Systematic review

Network meta-analysis of antibiotic prophylaxis for prevention of surgical-site infection after groin hernia surgery

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Background: **First-generation cephalosporins (such as cefazolin) are recommended as antibiotic prophylaxis in groin hernia repair, but other broad-spectrum antibiotics have also been prescribed in clinical practice. This was a systematic review and network meta-analysis to compare the efficacy of different antibiotic classes for prevention of surgical-site infection (SSI) after hernia repair.**

Methods: **RCTs were identified that compared efficacy of antibiotic prophylaxis on SSI after inguinal or femoral hernia repair from PubMed and Scopus databases up to March 2016. Data were extracted independently by two reviewers. Network meta-analysis was applied to assess treatment efficacy. The probability of being the best antibiotic prophylaxis was estimated using surface under the cumulative ranking curve (SUCRA) analysis.**

Results: **Fifteen RCTs (5159 patients) met the inclusion criteria. Interventions were first-generation (7 RCTs, 1237 patients) and second-generation (2 RCTs, 532) cephalosporins, β-lactam/β-lactamase inhibitors (6 RCTs, 619) and fluoroquinolones (2 RCTs, 581), with placebo as the most common comparator (14 RCTs, 2190). A network meta-analysis showed that β-lactam/β-lactamase inhibitors and first-generation cephalosporins were significantly superior to placebo, with a pooled risk ratio of 0·44 (95 per cent c.i. 0·25 to 0·75) and 0·62 (0·42 to 0·92) respectively. However, none of the antibiotic classes was significantly different from the others. SUCRA results indicated that β-lactam/β-lactamase inhibitors and first-generation cephalosporins were ranked first and second respectively for best prophylaxis.**

Conclusion: **β-Lactam/β-lactamase inhibitors followed by first-generation cephalosporins ranked as the most effective SSI prophylaxis for adult patients undergoing groin hernia repair.**

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Introduction

Inguinal and femoral hernias account for around 70–75 per cent of all hernia operations[1]. The rate of hernia repair is ten per 100 000 population in the UK and 28 per 100 000 in the USA[2]. Groin hernia repairs can be performed as either open or laparoscopic procedures, with or without the use of a prosthetic mesh, termed hernioplasty and herniorrhaphy respectively. Although hernia repair is considered a clean procedure, the postoperative wound infection rate is higher than expected for other clean procedures, approximately 4–5 per cent[3]. The most common pathogen is *Staphylococcus aureus*[4,5].

Antibiotic prophylaxis is therefore recommended in many guidelines, particularly for reducing infection risk when prosthetic material is employed[4–7]. The prophylactic efficacy of different antibiotic classes has been studied, including first-generation (such as cephaloridine, cefazolin), second-generation (cefuroxime) and third-generation (cefonicid, cefotaxime) cephalosporins, β-lactam/β-lactamase inhibitors (amoxicillin–clavulanic acid, ampicillin–sulbactam) and fluoroquinolones (ciprofloxacin, levofloxacin)[8–25]. First-generation cephalosporins are the most commonly recommended for several reasons (cost, tolerability, efficacy, safety and acceptable pharmacokinetics[4,5]), but other classes are being used increasingly in clinical practice[26,27].

The efficacy of antibiotic prophylaxis in hernioplasty remains controversial, and some surgeons still feel that antibiotic prophylaxis is not necessary, even for procedures with a mesh[27]. Results of previous systematic reviews

and meta-analyses[3,28,29] pooling nine to 12 RCTs showed benefits of antibiotic prophylaxis in reducing the risk of surgical-site infection (SSI) compared with placebo. The rate of SSI ranged from 2·4 to 3·0 per cent with antibiotic prophylaxis, and 4·2 to 6·0 per cent in placebo groups. However, the most recent meta-analysis[30] in 2014, pooling 12 RCTs, found an incidence of infection of 2·6 and 4·4 per cent respectively, which did not reach statistical significance. Since that meta-analysis was performed, three additional RCTs[23–25] have been published, with conflicting results. Despite these findings, the use of antibiotic prophylaxis in hernioplasty is still recommended when there is a risk of wound infection[5,30–32]. Given the concerns about the increasing use of broad-spectrum antibiotics and drug resistance, it remains unknown which antibiotic is the best for groin hernia surgical-site prophylaxis.

Network meta-analysis of available data can compare efficacy between antibiotics by borrowing information from a common comparator such as placebo[33,34]. In addition, a network meta-analysis can rank the most effective antibiotic classes. The present systematic review used network meta-analysis to map all antibiotic classes, with the aim of determining and ranking the efficacy of each antibiotic prophylaxis regimen compared with an active comparator for prophylaxis in groin hernia repair.

Methods

This systematic review and network meta-analysis was conducted following guidelines in the PRISMA extension of network meta-analyses[35]. The review protocol was registered in the international prospective register of systematic reviews (CRD42015025398).

Search strategies and study selection

PubMed and Scopus databases were used to identify previous meta-analyses and RCTs of antibiotic prophylaxis for groin hernia repair up to 23 March 2016.

The search terms and strategies were constructed as follows: Patient: herni*; intervention: antibiotic*, antimicrob*, Cephalosporins, Cefazolin, Cefuroxime, Cefotaxime, Cefoxitin, Cefotetan, Ceftriaxone, Penicillins, Beta-lactams, Amoxicillin, Ampicillin, Piperacillin, Beta-lactamase Inhibitors, Sulbactam, Clavulan*, Tazobactam, Sultamicillin, Amoxicillin–potassium clavulanate combination, Fluoroquinolones, Levofloxacin, Ciprofloxacin, Moxifloxacin; comparator: placebo, no treatment; outcome: prophyla*, prevent*, surgical wound infection, wound infection. Search strategies for each electronic database are described in *Appendix S1* (supporting information).

Two reviewers independently screened all titles and abstracts of studies identified in previous meta-analyses, and those identified from electronic databases. Full papers were retrieved if a decision could not be made. Disagreement was resolved by consensus and discussion with a third party.

Any RCT regardless of sample size was included if it met the following criteria: included adult patients who underwent groin hernia repair (inguinal or femoral hernia, laparoscopic or open repair) with, or without using prosthetic material; compared any systemic administration of antibiotic with antibiotic, placebo or no treatment; prophylactic antibiotics included any generation of cephalosporins, β-lactam antibiotics combined with β-lactamase inhibitors, or fluoroquinolones; and had SSI as the outcome. Studies were excluded if there were insufficient data for pooling after three failed attempts to contact the authors regarding data provision, or if they compared different doses of the same antibiotic class.

Interventions and comparators

The interventions were systemic administration of antibiotic prophylaxis before surgery. Antibiotics were then categorized according to class: first-generation cephalosporins (such as cefazolin, cephaloridine), second-generation cephalosporins (cefotetan, cefuroxime, cefotaxime, cefoxitin), third-generation cephalosporins (ceftriaxone), β-lactam combined with β-lactamase inhibitors (combinations of amoxicillin and clavulanate, ampicillin and sulbactam, or ampicillin and clavulanate) and fluoroquinolones (levofloxacin, ciprofloxacin, moxifloxacin). The comparators were placebo or no treatment, and active controls if any of the antibiotics described above were used.

Outcome of interest

The outcome of interest was SSI, defined according to the original studies using either the Centers for Disease Control and Prevention (CDC) criteria[4] or clinical signs and symptoms. Briefly, SSI was an infection involving superficial or deep soft tissues at the incision site that occurred within 30 days or 1 year respectively after the operation. Superficial SSI was defined by the presence of at least one of the following: purulent drainage with, or without laboratory confirmation; positive organisms isolated from fluid or tissue from the superficial incision; having one or more signs or symptoms (pain or tenderness, localized swelling, redness, opened superficial incision by surgeon); and diagnosis of superficial incisional SSI by the surgeon or attending physician. Deep SSI involved deep

soft tissues (fascial and muscle layers) of the incision with at least one of the following: purulent drainage from the deep incision; a deep incision deliberately opened by a surgeon; abscess; or diagnosis by surgeon or attending physician.

Risk-of-bias assessment

The methodological quality of the included studies was evaluated by risk-of-bias assessment[36]. This included random sequence generation, allocation concealment, blinding of participants and personnel, blinded outcome assessment, incomplete outcome data, and selective outcome reporting. Disagreement was resolved by consensus and discussion with a third party.

Data extraction

Data extraction was done by two authors independently. Characteristics of studies and patients were extracted. These included: setting, follow-up interval, mean age, BMI, percentage of men, percentage with diabetes, SSI criteria, percentage with ASA fitness grade higher than II, duration of surgery, and type of intervention and comparator. Cross-tabulated data between intervention and SSI were also extracted. Any disagreement was resolved by discussion.

Statistical analysis

Direct comparison

The efficacies of each antibiotic class *versus* placebo, no treatment or another antibiotic were compared directly. The risk ratios (RRs) from each study were calculated and pooled using a fixed-effect model if there was no evidence of heterogeneity; otherwise a random-effects model was applied. Heterogeneity was assessed using Cochrane Q test and the I^2 statistic, and was considered present if $P < 0{\cdot}100$ or the I^2 value was 25 per cent or greater. The source of heterogeneity was explored using meta-regression by fitting clinical (age, diabetes, weight, ASA grade) or methodological (criteria for diagnosing SSI, follow-up interval, study setting) factors in the model. If heterogeneity was present, a subgroup analysis was performed. Publication bias was assessed using funnel plots and Egger's tests. If one of these indicated asymmetry, a contour-enhanced funnel plot was constructed to distinguish whether the cause of asymmetry was publication bias or heterogeneity.

Network meta-analysis

Network meta-analysis was used to assess treatment effects between different antibiotic classes. Indirect comparisons between two antibiotic classes were made by borrowing information from a common comparator (placebo/no prophylaxis). Treatments were coded as 1, 2, 3, 4 and 5 for placebo/no treatment, first-generation cephalosporins, second-generation cephalosporins, β-lactam combined with β-lactamase inhibitors, and fluoroquinolones respectively. A network of all treatments was mapped in which nodes and edges were weighted by number of subjects and studies for that comparison respectively. A contribution plot was constructed to display the contribution of each direct comparison to the network meta-analysis estimates.

Two approaches were applied for assessing relative treatment effects: one-stage and two-stage network meta-analyses. For the one-stage approach, aggregate data were expanded to individual-patient data (*Appendix S2*, supporting information). A mixed-effect Poisson regression was applied to estimate relative treatment effects across studies using placebo/no treatment as the reference group[37]. The treatment effect was considered as a fixed effect, whereas study was considered as a random effect. RRs were then estimated by exponential coefficients.

For the two-stage approach, a relative treatment effect (coefficient or lnRR) and its variance–co-variance was estimated for each study using a generalized linear model with a log-link function and binomial distribution of SSI. These relative treatment effects were then pooled across studies using a multivariable meta-analysis with maximum likelihood function[38,39]. Relative treatment effects between antibiotics were then compared using a linear combination of the multivariable meta-analysis model. Treatment efficacy was then ranked as estimated probability of being best prophylaxis using the surface under the cumulative ranking curve (SUCRA) method[33,40]. Predictive intervals were estimated and plotted by taking into account heterogeneity within and between treatment comparisons. This allowed an assessment of whether relative treatment effects would work well when applied in other studies/populations[33,34]. The inconsistency assumption, that is agreement between direct and indirect treatment effects, was assessed using a design-by-treatment interaction model.

Finally, a number needed to treat (NNT) was estimated by the following equation[41]:

$$\text{NNT} = \frac{1}{I_{\text{placebo}} \times \left(1 - \text{pooled RR}\right)}$$

where I_{placebo} is the pooled incidence of SSI in the placebo group, and pooled RR is the relative treatment effect estimated from the network meta-analysis.

All analyses were performed using STATA® software version 14.0 (StataCorp, College Station, Texas, USA). $P < 0{\cdot}050$ was considered statistically significant unless

otherwise specified. More details of the analysis plan and STATA® commands used can be found in *Appendix S2* (supporting information).

Results

Identification of eligible studies

A total of 1683 studies were identified from PubMed and Scopus databases. Of these, 11[3,28–30,42–48] were systematic reviews/meta-analyses, which included a total of 19 individual studies. Only 14 of the 19 studies met the inclusion criteria; reasons for not including five RCTs[49–53] are described (*Fig. 1*). Of 1683 original studies, 17 RCTs[9–25] met the inclusion criteria, of which 13 had already been identified and included in previous meta-analyses; four additional studies were identified, giving a total of 18 eligible RCTs.

Characteristics of eligible studies

Characteristics of the 18 RCTs[8–25] are described in *Tables 1* and *2*. Three[8–10] and 15[11–25] trials respectively included herniorrhaphy and hernioplasty (prosthetic

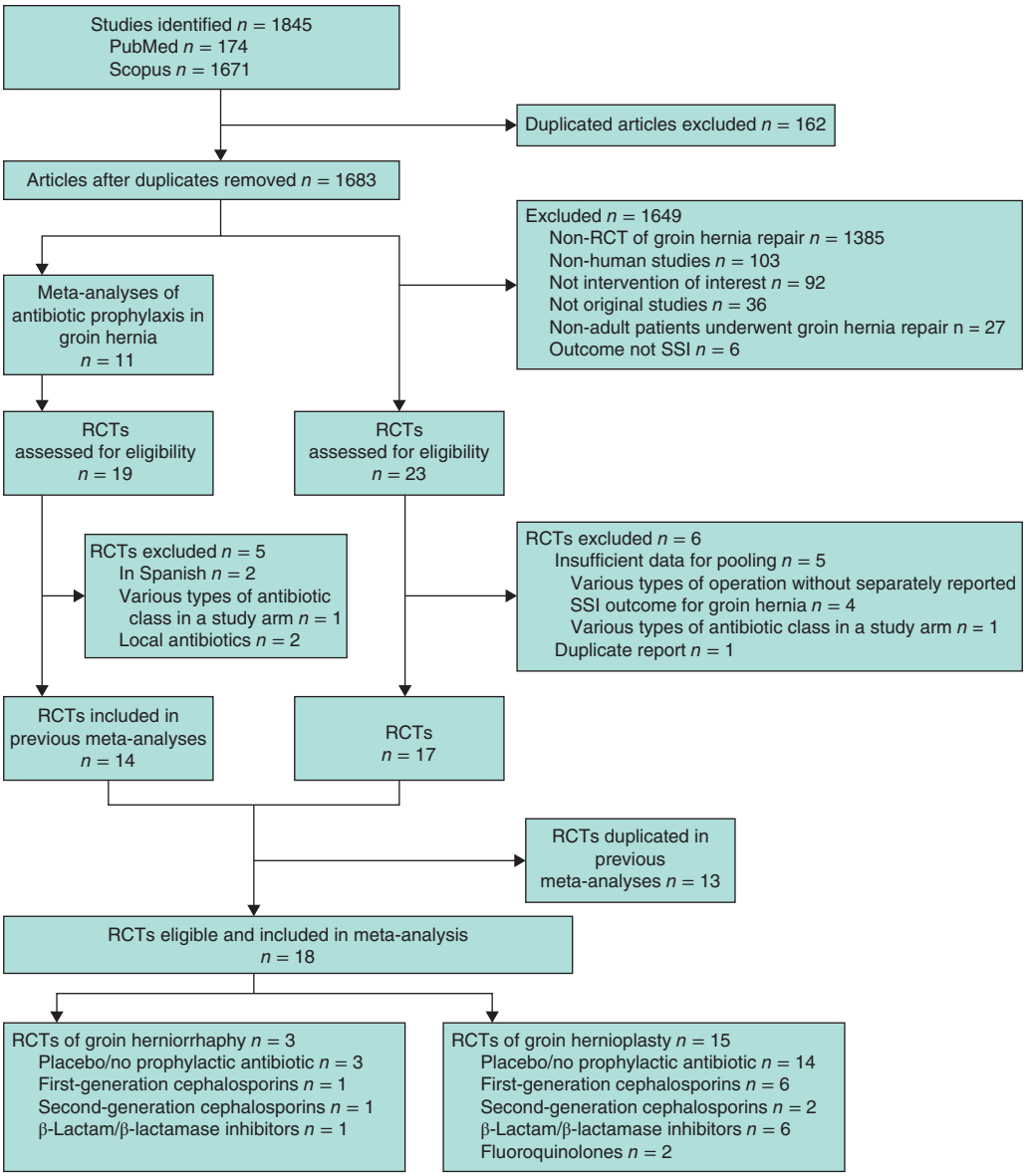

Fig. 1 Flow diagram showing selection of articles for review. SSI, surgical-site infection

Table 1 Characteristics of included RCTs

Reference	Antibiotic regimen	Class of antibiotic	Setting	SSI definition	Country	Follow-up (days)
Herniorrhaphy						
8	Cephaloridine 1 g single dose i.m. followed by 1 g i.m. × 2 doses *versus* no antibiotic	First-generation cephalosporins *versus* no antibiotic	Single	n.r.	UK	At least 28
9	Cefonicid 1 g i.v. *versus* placebo	Second-generation cephalosporins *versus* placebo	Multi	S/S	USA	At least 42
10	Amoxicillin–clavulanate 1·2 g i.v. *versus* placebo	β-Lactam/β-lactamase inhibitors *versus* placebo	Multi	S/S	UK	28–42
Hernioplasty						
11	Ampicillin–sulbactam 1·5 g i.v. *versus* placebo	β-Lactam/β-lactamase inhibitors *versus* placebo	Single	CDC	Turkey	365
12	Cefuroxime 1·5 g i.v. *versus* placebo	Second-generation cephalosporins *versus* placebo	Multi	CDC	The Netherlands	84
13	Cefazolin 1 g i.v. *versus* placebo	First-generation cephalosporins *versus* placebo	Single	CDC	Spain	730
14	Cefazolin 1 g i.v. *versus* placebo	First-generation cephalosporins *versus* placebo	Single	CDC	Philippines	At least 28
15	Cefazolin 1 g i.v. *versus* ciprofloxacin 500 mg oral	First-generation cephalosporins *versus* fluoroquinolones	Single	CDC	Turkey	365
16	Ampicillin–clavulanate 1·2 g i.v. *versus* placebo	β-Lactam/β-lactamase inhibitors *versus* placebo	Single	S/S	Greece	30
17	Amoxicillin–clavulanate 1·2 g i.v. *versus* placebo	β-Lactam/β-lactamase inhibitors *versus* placebo	Single	CDC	India	365
18	Cefazolin 1 g i.v. *versus* placebo	First-generation cephalosporins *versus* placebo	Single	CDC	India	30
19	Cefuroxime 1·5 i.v. *versus* placebo	Second-generation cephalosporins *versus* placebo	Single	CDC	India	30
20	Amoxicillin–clavulanate 1·2 g i.v. *versus* placebo	β-Lactam/β-lactamase inhibitors *versus* placebo	Single	S/S	India	8
21	Amoxicillin-clavulanate 1·2 g i.v. *versus* placebo	β-Lactam/β-lactamase inhibitors *versus* placebo	Single	CDC	Egypt	30
22	Cefazolin 1 g i.v. *versus* placebo	First-generation cephalosporins *versus* placebo	Single	CDC	Turkey	30
23	Amoxicillin–clavulanate 1 g i.v. *versus* placebo	β-Lactam/β-lactamase inhibitors *versus* placebo	Single	n.r.	Pakistan	14
24	Cefazolin 1 g i.v. *versus* levofloxacin 200 g i.v. *versus* placebo	First-generation cephalosporins *versus* fluoroquinolones *versus* placebo	Multi	CDC	China	30
25	Cefazolin 1 g i.v. *versus* placebo	First-generation cephalosporins *versus* placebo	Single	CDC	Japan	90

SSI, surgical-site infection; i.m., intramuscular; single, single centre; n.r., not reported; i.v., intravenous; multi, multicentre; S/S, signs and symptoms; CDC, Centers for Disease Control and Prevention.

mesh). Four antibiotic classes were used in these studies: first-generation cephalosporins, second-generation cephalosporins, β-lactam/β-lactamase inhibitors and fluoroquinolones.

Of the three RCTs that examined antibiotic prophylaxis for herniorrhaphy, the prophylactic antibiotics were first-generation cephalosporin (intramuscular cephaloridine)[8], second-generation cephalosporin (intravenous cefonicid)[9] and β-lactam/β-lactamase inhibitors (intravenous amoxicillin–clavulanate)[10]; placebo or no treatment was the comparator for all three RCTs. Follow-up ranged from 4 to 6 weeks. Because data

Table 2 Further details of included RCTs

Reference	No. of subjects	Mean age (years)	% men	Mean BMI (kg/m^2)	ASA grade (I/II/III/IV)	% ASA grade > II	% diabetes mellitus	% resident/non-certified surgeon	Mean duration of surgery (min)
Herniorrhaphy									
8	97	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
9	612	50	90·4	24·7	n.r.	n.r.	4·0	n.r.	n.r.
10	563	57	94·7	73*	n.r.	n.r.	n.r.	n.r.	50% > 35 min
Hernioplasty									
11	269	56	92·6	25·0	198/71/0/0	0	0	n.r.	63·5
12	1008	58	96·3	n.r.	n.r.	n.r.	0	43·4	39·9
13	99	58	90	26·1	I or II	0	18	24	64·5
14	360	61	98·1	n.r.	284/76/0/0	0	n.r.	n.r.	53·1
15	395	56	89·6	25·7	n.r.	n.r.	6·1	n.r.	73·3
16	379	58	93·9	26·1	269/100/10/0	2·6	3·4	n.r.	48·8
17	120	41	100	n.r.	101/19/0/0	0	0	n.r.	58·3
18	450	45	98·8	n.r.	308/26/0/0	0	0	n.r.	53·1
19	55	n.r.	0	n.r.	n.r.	n.r.	n.r.	n.r.	85% > 1 h
20	200	n.r.	n.r.	n.r.	n.r.	n.r.	0	n.r.	n.r.
21	98	44	98	n.r.	n.r.	n.r.	n.r.	n.r.	39·2
22	200	49	92	n.r.	111/71/18**	9·0	6·0	n.r.	76·3
23	166	53	100	n.r.	n.r.	n.r.	0	n.r.	n.r.
24	1160	55	90·1	67*	82·5% ≥ I	n.r.	n.r.	n.r.	n.r.
25	200	69	91·5	22·9	89/101/10/0	5·0	6·5	83·5	65·8

*Weight in kilograms; **III–IV. n.r., Not reported.

available were insufficient for pooling (only 1 RCT for each comparison), the remainder of the analyses focused on hernioplasty.

Of the 15 RCTs that examined antibiotic prophylaxis for hernioplasty, 14 had placebo as comparator and only one had an active comparator[15] (fluoroquinolone *versus* first-generation cephalosporin) (*Table 1*). Among the 14 placebo-controlled studies, one[24] had three treatment arms (first-generation cephalosporin, fluoroquinolone and placebo); the remaining 13 RCTs each had two treatment arms. Comparisons made were: first-generation cephalosporins *versus* placebo (6 RCTs)[13,14,18,22,24,25], second-generation cephalosporins *versus* placebo (2 RCTs)[12,19], β-lactam/β-lactamase inhibitors *versus* placebo (6 RCTs)[11,16,17,20,21,23], and fluoroquinolone *versus* placebo (1 RCT)[24]. For the first- and second-generation cephalosporin trials, intravenous cefazolin 1 g and cefuroxime in a 1·5-g single dose were used respectively. For the two studies that examined fluoroquinolones, one RCT[24] compared a single dose of intravenous levofloxacin 200 g with first-generation cephalosporin and placebo (3-arm study), and another[15] compared oral ciprofloxacin 500 mg *versus* intravenous cefazolin 1 g. For the trials that examined β-lactam/β-lactamase inhibitors, two[11,16] used a single combination dose of ampicillin and β-lactamase inhibitor (ampicillin–sulbactam 1·5 g[11] and ampicillin–clavulanate 1·2 g[16]), whereas four RCTs[17,20,21,23] used a single dose of amoxicillin–clavulanate in a dose ranging from 1 to 1·2 g.

Mean age of study participants ranged from 41 to 69 years (*Table 2*). Follow-up ranged from 8 days to 2 years. The proportion of men ranged from 89·6 to 100 per cent. Most RCTs[11,13,14,16–18,22,25] included mainly patients with an ASA fitness grade of I or II. The majority used CDC criteria[4] for diagnosis of SSI[11–15,17–19,21,22,24,25]; four studies[9,10,16,20] used clinical signs and symptoms for diagnosis, including wound erythema[16,20], purulent drainage[9,16], opened wound[9], requirement for antibiotics[10], stitch abscess[10,20] and wound breakdown/dehiscence[10,16].

Thirteen hernioplasty studies reported micro-organism for SSIs, which were mainly *S. aureus/Staphylococcus* spp.[11–19,21,22,24,25], followed by *Escherichia coli*[15,18,24], *Pseudomonas aeruginosa/Pseudomonas* spp.[14,21,24] and *Streptococcus* spp.[12,16,18,24] (*Table S1*, supporting information).

Risk-of-bias assessment

Among the 15 studies that examined antibiotic prophylaxis for hernioplasty, all studies were considered at low risk of bias in terms of random sequence generation (selection bias). More than 60 per cent of included studies were considered at low risk of bias in terms of allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias) and selective outcome reporting (reporting bias) (*Figs S1* and *S2*, supporting information).

Direct meta-analysis

Relative treatment effects of direct comparisons between antibiotics *versus* placebo were estimated, with little heterogeneity ($I^2 = 0–8{\cdot}9$ per cent) (*Table S2*, supporting information). The treatment effects were then pooled using fixed-effect models, which indicated that only first-generation cephalosporins and β-lactam/β-lactamase inhibitors reached statistical significance, with pooled RRs of 0·62 (95 per cent c.i. 0·41 to 0·92) and 0·44 (0·25 to 0·75) *versus* placebo respectively. This suggests that use of the first-generation cephalosporins or β-lactam/β-lactamase inhibitors could lower SSI rates by approximately 40 and 60 per cent respectively compared with placebo. In contrast, there were no significant treatment effects on SSI observed between second-generation cephalosporins *versus* placebo, and fluoroquinolones *versus* first-generation cephalosporins.

Publication bias was assessed for these two pooled estimates using funnel plots (*Fig. S3*, supporting information). Egger's test showed significant bias for first-generation cephalosporins (coefficient −1·98, s.e. 0·70, $P = 0{\cdot}047$), but not for β-lactam/β-lactamase inhibitors (coefficient −0·51, s.e. 1·02, $P = 0{\cdot}641$), although this may be due to lack of power. The contour-enhanced funnel plot for first-generation cephalosporins *versus* placebo showed that a few studies in the significant (not non-significant) area might be not reported (missing). Thus, publication bias might be present but should not have much effect on pooled results.

Network meta-analysis

All 15 RCTs[11–25] that examined antibiotic prophylaxis for SSI in hernioplasty (5159 subjects) were included in a network meta-analysis (*Table S3*, supporting information). All antibiotic contrasts were mapped in a network plot, in which five indirect active comparisons were estimated from the network: second- *versus* first-generation cephalosporins, β-lactam/β-lactamase inhibitors *versus* first-generation cephalosporins, β-lactam/β-lactamase inhibitors *versus* second-generation cephalosporins, fluoroquinolones *versus* second-generation cephalosporins and fluoroquinolones *versus* β-lactam/β-lactamase inhibitors (*Fig. 2*). Data were mostly contributed from direct comparisons of first-generation cephalosporins *versus* placebo, second-generation cephalosporins *versus* placebo and β-lactam/β-lactamase inhibitors *versus* placebo (23·6, 23·2 and 23·2 per cent respectively) (*Fig. S4*, supporting information).

Effects of antibiotic prophylaxis were next estimated using two-stage network meta-analysis with a consistency model[38,54,55]. The pooled RRs of SSI for antibiotics *versus* placebo and *versus* antibiotics were plotted (*Fig. S5*,

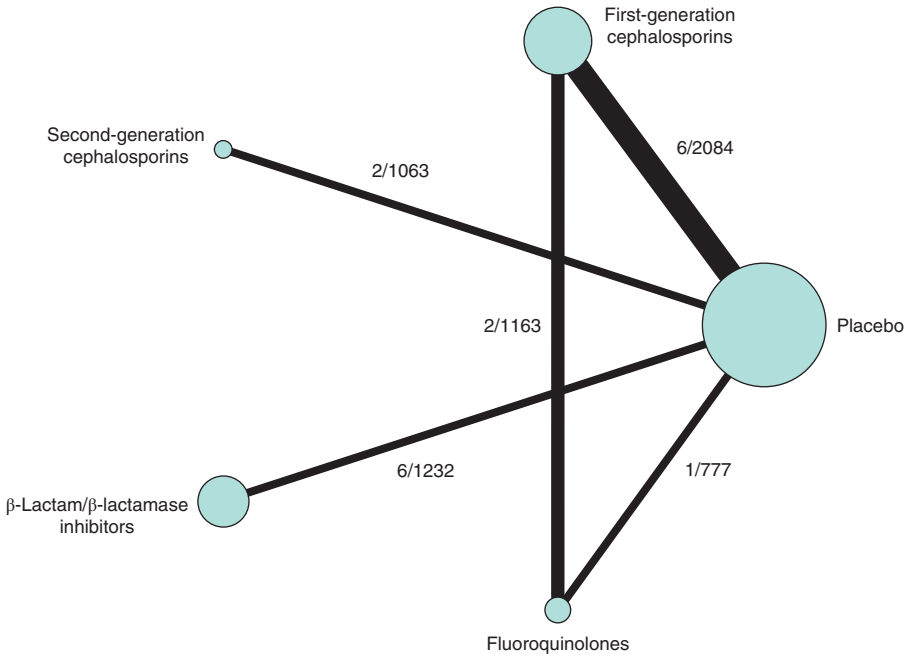

Fig. 2 Network plot of uses of antibiotic prophylaxis for reducing surgical-site infection after hernioplasty. Nodes are weighted by number of studies; edges are weighted by numbers of included subjects. Numbers of studies/subjects are shown

supporting information), and all possible pairwise comparisons were further estimated (*Table 3*). The results indicated that β-lactam/β-lactamase inhibitors provided the most effective antibiotic prophylaxis compared with placebo, with a pooled RR of 0·44 (95 per cent c.i. 0·25 to 0·75), followed by first-generation cephalosporins, with a pooled RR of 0·62 (0·42 to 0·92). Multiple comparisons between antibiotics were also done (*Table 3*). Compared with first-generation cephalosporins, β-lactam/β-lactamase inhibitors were most effective, whereas second-generation cephalosporins and fluoroquinolones were least effective; however, these effects were not statistically significant, with pooled RRs of 0·70 (0·36 to 1·38), 1·32 (0·55 to 3·16) and 1·23 (0·71 to 2·15) respectively. β-Lactam/β-lactamase

Table 3 Comparisons of antibiotic prophylaxis effects on surgical-site infection in hernioplasty

	Risk ratio			
	First-generation cephalosporins	Second-generation cephalosporins	β-Lactam/ β-lactamase inhibitors	Fluoroquinolones
Reference antibiotic				
First-generation cephalosporins	0·62 (0·42, 0·92)* [65·5; 11·5]	1·32 (0·55, 3·16)	0·70 (0·36, 1·38)	1·23 (0·71, 2·15)
Second-generation cephalosporins	0·76 (0·32, 1·82)	0·82 (0·37, 1·79)* [40·7; 10·7]	0·54 (0·21, 1·39)	0·94 (0·36, 2·45)
β-Lactam/β-lactamase inhibitors	1·42 (0·73, 2·78)	1·87 (0·72, 4·84)	0·44 (0·25, 0·75)* [91·0; 74·4]	1·75 (0·80, 3·82)
Fluoroquinolones	0·81 (0·46, 1·42)	1·07 (0·41, 2·80)	0·57 (0·26, 1·25)	0·77 (0·44, 1·34)* [41·0; 3·4]

Values are the risk ratio, with 95 per cent confidence intervals in parentheses, of surgical-site infection with use of test antibiotic (in column heading) *versus* reference antibiotic or *placebo. Values below 1·00 show benefit for test antibiotic compared with reference antibiotic. Values in square brackets are surface under the cumulative ranking curve area; percentage probability of test antibiotic being best prophylaxis.

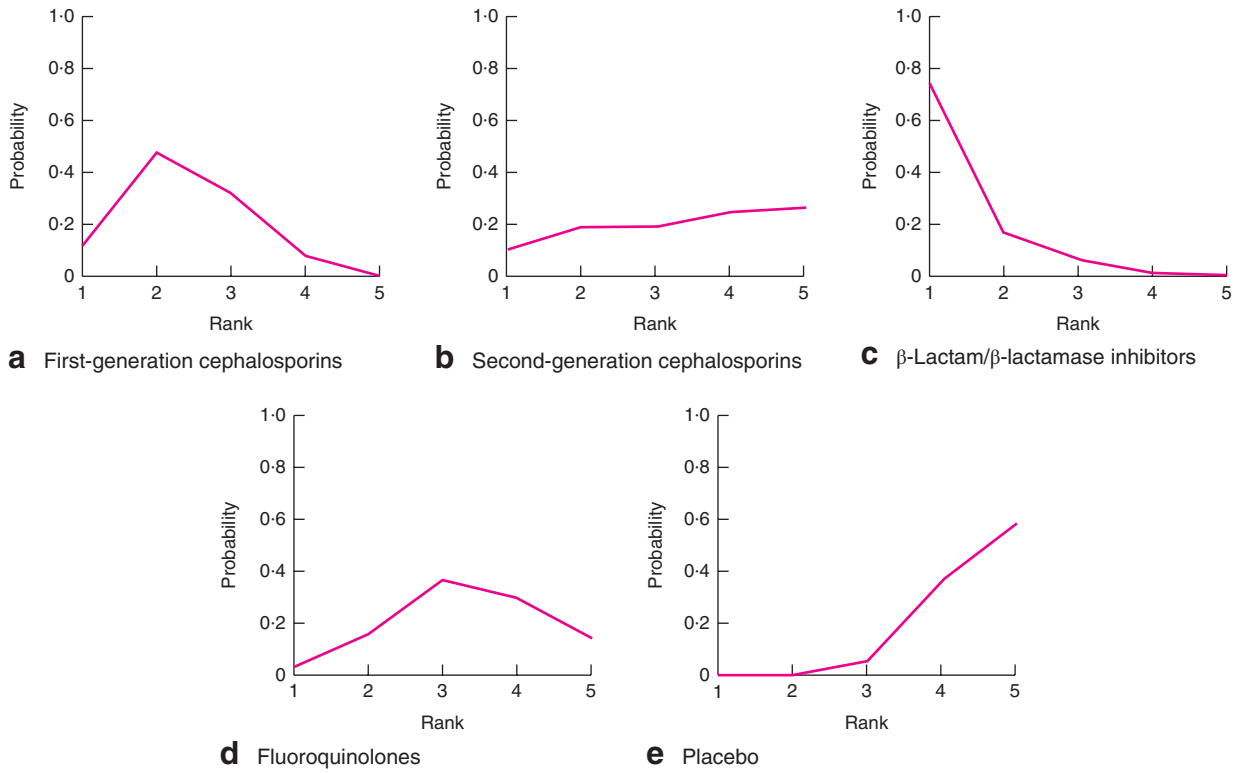

Fig. 3 Rankograms showing use of antibiotic prophylaxis for reducing surgical-site infection after hernioplasty: **a** first-generation cephalosporins, **b** second-generation cephalosporins, **c** β-lactam/β-lactamase inhibitors, **d** fluoroquinolones and **e** placebo

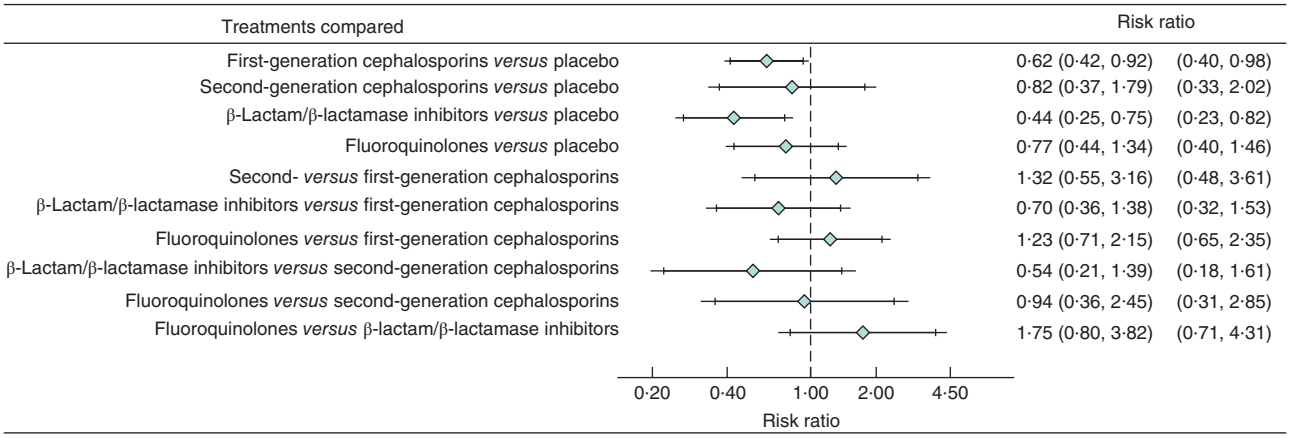

Fig. 4 Predictive interval plots for antibiotic prophylaxis network of groin hernioplasty. Values in parentheses are 95 per cent confidence intervals, followed by 95 per cent predictive intervals that take future uncertainty into account. These are also plotted as bold and extended lines respectively. The dashed line indicates no treatment effect (risk ratio = 1·00)

inhibitors and fluoroquinolones seemed to be superior to second-generation cephalosporins but this was not statistically significant, with pooled RRs of 0·54 (0·21 to 1·39) and 0·94 (0·36 to 2·45) respectively. Finally, fluoroquinolone prophylaxis was associated with a 75 per cent higher risk of SSI compared with β-lactam/β-lactamase inhibitors (RR 1·75, 0·80 to 3·82), but this was not statistically significant. The one-stage network meta-analysis yielded similar results to the two-stage approach (*Appendix S2*, supporting information); only the first-generation cephalosporins and β-lactam/β-lactamase inhibitors were effective *versus* placebo, with pooled RRs of 0·56 (0·38 to 0·81) and 0·40 (0·24 to 0·69) respectively.

The probability of being the best prophylaxis regimen was estimated by the SUCRA method, with probability and SUCRA closest to 100 reflecting best prophylaxis. These results suggested that β-lactam/β-lactamase inhibitors had 74·4 per cent chance of being the best prophylaxis (SUCRA 91·0), followed by first-generation cephalosporins (11·5 per cent chance, SUCRA 65·5), second-generation cephalosporins (10·7 per cent) and fluoroquinolones (3·4 per cent) (*Table 3* and *Fig. 3*).

Predictive intervals were also estimated (*Fig. 4*). This suggested that, after taking into account uncertainty from both heterogeneity and inconsistency, predictive intervals of first-generation cephalosporin and β-lactam/β-lactamase inhibitor effects were slightly wider than the network meta-analysis confidence intervals, but did not change the conclusions. These two antibiotics will still be beneficial in the future compared with placebo, with pooled RRs of 0·62 (95 per cent predictive interval 0·40 to 0·98) and 0·44 (0·23 to 0·82) respectively

The NNTs for first-generation cephalosporins and β-lactam/β-lactamase inhibitors were estimated. The pooled SSI incidence in the placebo group was 6·1 (95 per cent c.i. 4·2 to 8·1) per cent. The estimated NNTs for first-generation cephalosporins and β-lactam/β-lactamase inhibitors were 43 (95 per cent c.i. 28 to 202) and 29 (21 to 66) respectively.

Finally, the inconsistency assumption was checked by applying a design-by-treatment interaction model, which indicated no evidence of inconsistency effects (global $\chi^2 = 0{\cdot}719$, $P = 0{\cdot}472$).

Discussion

This systematic review and network meta-analysis of antibiotic prophylaxis for SSI in hernioplasty included four classes of antibiotic prophylaxis. The most effective antibiotics were β-lactam/β-lactamase inhibitors followed by first-generation cephalosporins, which reduced SSI rates by 56 and 38 per cent respectively compared with placebo; probabilities of being the best prophylaxis were 74·4 and 11·5 per cent respectively. A total of 29 and 43 patients respectively need antibiotic prophylaxis with β-lactam/β-lactamase inhibitors and first-generation cephalosporins to prevent one SSI.

Efficacy of antibiotic prophylaxis in herniorrhaphy could not be assessed because there were only three studies and each examined a different antibiotic class. However, using mesh in groin hernia repair is more common in practice because it reduces recurrence[56].

Applying a network meta-analysis framework provides some benefit over direct meta-analysis, even though their results are quite similar, because it allows an estimation of

treatment ranking and predictive interval. The results from the network meta-analysis are consistent with those of the direct meta-analysis, indicating that only first-generation cephalosporins and β-lactam/β-lactamase inhibitors have a significant prophylactic effect compared with placebo in groin hernioplasty. As a result, consistency and thus transitivity assumptions should hold[54]. In addition, the predictive intervals from network meta-analysis suggested that using first-generation cephalosporins and β-lactam/β-lactamase inhibitors will still be effective in the future. Although β-lactam/β-lactamase inhibitors provided the best prophylaxis, it was not significantly different from that of first-generation cephalosporins or other antibiotic classes (second-generation cephalosporins and fluoroquinolones).

Based on NNTs, prescribing first-generation cephalosporin or β-lactam/β-lactamase inhibitors to 100 patients having groin hernioplasty should prevent about two and three SSIs respectively. A further assessment is needed to determine whether β-lactam/β-lactamase inhibitors are more cost-effective than first-generation cephalosporins. Moreover, the virulence and frequency of the responsible micro-organism should also be considered in order to select antibiotic type properly.

This study has some limitations. A few treatment comparisons had a small number of studies. For instance, second-generation cephalosporin and fluoroquinolone results were based on only two trials, with poor precision of the estimated treatment effects. Sample size and the number of studies and subjects may play a role. This network meta-analysis needs to be updated when further studies become available. In addition, the study focused only on systemic antibiotic use and this may need to be compared with other routes (topical antibiotic, antibiotic-eluting mesh) when data are published[57].

At present, β-lactam/β-lactamase inhibitors followed by first-generation cephalosporins are most effective in SSI prophylaxis for adult patients undergoing groin hernioplasty; however, the efficacies of these two antibiotics are not significantly different. Further economic evaluation is needed to assess their cost-effectiveness.

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Supporting information

Additional supporting information may be found in the online version of this article:

Appendix S1 Search terms and results (Word document)

Appendix S2 STATA commands for direct meta-analysis, network meta-analysis and number needed to treat (Word document)

Fig. S1 Risk-of-bias assessment (Word document)

Fig. S2 Summary of risk-of-bias assessments (Word document)

Fig. S3 Funnel and contour-enhanced funnel plots for direct meta-analysis of groin hernioplasty (Word document)

Fig. S4 Contribution plot for network meta-analysis of antibiotic prophylaxis in hernioplasty (Word document)

Fig. S5 Forest plot of antibiotic prophylaxis *versus* placebo: network meta-analysis (Word document)

Table S1 Micro-organisms isolated from surgical-site infections (Word document)

Table S2 Efficacy of antibiotic prophylaxis against surgical-site infection in groin hernioplasty: direct meta-analysis (fixed-effect model) (Word document)

Table S3 Data from hernioplasty studies that contributed to network meta-analysis (Word document)