from TKRs
Soave et al.,1986 [18]	Only compared two antibiotic agents
Vainionpää et al.,1988 [19]	Only compared two antibiotic agents
Wall et al.,1988 [20]	Without separating THRs from TKRs
Wollinsky et al.,1997 [21]	The purpose of the study was to examine bacterial contamination
Evrard et al.,1988 [22]	Only compared two different types of antibiotic agents
Wymenga et al.,1992 [23]	Only compared different doses of an antibiotic agent
Suter et al.,1994 [24]	Only compared two different types of antibiotic agents
Pollard, et al.,1979 [25]	Only compared two different types of antibiotic agents

b. Studies excluded and reasons for exclusion (antibiotic-impregnated cement)

Studies excluded from MTC	Reasons for exclusion
Josefsson et al.,1993 [26]	This study had same patient population as that in the study by Josefsson et al (1981), but had longer follow-up period (10-year follow-up period). So the latter was chosen.
McQueen et al., 1987 [27]	This study did not report the number of THRs assigned to systemic or cement antibiotics treatment
Lieberman, et al, 1994	The study could not be located in the author's references
Josefsson et al.,1990 [28]	The study had the same patient population as that in the study by Josefsson et al. (1981) . So the latter was chosen for shorter follow-up period
Pfarr and Burri (1979); Wannske and Tscherne et al., (1979); Buchholz and Engelbrecht (1970); Buchholz and Gartman (1972); Buchholz et al., (1977); Thierse et al., (1978);Rottger et al (1979)	In German
Chiu et al.,2001 [2]	Outcome measure was TKR-related infection
Chiu et al.,2002 [3]	Outcome measure was TKR-related infection
Persson et al.,1999 [29]	An economic evaluation study citing infection data from Lidwell (1982)
Malchau et al.,1993 [30]	Only investigated risk factors for revision
Havelin et al.,1995 [31]	Revision was the outcome measure
Espehaug et al.,1997 [32]	Only investigated patient-related risk factors for early revision
Buchholz et al.,1984 [33]	A semi review rather than a primary study
Murry 1984 [34]	THRs were not separated from revisions
Lynch et al.,1987 [35]	The study could not be connected to the mixed treatment comparison network

c. Studies excluded and reasons for exclusion (ventilation systems in operating theatres)

Studies excluded from MTC	Reasons for exclusion
Charnley 1972 [36]	Information about the use of antibiotic was unavailable
Berthelot et al.,2006 [37]	Outcome measure was pulmonary aspergillosis infection
Clark et al.,1976 [38]	Outcome measure was cardiac infection
Davison et al.,1971 [39]	Outcome measure was wound infection in general
Drake et al.,1977 [40]	Outcome measure was wound infection in general
Franco et al.,1977 [41]	THRs were not separated from TKRs, with culture bacteria being the outcome measure
Gruenberg et al.,2004 [42]	Outcome measure was not THR-related infection
Lidwell et al.,1982 [43]	THRs was not separated from TKRs
Millar 1979 [44]	Outcome measure was not THR-related infection
Oren et al.,2001 [45]	Outcome measure was not THR-related infection
Sanderson and Bentley 1976 [46]	THRs were not separated from joint replacements
Simsek et al.,2006 [47]	Outcome measure was not THR-related infection
Wilson1982 [48]	Irrelevant outcome
Nelson et al.,1980 [49]	Previous surgery history was suspected to be a serious confounder masking true treatment effect and no pertinent data was available to explain the observed difference in the incidence of infection by the authors

Appendix 3

a. Study Type (Based on methods for development of NICE public health guidance[50])

Study Type	Studies included
1	Meta-analysis, systematic reviews of randomized control trials (RCTs), or RCTs including cluster RCTs
2	Systematic reviews of, or individual, non-randomised controlled trials, case-control studies, cohort studies, controlled before-and-after (CBA) studies, interrupted time series (ITS) studies and correlation studies
3	Non-analytic studies such as case reports and case series studies
4	Expert opinion and formal consensus

b. Study Quality (Based on methods for development of NICE public health guidance[50])

Study Quality	Evaluation
++	All or most of the quality criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or the review are thought to be very unlikely to alter
+	Some of the criteria have been fulfilled. Where they have not been fulfilled, the conclusions of the study or the review are thought to be unlikely to alter
–	Few or no criteria have been fulfilled. The conclusions of the study are thought to be likely or very likely to alter

c. Level of Evidence (Based on methods for development of NICE public health guidance[50])

Level of evidence	Explanations
1^{++}	High quality meta-analysis, systematic reviews of RCTs, or RCTs (including cluster RCTs) with a very low risk of bias
1^{+}	Well-conducted meta-analysis, systematic reviews of RCTs, or RCTs (including cluster RCTs) with a low risk of bias
1^{-}	Meta-analyses, systematic reviews of RCTs, or RCTs (including cluster) with a high risk of bias
2^{++}	High quality systematic reviews of these types of studies, or individual, non-RCTs, case control studies, cost benefit analysis (CBA) studies, and correlation studies with a low risk of confounding, bias or chance and a high probability that the relationship is causal
2^{+}	Well conducted non-RCT, case control studies, cohort studies, cost benefit analysis (CBA) studies and correlation studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2^{-}	Non-RCTs, case control studies, cohort studies, CBA studies, ITS and correlation studies with a high risk or chance of confounding bias, and a significant risk that that relationship is not causal.
3	Non-analytical studies (for example, case reports, case series)
4	Expert opinion and formal consensus

Appendix 4

a. Quality Assessment of RCTs and Quality Score Allocation (Based on the Joanna Briggs Institute Reviewer's Manual [51])

Criterion1	**Random Sequence Generalization** **Was the assignment to the treatment groups truly random**	**Adequate: sequence generalization was truly random (computer generated, random numbers table or coded packages) _3** **Inadequate: use of such means as alternation, case record number, birth date, etc_2** **Unknown: No details were provided in the paper as to random sequence generalization_1**
Criterion 2	Blinding of Subjects Were patients blinded to treatment allocation?	Adequate: adequate measures were adopted to ensure patients were blinded to treatment allocation_3 Inadequate: there was some possibility of disclosure of treatment allocation_2 Unknown: No details were provided in the paper as to treatment allocation_1
Criterion 3	Blinding of Assessors Were the assessors of the outcome blinded to treatment status?	Adequate: actions were taken to blind assessors or outcomes so that bias is unlikely_3 Inadequate: there may be some possibility that assessors or outcomes were not blinded_2 Unknown: No details were provided in the text_1
Criterion 4	Sample Size Was a priori calculation of sample size undertaken	Yes_2 No/not mentioned_1
Criterion 5	Baseline Characteristics and Comparability Were the treatment and control groups similar at baseline in terms of prognostic factors?	Un-confounded: treatment and control groups were comparable at baseline/ or confounding were adjusted for_3 Some degree of confounding: mentioned, but not adjusted for_2 Significant potential for confounding or confounding not discussed_1
Criterion 6	Intention to Treat (ITT) Were the outcomes of subjects who withdrew described and included in the analysis? (Intention to treat)	ITT: Primary analysis based all randomized cases_3 Analysis was unmodified: numbers and reasons for withdraw were indicted, but not considered in the analysis_2 No mention: ITT was not mentioned_1
Criterion 7	Outcome Assessment Were the assessment of the methods of wound infection defined and applied consistently between patient groups?	Microbiological diagnosis was based on a predefined protocol_3 Microbiological diagnosis may be included in definite criteria_2 Clinical decision as made with no specific criteria or assessment methods was unstated_1
Criterion 8	Statistical Analysis Was appropriate statistical analysis used?	Appropriate statistical analysis was used_3 It was unclear whether appropriate statistical analysis was used_2 Inappropriate statistical analysis was used_1

b. Quality Assessment of Observational Studies and Quality Score Allocation (Based on the Joanna Briggs Institute Reviewer's Manual and the quality of reporting of observational longitudinal research by Tooth et al [51,52])

Criterion 1	**Were the patients at a similar point in their disease progression?**	**The patients were at a similar point in their disease progression_3** **It was unclear whether the patients were at a similar point in their disease progression_2** **The patients were not at a similar point in their disease progression_1**
Criterion 2	Were confounding variables identified and their effects adequately adjusted for?	Confounding variables were identified and their effects adequately adjusted for_3 It was unclear whether confounding variables were identified and their effects adequately adjusted for _2 Confounding variables were not identified and their effects were not adequately adjusted for_1
Criterion 3	Was bias minimized regarding the selection of cases and controls? (cases and control groups comparable on all the prognostic confounding factors)	The bias regarding the selection of cases and controls was minimized_3 The bias regarding the selection of cases and controls was inadequately addressed_2 The bias regarding the selection of cases and controls was not addressed_1
Criterion 4	Were outcomes assessed using objective measures or criteria? (self-recall questionnaire is not)	Outcomes were assessed using objective measures or criteria_3 Outcomes were assessed using limited objective measures and criteria_2 Outcomes were not assessed using objective measures and criteria_1
Criterion 5	Was outcome assessment blind to exposure status?	Outcome assessment was blind to exposure status_3 It was unclear whether outcome assessment was blind to exposure status_2 Outcome assessment was not blind to exposure status_1
Criterion 6	Was follow up carried out over a sufficient period of time? (long enough for the outcome to occur)	Follow-up was carried out over a sufficient period of time_3 It was unclear whether follow-up was carried out over a sufficient period of time_2 Follow-up was carried out over an insufficient period of time_1
Criterion 7	Were the outcomes of the patients who withdrew described and included in the analysis	The outcomes of the patients who withdrew were described and included in the analysis_3 The outcomes of the patients who withdrew were unclear nor were their inclusion in the analysis_2 The outcomes of the patents who withdrew were not included in the analysis_1
Criterion 8	Was appropriate statistical analysis used?	Appropriate statistical analysis was used_ 3 It was unclear whether appropriate statistical analysis was used_2 Statistical analysis used was inappropriate_1

Appendix 5

Random effect mixed treatment comparison models

Regression-based methods have been developed to fit MTC models [53-56]. The basic model specification is an extension of the Bayesian specification for standard pair-wise meta-analysis of binary data using a logistic regression model:[53,57,58]

$$\text{logit}\left(p_{j,k}\right) = \begin{cases} \mu_{jb} \text{ for baseline treatment } b;\ b=A, B, C\ldots \\ \mu_{jb} + \delta_{jbk} \text{ for treatment } k;\ k>A, B, C\ \ldots \end{cases} \qquad (1)$$

Where $p_{jk}$is the probability of the event for treatment k in trial j;$\mu_{jb}$is the log odds of the event for the reference (baseline) treatment b in trial j. The study effects: μ_{jb}, are treated as unrelated nuisance parameters. $\delta_{jbk}$is the trial specific log odds ratio of treatment k relative to the reference treatment b in trial j ($k>b$ signifies that k is numerically after b). For our purposes the event will be an infection.

The Random Effect Model

The trial specific log odds δ_{jbk} are assumed to be normally distributed with mean d_{bk} and a between-study variance τ^2 as specified below:

$\delta_{jbk} \sim$ Normal (d_{bk}, τ^2), where $d_{bk} = d_{jk} - d_{jb}$ (2)

τ^2 accounts for between-study variation in treatment effectiveness.

If *A* is treated as the overall MTC reference (baseline) treatment, then the effects of treatment *B, C, D, ... K* relative to *A*, d_{AB}, d_{AC}, d_{AD} ...., d_{AK} are considered to be *basic parameters* and $d_{AA}=0$. All other parameters that define effects of one treatment relative to another are called *functional parameters*. These functional parameters are derived from the basic parameters under the assumption that both the direct and indirect evidence estimate the same underlying treatment effect for each pair-wise comparison:

$d_{BC} = d_{AC} - d_{AB}$

$d_{BD} = d_{AD} - d_{AB}$ ..... *(3)*

$d_{CD} = d_{AD} - d_{AC}$

…

$d_{XY} = d_{AY} - d_{AX}$

The model takes into account the correlation in multi-arm trials [55,57,59-61]. Multi-arm trials on treatments *A, X* and *Y*, for instance, will have a correlation between δ_{jAX} andδ_{jAY}. Under the assumption of homogenous variance in these trials, this covariance is given by $\tau^2/_2$ [55,57,60] and is accounted for in the model for any

multi-arm trials. This covariance is modelled using the following correlation formulation for any number of arms by decomposition of a multivariate normal distribution as a series of conditional univariate distributions: [55,56,60,62]

$$\begin{pmatrix} x_1 \\ \vdots \\ x_p \end{pmatrix} \sim N\left(\begin{pmatrix} \mu_1 \\ \vdots \\ \mu_p \end{pmatrix}, \begin{pmatrix} \tau^2 & \tau^2/2 & \cdots & \tau^2/2 \\ \tau^2/2 & \tau^2 & \cdots & \tau^2/2 \\ \vdots & \vdots & \ddots & \vdots \\ \tau^2/2 & \tau^2/2 & \cdots & \tau^2 \end{pmatrix} \right) \qquad (4)$$

with the conditional univariate distributions being:

$$x_1 \Big| \begin{pmatrix} x_1 \\ \vdots \\ x_{i-1} \end{pmatrix} \sim N\left(\mu_i + \frac{1}{i}\sum_{j=1}^{i-1}(x_j - \mu_j), \frac{(i+1)}{2i}\tau^2\right) \qquad (5)$$

We used the above MTC models as the main model for the evidence synthesis.
In order to model inevitable variations across all included studies in terms of study population, study setting, and study design, etc, we used the random effect model for our analysis.

Appendix 6

Modelling variation in follow-up durations with the log-log link model

Although the logit link MTC model adjusts for multi-arm trials, it does not account for variation in follow-up durations. As the included studies varied significantly in follow-up period, we also included the following complementary log-log link model to assess the effect of variation in follow-up durations, if any, on the incidence of THR-related SSIs:[63,64]

$$\theta_{ik} = cloglog(p_{ik}) = log(f_i) + log(\varphi_{i,bk}) = log(f_i) + \mu_i + \delta_{i,bk} I_{\{k \neq 1\}} \quad (6)$$

where φ_{ik} is the event rate, taking into account different follow-up durations f_i; $\delta_{i,bk}$ the treatment effects representing log-odds ratios; $I_{\{u\}} = \begin{cases} 1 & if u \text{ is true} \\ 0 & otherwise \end{cases}$

Appendix 7

The posterior mean residual deviance and the deviance information criterion (DIC)

The posterior mean residual deviance $\bar{D}_{res}$ is defined as the deviance for the fitted model minus the deviance for the saturated model. Each unconstrained data point has a contribution $\bar{D}_i$ to the residual deviance, such that

$\bar{D}_{res} = \sum_i \bar{D}_i$.

It is expected that each data point should contribute approximately 1 to the posterior mean deviance [56,65]. Therefore, under the null hypothesis that the model adequately fits the data, $\bar{D}_{res}$ would have a mean equal to the number of unconstrained data points for a perfectly fitted model [56,65,66].

The DIC is defined as:

$DIC = \bar{D}_{res} + pD$,

where p_D denotes the effective number of parameters, which is defined as the relative influence that each observation has on its own fitted value.

$pD = \bar{D}_{res} - \hat{D}$,

where $\hat{D}$ is the deviance calculated at the posterior mean of the model parameters or the posterior mean of the fitted values when nonlinearity exists between the likelihood and the model parameters [65,66].

The DIC provides a measure of model fit that penalizes model complexity. Lower DIC values suggest a better fitted model [66].

Appendix 8

Diagnostic tests for model fit

Where the model fit was poor, we explored how each data point influenced the model fit by plotting $\bar{D}_i$ (each data point's contribution to $\bar{D}_{res}$) against its contribution to pD (leverage) [66]. These summaries were displayed in a plot of leverage versus dr_i for each data point, where $dr_i = \pm\sqrt{\bar{D}_i}$ with sign given by the difference between the posterior mean of the predicted and observed values for observation *i*. Curves of the quadratic function $y = -x^2 + c$ with *c* = 1, 2, 3 and 4 were plotted as they represented the lines of each contribution to DIC. Points lying on such parabolas each contributed an amount *c* to DIC, with points lying outside the line *c* = 3 identified as contributing to the model's poor fit [65,66].

Appendix 9

The node-splitting method

Node-splitting is based on splitting sources of information about a node in a directed acyclic graph (DAG) which represents the dependency structure of a model. It allows the conflict between the inferences on a node from different sources of information to be examined [65-67].

Given that only pairs of treatments which are part of a closed loop have both direct and indirect evidence available, and that there is no inconsistency assumed within a multi-arm trial [68], all three-way closed loops were checked for inconsistency except for three closed loops in bold lines as they were formed only by a multi-arm trial (Figure 2)

Two posterior distributions were obtained from the mean infection control effect d_{XY}: one based on studies comparing strategy X and Y directly, with mean d_{XY}^{Dir}; and another indirectly with mean d_{XY}^{Ind} from the MTC of all the remaining indirect evidence. The inconsistency parameter was:

$$\omega_{XY} = d_{XY}^{Dir} - d_{XY}^{Ind}$$

A test of the null hypothesis that $\omega_{XY} = 0$ would provide evidence of consistency [65,66]. We also used the posterior mean residual deviance $\bar{D}_{res}$ and DIC to compare the full MTC model with the model where a particular node was split.

Appendix 10

The meta-regression model on potential interaction effects of studies with mixed quality

Since there were only a limited number studies available for the evidence synthesis, we included both RCTs and observational studies in the MTC. In order to estimate and adjust for potential confounding by studies with mixed quality, we conducted meta-regression analysis using the following subgroup interaction random effect model: [69,70]

$$\theta_{ik} = logit(p_{ik}) = \mu_i + (\delta_{ik} + \beta x_i) I_{(k \neq 1)} \quad (8)$$

Where θ_{ik} is the linear predictor in arm k of trial i; μ_i the trial specific baseline effects in trial i; x_i is the trial-level covariate for trial i, which is:

$$x_i = \begin{cases} 0 \ if \ the \ trial \ is \ a \ RCT \\ 1 \ if \ the \ trial \ is \ an \ observational \ study \end{cases}$$

β the estimated change for observational studies; δ_{ik} is the trial-specific log-odds ratios of the infection control effects in arm *k* relative to the referent.

Appendix 11

Odds ratio with 95% creditable intervals of all infection control strategies based on the random effect, cloglog link MTC model adjusting for follow-up durations

Comparison of infection control strategies	Odds ratio and 95% credible interval							
OR[1,2] 0.32 (0.12–0.65)								
OR[1,3] 0.26 (0.03–0.94)	OR[2,3] 0.90 (0.11–3.30)							
OR[1,4] 0.26 (0.07–0.67)	OR[2,4] 0.83 (0.28–1.95)	OR[3,4] 1.93 (0.21–7.52)						
OR[1,5] 0.39 (0.09–1.12)	OR[2,5] 1.27 (0.38–3.32)	OR[3,5] 3.24 (0.27–13.95)	OR[4,5] 1.95 (0.37–6.39)					
OR[1,6] 0.13 (0.03–0.35)	OR[2,6] 0.44 (0·13–1.11)	OR[3,6] 1.11 (0.09–4.53)	OR[4,6] 0.67 (0.13–2.09)	OR[5,6] 0.43 (0.09–1.23)				
OR[1,7] 0.26 (0.04–0.93)	OR[2,7] 0.89 (0.14–3.10)	OR[3,7] 2.43 (0.11–10.03)	OR[4,7] 1.40 (0.14–5.26)	OR[5,7] 0.85 (0.10–3.02)	OR[6,7] 1.95 (0.54–5.29)			
OR[1,8] 0.54 (0.03–2.10)	OR[2,8] 1.76(0.11–7.00)	OR[3,8] 5.45 (0.10–20.56)	OR[4,8] 2.97 (0.12–11.73)	OR[5,8] 1.67 (0.08–6.81)	OR[6,8] 3.70 (0.38–13.46)	OR[7,8] 2.30 (0.22–8.20)		
OR[1,9] 0.73 (0.05– 2.66)	OR[2,9] 2.46 (0.21–8.89)	OR[3,9] 13.54 (0.18–26.37)	OR[4,9] 4.14 (0.22–14.49)	OR[5,9] 2.27 (0.15–8.48)	OR[6,9] 4.92 (0.74–16.52)	OR[7,9] 3.00 (0.43–10.14)	OR[8,9] 2.51 (0·23–10.16)	
	Model fit statistic (Posterior mean residual deviance) 34.4*			Model fit statistic (DIC) 180.6			Heterogeneity (between-study standard deviation) 0.62	

*Compared with 32 data points.
Note: Model fit is considered to be adequate if posterior mean residual deviance is approximately equal to the total number of data points [71];
OR: odds ratio

The results based on the cloglog link model that accounted for variations in follow-up were almost identical to the results based on the logit link random effect model, suggesting that significant variation in follow-up durations had little effect on the relative efficacy of various infection control strategies in reducing THR-related SSIs.

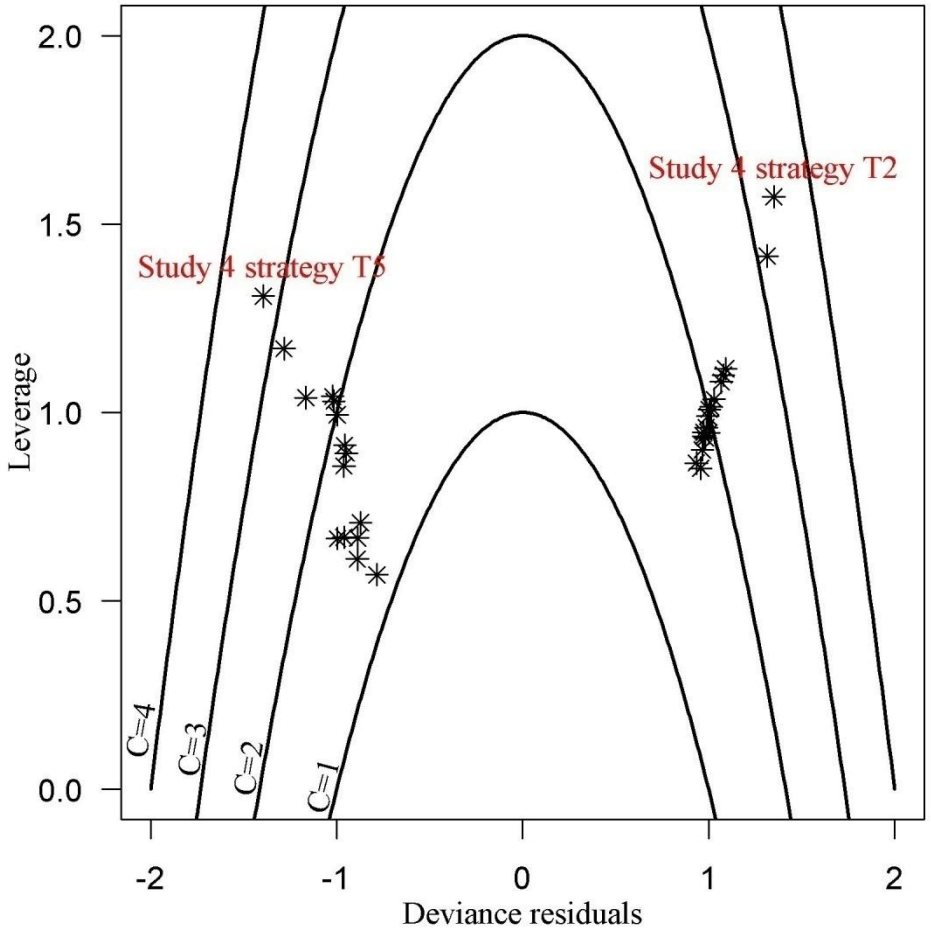
Table 12 The probability of each infection control strategy being the best strategy and its median rank

Infection control strategies	Probability	Median rank (95% Credible interval)
T1	0.00	9 (7 – 9)
T2	0.00	6 (3 – 8)
T3	0.24	3 (1 – 8)
T4	0.06	4 (1 – 8)
T5	0.02	6 (2 – 8)
T6	0.47	2 (1 – 5)
T7	0.08	3 (1 – 8)
T8	0.10	5 (1 – 9)
T9	0.02	7 (2 – 9)

Note: T1-T9 representing 9 infection control strategies (refer to Table 2 for denotations)

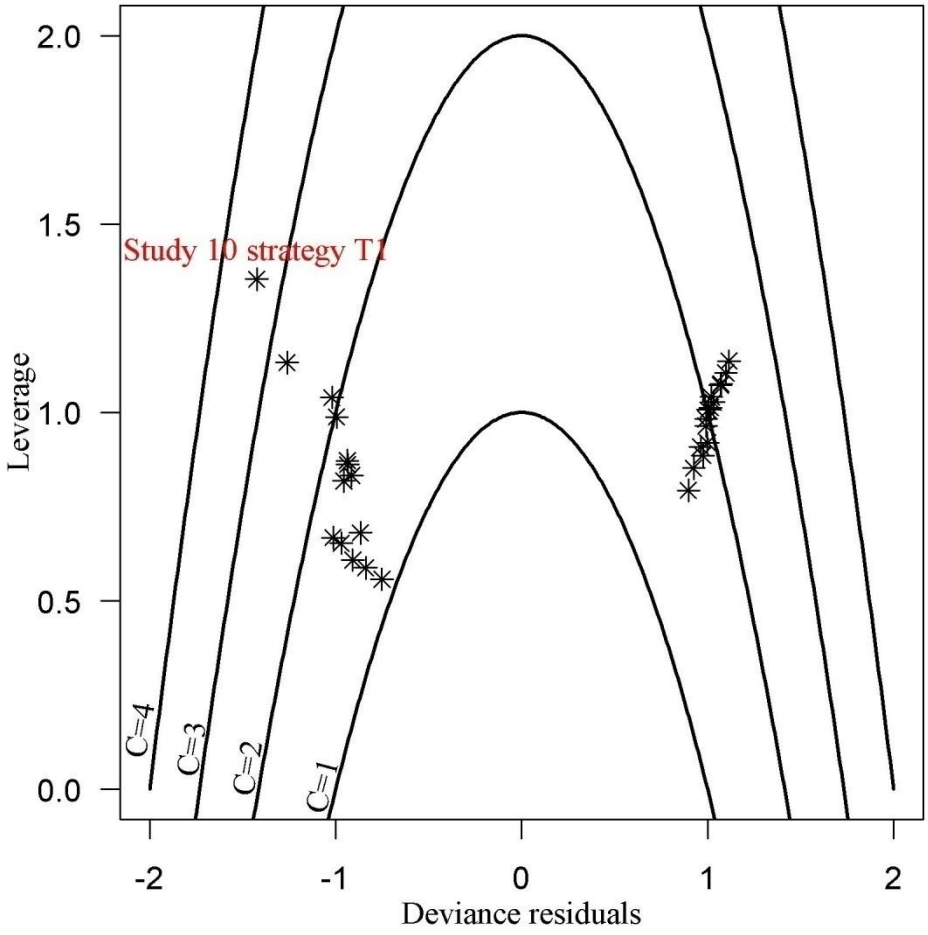
Appendix 13

a. Leverage versus deviance residual superimposed on curves: $y= -x^2 + c$, where c=1,2,3,4, representing the amount contributed to DIC



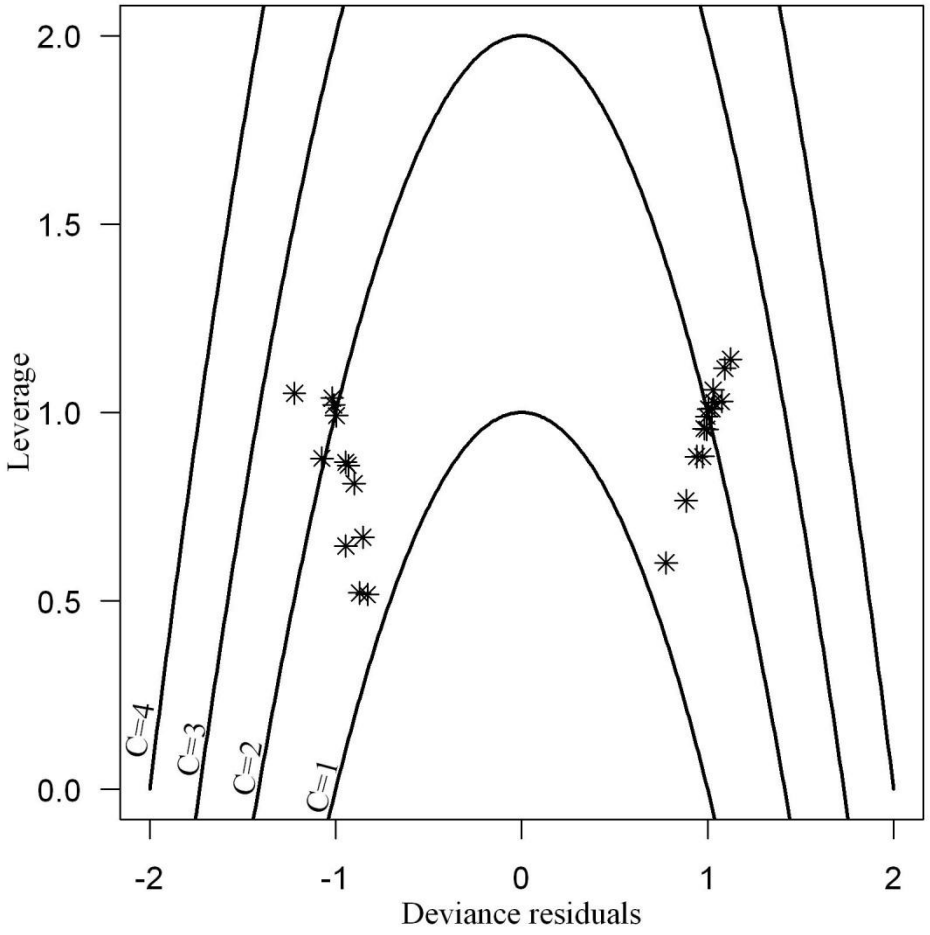
Curves of the quadratic function $y = -x^2 + c,\ \ c = 1, 2, 3, 4$, were plotted as they represented the lines of each contribution to deviance information criterion (DIC). Points lying outside the line $c = 3$, were identified as contributing to the inadequate model fit. As the diagnostic plot showed that the first and second arm (infection control strategy T2 and T5) of study 4 were outliers contributing to the inadequate model fit.

b. Sensitivity analysis by excluding the first and second arm of study 4((4, 1) and (4, 2))
Leverage versus deviance residual superimposed on curves: $y= -x^2 + c$, where c=1, 2, 3, 4, representing the amount contributed to DIC



After excluding study 4 from the MTC network, the diagnostic plot showed that the first arm (infection control strategy T1) of study 10 was an outlier contributing to the inadequate model fit.

c. Sensitivity analysis by further excluding the first arm of study 10 (1, 10)
Leverage versus deviance residual superimposed on curves: $y= -x^2 + c$, where c=1, 2, 3, 4, representing the amount contributed to DIC



After excluding study 10 from the network, all the remaining data points lay below the quadratic curve with c = 3, suggesting that the contribution by the remaining data points to the DIC were unimportant, which in turn should improve the model fit.

Appendix 14 Sensitivity analysis with the exclusion of study 4[72] and study 10[73] from the MTC network

Comparison of infection control strategies	Odds ratio and 95% credible interval						
OR[1,2] 0.22 (0.08-0.43)							
OR[1,3] 0.20 (0.03-0.60)	OR[2,3] 1.00 (0.15-3.21)						
OR[1,4] 0.19 (0.06-0.43)	OR[2,4] 0.87 (0.35-1.86)	OR[3,4] 1.61 (0.23-5.78)					
OR[1,5] 0.76 (0.11-2.23)	OR[2,5] 3.39 (0.61-10.42)	OR[3,5] 7.09 (0.48-28)	OR[4,5] 4.80 (0.62-16.16)				
OR[1,6] 0.09 (0.02-0.25)	OR[2,6] 0.43 (0.09-1.27)	OR[3,6] 0.63 (0.09-1.92)	OR[4,6] 0.63 (0.09-1.92)	OR[5,6] 0.19 (0.24-0.69)			
OR[1,7] 0.33 (0.02-0.56)	OR[2,7] 1.05 (0.11-2.90)	OR[3,7] 3.92 (0.09-6.67)	OR[4,7] 1.74 (0.12-4.22)	OR[5,7] 0.46 (0.03-1.43)	OR[6,7] 1.85 (0.67-4.20)		
OR[1,8] 0.83 (0.02-1.16)	OR[2,8] 10.75 (0.09-5.88)	OR[3,8] 43.12 (0.08-12.92)	OR[4,8] 6.84 (0.10-8.44)	OR[5,8] 1.04 (0.03-2.83)	OR[6,8] 3.83 (0.44-10.33)	OR[7,8] 2.05 (0.27-6.33)	
OR[1,9] 0.66 (0.03-1.44)	OR[2,9] 3.42 (0.19-7.35)	OR[3,9] 10.32 (0.16-16.24)	OR[4,9] 4.60 (0.20-10.58)	OR[5,9] 1.29 (0.06-3.57)	OR[6,9] 4.72 (1.00-10.27)	OR[7,9] 3.23 (0.58-7.56)	OR[8,9] 2.39 (0.31-8.37)
	Model fit statistic (posterior mean of residual deviance) 25.3*			Model fit statistic (DIC) 141.8		Heterogeneity (between-study standard deviation) 0.43	

* Compare with 26 total data points. OR: odds ratio.

Model fit is considered to be adequate when posterior mean residual deviance is approximately equal to the total number of data points The sensitivity analysis by excluding study 4 and 10 from the MTC network showed that the model fit was improved as the DIC was reduced from 180.6 corresponding to 32 data points down to 141.8 corresponding to 26 data points. The posterior mean residual deviance was also reduced from 34.3 (compared to 32 data points) down to 25.3 (compared to 26 data points), suggesting that the MTC model fitted the data well. Heterogeneity measured in between-study standard deviation across the MTC network was also significantly reduced from 0.63 to 0.43

Appendix 15

The probability of each infection control strategy being the best strategy and its median rank

- **Sensitivity analysis by excluding study 4[72] and study 10[73] from the MTC network**

Infection control strategy	RE MTC model (10 studies)	
	Probability of each strategy being the best	Median Rank (95% CrI)
T1. No systemic antibiotics + Plain cement + Conventional ventilation	0.00	9 (7 – 9)
T2. Systemic Antibiotics + Plain Cement + Conventional ventilation	0.01	6 (2 – 8)
T3. No systemic antibiotics + Plain cement + Laminar airflow	0.14	4 (1 – 8)
T4. Systemic antibiotics + Plain cement + Laminar airflow	0.05	4 (1 – 7)
T5. No systemic antibiotics + Antibiotic-impregnated cement + Conventional ventilation	0.00	8 (4 – 9)
T6. Systemic antibiotics + Antibiotic-impregnated cement + Conventional ventilation	0.64	1 (1 – 4)
T7. Systemic antibiotic + Antibiotic-impregnated cement + Laminar airflow	0.05	3 (1 – 7)
T8. Systemic antibiotics + Antibiotic-impregnated cement+ conventional ventilation + Space suit	0.10	4 (1 – 8)
T9. Systemic antibiotics + Antibiotic-impregnated cement + laminar ventilation + Space suit	0.01	6 (2 – 9)

The sensitivity analysis by excluding study 4 and 10 from the network showed that results were little changed. Infection control strategy T6 (systemic antibiotics + antibiotic-impregnated cement + conventional ventilation) remained dominant with the highest median rank the highest probability (64%) of being the best the infection control strategy for preventing THR-related SSIs.

Appendix 16 **Evidence from the MTC of 10 studies (excluding study 4[72] and 10[73] from the MTC network), direct evidence from pair-wise meta-analysis, and direct and indirect evidence from node-splitting (relative intervention effects are in log odds ratio)**

Treatments		All Evidence	Direct		Indirect Evidence	Inconsistency Estimate	Test for Inconsistency	Posterior mean residual deviance	DIC	Heterogeneity
		MTC	Pairwise meta-analysis	Node-split	Node-split	Node-split	Node-split			
X	Y	Mean 95% CrI	Mean (95% CI)	Mean (95% CrI)	Mean (95% CrI)	Mean (95% CrI)	Bayesian p-value	(MTC) 25.3	(MTC) 141.8	(MTC) 0.4
T1	T2	-1.6 (-2.5 – -0.8)	-1.7 (-2.6 – -0.8) *I^2 =24.5%	-1.7 (-2.8 – -0.9)	-1.0 (-2.7 – 0.6)	-0.7 (-2.6 – 1.1)	0.2	25.0	142.4	0.5
T1	T3	-1.9 (-3.5 – -0.5)	-1.86 (-2.91 – -0.81) I^2 =0%	-1.9 (-3.5– -0.5)	0.0 (-196.2 – 195·5)	-2 (-197.5 – 194.2)	0.5	25.4	141.9	0.4
T1	T4	-1.8 (-2.9 – -0.8)	-1.47 (-2.35 – -0.58) I^2 =0%	-1.5 (-3.0 – -0.1)	-2.2 (-3.8 – -0.9)	0.7 (-1.2 – 2.8)	0.8	25.1	142.5	0.5
T2	T3	-0.3 (-1.9 – -1.2)	0.23(-1.16 – 1.62) I^2 =0%	-0.2 (-1.8 – 1.4)	1.7 (-193.7 – 197.7)	-1.9 (-198.0– 193.5)	0.5	25.5	141.8	0.4
T2	T4	-0.2 (-1.1 – 0.6)	-0.2 (-0.9 – 0.5) I^2=19%	-0.2 (-1.0 – 0.7)	1.7 (-194.6 – 198.3)	-1.9 (-198.5– 194.3)	0.5	25.4	141.8	0.4
T3	T4	0.1 (-1.5 – 1.8)	0.39 (-0.88 – 1.66) I^2 =0%	0.4 (-1.3 – 2.2)	- 0.4 (-2.5 – 1.6)	0.8 (-1.4 – 3.2)	0.8	25.1	142.5	0.5
T1	T5	-0.7 (-2.2 – 0.8)	0.1 (-1.0 – 1.3) I^2=0%	-0.4 (-2.3 – 1.5)	-0.6 (-3.7 – 3.1)	0.1 (-3.8 – 3.9)	0.5	26.2	143.8	0.5
T2	T5	0.9(-0.5 – 2.3)	0.6 (-0.2 – 1.4) I^2= 0%	0.8 (-0.7 – 2.1)	1.5 (-194.8 – 197.8)	-0.7 (-196.9 –195.6)	0.5	25.3	141.8	0.4
T1	T6	-2.8 (-4.1 – -1.4)	-2.0 (-2.5 – -0.7) I^2= 0%	-2.6 (-3.9 – -1.0)	-3 (-107.3 – 95.1)	-0·4 (-97.8 – 104.7)	0.5	25.3	141.8	0.4
T2	T6	-1.2 (-2.4 – 0.2)	-1.0 (-1.4 – -0.6) I^2= 13·9%	-1.3 (-2.7 – -0.1)	-25 (-126.1 – 99.2)	23.6 (-100.6–124.8)	0.7	25.3	141.9	0.4
T5	T6	-2.1 (-3.7 – -0.4)	-1.7 (-2.6 – -0.8) I^2= 0%	-2.1 (-3.7 – -0.4)	-12.1 (-98.7– 73.8)	10.0 (75.8 – 96.8)	0.6	25.3	141.8	0.4
T6	T7	0.5 (-0.4 – 1.4)	0.4 (0.2 – 0.7) I^2= 0%	0.5 (-0.4 – 1.5)	2.6 (-193.9 – 199.1)	-2.1 (-198.7 – 194.4)	0.5	25.2	141.7	0.4
T6	T8	0.9 (-0.8 – 2.3)	1.03 (-0.06 – 2.12) I^2 =0%	0.9 (-0.7 – 2.3)	2.6 (-193.5 – 198.2)	-1.7 (-197.4 –194.3)	0.5	25.4	141.9	0.4
T7	T8	0.4 (-1.3 – 1.8)	0.37 (-0.81 – 1.55) I^2 =0%	0.4 (-1.3 – 1.8)	2.2 (-193.0 – 197.8)	-1.9 (-197.4 –193.4)	0.5	25.3	141.8	0.4
T6	T9	1.2 (0.0 – 2.5)	1.32 (0.63 – 2.00) I^2 =0%	1.3 (0.1 – 2.5)	2.9 (-192.9 – 199.0)	-1.6 (-197.7– 194.1)	0.5	25.3	141.8	0.4
T7	T9	0.8 (-0.5 – 2.0)	0.66 (-0.16 – 1.48) I^2=0%	0.7 (-0.6 – 2.0)	2.0 (-193.8 – 198.0)	-1.3 (-197.3–194.4)	0.5	25.3	141.8	0.4

Sixteen pair-wise comparisons that formed nine 3-way closed loops in the network were checked for consistency.

Despite some variations in the point estimates, there was a broad agreement among the direct evidence from pair-wise meta-analyses and splitting corresponding nodes, and the evidence from the full MTC model. Tests for inconsistency between direct and indirect evidence from node splitting suggested that there was no statistically significant inconsistency between direct and direct evidence.

It is worth noting that the 95% credible intervals for some pair-wise comparisons widened greatly following node splitting. This may be explained by the fact that the node splitting has led to less evidence available to inform the variance parameter.

Appendix 17

Meta-regression on subgroup interaction effect between RCTs and observational studies (based on 10 studies)

Models	The posterior mean residual deviance	DIC	β (subgroup interaction term)	Heterogeneity (between-study standard deviation)
The random effect meta-regression model	24.3*	141.0	1.4 (95%CrI: -0.3 – 3.5)	0.4
The random effect MTC model	25.3*	141.8	(not applicable)	0.4

*Compared with 26 data points

The test for subgroup interaction showed that the effect of interaction between the RCT group and the observational study group was not statistically significant. The interaction term β was estimated to be 1.4 with 95% credible interval (95%CrI: -0.3–3.5) containing a 0 value, indicative of the possibility of no interaction effect between the RCT group and the observational study group.

Appendix 18

(a) The probability of each infection control strategy being the best strategy: sensitivity analysis by excluding the RCT by Hill et al [74] from the MTC network

Infection control strategy	RE MTC model (11 studies)	
	Probability of each strategy being the best	Median Rank (95% CrI)
T1. No systemic antibiotics + Plain cement + Conventional ventilation	0.00	8 (5 – 8)
T2. Systemic Antibiotics + Plain Cement + Conventional ventilation	0.01	5 (2 – 7)
T4. Systemic antibiotics + Plain cement + Laminar airflow	0.16	3 (1 – 7)
T5. No systemic antibiotics + Antibiotic-impregnated cement + Conventional ventilation	0.01	7 (3 – 8)
T6. Systemic antibiotics + Antibiotic-impregnated cement + Conventional ventilation	0.63	1 (1 – 4)
T7. Systemic antibiotic + Antibiotic-impregnated cement + Laminar airflow	0.06	3 (1 – 6)
T8. Systemic antibiotics + Antibiotic-impregnated cement+ conventional ventilation + Space suit	0.11	4 (1 – 8)
T9. Systemic antibiotics + Antibiotic-impregnated cement + laminar ventilation + Space suit	0.02	5 (2 – 8)

The sensitivity analysis by excluding the RCT by Hill et al [74] from the network showed that results were little changed. Infection control strategy T6 (systemic antibiotics + antibiotic-impregnated cement + conventional ventilation) remained dominant with the highest median rank and highest probability (63%) of being the most effective control strategy for preventing THR-related SSIs.

(b) The probability of each infection control strategy being the best strategy: sensitivity analysis by including the RCT by Lidwell et al [43]

Infection control strategy	RE MTC model (11 studies)	
	Probability of each strategy being the best	Median Rank (95% CrI)
T1. No systemic antibiotics + Plain cement + Conventional ventilation	0.00	9 (7 – 9)
T2. Systemic Antibiotics + Plain Cement + Conventional ventilation	0.00	5 (3 – 7)
T3. No systemic antibiotics + Plain cement + Laminar airflow	0.01	7 (2 – 8)
T4. Systemic antibiotics + Plain cement + Laminar airflow	0.03	4 (1 – 7)
T5. No systemic antibiotics + Antibiotic-impregnated cement + Conventional ventilation	0.00	8 (3 – 9)
T6. Systemic antibiotics + Antibiotic-impregnated cement + Conventional ventilation	0.83	1 (1 – 3)
T7. Systemic antibiotic + Antibiotic-impregnated cement + Laminar airflow	0.04	2 (1 – 6)
T8. Systemic antibiotics + Antibiotic-impregnated cement+ conventional ventilation + Space suit	0.09	4 (1 – 8)
T9. Systemic antibiotics + Antibiotic-impregnated cement + laminar ventilation + Space suit	0.01	5 (2 – 8)

(The data from the RCT by Lidwell et al [43] used for this sensitivity analysis: T1: 39/1161; T2: 24/2968; T3: 8/516; T4: 9/1279)

The sensitivity analysis by including the RCT by Lidwell et al [43] in the network showed that results were little changed. Infection control strategy T6 (systemic antibiotics + antibiotic-impregnated cement + conventional ventilation) remained dominant with the highest median rank and highest probability (83%) of being the best infection control strategy for preventing THR-related SSIs.

Appendix 19

Re-analysis of the meta-analysis by Parvizi et al [75] 2008

The study by Espehaug et al [32] had four treatment arms compared: *A:* no antibiotics (neither systemically nor through cement); B: systemic antibiotics only*;* C*:* antibiotics delivered through cement only; D: antibiotics delivered both systemically and through cement. Instead of selecting treatment arm B and C from the observational study to pool with the rest of studies on a comparable basis, the authors of the meta analysis [75] added treatment A and B together as one arm, and added C and D together as another arm to pool with the rest of the studies, which significantly cofounded the treatment effect of the infection control strategies compared. We replicated the meta-analysis and re-analysed the data by pooling treatment arm B and C from the observational study with the rest of the studies on a comparable basis for summary estimation.

Our data re-analysis showed that the pooled relative risk of antibiotic-impregnated cement compared with plain cement was 0.76 (95% CI: 0.45 – 1.28), I^2 =18.5%, suggesting that there was no strong evidence that antibiotic-impregnated cement without systemic antibiotics was effective in reducing THR-related infection as compared with plain cement with systemic antibiotics.

Author/year	**Antibiotic-impregnated cement only**	**Systemic antibiotics only**	**Odds ratios with 95% confidence intervals**
McQueen (1987)	1/146	2/149	0.51(0.045 – 5.65)
Lynch (987)	7/424	11/640	0.96 (0.37 – 2.50)
Lynch (1987)	1/194	3/109	0.18 (0.02 -1.78)
Lieberman (1994)	2/19	1/16	1.77 (0.15 – 21.47)
Josefsson (1993)	9/565	13/550	0.67 (0.28 – 1.58)
Josefsson (1990)	7/711	16/698	0.42 (0.17 – 1.04)
Espehaug (1997)	3/239	25/4586	2.32 (0.70 – 7.74)
Pooled relative risk with 95% confidence interval		0.76 (0.46 – 1.28)	
Heterogeneity		I squared = 18.8%	
The original pooled relative risk with 95% confidence interval by Parvizi et al		0.506 (0.341 – 0.751)	

Note: Parvizi et al [75] also incorrectly presented the data from the study by Lynch et al [76]. For the treatment arm 'systemic antibiotics only', the number of THR-related infections and the total number of THRs should be: 11/640, but the authors presented as 11/651.

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