National Institute for Health and Care Excellence

Final

Joint replacement (primary): hip, knee and shoulder

[I] Evidence review for ultra-clean air

NICE guideline NG157

Intervention evidence review underpinning recommendation 1.5.2 in the NICE guideline

June 2020

Final

This evidence review was developed by the National Guideline Centre, hosted by the Royal College of Physicians

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1.1 Review question: In adults having primary elective joint replacement or orthopaedic surgery utilising metallic implants, what is the clinical and cost effectiveness of using ultra-clean air theatres?

1.2 Introduction

Infection following hip, knee or shoulder replacement is a catastrophic complication. Microbial colonisation of the implant can result in both local and systemic sepsis. Failure to eradicate infection at an early stage can result in biofilm formation on the implant which makes it difficult to eradicate the infection with antibiotic therapy alone. In these circumstances further surgery to remove infected implants alongside debridement of infected tissue as part of a revision procedure is typically required.

There are multiple strategies to reduce the risk of infection in implant surgery. These include the use of ultra-clean air theatres in addition to other strategies. Ultra-clean air theatres are believed to reduce bacterial cell counts and surgical wound contamination within theatre. It is currently advised by the BOA and GIRFT that all arthroplasty surgery is performed in a ultra-clean air theatres.[15]

Recent joint registry evidence has questioned the need to use ultra-clean air theatres for all arthroplasty cases. This has prompted debate about their use and cost effectiveness. This review therefore seeks to understand the role of ultraclean air theatres and make recommendation about their ongoing use within primary elective hip, knee and shoulder joint replacement surgery.

1.3 PICO table

For full details, see the review protocol in Appendix A:

Table 1: PICO characteristics of review question

Population	Adults having primary elective joint replacement or orthopaedic surgery utilising metallic implants.
Intervention	Ultra clean-air theatres (including laminar flow and ex flow systems)
Comparison	Conventional airflow theatres
Outcomes	**Critical** • Mortality: 30 day (dichotomous) • Quality of life (continuous) • Deep surgical site infection (dichotomous) • Superficial surgical site infection (dichotomous) **Important** • Return to theatre (dichotomous) • Hospital readmission (dichotomous) • Length of stay (continuous)
Study design	Randomised controlled trials If no well-conducted RCTs are available, observational studies with multivariate analysis will be investigated.

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The population was expanded from adults having primary elective joint replacement to include orthopaedic surgery utilising metallic implants because issues around infection are common to a wider population. Infection is linked to the usage of implants during orthopaedic surgery and as these materials are not organic, it is harder for the body to kill bacteria on them.

1.4 Clinical evidence

1.4.1 Included studies

A search was conducted for randomised trials and observational studies comparing the effectiveness of ultra clean-air theatres versus conventional air flow theatres in people who are undergoing joint replacement surgery or orthopaedic surgery utilising metallic implants.

The RCT evidence found were for surgeries undertaken before 1990 and the ventilation technology in that period is considered to be of limited comparability to modern ventilation systems. Therefore it was decided to include observational evidence in the review.

Two randomised controlled trials[20, 33, 35] and 7 observational studies[13, 14, 18, 46, 53, 54, 59] were included in the review; these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 3).

See also the study selection flow chart in Appendix C: study evidence tables in Appendix D: forest plots in Appendix E: and GRADE tables in Appendix H:

1.4.2 Excluded studies

See the excluded studies list in Appendix I:

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1.4.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Randomised controlled trials				
Fitzgerald Jr 1992[20]	Horizontal ultra clean-air operating theatre versus Conventional ventilated operating theatre with turbulent airflow	People having primary total hip or knee replacement surgery N=6,050 USA	Deep surgical site infection Follow-up was varied: 1 to 8 years.	Prophylactic antibiotic therapy utilised. Traffic in theatre controlled. Personnel isolator systems (body suits) not used.
Lidwell 1982[33, 35]	Ultra-clean air ventilation versus Conventionally ventilated operating room using positive-pressure air supply 4 hospitals utilised either body-exhaust suits or conventional clothing in ultra clean-air surgeries. 15 hospitals used one or the other at all times. Additional results were presented for this subgroup The decision whether to give prophylactic antibiotics was made by the surgeon. Additional results were presented for this subgroup.	People having total hip or knee replacement N= 8,136 15 hospitals in United Kingdom and 4 hospitals in Sweden	Confirmed sepsis within 1-4 years after surgery Median follow-up of 2.5 years. 45% of people followed up for more than 2 years.	Each surgeon operated on people randomly allocated to rooms with ultra clean-air ventilation or conventional ventilation. At 14 hospitals, prophylactic antibiotics were given routinely either to the great majority of people or to only a small minority. At 5 hospitals, prophylactic antibiotics were given by almost every surgeon to 38-58 per cent of the people.
Observational studies				
Brandt 2008[13]	HEPA-filtered (vertical) laminar airflow ventilation	• Hip replacement. N=28,623 (44 hospitals)	Severe surgical site infection with unclear follow up	Data from the German National Nosocomial Infections

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Study	Intervention and comparison	Population	Outcomes	Comments
	versus HEPA-filtered turbulent ventilation	• Knee replacement. N=9,396 (18 hospitals) Germany	Follow-up duration varied according to routine post discharge surveillance Follow-up: unclear period Logistic regression analysis. Multivariate analysis utilised to control for potentially confounding factors: sex, age, NNIS risk index variables (ASA score, wound class, surgery duration), frequency of operative procedure, number of beds in hospital, academic status of hospital, long term participation in KISS.	Surveillance System (KISS) from 2000 until 2004. Surveys sent to hospitals to find out about ventilation systems installed. Perioperative antibiotic prophylaxis given to 98% of people undergoing hip or knee replacement in 2004 Body exhaust systems are not routinely used in Germany. Liquid resistant surgical gowns and drapes well established. Unclear if dedicated orthopaedic theatres were used.
Breier 2011[14]	Laminar airflow ceilings with woven textile distribution versus Non-laminar airflow ventilation systems installed between 1990 and 2004	Results presented for 3 populations: • Elective primary hip replacement. N=33,463 (48 hospitals) • Primary hip replacement surgery due to fracture. N=7,749 (41 hospitals) • Primary knee replacement. N=20,554 (38 hospitals) Germany	Severe surgical site infections: deep SSIs and organ/space infections with unclear follow up Follow-up duration varied according to routine post discharge surveillance Follow-up: unclear period Logistic regression analysis. Multivariate analysis was adjusted for age, duration of	Data from the German National Nosocomial Infections Surveillance System (KISS) from 2004 until 2009 Surveys sent to hospitals to find out about ventilation systems installed. Perioperative antibiotic prophylaxis given to 99% of people undergoing hip or knee replacement in 2008.

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Study	Intervention and comparison	Population	Outcomes	Comments
			surgery, ASA score. Hospital factors were not included as they did not show a significant influence.	Body exhaust systems are not routinely used in Germany. Liquid resistant surgical gowns and drapes well established. Unclear if dedicated orthopaedic theatres were used. Data was also presented on laminar flow with larger or smaller ceiling areas.
Dale 2009[18]	Laminar flow ventilation versus "ordinary" ventilation	Primary total hip replacement (THR). N=97,344 Norway	Revision due to deep infection of the implant Follow up ranged from 0-20 years All THAs were followed until their first revision due to deep infection or revision for other causes, until date of death or emigration of the patient, or until January 1, 2008. Cox regression model Adjusted for sex, age, diagnosis (osteoarthritis, inflammatory disease, other), monoblock or modular prosthesis, type of fixation (uncemented, cement containing or not containing antibiotics), antibiotic prophylaxis, duration of surgery	Data from Norwegian Arthroplasty Register from 15 September 1987 to 1 January 2008 ASA score not recorded in the register until 2005. Unclear what clothing was worn in theatre or if dedicated orthopaedic theatres were utilised.
Namba 2012[46]	Laminar flow ventilation	Primary elective total hip	Deep surgical site infection	Data from Kaiser Permanente

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Study	Intervention and comparison	Population	Outcomes	Comments
	versus not using laminar flow ventilation.	replacement N=30,491 USA	within one year post-operatively Cox's proportional hazard regression model. All variables found to be independently associated with the outcome were included in the final multivariate model: ASA grade, bilateral procedures, sex, age, diabetes, and body mass index.	Total Joint Replacement Registry (TJRR) between 2001 and 2009. 46 medical centres Obesity and chronic medical conditions should be addressed prior to THR. Unclear if dedicated orthopaedic theatres were used. Use of a body exhaust system was a factor investigated.
Pedersen 2010[53]	Laminar air flow ventilation (n=72423) versus conventional Ventilation (n=8333)	Primary total hip replacement N=80,756 Denmark	Revision due to infection follow up ranged from 0 to 14 years. The follow-up period started on the day surgery and ended on the day of revision, death, emigration, or 1st January 2009. Cox regression model. Adjusted for: age, sex, indication for primary THA, previous surgery on the same hip, Charlson co-morbidity index, fixation technique, duration of surgery, type of anaesthesia, and ossification prophylaxis, year of surgery	Data from the Danish Hip Arthroplasty Registry (DHR) from 1995 to 2008. Unclear what clothing was worn by the surgical staff and whether dedicated orthopaedic theatres were used.
Pinder 2016[54]	Laminar flow utilised	People undergoing	Surgical site infection within	Data taken from the Hospital

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Study	Intervention and comparison	Population	Outcomes	Comments
	throughout the study period. (n=73112) versus plenum ventilation throughout the study period. (n=12497)	hemiarthroplasty of the hip due to trauma N=85,609 United Kingdom	90 days of surgery (SSI90) Confounding variables adjusted for in analysis. It is unclear what factors were adjusted for. The following factors were mentioned: age, sex, Charlson co-morbidity index, socio-economic deprivation, and number of trauma operations performed.	Episodes Statistics database for 2008 to 2013. Data from 184 hospitals used. Hospitals were sent questionnaires to determine use of laminar flow theatres. Unclear what clothing was worn by the surgical staff and whether dedicated orthopaedic theatres were used.
Song 2012[59]	HEPA-filtered laminar flow ventilation versus conventional HEPA-filtered turbulent ventilation	Total hip replacement (n=3,422) or total knee replacement (n=3,426) N=6,848 Korea Included people having revision joint replacement surgery.	Severe surgical site infections: deep incisional and organ/space infections Follow-up: 1 year after surgery Factors with a p<0.1 in univariate analysis were included in a stepwise multiple logistic regression model. The final model was adjusted for hospital volume of surgery, sex, preoperative hospital stay, diabetes, anaesthesia, revision surgery, duration of surgery, trauma, infections at other sites.	Data from Korean Nosocomial Infections Surveillance System (KONIS) from 2006 to 2009. 26 hospitals participated. Hospital must employ 1 full time infection control practitioner to be included in analysis Unclear what clothing was worn by the surgical staff and whether dedicated orthopaedic theatres were used.

See Appendix D: for full evidence tables.

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1.4.4 Quality assessment of clinical studies included in the evidence review

Table 3: RCT evidence summary: ultra clean-air theatres versus conventional ventilation theatres

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Conventional air flow theatres	Risk difference with Ultra clean-air theatres (95% CI)
Randomised group data from Fitzgerald 1992: prophylactic antibiotic therapy used in all people and body exhaust suits not used by surgical staff.					
Deep surgical site infection	6050 (1 study) 1-8 years	⨁⊖⊖⊖ VERY LOW[1,3] due to risk of bias, imprecision	RR 0.9 (0.36 to 2.28)	3 per 1000	0 fewer per 1000 (from 2 fewer to 4 more)
Randomised group data from Lidwell 1982: prophylactic antibiotics used in 72% of people and ultra clean-air surgical staff could wear either body exhaust suits or conventional clothing					
Confirmed sepsis	8055 (1 study) 2.5 years	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, indirectness	RR 0.38 (0.24 to 0.62)	15 per 1000	9 fewer per 1000 (from 6 fewer to 12 fewer)
2 subgroup analyses reported in Lidwell 1982 where all people received prophylactic antibiotics as is standard care today					
Confirmed sepsis: all people given prophylactic antibiotics and ultra clean-air operating teams either wore body exhaust suits or conventional clothing	5831 (1 study) 2.5 years	⨁⊖⊖⊖ VERY LOW[1,3,4] due to risk of bias, imprecision, indirectness	RR 0.43 (0.21 to 0.9)	8 per 1000	5 fewer per 1000 (from 1 fewer to 6 fewer)
Confirmed sepsis: all people given prophylactic antibiotics and ultra clean-air operating teams either wore conventional clothing	4247 (1 study) 2.5 years	⨁⊖⊖⊖ VERY LOW[1,3] due to risk of bias, imprecision	RR 0.87 (0.41 to 1.87)	8 per 1000	1 fewer per 1000 (from 5 fewer to 7 more)

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] Usage of prophylactic antibiotics or body exhaust suits was not standardised across that trial. Both could affect the outcome.
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[4] Usage of body exhaust suits was not standardised across this subgroup. This could affect the outcome.

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Table 4: Observational studies evidence summary: ultra clean-air theatres versus conventional ventilation theatres

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Adjustment for confounding factors
Revision due to infection Follow-up ranged from 0-14 years	80,756 (1 study)	VERY LOW[2] due to imprecision	Adjusted RR 0.9 (0.7 to 1.14)	Cox regression model that was adjusted for: age, sex, indication for primary THA, previous surgery on the same hip, Charlson co-morbidity index, fixation technique, duration of surgery, type of anaesthesia, and ossification prophylaxis, year of surgery
Revision due to infection Follow-up ranged from 0-20 years	N=97,344 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	Adjusted RR 1.3 (1.1 to 1.5)	Risk ratio estimates adjusted for sex, age, diagnosis, type of prosthesis, duration of operation, antibiotic prophylaxis systemically, and type of fixation
Severe surgical site infection Follow-up: unclear People having hip replacement	28,623 (1 study)	VERY LOW[2] due to imprecision	Adjusted OR 1.63 (1.06 to 2.52)	Logistic regression model utilising multivariate analysis including: sex, age, NNIS risk index variables (ASA score, wound class, duration of operation), frequency of this operative procedure in the hospital, number of hospital beds, academic status of hospital, long term participation in KISS.
Severe surgical site infection Follow-up: unclear People having knee replacement	9,396 (1 study)	VERY LOW[2] due to imprecision	Adjusted OR 1.76 (0.8 to 3.85)	Logistic regression model utilising multivariate analysis including: sex, age, NNIS risk index variables (ASA score, wound class, duration of operation), frequency of this operative procedure in the hospital, number of hospital beds, academic status of hospital, long term participation in KISS.
Severe surgical site infection Follow-up: unclear People having elective primary hip joint replacement	33,463 (1 study)	VERY LOW[2] due to imprecision	Adjusted OR 1.1 (0.56 to 2.17)	Logistic regression model adjusted for sex, age, duration of operation, ASA score
Severe surgical site infection Follow-up: unclear	7,749 (1 study)	VERY LOW[2] due to imprecision	Adjusted OR 1.28 (0.67 to	Logistic regression model adjusted for sex, age, duration of operation, ASA score

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Adjustment for confounding factors
People having primary hip joint replacement after fracture			2.43)	
Severe surgical site infection Follow-up: unclear People having primary knee joint replacement after	20,554 (1 study)	VERY LOW[2] due to imprecision	Adjusted OR 0.95 (0.37 to 2.41)	Logistic regression model adjusted for sex, age, duration of operation, ASA score
Deep surgical site infection at 1 year postoperatively Follow-up: unclear Primary elective total hip replacement	30,491 (1 study)	LOW	Laminar airflow was not found to be independently associated with deep SSI	Final Cox's proportional hazard regression model included: ASA grade, bilateral procedures, sex, age, diabetes, and body mass index.
Surgical Site Infection within 90 days of surgery	85,609 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	Adjusted OR 1.45 (1.17 to 1.8)	It was indicated that confounding variables adjusted for in analysis though it is unclear what these factors were. The following factors were mentioned: age, sex, Charlson co-morbidity index, socio-economic deprivation, and number of trauma operations performed.
Severe surgical site infection within 1 year of surgery	6,848 (1 study)	LOW	Not significant in multivariate analysis	Stepwise multiple logistic model used. Risk factors with a p value of less than 0.1 were included in the initial model. p values of less than 0.5 were considered statistically significant in multivariate analysis. Factors included: surgeries performed each month, OR airflow, sex, preoperative hospital stay, diabetes, anaesthesia, revision surgery, duration of surgery, trauma, other infections.

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Adjustment for confounding factors

[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

See Appendix F: for full GRADE tables.

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1.5 Economic evidence

1.5.1 Included studies

One health economic study was identified with the relevant comparison and has been included in this review. [24] It is summarised in the health economic evidence profile below (Table 5) and the health economic evidence table in Appendix H:

1.5.2 Excluded studies

One economic study relating to this review question was identified but was excluded due to the availability of more applicable evidence. [43] It is listed in Appendix I: with reasons for exclusion given.

See also the health economic study selection flow chart in Appendix G:

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1.5.3 Summary of studies included in the economic evidence review

Table 5: Health economic evidence profile: 8 different combinations of infection prevention strategies after total hip replacement versus no infection prevention

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Graves 2016[24] (UK)	Partially applicable[(a)]	Potentially serious limitations[(b)]	Eight interventions[(c)] (T2-T9) with different combinations of systemic antibiotics, antibiotic impregnated cement, laminar air flow and body exhaust suits compared with no systemic antibiotics, normal cement, conventional ventilation and no body exhaust suits (T1).	**Total costs (mean £ per patient) vs T1:** T2: -93.46 T3: -79.58 T4: -68.17 T5: -59.94 T6: -107.67 T7: -42.31 T8: -51.23 T9: 10.10	**QALYs (mean per patient) vs T1:** T2: 0.0013 T3: 0.0016 T4: 0.0015 T5: 0.0012 T6: 0.0019 T7: 0.0016 T8: 0.0014 T9: 0.0008	T6 dominates (less costly and more effective) all interventions including those which involve laminar air flow **Addition of laminar flow by set of co-interventions:** T3 vs T1: T3 dominates T4 vs T2: £115,041 per QALY gained T7 vs T6: T6 dominates T9 vs T8: T8 dominates	T6 probability of dominance = 32%. A probabilistic sensitivity analyses was conducted for interventions T2-9 being cost saving, increasing QALYs and being cost-effective, when compared with T1. T2 and T5 had the greatest probability of being cost saving (96%). T6 had the greatest probability of increasing QALYs (70%) and being cost effective (32%).

Abbreviations: QALY: quality-adjusted life years

(a) UK NHS perspective with relevant comparators. QALYs not derived using EQ-5D

(b) The baseline risk of deep infection was from a very old study, the cost of laminar flow units was sourced from the USA; 3 out of the 6 studies used to estimate laminar flow effect were not included in this guideline's clinical review because they did not adequately control for confounding and a fourth was in the wrong population

(c) T1; No systemic antibiotics, plain cement and conventional ventilation; T2: Systemic antibiotics, plain cement and conventional ventilation; T3: No systemic antibiotics, plain cement and laminar airflow; T4: Systemic antibiotics, plain cement and laminar airflow; T5: No systemic antibiotics, antibiotic-impregnated cement and conventional ventilation; T6: Systemic antibiotics, antibiotic-impregnated cement and conventional ventilation; T7: Systemic antibiotics, antibiotic-impregnated cement and laminar airflow; T8: Systemic antibiotics, antibiotic-impregnated cement, conventional ventilation and body exhaust suit; T9: Systemic antibiotics, antibiotic-impregnated cement, laminar ventilation and body exhaust suits

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1.5.4 Unit costs

Relevant unit costs are provided below to aid consideration of cost effectiveness.

Table 6: UK costs of laminar airflow in operating rooms

Equipment	Cost (per surgery)
Laminar air flow system	£6.33-£9.50[(a)]

Source: Graves 2016 [24]

(a) Conversion made from a USA estimation for the 2011/2012 range. Costs of construction and installation were considered with a 5 year lifetime assumed. The cost per case was then calculated by dividing the annual cost by an assumed case load of 25 surgeries per week for 50 weeks.

1.6 Evidence statements

1.6.1 Clinical evidence statements

Evidence from 2 randomised controlled trials and 7 observational studies reported on infection prevention in joint replacement surgery through the use of ultra clean-air ventilation compared to conventional ventilation. 1 RCT (very low quality, n=6050) found no difference in deep surgical site infection. The second RCT was analysed using the original randomised groups and found a benefit of ultra clean-air in confirmed sepsis (very low quality, n=8055). This same evidence was also sub-grouped in 2 ways. The first where all people were given prophylactic antibiotics and ultra clean-air operating teams either wore body exhaust suits or conventional clothing and that found a benefit of ultra clean-air in confirmed sepsis (very low quality, n=5831). The second where all people given prophylactic antibiotics and ultra clean-air operating teams wore conventional clothing found no clinically important difference between interventions in confirmed sepsis (very low quality, n=4247). Evidence from observational studies was not meta-analysed due to control of different confounding factors and variation in data gathering of the outcome of interest. 2 studies reported revision due to infection and one found no clinical difference and the other found a benefit for conventional ventilation (very low quality, n=80,756-97,344). 5 studies reported on surgical site infection across 8 outcomes and 4 indicated no clinical difference and 4 indicated a clinically important benefit of conventional ventilation (low to very low quality, n=6,848-85,609). No evidence was available for 30-day mortality or quality of life.

1.6.2 Health economic evidence statements

One comparative cost utility analysis found that use of laminar airflow in theatres was: dominant (less costly and more effective) compared to not using any other infection prevention strategy; not cost effective when used as an adjunct to systemic antibiotics; dominated when used as an adjunct to systemic antibiotics and antibiotic impregnated cement; and dominated (cost more and less effective) when used as an adjunct to systemic antibiotics, antibiotic impregnated cement and body exhaust suits. This analysis was assessed as partially applicable with potentially serious limitations.

1.7 The committee's discussion of the evidence

1.7.1 Interpreting the evidence

1.7.1.1 The outcomes that matter most

The critical outcomes are 30-day mortality, quality of life, deep surgical site infection and superficial surgical site infection. The choice of ventilation systems used during orthopaedic surgery with implants was made based on the concept of reduction of infection. This review

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includes 2 critical outcomes on infection. The committee spoke about the devastating possibilities to the person who has surgical site infection after joint replacement surgery. Addressing these infections is a significant cost to the NHS. Infections can recur after they initially happen, and a committee member spoke about people being operated on 9 or 10 times due to infection.

The important outcomes are also designed to pick up the negative impacts of infection through return to theatre, hospital readmission, and length of stay.

No evidence was found for the following critical outcomes: 30-day mortality or quality of life.

1.7.1.2 The quality of the evidence

All of the outcomes were judged to be low or very low quality.

The RCT evidence was at very high risk of bias. The method of randomisation was unclear, there was imprecision for one outcome and the data was not directly applicable to current practice for 2 others due to intermittent use of prophylactic antibiotics and body exhaust suits.

Subgroup data was also presented from 1 RCT and it should be noted that this breaks randomisation. This subgroup is more relevant to current practice as it relates to people who were given prophylactic antibiotics and where the operating room staff did not wear body exhaust suits. However, the decision to give antibiotics was made by the operating surgeon and the decision to use body exhaust suits was based on local hospital policy. All the evidence from the RCTs were deemed to be of very low quality.

Much of the observational data was from registries and was consequently influenced by confounding factors. These factors were numerous but included surgeon experience and effectiveness, type of prosthesis, duration of operation, and variations in the clinical condition of people selected for ultra clean-air or conventional ventilation. Only studies that used multivariate analysis to address confounding factors were included and the factors adjusted for varied between studies. In addition, infection reporting policies, revision policy, diagnostics, and surgeon awareness, could influence the results. All outcomes were downgraded to very low quality for risk of bias due to unclear control of important confounding factors or for imprecision around the resulting effect estimate.

1.7.1.3 Benefits and harms

The committee spoke about the consequences of surgical site infection after joint replacement surgery. It can be a catastrophic complication and lead to considerable morbidity and cause amputation or revision surgery. Also people are more likely to have further infections after joint replacement surgery if it has happened before.

2 RCTs were included in the evidence review. All surgeries in both trials were completed before 1990. Personnel isolator systems (body exhaust suits) were occasionally utilised in 1 RCT but not in the other. Similarly, 1 RCT gave all people prophylactic antibiotics, and the other study gave prophylactic antibiotics to 72% of people in the study. The operating surgeon made the decision on whether they should be administered. The original randomised data from this trial and 2 additional subgroup analyses were presented. These 2 subgroups contain only people who were given prophylactic antibiotics and in 1 case only people operated on by staff who were not wearing body exhaust suits. These 2 subgroups are a closer match to how current NHS joint replacement surgery is undertaken than the original randomised intervention groups. The RCT outcomes varied in clinical importance and no meta-analysis was undertaken due to variation in care and the breaking of randomisation though subgroup analysis. The study where prophylactic antibiotics were given to all people and surgery was completed without the use of personnel isolator systems did not find a clinically important benefit of ultra clean air in deep surgical site infection.

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However, it was mentioned that this study used a horizontal laminar flow system and these are harder to run effectively. The other RCT found a clinically important benefit of ultra clean air with the truly randomised data (72% of people having prophylactic antibiotics and body exhaust suits occasionally worn) and a clinically important benefit in the subgroup of people who all had prophylactic antibiotics and body exhaust suits occasionally worn. However, there was no clinically important benefit in the subgroup of people who had prophylactic antibiotics and body exhaust suits were not worn. All surgery undertaken in the 2 RCTs were completed before 1990. The committee agreed that ultra clean air systems utilised in the 1980s are different from those used today, and the conventional ventilation systems likewise are different from today's turbulent ventilation, as they exist today. Thus, the committee could not draw firm conclusions on the effectiveness of ultra clean air from the RCT data.

A number of other systematic reviews investigating ventilation systems during joint replacement surgery had excluded studies undertaken before 1990 due to the technology in that period being outdated by modern standards. The committee agreed that it would be prudent to include more recent observational studies that use multivariate analysis to control for confounding factors.

Seven observational studies were included; these analysed data from national registries and surveys and consequently encompassed very large numbers of people. NJR data would have only been considered if it was adjusted for confounding factors. Five outcomes, 1 revision due to infection and 4 surgical site infection outcomes indicated no clinically important difference. Five outcomes, 1 revision due to infection and 4 surgical site infection outcomes indicated a clinically important benefit for conventional ventilation over ultra clean-air. The imprecision of the studies was noted. The confidence intervals, where reported, of all outcomes crossed at least 1 minimally important difference (MID) and 3 outcomes crossed both MIDs. The committee spoke of the importance of the follow-up in terms of picking up the number of surgical site infections accurately. Studies reporting on revision due to infection followed up people for the length of the studies and this was 0 to 14 years in 1 case and 0 to 20 years in the other. The surgical site infection outcomes varied more. Five outcomes from the KISS registry were followed-up in routine post discharge surveillance, and this was variable. Two outcomes were limited to infections within 1 year of surgery and 1 outcome within 90 days of surgery. The committee did not consider periods under 2 years to be sufficient to give an accurate picture of infection after joint replacement surgery. Deep infection often presents late and diagnosis can be difficult. This could be missed in registry data whereas RCTs, where infection is the most significant outcome, may be more focussed on accurately collecting this follow-up data. The committee also spoke about the collection of registry data. It is not a comprehensive enough process to give an accurate summary of the infection risk of ventilation systems in operating theatres. A further weakness was the usage of 'infections that lead to revision' as an outcome. A committee member did not consider this to be an effective way to judge the number of infections as many infections happen that lead to negative outcomes but not necessarily revision surgery.

The committee indicated that the ventilation technology used in the 2 RCTs may not accurately represent either ultra clean-air or conventional ventilation as they stand today. They also agreed the registry data utilised in the observational studies was flawed. The committee consensus was that ultra clean-air ventilation is more effective at reducing surgical site infections than conventional turbulent air ventilation and the inconclusive results of the evidence review were not strong enough to alter current practice. The current BOA Consultant Advisory Book (2014) recommends that ultra clean-air vertical laminar flow systems or equivalent are mandatory for joint replacements and major orthopaedic implant surgery. In line with standard orthopaedic UK practice, the committee's assessment of the evidence and consensus, a recommendation was made to use ultra clean-air ventilation for primary joint replacement surgeries.

It was also noted by the committee that the observational studies included did not always report whether people received prophylactic antibiotics.

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1.7.2 Cost effectiveness and resource use

One economic study was found which suggested that when antibiotic prophylaxis (or any other infection prevention strategy) is not used, laminar airflow is cost effective. This highlights the importance of whether antibiotic prophylaxis is used routinely or not. In current practice, antibiotics are commonly used; however, the issue of antibiotic resistance may change guidance on the use of antibiotics. The study also suggested that when other infection prevention strategies are used, the addition of laminar flow is not cost effective. This model was based on a mixture of randomised and observational evidence that only partially overlapped with the evidence in this guideline's clinical review.

The unit costs presented for laminar flow were for construction and installation and therefore concerned new builds. A few committee members agreed that the unit cost for the new build seemed less expensive than what they had expected. The costs presented had limited applicability in that the estimate was from the USA and for 2011/12. Committee members thought that it could be more relevant to focus on the cost effectiveness of building additional laminar airflow theatres. It was not known exactly how many hospitals do not have laminar flow operating theatres; however, their use is widespread and considered current practice. Installation of new ultra clean-air facilities may have an initial resource impact; however, running costs once built would be minimal. It was suggested that anecdotally over the lifetime of a theatre, it would be surprising if the use of laminar airflow costed more than £2–3 per person over conventional ventilation. Therefore, where laminar flow operating theatres already exist, their use does not have a large resource impact. Alternatively, if a recommendation were made against the use of the intervention, there would also be a cost associated with dismantling the existing laminar airflow operating theatres. There may be additional costs to the NHS due to emergency surgery overflow reducing elective capacity. This means that, at times, private facilities with ultra clean-air theatres must be hired out in order to carry out elective joint replacement procedures. However, these costs also form part of current practice.

The poor quality and conflicting results of the clinical RCT and observational data (as discussed in Section1.7.1) means that it was not possible to draw conclusions about the effectiveness or cost effectiveness of ultra clean air compared with conventional ventilation from the evidence. The committee also agreed that original cost effectiveness modelling would not be informative for their decision, since it would have to be based on the existing flawed clinical effectiveness evidence base.

The committee consensus was that ultra clean-air ventilation is more effective at reducing surgical site infections than conventional turbulent air ventilation and the inconclusive results of the evidence review were not strong enough to alter current practice. A recommendation was made to use ultra clean-air ventilation for primary joint replacement surgeries. As recommending the use of ultra clean air theatres will not change current practice, no resource impact is expected.

1.7.3 Other factors the committee took into account

The committee discussed the theoretical advantages of ultra clean air systems. They have been shown to reduce bacterial colonies settling and it is believed that this consequently reduces surgical site infection.

It was also noted that there are other known factors that are thought to influence the occurrence of infection. Airborne bacteria that cause infections can still be present after previous operations and this is particularly associated with 'dirty' surgery such as gastrointestinal surgery or surgery on ischaemic vascular limbs. The bacteria left by these types of surgery are believed to present a much higher infection risk for joint replacement surgery. Thus having dedicated orthopaedic operating rooms where such surgeries do not occur are very important to infection control.

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The committee also discussed the increase in antimicrobial resistance. 1 RCT did indicate a more pronounced effect of ultra clean-air when including people with and without prophylactic antibiotics. Therefore, rising antibiotic resistance could make the effect of ultra clean-air more important if this continues.

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Appendices

Appendix A: Review protocols

Table 7: Review protocol: ultra clean-air

ID	Field	Content
0.	PROSPERO registration number	Not registered
1.	Review title	Ultra clean-air theatres
2.	Review question	In adults having primary elective joint replacement or orthopaedic surgery utilising metallic implants, what is the clinical and cost effectiveness of using ultra clean-air theatres?
3.	Objective	Joint infection post total joint arthroplasty is a costly and devastating occurrence. Ultra clean-air theatres have ventilation systems designed to reduce infection in people undergoing joint replacement surgery. This review question asks whether these ventilation systems are clinically and cost effective for the purpose of primary elective joint replacement procedures.
4.	Searches	The following databases will be searched: Cochrane Central Register of Controlled Trials (CENTRAL) Cochrane Database of Systematic Reviews (CDSR) Embase MEDLINE Searches will be restricted by: English language Human studies Letters and comments are excluded. Other searches: Inclusion lists of relevant systematic reviews will be checked by the reviewer. The searches may be re-run 6 weeks before final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review.

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ID	Field	Content
5.	Condition or domain being studied	Primary elective hip, knee or shoulder joint replacement surgery
6.	Population	Inclusion: Adults having primary elective joint replacement or orthopaedic surgery utilising metallic implants. Exclude studies including people meeting any of the following criteria: Adults having revision joint replacement. Adults having joint replacement as treatment for primary or secondary cancer affecting the bones.
7.	Intervention/Exposure/Test	Ultra clean-air theatres (including laminar flow and ex flow systems)
8.	Comparator/Reference standard/Confounding factors	Conventional air flow theatres
9.	Types of study to be included	Systematic reviews RCTs If no well-conducted RCTs are available, then observational studies with multivariate analysis will be investigated.
10.	Other exclusion criteria	Non-English language studies. Abstracts will be excluded as it is expected there will be sufficient full text published studies available.
11.	Context	N/A
12.	Primary outcomes (critical outcomes)	Mortality: 30 day (dichotomous) Quality of life (continuous) Superficial Surgical site infection (dichotomous) Deep surgical site infection (dichotomous)
13.	Secondary outcomes (important outcomes)	Return to theatre (dichotomous) Hospital readmission (dichotomous) Length of stay (continuous)
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. Titles and/or abstracts of studies retrieved using the search strategy and those from additional sources will be screened for inclusion.

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ID	Field	Content
		The full text of potentially eligible studies will be retrieved and will be assessed for eligibility in line with the criteria outlined above. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. An in-house developed database; EviBase, will be used for data extraction. A standardised form is followed to extract data from studies (see Developing NICE guidelines: the manual section 6.4) and for undertaking assessment of study quality. Summary evidence tables will be produced including information on: study setting; study population and participant demographics and baseline characteristics; details of the intervention and control interventions; study methodology' recruitment and missing data rates; outcomes and times of measurement; critical appraisal ratings. A second reviewer will quality assure the extracted data. Discrepancies will be identified and resolved through discussion (with a third reviewer where necessary).
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. For Intervention reviews the following checklist will be used according to study design being assessed: Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) Randomised Controlled Trial: Cochrane RoB (2.0) Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
16.	Strategy for data synthesis	Where possible, data will be meta-analysed. Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5) to combine the data given in all studies for each of the outcomes stated above. A fixed effect meta-analysis, with weighted mean differences for continuous outcomes and risk ratios for binary outcomes will be used, and 95% confidence intervals will be calculated for each outcome. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. We will consider an I^2 value greater than 50% indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented using random-effects. GRADE pro will be used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome.

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ID	Field	Content			
		If the population included in an individual study includes children aged under 12, it will be included if the majority of the population is aged over 12, and downgraded for indirectness if the overlap into those aged less than 12 is greater than 20%. Publication bias is tested for when there are more than 5 studies for an outcome. Other bias will only be taken into consideration in the quality assessment if it is apparent. Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. If sufficient data is available to make a network of treatments, WinBUGS will be used for network meta-analysis.			
17.	Analysis of sub-groups	Size of the vertical laminar airflow area: airflow area ≥ 320cm x 320cm, airflow area < 320cm x 320cm Types of ultra clean air flow: vertical, horizontal, ex-flow Theatre use: mixed theatres, dedicated orthopaedic theatres			
18.	Type and method of review	☒	Intervention		
		☐	Diagnostic		
		☐	Prognostic		
		☐	Qualitative		
		☐	Epidemiologic		
		☐	Service Delivery		
		☐	Other (please specify)		
19.	Language	English			
20.	Country	England			
21.	Anticipated or actual start date	07/07/18			
22.	Anticipated completion date	20/03/20			
23.	Stage of review at time of this submission	Review stage		Started	Completed
		Preliminary searches		☑	☐
		Piloting of the study selection process		☑	☐

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ID	Field	Content		
		Formal screening of search results against eligibility criteria	☐	☐
		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail Headches@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre		
25.	Review team members	From the National Guideline Centre: Carlos Sharpin [Guideline lead] Alex Allen [Senior Systematic Reviewer] Rafina Yarde [Systematic reviewer] Robert King [Health economist] Agnès Cuyàs [Information specialist] Eleanor Priestnall [Project Manager]		
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.		
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.		
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the		

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ID	Field	Content	
		development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: [NICE guideline webpage].	
29.	Other registration details		
30.	Reference/URL for published protocol		
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: notifying registered stakeholders of publication publicising the guideline through NICE's newsletter and alerts issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Joint replacement surgery, arthroplasty, ventilation, ultra clean-air, turbulent flow	
33.	Details of existing review of same topic by same authors	N/A	
34.	Current review status	☒	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information	N/A	
36.	Details of final publication	www.nice.org.uk	

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Table 8: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2003, abstract-only studies and studies from low or middle-income countries (for example, most non-OECD countries) or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[47] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example,

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	Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2003 or later but that depend on unit costs and resource data entirely or predominantly from before 2003 will be rated as 'Not applicable'. • Studies published before 2003 will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

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Appendix B: Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[47]

For more detailed information, please see the Methodology Review.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the searches where appropriate.

Table 9: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 01 May 2019	Exclusions
Embase (OVID)	1974 – 01 May 2019	Exclusions
The Cochrane Library (Wiley)	Cochrane Reviews to 2019 Issue 5 of 12 CENTRAL to 2019 Issue 5 of 12 DARE, and NHSEED to 2015 Issue 2 of 4 HTA to 2016 Issue 4 of 4	None

Medline (Ovid) search terms

1.	arthroplasty/ or arthroplasty, replacement/ or arthroplasty, replacement, hip/ or arthroplasty, replacement, knee/ or arthroplasty, replacement, shoulder/ or hemiarthroplasty/
2.	joint prosthesis/ or hip prosthesis/ or knee prosthesis/ or shoulder prosthesis/
3.	((joint* or knee* or shoulder* or hip*) adj5 (surger* or replace* or prosthe* or endoprosthe* or implant* or artificial or arthroplast* or hemiarthroplast*)).ti,ab.
4.	or/1-3
5.	Orthopedics/
6.	Orthopedic Procedures/
7.	(orthopedic* or orthopaedic*).ti,ab.
8.	Metal-on-Metal Joint Prostheses/
9.	Fracture Fixation, Internal/
10.	exp Internal Fixators/
11.	(metal* adj3 (prosthes* or implant* or fixator* or nail* or plate* or screw* or wire* or pin* or rod*)).ti,ab.
12.	dynamic compression plate*.ti,ab.
13.	((surgical or fracture*) adj2 fixation*).ti,ab.
14.	osteosynthes*.ti,ab.
15.	(open reduction adj2 internal fixation*).ti,ab.
16.	ORIF.ti,ab.
17.	Spinal Fusion/

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18.	((spine or spinal or vertebral or anterior or posterior or posterolateral or postero lateral or transforaminal or trans foraminal or interbody or inter body) adj3 fusion*).ti,ab.
19.	(PLF or ALIF or PLIF or TLIF or DLIF or XLIF).ti,ab.
20.	(spondylodesis or spondylosyndesis).ti,ab.
21.	or/5-20
22.	4 or 21
23.	letter/
24.	editorial/
25.	news/
26.	exp historical article/
27.	Anecdotes as Topic/
28.	comment/
29.	case report/
30.	(letter or comment*).ti.
31.	or/23-30
32.	randomized controlled trial/ or random*.ti,ab.
33.	31 not 32
34.	animals/ not humans/
35.	exp Animals, Laboratory/
36.	exp Animal Experimentation/
37.	exp Models, Animal/
38.	exp Rodentia/
39.	(rat or rats or mouse or mice).ti.
40.	or/33-39
41.	22 not 40
42.	limit 41 to English language
43.	Operating Rooms/
44.	Environment, Controlled/
45.	Ventilation/
46.	Air Filters/
47.	((operat* or surger* or surgical or theat* or room*) adj5 (ventilat* or air* or environment* or climate*)).ti,ab.
48.	((air* or technolo*) adj3 (filter* or filtration or purifi* or purify* or condition* or quality)).ti,ab.
49.	(high efficiency particulate or HEPA).ti,ab.
50.	((exponential or vertical or horizontal or laminar or plenum or "ceiling to floor" or "wall mounted") adj3 air*).ti,ab.
51.	(LAF or Exflow).ti,ab.
52.	((ultraclean or clean* or Charnley or Howorth) adj3 (air* or ventilat* or enclosure* or technolo*)).ti,ab.
53.	(UCA or UCV).ti,ab.
54.	or/43-53
55.	42 and 54

Embase (Ovid) search terms

1.	*arthroplasty/ or *replacement arthroplasty/ or *hip replacement/ or *knee replacement/ or *shoulder replacement/ or *hemiarthroplasty/

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2.	*joint prosthesis/ or *hip prosthesis/ or *knee prosthesis/ or *shoulder prosthesis/
3.	((joint* or knee* or shoulder* or hip*) adj5 (surger* or replace* or prosthe* or endoprosthe* or implant* or artificial or arthroplast* or hemiarthroplast*)).ti,ab.
4.	or/1-3
5.	*orthopedics/
6.	*orthopedic surgery/
7.	(orthopedic* or orthopaedic*).ti,ab.
8.	*metal on metal joint prosthesis/
9.	osteosynthesis/
10.	exp internal fixator/
11.	(metal* adj3 (prosthes* or implant* or fixator* or nail* or plate* or screw* or wire* or pin* or rod*)).ti,ab.
12.	dynamic compression plate*.ti,ab.
13.	((surgical or fracture*) adj2 fixation*).ti,ab.
14.	osteosynthes*.ti,ab.
15.	(open reduction adj2 internal fixation*).ti,ab.
16.	ORIF.ti,ab.
17.	spine fusion/
18.	((spine or spinal or vertebral or anterior or posterior or posterolateral or postero lateral or transforaminal or trans foraminal or interbody or inter body) adj3 fusion*).ti,ab.
19.	(PLF or ALIF or PLIF or TLIF or DLIF or XLIF).ti,ab.
20.	(spondylodesis or spondylosyndesis).ti,ab.
21.	or/5-20
22.	4 or 21
23.	letter.pt. or letter/
24.	note.pt.
25.	editorial.pt.
26.	case report/ or case study/
27.	(letter or comment*).ti.
28.	or/23-27
29.	randomized controlled trial/ or random*.ti,ab.
30.	28 not 29
31.	animal/ not human/
32.	nonhuman/
33.	exp Animal Experiment/
34.	exp Experimental Animal/
35.	animal model/
36.	exp Rodent/
37.	(rat or rats or mouse or mice).ti.
38.	or/30-37
39.	22 not 38
40.	limit 39 to English language
41.	operating room/
42.	*microclimate/
43.	*air conditioning/
44.	*air filter/

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45.	((operat* or surger* or surgical or theat* or room*) adj5 (ventilat* or air* or environment* or climate*)).ti,ab.
46.	((air* or technolo*) adj3 (filter* or filtration or purifi* or purify* or condition* or quality)).ti,ab.
47.	(high efficiency particulate or HEPA).ti,ab.
48.	((exponential or vertical or horizontal or laminar or plenum or "ceiling to floor" or "wall mounted") adj3 air*).ti,ab.
49.	(LAF or Exflow).ti,ab.
50.	((ultraclean or clean* or Charnley or Howorth) adj3 (air* or ventilat* or enclosure* or technolo*)).ti,ab.
51.	(UCA or UCV).ti,ab.
52.	or/41-51
53.	40 and 52

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Arthroplasty] this term only
#2.	MeSH descriptor: [Arthroplasty, Replacement] this term only
#3.	MeSH descriptor: [Arthroplasty, Replacement, Hip] this term only
#4.	MeSH descriptor: [Arthroplasty, Replacement, Knee] this term only
#5.	MeSH descriptor: [Arthroplasty, Replacement, Shoulder] this term only
#6.	MeSH descriptor: [Hemiarthroplasty] this term only
#7.	(or #1-#6)
#8.	MeSH descriptor: [Joint Prosthesis] this term only
#9.	MeSH descriptor: [Hip Prosthesis] this term only
#10.	MeSH descriptor: [Knee Prosthesis] this term only
#11.	MeSH descriptor: [Shoulder Prosthesis] this term only
#12.	(or #8-#11)
#13.	((joint* or knee* or shoulder* or hip*) near/5 (surger* or replace* or prosthe* or endoprosthe* or implant* or artificial or arthroplast* or hemiarthroplast*)):ti,ab
#14.	(or #7, #12-#13)
#15.	MeSH descriptor: [Orthopedics] this term only
#16.	MeSH descriptor: [Orthopedic Procedures] this term only
#17.	(orthopedic* or orthopaedic*):ti,ab
#18.	MeSH descriptor: [Metal-on-Metal Joint Prostheses] this term only
#19.	MeSH descriptor: [Fracture Fixation, Internal] this term only
#20.	MeSH descriptor: [Internal Fixators] explode all trees
#21.	(metal* near/3 (prosthes* or implant* or fixator* or nail* or plate* or screw* or wire* or pin* or rod*)):ti,ab
#22.	dynamic compression plate*:ti,ab
#23.	((surgical or fracture*) near/2 fixation*):ti,ab
#24.	osteosynthes*:ti,ab
#25.	(open reduction near/2 internal fixation*) ti,ab
#26.	ORIF:ti,ab
#27.	MeSH descriptor: [Spinal Fusion] this term only
#28.	((spine or spinal or vertebral or anterior or posterior or posterolateral or postero lateral or transforaminal or trans foraminal or interbody or inter body) near/3 fusion*):ti,ab
#29.	(PLF or ALIF or PLIF or TLIF or DLIF or XLIF):ti,ab
#30.	(spondylodesis or spondylosyndesis):ti,ab

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#31.	(or #15-#30)
#32.	#14 or #31
#33.	MeSH descriptor: [Operating Rooms] this term only
#34.	MeSH descriptor: [Environment, Controlled] this term only
#35.	MeSH descriptor: [Ventilation] explode all trees
#36.	MeSH descriptor: [Air Filters] this term only
#37.	((operat* or surger* or surgical or theat* or room*) near/5 (ventilat* or air* or environment* or climate*)):ti,ab
#38.	((air* or technolo*) near/3 (filter* or filtration or purifi* or purify* or condition* or quality)):ti,ab
#39.	(high efficiency particulate or HEPA):ti,ab
#40.	((exponential or vertical or horizontal or laminar or plenum or "ceiling to floor" or "wall mounted") near/3 air*):ti,ab
#41.	(LAF or Exflow):ti,ab
#42.	((ultraclean or clean* or Charnley or Howorth) near/3 (air* or ventilat* or enclosure* or technolo*)):ti,ab
#43.	(UCA or UCV):ti,ab
#44.	(or #33-#43)
#45.	#32 and #44

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to joint replacement population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional health economics searches were run in Medline and Embase.

Table 10: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	2014 – 04 July 2018	Exclusions Health economics studies
Embase	2014 – 04 July 2018	Exclusions Health economics studies
Centre for Research and Dissemination (CRD)	HTA - Inception – 04 July 2018 NHSEED - Inception to March 2015	None

Medline (Ovid) search terms

1.	Operating Rooms/
2.	Environment, Controlled/
3.	Ventilation/
4.	Air Filters/
5.	((operat* or surger* or surgical or theat* or room*) adj5 (ventilat* or air* or environment* or climate*)).ti,ab.
6.	((air* or technolo*) adj3 (filter* or filtration or purifi* or purify* or condition* or quality)).ti,ab.

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7.	(high efficiency particulate or HEPA).ti,ab.
8.	((exponential or vertical or horizontal or laminar or plenum or "ceiling to floor" or "wall mounted") adj3 air*).ti,ab.
9.	(LAF or Exflow).ti,ab.
10.	((ultraclean or clean* or Charnley or Howorth) adj3 (air* or ventilat* or enclosure* or technolo*)).ti,ab.
11.	(UCA or UCV).ti,ab.
12.	or/1-11
13.	letter/
14.	editorial/
15.	news/
16.	exp historical article/
17.	Anecdotes as Topic/
18.	comment/
19.	case report/
20.	(letter or comment*).ti.
21.	or/13-20
22.	randomized controlled trial/ or random*.ti,ab.
23.	21 not 22
24.	animals/ not humans/
25.	exp Animals, Laboratory/
26.	exp Animal Experimentation/
27.	exp Models, Animal/
28.	exp Rodentia/
29.	(rat or rats or mouse or mice).ti.
30.	or/23-29
31.	12 not 30
32.	limit 31 to English language
33.	Economics/
34.	Value of life/
35.	exp "Costs and Cost Analysis"/
36.	exp Economics, Hospital/
37.	exp Economics, Medical/
38.	Economics, Nursing/
39.	Economics, Pharmaceutical/
40.	exp "Fees and Charges"/
41.	exp Budgets/
42.	budget*.ti,ab.
43.	cost*.ti.
44.	(economic* or pharmaco?economic*).ti.
45.	(price* or pricing*).ti,ab.
46.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
47.	(financ* or fee or fees).ti,ab.
48.	(value adj2 (money or monetary)).ti,ab.
49.	or/33-48

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50.	32 and 49

Embase (Ovid) search terms

1.	operating room/
2.	*microclimate/
3.	*air conditioning/
4.	*air filter/
5.	((operat* or surger* or surgical or theat* or room*) adj5 (ventilat* or air* or environment* or climate*)).ti,ab.
6.	((air* or technolo*) adj3 (filter* or filtration or purifi* or purify* or condition* or quality)).ti,ab.
7.	(high efficiency particulate or HEPA).ti,ab.
8.	((exponential or vertical or horizontal or laminar or plenum or "ceiling to floor" or "wall mounted") adj3 air*).ti,ab.
9.	(LAF or Exflow).ti,ab.
10.	((ultra clean or ultraclean or clean* or Charnley or Howorth) adj3 (air* or ventilat* or enclosure* or technolo*)).ti,ab.
11.	(UCA or UCV).ti,ab.
12.	or/1-11
13.	letter.pt. or letter/
14.	note.pt.
15.	editorial.pt.
16.	case report/ or case study/
17.	(letter or comment*).ti.
18.	or/13-17
19.	randomized controlled trial/ or random*.ti,ab.
20.	18 not 19
21.	animal/ not human/
22.	nonhuman/
23.	exp Animal Experiment/
24.	exp Experimental Animal/
25.	animal model/
26.	exp Rodent/
27.	(rat or rats or mouse or mice).ti.
28.	or/20-27
29.	12 not 28
30.	limit 29 to English language
31.	health economics/
32.	exp economic evaluation/
33.	exp health care cost/
34.	exp fee/
35.	budget/
36.	funding/
37.	budget*.ti,ab.
38.	cost*.ti.

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39.	(economic* or pharmaco?economic*).ti.
40.	(price* or pricing*).ti,ab.
41.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
42.	(financ* or fee or fees).ti,ab.
43.	(value adj2 (money or monetary)).ti,ab.
44.	or/31-43
45.	30 and 44

NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Operating Rooms
#2.	MeSH DESCRIPTOR Environment, Controlled
#3.	MeSH DESCRIPTOR Ventilation
#4.	MeSH DESCRIPTOR Air filters
#5.	(((operat* or surger* or surgical or theat* or room*) adj5 (ventilat* or air* or environment* or climate*)))
#6.	(((air* or technolo*) adj3 (filter* or filtration or purifi* or purify* or condition* or quality)))
#7.	(high efficiency particulate or HEPA)
#8.	(((exponential or vertical or horizontal or laminar or plenum or "ceiling to floor" or "wall mounted") adj3 air*))
#9.	(LAF or Exflow)
#10.	(((ultra clean or ultraclean or clean* or Charnley or Howorth) adj3 (air* or ventilat* or enclosure* or technolo*)))
#11.	(UCA or UCV)
#12.	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11) IN HTA
#13.	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11) IN NHSEED

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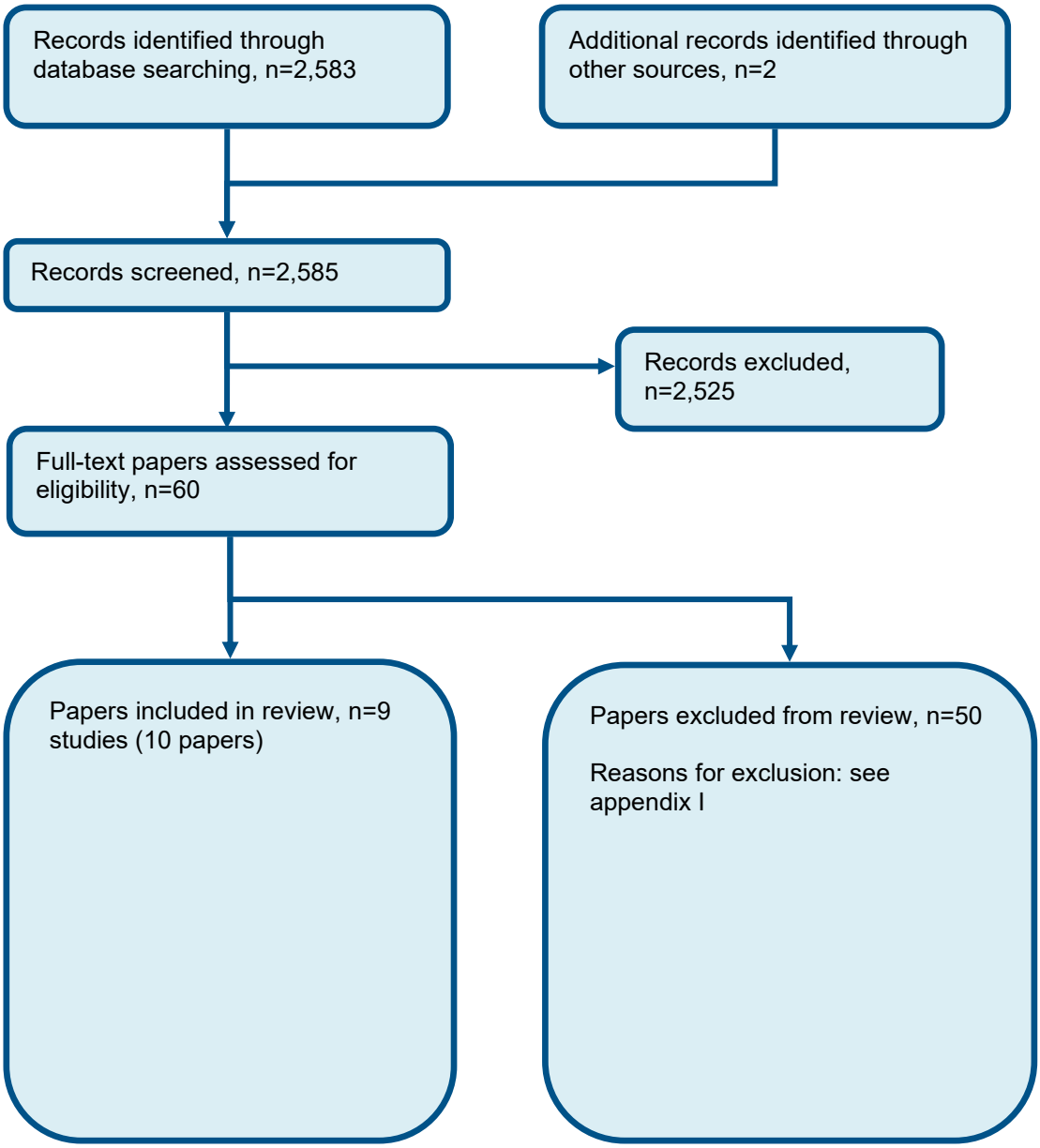
Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of ultra clean-air



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Appendix D: Clinical evidence tables

Study	Brandt 2008-1[13]
Study type	Non randomised study
Number of studies (number of participants)	1 (n=39,589)
Countries and setting	Conducted in Germany; Setting: Data from 44 hospitals in Germany.
Line of therapy	Adjunctive to current care
Duration of study	Not clear:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: People undergoing hip replacement surgery
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People who have had primary hip joint replacement
Exclusion criteria	None detailed
Recruitment/selection of patients	The data utilised for this analysis came from the 2000-2004 KISS surveillance in Germany.
Age, sex and family origin	Age - --: Not detailed. Sex (M:F): Not detailed. Family origin: Not reported
Indirectness of population	No indirectness
Interventions	(n=17,657) Intervention 1: Ultra clean-air theatres . HEPA-filtered laminar airflow ventilation (vertical). Duration During joint replacement surgery. Concurrent medication/care: Background treatment dependent on local policy in the hospital and a person's specific clinical needs. Indirectness: No indirectness Further details: 1. Size of the vertical laminar airflow area:: Mixed airflow area 2. Theatre use: Not stated / Unclear 3. Type of ultra clean air flow system: vertical laminar (n=10,966) Intervention 2: Conventional air flow theatres. HEPA-filtered conventional turbulent ventilation. Duration During joint replacement surgery. Concurrent medication/care: Background treatment dependent on local policy in the hospital and a person's specific clinical needs. Indirectness: No indirectness Further details: 1. Size of the vertical laminar airflow area: Not applicable 2. Theatre use: Not stated / Unclear 3. Type of ultra clean air flow system: Not applicable
Funding	Academic or government funding (German national nosocomial infection surveillance system (KISS) is supported by the German Federal Ministry of Health)

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RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ULTRA CLEAN-AIR THEATRES versus CONVENTIONAL AIR FLOW THEATRES Protocol outcome 1: Deep surgical site infection at 1 month - Actual outcome: Severe surgical site infection at Unclear; OR; 1.63 (95%CI 1.06 to 2.52, Comments: Adjusted OR: multivariate analysis including: sex, age, NNIS risk index variables (ASA score, wound class, duration of operation), frequency of this operative procedure in the hospital, number of hospital beds, academic status of hospital, long term participation in KISS.); Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Key confounders: No mention of space suits; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day ; Quality of life at 1 month; Superficial surgical site infection at 1 month; Return to theatre at within 3 months; Hospital readmissions at within 90 days; Length of stay at time until hospital discharge

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Study	Brandt 2008-2[13]
Study type	Non randomised study
Number of studies (number of participants)	1 (n=9,396)
Countries and setting	Conducted in Germany; Setting: Data from 18 hospitals in Germany.
Line of therapy	Adjunctive to current care
Duration of study	Not clear:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: People undergoing knee replacement surgery
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People who have had primary knee replacement surgery
Exclusion criteria	None detailed
Recruitment/selection of patients	The data utilised for this analysis came from the 2000-2004 KISS surveillance in Germany.
Age, sex and family origin	Age - --: Not detailed. Sex (M:F): Not detailed. Family origin: Not reported
Interventions	(n=5,993) Intervention 1: Ultra clean-air theatres . HEPA-filtered laminar airflow ventilation (vertical). Duration During joint replacement surgery. Concurrent medication/care: Background treatment dependent on local policy in the hospital and a person's specific clinical needs. Indirectness: No indirectness Further details: 1. Size of the vertical laminar airflow area:: Mixed airflow area 2. Theatre use: Not stated / Unclear 3. Type of ultra clean air flow system: vertical laminar (n=3,403) Intervention 2: Conventional air flow theatres. HEPA-filtered conventional turbulent ventilation. Duration During joint replacement surgery. Concurrent medication/care: Background treatment dependent on local policy in the hospital and a person's specific clinical needs. Indirectness: No indirectness Further details: 1. Size of the vertical laminar airflow area:: Not applicable 2. Theatre use: Not stated / Unclear 3. Type of ultra clean air flow system: Not applicable
Funding	Academic or government funding (German national nosocomial infection surveillance system (KISS) is supported by the German Federal Ministry of Health)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ULTRA CLEAN-AIR THEATRES versus CONVENTIONAL AIR FLOW THEATRES

Protocol outcome 1: Deep surgical site infection at 1 month
- Actual outcome: Severe surgical site infection at Unclear; OR; 1.76 (95%CI 0.8 to 3.85, Comments: Adjusted OR: multivariate analysis including: sex, age, NNIS risk index variables (ASA score, wound class, duration of operation), frequency of this operative procedure in the hospital, number of hospital

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beds, academic status of hospital, long term participation in KISS.); Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Key confounders: No mention of space suits; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day ; Quality of life at 1 month; Superficial surgical site infection at 1 month; Return to theatre at within 3 months; Hospital readmissions at within 90 days; Length of stay at time until hospital discharge

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Study	Breier 2011-1[14]
Study type	Non randomised study
Number of studies (number of participants)	1 (n=33,463)
Countries and setting	Conducted in Germany; Setting: Data from 48 hospitals in Germany.
Line of therapy	Adjunctive to current care
Duration of study	Not clear:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: People undergoing hip replacement
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People who have had primary hip joint replacement due to arthrosis
Exclusion criteria	Revision joint replacement surgeries were not included in the analysis.
Recruitment/selection of patients	The data utilised for this analysis came from the KISS surveillance 2004-2009 in Germany.
Age, sex and family origin	Age - --: Not detailed. Sex (M:F): 13158/20305. Family origin: Not reported
Indirectness of population	No indirectness
Interventions	(n=23,017) Intervention 1: Ultra clean-air theatres . Laminar airflow system. Duration During joint replacement surgery. Concurrent medication/care: Background treatment dependent on local policy in the hospital and a person's specific clinical needs. Indirectness: No indirectness Further details: 1. Size of the vertical laminar airflow area:: Mixed airflow area (Subgroup data available if required). 2. Theatre use: Not stated / Unclear 3. Type of ultra clean air flow system: Mixed type (n=10,466) Intervention 2: Conventional air flow theatres. Non laminar flow ventilation systems installed from 1990 and 2004. . Duration During joint replacement surgery. Concurrent medication/care: Background treatment dependent on local policy in the hospital and a person's specific clinical needs. Indirectness: No indirectness Further details: 1. Size of the vertical laminar airflow area:: Not applicable 2. Theatre use: Not stated / Unclear 3. Type of ultra clean air flow system: Not applicable
Funding	Academic or government funding (German national nosocomial infection surveillance system (KISS) is supported by the German Ministry of Health)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ULTRA CLEAN-AIR THEATRES versus CONVENTIONAL AIR FLOW THEATRES Protocol outcome 1: Deep surgical site infection at 1 month	

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- Actual outcome: Severe surgical site infection at Unclear; OR; 1.1 (95%CI 0.56 to 2.17, Comments: Adjusted for sex, age, duration of operation, ASA score); Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Key confounders: Space suits not mentioned; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day ; Quality of life at 1 month; Superficial surgical site infection at 1 month; Return to theatre at within 3 months; Hospital readmissions at within 90 days; Length of stay at time until hospital discharge

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Study	Breier 2011-2[14]
Study type	Non randomised study
Number of studies (number of participants)	1 (n=7749)
Countries and setting	Conducted in Germany; Setting: Data from 41 hospitals in Germany.
Line of therapy	Adjunctive to current care
Duration of study	Not clear:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: People who have undergone hip replacement due to trauma
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People who have had primary hip joint replacement due to trauma
Exclusion criteria	Revision joint replacement surgeries were not included in the analysis.
Recruitment/selection of patients	The data utilised for this analysis came from the KISS surveillance in Germany.
Age, sex and family origin	Age - --: Not reported. Sex (M:F): 2090/5659. Family origin: Not reported
Indirectness of population	No indirectness
Interventions	(n=6,513) Intervention 1: Ultra clean-air theatres . Laminar airflow system. Duration During joint replacement surgery. Concurrent medication/care: Background treatment dependent on local policy in the hospital and a person's specific clinical needs. Indirectness: No indirectness Further details: 1. Size of the vertical laminar airflow area:: Mixed airflow area 2. Theatre use: Not stated / Unclear 3. Type of ultra clean air flow system: Mixed type (n=1,236) Intervention 2: Conventional air flow theatres. Non laminar flow ventilation systems installed from 1990 and 2004. . Duration During joint replacement surgery. Concurrent medication/care: Background treatment dependent on local policy in the hospital and a person's specific clinical needs. Indirectness: No indirectness Further details: 1. Size of the vertical laminar airflow area:: Not applicable 2. Theatre use: Not stated / Unclear 3. Type of ultra clean air flow system: Not applicable
Funding	Academic or government funding (German national nosocomial infection surveillance system (KISS) is supported by the German Ministry of Health)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ULTRA CLEAN-AIR THEATRES versus CONVENTIONAL AIR FLOW THEATRES Protocol outcome 1: Deep surgical site infection at 1 month	

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- Actual outcome: Severe surgical site infection at Unclear; OR; 1.28 (95%CI 0.67 to 2.43, Comments: Adjusted for sex, age, duration of operation, ASA score); Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Key confounders: Space suits not mentioned; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day ; Quality of life at 1 month; Superficial surgical site infection at 1 month; Return to theatre at within 3 months; Hospital readmissions at within 90 days; Length of stay at time until hospital discharge

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Study	Breier 2011-2[14]
Study type	Non-randomised study
Number of studies (number of participants)	1 (n=20,554)
Countries and setting	Conducted in Germany; Setting: Data from 38 hospitals in Germany.
Line of therapy	Adjunctive to current care
Duration of study	Not clear:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: People undergoing knee prosthesis procedures
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People who have had primary knee joint replacement
Exclusion criteria	Revision joint replacement surgeries were not included in the analysis.
Recruitment/selection of patients	The data utilised for this analysis came from the KISS surveillance in Germany.
Age, sex and family origin	Age - --: Not detailed. Sex (M:F): 6559/13995. Family origin: Not reported
Indirectness of population	No indirectness
Interventions	(n=14,456) Intervention 1: Ultra clean-air theatres . Laminar airflow system. Duration During joint replacement surgery. Concurrent medication/care: Background treatment dependent on local policy in the hospital and a person's specific clinical needs. Indirectness: No indirectness Further details: 1. Size of the vertical laminar airflow area:: Mixed airflow area (Specific laminar flow size data available if required). 2. Theatre use: Not stated / Unclear 3. Type of ultra clean air flow system: Mixed type (n=6,098) Intervention 2: Conventional air flow theatres. Non laminar flow ventilation systems installed from 1990 and 2004. . Duration During joint replacement surgery. Concurrent medication/care: Background treatment dependent on local policy in the hospital and a person's specific clinical needs. Indirectness: No indirectness Further details: 1. Size of the vertical laminar airflow area:: Not applicable 2. Theatre use: Not stated / Unclear 3. Type of ultra clean air flow system: Not applicable
Funding	Academic or government funding (German national nosocomial infection surveillance system (KISS) is supported by the German Ministry of Health)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ULTRA CLEAN-AIR THEATRES versus CONVENTIONAL AIR FLOW THEATRES	

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Protocol outcome 1: Deep surgical site infection at 1 month - Actual outcome: Severe surgical site infection at Unclear; OR; 0.95 (95%CI 0.37 to 2.41, Comments: Adjusted for sex, age, duration of operation, ASA score); Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Key confounders: Space suits not mentioned; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day ; Quality of life at 1 month; Superficial surgical site infection at 1 month; Return to theatre at within 3 months; Hospital readmissions at within 90 days; Length of stay at time until hospital discharge

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Study	Dale 2009[18]
Study type	Non-randomised study
Number of studies (number of participants)	1 (n=97,344)
Countries and setting	Conducted in Norway; Setting:
Line of therapy	Part of comparison
Duration of study	Follow up (post intervention): 0-20 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: People who underwent primary total hip replacement
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People who underwent primary total hip replacement.
Exclusion criteria	In order to have homogeneous subgroups concerning type of fixation, 4,392 hybrids and 3,727 reversed hybrids were excluded. 3,730 arthroplasties had incomplete data on fixation method or were registered with different brands of cement for different components, and were also excluded. 1,689 additional THAs were excluded because of missing values for other adjustment variables.
Recruitment/selection of patients	Norwegian Arthroplasty Register (NAR) data utilised. From September 15th 1987 to January 1st 2008.
Age, sex and family origin	Age - --: Not detailed. Sex (M:F): 70% male, 30% female. Family origin: Not detailed
Indirectness of population	No indirectness
Interventions	(n=45,620) Intervention 1: Ultra clean-air theatres . Laminar flow ventilation. Duration During joint replacement surgery. Concurrent medication/care: Background treatment depended on local hospital guidelines. Indirectness: No indirectness Further details: 1. Size of the vertical laminar airflow area:: Not stated / Unclear 2. Theatre use: Not stated / Unclear 3. Type of ultra clean air flow system: Not stated / Unclear (n=48,338) Intervention 2: Conventional air flow theatres. Reported as ordinary airflow ventilation. Duration During joint replacement surgery. Concurrent medication/care: Background treatment depended on local hospital guidelines. Indirectness: No indirectness Further details: 1. Size of the vertical laminar airflow area: Not applicable 2. Theatre use: Not stated / Unclear 3. Type of ultra clean air flow system: Not applicable
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ULTRA CLEAN-AIR THEATRES versus CONVENTIONAL AIR FLOW THEATRES	

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Protocol outcome 1: Return to theatre at within 3 months - Actual outcome: Revision due to infection at within 1 year of surgery; RR; 1.3 (95%CI 1.1 to 1.5, Comments: Adjusted risk ratio estimates for sex, age, diagnosis, type of prosthesis, duration of operation, antibiotic prophylaxis systemically, and type of fixation); Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Key confounders: No mention of space suits; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day ; Quality of life at 1 month; Superficial surgical site infection at 1 month; Deep surgical site infection at 1 month; Hospital readmissions at within 90 days; Length of stay at time until hospital discharge

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Study	Fitzgerald jr 1992[20]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=5,868)
Countries and setting	Conducted in USA; Setting: Wayne State University School of Medicine, Detroit, USA. All procedures performed by one group of surgeons with standardised protocols.
Line of therapy	Adjunctive to current care
Duration of study	Follow up (post intervention): 1 year to 8 years.
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Primary hip or knee joint replacement
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Define
Exclusion criteria	Define
Age, sex and family origin	Age - --: Not detailed. Sex (M:F): Define. Family origin: Not detailed
Indirectness of population	No indirectness
Interventions	(n=2,848) Intervention 1: Ultra clean-air theatres . Horizontal ultra clean-air theatre. Duration During joint replacement surgery. Concurrent medication/care: Prophylactic antibiotic therapy utilised. Traffic in theatre controlled. . Indirectness: No indirectness Further details: 1. Size of the vertical laminar airflow area:: Not stated / Unclear 2. Theatre use: Not stated / Unclear 3. Type of ultra clean air flow system: horizontal laminar (n=3,202) Intervention 2: Conventional air flow theatres. Conventional ventilated operating room with turbulent airflow. Duration During joint replacement surgery. Concurrent medication/care: Prophylactic antibiotic therapy utilised. Traffic in theatre controlled. . Indirectness: No indirectness Further details: 1. Size of the vertical laminar airflow area:: Not applicable 2. Theatre use: Not stated / Unclear 3. Type of ultra clean air flow system: Not applicable
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ULTRA CLEAN-AIR THEATRES versus CONVENTIONAL AIR FLOW THEATRES Protocol outcome 1: Deep surgical site infection at 1 month - Actual outcome: Deep surgical site infection at From 1 to 8 years follow-up; Group 1: 8/2848, Group 2: 10/3202 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low,	

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Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day ; Quality of life at 1 month; Superficial surgical site infection at 1 month; Return to theatre at within 3 months; Hospital readmissions at within 90 days; Length of stay at time until hospital discharge

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Study (subsidiary papers)	Lidwell 1982[35] (Lidwell 1987[33])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=8136)
Countries and setting	Conducted in Sweden, United Kingdom; Setting: Hospitals in England (11), Scotland (4), and Sweden (4)
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: 4 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: People undergoing total hip or knee joint replacement
Stratum	Overall
Subgroup analysis within study	Post-hoc subgroup analysis: People administered prophylactic antibiotics
Inclusion criteria	People undergoing total hip or knee joint replacement.
Exclusion criteria	None detailed
Recruitment/selection of patients	Recruited from 1974 until 1979.
Age, gender and ethnicity	Age - --: Not detailed. Gender (M:F): Not detailed. Ethnicity: Not detailed
Further population details	
Indirectness of population	No indirectness
Interventions	(n=1279) Intervention 1: Ultra clean-air theatres . Ultra-clean air operating theatres. . Duration Operative period. Concurrent medication/care: Conventional clothing. All people in this subgroup were given prophylactic antibiotics. . Indirectness: No indirectness Further details: 1. Size of the vertical laminar airflow area:: Not stated / Unclear 2. Theatre use: Not stated / Unclear 3. Type of ultra clean air flow system: Not applicable (Mixed). (n=2968) Intervention 2: Conventional air flow theatres. Operating theatre with positive-pressure air supply.. Duration During surgery. Concurrent medication/care: Conventional operating-room clothing. Prophylactic antibiotics utilised. . Indirectness: No indirectness Further details: 1. Size of the vertical laminar airflow area:: Not stated / Unclear 2. Theatre use: Not stated / Unclear 3. Type of ultra clean air flow system: Not applicable (Mixed). (n=3922) Intervention 3: Ultra clean-air theatres . Ultra-clean air operating theatres. . Duration Operative period. Concurrent medication/care: Some hospitals utilised body exhaust ventilated suits for the operation. Prophylactic antibiotics given as decided by surgeon. . Indirectness: No indirectness Further details: 1. Size of the vertical laminar airflow area:: Not stated / Unclear 2. Theatre use: Not stated / Unclear 3. Type of ultra clean air flow system: Not stated / Unclear

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	(n=4133) Intervention 4: Conventional air flow theatres. Operating theatre with positive-pressure air supply.. Duration During surgery. Concurrent medication/care: Conventional operating-room clothing. Prophylactic antibiotic use decided by surgeon. Indirectness: No indirectness Further details: 1. Size of the vertical laminar airflow area:: Not applicable 2. Theatre use: Not stated / Unclear 3. Type of ultra clean air flow system: Not applicable (n=2863) Intervention 5: Ultra clean-air theatres . Ultra-clean air operating theatres. . Duration Operative preiod. Concurrent medication/care: Everyone in this group was given prophylactic antibiotics. Indirectness: No indirectness Further details: 1. Size of the vertical laminar airflow area:: Not stated / Unclear 2. Theatre use: Not stated / Unclear 3. Type of ultra clean air flow system: Not stated / Unclear
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ULTRA CLEAN-AIR THEATRES: ANTIBIOTICS & CONVENTIONAL CLOTHING versus CONVENTIONAL AIR FLOW THEATRES: ANTIBIOTICS

Protocol outcome 1: Deep surgical site infection at 1 month
- Actual outcome: Confirmed sepsis at at a median of 2.5 years; Group 1: 9/1279, Group 2: 24/2968
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ULTRA CLEAN-AIR THEATRES versus CONVENTIONAL AIR FLOW THEATRES

Protocol outcome 1: Deep surgical site infection at 1 month
- Actual outcome: Confirmed sepsis at at a median of 2.5 years; Group 1: 3922/23, Group 2: 4133/63
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - High, Other 1 - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ULTRA CLEAN-AIR THEATRES: ANTIBIOTICS & ANY CLOTHING versus CONVENTIONAL AIR FLOW THEATRES: ANTIBIOTICS

Protocol outcome 1: Deep surgical site infection at 1 month
- Actual outcome: Confirmed sepsis at at a median of 2.5 years; Group 1: 2863/10, Group 2: 2968/24
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcomes not reported by the	Mortality at 30 day ; Quality of life at 1 month; Superficial surgical site infection at 1 month; Return to theatre

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study	at within 3 months; Hospital readmissions at within 90 days; Length of stay at time until hospital discharge

Study	**Namba 2012[46]**
Study type	Non-randomised study

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Number of studies (number of participants)	1 (n=30,491)
Countries and setting	Conducted in USA; Setting: 46 medical centres in six regions in the United States. Data from Kaiser Permanente Total Joint Replacement Registry (TJRR)
Line of therapy	Part of comparison
Duration of study	Follow up (post intervention): 1 year postoperative follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: People who underwent total hip replacement
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Primary elective total hip replacements
Exclusion criteria	None detailed
Recruitment/selection of patients	All primary elective THRs registered in the TJRR from 1st April 2001 until 30th December 2009 2001 and 30 December 2009
Age, sex and family origin	Age - Mean (SD): 65.5 (11.8). Sex (M:F): 13017/17474. Family origin: Not detailed
Indirectness of population	No indirectness
Interventions	(n=8,478) Intervention 1: Ultra clean-air theatres . Laminar flow operating theatres. Duration During THR surgery. Concurrent medication/care: Background treatment was local orthpaedic centre policy. Indirectness: No indirectness Further details: 1. Size of the vertical laminar airflow area:: Not stated / Unclear 2. Theatre use: Not stated / Unclear 3. Type of ultra clean air flow system: Not stated / Unclear (n=22,013) Intervention 2: Conventional air flow theatres. No details, defined as not laminar flow. Duration During THR surgery. Concurrent medication/care: Background treatment was local orthpaedic centre policy. Indirectness: No indirectness Further details: 1. Size of the vertical laminar airflow area:: Not applicable 2. Theatre use: Not stated / Unclear 3. Type of ultra clean air flow system: Not applicable
Funding	Academic or government funding (No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article).
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ULTRA CLEAN-AIR THEATRES versus CONVENTIONAL AIR FLOW THEATRES Protocol outcome 1: Deep surgical site infection at 1 month - Actual outcome: Deep surgical site infection	

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at 1 year postoperatively; HR; 1.08 (95%CI 0.77 to 1.53, Comments: Univariate Cox's proportional hazard regression model. All variables found to be independently associated with the outcome were included in the multivariable Cox models but laminar flow was not. Factors investigated: age, sex, race, body mass index (BMI), weight, diabetic status, ASA score, diagnosis (osteoarthritis, rheumatoid arthritis, post-traumatic arthritis, osteonecrosis, and other), yearly volumes for hospitals, surgeon annual volume, surgeon arthroplasty fellowship training status, unilateral or bilateral procedure, anaesthesia (epidural, general, spinal, other), infection prophylaxis, use of a body exhaust system, surgical approach and duration of surgery); Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day ; Quality of life at 1 month; Superficial surgical site infection at 1 month; Return to theatre at within 3 months; Hospital readmissions at within 90 days; Length of stay at time until hospital discharge

Study	**Pedersen 2010[53]**
Study type	Non randomised study
Number of studies (number of participants)	1 (n=80,756)

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Countries and setting	Conducted in Denmark; Setting: All orthopedics departments performing total hip replacement, including private hospitals from Jan 1st 1995 to Dec 31st 2008. Danish Hip Arthroplasty Registry data
Line of therapy	Part of comparison
Duration of study	Other: Data on surgery undertaken Jan 1st 1995 and Dec 31st 2008.
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: People who underwent total hip athroplasty
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People undergoing primary total hip arthrosplasty
Exclusion criteria	None detailed
Recruitment/selection of patients	Nationwide clinical database of all primary THAs performed in Denmark
Age, sex and family origin	Age - Other: median group 70-79. Sex (M:F): 33925/46831. Family origin: Not detailed
Indirectness of population	No indirectness
Interventions	(n=72,423) Intervention 1: Ultra clean-air theatres . Laminar air flow ventilation. Duration During joint replacement surgery. Concurrent medication/care: Followed local orthopaedic department policy. Indirectness: No indirectness Further details: 1. Size of the vertical laminar airflow area:: Not stated / Unclear 2. Theatre use: Not stated / Unclear 3. Type of ultra clean air flow system: Not stated / Unclear (n=8,333) Intervention 2: Conventional air flow theatres. Conventional ventilation. Duration During joint replacement surgery. Concurrent medication/care: Followed local orthopaedic department policy. Indirectness: No indirectness Further details: 1. Size of the vertical laminar airflow area:: Not applicable 2. Theatre use: Not stated / Unclear 3. Type of ultra clean air flow system: Not applicable
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ULTRA CLEAN-AIR THEATRES versus CONVENTIONAL AIR FLOW THEATRES

Protocol outcome 1: Deep surgical site infection at 1 month
- Actual outcome: Revision due to infection at Median follow-up: 4.6 years (0-14); RR; 0.9 (95%CI 0.7 to 1.14, Comments: Adjusted for type of anaesthesia, ossification prophylactic treatment, duration of surgery, fixation technique, previous surgery to same hip, primary diagnosis for THA, Charlson co-morbidity index, age, sex, calendar year of surgery.
);
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

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- Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day ; Quality of life at 1 month; Superficial surgical site infection at 1 month; Return to theatre at within 3 months; Hospital readmissions at within 90 days; Length of stay at time until hospital discharge

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Study	Pinder 2016[54]
Study type	Non-randomised study
Number of studies (number of participants)	1 (n=114,967)
Countries and setting	Conducted in United Kingdom; Setting: 184 NHS hospitals were surveyed
Line of therapy	Part of comparison
Duration of study	Follow up (post intervention): Outcome follow-up was 90 days after surgery
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: People undergoing hip arthroplasty
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People undergoing hip arthroplasty
Exclusion criteria	Hospitals where <20 hemiarthroplasties performed annually, elective hospitals, children's hospitals, treatmen centres, non orthpaedic hospitals.
Recruitment/selection of patients	Questionnaires sent to 184 NHS hospitals who conduct orthopaedic trauma surgery
Age, sex and family origin	Age - Other: Not detailed. Sex (M:F): Not detailed. Family origin: Not detailed
Indirectness of population	No indirectness
Interventions	(n=73,112) Intervention 1: Ultra clean-air theatres . Laminar flow ventilation utilised throughout the study period for hemiarthroplasty. Duration During hemiarthroplasty. Concurrent medication/care: Dependent on the hospital policy. Indirectness: No indirectness Further details: 1. Size of the vertical laminar airflow area:: Not stated / Unclear 2. Theatre use: Not stated / Unclear 3. Type of ultra clean air flow system: Not stated / Unclear (n=12,497) Intervention 2: Conventional air flow theatres. Plenum ventilation throughout the study period.. Duration During hemiarthroplasty surgery. Concurrent medication/care: Dependent on the hospital policy. Indirectness: No indirectness Further details: 1. Size of the vertical laminar airflow area:: Not applicable 2. Theatre use: Not stated / Unclear 3. Type of ultra clean air flow system: Not applicable
Funding	No funding (No funding from a commercial entity.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ULTRA CLEAN-AIR THEATRES versus CONVENTIONAL AIR FLOW THEATRES Protocol outcome 1: Deep surgical site infection at 1 month - Actual outcome: Surgical Site Infection at Within 90 days; OR; 1.45 (95%CI 1.17 to 1.8) ( ) , Comments: Confounding variables adjusted for in analysis	

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though it is unclear what these factors were. The following factors were mentioned: age, sex, Charlson co-morbidity index, socio-economic deprivation, and number of trauma operations performed.; Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day ; Quality of life at 1 month; Superficial surgical site infection at 1 month; Return to theatre at within 3 months; Hospital readmissions at within 90 days; Length of stay at time until hospital discharge

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Study	Song 2012[59]
Study type	RCT (randomised; Parallel)
Number of studies (number of participants)	1 (n=6,848)
Countries and setting	Conducted in South Korea; Setting:
Line of therapy	Part of comparison
Duration of study	Follow up (post intervention): At least 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: People who underwent total knee arthroplasty of total hip arthroplasty
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People who underwent total knee arthroplasty of total hip arthroplasty. All hospitals must have had 1 full-time infection control practitioner on staff.
Exclusion criteria	People having preoperative antibiotics for infections.
Recruitment/selection of patients	26 hospitals participating in the Korean Nosocomial Infections Surveillance System (KONIS).
Age, sex and family origin	Age - --: Not detailed. Sex (M:F): Not detailed. Family origin: Not detailed
Indirectness of population	No indirectness
Interventions	(n=4,188) Intervention 1: Ultra clean-air theatres . High-efficiency particulate air HEPA-filtered laminar airflow ventilation. Duration Airflow during joint replacement surgery. Concurrent medication/care: Antimicrobial prophylaxis administered. . Indirectness: No indirectness Further details: 1. Size of the vertical laminar airflow area:: Not stated / Unclear 2. Theatre use: Not stated / Unclear 3. Type of ultra clean air flow system: Not stated / Unclear (n=2,086) Intervention 2: Conventional air flow theatres. Conventional turbulent ventilation with HEPA-filtered air. Duration Airflow during joint replacement surgery. Concurrent medication/care: Parenteral antimicrobial prophylactic antibiotics were administered. Indirectness: No indirectness Further details: 1. Size of the vertical laminar airflow area:: Not applicable 2. Theatre use: Not stated / Unclear 3. Type of ultra clean air flow system: Not applicable
Funding	Academic or government funding (The Korean Nosocomial Infections Surveillance System is supported by a grant from the Korean Centers for Disease Control and Prevention.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ULTRA CLEAN-AIR THEATRES versus CONVENTIONAL AIR FLOW THEATRES Protocol outcome 1: Deep surgical site infection at 1 month	

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- Actual outcome: Severe surgical site infection at 1 year after surgery; OR; Not significant, Comments: Stepwise multiple logistic model used. Risk factors with a p value of less than 0.1 were included in the initial model. p values of less than 0.5 were considered statistically significant in multivariate analysis. Factors included: surgeries performed each month, OR airflow, sex, preoperative hospital stay, diabetes, anaesthesia, revision surgery, duration of surgery, trauma, other infections. ; Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day ; Quality of life at 1 month; Superficial surgical site infection at 1 month; Return to theatre at within 3 months; Hospital readmissions at within 90 days; Length of stay at time until hospital discharge

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Appendix E: Forest plots

E.1 Randomised controlled trial evidence

Figure 2: Deep surgical site infection

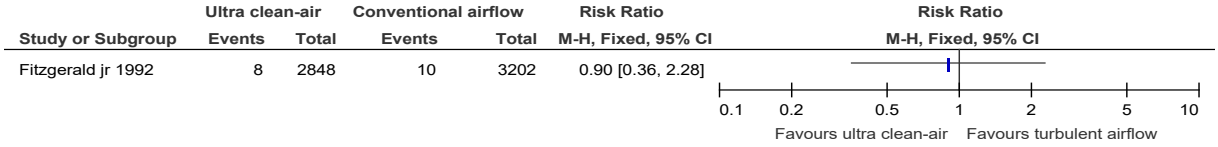


Figure 3: Confirmed sepsis: original randomised groups

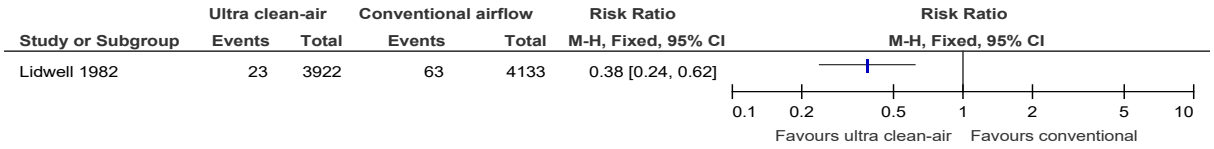


Figure 4: Confirmed sepsis: subgroup analysis of people given preoperative antibiotics and operating room staff wore either body exhaust suits or conventional clothing

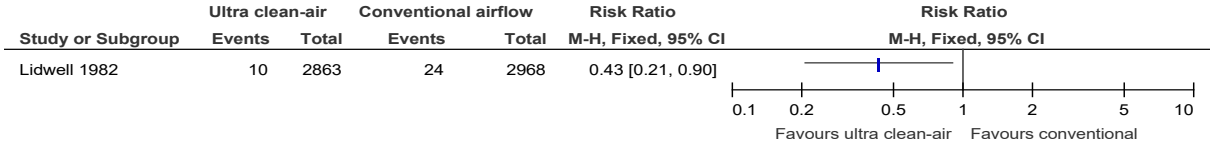
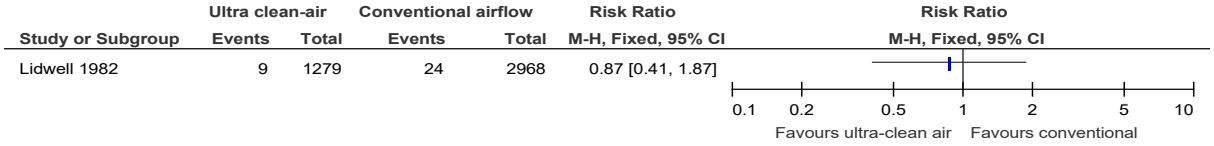


Figure 5: Confirmed sepsis: subgroup analysis of people given preoperative antibiotics and operating room staff wore conventional clothing



E.2 Observational study evidence

Figure 6: Revisions due to infection

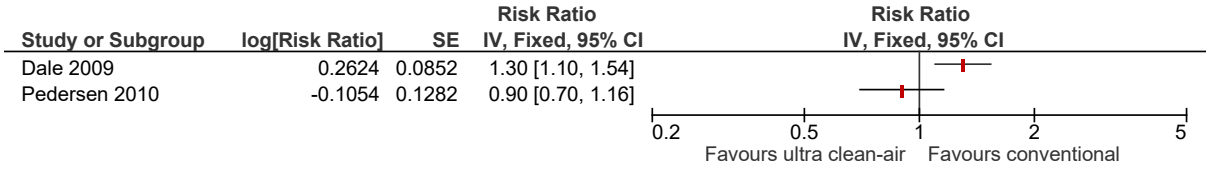


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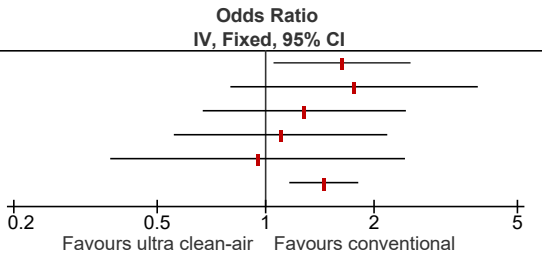
Figure 7: Deep surgical site infection

Study or Subgroup	log[Odds Ratio]	SE	Odds Ratio IV, Fixed, 95% CI
Brandt 2008-hip JR	0.48858	0.220916	1.63 [1.06, 2.51]
Brandt 2008-knee JR	0.565314	0.400821	1.76 [0.80, 3.86]
Breier 2011-hip frac JR	0.24686	0.328666	1.28 [0.67, 2.44]
Breier 2011-hip JR	0.09531	0.345547	1.10 [0.56, 2.17]
Breier 2011-knee JR	-0.05129	0.47803	0.95 [0.37, 2.42]
Pinder 2016	0.371564	0.109894	1.45 [1.17, 1.80]



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Appendix F: GRADE tables

Table 11: Clinical RCT evidence profile: ultra clean-air versus conventional ventilation

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ultra clean-air theatres	Conventional air flow theatres	Relative (95% CI)	Absolute		
Confirmed sepsis (follow-up median 2.5 years)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	23/3922 (0.59%)	63/4133 (1.5%)	RR 0.38 (0.24 to 0.62)	9 fewer per 1000 (from 6 fewer to 12 fewer)	⊕OOO VERY LOW	CRITICAL
Confirmed sepsis: subgroup analysis of people who had antibiotics and any clothing was worn by operating room staff (follow-up median 2.5 years)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	10/2863 (0.35%)	24/2968 (0.81%)	RR 0.43 (0.21 to 0.9)	5 fewer per 1000 (from 1 fewer to 6 fewer)	⊕OOO VERY LOW	CRITICAL
Confirmed sepsis: subgroup analysis of people who had antibiotics and conventional clothing was worn by operating room staff (follow-up median 2.5 years)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	9/1279 (0.7%)	24/2968 (0.81%)	RR 0.87 (0.41 to 1.87)	1 fewer per 1000 (from 5 fewer to 7 more)	⊕OOO VERY LOW	CRITICAL
Deep surgical site infection (follow-up 1-8 years)												
1	randomised	serious[1]	no serious	no serious	very serious[3]	none	8/2848	10/3202	RR 0.9 (0.36	0 fewer per 1000 (from 2 fewer to 4	⊕OOO VERY	CRITICAL

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	trials		inconsistency	indirectness			(0.28%)	(0.31%)	to 2.28)	more)	LOW	

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] Usage of prophylactic antibiotics or body exhaust suits was not standardised across that trial. Both affect the outcome.
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

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Appendix G: Health economic evidence selection

Figure 8: Flow chart of health economic study selection for the guideline

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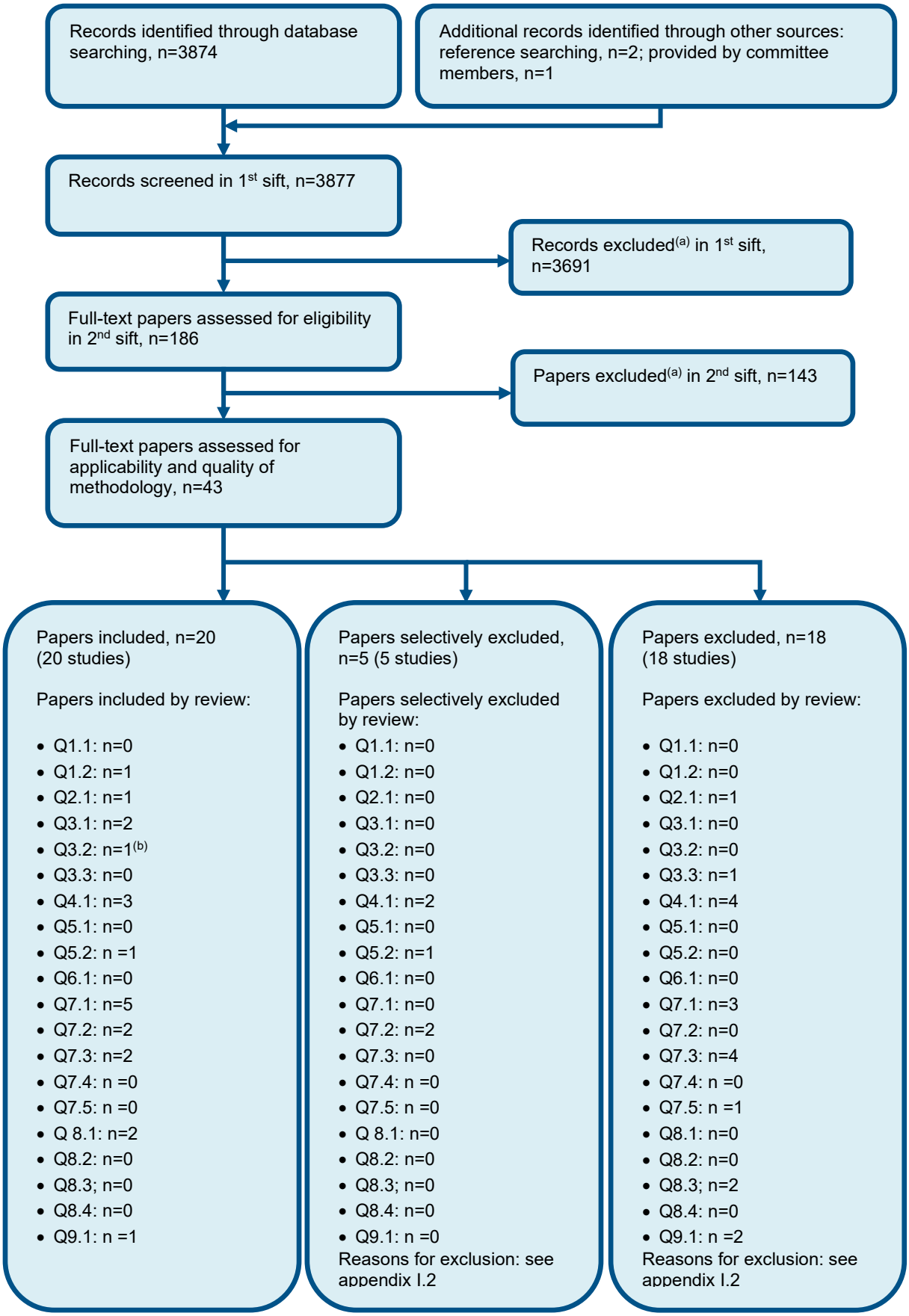

a) Non-relevant population, intervention, comparison, design or setting; non-English language
b) One study was applicable to both Q3.1 and Q3.2

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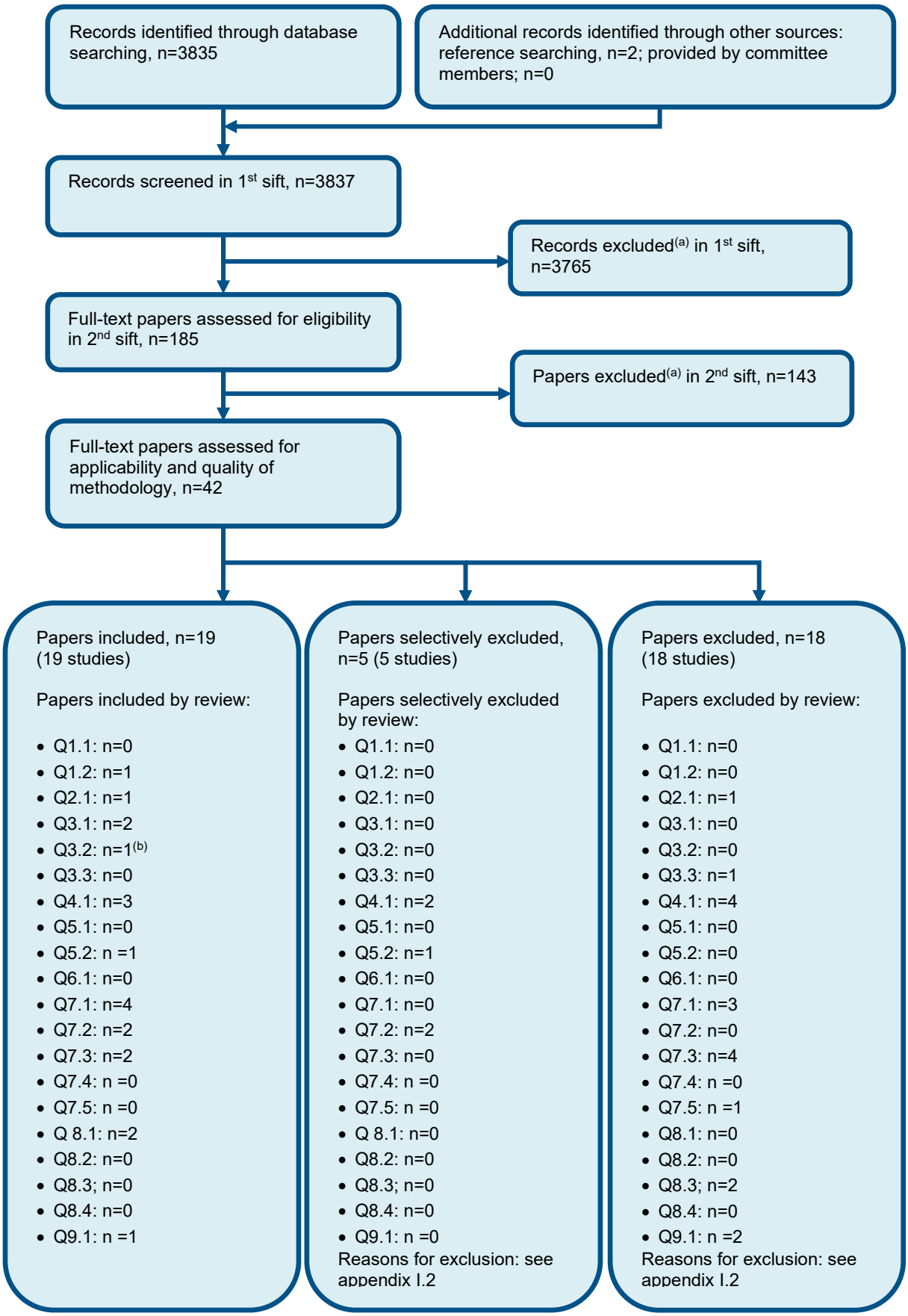

c) Non-relevant population, intervention, comparison, design or setting; non-English language
d) One study was applicable to both Q3.1 and Q3.2

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Appendix H: Health economic evidence tables

Study	Graves 2016[24]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost-utility analysis **Study design:** Probabilistic decision analytic model **Approach to analysis:** Individual patient simulation with a Markov model structure to compare competing approaches to managing the risk of SSI. People who get a deep infection will receive either one of the standard treatment options (DAIR, one-stage revision or two-stage revision) or permanent resection for severe cases. **Perspective:** UK NHS **Time horizon**: 5 years **Discounting:** Costs: 3%; Outcomes: 3%	**Population:** Adults >18 years old who underwent THR **Cohort settings:** 77,321 patients from the National Joint Registry in 2012. Mean age: NR Female: NR **Interventions** **T1:** No systemic antibiotics, plain cement and conventional ventilation **T2:** Systemic antibiotics, plain cement and conventional ventilation **T3:** No systemic antibiotics, plain cement and laminar airflow **T4:** Systemic antibiotics, plain cement and laminar airflow **T5:** No systemic antibiotics, antibiotic-impregnated cement and conventional ventilation **T6:** Systemic antibiotics, antibiotic-impregnated cement and conventional ventilation **T7:** Systemic antibiotics, antibiotic-impregnated cement and laminar airflow **T8:** Systemic antibiotics, antibiotic-impregnated cement, conventional ventilation and body exhaust suit **T9:** Systemic antibiotics, antibiotic-impregnated cement, laminar ventilation and body exhaust suit	**Total costs (mean £ per patient) vs T1:** T2: -93.46, T3: -79.58, T4: -68.17, T5: -59.94, T6: -107.67, T7: -42.31, T8: -51.23, T9: 10.10 **Currency & cost year:** 2012 GBP (£) **Cost components incorporated:** NHS costs including intervention costs and costs of treating infections including revision surgery and hospital stay.	**QALYs (mean per patient) vs T1:** T2: 0.0013, T3: 0.0016, T4: 0.0015, T5: 0.0012, T6: 0.0019, T7: 0.0016, T8: 0.0014, T9: 0.0008	T6 dominated all other interventions (p=0.32) **Addition of laminar flow by set of co-interventions:** T3 vs T1: T3 dominates T4 vs T2: £115,041 per QALY gained T7 vs T6: T6 dominates T9 vs T8: T8 dominates **Analysis of uncertainty:** Probabilistic sensitivity analysis for the probability that T2-9 are cost saving, increases QALYs and are cost-effective, compared with T1. T2 and T5 had the greatest probability of being cost saving (96%). T6 had the greatest probability of increasing QALYs (70%) and being cost effective (32%).

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Data sources
Health outcomes: A network meta-analysis of 12 studies, of which 6 compared a laminar flow strategy with a conventional ventilation strategy; 4 of these are observational studies and 2 are RCTs. **Quality-of-life weights:** 15D HRQoL, AQoL and expert opinion sourced from published literature. **Cost sources:** Antibiotics commonly used in the NHS. Antibiotic impregnated cement and normal cement. Costs of laminar airflow construction and installation were £39,600-£59,400 and made from an estimation based in the USA for 2011-2012. Annual capital costs were made by assuming a 5-year lifetime. A typical caseload of 25 surgeries per week for 50 weeks of the year was assumed to find the laminar airflow cost per case. Costs of body exhaust suits also made from US data, as UK data was unavailable. Costs of treating infection from NHS Reference Costs 2012 to 2013, British National Formulary and published literature.
Comments
Source of funding: The National Institute for Health Research Health Technology Assessment programme and the Queensland Health Quality Improvement and Enhancement Programme. **Limitations:** The baseline risk of deep infection was from a very old study, Lidwell 1982 [35]; the costs for laminar flow units have been converted from US dollars as no UK data was available; 3 out of the 6 studies used to estimate laminar flow effect were not included in this guideline's clinical review because they did not adequately control for confounding and a fourth's population was orthopaedic surgery which is broader than just orthopaedic implants; utility values were not derived from EQ-5D.
Overall applicability:(a) Partially applicable **Overall quality:**(b) Potentially serious limitations

Abbreviations: 15D HRQoL; 15 dimension health related quality of life; AQoL: assessment quality of life; DAIR: debridement, antibiotics and implant retention; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); QALYs: quality-adjusted life years; SSI: surgical site infection; THR; total hip replacement

(a) Directly applicable / Partially applicable / Not applicable

(b) Minor limitations / Potentially serious limitations / Very serious limitations

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Appendix I: Excluded studies

I.1 Excluded clinical studies

Table 12: Studies excluded from the clinical review

Study	Exclusion reason
Agarwal 2017[1]	Inappropriate comparison
Aglietti 1973[2]	Observational study without adjustment for confounding factors
Aglietti 1974[3]	Observational study without adjustment for confounding factors
Agodi 2015[4]	Study investigates microbial air contamination rather than patient infection
Ahl 1995[5]	Study investigating air contamination
Andersson 2012[6]	Inappropriate comparison
Asaid 2013[7]	Inappropriate comparison
Babkin 2007[8]	Incorrect interventions
Benson 1975[9]	Non-comparative study
Bischoff 2017[10]	Incorrect population. Included studies were checked for inclusion in this evidence review.
Blom 2004[11]	Inappropriate comparison
Brady 1975[12]	Observational study without adjustment for confounding factors
Clarke 2004[16]	Study investigates microbial air contamination rather than patient infection
Curtis 2018[17]	Incorrect interventions
Darouiche 2017[19]	Incorrect interventions
Freeman 1977[21]	Observational study without adjustment for confounding factors
Gastmeier 2012[22]	Incorrect population. Included studies were checked for inclusion in this evidence review.
Gould 1974[23]	Observational study without adjustment for confounding factors
Gruenberg 2004[25]	Not review population
Hooper 2011[26]	Observational study without adjustment for confounding factors
Illingworth 2013[27]	Not a primary study
Irvine 1972[28]	Observational study without adjustment for confounding factors
Kakwani 2007[29]	Observational study without adjustment for confounding factors
Kelly 1996[30]	Not review population
Knobben 2006[31]	Incorrect interventions
Levent 2010[32]	Non-comparative study
Lidwell 1983[36]	Inappropriate comparison
Lidwell 1983[37]	Not a comparative study
Lidwell 1984[38]	Risk factors for sepsis
Lidwell 1985[34]	Inappropriate comparison
Maksimovic 2008[39]	Inappropriate comparison
Mandal 1980[40]	Observational study without adjustment for confounding factors
Marotte 1987[41]	Observational study without adjustment for confounding factors
Mchugh 2015[42]	Incorrect population. Included studies were checked for inclusion in this evidence review.
Miner 2007[44]	Observational study without adjustment for confounding factors

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Study	Exclusion reason
Minns 1979[45]	Non-comparative study
Nelson 1973[48]	Literature review
Nelson 1973[49]	Literature review
Nelson 1973[51]	Observational study without adjustment for confounding factors
Nelson 1980[50]	Observational study without adjustment for confounding factors
Pasquarella 2018[52]	Unclear if the population is having primary joint arthroplasty
Ritter 1980[55]	Observational study without adjustment for confounding factors
Salvati 1982[56]	Observational study with inadequate control of confounding factors
Singh 2017[57]	Observational study without adjustment for confounding factors
Singh 2017[58]	Observational study without adjustment for confounding factors
Stocks 2011[60]	Incorrect interventions
Whyte 1974[62]	Literature review
Whyte 1983[61]	Inappropriate comparison
Wiley 1973[63]	Observational study without adjustment for confounding factors
Wu 2013[64]	Not in English language

I.2 Excluded health economic studies

Table 13: Studies excluded from the health economic review

Reference	Reason for exclusion
Merollini 2013[43]	This study was selectively excluded because it was conducted by the same team as the Graves2016 NHS HTA [24] using similar methods and clinical effects but with an Australian perspective.

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