Systematic review of the cost-effectiveness of preoperative antibiotic prophylaxis in reducing surgical-site infection

J. Allen1,2, M. David2,4 and J. L. Veerman2,3,5

1Queensland Audit of Surgical Mortality, Royal Australasian College of Surgeons, and 2School of Public Health, University of Queensland, Brisbane, 3School of Medicine, Griffith University, Southport, Queensland, 4School of Medicine and Public Health, University of Newcastle, Callaghan, and 5Cancer Council NSW, Woolloomooloo, New South Wales, Australia

Correspondence to: Mrs J. Allen, Queensland Audit of Surgical Mortality, PO Box 7476, East Brisbane, Queensland 4169, Australia (e-mail: jenny.allen@surgeons.org)

Background: Surgical-site infections (SSIs) increase the length of hospital admission and costs. SSI prevention guidelines include preoperative antibiotic prophylaxis. This review assessed the reporting quality and cost-effectiveness of preoperative antibiotics used to prevent SSI.

Methods: PubMed, Web of Science, Cumulative Index to Nursing and Allied Health Literature, Index of Economic Articles (EconLit), Database of Abstracts of Reviews of Effect (including the National Health Service Economic Evaluation Database) and Cochrane Central databases were searched systematically from 1970 to 2017 for articles that included costs, preoperative antibiotic prophylaxis and SSI. Included were RCTs and quasi-experimental studies conducted in Organisation for Economic Co-operation and Development countries with participants aged at least 18 years and published in English. Two reviewers assessed eligibility, with inter-rater reliability determined by Cohen’s 𝜗 statistic. The Consolidated Health Economic Evaluation and Reporting Standards (CHEERS) and modified Drummond checklists were used to assess reporting and economic quality. Study outcomes and characteristics were extracted, and incremental cost-effectiveness ratios were calculated, with costs adjusted to euros (2016) (€1 = US $1.25; £1 sterling = €1.28).

Results: Twelve studies published between 1988 and 2014 were included from 646 records identified; nine were RCTs, two were nested within RCTs and one was a retrospective chart review. Study quality was highest in the nested studies. Cephalosporins (first, second and third generation) were the most frequent prophylactic interventions. Eleven studies demonstrated clinically effective interventions; ten were cost-effective (the intervention was dominant); in one the intervention was dominated by the control; and in one the intervention was more effective and more expensive than the control.

Conclusion: Preoperative antibiotic prophylaxis does reduce SSI, costs to hospitals and health providers, but the reporting of economic methods in RCTs is not standardized. Routinely nesting economic methods in RCTs would improve economic evaluations and ensure appropriate selection of prophylactic antibiotics.

Funding information
No funding

Paper accepted 13 December 2017
Published online 14 April 2018 in Wiley Online Library (www.bjopen.com). DOI: 10.1002/bjo.545

Introduction

Surgical-site infections (SSIs) occur in 1–25 per cent of surgical patients, although the occurrence and severity vary. These variations depend on the type, duration and time of day of the operation, and the time from infection onset to detection and successful treatment. SSI leads to longer hospital stays and higher costs to patients, hospitals and health systems. In Europe, a minimum estimate of increased health cost due to SSI in 2004 was €1.47–19.1 billion, and more recently in the USA (2014) SSI was associated with double the costs compared with those for a patient without SSI.

Jointly, the Centers for Disease Control and Prevention (CDC) in the USA, the National Institute for Health and Care Excellence in the UK and the World Health Organization developed SSI prevention guidelines.
These include several prevention measures: preoperative screening of patients and decolonization of nasal cavities, showering, hair removal, intraoperative skin preparation using chlorhexidine, preoperative prophylactic antibiotic administration (within 1 h before surgery), normothermia and body temperature regulation, use of incision drapes, administration of supplemental oxygen throughout the operation, control of the patient’s glucose level, and postoperative use of surgical dressings and appropriate hand hygiene. The prevention measures may be implemented individually or as a bundle (3–5 interventions are grouped together).

Several systematic reviews have reported on aseptic skin preparation (including surgical hand asepsis, intraoperative skin antisepsis and skin preparation with chlorhexidine)\textsuperscript{14–16}, dressings including wound edge protection devices\textsuperscript{16,17}, increased oxygen supplementation\textsuperscript{18}, glucose control\textsuperscript{19} and thermoregulation\textsuperscript{20}. Two reviews have reported on the cost-effectiveness of the interventions\textsuperscript{14,16} and the quality of health economic reporting\textsuperscript{16}.

Despite the routine use of antibiotic prophylaxis, which is inexpensive\textsuperscript{21–23}, SSIs continue to occur. This suggests that implementation of SSI prevention is suboptimal – that more can be done, and done cost-effectively. To date, no cost-effectiveness review of preoperative antibiotic prophylaxis has been performed, despite the existence of clinical guidelines for antibiotic prophylaxis in surgery\textsuperscript{21–23}.

The aim of this review was to evaluate the cost-effectiveness of preoperative antibiotic prophylaxis used to prevent SSIs, and to assess the reporting quality of clinical effectiveness and cost-effectiveness for each study.

### Methods

#### Data sources

Published studies were identified by following the Cochrane Review Group search strategy\textsuperscript{24}, the University of York Centre for Reviews and Dissemination\textsuperscript{25} and the PRISMA statement\textsuperscript{26}. Six databases were searched: the Cochrane Library (Cochrane Central), PubMed, Cumulative Index to Nursing and Allied Health Literature (CINAHL via EBSCO), Web of Science core collection, Journal of Economic Literature and the Index of Economic Articles (EconLit via EBSCO), and Database of Abstracts of Reviews of Effect (DARE, via the University of York Centre for Reviews and Dissemination, which incorporates the National Health Service Economic Evaluation Database (NHS EED)). Earlier databases were
Table 1 Characteristics of included studies

| Reference | Population | Follow-up | Control | Intervention | Preoperative prophylaxis outcome measures | Conclusion |
|-----------|------------|-----------|---------|--------------|-----------------------------------------|------------|
| Blair et al. (1995) | ‘Clean’ neck dissection: 192 | n.s. | No prophylaxis | Cefazolin 600mg* Clindamycin 2g* Penicillin* Drug name n.s.* | First-generation cephalosporin; clindamycin and penicillin versus no antibiotic to prevent postoperative wound infection | Cost-benefit analysis (hospital stay and cost) No significant difference in infections. Preoperative antibiotic prophylaxis advocated. Cost-effective |
| Bold et al. (1998) | Axillary lymph node dissection: 178 | 4 weeks after surgery | Placebo (normal saline) | Cefonicid 1g (single dose) | Second-generation cephalosporin versus placebo to decrease postoperative wound complications | Cost-benefit analysis No significant difference in infections. Preoperative antibiotic prophylaxis advocated |
| Davey et al. (1988) | Abdominal or vaginal hysterectomy: 400 | Every 3 days, then after discharge (visit week 2, phone call week 6) | Placebo (normal saline) | Cephradine 2g (single dose) Meclocillin 5g (single dose) | First-generation cephalosporin versus broad-spectrum penicillin to prevent wound infection | Cost-benefit analysis (patient, hospital and community services) Cephradine antibiotic prophylaxis advocated in abdominal hysterectomy. Antibiotic prophylaxis questionable in vaginal hysterectomy |
| Dhadwal et al. (2007) | Median sternotomy for primary CABG of at least 1 thoracic artery and at least 1 of 4 defined risk factors: 201‡ and 186§ Daily until discharge, then after discharge (week 6 and 90 days) | Cefuroxime 1.5g (single dose), then cefuroxime 750mg at reversal of anti-coagulation, 8 and 16h after surgery | Rifampicin 600mg (single dose), then gentamicin 2mg/kg + vancomycin 15mg/kg on induction of anaesthesia. Postoperative vancomycin 7.5mg/kg at 12, 24 and 36h | Second-generation cephalosporin versus gentamicin combined with rifampicin and vancomycin to prevent sternal wound infection | Cost-benefit analysis Longer and broader-spectrum preoperative antibiotic prophylaxis advocated. Cost-effective |
| Dijksman et al. (2012) | Intestinal resection with primary anastomosis, with or without a diverting ileostomy or closure of a temporary colostomy: 289 | 1 year Placebo for 2 days before surgery, then parenteral perioperative cefuroxime 1500mg + metronidazole 500mg 30min before surgery. Cefuroxime 1500mg + metronidazole 500mg continued 8-hourly for 24h | SDD (polymyxin B sulphate 100mg + tobramycin 80mg + amphotericin B 500mg) for 2 days before surgery and continued for at least 3 days after surgery or until normal bowel function. Parenteral perioperative antibiotic cefuroxime 1500mg + metronidazole 500mg 30min before surgery. Cefuroxime 1500mg + metronidazole 500mg continued 8-hourly for 24h | Perioperative selective decontamination of digestive tract (polymyxin B sulphate with tobramycin and amphotericin B) versus placebo to reduce infection | Cost-effectiveness analysis Selective decontamination of digestive tract advocated. Cost-effective |
## Table 1  Continued

| Reference | Population | Follow-up | Control | Intervention | Primary outcome measures | Secondary outcome measures | Conclusion |
|-----------|------------|-----------|---------|--------------|--------------------------|---------------------------|------------|
| Garcia-Rodriguez et al.\(^4\) (1989) | Gastroduodenal or biliary surgery with at least 1 of 11 defined risk factors: 1451 | 16 days | Cefoxitin 2 g (single i.v. dose), then cefoxitin 2 g 6, 12 and 18 h after surgery | Cefotaxime 1 g (single i.v. dose) | Second- and third-generation cephalosporin to reduce postoperative infection | Cost-benefit analysis | Cefotaxime antibiotic prophylaxis advocated. Cost-effective |
| Jones et al.\(^5\) (1997) | Obstetrics and gynaecology, gastrointestinal, orthopaedics and other (total joint replacement and open reduction of fractures) surgical procedures: 812 | 30 days | Cefotaxime 1 0 g (slow i.v. bolus after anaesthesia but 30 min before incision). Additional cefotaxime 1 0 g given during surgery if procedure duration 2 h or more. For bowel surgery, standard bowel preparation before prophylaxis | Cefoperazone 1 0 g (slow i.v. bolus after anaesthesia but 30 min before incision). For bowel surgery, standard bowel preparation before prophylaxis | Two third-generation cephalosporins to prevent perioperative infection | Cost containment | Both cefoperazone and cefotaxime antibiotic prophylaxis advocated. Both cost-effective |
| Marroni et al.\(^6\) (1999) | Abdominal aortic or lower limb prosthetic vascular surgery: 238 | Daily until discharge, then after discharge (3 months for 1 year, then at 24 months) | Cefazolin 2 g (single i.v. dose) | Teicoplanin 400 mg (single dose) | Efficacy and tolerability of first-generation cephalosporin and a glycopeptide to prevent postoperative infection | Cost-benefit analysis | Cefazolin antibiotic prophylaxis advocated. Cost-effective |
| Matkaris et al.\(^7\) (1991) | Abdominal hysterectomy: 200 | 4–5 days if no SSI, otherwise kept in hospital until infection resolved | No prophylaxis | Ceftriaxone 2 g (single dose). Additional dose if postoperative infection | Cefotaxime 2 g (single dose). Additional dose if postoperative infection | Efficacy and safety of three third-generation cephalosporins to prevent postoperative infection | Cost-benefit analysis | Single dose of any of the three antibiotic prophylaxes advocated. Cefotaxime was most cost-effective |
| Matsui et al.\(^8\) (2014) | Laparoscopic cholecystectomy for gallbladder stones or polyps: 437 | 8 days after surgery in outpatient setting | No prophylaxis | Cefazolin 1 g (3 doses before skin incision, then 12 and 24 h after surgery). Additional cefazolin 1 g in theatre if duration of surgery more than 3 h | First-generation/second-generation cephalosporin to reduce postoperative complications, including SSI and distant infection | Cost-effectiveness analysis | Antibiotic prophylaxis advocated. Cost-effective |
| Sisto et al.\(^9\) (1994) | CABG: 551 | Daily until discharge (10–12 days) or to another hospital (6–7 days) | Ceftriaxone 2 g (single dose) | Cefoxime 1 5 g (single dose), then cefuroxime 1 5 g (8-hourly to end of postoperative day 2) | Efficacy and side-effects of single-dose third-generation cephalosporin versus multiple doses of second-generation cephalosporin to prevent postoperative infection | Cost-benefit analysis | Efficacy of ceftriaxone and cefuroxime equivalent. Ceftriaxone cheaper and simpler to use |
| Wilson et al.\(^10\) (2008) | Colorectal surgery: 672# | 4 weeks after surgery | Ertapenem 1 g (single dose) | Cefotetan 2 g (single dose) | Preoperative prophylaxis of second-generation cephalosporin and a β-lactam to reduce postoperative infectious complications | Cost-benefit analysis | Ertapenem antibiotic prophylaxis advocated. Cost-effective |

*Prophylactic antibiotic dose not stated; †antibiotic trade name or generation of the cephalosporin not stated; ‡intention-to-treat data for antibiotic efficacy; §per-protocol data for costs; \(^4\)blinding not stated; \(^5\)per-protocol data. n.s., Not stated; CABG, coronary artery bypass graft; SDD, selective decontamination of digestive tract; i.v., intravenous; SSI, surgical-site infection. A more detailed version of this table is available as Table S3, supporting information\(^11\).
searched from 1970 (PubMed, EconLit) and others from 1994 (DARE and NHS EED), 1996 (Cochrane Central) and 1982 (CINAHL). The search of all databases was concluded on 28 June 2017.

**Search strategy**

Keywords and search terms were matched with database-specific medical subject heading (MeSH) terms or title fields. Keywords for four different themes were linked with AND (cost AND prophylaxis AND prevention AND surgical-site infection). Full search strategies can be found in Table S1 (supporting information). Search results were exported into EndNote® version X7 (Thomson Reuters, New York, USA) and duplicates were removed. Manual screening of references from included articles was performed to identify additional publications not identified by the search.

**Selection criteria**

Systematic reviews, guidelines, conference proceedings and letters were excluded. Only articles published in English and in peer-reviewed journals were included. The studies had to define a SSI, even if it did not conform to the CDC definition: an infection related to an operative procedure that occurs at or near the surgical incision within 30 days of the procedure or within 1 year if an implant is left in place. PICO (population, intervention, comparison and outcomes) were used to evaluate study eligibility. Studies were included if they were economic evaluations in RCTs or quasi-experimental studies that compared the efficacy between different antibiotic prophylaxis regimens or placebo. Economic evaluations were defined as the comparative analysis of the costs and consequences of alternative programmes. Studies were excluded if they were performed in non-OECD (Organisation for Economic Co-operation and Development) countries. OECD countries were defined as high-income-earning economies, and included 31 OECD members (Table S2, supporting information). Other exclusion criteria were: study participants younger than 18 years of age and surgery that did not require a general anaesthetic.

**Data extraction**

Data from outcomes and resource use studies were used to construct and judge the cost-effectiveness. Two reviewers independently applied the inclusion and exclusion criteria to the eligible studies. They first screened the titles, then abstracts and finally the full text. At each step their agreement was assessed using Cohen’s κ statistic with a 95 per cent c.i. Cohen’s κ statistic adjusts the proportion of articles for which there is agreement by the amount of agreement expected by chance alone. Agreement strengths for Cohen’s κ are defined as: poor, κ < 0·00; slight, κ = 0·00–0·20; fair, κ = 0·21–0·40; moderate, κ = 0·41–0·60; substantial, κ = 0·61–0·80; and almost perfect, κ = 0·81–1·00.

Disagreements were resolved by discussion, and when consensus could not be reached a third reviewer acted as referee. Reasons for exclusion were documented. All eligible articles that passed the full-text screening were included in the review.

Extracted study data were recorded in a data collection form; they included year and country of study, study design, definition of SSI, population demographics, surgical procedures, antibiotic prophylaxis (costs, dosage and mode of administration), mean hospital and patient costs, and outcome data (duration of hospital stay, mortality, incidence of SSI, bacteria identified and antimicrobial resistance).

**Reporting quality assessment**

The 24-item Consolidated Health Economic Evaluation and Reporting Standards (CHEERS) checklist was used to assess comprehensively the quality of the clinical and methodological reporting relating to title, structured abstract, methods, results, discussion, conclusion, funding and conflicts of interest. Two of the checklist items (choice of a model and assumptions) were not included as they were not applicable to any of the studies. Each of the remaining 22 items were assigned a weighted rating: 0, did not report; 1, reported poorly; 2, reported well. The overall quality rating is the proportion of items reported well: high quality, 17 or more of 22 (77 per cent or above); medium/acceptable quality, 11 or more and fewer than 17 of 22 (50 per cent or above and less than 77 per cent); and low/unacceptable quality, fewer than 11 of 22 (less than 50 per cent). There is methodological reporting overlap between the CHEERS checklist and the economic quality checklist described below.

**Economic quality assessment**

A modified version of the Drummond et al. checklist was used to assess the quality of the economic and methodological reporting. The checklist includes ten questions, of which two have subquestions. These 12 questions enabled assessment of the following elements for each study: methods used (appropriate and accurate measurement of costs and outcomes), clinical effectiveness, limitations, uncertainty, relevance, generalizability and conclusions. Answers
Table 2 CHEERS checklist summary of reporting quality

| Questions                                      | No. of studies reporting (n = 12) |
|------------------------------------------------|-----------------------------------|
| Title and abstract                             |                                    |
| Title                                          | 6                                 |
| Abstract                                       | 3                                 |
| Introduction                                   |                                    |
| Background and objectives                      | 0                                 |
| Methods                                        |                                    |
| Target population and subgroups                | 6                                 |
| Setting and location                           | 6                                 |
| Study perspective                              | 5                                 |
| Comparators                                    | 5                                 |
| Time horizon                                   | 7                                 |
| Discount rate                                  | 3                                 |
| Choice of health outcomes                      | 7                                 |
| Measurement and valuation of effectiveness     | 7                                 |
| Estimating resources and costs                 | 7                                 |
| Currency, price date and conversion            | 3                                 |
| Choice of model                                | 0                                 |
| Assumptions                                    | 0                                 |
| Analytical methods                             | 0                                 |
| Results                                        | 0                                 |
| Study parameters                               | 0                                 |
| Incremental costs and outcomes                 | 0                                 |
| Characterizing uncertainty                     | 2                                 |
| Characterizing heterogeneity                    | 3                                 |
| Discussion                                     |                                    |
| Study findings, limitations, generalizability and current knowledge | 8 |
| Other                                          | 0                                 |
| Source of funding                              | 0                                 |
| Conflict of interest                           | 0                                 |

n.a., Not applicable.

assigned to each question could be: ‘yes’, ‘no’ or ‘not applicable’. The overall quality ratings are based on the number of questions answered as ‘yes’: high quality, nine or more of 12 (75 per cent or above); medium/acceptable quality, six or more and fewer than nine of 12 (50 per cent or more and less than 75 per cent); and low/unacceptable quality, fewer than six of 12 (less than 50 per cent).

**Incremental cost-effectiveness ratio**

When treatment effect (TE) and incremental cost-effectiveness ratios (ICERs) were not reported, they were calculated using the study data. Treatment effect is defined as the difference between the control and intervention effect (TEc − TEi). To determine the incremental cost saving of SSIs averted, the difference in mean total cost between the intervention and control prophylaxis was divided by the treatment effect. Calculated ICER costs were then adjusted to British pounds (£) in a two-step process, using the Campbell and Cochrane Economics Methods Group—Evidence for Policy and Practice Information and Coordinating Centre cost converter web-based tool. Step 1 inflates the cost from the original price year to April 2016, using a Gross Domestic Product deflator index (GDPD values), obtained from the International Monetary Fund World Economic Outlook Database GDP deflator index data set. Step 2 converts the original currency to British pounds, using conversion rates based on Purchasing Power Parities for GDP (PPP values). Using a web-based tool, the 2016 British pound to euro conversion factor for £1 sterling is €1.28. When not stated, accepted standard practice to infer price year and/or currency was used. The price year was assumed to be either the year the study ended or the year of publication, and the original currency to be the same as that in the study setting.

**Results**

The search yielded 628 articles; 508 remained once duplicates had been removed. The remaining articles were subjected to a systematic review by two independent reviewers who applied the inclusion criteria. A further 18 articles were identified by hand-searching. The inclusion criteria were first applied to the article titles, then abstracts and finally the full text. Cohen’s κ statistic calculated for each step showed almost perfect (κ = 0.89, 95 per cent c.i. 0.80 to 0.98), substantial (κ = 0.64, 0.53 to 0.75) and moderate (κ = 0.55, 0.45 to 0.65) agreement respectively. Five full-text articles required review by a third reviewer, and
| Reference        | Surgical procedure | Definition of postoperative infection | Preoperative prophylaxis | Sample size | Postoperative infections |
|------------------|--------------------|--------------------------------------|--------------------------|-------------|--------------------------|
| Blair et al.     | Neck dissection    | Wound infection: based on wound grading scale developed by Johnson et al.49 | Cefazolin 600 mg Clindamycin 2 g Penicillin Drug n.s. | 192 (139 : 53) | Control* 58 (30 : 2) Intervention* 13 (6 : 8) Control* 17 (8 : 6) Intervention* 5 (2 : 6) P 0.08 |
| Bold et al.      | Axillary lymph node dissection | Infection of surgical wound in the absence of any other site of infection | Placebo (normal saline) Cefonicid 1 g | 178 (24 : 154) | Control* 90 (50 : 6) Intervention* 88 (49 : 4) P 0.08 |
| Davey et al.     | AH or VH           | Infected wound; pelvic infection | Placebo (normal saline) Cephradine 2 g | 400 (0 : 400) | AH 102 (25 : 5) VH 97 (24 : 3) Hospital wound Pelvic VH 29 (7 : 2) VH 34 (8 : 5) AH 20 (19 : 6) VH 6 (21) AH 6 (6) VH 1 (3) < 0.05 Hospital total AH 42 (41 : 2) AH 16 (16) VH 10 (34) VH 8 (24) P 0.41 Home wound Pelvic AH 9 (8 : 8) AH 10 (10) VH 2 (7) VH 1 (3) VH 0 (0) 0.81 Home total AH 15 (14 : 7) AH 25 (26) VH 7 (24) VH 10 (29) VH 0 (0) 0.02 Hospital total AH 42 (41 : 2) AH 30 (29 : 7) VH 10 (34) VH 6 (16) P 0.11 Mezlocillin 5 g AH 102 (25 : 5) AH 101 (25 : 3) Hospital wound Pelvic VH 29 (7 : 2) VH 37 (9 : 2) AH 20 (19 : 6) AH 18 (17 : 8) VH 6 (21) VH 0 (0) 0.86 Hospital total AH 42 (41 : 2) AH 30 (29 : 7) VH 10 (34) VH 6 (16) P 0.15 Mezlocillin 5 g AH 102 (25 : 5) AH 101 (25 : 3) Hospital wound Pelvic VH 29 (7 : 2) VH 37 (9 : 2) AH 20 (19 : 6) AH 18 (17 : 8) VH 6 (21) VH 0 (0) 0.86 Hospital total AH 42 (41 : 2) AH 30 (29 : 7) VH 10 (34) VH 6 (16) P 0.15 Mezlocillin 5 g AH 102 (25 : 5) AH 101 (25 : 3) Hospital wound Pelvic VH 29 (7 : 2) VH 37 (9 : 2) AH 20 (19 : 6) AH 18 (17 : 8) VH 6 (21) VH 0 (0) 0.86 Home total AH 15 (14 : 7) AH 14 (13 : 9) VH 7 (24) VH 2 (5) VH 0 (0) 0.19 Home total AH 15 (14 : 7) AH 14 (13 : 9) VH 7 (24) VH 2 (5) VH 0 (0) 0.19 Dhadwal et al. | CABG | NNIS infection risk score35 CDC sternal wound40 | Cefuroxime 15 g | 201 (165 : 36) 106 (52 : 8) 95 (47 : 2) 0.063 Sternal wound (90 days) 25 (23 : 6) 8 (8) 0.004$ Superficial 11 (10 : 4) 4 (4) 0.097 Deep 8 (7 : 5) 2 (2) 0.15# Organ space 6 (5 : 7) 2 (2) 0.36# Deep + organ space 14 (13 : 2) 4 (4) 0.03 Sternal debridement 19 (17 : 9) 4 (4) 0.002 Harvest site infection 7 (6 : 6) 45 (5) 0.69 |
| Reference          | Surgical procedure                                  | Definition of postoperative infection                                                                 | Preoperative prophylaxis                                                                 | Sample size | Postoperative infections |
|--------------------|-----------------------------------------------------|--------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|-------------|----------------------------|
|                    |                                                     |                                                                                                        | Control: Intervetion*                                                                    | Total (M : F) | Inter-vention* P          |
| Dijksman et al.    | Digestive tract surgery                            | Wound infection, intra-abdominal abscess and anastomatic leak. Calculated event rate was percentage of patients who suffered at least 1 infectious complication | Placebo. Parenteral perioperative antibiotic cefuroxime 1500 mg + metronidazole 500 mg | 289 (156 : 133) | 45 (30 : 6) 0.03†        |
|                    |                                                     |                                                                                                        | SDD (polymyxin B sulphate100 mg + tobramycin 80 mg + amphotericin B 500 mg). Parenteral perioperative antibiotic cefuroxime 1500 mg + metronidazole 500 mg | 146 (50 : 5) 143 (49 : 5) |                          |
| Garcia-Rodriguez et al. | Gastroduodenal or biliary surgery                  | Surgical wound infection: cellulitis with purulent secretion, with or without dehiscence (NRC)          | Cefoxitin 2 g Cefotaxime 1 g                                                              | 1451 (824 : 827) | 716 (50 : 2) 722 (49 : 8) |
|                    |                                                     |                                                                                                        | Wound infection                                                                         | 54 (7 : 5) 24 (3 : 3) | < 0.002                   |
| Jones et al.       | Gastrointestinal, gynaecological, orthopaedic (total joint replacement and open reduction of fractures) and other surgery | Postoperative surgical incision or peritoneal cavity infection                                      | Cefotaxime 1 g Cefoperazone 1 g                                                          | 812 (42 : 770) 401 (49 : 4) 411 (50 : 6) | Wound infection 12 (3 : 0) 9 (2 : 2) > 0.05 |
|                    |                                                     |                                                                                                        | Total general                                                                           | 96 (22 : 74) 89 (9 : 75) 1 (0 : 1) 2 (1 : 0) 1 (0 : 1) 1 (0 : 1) | 1 (0 : 1) 0 (0 : 1) 0.05 |
|                    |                                                     |                                                                                                        | UGITT                                                                                   | 72 (22 : 50) 66 (6 : 56) 0 (0 : 66) 0 (0 : 66) 0 (0 : 66) 0 (0 : 66) | 0 (0 : 1) 0 (0 : 1) 0.00 |
|                    |                                                     |                                                                                                        | Colorectal                                                                               | 24 (22 : 2) 23 (2 : 21) 1 (0 : 21) 2 (1 : 19) 2 (1 : 19) 2 (1 : 19) | 0 (0 : 2) 0 (0 : 2) 0.00 |
|                    |                                                     |                                                                                                        | Total O + G                                                                             | 168 (22 : 146) 168 (2 : 166) 9 (1 : 87) 9 (1 : 87) 9 (1 : 87) 9 (1 : 87) | 6 (0 : 6) 6 (0 : 6) 0.00 |
|                    |                                                     |                                                                                                        | Hysterectomy                                                                            | 119 (22 : 97) 125 (2 : 123) 8 (1 : 111) 8 (1 : 111) 8 (1 : 111) 8 (1 : 111) | 6 (0 : 6) 6 (0 : 6) 0.00 |
|                    |                                                     |                                                                                                        | C-section                                                                               | 19 (2 : 17) 18 (2 : 16) 1 (0 : 16) 1 (0 : 16) 1 (0 : 16) 1 (0 : 16) | 0 (0 : 0) 0 (0 : 0) 0.00 |
|                    |                                                     |                                                                                                        | Other O + G                                                                             | 30 (2 : 28) 25 (2 : 23) 0 (0 : 23) 0 (0 : 23) 0 (0 : 23) 0 (0 : 23) | 0 (0 : 0) 0 (0 : 0) 0.00 |
|                    |                                                     |                                                                                                        | Total orthopaedic                                                                        | 74 (2 : 72) 77 (2 : 75) 7 (5 : 69) 7 (5 : 69) 7 (5 : 69) 7 (5 : 69) | 0 (0 : 0) 0 (0 : 0) 0.00 |
|                    |                                                     |                                                                                                        | Total joints                                                                            | 51 (2 : 49) 59 (2 : 57) 5 (3 : 44) 5 (3 : 44) 5 (3 : 44) 5 (3 : 44) | 0 (0 : 0) 0 (0 : 0) 0.00 |
|                    |                                                     |                                                                                                        | Other orthopaedic                                                                        | 23 (2 : 21) 18 (2 : 16) 1 (0 : 16) 1 (0 : 16) 1 (0 : 16) 1 (0 : 16) | 0 (0 : 0) 0 (0 : 0) 0.00 |
|                    |                                                     |                                                                                                        | Other surgery                                                                            | 61 (2 : 59) 77 (2 : 75) 1 (0 : 74) 1 (0 : 74) 1 (0 : 74) 1 (0 : 74) | 1 (0 : 1) 1 (0 : 1) 1.00 |
| Marroni et al.     | Abdominal aortic or lower limb prosthetic vascular surgery | Surgical wound infection; deep wound infection (CDC)                                                  | Cefazolin 2 g Teicoplanin 400 mg                                                          | 238 (220 : 18) 119 (50 : 0) 119 (50 : 0) | SSI 2 (1 : 7) 7 (5 : 9) 0.19 |
|                    |                                                     |                                                                                                        | Wound infection                                                                         | 2 (1 : 7) 1 (0 : 6) 0 (0 : 6) 0 (0 : 6) 0 (0 : 6) 0 (0 : 6) | 0.49 |
| Matkaris et al.    | AH                                                  | Fever > 38°C for 24 h, blood analysis, urine analysis, clinical evaluation                             | No prophylaxis                                                                          | 200 (0 : 200) 50 (25 : 0) 50 (25 : 0) | SSI 19 (3 : 7) 4 (0 : 8) 0.001 |
| Matsui et al.      | Laparoscopic cholecystectomy for removal of gallbladder stones or polyps                              | SSI (surgical wound and subhepatic abscess)                                                        | Ceftriaxone 2 g Cefotaxime 2 g Cefazidime 2 g                                            | 1037 (490 : 547) 519 (50 : 0) 518 (50 : 0) | Wound 16 (3 : 1) 4 (0 : 8) 0.005 |
|                    |                                                     |                                                                                                        | Cefazolin 1 g                                                                          | 19 (3 : 7) 4 (0 : 8) 0.001 | Subhepatic 3 (0 : 3) 0 (0 : 0) 0.249 |
|                    |                                                     |                                                                                                        |                                                                                         | 35 (6 : 7) 6 (1 : 2) 0.001 |

© 2018 The Authors. www.bjsopen.com BJS Open 2018; 2: 81–98

BJS Open published by John Wiley & Sons Ltd on behalf of BJS Society Ltd
Table 3 Continued

| Reference       | Surgical procedure | Definition of postoperative infection                                                                 | Preoperative prophylaxis | Sample size | Postoperative infections |
|-----------------|--------------------|--------------------------------------------------------------------------------------------------------|--------------------------|-------------|--------------------------|
|                 |                    |                                                                                                         |                          |             |                          |
|                 |                    | Superficial and deep sternal wound infection; donor-site infection                                      | Ceftriaxone 1.5 g        | 551         | Superficial              |
|                 |                    |                                                                                                         |, then cefuroxime 1.5 g   |              |                           |
|                 |                    |                                                                                                         | 8-hourly until end of    | 274         | Deep                     |
|                 |                    |                                                                                                         | operation day 2 after    | 277         |                           |
|                 |                    |                                                                                                         | surgery                  |             |                           |
|                  |                    | Superficial and deep incisional; either superficial infection or anastomotic leak (NNIS)                 | Cefotaxime 2 g           | (437 : 114) |                           |
|                  |                    | (Surgical site)                                                                                         |                          |             |                           |
|                  |                    |                                                                                                         |                           |             |                           |
|                  |                    | Superficial                                                                                           | Ertapenem 1 g            | 672         | Donor site               |
|                  |                    |                                                                                                         |                          | (365 : 307) |                           |
|                  |                    |                                                                                                         | Celotetan 2 g            |             |                           |
|                  |                    |                                                                                                         |                          | (50 : 3)    | SSI                      |
|                  |                    |                                                                                                         |                          | (49 : 7)    |                           |
|                  |                    |                                                                                                         |                           |             |                           |
|                  |                    |                                                                                                         |                           |             |                           |

*Values in parentheses are percentages. †Intervention failure results for cefazolin, clindamycin and cefoperazone were pooled as individual results were not stated; statistical method was not stated, but assumed to be Fisher's exact test. ‡Fisher's exact test (P < 0.050 was considered significant with 80 per cent confidence level). §Analysis of significance in fourfold tables was done with the χ² test with Yates’ correction unless the total number of observations was less than 60 or the number in any cell was zero, when Fisher’s exact test was used; threefold or greater tables were analysed with the χ² test. ¶χ² or Fisher's exact test with two-sided significance level of 0.05. #χ² test with Yates’ correction. **Intention-to-treat data; statistical analysis with Fisher’s exact test; infection data were missing for six patients in the control group and seven in the intervention group. ††Per-protocol data; statistical analysis with Fisher’s exact test or χ² test; P < 0.050 considered significant; ‡‡χ² test with a two-sided significance level of 0.05 when expected frequencies were less than 5. §§Statistical method not stated. §§§χ² test with significance level of 0.05; Fisher’s exact test used for subhepatic comparison as expected frequencies in cells were less than 5. #§§Student’s t test for parametric data and Mann–Whitney or χ² test for non-parametric data; significance level of 0.05. ***Per-protocol data; absolute difference and 95 per cent c.i. for percentage prophylactic failure were determined in a statistical model adjusting for surgical procedure; 95 per cent c.i. that did not overlap zero indicated significant difference between groups at P < 0.050, n.s., Not stated; AH, abdominal hystectomy; VH, vaginal hysterectomy; CABG, coronary artery bypass graft; NNIS, National Nosocomial Infections Surveillance; CDC, Centers for Disease Control and Prevention; SDD, selective decontamination of digestive tract; NRC, National Research Council; UGIT, upper gastrointestinal tract; O+G, obstetrics and gynaecology; C-section, caesarean section; SSI, surgical-site infection.

one was included. The five main reasons for full-text exclusion were: age restriction (81 articles), inadequate or no cost data (34), discussion or symposium paper (16), systematic review (14) and studies performed in non-OECD country (13). Twelve articles met the inclusion criteria (Fig. 1).

Table 1 included studies35–46. These were published between 1988 and 2014 with four published after 200038,39,44,46. Nine36–38,40–45 were RCTs, two39,46 were nested within an RCT and one35 was a retrospective chart review. Eight were conducted in Europe (Greece35,43, Scotland37, UK38, Spain40, Italy42, Finland45 and the Netherlands19), three in the USA36,41,46 and one in Japan44. The studies encompassed head and neck, gynaecological, vascular, cardiothoracic, general (breast and endocrine, intestinal and colorectal, and hepatopancreatobiliary) and orthopaedic surgery. Eleven studies35–38,40–46 evaluated the effectiveness of preoperative prophylaxis of the antibiotic cephalosporin (either first, second or third generation).

These included ‘clean’ surgery (neck dissection35, axillary lymph node dissection36, coronary artery bypass graft (CABG)38,43, abdominal aortic or lower limb prosthetic vascular surgery42) and ‘clean-contaminated’ surgery (abdominal or vaginal hysterectomy37,41,43, digestive tract resection with anastomosis19, colonic resection and colorectal surgery41,46, biliary40 and gallbladder surgery44). One study39 evaluated selective decontamination of the digestive tract in clean-contaminated surgery of the digestive tract with anastomosis.

Quality assessment of reporting

The reporting quality of most of the studies was low to moderate using the CHEERS statement checklist31 (Table 2, Table S4, supporting information). Only one study39 had a high reporting quality for 18 of the 22 items. Three studies37–39 reported economic evaluations in their titles. In most studies the objectives, methods (settings, populations and comparators) were well...
### Table 4 Length of hospital stay and mortality associated with preoperative prophylactic antibiotics

| Reference                  | Surgical procedure | Preoperative prophylaxis | Population | Length of hospital stay* | Mortality ‡ |
|----------------------------|--------------------|--------------------------|------------|--------------------------|-------------|
|                           |                    |                          | C          | I                        | P           |
|                            |                    |                          | No infection | Infec-        |             |
|                            |                    |                          |            | tion | P | C   | I | P |
| Blair et al. ²⁵‡           | Neck dissection    | No prophylaxis versus    | 99         | 93                      | n.c.        | n.s. | n.s. |
|                            |                    | cefazolin, clindamycin    |            |               |             |     |     |
|                            |                    | and cefoperazone         |            |               |             |     |     |
| Bold et al. ²⁶‡            | Axillary lymph node| Placebo (normal saline)  | 90         | 88                      | n.c.        | n.s. | n.s. |
|                            | dissection         | versus cefonicid         |            |               |             |     |     |
| Davey et al. ²⁷            | AH or VH           | AH: placebo (normal      | 102        | 97                      | n.c.        | n.s. | n.s. |
|                            |                    | saline) versus cephradine|            |               |             |     |     |
|                            |                    | AH: placebo (normal      | 101        | 97                      | n.c.        | n.s. | n.s. |
|                            |                    | saline) versus            |            |               |             |     |     |
|                            |                    | mezlocillin               |            |               |             |     |     |
|                            |                    | VH: placebo (normal       | 29         | 34                      | n.c.        | n.s. | n.s. |
|                            |                    | saline) versus cephradine|            |               |             |     |     |
|                            |                    | VH: placebo (normal       | 37         | 37                      | n.c.        | n.s. | n.s. |
|                            |                    | saline) versus            |            |               |             |     |     |
|                            |                    | mezlocillin               |            |               |             |     |     |
| Dhadwal et al. ²⁸‡         | CABG                | Cefuroxime versus         | 106        | 95                      | 0.063       | 4 (4) | 1 (1) | 0.630 |
|                            |                    | rifampicin + gentamicin + |            |               |             |     |     |
|                            |                    | vancomycin +             |            |               |             |     |     |
|                            |                    | vancomycin               |            |               |             |     |     |
| Dijskman et al. ²⁹         | Digestive tract surgery | Placebo, cefuroxime      | 146        | 143                     | 0.055       | 5 (3.4) | 6 (4.2) | 0.732 |
|                            |                    | and metronidazole versus  |            |               |             |     |     |
|                            |                    | SDD, cefuroxime and       |            |               |             |     |     |
|                            |                    | metronidazole             |            |               |             |     |     |
| García-Rodríguez et al.   | Gastrointestinal   | Cefotaxime versus         | 716        | 722                     | < 0.001     | 7 (0.6) | 4 (0.6) | n.s. |
| et al. ²⁰                  | surgery            | cefotaxime                |            |               |             |     |     |
| Jones et al. ²¹           | Hysterectomy,      | Cefotaxime versus         | 401        | 411                     | n.c.        | n.s. | n.s. |
|                            | genitourinary and   | cefoperazone              |            |               |             |     |     |
|                            | other (mainly      |                          |            |               |             |     |     |
|                            | orthopaedic total  |                          |            |               |             |     |     |
|                            | joint replacement  |                          |            |               |             |     |     |
|                            | and open reduction  |                          |            |               |             |     |     |
|                            | of fractures)      |                          |            |               |             |     |     |
|                            | surgery            |                          |            |               |             |     |     |
| Marroni et al. ²²         | Abdominal aortic or| Cefazolin versus          | 119        | 119                     | 3 (2.5)     | 4 (3.4) | 1.000 |
|                            | lower limb         | teicoplanin               |            |               |             |     |     |
|                            | prosthetic vascular|                          |            |               |             |     |     |
| Matkaris et al. ²³        | AH                  | No antibiotic prophylaxis | 50         | 50                      | < 0.001     | n.s. | n.s. |
|                            |                    | versus ceftriaxone        |            |               |             |     |     |
|                            |                    | No antibiotic prophylaxis | 50         | 50                      | < 0.001     | n.s. | n.s. |
|                            |                    | versus cefotaxime         |            |               |             |     |     |
|                            |                    | No antibiotic prophylaxis | 50         | 50                      | < 0.001     | n.s. | n.s. |
| Matsui et al. ²⁴‡         | Laparoscopic        | No antibiotic prophylaxis | 519        | 518                     | 0.010       | 0 (0)  | 0 (0) |
|                            | cholecystectomy    | versus cefazolin         |            |               |             |     |     |
|                            | for removal of     |                          |            |               |             |     |     |
|                            | gallbladder stones |                          |            |               |             |     |     |
|                            | or polyps          |                          |            |               |             |     |     |
|                            |                    |                          |            |               |             |     |     |
| Sisto et al. ²⁵           | CABG                | Ceftriaxone versus        | 274        | 277                     | n.c.        | 3 (1.1) | 4 (1.4) | 1.000 |
|                            |                    | cefuroxime                |            |               |             |     |     |
| Wilson et al. ²⁶‡         | Colorectal surgery | Ertapenem versus          | 338        | 334                     | 3 of 451    | 7 of 450 | 0.340 |
|                            |                    | cefotaxime                |            |               |             |     |     |

*Values are mean (median, range) unless indicated otherwise; †values are mean(s.d.); ‡Values in parentheses are percentages. §Values in parentheses are percentages. ¶Values in parentheses are percentages. ††Values in parentheses are percentages. †‡Values in parentheses are percentages. †§Values in parentheses are percentages. §§Values in parentheses are percentages. †¶Values in parentheses are percentages. †∥Values in parentheses are percentages. **Intention-to-treat data; infection data were missing for six patients in the control group and seven in the intervention group. ††Per-protocol data. †‡Intention-to-treat data. †§§Per-protocol data; intention-to-treat data used for mortality reported in the nested study of Itani et al. ⁴⁶; C, control; I, intervention; n.c., not calculated (insufficient data in article); n.s., not stated; AH, abdominal hysterectomy; VH, vaginal hysterectomy; CABG, coronary artery bypass graft; SDD, selective decontamination of the digestive tract. P values are those reported in the article.
## Table 5  Evidence of preoperative prophylactic antibiotics in bacterial isolates and resistance patterns

| Reference               | Population                                                                 | Preoperative prophylaxis | Bacterial isolates | Bacterial resistance patterns |
|-------------------------|-----------------------------------------------------------------------------|---------------------------|--------------------|-----------------------------|
| Dhadwal et al.          | Median sternotomy for primary CABG of at least one thoracic artery and at least one of four defined risk factors: 201 | Cefuroxime 1.5 g (single dose), then cefuroxime 750 mg at reversal of anticoagulation 8 and 16 h after surgery | Rifampicin 600 mg (single dose), then gentamicin 2 mg/kg + vancomycin 15 mg/kg on induction of anaesthesia. Postoperative vancomycin 7.5 mg/kg at 12, 24 and 36 h | 19 of 99 GNB: 15 GPB: 10 Rifampicin-resistant GNB: 4 Vancomycin-resistant GPB: 0 Anaerobic: 2 Yeast: 1 | No increase in vancomycin-resistant *Enterococcus* or MRSA |
| Garcia-Rodriguez et al. | Gastroduodenal or biliary surgery with at least one of the 11 defined risk factors: 1451 | Cefoxitin 2 g (single i.v. dose), then cefoxitin 2 g 6,12 and 18 h after surgery | Cefotaxime 1 g (single dose) | *Escherichia coli* and *Staphylococcus aureus* most common; frequency and study group not mentioned | 12 of 21 GNB: 2 GPB: 5 Anaerobic: 3 | Not stated |
| Jones et al.            | Hysterectomy, genitourinary, gastrointestinal or other (total joint replacement and open reduction of fractures) surgical procedures: 812 | Cefotaxime 1.0 g (slow i.v. bolus after anaesthesia but 30 min before incision). Additional cefotaxime 1.0 g given during surgery if procedure duration 2 h or more. For bowel surgery, standard bowel preparation before prophylaxis | Cefoperazone 1.0 g (slow i.v. bolus after anaesthesia but 30 min before incision). For bowel surgery, standard bowel preparation before prophylaxis | 18 of 21 GNB: 2 GPB: 3 Anaerobic: 2 | Aerobic organisms 92% susceptible to cefoperazone and 72% inhibited by cefotaxime |
| Marroni et al.          | Abdominal aortic or lower limb prosthetic vascular surgery: 238            | Cefazolin 2 g (single i.v. dose) | Teicoplanin 400 mg (single dose) | MRSA: 0 GNB: 1 | MRSA: 0 GNB: 2 SWI GNB: 1 GPB: 1 UTI GNB: 3 Bloodstream GNB: 2 Mediatinitis GNB: 1 GPB: 6 Anaerobic: 0 | n.s. |
| Sisto et al.            | CABG: 551                                                                  | Ceftriaxone 2 g (single dose) | Cefuroxime 1.5 g (single dose), then cefuroxime 1.5 g 8-hourly until end of postoperative day 2 | GNB: 1 GPB: 6 Anaerobic: 0 *Clostridium difficile: 0* | GNB: 5 GNB: 17 C. difficile: 2 | 67% resistant to cefotetan; 16% resistant to ertapenem |
| Wilson et al.           | Colorectal surgery: 672                                                    | Ertapenem 1 g (single dose) | Cefotetan 2 g (single dose) | GNB: 42 Anaerobic: 36 C. difficile: 2 | GNB: 51 Anaerobic: 44 C. difficile: 2 | © 2018 The Authors. www.bjsopen.com BJS Open 2018; 2: 81–98 |

*Intention-to-treat data for antibiotic efficacy. †Infection data were missing for six patients in the control group and seven in the intervention group. ‡Per-protocol data; bacterial isolates and susceptibility data from nested study by Itani et al. GNB, Gram-negative bacteria; GPB, Gram-positive bacteria; MRSA, methicillin-resistant *Staphylococcus aureus*; SWI, surgical wound infection; UTI, urinary tract infection; CABG, coronary artery bypass graft.
Table 6 Summary of quality assessment checklist for assessing economic evaluations of included studies

| Question                                      | Yes | No  | Unsure | Not applicable |
|-----------------------------------------------|-----|-----|--------|----------------|
| Well defined question stated?                 | 12  | 0   | 0      | 0              |
| Description of alternatives?                  | 12  | 0   | 0      | 0              |
| Evidence of clinical effectiveness established?| 10  | 1   | 1      | 0              |
| Relevant costs and outcomes identified?       | 7   | 5   | 0      | 0              |
| Costs measured accurately in appropriate units?| 8   | 4   | 0      | 0              |
| Outcomes measured accurately in appropriate units?| 8   | 4   | 0      | 0              |
| Costs valued credibly?                        | 10  | 2   | 0      | 0              |
| Outcomes valued credibly?                     | 10  | 2   | 0      | 0              |
| Costs discounted? (n = 6)                     | 0   | 6   | 0      | 0              |
| Was incremental analysis performed?           | 1   | 11  | 0      | 0              |
| Was sensitivity analysis performed?           | 1   | 11  | 0      | 0              |
| Was generalizability discussed?               | 2   | 10  | 0      | 0              |

reported\(^{35-39, 41, 43-46}\), although time horizons and discounting were poorly reported\(^{35, 37, 38, 40-44, 46}\). Overall the results were poorly reported, including study parameters, incremental costs and characterization of uncertainty and heterogeneity\(^{36-46}\). Discussion around the individual study findings, their limitations and generalizability was also of poor quality\(^{37, 40-46}\). Source of funding and conflict of interest was poorly reported: four\(^{35, 36, 41, 44}\) reported funding and two\(^{38, 44}\) reported conflict of interest. Only one\(^{44}\) of these studies reported on both funding and conflict of interest.

**Clinical effectiveness of antibiotic prophylaxis, length of hospital stay and mortality**

All studies included a definition for postoperative SSI (Table 3). Four studies\(^{38, 40, 42, 46}\) used several variations of recognized definitions: the National Nosocomial Infections Surveillance\(^{54-56}\), variations of the CDC definition\(^{50, 53}\) and the National Research Council definition\(^{50, 52}\). The definition used by Blair and colleagues\(^{35}\) was developed by Johnson and co-workers\(^{49}\) in 1984, and the definition reported by Dijksman\(^{51}\) was that of Rommes et al.\(^{51}\), used in the nested study of Roos and colleagues\(^{37}\).

All studies reported SSI rates and the effectiveness of the preoperative antibiotic prophylaxis. Prophylactic effectiveness was demonstrated in 11 studies\(^{35-44, 46}\), although effectiveness was statistically significant in only seven\(^{37-40, 43, 44, 46}\). Blair and colleagues\(^{35}\) demonstrated effectiveness of the intervention compared with placebo, but failed to stipulate which of the three interventions was effective (cefazolin, clindamycin or cefoperazone). Effectiveness was therefore calculated for the pooled interventions. Matkaris et al.\(^{45}\) demonstrated significant effectiveness of three prophylactic antibiotics versus the no-antibiotic control, and also reported comparable differences between the three prophylactic antibiotics. The study that did not demonstrate prophylactic effectiveness for the intervention compared a single dose of ceftriaxone (third-generation cephalosporin) with three doses of cefuroxime (second generation) given three times daily, in patients undergoing CABG\(^{45}\).

Eleven studies\(^{35-44, 46}\) reported length of hospital stay (LOS), although the reporting was inconsistent between treatment groups as well as between infected and non-infected patients (Table 4). Overall LOS was reduced in the intervention group for all of the studies, although this was significant in only one study\(^{44}\). LOS was increased in the presence of infection compared with no infection in two studies\(^{35, 40}\). Five studies\(^{38-40, 42, 45}\) reported on mortality, although none stated the day of admission when the death occurred; there was no significant difference in mortality rates between intervention and control groups in the five studies\(^{38-40, 42, 45}\). There was one death from infection in each arm of the Marroni study\(^{52}\), whereas in the Sisto study\(^{45}\) no death was from infection. Mortality was not reported in the paper by Wilson et al.\(^{46}\), but was reported in the nested study of Itani and co-workers\(^{48}\); the difference was not statistically significant and was not directly related to the prophylaxis.

**Bacterial isolates and antimicrobial resistance**

Six studies\(^{38, 40, 42, 45, 46}\) reported and identified the bacterial pathogens responsible for SSIs; the pathogens were similar across the studies (Table 5). Clostridium difficile, a toxic organism found in the intestine causing colitis, was identified in one study\(^{45}\) after surgery following a second dose of cefuroxime. Wilson et al.\(^{46}\) also reported C. difficile colitis (in 2 patients who received ertapenem) and antimicrobial resistance of the pathogens to ertapenem versus cefotetan in the nested study\(^{46}\). Resistance of pathogens to ertapenem was much lower (16 per cent) than that to cefotetan (67 per cent). Only two other studies\(^{38, 41}\) reported antimicrobial resistance. Dhadwal and colleagues\(^{38}\) found no increase in vancomycin-resistant Enterococcus or methicillin-resistant Staphylococcus aureus.
Table 7 Summary of reported costs and incremental cost-effectiveness ratio calculated from study data

| Reference | Intervention versus control | Intervention failure* | Control failure* | Treatment effect (TEc – TEi) | Mean cost of intervention (includes treatment cost) | Mean cost of control (includes treatment cost) | Incremental cost per patient | Incremental cost per patient (2016 €)† | ICER (2016 €)† |
|-----------|----------------------------|-----------------------|-----------------|-----------------------------|-----------------------------------------------|-----------------------------------------------|-------------------------------|-----------------------------------|-----------------|
| Blair et al.35‡ | Cefazolin, clindamycin and cefoperazone versus placebo | 3 of 93 (3) | 10 of 99 (10) | 7 | $36 240.00 | $36 030.00 | $210.00 | 293.79 | Dominant |
| Bold et al.36‡ | Cefoxitin versus placebo | 5 of 88 (6) | 12 of 90 (13) | 7 | $149 80 | $364.87 | −$215.07 | −$269.26 | Dominant |
| Davey et al.37‡ | AH: cephadrine versus placebo | 40 of 97 (41) | 53 of 102 (52.0) | 11 | $18 26 | $31.34 | −$13.08 | −$37.92 | Dominant |
|             | AH: mezlocillin versus placebo | 40 of 101 (39.6) | 53 of 102 (52.0) | 12.4 | $17.61 | $31.34 | −$13.73 | −$37.92 | Dominant |
|             | VH: cephadrine versus placebo | 14 of 34 (41) | 15 of 29 (52) | 11 | $40.60 | $41.20 | −$0.60 | −$1.65 | Dominant |
|             | VH: mezlocillin versus placebo | 7 of 37 (19) | 15 of 29 (52) | 33 | $8.80 | $41.20 | −$33.40 | −$89.50 | Dominant |
| Dhandwal et al.38‡ | Rifampicin + gentamicin + vancomycin versus cefuroxime | 8 of 87 (9) | 25 of 99 (25) | 16 | $15 158.00 | $19 054.00 | −$3896.00 | −$4315.99 | Dominant |
| Dijksman et al.39++, SDD (ampicillin B, polymyxin B sulphate + tobramycin) versus placebo | 28 of 143 (19.6) | 45 of 146 (30.8) | 11.2 | $12 031.00 | $14 635.00 | −$2604.00 | −$2731.28 | Dominant |
| Garcia-Rodriguez et al.40‡‡ | Cefotaxime versus cefotaxin | 22 of 722 (3.3) | 54 of 716 (7.7) | 4.4 | $28.64 | $104.43 | −$75.79 | −$120.72 | Dominant |
| Jones et al.41 ‡|| Cefoperazone versus cefotaxime | 9 of 411 (2.2) | 12 of 401 (3.0) | 0.8 | $14.50 | $12.90 | $1.60 | 2.64 | 5.12 |
| Mannoni et al.42‡‡ | Cefazolin versus teicoplanin | 7 of 119 (5.9) | 2 of 119 (1.7) | −4.2 | $4803.13 | $4361.86 | $441.27 | $525.42 | Dominated by control |
| Matkaris et al.43‡‡ | Ceftriaxone versus no antibiotic | 3 of 50 (6) | 15 of 50 (30) | 24 | $150.12 | $248.03 | −$97.91 | −$140.10 | Dominant |
|             | Ceftriaxone versus no antibiotic | 4 of 50 (8) | 15 of 50 (30) | 22 | $128.06 | $248.03 | −$119.97 | −$171.67 | Dominant |
|             | Cefazolin versus no antibiotic | 4 of 50 (8) | 15 of 50 (30) | 22 | $137.81 | $248.03 | −$110.22 | −$157.71 | Dominant |
| Matsui et al.44## | Cefazolin versus no antibiotic | 6 of 518 (1.2) | 35 of 519 (6.7) | 5.5 | $766.10 | $831.90 | −$65.80 | −$60.75 | Dominant |
| Sisto et al.45+++ | Cefetazidime versus ceftazidime | 21 of 274 (7.7) | 23 of 277 (8.3) | 0.6 | $36.11 | $107.82 | −$71.71 | −$95.95 | Dominant |
| Wilson et al.46+++ | Ertapenem versus ceftobuten | 143 of 334 (42.8) | 95 of 338 (28.1) | −14.7 | $15 230.00 | $17 411.00 | −$2181.00 | −$2340.81 | Dominant |

*Values in parentheses are percentages. †‘Discounted’ cost per patient and incremental cost-effectiveness ratio (ICER) calculated by means of a two-step discounting process using the Campbell and Cochrane Economics Methods Group—Evidence for Policy and Practice Information and Coordinating Centre cost converter web-based tool.12,33. The 2016 implied conversion factor is US $1 = €0.70 sterling; the 2016 euro conversion factor is £1 sterling = €1.28. ‡Treatment effects of cefazolin, clindamycin and cefoperazone were pooled, and costs were pooled and averaged; cost inferred from study setting to be US$; for conversion of 1992 US dollars to 2016 British pounds, the implied inflation factor for US $1 in 1992 to 2016 value is 1.57. §§Price year inferred from publication date; for conversion of 1998 US dollars to 2016 British pounds, the implied inflation factor for US $1 in 1998 to 2016 is 1.41. ¶¶Price year inferred from publication date; for conversion of 1988 British pounds to 2016 British pounds, the implied inflation factor for £1 sterling in 1988 to 2016 is 2.16. #Price year inferred from study end date; cost data based on per-protocol analysis; for conversion of 2004 US dollars to 2016 British pounds, the implied inflation factor for US $1 in 2004 to 2016 is 1.24. **For conversion of 2008 euros to 2016 euros, the implied inflation factor for €1 in 2008 to 2016 is 1.05. ††Cost inferred from study setting to be US$; for conversion of 1998 US dollars to 2016 British pounds, the implied inflation factor for US $1 in 1998 to 2016 is 1.79; infection data were missing for six patients in the control group and seven in the intervention group. ‡‡‡Price year inferred from publication date; all treatment failures; for conversion of 1987 US dollars to 2016 British pounds, the implied inflation factor for US $1 in 1987 to 2016 is 1.87. §§§Price year inferred from study end date; for conversion of 1998 US dollars to 2016 British pounds, the implied inflation factor for US $1 in 1998 to 2016 is 1.41. †††Price year inferred from publication date; for conversion of 1991 US dollars to 2016 British pounds, the implied inflation factor for US $1 in 1991 to 2016 is 1.61. ###Price year inferred from publication date; for conversion of 2013 US dollars to 2016 British pounds, the implied inflation factor for US $1 in 2013 to 2016 is 1.04. ####Price year inferred from study end date; for conversion of 1994 US dollars to 2016 British pounds, the implied inflation factor for US $1 in 1994 to 2016 is 1.50. ††Cost inferred from study setting to be US$; cost data based on per-protocol analysis; for conversion of 2005 US dollars to 2016 British pounds, the implied inflation factor for US $1 in 2005 to 2016 is 1.21. TEC, treatment effect for control; TEi, treatment effect for intervention; AH, abdominal hysterectomy; VH, vaginal hysterectomy; SDD, selective decontamination of digestive tract. A more detailed version of this table is available as Table S6, supporting information.
(MRSA) in CABG, although Gram-positive bacteria resistant to rifampicin were identified in both control (cefuroxime) and investigation (rifampicin, vancomycin and gentamicin) groups. Jones and co-workers found few pathogens (8 per cent) resistant to cefoperazone and, although no pathogens were resistant to cefotaxime, 72 per cent were inhibited by cefotaxime in several surgical procedures.

Quality assessment of economic evaluation

A modified Drummond checklist was used to assess economic methodological quality for each study (Table 6; Table S5, supporting information). Overall four studies were evaluated as being of high quality, six as moderate/acceptable quality, and two as low/unacceptable quality. All studies defined an answerable question and included an alternative treatment. Eight studies accurately measured their outcomes and costs, which were both reported in the appropriate units. No study performed sensitivity analysis or discounted cost, although discounting was not applicable in six studies. Only one study performed an ICER analysis.

Cost analysis of antibiotic prophylaxis

Of the included studies, nine were cost-benefit studies, two were cost-effectiveness studies and one was a cost containment study (Table 1; Table S3, supporting information). These were all from the perspective of the healthcare provider, with costs reported as mean cost per patient or per patient episode. Sources for the cost data were reported in all studies, and costs included prophylactic antibiotic, daily hospital charge, nursing/staff time, hospital care, care after discharge, and treatment of the SSIs (Table 7). The currencies reported were: euros, British pounds, US dollars, drachma and pesetas; both drachma and pesetas were converted to US dollars, which was the currency used in all cost analyses. Only four studies reported the price year for the currency conversion. Nine studies reported cost savings favouring the use of the preoperative prophylaxis intervention and two reported cost savings favouring the control prophylaxis. Davey and colleagues showed significant clinical effectiveness for cephradine and mezlocillin in abdominal and vaginal hysterectomy, but neither intervention was considered cost-effective. One study reported an ICER when using selective decontamination of the digestive tract versus placebo in gastrointestinal surgery, with the prevention of at least one infection leading to a reported saving of €23 164 per patient. No study discounted costs, although Dijksman et al. stated that the reason for not discounting costs included a 1-year time horizon, and they did perform a sensitivity analysis. One study considered only the acquisition and delivery cost of the antibiotic prophylaxis and not the treatment failures.

Calculated incremental cost-effectiveness ratio

The calculated ICER was based on the results of each study, their reported currency and euros (2016) (Table 7; Table S6, supporting information). Eight studies did not clearly state the price year for the cost calculations, so the year in which the study ended and date of publication were used. The calculated treatment effect showing the proportion of infections averted ranged from 0.06 per cent in clean CABG surgery to 0.33 per cent in clean-contaminated vaginal hysterectomy, with one study showing a negative effect in vascular prosthetic surgery. The intervention in ten studies was dominant (more effective and cheaper than the control) and in one study the intervention was dominated by the control (it was less effective and more expensive). In the remaining study, the intervention was more effective and more expensive than the control. This resulted in an incremental increase of €2.64 per patient and a resultant ICER of €5.12 for the year 2016.

Discussion

This review aimed to evaluate the cost-effectiveness of pre-operative antibiotic prophylaxis in preventing SSIs, including assessment of the reporting quality of the clinical and cost-effectiveness. Twelve studies published between 1988 and 2014 were identified, and included preoperative antibiotic prophylaxis as well as costs. Most of the studies had a large sample size; five had more than 500 participants, four had between 200 and 500 participants and three had fewer than 200 participants. All studies reported some measure of costs, but only two reported on incremental cost-effectiveness and none included any of the recommended economic checklists. All identified studies reported on prophylactic effectiveness, although few included antibiotic resistance and none addressed the appropriateness of antibiotic stewardship.

Prophylactic effectiveness was achieved in ten studies. The size of these effects is considered clinically important, particularly in contaminated and clean-contaminated surgery, which has a higher risk of baseline SSI compared with clean procedures. Five
of the included studies involved clean surgical procedures, so clinical effectiveness in four of these studies was not unexpected. Prophylactic effectiveness was also achieved even when the comparator was another antibiotic. Most of the prophylactic interventions involved first-, second- or third-generation cephalosporins compared with either placebo or a control. Cephalosporins are safe and have a long half-life, ensuring penetration of tissues. They offer cover against most S. aureus strains and some Gram-negative organisms, but not coagulase-negative staphylococci or MRSA. Only two studies mentioned screening for C. difficile. Cephalosporins, especially third-generation drugs, have been linked to patients having an increased risk of colonization with C. difficile, causing toxic C. difficile colitis, even when administered as a single dose. The size and dosage of antibiotic prophylaxis is important, as single-dose administration may precipitate resistance unless the prophylactic drug has a sufficient half-life and tissue penetration. One study showed that a single dose of the intervention (cefoperazone) was less effective clinically and cost more than control prophylaxis (cefotaxime). Both of these antibiotics are third-generation cephalosporins, and both were administered as a single bolus 30 min after anaesthesia but before incision. Cefotaxime was administered again during surgery if the duration of the procedure exceeded 2 h.

Teicoplanin, a glycopeptide, may also be administered as a single dose. Its use as an intervention, however, was less effective and more expensive compared with ceftazolin (a first-generation cephalosporin). Cefazolin remains the prophylactic choice in vascular surgery as it is effective against S. aureus (the most frequently isolated organism in infected vascular wounds). Cefazolin has been shown to be as effective as cefamandole and cefuroxime in prothetic vascular surgery. With the increase in MRSA, vancomycin is an alternative, but it is toxic. Teicoplanin is similar to vancomycin, but is less toxic and has a longer half-life, so may be administered once daily. Teicoplanin lacks activity against Gram-negative bacteria, however, and most infections in the teicoplanin study were caused by Gram-negative bacteria; this may have contributed to the increased costs per patient.

Combining the findings of economic evaluations with those of clinical-effectiveness trials provides healthcare policy-makers with evidence-based options for healthcare decision-making. The methodology of economic evaluations needs to be defined clearly at the study outset. This review identified low to acceptable reporting of the economic evaluations, but with great variation, whereas the reporting of clinical effectiveness was more standardized. The most recent studies were more consistent in terminology and reporting of costs and their units. Some of the studies did not include treatment failures in their cost analysis, and this may result in an intervention that is cost-saving but not necessarily cost-effective. In addition, cost-effectiveness may be more favourable in procedures that carry a higher baseline risk of SSI when the cost of prophylaxis is the same. Length of hospital stay is a recognized factor contributing to costs, and all studies reported a reduced length of stay compared with the control regimen; however, it was difficult to determine the exact costs of the stay. It is also recognized that mean daily costs decrease with extended length of stay, with the most intensive costs incurred in the period shortly after admission; this may be perceived as a disincentive for hospitals to eliminate all SSIs. None of the included studies reported decreasing costs of the hospital admission; all reported a daily hospital charge. Mortality also has an associated cost, and in cost-effectiveness studies is considered a permanent sequela. Only five studies and a nested study reported mortality, and none included deaths in the cost analysis.

The methodological quality of the included studies was not well reported, as evidenced by low scores on the CHEERS checklist, whereas economic reporting was moderate to high, with seven studies ranking 75 per cent or above on the modified Drummond quality checklist. Two of the highest-quality studies were among the most recent ones, published in 2008 and 2012. There was, however, no standard method of reporting costs, and some cost components were not always reported; discounting was not reported in any study. Consistent inclusion of standardized economic studies in clinical trials and quasi-experimental studies would allow evidence-based decision-making with respect to antibiotic efficacy and cost-effectiveness.

This review has five main limitations. First, the search terms used may not have identified all articles, as a wide variety of terms exist to describe economic evaluations, prophylaxis and infection. Second, the review was restricted to studies performed in OECD countries. The purpose of the restriction was to reduce the effect of differences in operating theatre conditions and surgical procedures on the incidence of SSI. Third, the ICER analysis is based on the published study data and, because there was heterogeneity between the studies and sensitivity analysis was not always reported, it was limited to point estimates. Fourth, in this review, an ICER was not sensitive enough to rank cost-effectiveness, as most of the interventions were dominant. For the dominant interventions using an ICER the range of difference could not be determined, and possibly a quality-adjusted...
life-year framework would be more suitable; however, this would require standardized reporting. Fifth, despite the importance of preventing primary antibiotic resistance, the review did not attempt to address the development of resistance or antibiotic stewardship, because no study reported on either. This also implies that the results of these studies have limited generalizability; if resistance patterns differ, a drug that is (cost-)effective in one context may not be in another. The specific findings of the studies reviewed here should therefore be treated with caution.

The strengths of this review are several. It is the first to include both clinical and economic effectiveness of preoperative prophylaxis; it included five databases, and the numerous keywords were matched with indexed terms specific to the databases. This review summarized large data sets that encompassed many surgical specialties and procedures. It is recommended that more than one reviewer should screen for papers to be included in a systematic review. This review used two independent reviewers, and the k statistic for each level of screening was at the higher end of the scale (from substantial to almost perfect).

This review of the cost-effectiveness of preoperative antibiotic prophylaxis found that most interventions were cost-effective. To ensure that preoperative prophylaxis continues to prevent SSI, there needs to be increased awareness of the prevalence of resistance within each facility and improved antibiotic stewardship to reduce the development of resistance. Antibiotic stewardship includes use of the appropriate recommended antibiotic prophylaxis based on the most common pathogens likely to cause SSI for a specific surgical procedure, following recommended timing of administration before incision to ensure maximum tissue concentration, adjusting the prophylaxis dose according to the patient’s bodyweight, redosing the prophylaxis at intervals of two half-lives, and discontinuing prophylaxis after surgery within recommended time frames. New antibiotic prophylaxis regimens may be implemented when they are less effective or more expensive if economic methods are not included routinely in RCTs and quasi-experimental studies. Economic methods would improve the understanding and true economic benefit of these new regimens. The economic methods need to be standardized against recommended guidelines and incorporate sensitivity analysis, discount rates, year and date of the study, unit costs, mortality, treatment effects, antibiotic resistance and quality-of-life costs.

**Disclosure**

The authors declare no conflict of interest.
Cost-effectiveness of preoperative antibiotic prophylaxis

15 Noorani A, Rabey N, Walsh SR, Davies RJ. Systematic review and meta-analysis of preoperative antisepsis with chlorhexidine versus povidone–iodine in clean-contaminated surgery. Br J Surg 2010; 97: 1614–1620.

16 Gillespie BM, Chaboyer W, Erichsen-Andersson A, Hettiarachchi RM, Kularatna S. Economic case for intraoperative interventions to prevent surgical-site infection. Br J Surg 2017; 104: e55–e64.

17 Gheorghe A, Roberts TE, Pinkney TD, Bartlett DC, Morton D, Calvert M. The cost-effectiveness of wound-edge protection devices compared to standard care in reducing surgical site infection after laparotomy: an economic evaluation alongside the ROSSINI trial. PLoS One 2014; 9: e95598.

18 Patel A, Bergman A, Moore B, Haglund U. The economic burden of complications occurring in major surgical procedures: a systematic review. Appl Health Econ Health Policy 2013; 11: 577–592.

19 Kao LS, Meeks D, Moyer VA, Lally KP. Peri-operative glycaemic control regimens for preventing surgical site infections in adults. Cochrane Database Syst Rev 2009; (3):CD006806.

20 Beltramini AM, Salata RA, Ray AJ. Thermoregulation and risk of surgical site infection. Infect Control Hosp Epidemiol 2011; 32: 603–610.

21 Bratzler DW, Dellinger EP, Olsen KM, Perl TM, Awuarter PG, Bolon MK et al.; American Society of Health-System Pharmacists; Infectious Disease Society of America; Surgical Infection Society; Society for Healthcare Epidemiology of America. Clinical practice guidelines for antimicrobial prophylaxis in surgery. Am J Health Syst Pharm 2013; 70: 195–283.

22 Scottish Intercollegiate Guidelines Network (SIGN). Antibiotic Prophylaxis in Surgery; SIGN Publication number 104; July 2008 [updated April 2014]. http://www.sign.ac.uk/assets/sign104.pdf [accessed 16 June 2017].

23 Anderson DJ, Podgorny K, Berrios-Torres SI, Bratzler DW, Dellinger EP, Greene L et al. Strategies to prevent surgical site infections in acute care hospitals: 2014 update. Infect Control Hosp Epidemiol 2014; 35: 605–627.

24 Higgins JPT, Green S (eds). Cochrane Handbook for Systematic Reviews of Interventions; Version 5.1.0; updated March 2011. http://handbook.cochrane.org [accessed 30 May 2014].

25 Centre for Reviews and Dissemination (CRD), University of York. Systematic Reviews: CRD’s Guidance for Undertaking Reviews in Health Care; 2009. https://www.crd.york.ac.uk/CRDWeb/GuideToSearching.asp [accessed 30 May 2014].

26 Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009; 339: 519–521.

27 Drummond MF, Sculpher MJ, Torrance GW, O’Brien BJ, Stoddart GL. Methods for the Economic Evaluation of Health Care Programmes (3rd ed.). Oxford University Press: New York, 2005.

28 World Bank Group. Data: Country and Lending Groups 2014. http://data.worldbank.org/about/country-and-lending-groups [accessed 16 July 2014].

29 Watson PF, Petrie A. Method agreement analysis: a review of correct methodology. Theriogenology 2010; 73: 1167–1179.

30 Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977; 33: 159–174.

31 Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D et al.; CHEERS Task Force. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. BMJ 2013; 346: f1049.

32 Campbell and Cochrane Economics Methods Group (CCEMG) and Evidence for Policy and Practice Information and Coordinating Centre (EPPi-Centre). CCEMG – EPPI-Center Cost Converter, v.1.5; April 2016. http://eppi.ioe.ac.uk/costconversion/default.aspx [accessed 20 May 2017].

33 Shemilt I, Thomas J, Morciano M. A web-based tool for adjusting costs to a specific target currency and price year. Evid Policy 2010; 6: 51–59.

34 International Monetary Fund. World Economic Outlook Database; April 2016. https://www.imf.org/external/pubs/ft/weo/2016/01/weodata/index.aspx [accessed 20 May 2017].

35 Blair EA, Johnson JT, Wagner RL, Carrau RL, Bizakis JG. Cost analysis of antibiotic prophylaxis in clean head and neck surgery. Arch Otolaryngol Head Neck Surg 1995; 121: 269–271.

36 Bold RJ, Mansfield PF, Berger DH, Pollock RE, Singletary SE, Ames FC et al. Prospective, randomized, double-blind study of prophylactic antibiotics in axillary lymph node dissection. Am J Surg 1998; 176: 239–243.

37 Davey PG, Duncan ID, Edward D, Scott AC. Cost-benefit analysis of cephapirin and mezlocillin prophylaxis for abdominal and vaginal hysterectomy. Br J Obstet Gynaecol 1988; 95: 1170–1177.

38 Dhadwal K, Al-Ruzzeh M, Athanasiou T, Choudhury M, Tekkis P, Vuddamalay P et al. A comparison of clinical and economic outcomes of two antibiotic prophylaxis regimens for sternal wound infection in high-risk patients following coronary artery bypass grafting surgery: a prospective randomised double-blind controlled trial. Heart 2007; 93: 1126–1133.

39 Dijskstra LM, Roos D, Gerhards MF, Tijssen JG, Gouma DJ, Dijkgraaf MG. Cost-effectiveness of perioperative selective decontamination of the digestive tract versus placebo in elective gastrointestinal surgery. Dig Surg 2012; 29: 384–390.

40 Garcia-Rodriguez JA, Puig-LaCalle J, Arnau C, Porta M, Vallve C. Antibiotic prophylaxis with cefotaxime in gastrointestinal and biliary surgery. Am J Surg 1989; 158: 428–432.
41 Jones RN, Wojeski WV. Single-dose cephalosporin prophylaxis of 929 surgical procedures in a prepaid group practice: a prospective, randomized comparison of cefotaxime and cefotaxime. *Diagn Microbiol Infect Dis* 1987; 6: 323–334.

42 Marroni M, Cao P, Fiorino M, Maghini M, Lenti M, Repetto A et al. Prospective, randomized, double-blind trial comparing teicoplanin and cefazolin as antibiotic prophylaxis in prosthesis vascular surgery. *Eur J Clin Microbiol Infect Dis* 1999; 18: 175–178.

43 Matkaris M, Markantes K, Stayannis K, Iatrakis G, Kourounis G, Tzingounis V. Reduction of hospital cost and administration of prophylactic antibiotherapy in gynecological surgery. *Isr J Med Sci* 1991; 27: 134–136.

44 Matsui Y, Satoi S, Kaibori M, Toyokawa H, Yanagimoto H, Matsui K et al. Antibiotic prophylaxis in laparoscopic cholecystectomy: a randomized controlled trial. *PLoS One* 2014; 9: e106702.

45 Sisto T, Laurikka J, Tarkka MR. Ceftriaxone vs cefuroxime for infection prophylaxis in coronary bypass surgery. *Scand J Thorac Cardiovac Surg* 1994; 28: 143–148.

46 Wilson SE, Turpin RS, Kumar RN, Itani KM, Jensen EH, Pellissier JM et al. Comparative costs of ertapenem and cefotetan as prophylaxis for elective colorectal surgery. *Surg Infect (Larchmt)* 2008; 9: 349–356.

47 Roos D, Dijksman LM, Oudemans-van Straaten HM, de Wit LT, Gouma DJ, Gerhards MF. Randomized clinical trial of perioperative selective decontamination of the digestive tract versus placebo in elective gastrointestinal surgery. *Br J Surg* 2011; 98: 1365–1372.

48 Itani KMF, Wilson SE, Awad SS, Jensen EH, Finn TS, Abramson MA. Ertapenem versus cefotetan prophylaxis in elective colorectal surgery. *N Engl J Med* 2006; 355: 2640–2651.

49 Johnson JT, Myers EN, Thearle PB, Sigler BA, Schramm VL Jr. Antimicrobial prophylaxis for contaminated head and neck surgery. *Laryngoscope* 1984; 94: 46–51.

50 Jonkers D, Elenbaas T, Terporten P, Nieman F, Stobberingh E. Prevalence of 90-days postoperative wound infections after cardiac surgery. *Eur J Cardiothorac Surg* 2003; 23: 97–102.

51 Rommes JH, Rios G, Zandstra DF. Therapy of infection. *Trends Anaesth Crit Care* 2001; 12: 25–33.

52 Berard F, Gandon J. Postoperative wound infections: the influence of ultraviolet irradiation of the operating room and of various other factors. *Ann Surg* 1964; 160(Suppl 2): 1–192.

53 Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. *Am J Infect Control* 1988; 16: 128–140.

54 Horan TC, Culver DH, Gaynes RP, Jarvis WR, Edwards JR, Reid CR. Nosocomial infections in surgical patients in the United States, January 1986–June 1992. National Nosocomial Infections Surveillance (NNIS) System. *Infect Control Hosp Epidemiol* 1993; 14: 73–80.

55 Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. Guideline for prevention of surgical site infection, 1999. Hospital Infection Control Practices Advisory Committee. *Infect Control Hosp Epidemiol* 1999; 20: 275–278.

56 Jarvis WR. Benchmarking for prevention: the Centers for Disease Control and Prevention's National Nosocomial Infections Surveillance (NNIS) system experience. *Infection* 2003; 31(Suppl 2): 44–48.

57 Bowater RJ, Stirling SA, Lilford RJ. Is antibiotic prophylaxis in surgery a generally effective intervention? Testing a generic hypothesis over a set of meta-analyses. *Ann Surg* 2009; 249: 551–556.

58 Privitera G, Scarpellini P, Ortisi G, Nicastro G, Nicolin R, de Lalla F. Prospective study of *Clostridium difficile* intestinal colonization and disease following single-dose antibiotic prophylaxis in surgery. *Antimicrob Agents Chemother* 1991; 35: 208–210.

59 Ambrose NS, Johnson M, Burdon DW, Keighley MR. The influence of single dose intravenous antibiotics on faecal flora and emergence of *Clostridium difficile* in gastrointestinal surgery. *J Antimicrob Chemother* 1985; 15: 319–326.

60 Edwards WH Jr, Kaiser AB, Tapper S, Edwards WH Sr, Martin RS III, Mulherin JL Jr et al. Cefamandole versus cefazolin in vascular surgical wound infection prophylaxis: cost-effectiveness and risk factors. *J Vasc Surg* 1993; 18: 470–476.

61 Edwards P, Clarke M, DiGuiseppi C, Pratap S, Roberts I, Wentz R. Identification of randomized controlled trials in systematic reviews: accuracy and reliability of screening records. *Stat Med* 2002; 21: 1635–1640.