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Review

Antimicrobial prophylaxis in total hip replacement: a systematic review

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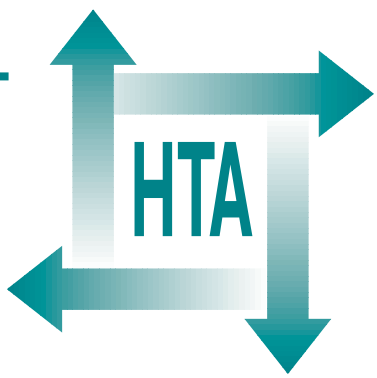
Health Technology Assessment
NHS R&D HTA Programme



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Antimicrobial prophylaxis in total hip replacement: a systematic review

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This report is one of a series covering acute care, diagnostics and imaging, methodology, pharmaceuticals, population screening, and primary and community care. It was identified as a priority by the Pharmaceutical Panel and funded as project number 94/29/01.

The views expressed in this publication are those of the authors and not necessarily those of the Standing Group, the Commissioning Board, the Panel members or the Department of Health. The editors wish to emphasise that funding and publication of this research by the NHS should not be taken as implicit support for the recommendations for policy contained herein. In particular, policy options in the area of screening will be considered by the National Screening Committee. This Committee, chaired by the Chief Medical Officer, will take into account the views expressed here, further available evidence and other relevant considerations.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

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Contents

List of abbreviations

b.d.	twice daily*
CI	confidence interval
df	degree of freedom*
ESR	erythrocyte sedimentation rate*
i.m.	intramuscularly*
ITT	intention to treat
i.v.	intravenously*
M/F	male/female*
NA	not available*
NS	not significant*
o.d.	once daily*
OT	operating theatre*
q.d.s.	four times daily*
RCT	randomised controlled trial
RR	relative risk
SD	standard deviation*
SWI	surgical wound infection
t.d.s.	three times daily*
THR	total hip replacement
TJR	total joint replacement*
TKR	total knee replacement
UTI	urinary tract infection*

* Used only in appendices and figures

Executive summary

Background

Total hip replacement (THR) has become one of the most successful and cost-effective operations ever introduced. The procedure has been practised widely in the UK for more than 25 years, with rates of THRs increasing all the time.

As with all surgery, THR has associated risks. These risks may include general risks such as vascular and/or neural injuries, thrombosis and infection. A recent survey of available data on hospital-acquired infections stated that one in 16 patients treated in hospital would develop an infection. Such hospital-acquired infections are thought to be costing the NHS in excess of £170 million in England alone.

Infection of a joint prosthesis can be devastating, increasing morbidity and hospitalisation. The role of antimicrobial prophylaxis in reducing infection rates is undisputed. However, uncertainty still remains over the choice of agent, the optimal duration, and mode of administration.

Objective

The aim of this review was to undertake a systematic review of the research evidence on the comparative efficacy and cost-effectiveness of antimicrobial prophylaxis used for patients undergoing a THR.

Methods

Data sources

Literature searches of the Cochrane Controlled Trials Register, MEDLINE and EMBASE were conducted to identify randomised controlled trials (RCTs) published between 1966 and 1998, which investigated antimicrobial prophylaxis in the prevention of postoperative wound infection following THR surgery. Reference lists of existing reviews in the area of antimicrobial prophylaxis in orthopaedic surgery were examined and experts in the field contacted to help identify further papers. Studies in all languages were considered.

Titles and abstracts of all studies identified by the searches were assessed by two reviewers to locate those that were potentially evaluations of antimicrobial prophylaxis in THR surgery.

Data extraction and validity

Data extraction and validity assessment were carried out by one reviewer and checked for accuracy by a second reviewer. Disagreements that could not be resolved through discussion were taken to a third party.

The principal outcome assessed in the review was the incidence of surgical wound infection (SWI). Data on systemic and remote infections, adverse events and resource use outcomes were also collected.

Data synthesis

Studies were grouped according to antimicrobial regimen used. Where appropriate, formal meta-analysis and investigation of heterogeneity among trials were conducted. If possible, the effect of antimicrobial prophylaxis was assessed according to the nature of the THR (i.e. primary or revision procedure) and the type of prosthesis used.

Results

A total of 25 RCTs were included in the review. The overall rate of SWI across all the included trials of antimicrobial prophylaxis for THR surgery was 1% (2.1% when total knee replacement (TKR) patients were included). *Staphylococcus aureus* and *Staphylococcus epidermidis* were the most frequently isolated pathogens in the trials included in the present review.

Trials of total joint replacement surgery have illustrated that SWI rates can be statistically significantly reduced when an antimicrobial is used prophylactically, compared with placebo or no intervention. However, trials to date provide inconclusive evidence on the optimal antimicrobial prophylaxis regimen. The comparative efficacy of antimicrobial prophylaxis for THR (and TKR) surgery was difficult to demonstrate, mainly due to the low infection rates and the small sample sizes of the trials.

Cephalosporins (first and second generation) were the most commonly studied antibiotics. There is no convincing evidence to suggest that third-generation cephalosporins are more effective than first- and second-generation cephalosporins in preventing SWIs in THR surgery.

The duration of the antimicrobial prophylactic regimen examined in the included trials varied from a single dose to a 14-day course. There is no evidence to suggest that administering antimicrobial prophylaxis for more than 1 day postoperatively reduces the number of infections following THR surgery. Extending the duration of a regimen for longer than 24 hours may not only be wasteful, but potentially hazardous in terms of toxicity, and the increased risk of developing bacterial resistance.

The antimicrobial prophylaxis examined in the review were administered parenterally, orally, or in antibiotic-loaded cement. The results of trials in this area are inconclusive. The cost and ease of administration should, therefore, be used to determine which route should be used.

Little information on the cost of the antibiotic regimens examined was provided in the RCTs included in the review.

It was not possible to carry out an assessment of the potential risk factors associated with total joint replacement surgery, due to inconsistencies in the reporting of such data within the included trials.

Conclusions

Antimicrobial prophylaxis is effective for the prevention of SWI in both TKR and THR surgery.

The efficacy of many of the regimens studied may be similar, and available data make it difficult to identify an optimal regimen. There is no convincing evidence to suggest that the new-generation cephalosporins are more effective at preventing postoperative SWI infections in THR/TKR surgery than the first-generation cephalosporins. Similarly, there is no convincing evidence to suggest that extending the duration of a regimen beyond 24 hours postoperatively reduces the number of SWI following THR/TKR surgery. Single-dose or short-term administration is not only as effective as long-term administration, but will lower overall costs and may reduce the risk of toxicity and the development of bacterial resistance.

Implications for policy

There is evidence to support the use of antimicrobial prophylaxis in elective THR. However, the universal acceptance of a fixed antimicrobial regimen should be avoided in order to minimise the development of antibiotic resistant bacteria. Guidelines, based on available research evidence, should be developed locally by surgeons, microbiologists and pharmacists, taking into account local sensitivities to organisms commonly implicated in wound infection post THR. Cost, patient acceptability and the minimisation of adverse effects should also be taken into consideration. Such guidelines should be constantly reviewed and updated, as no definitive version can be established.

Recommendations for research

No further small, under-powered trials examining antimicrobial prophylaxis for the prevention of SWI following THR/TKR should be funded. Given the low infection rates following THR/TKR surgery, and the possible changing pattern of bacteria resistance, it may not be cost-effective to carry out mega-trials of antimicrobial prophylaxis in this area. Future research needs to examine the risk factors that determine the level of SWIs in patients undergoing THR. Risk factors could be used to identify a high-risk group on whom trials of new or additional prophylactic measures could be performed. However, if such trials were to be undertaken they must be able to recruit sufficient patients to have the power to show a statistically significant difference.

Chapter 1
Background

Prevalence

Total hip replacement (THR) has become one of the most successful and cost-effective operations ever introduced.[1] The procedure has been practised widely in the UK for more than 25 years, with the rates of THRs increasing all the time. In 1989 it was estimated that around 60,000 primary and revision THRs were inserted per annum in the UK.[2] More recent data show that over 42,000 THRs were performed by the NHS in England alone during the period of 1994/95.[3]

THRs may be either primary or revision in nature. The revision of a THR is undertaken when a replacement fails due to the breaking, loosening or wearing of the prosthesis, or when the prosthesis becomes infected. It is thought that the demand for primary THRs will continue to increase because disease of the hip is age-related and life expectancy is increasing.[4] In addition to this, the number of revisions required will also increase. Indeed, as the length of life of those receiving hip replacements increases, revisions are forming a growing proportion of the total THR workload, accounting for 4.1% of procedures in 1980, rising to 12.1% in 1989/90.[5]

Principal underlying conditions necessitating THR

THR is performed primarily to relieve the joint pain, stiffness and deformity caused by arthropathies of the hip, namely osteoarthritis and rheumatoid arthritis. In approximately 50% of all patients undergoing a primary THR (including those for fractured neck of femur), the principal diagnosis is osteoarthritis. Surgery is not the only approach used in the management of such arthropathies of the hip. Medication, rehabilitation and surgery of varying complexities all play a role in symptom control and preservation and restoration of function.[5] There is little literature examining the appropriate indications for surgery, and there has been criticism over the lack of standardisation of criteria used by clinicians when considering THR. However, a recent set of patient referral appropriateness ratings and urgency rankings[6] may provide a useful tool for practitioners to rapidly assess the need, urgency and appropriateness of referral for THR.

Types of prostheses used

The number of hip joints available to surgeons is rapidly increasing, with over 60 different types available in the UK, ranging in cost from £250–2000.[7] The different types of hip replacements can be broadly categorised as follows:

- cemented THR, where the prosthesis is fixed by cement at both the acetabulum and femur
- cementless THR, where the prosthesis is not fixed by cement
- hybrid THR, where there is a cementless acetabulum but the prosthesis is fixed by cement at the femur.

A recent systematic review of total hip replacements highlights the problem that very few of the hip replacements in use in the UK have undergone proper, long-term evaluation.[4] The most thoroughly evaluated were the standard cemented implants, such as the Charnley and the Stanmore implants, which were shown to have the lowest long-term failure rates over 10–20 years follow-up. Both the Charnley and the Stanmore are amongst the cheaper of the implants, costing around £250–320 each.[7]

Infection following THR

As with any surgery, THR has associated risks. These risks may include general risks, such as vascular and/or neural injuries, thrombosis and infection. There are also more specific risks associated with surgical technique. The current review focuses on the incidence of infection following THR surgery. A recent survey of available data on hospital-acquired infections (the most common of which were SWIs and those of the urinary and respiratory tract) stated that one in 16 patients treated in hospital would develop an infection. Such hospital-acquired infections are thought to be costing the NHS in excess of £170 million in England alone.[8]

Infection of a joint prosthesis can be devastating, and while rarely causing death, infection is associated with increased morbidity and hospitalisation. Both ultraclean operating theatres and antimicrobial prophylaxis have been shown to reduce the incidence of wound infections following orthopaedic surgery.[9] Clinical trials have shown that antimicrobials reduce infection rates from between 5–8% to less than 1% when compared with placebo.[10,11] Although it is thought unlikely that in practice infection rates will be this low, the role of antimicrobial prophylaxis in reducing infection rates is undisputed. However, uncertainty still remains over the choice of agent, the optimal duration and the mode of administration.

Objective

The aim of this research was therefore to undertake a systematic review of the research evidence on the comparative efficacy and cost-effectiveness of antimicrobial prophylaxis used in patients undergoing a THR. (It should be noted that the following agents are not available in the UK: cefonicid, cefoperazone, ceforanide, cephalothin, dicloxacillin, lincomicin and nafcillin.)

Chapter 2
Methods

The review built on methods used during a systematic review of antimicrobial prophylaxis in colorectal surgery,[12,13] and was undertaken in collaboration with the Cochrane Musculoskeletal Injuries Group.

Search strategy

A search strategy was devised with the assistance of the Centre for Reviews and Dissemination information staff (appendix 1). This included searching electronic databases (Cochrane Controlled Trials Register, MEDLINE, EMBASE) up to November 1998. In addition, the reference lists of existing reviews in the area of antimicrobial prophylaxis in orthopaedic surgery were examined, and experts in the field were also contacted to help identify further papers. Studies in all languages were considered.

Inclusion criteria

Types of participants

All patients undergoing an elective THR, regardless of prostheses used, were included in the review (type of prosthesis was recorded when available). Both primary and revision procedures (see *Box 1*) were included in the review, and the results analysed separately where possible. Patients in whom the principal diagnosis was infection of the hip were excluded from the review.

Following the initial searches for trials, it became apparent that trials in this area often recruited both THR patients and total knee replacement (TKR) patients. Trials examining antimicrobial prophylaxis in both these patient groups were included, with the results for THR analysed separately where possible.

BOX 1: The definitions of THRs[5]

Primary THR	The replacement of the femoral head and the acetabulum.
Revision THR	The replacement of the acetabular or femoral components, or both, following the failure of a primary THR.

Types of intervention

Intervention was defined as any antimicrobial prophylaxis administered at the time of THR surgery. The antimicrobial agent used, and the mode and duration of administration were recorded. The type of operating theatre used (conventional/ultraclean) was also recorded.

Outcome measures

For a study to be included it had to report on wound infection, which was considered the primary outcome measure for the review. The definitions used (based on the USA Centres for Disease Control 1988 definitions) were:

- major deep wound infection – a deep SWI occurring at the incision site within 1 year and involving tissues or spaces at or beneath the fascial layer
- minor superficial wound infection – an infection occurring at the incision site within 30 days after surgery, involving the skin, subcutaneous tissue, or muscle located above the fascial layer.

It is noted that late prosthetic infections, the source of which is likely to be haematogenous, may occur after 1 year of surgery.[14] These were also recorded if reported.

Additional outcome measures included:

- mortality related to infection
- systemic infection (e.g. septicaemia)
- remote infection (e.g. urinary tract and respiratory tract infections)
- adverse effects
- resource use outcomes (e.g. length of hospital stay, reoperation, postoperative antibiotic therapy).

Study designs

All randomised controlled trials (RCTs) meeting the above inclusion criteria for participant and intervention type, and for outcome measures, were used to assess the efficacy of antimicrobial prophylaxis in THR. Data reported in the included studies on the cost-effectiveness of antimicrobial prophylaxis were also recorded, though no further analysis was undertaken on these data.

Identification of primary studies

Titles and, when available, abstracts of all studies identified by the searches were assessed by two reviewers to locate those that might be evaluations of antimicrobial prophylaxis in THR surgery. Full articles were obtained and, again, independently assessed by two reviewers to identify those meeting the inclusion criteria. Discrepancies were solved through discussion.

Validity assessment

Trials meeting the inclusion criteria were assessed for validity by one reviewer and checked by a second. Discrepancies were taken to a third party. Details of the following items were examined:

- What was the method of randomisation?
- Was an *a priori* calculation of sample size carried out?
- Was analysis carried out on an intention-to-treat (ITT) basis?
- Was the assessment of outcome blind?
- Were the groups comparable at baseline?
- Were inclusion/exclusion criteria clearly defined?
- What was the method of assessment of wound infection?
- What was the duration of follow-up?

Each item was individually scored using an adaptation of the system used by the Cochrane Musculoskeletal Injuries Group (see *Table 1*, page 5). A scale approach to validity assessment, providing an overall score for each trial, was not used because our main aim was to assess the internal validity of the trials. In addition, it has been demonstrated that different scales, when applied to the same RCT, can produce important differences in terms of quality assessment.[15]

Data extraction

Data were extracted by one reviewer using a predefined data extraction tool. This process was checked for accuracy by a second reviewer. If disagreements could not be resolved through discussion they were taken to a third party.

Data synthesis

Studies were grouped according to the antimicrobial regimen used. Where appropriate, formal meta-analysis and investigation of heterogeneity among trials were conducted using the Cochrane Collaboration's Metaview software (Revman®, v. 3.1). If possible, the effect of antimicrobial prophylaxis was assessed according to the nature of the THR (i.e. primary or revision procedure) and the type of prosthesis.

Chapter 3
Results

Over 1500 titles and abstracts were examined, of which 38 full articles were retrieved. A total of 25 RCTs, published in 32 articles, were identified as meeting the inclusion criteria for this review.[10,11,16–45] Details of the individual trials included in the review are shown in appendix 2. A list of excluded studies and reasons for exclusion is available in appendix 3.

The MEDLINE search identified the greatest number of included RCTs (84%), followed by the Cochrane Controlled Trials Register (80%) (see appendix 4). Of the four RCTs included in the review and not identified by the MEDLINE search, two were located through Cochrane Controlled Trials Register[11,18] and two through contact with experts in the field.[37,39]

Both THR patients and TKR patients were included in 15 of the identified RCTs,[16,19,24–27,32,34,35,37,38,40,42,43] only two of which presented data in a manner that enabled the results of the THR and TKR patients to be analysed separately.[32,34] The review's search strategy did not identify any RCTs that included TKR patients only. Over one-third of the RCTs were conducted in the USA, 16% in the UK and the remainder in Sweden, France, Italy, Germany, The Netherlands and Finland.

Quality of the studies

Table 1 provides a summary of the validity assessment of the 25 RCTs. (The results of the validity assessment for the individual trials, along with study details, are shown in appendix 2.) Only four trials used a truly concealed method of randomisation.[11,16,22,32] The number of patients randomised to a treatment arm within a trial ranged from 18 to 1600, with nearly half of all trials recruiting fewer than 100 patients to each arm. Only two trials gave details of an *a priori* calculation of sample size.[11,22] With regard to analysis, the majority of trials provided some discussion of withdrawals, however, only 36% included all randomised patients in the analysis. The proportion of trials in which the assessors of outcome were blinded to treatment status was low (28%), and the majority of studies did not discuss or did not adjust for confounding

TABLE 1 *Summary of validity assessment of included RCTs*

	Included RCTs (%)
A. Was randomisation of the study group blinded?	
0. States random, but no description, or quasi-randomisation	72
1. Small but real chance of disclosure of assignment	12
2. Method did not allow disclosure of assignment	16
B. Was an a priori calculation of sample size undertaken?	
0. No/not mentioned	92
1. Yes	8
C. Were the outcomes of patients who withdrew described and included in the analysis (ITT)?	
0. Not mentioned	32
1. States numbers and reasons for withdrawal, but analysis unmodified	32
2. Primary analysis based on all randomised cases	36
D. Were the assessors of outcome blinded to treatment status?	
0. Not mentioned/not done	56
1. Moderate chance of unblinding of assessors	16
2. Action taken to blind assessors, or outcomes such that bias is unlikely	28
E. Comparability of groups at baseline	
0. Large potential for confounding or not discussed	40
1. Confounding small; mentioned but not adjusted for	20
2. Unconfounded; good comparability of groups or confounding adjusted for	40
F. Was a placebo treatment assigned as part of the randomisation procedure?	
0. No	88
1. Yes	12
G. Were inclusion/exclusion criteria clearly defined?	
0. Not defined	12
1. Poorly defined	20
2. Well defined	68
H. Method of assessment of wound	
0. Not stated	8
1. Non-specific criteria; clinical decision	24
2. Definite criteria which might include a microbiological diagnosis	40
3. Microbiological diagnosis within a predetermined protocol	28
I. Duration of surveillance for wound infection	
0. Not stated	8
1. Less than 4 weeks	4
2. At least 4 weeks, but less than 2 years	60
3. At least 2 years	28

TABLE 2 *Number of quality items with highest possible score in the included trials*

No. of quality items with highest possible score*	Studies
6	Mauerhan, *et al.,* 1994[32]
5	Doyon, *et al.,* 1987,[11] Evrard, *et al.,* 1988[22]
4	Bryan, *et al.,* 1988,[16] Wollinsky, *et al.,* 1997[44]
3	McQueen, *et al.,* 1990,[34] Periti, *et al.,* 1994,[37] Vainionpää, *et al.,* 1988,[42] Wall, *et al.,* 1988[43]
2	Carlsson, *et al.,* 1977,[17] DeBenedictis, *et al.,* 1984,[19] Gunst, *et al.,* 1984,[23] Jones, *et al.,* 1987/88,[25–28] Schulitz, *et al.,* 1980[39]
1	Davies, *et al.,* 1986,[18] Josefsson, *et al.,* 1981/90/93,[29–31] Mollan, *et al.,* 1992,[35] Ritter, *et al.,* 1989,[38] Soave, *et al.,* 1986,[40] Suter, *et al.,* 1994,[41] Wymenga, *et al.,* 1992[45]
0	Heydemann & Nelson, 1986[24]

* *Out of a total of eight quality components*

factors (60%). In general, the inclusion criteria and method of wound assessment were well defined, though the definition of wound infection varied greatly between trials. Over 80% of trials followed patients for over 28 days, 28% included a follow-up period of at least 2 years.

When the use of placebo treatment (F) is not considered no trial scored the highest possible score for the eight remaining quality components (*Table 2*). Only three trials achieved the highest possible score for more than half of the eight quality components,[11,22,32] while 88% of the included trials achieved the highest possible score for less than 4 of the eight quality components.

Antimicrobial prophylaxis versus no antimicrobial prophylaxis/placebo

Lincomicin, cefuroxime, cefamandole, cephazolin and cloxacillin have all been compared with no antimicrobial prophylaxis,[23,39,44] or placebo,[11,17] for the prevention of SWI following either THR or TKR. The results of the individual trials are presented under their respective antimicrobial sections. Four of the five trials reported a reduction in wound infection rate for patients receiving antimicrobial prophylaxis, though the difference was statistically significant in only two trials (*Figure 1*). Pooling of the data from the five trials demonstrated a statistically significant reduction in SWIs in patients receiving antibiotic prophylaxis (SWI rate, 1.0% vs. 4.3%; relative risk (RR), 0.24; 95% confidence interval (CI), 0.14–0.43; number needed to treat, 30).

Different antimicrobial agents

A matrix illustrating the number of comparisons of antibiotics examined in the included RCTs is presented in appendix 5.

Cefonicid

Cefonicid is a second-generation cephalosporin, which is administered intravenously or intramuscularly. The bactericidal action of cefonicid results from inhibition of cell wall synthesis.

Cefonicid was studied in only one of the included RCTs.[19] The trial compared 3-day, prophylactic courses of cefonicid and cephazolin. During the follow-up period (4–12 months) no wound infection was identified in either the cefonicid patients ($n = 37$) or the cefamandole patients ($n = 39$).

Cefoperazone

Cefoperazone is a semisynthetic broad-spectrum cephalosporin. Its role as a prophylactic agent in comparison with cefotaxime has been examined in one RCT.[27] Infection rates were low in both groups, with no statistically significant differences between the two groups. Further details are presented under cefotaxime.

Ceforanide

Ceforanide, a semisynthetic parenteral cephalosporin, was compared with cephalothin in one RCT.[40] Both THR and TKR patients were included in the trial. The trial presents data on bone and plasma concentrations, but was too small to detect any differences in wound infection rates.

Cefotaxime

Cefotaxime is a semisynthetic broad-spectrum, third-generation, cephalosporin with good activity against Gram-negative bacteria.

Cefotaxime has been compared with cephazolin, cefoxitin, ticarcillin/clavulanic acid and cefoperazone in a series of three RCTs.[25–27] A fourth publication, combining the results from the three

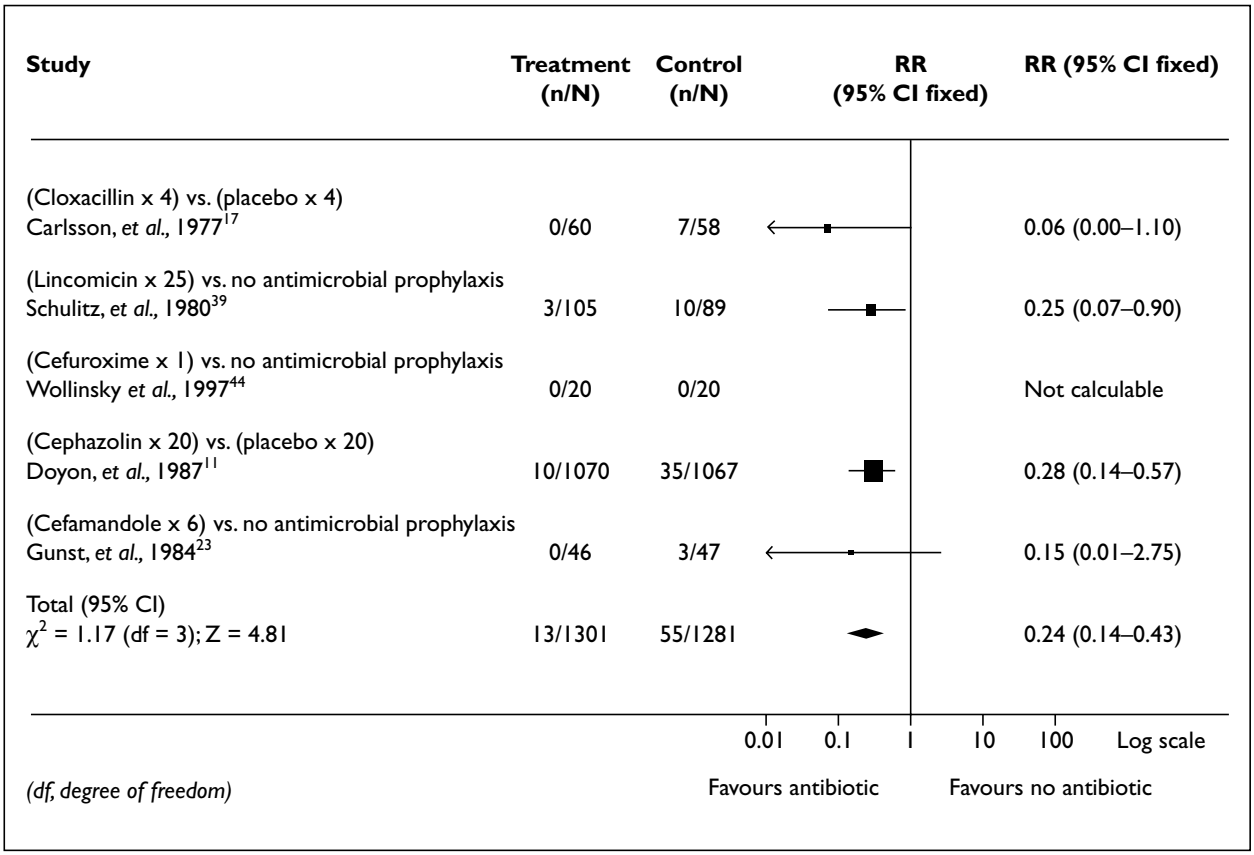

FIGURE 1 *Antimicrobial prophylaxis versus no antimicrobial prophylaxis/placebo*

trials, makes indirect comparisons between the antibiotics, using cefotaxime as the common factor in each trial.[28] All three trials included gastrointestinal, obstetrics and gynaecology, orthopaedic and other surgical procedures. Few data relating specifically to total joint replacement surgery are available in any of the publications. All regimens were found to be equally effective at preventing postoperative wound infections, though the number of total joint replacement patients was low, and the follow-up short (maximum of 30 days).

Cefoxitin

Cefoxitin is a second-generation, semisynthetic cephamycin antibiotic resistant to beta-lactamase.

Only one RCT examining the effectiveness of cefoxitin as a prophylactic agent in total joint replacement surgery was identified.[25] A multiple-dose regimen of cefoxitin was compared with single-dose cephazolin and cefotaxime. No statistically significant differences were demonstrated between infection rates for the three groups (see under cefotaxime).

Cefuroxime

Cefuroxime is a bactericidal, second-generation cephalosporin with a broad spectrum of activity. It is resistant to most beta-lactamases and active against many Gram-negative and Gram-positive organisms.

Seven RCTs examining cefuroxime were included in the review (*Figure 2*).[18,32,34,38,43–45] One trial compared 1.5 g of cefuroxime, administered after induction of anaesthesia, with no antibiotic therapy.[44] No SWIs were identified in either group. This is not surprising given the trial's small sample size (20 patients in each group) and lack of long-term follow-up.

Three studies compared cefuroxime with other antibiotics (cephradine and cefamandole,[18] cephazolin,[32] and teicoplanin[43]). The comparison of cefuroxime with cephradine and cefamandole was undertaken in a trial of 60 patients.[18] Because this trial's main aim was to assess bone, serum and tissue concentrations after antibiotic administration, outcome assessment was carried out in the immediate postoperative period, limiting the trials ability to detect significant differences in SWI rates.

No statistically significant differences were demonstrated in a well-conducted RCT of both THR and TKR patients, comparing three doses

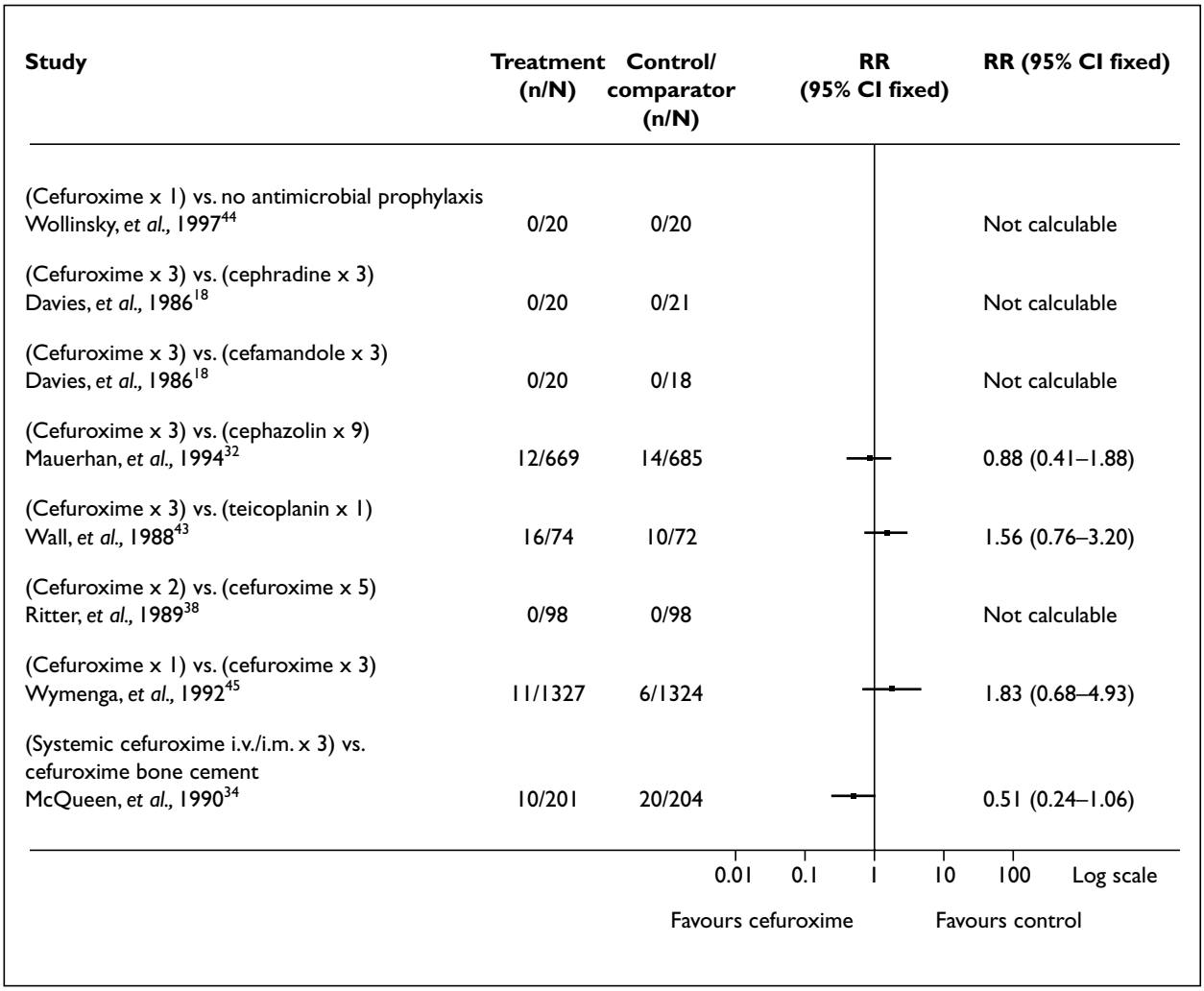

FIGURE 2 *Cefuroxime versus other antibiotics*

of cefuroxime (1.5 g) with nine doses of cephazolin (RR, 0.88; 95% CI, 0.41–1.88).[32] The overall SWI rate was 1.62% for the THR patients and 2.22% for the TKR. Analysing the data separately for the different surgical procedures again demonstrated no statistically significant differences in SWI rates for the two antibiotic regimens.

The interim results of a trial, published in 1988, comparing the efficacy of cefuroxime (three doses of 750 mg) to a single dose of teicoplanin (400 mg) was unable to demonstrate any statistically significant difference between the two regimens.[43] The present review failed to identify any long-term follow-up data for this trial.

Two RCTs examined the effect of postoperative doses of cefuroxime in addition to pre-/ intraoperative doses.[38,45] In one trial, a single dose of cefuroxime was associated with a higher rate of wound infection than three doses of cefuroxime, though the difference was not statistically significant (RR, 1.83; 95% CI, 0.68–4.93).[45] The trials suggest no significant advantage of additional postoperative doses for the prevention of SWIs; however, the methodology of one trial is poor, with little detail given on the method of randomisation, outcome assessment or the comparability of the groups at baseline.[38]

Cefuroxime bone cement was studied in one RCT.[34] THR and TKR patients were randomised to receive either cefuroxime-loaded cement or the same antibiotic administered systemically. Results were presented in a manner that enabled THR to be analysed separately from TKR. No statistically significant difference was demonstrated between the two routes of administration, whether THR patients were analysed separately (RR, 0.56; 95% CI, 0.25–1.24) or in combination with TKR patients (RR, 0.51; 95% CI, 0.24–1.06), though the reported rate of SWI was higher in the group of patients receiving cefuroxime bone cement (5.0% versus 9.8%).

Cephalothin

Only one RCT that was included in the review examined the role of cephalothin for the prevention of SWI.[40] The results of the trial were inconclusive (see under ceforanide).

Cefamandole

Cefamandole is a semisynthetic, second-generation cephalosporin with a broad spectrum of activity. It is active against both Gram-negative and Gram-positive organisms and has prolonged action, possibly due to beta-lactamase resistance.

Seven RCTS examined the relative efficacy of cefamandole to either no antibiotic therapy or an alternative antibiotic (*Figure 3*).[16,18,22,23,35,41,42] The comparison of a 1-day prophylactic course of cefamandole with no antibiotic treatment was undertaken in a trial of 93 THR patients.[23] The author's of the trial state that such a prophylactic course of antibiotic decreases the incidence of major SWIs. The difference between the two groups was not statistically significant in terms of early or late major SWIs, or of latent sepsis. The lack of statistically significant differences may be due, in part, to the small sample size, particularly as all operations were carried out with the use of a 'clean air' system, which may play a role in reducing the rate of SWIs.

Two RCTs compared cefamandole with cephazolin.[16,22] The smaller trial included both THR and TKR patients, the results for which could not be separated.[16] No statistically significant differences were identified between the two groups at any stage of the follow-up, suggesting that cefamandole and cephazolin may be equally effective for the prevention of SWIs in patients undergoing total joint replacements. This result is reinforced by the findings of a large, well-conducted RCT comparing a 2-day course of cefamandole with a 5-day course of cephazolin.[22] All patients included

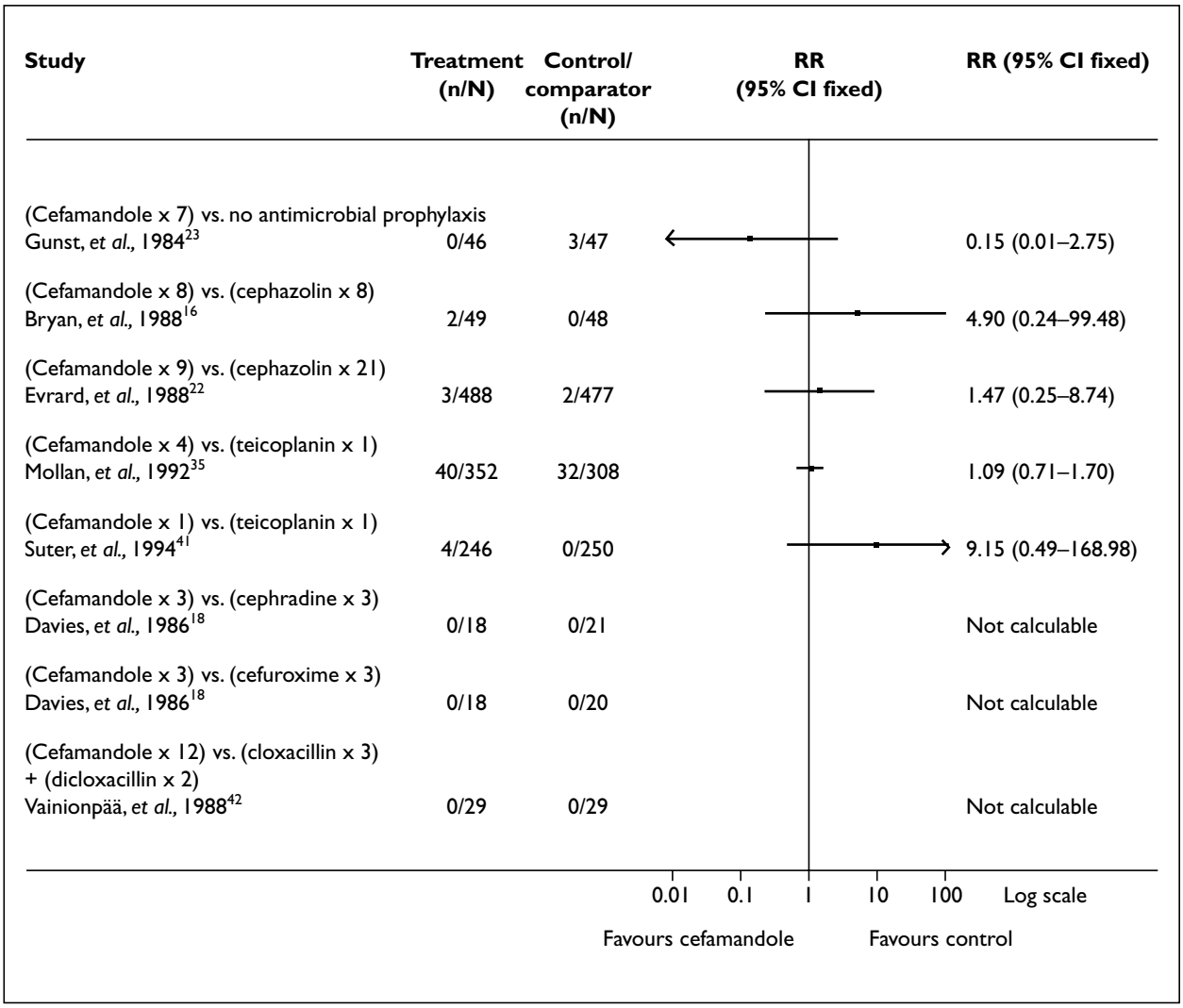

FIGURE 3 *Cefamandole versus other antibiotics*

in the trial (n = 965) received a THR. Infection rates were low in both groups (less than 1%), but did not differ significantly. Pooling the results of the two trials showed no statistically significant difference between the prophylactic use of cefamandole and cephazolin (RR, 2.15; 95% CI, 0.49–9.53).

Two trials compared cefamandole (single[41] and multiple[35] doses) with single-dose teicoplanin. Teicoplanin was found to be equally as effective at preventing SWI as both single- and multiple-dose cefamandole. However, the results presented by Mollan and co-workers[35] are the interim analysis of an ongoing trial. The author's comment on the lack of power within the study, despite recruiting 850 patients, to detect statistically significant differences between the antibiotics. Further recruitment of patients (both THR and TKR) will increase the power of this study, enabling it to better identify any potentially significant differences between the two antibiotics. Pooling of data from both trials failed to demonstrate any statistically significant difference in infection rates between prophylactic cefamandole and teicoplanin (RR, 1.21; 95% CI, 0.79–1.85).

Cefamandole was also compared with cloxacillin, cephradine and cefuroxime.[18,42] Both trials lacked the power to detect any statistically significant differences. In fact, no SWI was observed in any group of these small trials.

Cephazolin

Cephazolin is a semisynthetic, first-generation cephalosporin with a bactericidal action. It has a broad-spectrum of activity, attains high serum levels and is excreted quickly via the urine.

Six RCTS compared cephazolin with alternative antimicrobial prophylaxis (*Figure 4*).[16,19,22,25,32,37] The regimens varied in terms of duration and dosage. Two of the trials recruited fewer than 100 patients.[16,19] The four remaining RCTs were unable to demonstrate a statistically significant difference between cephazolin and cefamandole,[22] cefuroxime,[32] cefotaxime and cefoxitin,[25] and teicoplanin.[37] In three of the four trials, the number and duration of doses administered was greater in the cephazolin regimen.[22,32,37]

The efficacy of short-term versus long-term cephazolin (or naficillin) for the prevention of SWI in patients undergoing total joint replacements (THR and TKR) was studied in two RCTs, published in the same article.[24] All procedures were carried out in an ultraclean air environment and with a total body exhaust system. The overall rate of deep wound infections was found to be 0.6%, with no significant differences between groups.

Cephazolin was compared with placebo in a multicentre study involving 2137 THR patients.[10,11] Four of the centres carried out procedures in a hypersterile operating theatre, the others in a conventional theatre. The trial demonstrated a statistically significant reduction in hip infections 2 years postoperatively for patients receiving a 5-day prophylactic course of cephazolin. The benefit of the antimicrobial was, however, restricted to procedures carried out in the conventional operating theatres. Hip infection rates were not found to differ for procedures carried out in a conventional theatre with antibiotics and those carried out in a hypersterile theatre with or without antibiotics.

Cephradine

The first-generation cephalosporin, cephradine, is a broad-spectrum antibiotic with bactericidal action. It is active against both Gram-positive and Gram-negative bacteria.

Only one trial examined the role of cephradine in the prevention of SWI following THR.[18] The main aim of this study was to assess bone, serum and tissue concentrations. The small sample size and lack of follow-up severely limit the trial in its ability to provide meaningful data on wound infection rates.

Cloxacillin

Cloxacillin is a semisynthetic antibiotic. An early RCT of antimicrobial prophylaxis for the prevention of SWI following THR surgery compared cloxacillin with placebo.[17] A 14-day course of cloxacillin was shown to be more effective than placebo at 1–2$^1/_2$ years (RR, 0.06; 95% CI, 0.00–1.10) and 5–6$^1/_2$ years follow-up (RR, 0.14; 95% CI, 0.03–0.58). Both groups received 1 g of oral probenicid for 14 days, commencing on the day of surgery.

Cloxacillin, phenoxyphenyl penicillin, dicloxacillin and cephalexin formed a single treatment arm in a large, multicentre trial, comparing systemic administration of a prophylactic antibiotic with gentamicin-loaded bone cement.[31] The results of this trial are presented under gentamicin.

Cloxacillin was also compared with cefamandole (29 patients in each group).[42] No deep infections were reported in either group during the 2-year follow-up.

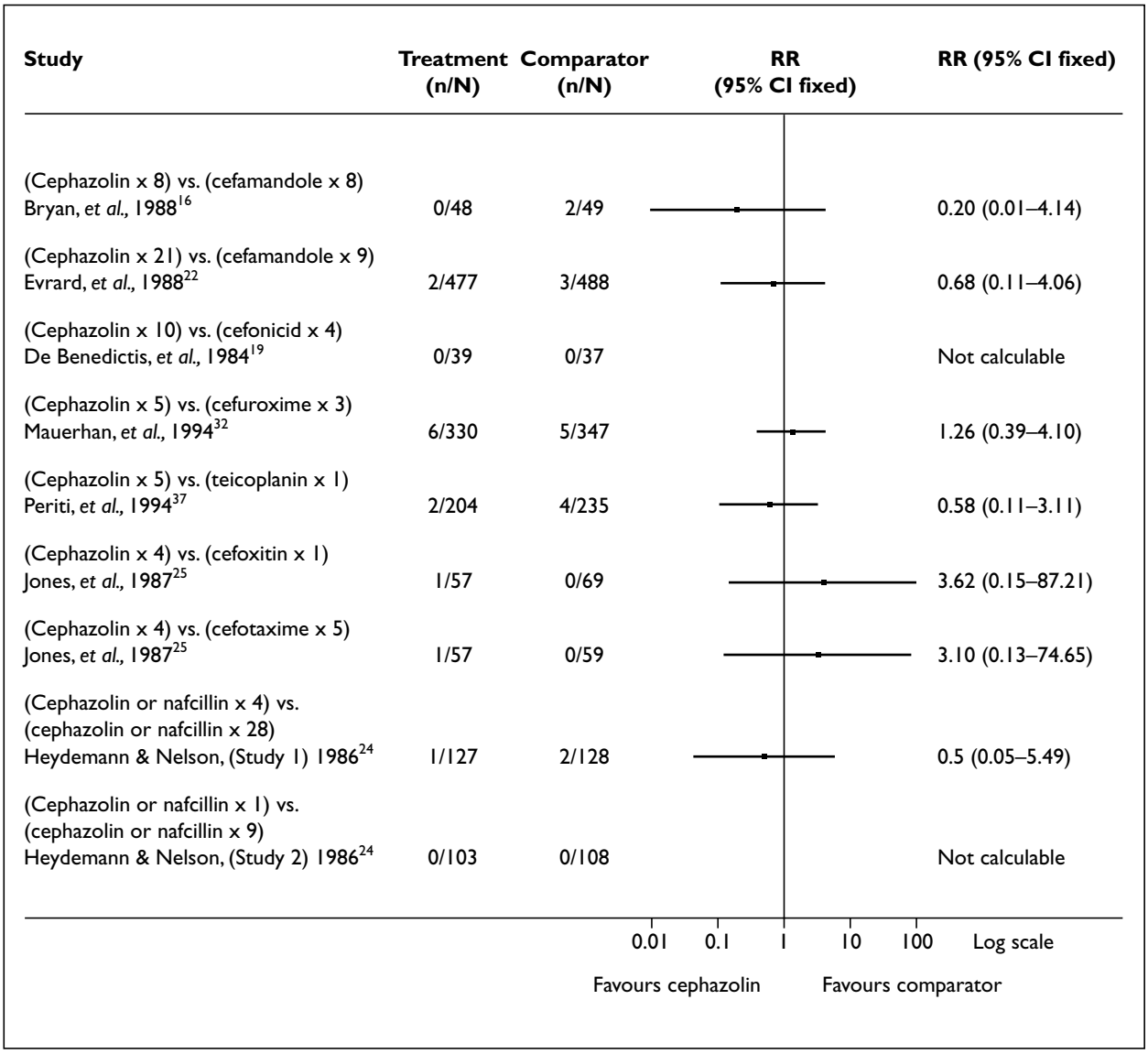

FIGURE 4 *Cephazolin versus other antibiotics*

Gentamicin

Gentamicin, a broad-spectrum aminoglycoside, is usually bactericidal in action. In general, gentamicin is active against aerobic Gram-negative bacteria and some aerobic Gram-positive bacteria. Gentamicin is inactive against anaerobic bacteria and, as with other aminoglycosides, is poorly absorbed through the gut.

One RCT compared the efficacy of gentamicin bone cement with phenoxyphenyl penicillin, cloxacillin, dicloxacillin or cephalexin, administered systemically.[31] This was a large, multicentre study, which provided 10-year follow-up data for 1115 patients. There was variation in the prostheses used and the systemic antibiotic regimens. However, at 1–2 years follow-up the trial showed a statistically significant difference in deep infection rates in favour of gentamicin-loaded cement (RR, 4.38; 95% CI, 1.25–15.32). This difference was maintained at 5 years, but was not statistically significant at the 10-year follow-up.

Lincomicin

An early trial of prophylactic lincomicin, for the prevention of wound infections following THR, recruited 259 patients.[39] All procedures were carried out in a conventional operating theatre. Patients were randomised to receive a 10-day course of lincomicin or no prophylactic antibiotic. Patients were followed for a period of 2 years, at which time no statistically significant difference was demonstrated in terms of superficial wound infections. However, the use of lincomicin was shown to significantly reduce the number of deep wound infections following THR. Combining the

data on both superficial and deep wound infections also provided a statistically significant difference in favour of the prophylactic antimicrobial (RR, 0.25; 95% CI, 0.07–0.90).

Teicoplanin

Teicoplanin, a bactericidal glycopeptide, is active against both aerobic and anaerobic Gram-positive bacteria. It is ineffective against Gram-negative bacteria. Four RCTs studying teicoplanin and meeting the review's inclusion criteria were identified (*Figure 5*).[35,37,41,43]

As discussed previously, teicoplanin was compared with cefamandole in two RCTs.[35,41] The trials demonstrated no statistically significant difference in infection rates between groups, either individually or pooled (RR, 1.21; 95% CI, 0.79–1.85).

No statistically significant differences were demonstrated, in terms of SWI rates, between single-dose teicoplanin and multiple-dose cephazolin[37] or multiple-dose cefuroxime.[43] Both trials report short-term follow-up data only.

Ticarcillin/clavulanic acid

Ticarcillin is derived from penicillin. Clavulanic acid inactivates penicillinases produced by bacteria resistant to ticarcillin. Jones and co-workers compared ticarcillin/clavulanic acid with cefotaxime in a large RCT of a range of surgical procedures.[26] Both regimens were single dose, and no statistically significant differences were found between the two antibiotics in terms of infection rates. However, there are few data relating specifically to total joint replacements within this study (see under cefotaxime).

Route of administration

The role of antibiotic-loaded bone cement, in comparison with the better established, systemically administered antimicrobial prophylaxis, has been evaluated in two RCTs (*Figure 6*).[31,34] Josefsson and Kolmert[31] used gentamicin as the antibiotic to be administered through the bone cement. This was compared with four systemically administered antibiotics (cloxacillin, dicloxacillin, cephalexin and phenoxymethyl penicillin), the results of which are presented together. The rate of deep infections at 1–2 years follow-up was found to be statistically significantly different in favour of gentamicin bone cement (RR, 4.38; 95% CI, 1.25–15.32). This difference remained significantly different up to the 5-year follow-up, but was not apparent 10 years postoperatively. Problems associated with the study include variation in antibiotics and prostheses, difficulties encountered in the correct diagnosis of a deep infection, and lack of blind outcome assessment.

McQueen and co-workers[34] compared systemic cefuroxime with cefuroxime bone cement. The groups were comparable in terms of the use of

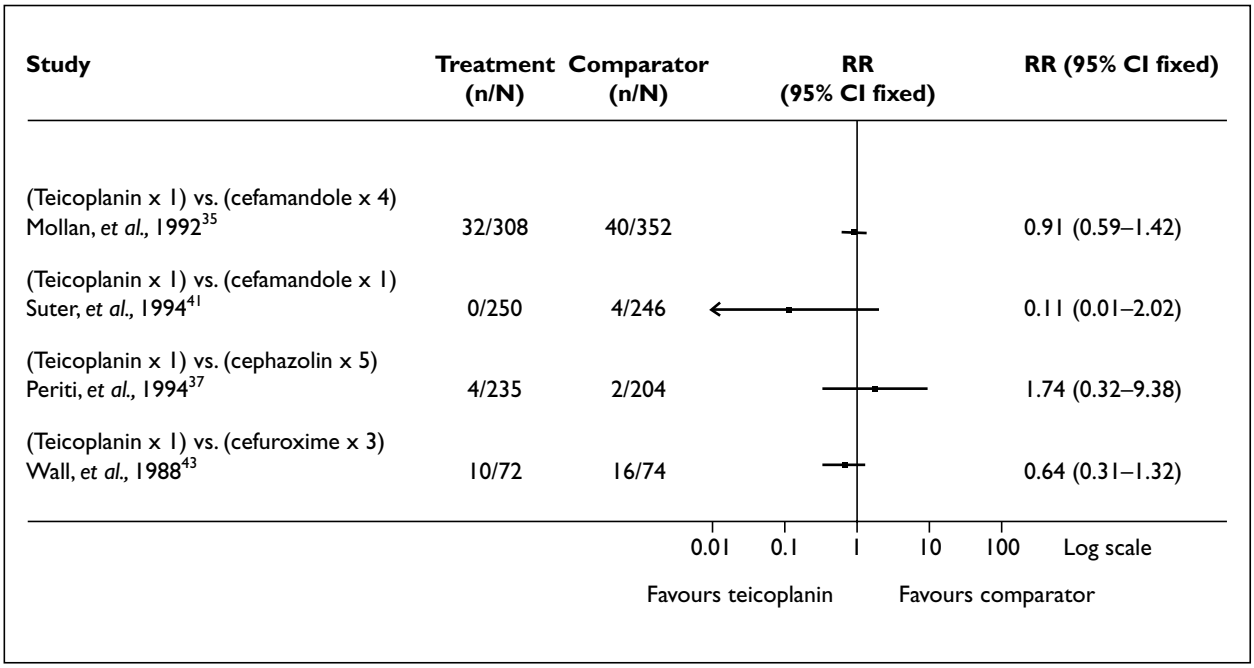

FIGURE 5 *Teicoplanin versus other antibiotics*

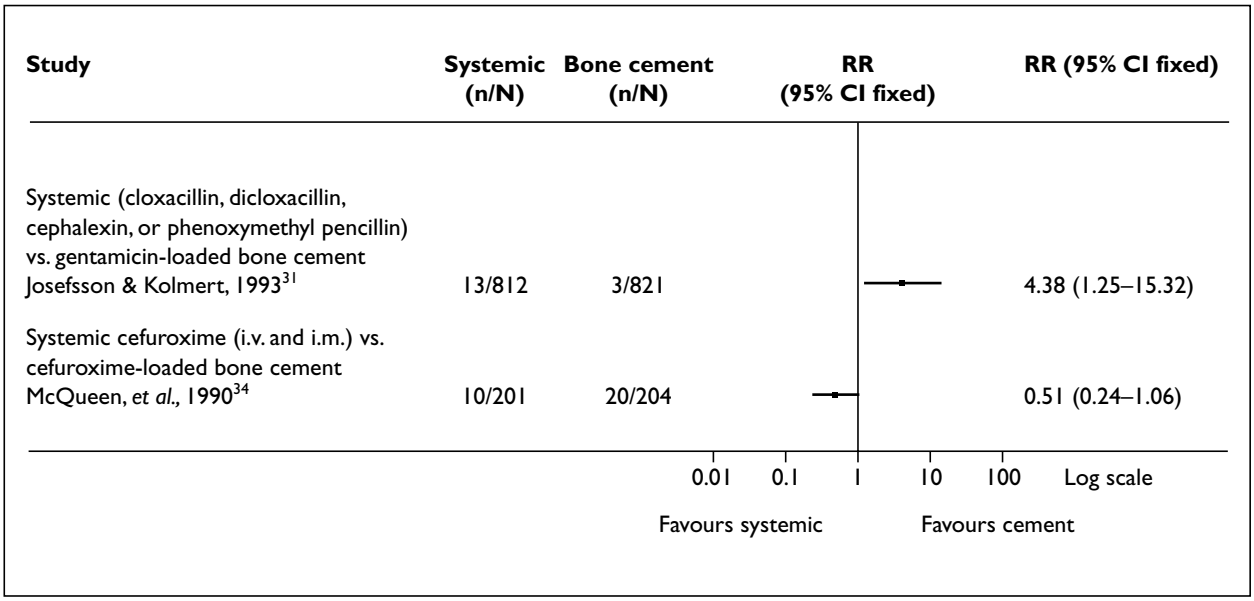

FIGURE 6 *Systemic administration versus antibiotic-loaded bone cement*

drainage, type of approach to the hip joint, type of prosthesis and duration of the operation. No statistically significant differences in superficial/deep wound infections were demonstrated at the 2-year follow-up.

Outcomes other than SWI

Cefamandole bone and serum concentrations were shown to be statistically significantly greater than those of cephazolin in one RCT of both THR and TKR patients.[16] However, the dose of cefamandole administered prophylactically was double that of cephazolin. The serum concentrations of cefamandole were compared with serum concentrations of cloxacillin in a second RCT. Again the dose and timing of administration varied between the two regimens.[42] Davies and co-workers also examined bone, serum and tissue concentrations of cefamandole in comparison with cephradine and cefuroxime.[18] The dose of antibiotic administered in each group was identical. All three antibiotics showed similar bone, serum and tissue concentrations at 20, 35 and 60 minutes after the initial injection of antibiotic. One RCT demonstrated higher, and more sustained bone and serum concentrations for ceforanide (two doses) than for cephalothin (five doses).[40]

Sixteen studies reported the results of bacteriological testing (see appendix 6). The most frequently isolated pathogens were *Staphylococcus aureus* and *Staphylococcus epidermidis*. Nine papers commented on the sensitivity of the pathogens to antibiotics, five commenting on the presence of strains resistant to the antibiotic administered prophylactically.[17,22,28,32,39] The percentage of resistant isolates varied greatly amongst these trials. For example, Jones and co-workers[28] reported that over half of the causative organisms in patients receiving cephazolin were resistant to the antibiotic. However, in the RCT by Mauerhan and co-workers it is stated that 'all but a few of the isolated pathogens were sensitive to cefuroxime and cephazolin'.[32] Only one trial identified methicillin-resistant staphylococci.[22]

The aim of the RCT conducted by Evrard and co-workers was to assess the rate of resistant colonising organisms and the percentage of positive drain samples in patients receiving either 2-day cefamandole or 5-day cephazolin prophylaxis.[22] There was no statistically significant difference in the number of infected drains. Patients receiving cefamandole did demonstrate a lower rate of Gram-negative organisms ($p < 0.01$).

Two trials report on aseptic loosening of the joint.[31,42] No statistically significant differences were demonstrated in either trial. Similarly, trials reporting on urinary and respiratory tract infections showed no statistically significant differences between the antimicrobial regimens examined.[22,34,40,41,44] None of the 25 RCTs reported deaths related to infection.

Adverse events

Twelve of the 25 RCTs included in the review reported adverse events such as nausea, vomiting,

erythema on administration of antibiotic, gastric pyrosis, cutaneous rash and mild dyspnoea.[11,16,18,19,25–27,32,35,37,41,43] No serious toxicity or adverse events were reported in any trial.

Cost

Only six of the included RCTs provided quantitative information relating to the cost of the antimicrobial prophylaxis used.[16,24–27,32] The cost information reported in these trials should be interpreted with caution due to incomplete measures of cost and benefit and the fact that the most recent of these studies was published in 1994. All seven trials were conducted in the USA. (Conversions to pound sterling are based on current exchange rates.)

The trial by Bryan and co-workers[16] was too small to demonstrate a statistically significant difference between prophylactic regimens of cephazolin and cefamandole. The authors state that pharmacological differences and cost should be considered when choosing an antimicrobial agent for the prevention of SWIs. They report the average wholesale prices of cephazolin and cefamandole to be similar (US$6.55/g and US$6.99/g (approx. £3.93 and £4.20), respectively). However, it should be noted that the cefamandole regimen used in their RCT required the administration of up to 10 g of the antibiotic, whereas the cephazolin regimen used only 5 g of antibiotic.

The efficacy of single-dose/short-term antimicrobial prophylaxis compared with multiple-dose/long-term antimicrobial prophylaxis was evaluated in two RCTs of total joint replacements.[24] Findings suggest that there is no added benefit of extending the duration of administration of an antibiotic when procedures are carried out in an ultraclean environment. They report that approximately US$7,700,000 (approx. £4,622,000) could be saved per 100,000 patients by reducing the administration of cephazolin from 48 hours to one dose (based on the cost of the drug to the authors' patients). Reducing the regimen from 7 days to one dose would save approximately US$29,700,000 (approx. £17,827,000).

Mauerhan and co-workers[32] also provide data in favour of antimicrobial prophylaxis regimens of reduced duration. They report the findings of a cost-minimisation analysis comparing total costs of a 1-day regimen of cefuroxime with total costs of a 3-day regimen of cephazolin. The total cost of prophylaxis per patient was calculated at US$37.03 for cefuroxime and US$56.07 for cephazolin (approx. £27.23 and £33.66, respectively).

Jones and co-workers calculated the total prophylaxis costs of the five antimicrobial regimens used in their three RCTs.[25–27] The three single-dose regimens of cefotaxime, ticarcillin/clavulanic acid and cefoperazone were shown to cost US$12.90, US$14.15 and US$14.50 (approx. £7.74, £8.49 and £8.70), respectively. In comparison, the multiple-dose regimen of cephazolin cost US$30 (approx. £18.01), and the cefoxitin regimen (five doses) cost $100 (approx. £60.02).

Chapter 4

Discussion

Methodological limitations of the included RCTs

Many of the trials included in the review are methodologically weak, providing little conclusive evidence on the relative efficacy of antimicrobial prophylaxis for the prevention of wound infections following THRs.

First, there is a lack of truly randomised trials examining antimicrobial prophylaxis in THR. In only 16% of the trials included in the present review was it clear that concealed patient allocation had occurred. By using inappropriate methods of patient allocation, trials are likely to be susceptible to selection bias, distorting the estimation of relative efficacy of the antimicrobials being examined. This bias is compounded by the fact that 60% of the papers did not mention or did not adjust for confounding factors.

The overall wound infection rate for patients (both THR and TKR patients) receiving some form of antimicrobial prophylaxis was found to be 2.1% in the included RCTs (255/12,143). When THR patients were examined separately, the overall infection rate was reduced to 1.0%. In either case, the infection rate is low. For an individual trial to have sufficient power to detect a statistically significant difference in infection rates between two antimicrobial prophylaxis regimens, its sample size would have to be large. In order to show a 50% reduction in an infection rate of 2%, for example, at the 5% significance level and 80% power, over 2300 patients would be required in each treatment arm. The fact that few studies included in the review were able to demonstrate statistically significant findings is not surprising, given that nearly half of all trials recruited fewer than 100 patients to each arm.

The main aim of several of the studies was to examine the concentrations of antibiotics in the bone and serum, and not SWI rates. This may account for some of the small sample sizes. It is not possible to conclude from the results of the trials that non-significant findings indicate regimens of equivalent efficacy in terms of preventing SWIs, due to lack of statistical power.

The definitions of wound infections used within the RCTs were generally well reported, with over a third of trials including a microbiological diagnosis. However, definitions did vary, making comparability between groups problematic. In addition to this, the duration of follow-up varied between RCTs. Over 10% of the trials followed patients for less than 4 weeks, or did not provide information on the duration of the follow-up period. The majority of trials followed patients for 4 weeks to 2 years, with 28% of trials observing patients for longer than 2 years. This variation in follow-up period, again, makes it difficult to compare infection rates between studies. Trials only reporting data collected during the period of hospitalisation, for example, will not identify all major, deep wound infections (those occurring at the incision site within 1 year, involving tissues or spaces at or beneath the fascial layer), and are likely to demonstrate lower infection rates than trials with a longer follow-up period. Late prosthetic infections, occurring after 1 year of surgery are thought more likely to be haematogenous in source, rather than due to intraoperative seeding.[14] The role of antimicrobial prophylaxis, at the time of total joint replacement surgery, in reducing late onset infections has been questioned. However, statistically significant differences in infection rates for patients receiving antimicrobial prophylaxis and those receiving placebo, have been demonstrated 5 years postoperatively.[17] Carlsson and co-workers, combining data from an RCT and a retrospective study, demonstrated a reduction in late infection rates from 15.4% to 2% with the use of antimicrobial prophylaxis.[17] Further analysis of their data led them to conclude the rate of haematogenous infections was less than 1%. RCTs of antimicrobial prophylaxis in total joint replacement surgery should include a long-term follow-up period to allow a full assessment of all infection types – superficial, deep and late onset.

The generalisability of the results of the RCTs must also be questioned. Although the inclusion and exclusion criteria were often clearly stated, patient characteristics were often sparse. The number of primary or revision procedures, or the types of hip replacements used (i.e. cemented, cementless or hybrid) were not always reported.

In addition, the type of operating theatre used was seldom noted. The RCTs included in the review span over 20 years, from 1977–98; changes in practice, such as developments in technology and the increasing proportion of revision procedures, and the emergence of antibiotic-resistant bacteria, may mean that results of earlier trials have little bearing on current practice.

The systematic review itself has its limitations. First, it relies wholly on reported data. Lack of contact with the authors of the RCTs included in the review means that the primary data are not the subject of analysis. Publication bias may also be present within the review. However, over 80% of the included trials reported results that did not show a statistically significant difference in wound infection rates between groups. It is unlikely, therefore, that treatment effects have been over-estimated due to publication bias, though the review might still have been improved by contacting antibiotic manufacturers to identify unpublished literature. It is unclear whether bias exists due to unrepresentative inclusion of non-English language publications.

Efficacy of antimicrobial prophylaxis

Trials of total joint replacement surgery have illustrated that infection rates can be statistically significantly reduced when an antimicrobial is used prophylactically, in comparison with placebo or no intervention.[17,23,39] Given the disastrous effects of infections of a joint prosthesis, causing increased patient morbidity and increased costs in terms of prolonged hospitalisation, additional therapy and the possibility of further surgery, it is apparent that antimicrobial prophylaxis is necessary for THR surgery. However, trials to date provide inconclusive evidence on the optimal antimicrobial prophylaxis regimen, because of the low infection rates and/or lack of statistical power of small studies.

Antimicrobial agent

It was not possible to identify the most effective antimicrobial agent within the review. In order to choose an appropriate prophylactic antibiotic, consideration needs to be given to the bacteriological coverage given by an antibiotic, and the types of bacteria likely to cause wound infection and also their sensitivity to antibiotics. This information should come from continuous detailed environmental bacteriological examination and cultures from wound infections.[39] In addition, the toxicity profile of the antibiotic and the cost of the drug should be considered.

S. aureus and *S. epidermidis* were the most frequently isolated pathogens in the trials included in the present review. Other bacteria were also identified, including aerobic streptococci and anaerobic cocci. Cephalosporins (first and second generation) were the most commonly studied antibiotics. These antibiotics provide cover for a broad spectrum of bacteria, and are relatively non-toxic, the main adverse effects being hypersensitivity reactions.[46] Third-generation cephalosporins have a similar activity to first- and second-generation cephalosporins, but are generally more expensive. When there is no difference in the efficacy and safety of prophylactic antimicrobial agents, the cost and ease of administration need to be considered.[47] Little information on the cost of the antibiotic regimens examined was provided in the RCTs included in this review.

Timing and duration of administration

To obtain maximal prophylactic effect, an antibiotic must be able to achieve adequate concentrations in the bone and tissue surrounding the area of surgery at the moment of wound contamination. The pharmacokinetic properties of an antibiotic may need to be considered when establishing the required timing and duration of a prophylactic regimen.

All RCTs included in the review administered the first antimicrobial within 1 hour prior to anaesthesia, the majority of trials administering the first dose at the induction of anaesthesia. The duration of the antimicrobial prophylactic regimen postoperatively varied from a single dose to a 14-day course.[31] There is no evidence to suggest that administering antimicrobial prophylaxis for more than 1 day postoperatively reduces the number of infections following THR surgery. Extending the duration of a regimen for longer than 24 hours may not only be wasteful, but potentially hazardous in terms of toxicity and the increased risk of developing bacterial resistance.

Route of administration

The antimicrobial prophylactic agents examined in the review were administered parenterally (intravenously or intramuscularly), orally, or in antibiotic-loaded cement. Comparisons were made between systemic administration and the use of antibiotic-loaded cement.[31,34] The results of trials in this area are inconclusive. The cost and ease of administration should, therefore,

be used to determine which route should be used.

Other factors influencing the outcome of THRs

Patient characteristics

Several patient characteristics have been identified as potential risk factors for wound infections in THR surgery. The underlying arthropathy and the condition of the tissue may play an important role in determining whether bacterial contamination of a wound will produce an infection.[48] The less viable the tissue, the more likely it is that bacteria will invade it. This risk of infection may also increase if the patient's natural resistance is compromised due to, for example, old age, obesity or weight loss, diabetes mellitus, sickle-cell anaemia, cirrhosis, or the use of steroids.[12,13,48] However, one large RCT and its follow-up was unable to confirm the prognostic value of obesity, diabetes or previous hip surgery as risk factors for hip infection.[10,11]

Operative factors

It has been estimated that approximately 95% of wound contamination is derived from the operating room air.[49] The use of ultraclean operating theatres, with laminar airflow have been shown to reduce the number of total joint infections from 1.5% (conventional operating theatres) to 0.6%.[50] The study did not aim to evaluate the role of antimicrobial prophylaxis, but the findings suggest that there may be an added benefit of utilising both antimicrobial prophylaxis and ultraclean operating theatres.

Infection rates may also be influenced by a surgeon's training and experience of performing total joint replacement surgery,[6] and the type of implant used.[31]

It was not possible to carry out an assessment of the potential risk factors associated with total joint replacement surgery, due to inconsistencies in the reporting of such data within the included trials.

Chapter 5
Conclusions

Antimicrobial prophylaxis is effective for the prevention of SWI in both TKR and THR surgery. The added benefit of antimicrobial prophylaxis when used in conjunction with ultraclean operating theatres, remains unclear.

The efficacy of many of the regimens studied for the prevention of SWI may be similar, and available data make it difficult to identify an optimal regimen. However, there is no convincing evidence to suggest that extending the duration of a regimen beyond 24 hours postoperatively reduces the number of SWI following THR or TKR surgery. Single-dose or short-term administration is not only as effective as long-term administration, but will lower overall costs, and may reduce the risk of both toxicity and the development of bacterial resistance.

Similarly, there is no convincing evidence to suggest that the new-generation cephalosporins are more effective at preventing postoperative SWI infections in THR and TKR surgery than the first-generation cephalosporins.

The volume of research in this area is decreasing, with only four trials published in the last 5 years. Given the low infection rates following THR, and the small sample size of trials comparing antimicrobial prophylaxis, it is unlikely that the current knowledge base is going to change drastically in the near future.

Implications for policy

There is evidence to support the use of antimicrobial prophylaxis in elective THR. However, the universal acceptance of a fixed antimicrobial regimen should be avoided in order to minimise the development of antibiotic-resistant bacteria. Guidelines, based on available research evidence, should be developed locally by surgeons, microbiologists and pharmacists, taking into account local sensitivities to organisms commonly implicated in wound infection post THR. The minimisation of adverse effects and cost, and patient acceptability should also be taken into consideration. Such guidelines should be constantly reviewed and updated, as no definitive version can be established.

Recommendations for research

No further small, under-powered trials examining antimicrobial prophylaxis for the prevention of SWI following THR/TKR should be funded. Given the low infection rates following THR/TKR surgery, and the possible changing pattern of bacteria resistance, it may not be cost-effective to carry out mega-trials of antimicrobial prophylaxis. The difference in infection rate between antimicrobial prophylaxis regimens is likely to be small, and may not be clinically significant, whereas the cost of recruiting large numbers of patients into a trial is high. In addition, local resistance profiles are likely to be ever-changing, meaning that results of such trials may not be relevant for long. Future research needs to examine the risk factors that determine the level of SWIs in patients undergoing THR. Risk factors could be used to identify a high-risk group on whom trials of new or additional prophylactic measures could be performed. However, if such trials were to be undertaken they must be able to recruit sufficient patients to have the power to show a statistically significant difference, and they should consider the issues of trial validity listed in *Table 1*. The type of operating theatre, the nature of the procedures undertaken and the types of prostheses used should all be recorded.

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References

1. Malchau H, Herberts P, Lennart A. Prognosis of total hip replacement in Sweden. Follow-up of 92,675 operations performed 1978–1990. *Acta Orthop Scand* 1993;**64**:497–506.
2. Court-Brown C. Orthopaedic surgery. In: Taylor E, Editor. Current problems in antibiotic prophylaxis and surgical infection. London: Royal Society of Medicine Services, 1989:47–8.
3. Department of Health. Hospital episode statistics (HES) and population data provided by the statistics division. London: DoH, 1996.
4. Nuffield Institute for Health University of Leeds, NHS Centre for Reviews and Dissemination University of York. Total hip replacement. *Effective Health Care* 1996;**2**(7):1–12.
5. Williams M, Frankel S, Nanchahal K, Coast J, Donovan J. Total hip replacement. In: Health Care Needs Assessment: the epidemiologically based needs assessment reviews. London: Office of Health Economics, 1982.
6. Naylor C, Williams J, The Ontario Panel on Hip and Knee Arthroplasty. Primary hip and knee replacement surgery: Ontario criteria for case selection and surgical priority. *Quality in Health Care* 1996;**5**:20–30.
7. Murray D, Carr A, Bulstrode C. Which primary total hip replacement? *J Bone Joint Surg [Br]* 1995;**77**:520–7.
8. McGuigan S. OHE compendium of health statistics. 10th ed. London: Office of Health Economics, 1997.
9. Norden C. Antibiotic prophylaxis in orthopedic surgery. *Rev Infect Dis* 1991;**13**(Suppl 10):S842–6.
10. Hill C, Flamant R, Mazas F, Evrard J. Prophylactic cefazolin versus placebo in total hip replacement. Report of a multicentre double-blind randomised trial. *Lancet* 1981;**1**:795–6.
11. Doyon F, Evrard J, Mazas F. Long-term results of prophylactic cefazolin versus placebo in total hip replacement. *Lancet* 1987;**1**(8573):860.
12. Song F, Glenny A. Antimicrobial prophylaxis in colorectal surgery: a systematic review of randomised controlled trials. *Br J Surg* 1998;**85**:1232–41.
13. Song F, Glenny AM. Antimicrobial prophylaxis in colorectal surgery: a systematic review of randomised controlled trials. *Health Technol Assess* 1998;**2**(7).
14. Strachan C. Antibiotic prophylaxis in peripheral vascular and orthopaedic prosthetic surgery. *J Antimicrob Chemother* 1993;**31**(Suppl B):65–78.
15. Moher D, Jadad A, Tugwell R. Assessing the quality of randomised controlled trials. *Int J Technol Assess Health Care* 1996;**12**:195–208.
16. Bryan C, Morgan S, Caton R, Lunceford E. Cefazolin versus cefamandole for prophylaxis during joint arthroplasty. *Clin Orthop* 1988;**228**:117–22.
17. Carlsson A, Lidgren L, Lindberg L. Prophylactic antibiotics against early and late deep infections after total hip replacements. *Acta Orthop Scand* 1977;**48**:405–10.
18. Davies A, Lockley R, Jones A, el Safty M, Clothier J. Comparative pharmacokinetics of cefamandole, cefuroxime and cephradine during total hip replacement. *J Antimicrob Chemother* 1986;**17**:637–40.
19. DeBenedictis K, Rowan N, Boyer B. A double-blind study comparing cefonicid with cefazolin as prophylaxis in patients undergoing total hip or knee replacement. *Rev Infect Dis* 1984;**6**(Suppl):S901–4.
20. Ericson C, Lidgren L, Lindberg L. Cloxacillin in the prophylaxis of postoperative infections of the hip. *J Bone Joint Surg [Am]* 1973;**55A**:808–13.
21. Evrard J, Mazas F, Acar J, Doyon F, Flamant R. [Comparison of two preventive antibiotic treatments in total hip arthroplasty.] *Rev Chir Orthop* 1985;**71**:37.
22. Evrard J, Doyon F, Acar J, Salord J, Mazas F, Flamant R. Two-day cefamandole versus five-day cefazolin prophylaxis in 965 total hip replacements. *Int Orthop* 1988;**12**:69–73.
23. Gunst J, Deletang S, Rogez J, Blanloiel Y, Baron D, Dixneuf B. Prophylactic antibiotic therapy by cefamandole in total hip replacement with use of a clean air system. A randomized study. *Path Biol* 1984;**32**:567–9.
24. Heydemann J, Nelson C. Short-term preventive antibiotics. *Clin Orthop* 1986;**205**:184–7.
25. Jones R, Wojeski W, Bakke J, Porter C, Searles M. Antibiotic prophylaxis of 1,036 patients undergoing elective surgical procedures: a prospective randomized comparative trial of cefazolin, cefoxitin and cefotaxime in a prepaid medical practice. *Am J Surg* 1987c;**153**:341–6.
26. Jones R, Wojeski W. Single-dose surgical prophylaxis using ticarcillin/clavulanic acid (timentin): a prospective, randomised comparison with cefotaxime. *Diagn Microbiol Infect Dis* 1987;**7**:219–23.

27. Jones R, Wojeski W. Single-dose cephalosporin prophylaxis of 929 surgical procedures in a prepaid group practice: a prospective, randomised comparison of cefoperazone and cefotaxime. *Diagn Microbiol Infect Dis* 1987a;**6**:323–34.

28. Jones R, Slepack J, Wojeski W. Cefotaxime single-dose surgical prophylaxis in a pre-paid group practice: comparisons with other cephalosporins and ticarcillin/clavulanic acid. *Drugs* 1988;**35**:116–23.

29. Josefsson G, Lindberg L, Wiklander B. Systemic antibiotics and gentamicin-containing bone cement in the prophylaxis of post-operative infections in total hip arthroplasty. *Clin Orthop* 1981;**159**:194–200.

30. Josefsson G, Gudmundsson G, Kolmert L, Wijkstrom S. Prophylaxis with systemic antibiotics versus gentamicin bone cement in total hip arthroplasty. *Clin Orthop* 1990;**253**:173–8.

31. Josefsson G, Kolmert L. Prophylaxis with systemic antibiotics versus gentamicin bone cement in total hip arthroplasty. A ten-year survey of 1,688 hips. *Clin Orthop* 1993:210–14.

32. Mauerhan D, Nelson C, Smith D, Fitzgerald R, Slama T, Petty R, *et al.* Prophylaxis against infection in total joint arthroplasty. One day of cefuroxime compared with three days of cefazolin. *J Bone Joint Surg [Am]* 1994;**76**:39–45.

33. McQueen M, Littlejohn A, Hughes S. A comparison of systemic Cefuroxime and Cefuroxime loaded bone cement in the prevention of early infection after total joint replacement. *Int Orthop* 1987;**11**:241–3.

34. McQueen M, Hughes S, May P, Verity L. Cefuroxime in total joint arthroplasty. Intravenous or in bone cement. *J Arthroplasty* 1990;**5**:169–72.

35. Mollan R, Haddock M, Webb C. Teicoplanin vs cephamandole for antimicrobial prophylaxis in prosthetic joint implant surgery: (preliminary results). *Eur J Surg (suppl)* 1992;**567**:19–21.

36. Nelson C, Green T, Porter R, Warren R. One day versus seven days of preventive antibiotic therapy in orthopedic surgery. *Clin Orthop* 1983;**176**:258–63.

37. Periti P, Stringa G, Donati L, Mazzei T, Mini E, Novelli A. Teicoplanin – its role as systemic therapy of burn infections and as prophylaxis for orthopaedic surgery. *Eur J Surg (suppl)* 1994;**567**:3–8.

38. Ritter M, Campbell E, Keating E, Faris P. Comparison of intraoperative versus 24 hour antibiotic prophylaxis in total joint replacement. A controlled prospective study. *Orthop Rev* 1989;**18**:694–6.

39. Schulitz K, Winkelmann W, Schoening B. The prophylactic use of antibiotics in alloarthroplasty of the hip joint for coxarthrosis. *Arch Orthop Trauma Surg* 1980;**96**:79–82.

40. Soave R, Hirsch J, Salvati E, Brause B, Roberts R. Comparison of ceforanide and cephalothin prophylaxis in patients undergoing total joint arthroplasty. *Orthopedics* 1986;**91**:1657–60.

41. Suter F, Avai A, Fusco U, Gerundini M, Caprioli S, Maggiolo F. Teicoplanin versus cefamandole in the prevention of infection in total hip replacement. *Eur J Clin Microbiol Infect Dis* 1994;**13**:793–6.

42. Vainionpää S, Wilppula E, Lalla M, Renkonen O-V, Rokkanen P. Cefamandole and isoxazyl penicillins in antibiotic prophylaxis of patients undergoing total hip or knee joint arthroplasty. *Arch Orthop Trauma Surg* 1988;**107**:228–30.

43. Wall R, Klenerman L, McCullough C, Fyfe I. A comparison of teicoplanin and cefuroxime as prophylaxis for orthopaedic implant surgery: a preliminary report. *J Antimicrob Chemother* 1988;**21**:141–6.

44. Wollinsky K, Oethinger M, Buchele M, Kluger P, Puhl W, Mehrkens H. Autotransfusion – bacterial contamination during hip arthroplasty and efficacy of cefuroxime prophylaxis. A randomized controlled study of 40 patients. *Acta Orthop Scand* 1997;**68**:225–30.

45. Wymenga A, van Horn J, Theeuwes A, Muytjens H, Sloof T. Cefuroxime for prevention of postoperative coxitis. One versus three doses tested in a randomized multicenter study of 2,651 arthroplasties. *Acta Orthop Scand* 1992;**63**:19–24.

46. Fitzgerald R, Thompson R. Cephalosporin antibiotics in the prevention and treatment of musculoskeletal sepsis. *J Bone Joint Surg Am* 1983;**65A**:1201–5.

47. Norrby S. Cost effective prophylaxis of surgical infections. *Pharmacoeconomics* 1996;**10**:129–39.

48. Eron L. Prevention of infection following orthopedic surgery. *Antibiot Chemother* 1985;**33**:140–64.

49. Gillespie W. Infection in total joint replacement. *Infect Dis Clin North Am* 1990;**4**(3):465–84.

50. Lidwell O, Lowbury E, Whyte W, Blowers R, Stanley S, Lowe D. Effect of ultraclean air in operating rooms on deep sepsis in the joint after total hip or knee replacement: a randomized study. *BMJ* 1982;**285**:10–14.

51. Bergstrom B, Lidgren L, Lindberg L. Radiographic abnormalities caused by postoperative infections following total hip arthroplasty. *Clin Orthop* 1974;**99**:94–102.

52. Wymenga A, Hekster Y, Theeuwes A, Muytjens H, van Horn J, Sloof T. Antibiotic use after cefuroxime prophylaxis in hip and knee joint replacement. *Clin Pharmacol Ther* 1991;**50**:215–20.

Appendix 1

MEDLINE search strategy

Set	Search
1	hip joint/su
2	hip prosthesis/
3	acetabulum/
4	hip replacement$.tw.
5	total-hip replacement$.tw.
6	total joint replacement$.tw.
7	hip surgery.tw.
8	hip operation$.tw.
9	(hip adj3 prosthe$).tw.
10	(hip adj3 arthroplasty).tw.
11	or/1-10
12	exp bacterial infections/pc,dt
13	exp postoperative complications/pc,dt
14	surgical wound infection/pc,dt
15	prosthesis-related infections/pc
16	sepsis/pc,dt
17	exp anti-infective agents/
18	exp infection control/
19	exp antibiotics/tu
20	antibiotic prophylaxis/
21	((bacteri$ or wound$) adj2 (infect$ or contamin$)).tw.
22	sepsis.tw.
23	antibiotic$.ti,ab.
24	antimicrobial$.ti,ab.
25	anti-microbial$.ti,ab.
26	(anti$ adj infect$).ti,ab.
27	ultraclean.tw.
28	hypersterile.tw.
29	or/12-28
30	11 and 29
31	thromboemb$.tw.
32	embolism$.tw.
33	thrombosis.tw.
34	exp thrombosis/
35	31 or 32 or 33 or 34
36	30 not 35
37	limit 36 to human

Appendix 2

Study details

Study and validity assessment*	Patient characteristics and definition of infection	Antibiotic regimen	Results	Comments and authors' conclusions
Bryan, *et al.,* 1988[16] USA Double-blind RCT A: 2 B: 0 C: 1 D: 2 E: 1 F: 0 G: 2 H: 1 I: 3	109 patients undergoing either THR or TKR (initial or revision procedures) were randomised. Characteristics only given for evaluable patients M/F = 39/58 Mean age = 59 years Definitions of infection were not given. However, febrile morbidity was defined as oral temperature greater than 100.4°F during any three consecutive 24-hour periods during the first 8 postoperative days. Preoperative and postoperative laboratory tests included complete blood counts, blood chemistry tests and urinalyses. Cultures were obtained from all suspected sites of infection	Group A: cephazolin, 1 g 1 hour prior to anaesthesia, followed by 1 g during surgery for procedures exceeding 2 hours, and then 500 mg 8-hourly for six doses (*n* = 55) Group B: cefamandole, 2 g $^1/_2$–1 hour prior to anaesthesia, followed by 2 g during surgery for procedures exceeding 2 hours, and then 1 g 8-hourly for six doses (*n* = 54) Antibiotics were given either i.v. or i.m. Type of OT: not stated	Analysis was not carried out on an ITT basis Febrile morbidity during first 8 postoperative days: Group A: 21/48 Group B: 26/49 (NS) SWI (short-term follow-up): Group A: 0/48 Group B: 2/49 (NS) Deep wound infection (at least 2 years after surgery): Group A: 0/48 Group B: 0/49 (NS) No statistically significant differences were found between the two groups in terms of UTI, pneumonia, laboratory tests or other postoperative complications. Serum and bone concentrations are reported in the paper	Cannot separate TKR results from THR results The study presents data suggesting that both cephazolin and cefamandole are equally effective for the prevention of postoperative wound infection in patients undergoing TJRs. The authors suggest that the choice of agent should include consideration of cost Supported in part by a grant from Smith Kline and French Laboratories
Carlsson, *et al.,* 1977[17] Sweden Follow-up of earlier trial[20] Multicentre double-blind RCT A: 0 B: 0 C: 1 D: 1 E: 0 F: 1 G: 1 H: 3 I: 3	Number originally randomised not clear. Paper reports data on 118 THR M/F = 476/654 Mean age (± SD) = 64.6 ± 9.3 years Only deep infections, both early and late, were considered. Deep infections were defined as: positive aerobic culture from fistulae or abscesses or with positive aerobic or anaerobic culture from tissue specimens adjacent to the prosthesis or the surface of cement; pain; roentgen signs of infection according to Bergstrom, *et al.*,[51] and elevated ESR (above 35 mm/hour)	Group A: cloxacillin, 1 g i.m. preoperatively followed by three further doses 6-hourly. Following this patients received 1 g orally 6-hourly until day 14 inclusive of the operation. In addition, patients received oral probenecid, 1 g b.d. during the same period as the cloxacillin (*n* = 60) Group B: placebo given as for cloxacillin. Patients also received probenecid as in Group A (*n* = 58) Type of OT: conventional	Analysis was not carried out on an ITT basis Deep infections 1–2$^1/_2$ years postoperative: Group A: 0/60 Group B: 7/58 ($p < 0.05$) Deep infections 5–6$^1/_2$ years postoperative: Group A: 2/60 Group B: 14/58 ($p < 0.01$) No cost information reported	The results of this trial suggest that cloxacillin is effective in preventing deep infection occurring after THR. The results are supplemented by a retrospective investigation presented in the same paper Supported by Swedish Medical Research Council

* *Please refer to* Table 1 *in main report for validity codes*

M/F, male/female; TJR, total joint replacement; ESR, erythrocyte sedimentation rate; UTI, urinary tract infection; OT, operating theatre; SD, standard deviation; b.d., twice daily; i.v., intravenously; i.m., intramuscularly; NS, not significant

continued

Study and validity assessment*	Patient characteristics and definition of infection	Antibiotic regimen	Results	Comments and authors' conclusions
Davies, *et al.,* 1986[18] UK Single-centre RCT A: 0 B: 0 C: 1 D: 0 E: 0 F: 0 G: 2 H: 0 I: 0	60 patients undergoing THR. Revision procedures were excluded M/F = 21/39 Mean age (range) = 72.5 years (61–80) No definition of wound infection reported. Bone, serum and tissue samples were taken 20, 35 and 60 minutes after the initial injection of antibiotic	Group A: cephradine, 1 g i.v. at induction of anaesthesia, followed by two similar doses 8-hourly (*n* = 21) Group B: cefuroxime, 1 g i.v. at induction of anaesthesia, followed by two similar doses 8-hourly (*n* = 20) Group C: cefamandole, 1 g i.v. at induction of anaesthesia, followed by two similar doses 8-hourly (*n* = 18) Comparability of groups not discussed Type of OT: not stated	98% of patients were assessed in the immediate postoperative period No prosthetic or wound infections and no significant side-effects were detectable during the observation period All three antibiotics showed similar serum:bone and serum:tissue ratios No cost information reported	The main aim of this study was to assess bone, serum and tissue concentrations. The follow-up period and sample size mean the trial is severely limited in its ability to detect wound infections. The authors conclude, however, that as concentration levels were comparable for all three antibiotics, the choice of prophylactic agent for THR should be guided by the pathogens causing the infection and the cost of the antibiotic Source of funding not stated
DeBenedictis, *et al.,* 1984[19] USA Single-centre, double-blind RCT A: 0 B: 0 C: 0 D: 1 E: 2 F: 0 G: 2 H: 0 I: 2	76 patients undergoing either THR or TKR (both initial and revision procedures) M/F = 31/45 Mean age (range) = 67.5 years (36–86) No definition of wound infection reported	Group A: cefonicid, 1 g i.m. or i.v. 30 minutes prior to incision, and then o.d. for 3 days (*n* = 37) Group B: cephazolin, 1 g i.m. or i.v. 30 minutes prior to incision and then 8-hourly for 72 hours post-operatively (*n* = 39) Groups were comparable with regard to age, sex, antecedent disease risk factors and duration of surgical procedure Previous surgery (prosthetic and non-prosthetic) on the joint operated on was more common in Group A (9 vs. 4) Type of OT: not stated	96% of patients were available for assessment. Follow-up period ranged from 4 months to 1 year There were no early or late wound infections evident in either group. All cultures performed on blood, synovial fluid and tissue samples showed no evidence of sepsis One patient in Group A had a prolonged febrile course and one patient in Group B had a bronchial infection. Neither case resulted in prosthetic sepsis No drug toxicity reported in either group No cost information reported	No statistically significant differences were reported between the groups. However, as discussed by the authors, a larger sample size and longer follow-up period would be required to demonstrate an increased efficacy of one regimen over another Supported in part by a grant from Smith Kline and French Laboratories

* *Please refer to* Table 1 *in main report for validity codes*
M/F, male/female; OT, operating theatre; o.d., once daily; i.v., intravenously; i.m., intramuscularly

continued

Study and validity assessment*	Patient characteristics and definition of infection	Antibiotic regimen	Results	Comments and authors' conclusions
Doyon, *et al.,* 1987[11] France Long-term results of previously published trial (Hill, *et al.,* 1981[10]). Data on trial methodology taken from previous paper Multicentre, double-blind RCT A: 2 B: 1 C: 2 D: 2 E: 0 F: 1 G: 2 H: 2 I: 3	2137 patients undergoing THR in nine centres M/F = 42/58% Mean age = 64.5 years Possible risk factors reported in the trial Samples taken for bacteriological examination. Hip infections were defined as abscess, septicaemia, or lethal infection. Hips were evaluated clinically, radiologically and biologically (ESR)	Group A: cephazolin, 1 g at induction of anaesthesia, followed by the same dose 6-hourly for 5 days (n = 1070) Group B: placebo, same timing as for Group A (n = 1067) Type of OT: four centres had hyper-sterile OTs; the remaining five centres had conventional OTs	Analysis was carried out on an ITT basis Hip infections 2 years postoperative: Group A: 10/1070 Group B: 35/1067 ($p < 0.01$) Hip infections were not found more frequently in the high-risk patients There were more infections in the centres with conventional OTs than those with a hyper-sterile OTs, and the difference between placebo and cephazolin is restricted to conventional OT UTIs were significantly fewer in Group A ($p < 0.01$), but were found not to be linked to hip infections No cost information reported	A well-designed multi-centre RCT, demonstrating the reduction of infections following the administration of antimicrobial prophylaxis. The benefit of antimicrobial prophylaxis was, however, restricted to procedures carried out in conventional OTs Source of funding not stated
Evrard, *et al.,* 1988[22] France Also published in French (1985)[21] Multicentre, double-blind RCT A: 2 B: 1 C: 2 D: 1 E: 2 F: 0 G: 2 H: 3 I: 2	965 THR in 912 patients M/F = 502/410 Mean age (± SD) = 65.8 ± 11 years Only deep infections of the hip, as defined below, were recorded: 1: subacute sepsis with isolation of pathogenic organisms obtained by direct aspiration 2: acute infection with clinical signs of sepsis (pain, fever, redness of the wound) 3: discharging sinus	Group A: cephazolin, 1 g at induction of anaesthesia. The dose was repeated 6-hourly for 5 days (n = 477) Group B: cefamandole, 1.5 g i.v. at induction of anaesthesia, followed by eight further doses of 0.75 g over 2 days (n = 488) Antibiotic-loaded cement was not used. Aseptic technique, conditions of operative field and conduct of the operation, did not vary between the two treatment groups Type of OT: conventional	84% of the patients followed-up for at least 1 year. Analysis carried out on an ITT basis Deep infections of the hip: Group A: 2/477 (one septic loosening, one sinus) Group B: 3/488 (two secondary acute, one sinus) There was no statistically significant difference in the number of infected drains Group B did demonstrate a lower rate of Gram-negative organisms ($p < 0.01$)	A well-designed trial demonstrating that cefamandole, given for 2 days, appears to be as effective as cephazolin, given for 5 days, in preventing infection following THRs Source of funding not stated

* *Please refer to* Table 1 *in main report for validity codes*
M/F, male/female; ESR, erythrocyte sedimentation rate; UTI, urinary tract infection; OT, operating theatre; SD, standard deviation; i.v., intravenously

continued

Study and validity assessment*	Patient characteristics and definition of infection	Antibiotic regimen	Results	Comments and authors' conclusions
Gunst, *et al.,* 1984[23] France A: 0 B: 0 C: 2 D: 1 E: 0 F: 0 G: 1 H: 3 I: 2	93 THR undertaken in 84 patients M/F = 42/51 Average age = 65 years Wounds infections were described as superficial or serious infections. Serious infections were those occurring around the prosthesis necessitating further surgery of the joint. Serious infections were subdivided into early (signs of infection within 1 month); late (signs of infection after 1 month); latent sepsis (diagnosed 6 months postoperatively according to recurrence of hip pain, radiographic signs of loosening and on the basis of previous positive cultures from Redon drains)	Group A: cefamandole, 1.5 g i.v. prior to incision, followed by 1.5 g 4-hourly up to 24 hours post-operatively (*n* = 46) Group B: no antibiotic treatment (*n* = 47) All patients were operated on by the same surgeons Type of OT: clean air system	All randomised patients were included in the analysis Early major infections: Group A: 1/46 Group B: 4/47 (NS) Late major infections: Group A: 0/46 Group B: 1/47 (NS) Latent sepsis: Group A: 0/46 Group B: 3/47 (NS) No cost information reported	The authors conclude that 1-day prophylatic antibiotic therapy with cefamandole decreases the incidence of major infection at the surgical site in THR with the use of a clean air system. However, no statistically significant differences were demonstrated between the two groups. The small sample size may have limited the trial in its ability to identify any significant differences Source of funding not stated
Heydemann & Nelson, 1986[24] USA Study 1 also published elsewhere (1983)[36] Two single-centre RCTs A: 0 B: 0 C: 0 D: 0 E: 0 F: 0 G: 0 H: 1 I: 2	*Study 1* 255 TJR (184 THR, 71 TKR). Age range = 23–88 years A wound was considered infected if it drained or contained purulent material, or if it had a haematoma from which an organism was cultured (data taken from Nelson, *et al.*[36]) *Study 2* 211 TJR (122 THR, 89 TKR). No details of patient characteristics or SWI definition	*Study 1* Group A: nafcillin or cephazolin, 1 g i.v. 6-hourly for 24 hours (THR = 88;TKR = 39) Group B: nafcillin or cephazolin, 1 g i.v. 6-hourly for 72 hours, followed by 500 mg 6-hourly for 4 days (THR = 96;TKR = 32) *Study 2* Group C: nafcillin or cephazolin, 1 g i.v. prior to incision of the skin (THR = 58;TKR = 45) Group D: nafcillin or cephazolin, 1 g i.v. prior to incision of the skin, followed by the same dose 6-hourly for 48 hours (THR = 64; TKR = 44) Type of OT: all procedures were carried out in an ultraclean air system	*Study 1* Deep wound infections at 1 year: Group A: 1/127 Group B: 2/128 (NS) No infections were noted in the TKR patients *Study 2* Deep wound infections at 1 year: Group C: 0/103 Group D: 0/108 (NS) Per 100,000 patients, the cost savings of giving antibiotics intraoperatvely rather than for 48 hours would have been US$7,700,000; with the reduction from 7 days to one-dose antibiotics, the savings would have been US$29,700,000	Cannot separate TKR results from THR results. No statistically significant differences were found between any of the regimens examined in terms of infection rates. Cost issues must be taken into account when deciding upon antimicrobial prophylaxis for elective TJRs Source of funding not stated

* *Please refer to* Table 1 *in main report for validity codes*
M/F, male/female; TJR, total joint replacement; OT, operating theatre; i.v., intravenously; NS, not significant

continued

Study and validity assessment*	Patient characteristics and definition of infection	Antibiotic regimen	Results	Comments and authors' conclusions
Jones, *et al.,* 1988[28] USA Three multicentre, single-blind RCTs (1987)[25–27] A: 0 B: 0 C: 0 D: 2 E: 2 F: 0 G: 2 H: 2 I: 2	Total of 2215 patients, 320 evaluable TJR patients. Patient characteristics are not supplied for TJR patients All three trials used the same methodology Postoperative infection was defined as presence of purulent material drained from the surgical incision or peritoneal cavity, regardless of bacteriological or laboratory investigation	*Study 1* Group A: cefotaxime, 1 g i.v. on arrival at OT. A further 1 g was administered if procedure lasted more than 2 hours (*n* = 59) Group B: cephazolin, 1 g i.v. on arrival at OT, followed by 1 g 8-hourly for 24 hours (*n* = 57) Group C: cefoxitin, 2 g i.v. on arrival at OT, followed by 2 g 6-hourly for 24 hours (*n* = 69) *Study 2* Group A: as above (*n* = 9) Group D: ticarcillin/clavulanic acid, 3.1 g (*n* = 16) *Study 3* Group A: as above (*n* = 51) Group E: cefoperazone, 1 g on arrival at OT (*n* = 59) Type of OT: ultraclean air	The results for the cefotaxime patients have been pooled. No statistically significant differences were observed between groups in terms of wound infection. Nearly 70% of wounds were late onset (8–30 days) Group A: 1/119 Group B: 1/57 Group C: 0/69 Group D: 0/16 Group E: 0/59 The total costs (US$) for the antibiotic regimen studied were calculated at: cefotaxime = $12.90 cephazolin = $30.00 cefoxitin = $100.00 ticarcillin/clavulanic acid = $14.15 cefoperazone = $14.50	The results of three RCTs are presented, covering gastrointestinal, obstetrics and gynaecology, orthopaedic and other procedures. Data relating specifically to TJR are limited. However, the results for all surgical procedures suggest that single-dose prophylaxis with cefotaxime, cefoperazone or ticarcillin/clavulanic acid provide safe, effective and economical prophylaxis Source of funding not stated
Josefsson & Kolmert, 1993[31] Sweden 10-year follow-up of multicentre RCT. More detailed methodology published elsewhere (1981, 1990)[29,30] A: 0 B: 0 C: 1 D: 0 E: 0 F: 0 G: 1 H: 2 I: 3	1688 consecutive THR in 1599 patients M/F = 853/835 Mean age at time of operation (range) = 69 years (25–98) Prostheses used included: Christiansen (*n* = 763); Brunswik/Lubinus (*n* = 606); Charnley (*n* = 199); computer-assisted design (*n* = 112); other (*n* = 8) The definition of superficial wound infection was based on the following criteria: abnormal redness of the wound, presence of secretion, initiation of antibiotics A diagnosis of deep infection was based on the following three criteria: pain, elevated ESR, and progressive radiographic resorption of the bone stock	Group A: systemic antibiotics; cloxacillin, 1 g q.d.s. for 7–14 days (*n* = 359); dicloxacillin, 1 g q.d.s. for 8–14 days (*n* = 192); cephalexin, 1 g q.d.s. for 9–11 days (*n* = 209); phenoxymethyl penicillin, 0.65 g q.d.s. for 10 days (*n* = 75) Group B: gentamicin bone cement (0.5 g gentamicin to each 40 g packet of cement) (*n* = 853) Type of OT: not stated	1115 hips were available for evaluation at the 10-year follow-up. The rate of infection was calculated including patients deceased during the study Deep infections at 1–2 years: Group A: 13/812 Group B: 3/821 ($p < 0.05$) Deep infections at 5 years: Group A: 16/800 Group B: 7/831 ($p < 0.05$) Deep infections at 10 years: Group A: 13/789 Group B: 9/813 (NS) No statistically significant difference in rates of aseptic loosening were demonstrated No cost information reported	A large multicentre trial examining the prophylactic effect of gentamicin-loaded cement compared with the effect of systemic antibiotics. Problems associated with the trial include both variation in systemic antibiotic use and prostheses used. Ideally, these should be standardised. There were also problems in correctly diagnosing deep infections The findings of the study indicate that gentamicin-loaded cement, when compared with systemic antibiotics, is significantly better at preventing deep wound infections up to 5 years postoperative. This statistically significant difference not detectable 10 years after surgery Source of funding not stated

* *Please refer to* Table 1 *in main report for validity codes*

M/F, male/female; TJR, total joint replacement; ESR, erythrocyte sedimentation rate; OT, operating theatre; q.d.s., four times daily; i.v., intravenously; NS, not significant

continued

Study and validity assessment*	Patient characteristics and definition of infection	Antibiotic regimen	Results	Comments and authors' conclusions
Mauerhan, *et al.*, 1994[32] USA Multicentre, double-blind RCT. A: 2 B: 0 C: 2 D: 2 E: 2 F: 1 G: 2 H: 3 I: 2	1354 patients undergoing either primary or revision TJR (hip or knee) M/F = 533/821 Mean age (range) = 65 years (17–93) Wound infections were classified as either superficial or deep, depending on whether they developed above or below the fascia. Acute wound infections were those that had developed during hospitalisation; early infections were those that had developed by the 2–3-month assessment; and late infections, those that had developed by the 1-year assessment	Patients were stratified according to the operative procedure prior to randomisation Group A: cefuroxime, 1.5 g i.v. followed by 750 mg 8 and 16 hours later. Normal saline solution was then given 8-hourly for six additional doses (n = 669) Group B: cephazolin, 1 g i.v. followed by 1 g 8-hourly for eight additional doses (n = 685) No antibiotics in the irrigation solutions or bone cement Groups were comparable except that there was a significantly higher proportion of female patients in Group A (p = 0.007) Type of OT: not stated	62% of patients followed up for 1 year. Analysis carried out on an ITT basis Wound infections in primary THR patients: Group A: 4/285 (one deep, three superficial) Group B: 4/261 (two deep, two superficial) Wound infections in revision THR patients: Group A: 1/62 (one deep) Group B: 2/69 (one deep, one superficial) Wound infections in primary TKR patients: Group A: 7/293 (one deep, six superficial) Group B: 7/322 (three deep, four superficial) Wound infections in revision TKR patients: Group A: 0/29 Group B: 1/33 (one superficial) Seven infections were acute; 16 early; three late No significant difference between groups with regard to UTI, pneumonia, adverse events, mortality	A well-designed RCT demonstrating no statistically significant difference in the prevalence of wound infections between the patients who had received a 1-day regimen of cefuroxime and those who had received a 3-day regimen of cephazolin Supported by Glaxo, Inc.
McQueen, *et al.*, 1990[34] UK See also McQueen, *et al.*, 1987[33] Multicentre, single-blind RCT A: 0 B: 0 C: 1 D: 0 E: 2 F: 0 G: 1 H: 3 I: 3	405 TJR (either hip or knee) in 378 patients M/F = 152/253 Mean age (range) = 67 years (19–93) Deep infections were classified as: those extending deep into the fascia, with persistent wound discharge or joint pain, positive or negative cultures from deep tissues and delay in wound healing Superficial infections were classified as: those superficial to the deep fascia with positive or negative bacteriological cultures and no delay in wound healing. Infections were further classified as early (up to 3 months postoperatively) or late (3 months to 2 years postoperatively)	Group A: cefuroxime, 1.5 g i.v. administered at induction of anaesthesia, followed by two doses of 750 mg i.m. at 6 and 12 hours postoperatively (n = 201) Group B: cefuroxime powder, 1.5 g mixed in the OT with each pack of CMW (a polymethylmethacrylate cement) type 1 cement. Barium sulphate was added as a marker. The liquid polymer was added and the operation continued in the usual way (n = 204) Type of OT: not stated	99% of patients were followed-up for 2 years Deep infections in THR: Group A: 1/190 (early) Group B: 2/190 (early) Superficial infections in THR: Group A: 8/190 (early) Group B: 14/190 (early) Deep infections in TKR: Group A: 1/11 (early) Group B: 0/14 Superficial infections in TKR: Group A: 0/11 Group B: 4/14 The use of drainage, type of approach to hip joint, type of prosthesis, length of operation, were analysed but no difference in infection rates were found. No significant difference in UTI or respiratory tract infection rates between the two groups No cost information reported	The trial demonstrates no statistically significant difference between cefuroxime given systemically or in bone cement for the prevention of wound infection in TJR. It is thought that systemic use of the antimicrobial agent may be more convenient Supported by Glaxo Group Research Ltd

* *Please refer to* Table 1 *in main report for validity codes*

M/F, male/female; TJR, total joint replacement; UTI, urinary tract infection; OT, operating theatre; i.v., intravenously

continued

Study and validity assessment*	Patient characteristics and definition of infection	Antibiotic regimen	Results	Comments and authors' conclusions
Mollan, *et al.*, 1992[35] UK Single-centre RCT A: 0 B: 0 C: 0 D: 0 E: 0 F: 0 G: 2 H: 2 I: 2	850 patients undergoing primary THR or TKR. Only data on evaluable patients provided M/F = NA Mean age = NA (all patients > 14 years) THR/TKR = 512/148 Wounds were scored from 0–6: 0: a normal wound 1: mild erythema 2: severe erythema 3: serous discharge 4: purulent discharge 5: minor dehiscence 6: complete dehiscence Primary failure defined as a microbiologically documented wound infection (either major or minor). Secondary clinical failure defined as signs of remote infection from the wound, either pyrexia over 38.5°C between day 1 and 10, or where antibiotics were prescribed, where further surgery was required, or where there was proven infection	Group A: teicoplanin, 400 mg at induction of anaesthesia (n = 308) Group B: cefamandole, 2 g i.v. at induction, followed by 1 g at 6, 12 and 18 hours post-operatively (*n* = 352) All patients had gentamicin-loaded bone cement Comparability of groups not discussed Type of OT: not stated	77.6% of enrolled patients were available for evaluation Primary failure at 8–10 days: Group A: 2/308 (one major, one minor) Group B: 2/352 (two major) Primary failure at 30-day evaluation: Group A: 0/308 Group B: 1/352 (one major) Secondary failure at 8–10 days: Group A: 30/308 Group B: 38/352 Secondary failure at 30-day evaluation: Group A: 5/308 Group B: 3/352 Adverse events occurred in 5.1% of Group A patients and 7.1% of Group B patients. One adverse event in Group A and two in Group B were thought to be related to the study drug No cost information reported	Cannot separate TKR results from THR results. Results from this interim analysis demonstrate similar incidences of major wound infections in the two groups. The authors comment on the lack of statistical power to show a statistically significant difference between the two antibiotics, but suggest that a single dose of teicoplanin is as effective as four doses of cefamandole in prophylaxis for THR and TKR At the time of publication, recruitment into the trial continued. No further publication reporting data from this trial was identified Source of funding not stated
Periti, *et al.*, 1994[37] Italy Mulitcentre RCT A: 0 B: 0 C: 2 D: 0 E: 2 F: 0 G: 2 H: 2 I: 2	359 THR and 80 TKR were undertaken in ten orthopaedic centres. 71% of all procedures were cemented. 70% were primary procedures M/F = 160/279 Mean age = 65 years Failure was defined as: early infection of the wound (any surgical wound which drained purulent or serous material, even with negative bacteriological culture); delayed deep prosthesis infection; fever exceeding 38°C (excluding first 24 hours postoperative); infectious complications at non-surgical site; antibiotic therapy during the postoperative period	Group A: teicoplanin, 400 mg i.v. at induction of anaesthesia (THR = 192; TKR = 43) Group B: cephazolin, 2 g i.v. at induction of anaesthesia, followed by 1 g i.v. 6-hourly for a further four doses (THR = 167; TKR = 37) Type of OT: 322/439 (73%) procedures were carried out in conventional OTs; 114/439 (26%) in hypersterile theatres; the remainder were unspecified	72% of enrolled patients were available for evaluation at 3 months. Analysis carried out on an ITT basis. The results for THR and TKR are presented together Wound infection at 3 months: Group A: 4/235 Group B: 2/204 (NS) Asymptomatic bacteriuria: Group A: 2/235 Group B: 9/204 ($p < 0.01$) No significant differences were demonstrated between the two groups in terms of bronchopneumonia, thrombophlebitis, fever, or the need for antibiotic therapy No cost information reported	Cannot separate TKR results from THR results. The preliminary results of this trial suggest that a single perioperative dose of teicoplanin is as effective as a multiple-dose regimen of cephazolin for the prevention of infection following TJR. As yet, no further publications reporting long-term follow-up have been identified

* *Please refer to* Table 1 *in main report for validity codes*

M/F, male/female; NA, data not available; TJR, total joint replacement; OT, operating theatre; i.v., intravenously; NS, not significant

continued

Study and validity assessment*	Patient characteristics and definition of infection	Antibiotic regimen	Results	Comments and authors' conclusions
Ritter, *et al.*, 1989[38] USA Single-centre RCT A: 0 B: 0 C: 2 D: 0 E: 0 F: 0 G: 0 H: 1 I: 2	276 TJR (hip or knee) were undertaken in 196 patients. All were primary procedures M/F = 73/123 Mean age (range) = 66.4 years (17–88) No definitions given for wound infection. Opening and closing cultures were taken during every surgery	Group A: cefuroxime, 1.5 g and 750 mg i.v. intraoperatively, followed by further doses of 750 mg 8-hourly for 24 hours (THR = 66; TKR = 32) Group B: cefuroxime, 1.5 g and 750 mg i.v. intraoperatively. No postoperative doses given (THR = 45; TKR = 53) Type of OT: not stated	All patients were followed for at least 1 year Five deaths occurred (four in Group A, one in Group B), none related to the arthroplastic surgery No deep wound infections occurred in either group Positive cultures (either opening or closing): Group A: 5/98 Group B: 10/98 (NS) Other recorded complications included positive urine culture (significantly higher in Group B), thromboembolic disorders, urinary retention and cystoscopy with transurethral resection No cost information reported	Cannot separate TKR results from THR results. Few data are given on the methodology of the trial. However, the results suggest that there may be no statistically significant advantage of postoperative doses of cefuroxime when intraoperative dose are given Source of funding not stated
Schulitz, *et al.*, 1980[39] Germany Single-centre RCT A: 0 B: 0 C: 1 D: 0 E: 1 F: 0 G: 2 H: 2 I: 3	259 patients requiring THR due to coxarthrosis. 65 excluded from final analysis M/F = 64/130 Mean age = NA Superficial wound infection: presence of temperature, signs of inflammation with superficial induration of the wound and purulent wound drainage Deep infection: signs of inflammation with deep induration in the wound area during the observation period	Group A: lincomicin, 600 mg, i.v. 1 and 6 hours postoperatively. On the next day two additional i.v. doses of 600 mg lincomicin were given, and then from day 3 until day 10 postoperatively, a dose of 1 g was given orally, t.d.s. (n = 137) Group B: no antibiotic therapy (n = 122) Antibiotic-loaded cement was not used. Both groups were comparable with regard to age, time of surgery, duration of surgery and blood loss Type of OT: conventional	75% of randomised patients available for evaluation 2 years postoperative Superficial wound infections: Group A: 2/105 Group B: 2/89 Deep infections: Group A: 1/105 Group B: 8/89 ($p < 0.025$) No statistically significant differences were found between the groups with regard to other postoperative infections (urethrocystitis, pyelonephritis, pneumonia, abscess of labium) No cost information reported	The study demonstrates that the prophylactic use of antimicrobial agents significantly reduces the rates of deep SWIs following THR. The trial would have been enhanced by the assignment of a placebo to the control group and further details on outcome assessment Source of funding not stated
Soave, *et al.*, 1986[40] USA Single-centre RCT A: 1 B: 0 C: 0 D: 0 E: 1 F: 0 G: 2 H: 1 I: 2	101 patients (THR/TKR) were randomised. Mean age = 63 years (range, 29–87) No definition of wound infection given All patients were examined for fever and wound infection daily until discharge, and at 6 weeks, and 12–18 months later	Group A: ceforanide, 1 g preoperatively, followed by 1 g 12 hours later (THR = 38; TKR = 18) Group B: cephalothin, 2 g preoperatively, 2 g intraoperatively, and 1 g 6-hourly for a further three doses. (THR = 35; TKR = 22) Type of OT: not stated	No infected implants in the 101 patients followed for 6 weeks, or in the 81 patients followed for 18 months Six patients in Group A had postoperative UTI, compared with three patients in Group B. Mean plasma and bone concentrations were higher in Group A No cost information reported	Little detail on the trial's methodology is presented. The results of the trial are inconclusive, due to the small sample size Source of funding not stated

* *Please refer to* Table 1 *in main report for validity codes*

M/F, male/female; NA, data not available; TJR, total joint replacement; UTI, urinary tract infection; OT, operating theatre; t.d.s., three times daily; i.v., intravenously; NS, not significant

continued

Study and validity assessment*	Patient characteristics and definition of infection	Antibiotic regimen	Results	Comments and authors' conclusions
Suter, *et al.*, 1994[41] Italy Single-centre, single-blind RCT A: 1 B: 0 C: 1 D: 0 E: 1 F: 0 G: 2 H: 2 I: 2	520 patients undergoing elective THR M/F = 140/256 Mean age = 67 years Deep infection or infection of the prosthetic device, defined as: pain, local tenderness, abnormal ESR, radiographical signs of infection or positive bacterial cultures of the periprosthetic space Wound complications defined as: erythema, superficial haematoma, serous exudate	Group A: teicoplanin, 400 mg i.v., 60–90 minutes pre-operatively (n = 260) Group B: cefamandole, 2 g i.v. 60–90 minutes preoperatively (n = 260) Orthopaedic procedures performed by the same two surgeons, in the same OT (without laminar flow). Preoperative preparation of the skin was identical in the two groups. The two groups were comparable with regard to major patient characteristics Type of OT: conventional	91% of patients followed for at least 1 year Deep infections of the prosthesis did not occur in either group Wound erythema: Group A: 4/250; Group B: 3/246 Serous non-infected exudate: Group A: 1/250; Group B: 0/246 Non-infected haematoma: Group A: 8/250; Group B: 4/246 Infected superficial haematoma: Group A: 0/250; Group B: 4/246 No significant difference between groups for duration of hospitalisation (17.04 ± 6.55 vs. 17.11 ± 5.02 days). No late infective complications observed in either group No cost information reported	A clear trial demonstrating no statistically significant difference between teicoplanin and cefamandole for the prevention of infection in THR Source of funding not stated
Vainionpää, *et al.*, 1988[42] Finland Single-centre RCT A: 0 B: 0 C: 2 D: 0 E: 2 F: 0 G: 2 H: 1 I: 3	58 consecutive patients undergoing either THR or TKR for osteoarthritis. Revision procedures were excluded M/F = 14/44 Mean age (range) = 67.4 years (54–79) Main outcome reported is serum concentration. No definition of wound infection provided	Both groups received 2 g of i.v. antibiotic over a 10-minute period after anaesthesia had been established Group A: cefamandole, 1 g parenterally, 6-hourly for 3 days (*n* = 29) Group B: cloxacillin, 2 g i.v. 8-hourly for 1 day, followed by dicloxacillin, 1 g orally, for 2 days (*n* = 29) Type of OT: not stated	There was no deep infection or loosening of the endoprosthesis during the 2 year follow-up in either group Serum C-reactive protein levels were also monitored No cost information reported	Both antibiotics regimens appeared effective at preventing SWIs Supported by Eli Lilly Corporation

* *Please refer to* Table 1 *in main report for validity codes*

M/F, male/female; ESR, erythrocyte sedimentation rate; OT, operating theatre; i.v., intravenously

continued

Study and validity assessment*	Patient characteristics and definition of infection	Antibiotic regimen	Results	Comments and authors' conclusions
Wall, *et al.,* 1988[43] UK A: 0 B: 0 C: 2 D: 1 E: 0 F: 0 G: 2 H: 3 I: 1	146 patients undergoing either THR or TKR M/F = NA Mean age (range) = 69 years (19–86) Wound healing was categorised as: 0: normal healing 1: erythema 2: serous exudate 3: purulent exudate 4: wound separation	Group A: teicoplanin, 400 mg i.v. at induction of anaesthesia (*n* = 72) Group B: cefuroxime, 750 mg i.v. with pre-medication, 750 mg i.v. at induction of anaesthesia, and a further 750 mg i.v. 8 hours postoperatively (*n* = 74) Type of OT: not stated	All randomised patients were monitored for 10 days Erythema at day 10: Group A: 0/72; Group B: 2/74 Serous exudate at day 10: Group A: 9/72; Group B: 11/74 Purulent exudate at day 10: Group A: 0/72; Group B: 3/74 Wound separation at day 10: Group A: 1/72; Group B: 0/74 There were more isolates from wounds in Group B, though most were of doubtful significance Possibly-related adverse events: Group A: 8.3%; Group B: 8.1% No cost information reported	Cannot separate TKR results from THR results. No statistically significant differences in the efficacy of the two regimens were demonstrated. The article reports the results as interim results, stating that the patients were to be followed to determine the frequency and microbiology of later onset sepsis Supported by Merrell Dow
Wollinsky, *et al.,* 1997[44] Germany Single-centre RCT A: 0 B: 0 C: 2 D: 2 E: 1 F: 0 G: 2 H: 3 I: 0	40 patients undergoing primary THR M/F = NA Mean age = 63.5 years No definition of wound infection given. Contamination of wound drainage blood was graded: 0: no growth on agar and in broth 1: growth only in broth 2: growth on agar with no more than ten colonies 3: growth on agar with 11–100 colonies 4: growth on agar with more than 100 colonies	Group A: cefuroxime, 1.5 g after induction of anaesthesia (*n* = 20) Group B: no antibiotics (*n* = 20) Both groups underwent autologous processed blood transfusion. Groups were comparable with regard to age and weight. However, several risks factors were found in combinations that led to a significantly higher ($p = 0.04$) total anaesthesiological risk, rated according to the five-point scale of the American Society of Anaesthesiologists Type of OT: not stated	All patients were monitored for the duration of the hospital stay No wound infections or pulmonary infections were found in either group The operative field and wound drainage blood were never contaminated in either group but some of the suction tips were. Parts of the blood collection bags for Group B showed contamination, and processed red blood cell concentrates in both groups showed bacterial growth No cost information reported	The main aim of this study was to examine bacterial contamination during THR and autotransfusion. The sample size and duration of follow-up severely limit the studies ability to detect differences in wound infection rates Supported by Hoechst AG, Stuttgart

* *Please refer to* Table 1 *in main report for validity codes*

M/F, male/female; NA, data not available; OT, operating theatre; i.v., intravenously

continued

Study and validity assessment*	Patient characteristics and definition of infection	Antibiotic regimen	Results	Comments and authors' conclusions
Wymenga, *et al.*, 1992[45] The Netherlands Multicentre RCT Data from the same trial also published earlier by same author (1991)[52] A: 1 B: 0 C: 1 D: 0 E: 2 F: 0 G: 1 H: 2 I: 2	3199 patients undergoing THR, hemiarthroplasty of the hip were randomised (primary or revision procedures). Characteristics reported for evaluable patients only M/F = 553/2098 Mean age = 69 years 91% of evaluable patients had undergone a THR Patients were categorised as: Category 1: confirmed joint sepsis (defined as a positive bacteriological culture at reoperation or a draining sinus), or strong evidence of sepsis (defined as four or more possible signs of infection) Category 2: two or three possible signs of sepsis, but a definite diagnosis could not be made Category 3: one or no signs or infection Conditions defined as possible infections were pain during weight bearing and/or rest; tenderness of the wound; fever; an abnormal radiograph; ESR > 20 mm above the preoperative value or > 35 mm; positive culture from fluid aspirate; positive arthrogram; bone scan showing typical signs of infection; or increased C-reactive protein Wound infection in the postoperative period was defined as erythema more than 1 cm from incision	Group A: cefuroxime, 1.5 g i.v. at induction of anaesthesia (n = 1600) Group B: cefuroxime, 1.5 g i.v. at induction of anaesthesia. Second and third doses of cefuroxime, 750 mg, were given after 8 and 16 hours (n = 1599) In three centres, the surgical wound was rinsed with a fluid containing an antibiotic Type of OT: conventionally ventilated OTs were used	Analysis was not carried out on an ITT basis Mean follow-up period was 13 months. 2651 patients were available for evaluation Category 1 (up to 24 months postoperative): Group A: 11/1327 Group B: 6/1324 (NS) Category 2: Group A: 7/1327 Group B: 9/1324 (NS) Postoperative wound infection (definition unclear): Group A: 25/1327 Group B: 31/1324 (NS) No differences were found between groups with respect to haematoma, wound drainage, the amount of additional antibiotics prescribed for wound problems, fever of unknown reason, or distant infections Only five patients in the study had allergic reactions associated with cefuroxime No cost information reported	No statistically significant differences in the efficacy of the two regimens were demonstrated. However, the authors state that they feel an extended follow-up study with more cases of joint sepsis may provide more conclusive data Supported by Glaxo B.V., The Netherlands

* *Please refer to* Table 1 *in main report for validity codes*

M/F, male/female; ESR, erythrocyte sedimentation rate; OT, operating theatre; i.v., intravenously; NS, not significant

Appendix 3

Excluded studies

Boyd R, Burke J, Colton T. A double-blind clinical trial of prophylactic antibiotics in hip fractures. *J Bone Joint Surg [Am]* 1973;**55A**:1251–8.

Reason for exclusion: Examined the role of antimicrobial prophylaxis for hip fracture patients.

Burnett J, Gustilo R, Williams D, Kind A. Prophylactic antibiotics in hip fractures. A double-blind prospective study. *J Bone Joint Surg [Am]* 1980;**62A**:457–62.

Reason for exclusion: Examined the role of antimicrobial prophylaxis for hip fracture patients.

Gatell J, Riba J, Lozano M, Mana J, Ramon R, SanMiguel J. Prophylactic cefamandole in orthopaedic surgery. *J Bone Joint Surg [Am]* 1984;**66**:1219–22.

Reason for exclusion: Does not include THR data.

Hughes S, Want S, Darrell J, Dash C, Kennedy M. Prophylactic cefuroxime in total joint replacement. *Int Orthop* 1982;**6**:155–61.

Reason for exclusion: No mention of randomisation.

Lindberg L, Onnerfalt R, Dingeldein E, Wahlig H. The release of gentamicin after total hip replacement using low or high viscosity bone cement. A prospective, randomized study. *Int Orthop* 1991;**15**:305–9.

Reason for exclusion: RCT, but measures concentration of gentamicin in serum, not rates of infection.

Periti P, Jacchia E. Ceftriaxone as short term antimicrobial chemoprophylaxis in orthopedic surgery: a 1-year multicenter follow up. *Eur Surg Res* 1989;**21** (Suppl):25–32.

Reason for exclusion: RCT, but cannot separate out data on THR from other orthopaedic procedures.

Appendix 4

Methods by which studies were identified

Author	MEDLINE	CCTR	Bibliography	Expert
Bryan, *et al.,* 1988[16]	✔	✔		
Carlsson, *et al.,* 1977[17]	✔	✔	✔	✔
Davies, *et al.,* 1986[18]	✗[a]	✔		
DeBenedictis, *et al.,* 1984[19]	✔	✔		✔
Doyon, *et al.,* 1987[11]	✗[a]	✔	✔	
Evrard, *et al.,* 1988[22]	✔	✔		✔
Gunst, *et al.,* 1984[23]	✔	✗[a]		✔
Heydemann & Nelson, 1986[24] (two RCTs)	✔	✗[b]		✔
Jones, *et al.,* 1988[28] (three RCTs)	✔	✔	✔	✔
Josefsson & Kolmert, 1993[31]	✔	✔		
Mauerhan, *et al.,* 1994[32]	✔	✔		✔
McQueen, *et al.,* 1990[34]	✔	✔		✔
Mollan, *et al.,* 1992[35]	✔	✔		✔
Periti, *et al.,* 1994[37]	✗[a]	✗[b]		✔
Ritter, *et al.,* 1989[38]	✔	✔		
Schulitz, *et al.,* 1980[39]	✗[a]	✗[a]	✔	✔
Soave, *et al.,* 1986[40]	✔	✔		
Suter, *et al.,* 1994[41]	✔	✔		
Vainiopää, *et al.,* 1988[42]	✔	✔		✔
Wall, *et al.,* 1988[43]	✔	✔		
Wollinsky, *et al.,* 1997[44]	✔	✔		
Wymenga, *et al.,* 1992[45]	✔	✔		✔

CCTR, Cochrane Controlled Trials Register

✗[a], study on database, but not identified through the search strategy
✗[b], study not on database

Appendix 5

Number of comparisons of antibiotics in included RCTs

	Cefonicid	Cefoperazone	Ceforanide	Cefotaxime	Cefoxitin	Cefuroxime	Cephalexin	Cephalothin	Cefamandole	Cephazolin	Cephradine	Cloxacillin	Dicloxacillin	Gentamicin	Lincomicin	Nafcillin	Phenoxymethyl penicillin	Teicoplanin	Ticarcillin/clavulanic acid	Placebo/no treatment
Cefonicid										1										
Cefoperazone				1																
Ceforanide								1												
Cefotaxime		1			1					1									1	
Cefoxitin				1						1										
Cefuroxime						3			1	1	1							1		1
Cephalexin														1						
Cephalothin			1																	
Cefamandole						1				2	1	1						2		1
Cephazolin	1			1	1	1			2	2						1		1		1
Cephradine						1			1											
Cloxacillin									1					1						1
Dicloxacillin														1						
Gentamicin							1					1	1				1			
Lincomicin																				1
Nafcillin										1										
Phenoxymethyl penicillin														1						
Teicoplanin						1			2	1										
Ticarcillin/ clavulanic acid				1																
Placebo/ no treatment						1			1	1		1			1					

Appendix 6

Micro-organisms identified and sensitivity patterns: data reported in the included trials

Study	Micro-organisms identified in SWIs, and sensitivity patterns
Bryan, *et al.,* 1998[16] USA	Two patients receiving cefamandole developed infection at the operative sites, due to *S. aureus* and *S. epidermidis*, respectively
Group A: cephazolin Group B: cefamandole	Both isolates susceptible to cefamandole
Carlsson, *et al.,* 1977[17] Sweden	Analysis of 12 infected patients who had received cloxacillin (data from RCT and a retrospective study):
Group A: cloxacillin Group B: placebo	Immediately postoperative – *Proteus,* enterococci, *S. albus, Escherichia coli,* anaerobic peptococci, anaerobic streptococci
	Never quite symptom free – *Propionibaci acnes, S. aureus*
	After 3 months postoperative – *Pseudomonas pyocyanea, S. aureus,* anaerobic streptococci, *S. albus, Propionibact acnes*
	Seven infections were caused by microbes sensitive to cloxacillin in spite of the fact that this antibiotic was given prophylactically
Davies, *et al.,* 1986[18] UK	No SWI in any group
Group A: cephradine Group B: cefuroxime Group C: cefamandole	
DeBenedictis, *et al.,* 1984[19] USA	No SWI in either group
Group A: cefonicid Group B: cephazolin	
Doyon, *et al.,* 1987[11] France	No details of micro-organisms provided
Group A: cephazolin Group B: placebo	
Evrard, *et al.,* 1988[22] France	Two samples were taken for bacteriological examination: blood from the deepest part of the wound during operation, and specimens from the tip of the vacuum drainage tube after its removal. Forty-four drains were colonised in the cefamandole group and 35 in the cephazolin group (NS). The number of strains was 47 in the cefamandole group and 39 in the cephazolin group
Group A: cephazolin Group B: cefamandole	Group A: 44% Gram-negative; 56% Gram-positive (mainly *S. epidermidis*) Group B: 23% Gram-negative; 77% Gram-positive (mainly *S. epidermidis*)
	No pathogen was identified from three of the five infected hips. *Proteus morganii* was identified from one infected hip and *S. aureus* from another
	The percentage of resistant-colonising organisms, whether Gram-negative or Gram-positive was lower in the cefamandole group ($p < 0.01$). The percentage of methicillin-resistant staphylococci was 11% in the cefamandole group and 20% in the cephazolin group ($p > 0.05$)

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Study	Micro-organisms identified in SWIs, and sensitivity patterns
Gunst, *et al.,* 1984[23] France Group A: cefamandole Group B: No anti-microbial prophylaxis	Group A: *S. aureus* (one case), *aureus* (three cases), *Klebsiella* (one case)
Heydemann & Nelson, 1986[24] USA All groups received nafcillin or cephazolin for different duration	No details of micro-organisms provided
Jones, *et al.,* 1987/88[25–28] USA Group A: cefotaxime Group B: cephazolin Group C: cefoxitin Group D: ticarcillin/ clavulanic acid Group E: cefoperazone	No details of micro-organisms provided for THR patients The following reported details are for all surgical procedures (including gastrointestinal, obstetrics and gynaecology, orthopaedic, and other surgery) Organisms isolated from cephazolin and cefotaxime patients were equally divided between Gram-positive cocci and Gram-negative aerobic/anaerobic bacilli. However, virtually all (13/14) isolates cultured from cefoxitin regimen patients were Gram-positive, dominated by *S. aureus* and coagulase-negative *Staphylococcus* spp. Half the organisms causing infection in the cephazolin group were resistant to cephazolin. The proportion of resistant isolates for the cefoxitin and cefotaxime regimens were 29% and 40%, respectively
Josefsson & Kolmert, 1993[31] Sweden Group A: systemic antibiotics Group B: gentamicin bone cement	Bacterial flora showed nearly identical patterns in both groups The dominant bacteria was *S. aureus* (7/15 deep infections with positive cultures) and *S. epidermidis* (3/15). Four hips had Gram-negative bacteria
Mauerhan, *et al.,* 1994[32] USA Group A: cefuroxime Group B: cephazolin	*S. aureus* and *S. epidermidis* were the most frequently isolated pathogens. However, most wound infections were polymicrobial All but a few of the isolated pathogens were sensitive to cefuroxime and cephazolin
McQueen, *et al.,* 1990[34] UK Group A: cefuroxime (i.v) Group B: cefuroxime bone cement	*S. aureus* and *S. epidermidis* were the most frequently isolated pathogens No resistance emerged in the study
Mollan, *et al.,* 1992[35] UK Group A: teicoplanin Group B: cefamandole	Group A: one major failure; coagulase-positive *Staphylococcus* (one case) Group B: three major failures; coagulase-positive *Staphylococcus* (one case) and coagulase-negative staphylococci (two cases) Methicillin-resistant staphylococci not encountered
Periti, *et al.,* 1994[37] Italy Group A: teicoplanin Group B: cefazolin	Pathogens isolated from infected surgical wound: *S. aureus* (three cases) and one case each of *S. epidermidis, Clostridium perfringens* and *Serratia marcescens*
Ritter, *et al.,* 1989[38] USA Group A: cefuroxime Group B: cefuroxime	Positive cultures (either opening or closing): Group A – *S. epidermidis* (four cases), *Streptococcus viridans* (one case) Group B – *S. epidermidis* (five cases), *Pseudomonas* (two cases), *Corynebacterium diptheriae* (two cases) and *S. aureus* (one case)

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Study	Micro-organisms identified in SWIs, and sensitivity patterns
Schulitz, *et al.,* 1980[39] Germany Group A: lincomicin Group B: no antimicrobial prophylaxis	Group A: *S. aureus* (one case) Group B: *S. aureus* (seven cases) *S. aureus* was resistant to lincomicin in two cases
Soave, *et al.,* 1986[40] USA Group A: ceforanide Group B: cephalothin	Group A: *S. epidermidis* (one case) Group B: *S. epidermidis* (one case)
Suter, *et al.,* 1994[41] Italy Group A: teicoplanin Group B: cefamandole	The following organisms were identified from wound infections: methicillin-sensitive *S. aureus, Peptococcus* spp, *Micrococcus* spp, *Strept. sanguis* (one case each) and *Enterococcus* spp (two cases) Two infections were due to mixed flora
Vainionpää, *et al.,* 1988[42] Finland Group A: cefamandole Group B: cloxacillin	No SWI in either group
Wall, *et al.,* 1988[43] UK Group A: teicoplanin Group B: cefuroxime	Organisms identified from suspected wound infection: Group A – *E. coli* (one case), coagulase-negative *Staphylococcus* (two cases), diphtheroid (one case) Group B – coagulase-negative *Staphylococcus* (four cases), *E. coli* (one case), *Pseudomonas* sp (one case), *S. aureus* (one case), *Streptococcus viridans* (one case)
Wollinsky, *et al.,* 1997[44] Germany Group A: cefuroxime Group B: no antimicrobial prophylaxis	No SWI in either group
Wymenga, *et al.,* 1992[45] The Netherlands Both groups received cefuroxime for different duration	Joint sepsis confirmed by positive culture at reoperation and/or a draining sinus in 14 patients. Three patients showed clear signs of joint sepsis. Two underwent reoperation, but their perioperative cultures were negative. The joint aspirate from a third patient contained *S. aureus*

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This report was identified as a priority by the Pharmaceutical Panel.

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