Systematic review

Meta-analysis of randomized and quasi-randomized clinical trials of topical antibiotics after primary closure for the prevention of surgical-site infection

C. F. Heal[1,2,3], J. L. Banks[2], P. Lepper[2], E. Kontopantelis[5] and M. L. van Driel[4]

[1]Department of General Practice and Rural Medicine, [2]College of Medicine and Dentistry, and [3]Mackay Institute of Research and Innovation, James Cook University, Mackay, and [4]Discipline of General Practice, School of Medicine, University of Queensland, Brisbane, Queensland, Australia, and [5]Centre for Health Informatics, Institute of Population Health, University of Manchester, Manchester, UK

Correspondence to: Professor C. F. Heal, General Practice and Rural Medicine, James Cook University, Mackay Base Hospital, Bridge Road, Mackay, Queensland, 4740, Australia (e-mail: clare.heal@jcu.edu.au)

Background: **Surgical-site infections (SSIs) increase patient morbidity and costs. The aim was to identify and synthesize all RCTs evaluating the effect of topical antibiotics on SSI in wounds healing by primary intention.**

Methods: **The search included Ovid MEDLINE, Ovid Embase, the Cochrane Wounds Specialized Register, Central Register of Controlled Trials and EBSCO CINAHL from inception to May 2016. There was no restriction of language, date or setting. Two authors independently selected studies, extracted data and assessed risk of bias. When sufficient numbers of comparable trials were available, data were pooled in meta-analysis.**

Results: **Fourteen RCTs with 6466 participants met the inclusion criteria. Pooling of eight trials (5427 participants) showed that topical antibiotics probably reduced the risk of SSI compared with no topical antibiotic (risk ratio (RR) 0·61, 95 per cent c.i. 0·42 to 0·87; moderate-quality evidence), equating to 20 fewer SSIs per 1000 patients treated. Pooling of three trials (3012 participants) for risk of allergic contact dermatitis found no clear difference between antibiotics and no antibiotic (RR 3·94, 0·46 to 34·00; very low-quality evidence). Pooling of five trials (1299 participants) indicated that topical antibiotics probably reduce the risk of SSI compared with topical antiseptics (RR 0·49, 0·30 to 0·80; moderate-quality evidence); 43 fewer SSIs per 1000 patients treated. Pooling of two trials (541 participants) showed no clear difference in the risk of allergic contact dermatitis with antibiotics or antiseptic agents (RR 0·97, 0·52 to 1·82; very low-quality evidence).**

Conclusion: **Topical antibiotics probably prevent SSI compared with no topical antibiotic or antiseptic. No conclusion can be drawn regarding whether they cause allergic contact dermatitis.**

This paper is based on a Cochrane Review: Heal CF, Banks JL, Lepper PD, Kontopantelis E, van Driel ML. Topical antibiotics for preventing surgical site infection in wounds healing by primary intention. *Cochrane Database Syst Rev* 2016; (11)CD011426.

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Introduction

Many surgical procedures are performed every year; the majority result in wounds that heal by primary intention. Surgical-site infections (SSIs) account for up to 20 per cent of all of healthcare-associated infections[1]. At least 5 per cent of patients who have a surgical procedure will develop an SSI[2]. SSIs can delay healing, impair cosmetic outcomes and potentially cause other morbidity, such as deeper infections, as well as increase costs and the consumption of healthcare resources[3].

The acceptable rate of SSI following clean surgery (class 1) is less than 5 per cent[4,5], although some patients and procedures are at higher risk. Therefore, oral antibiotic prophylaxis of clean surgical wounds is usually reserved for at-risk patients or high-risk procedures[3,6,7]. Although limited guidelines exist for the use of oral antibiotics as infection prophylaxis, there is no guidance on the prophylactic use of topical antibiotics.

The only information available on the frequency of topical antibiotic use on wounds is a survey of plastic

surgeons in the UK, which revealed that 66 per cent used chloramphenicol eye ointment in their practice[8,9].

Adverse effects include allergic contact dermatitis, anaphylaxis and antibiotic resistance[10–12].

There is little evidence in the literature regarding the efficacy of antibiotic ointment in preventing SSI, and some existing evidence is conflicting. A systematic review of trials is important to guide clinical practice. The authors conducted a Cochrane Review[13], which is summarized in this article. Better information on efficacy could assist in rationalizing use and contribute to controlling development of antibiotic resistance in the community. The primary aim of this review was to determine whether the application of topical antibiotics after primary closure reduces the incidence of SSI.

Methods

Criteria for considering studies for this review

All RCTs or quasi-randomized trials examining surgical wounds healing by primary intention were included. There was no limitation for age, sex, country of origin or surgical setting. Secondarily infected wounds, wounds healing by secondary intention and the application of prophylaxis before closure were excluded. Ointments, creams, lotions, solutions, gels, tinctures, foams, pastes, powders and impregnated dressings were included in the definition of topical antibiotic, but not silver or antiseptics. Excluded were antibiotic irrigation or washouts, subcutaneous infiltration of the antibiotic, any topical treatment applied before closure by primary intention and antibiotic-coated sutures. The topical antibiotic may have been applied with, or without a dressing. The comparison group was topical antiseptic or no treatment.

The primary outcome was SSI, as defined by the US Centers for Disease Control and Prevention. In this definition, infection must occur within 30 days of the procedure, so this time point was used as a cut-off for this primary outcome measure. The trial authors' definitions of infection were accepted. Adverse effects within 30 days of the procedure were also a primary outcome, and were defined as allergic contact dermatitis, anaphylaxis or infections with patterns of antibiotic resistance.

Literature search

The following electronic databases were searched to identify reports of relevant RCTs from inception to May 2016: the Cochrane Wounds Specialized Register (searched 12 May 2016); Ovid MEDLINE; Ovid MEDLINE (In-Process & Other Non-Indexed Citations); Ovid Embase; the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library); and EBSCO Cumulative Index to Nursing and Allied Health Literature (CINAHL). The Ovid MEDLINE search was combined with the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision)[14]. The Embase search was combined with the Ovid Embase filter developed by the UK Cochrane Centre[14]. The CINAHL searches were combined with the trial filters developed by the Scottish Intercollegiate Guidelines Network[15]. Studies were not restricted with respect to language or date of publication.

Clinical trials registries and bibliographies of all retrieved and relevant publications identified were searched for additional eligible trials, and manufacturers and pharmaceutical companies contacted regarding studies for inclusion.

Data extraction

Two review authors screened the titles and abstracts independently. They obtained a copy of the full article for potentially eligible studies. Any discrepancies were resolved by consensus discussion with a third author. Where necessary and possible, additional information was sought from the principal investigator of the trial concerned.

The following data were extracted: eligibility criteria, trial characteristics, methods, participants, intervention, control group, outcome definitions and outcome data for primary and secondary outcomes, and key conclusions of study authors.

Assessment of risk of bias in included studies

Two review authors independently assessed each included study for risk of bias (selection bias, performance bias and attrition bias)[16]. A threshold was set such that trials assessed as at risk of either random number generation, allocation concealment or assessor blinding were considered to be at high risk of bias. If missing outcome data were distributed unequally over the intervention arms, the study was deemed to be at high risk of attrition bias, and the authors considered performing an intention-to-treat analysis.

Statistical analysis

All outcomes measured in the review were dichotomous. Risk ratio (RR) was used as the effect measure, with 95 per cent c.i. I^2 was interpreted according to the Cochrane Handbook[14], taking into account factors such as overlap of confidence intervals, and whether heterogeneity was in the magnitude or in the direction of the effect. Where

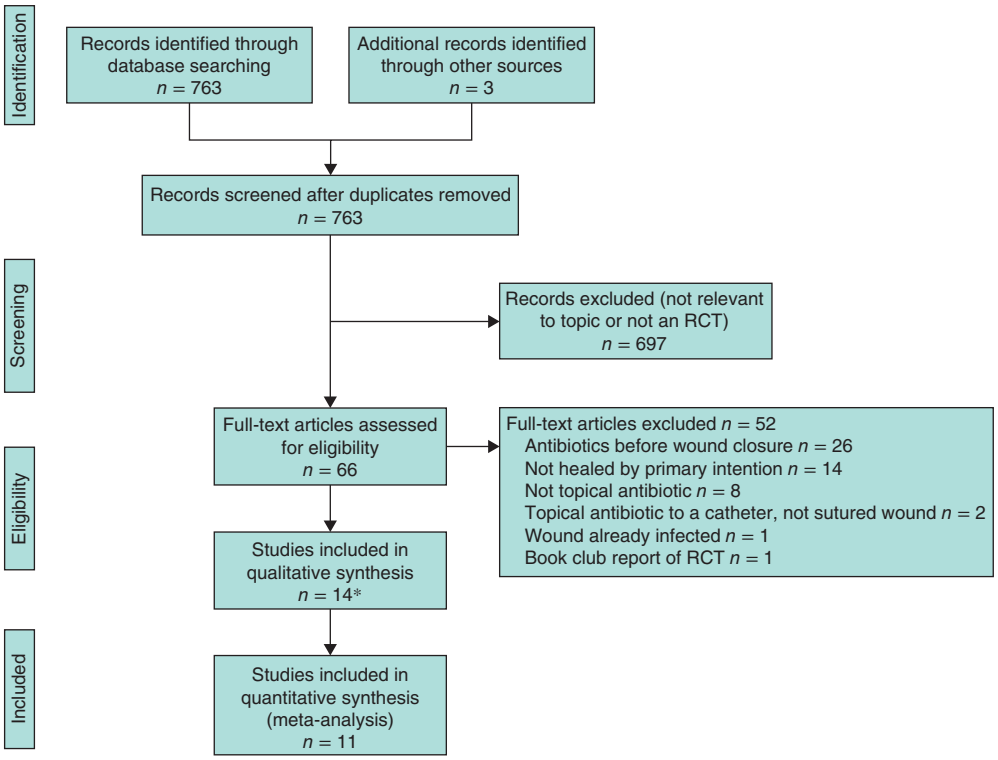

Fig. 1 PRISMA diagram for the systematic review. *Two of the 14 studies did not record the outcome of surgical-site infection (SSI), and one did not have extractable data for the outcome of SSI. All three of these studies were used in the meta-analysis of the outcome of wound healing, which is not presented in this abridged version of the original Cochrane Review[13]

levels of clinical and statistical heterogeneity permitted, the data were pooled in a meta-analysis using Review Manager 5.1 software (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark) with a random-effects model. Absolute risk differences were also calculated in order to determine the number needed to treat (NNTT). When insufficient data were available for meta-analyses, a narrative synthesis of the outcome across the included studies was presented.

The expected rate of SSI is 1–10 per cent. If missing randomized participants were assumed to indicate treatment failure (they had developed an infection), the rate of SSI would be increased falsely in the intervention group. As included trials had either complete data or minimal missing data, which was balanced over the intervention and control groups, complete case analysis was done for all trials in the review, recognizing the issue of trials with missing data when determining attrition bias in the risk-of-bias assessment.

If there were three or four arms in a study, where two or three of the arms were clinically similar for the purposes of the review, they were combined to create a single pairwise comparison. Where they could not be combined, multiple arms were included in the same analysis, but total results were not calculated in these tables.

One study[16] assessed multiple wounds per patient; randomization was at the level of the patient but the unit of analysis was the wound. The present authors could not find a published standard value for an inter-cluster correlation (ICC) for this scenario, so explored potential situations with different values used for ICC, and performed a sensitivity analysis on the overall effect. If the ICC was 1·0, as opposed to no adjustment for clustering, the RR did not change by a substantial amount, so no further adjustment was made.

Sensitivity analysis was done to assess the impact of risk of bias on the overall effect.

Results

The results of the search are shown in a PRISMA flow diagram (*Fig. 1*). The search identified 763 studies of potential relevance. After the first screening, 66 citations were considered potentially relevant. A total of ten RCTs and four quasi-randomized trials with 6466 participants met the inclusion criteria. Their study characteristics are shown in *Table 1*[16–28].

Table 1 Characteristics of included studies

Reference	Country	Setting and type of surgery	Interventions*	SSI	Allergic contact dermatitis
Caro *et al.*[17]†	UK	Emergency department; superficial lacerations	A: Neomycin–polymixin B–bacitracin aerosol (197)	A: 18 of 197	n.s.
			B: No treatment (235)*	B: 27 of 235	
			?500 patients randomized (unclear)	Unclear whether missing cases	
Dire *et al.*[18]	USA	Emergency department; lacerations	A: Bacitracin zinc ointment (109)	A: 6 of 109	A: 0 of 109
			B: Neomycin sulfate, bacitracin zinc, polymixin B ointment (110)	B: 5 of 110	B: 1 of 110
			C: Silver sulfadiazine cream 1% (99)	C: 12 of 99	C: 0 of 99
			D: Petroleum ointment (108)	D: 19 of 108	D: 0 of 108
			465 patients randomized	39 lost to follow-up (allocation not specified)	
Dixon *et al.*[16]	Australia	General practice skin cancer clinic; dermatological surgery	A: Mupirocin ointment 20 mg/g (262 patients; 562 wounds)	A: 13 of 562	A: 0 of 562
			B: Paraffin ointment (269 patients; 729 wounds)	B: 12 of 729	B: 0 of 729
			C: No ointment (247 patients; 510) wounds	C: 7 of 510	C: 0 of 510
				No missing cases	
Gilmore and Welbourn[19]	UK	General hospital setting; appendicectomy	A: Neomycin–bacitracin–polymixin B aerosol (84)	A: 8 of 84	n.s.
			B: 5% povidone–iodine aerosol (84)	B: 7 of 84	
			C: Control (no aerosol) (84)	C: 15 of 84	
				No missing cases	
Gough and Lawton[20] (1)†	UK	Children's hospital; circumcision	A: Soframycin-impregnated tulle gras (54)	n.s.	n.s.
			B: Benzoin compound-soaked gauze (54)		
Gough *et al.*[20] (2)†	UK	Children's hospital; circumcision	A: Soframycin-impregnated tulle gras (105)	n.s.	n.s.
			B: Paraffin tulle dressing (105)		
Heal *et al.*[21]	Australia	General practice; minor skin excisions	A: Chloromycetin ointment 1% (509)	A: 32 of 488	n.s.
			B: Paraffin ointment (505)	B: 53 of 484	
Hood *et al.*[22]	USA	Emergency department; uncomplicated soft tissue wounds	A: Bactroban (mupirocin) cream 2%	A: 2 of 50	n.s.
			B: Neosporin cream (neomycin–polymixin–bacitracin 3·5 mg/10 000 units/400 units)	B: 0 of 49	
			120 total randomized	99 total; 21 lost to follow-up (allocation not specified)	
Iselin *et al.*[23]†	France	Hospital inpatient and outpatient departments; hand surgery	A: Soaked pad of rifampicin (134?)	A: 8 of 114	A: 16 of 114
			B: Soaked pad of iodinated polyvidone solution (134)	B: 20 of 109	B: 16 of 109
Kamath *et al.*[24]	UK	Orthopaedic department; hip surgery	A: Chloramphencicol 1% ointment (50)	A: 4 of 47	n.s.
			B: No ointment (50)	B: 8 of 45	
Khalighi *et al.*[25]	USA	Hospital; cardiac implant insertions	A: Neomycin ointment 3·5 mg/g (263)	A: 2 of 263	n.s.
			B: Standard dressing (248)	B: 4 of 248	
			C: Povidone–iodine ointment 10% (257)	C: 4 of 257	
			D: Sterile non-adherent dressing (240)	D: 4 of 240	
Neri *et al.*[26]†	Italy	Hospital surgical ward; laparoscopic cholecystectomy	A: 3 ml rifampicin ointment (24)	Infection listed as outcome, but data could not be extracted	n.s.
			B: No ointment (24)		

Table 1 Continued

Reference	Country	Setting and type of surgery	Interventions*	SSI	Allergic contact dermatitis
Pradhan and Agrawal[27]	Nepal	Hospital; emergency caesarean section	A: Fusidic acid 2% (35) B: No ointment (35)	A: 1 of 35 B: 6 of 35 No missing cases	n.s.
Smack *et al.*[28]	USA	Outpatient dermatology clinic; dermatological surgery	A: Bacitracin ointment 500 units/g B: Petrolatum ointment 922 patients randomized with 1249 wounds; unclear whether 38 missing patients allocated to intervention or control	A: 4 of 444 patients, 597 wounds B: 9 of 440 patients, 610 wounds	A: 4 of 444 B: 0 of 440

*Values in parentheses are number of patients randomized. †Quasi-randomized study. SSI, surgical-site infection; n.s., not stated.

Ten two-arm studies were included, two three-arm studies[16,19] and two four-arm studies[18,25]. In all of the three- and four-arm trials, the intervention groups were considered to be receiving separate interventions and so all relevant comparisons were included.

Six studies[16–18,21,22,28] involved minor procedures that were all conducted in an outpatient or emergency department setting. Eight trials[19,20,23–27] involved general surgery performed in an operating theatre.

The surgical procedures in each trial were classified as clean[3,16,21,28], clean-contaminated[7,19,20,24–27] or contaminated[4,17,18,22,23]; there were no dirty procedures.

Eight trials compared topical antibiotics with no topical antibiotics, and six compared topical antibiotics with topical antiseptics. Three of these trials had multiple arms comparing topical antibiotics with both antiseptics and no treatment.

Risk of bias in included studies

In total, seven[16,17,19,20,23,26] of the 14 included trials were deemed to be at high risk of bias.

There were no trials in which participants were excluded from the analysis in sufficient numbers to cause potential bias. The dropout rate was no greater than 15 per cent in any trial, and numbers of dropouts were balanced between intervention and control groups when group allocation was recorded.

Two studies[19,22] reported pharmaceutical sponsorship from companies that supplied one or more of the study agents.

Effects of interventions: prevention of surgical-site infection

Of the 14 trials included in the review, only 11 reported SSI as an outcome. In one of these trials[26], the data for SSI were not extractable. This study was not included in data pooling for this outcome.

Topical antibiotic *versus* no topical antibiotic

Eight trials (5427 participants) were pooled to compare the effects of topical antibiotics with no topical antibiotics on SSI (*Fig. 2*). There were fewer infections with topical antibiotics than without (RR 0·61, 95 per cent c.i. 0·42 to 0·87). There was an absolute risk difference of 20 fewer SSIs per 1000 patients, and the number needed to benefit (NNTB) with topical antibiotic in order to avoid one additional SSI was 50. Most of these eight studies were at low or unclear risk of bias, and the quality of the evidence for this outcome was moderate. There was moderate interstudy heterogeneity ($I^2 = 44$ per cent).

The effect estimate was robust to removal of studies at high risk of bias (RR 0·49, 0·35 to 0·67; 3026 participants, 5 studies; $I^2 = 0$ per cent).

Pooling of three trials (3012 participants) that provided data on the risk of allergic contact dermatitis showed no difference (RR 3·94, 0·46 to 34·00; very low-quality evidence) (*Fig. S1*, supporting information).

There were no trials reporting anaphylaxis or patterns of antibiotic resistance.

Topical antibiotic *versus* topical antiseptic

In the pooling of five trials (1299 participants), topical antibiotics reduced the risk of SSI compared with topical antiseptics (RR 0·49, 95 per cent c.i. 0·30 to 0·80; moderate-quality evidence) (*Fig. 3*). This difference reflected an absolute difference in risk of 43 fewer cases of SSI per 1000 people treated with topical antibiotics rather than antiseptics (95 per cent c.i. 17 to 59 fewer per 1000; NNTB 24). There was minor interstudy heterogeneity ($I^2 = 12$ per cent).

The overall effect was robust to removal of studies at high risk of bias (RR 0·39, 0·20 to 0·76; 908 participants, 3 studies), and heterogeneity was reduced ($I^2 = 0$ per cent).

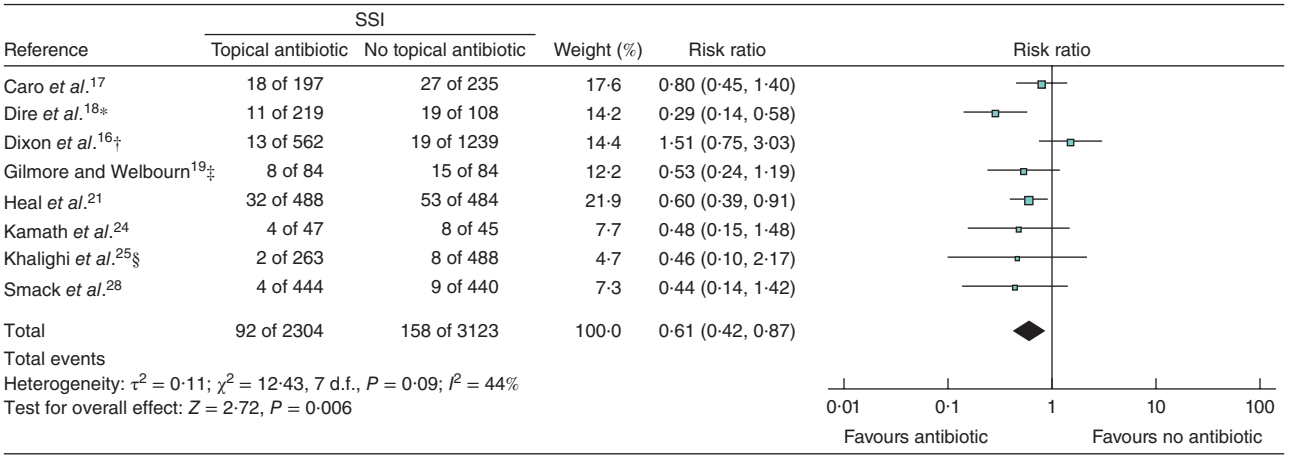

Fig. 2 Forest plot comparing the effects of topical antibiotics *versus* no topical antibiotic on surgical-site infection (SSI). A Mantel–Haenszel random-effects model was used for meta-analysis. Risk ratios are shown with 95 per cent confidence intervals. *Three of the four study arms are used here; the two antibiotic arms were combined and compared with the inert control arm. †There were two no-treatment arms in this three-arm study; this comparison is mupirocin *versus* combined petroleum and no ointment. ‡Two of the three study arms are used here: topical antibiotic *versus* no-treatment control. §Three of the four study arms are used here: neomycin *versus* combined non-adherent dressing and standard dressing

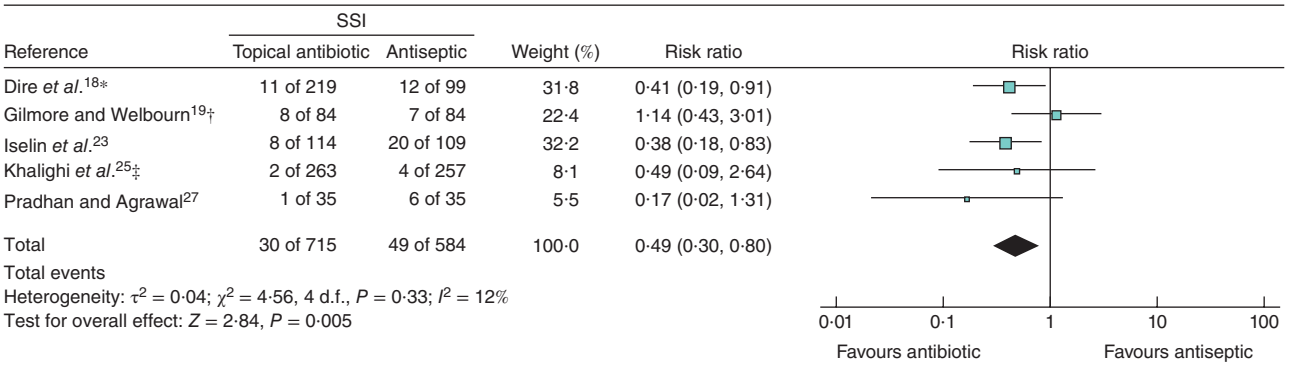

Fig. 3 Forest plot comparing the effects of topical antibiotics *versus* topical antiseptics on surgical-site infection (SSI). A Mantel–Haenszel random-effects model was used for meta-analysis. Risk ratios are shown with 95 per cent confidence intervals. *There were two antibiotic arms (bacitracin and neomycin), an antiseptic arm (silver) and an inert vehicle control arm (petroleum) in this four-arm study; this comparison is the two combined antibiotic arms *versus* the antiseptic arm. †Two of the three study arms are used here: topical antibiotic experimental *versus* antiseptic control arm. ‡Two of the four study arms are used here: neomycin *versus* povidone–iodine ointment

Pooling of two trials (541 participants) showed no clear difference in the risk of allergic contact dermatitis with topical antibiotics compared with antiseptics (RR 0·97, 0·52 to 1·82; very low-quality evidence) (*Fig. S2*, supporting information).

There were no trials reporting anaphylaxis or patterns of antibiotic resistance.

Discussion

This systematic review and meta-analysis found that topical antibiotics applied to surgical wounds healing by primary intention reduced the risk of SSI, whether compared with no antibiotic or no topical antiseptic (moderate-quality evidence). In clean (class 1) surgery, where the baseline infection rate is already low, the absolute risk reduction in SSI is probably smaller, and the case for use of topical antibiotics weaker.

It was not possible to draw conclusions regarding the effects of topical antibiotics on allergic contact dermatitis owing to lack of statistical power (small sample sizes). Any use of topical antibiotic needs to be tempered by consideration of side-effects such as allergic contact dermatitis, and

the evidence for this outcome, while critical, was found to be of very low quality. There were no patterns of antibiotic resistance or anaphylaxis in any of the studies identified. Subgroup analysis was not possible owing to lack of sufficient study numbers.

Some studies[16,25,28] had very low baseline rates of infection of around 2 per cent; for all other trials baseline rates were 10–20 per cent. In several of the studies[19,21,27] this baseline infection rate was higher than is considered to be acceptable[29], and this may limit the applicability of the evidence. The mean absolute risk reduction was 4·3 per cent when compared with antiseptics, and 2 per cent when compared with no treatment, but this result was heterogeneous in both comparisons and much lower in studies with low baseline infection rates. Two of the three studies with low baseline infection rates involved class 1 wounds. The baseline results in these studies and the results of the meta-analysis raise the question of whether prophylaxis is necessary in populations with clean class 1 wounds. The NNTT for an additional beneficial outcome was 24 in the antiseptic comparator group and 50 in the no-treatment comparator group, but again would be much higher in situations where the baseline infection rate was low.

RCTs need to be adequately powered so that they are able to detect treatment effects of a specified size, should they exist. As the incidence of SSI is often low, an adequate number of patients need to be recruited to detect a clinically significant difference. Only three of the trials reported sample size calculations. One study[16] was underpowered because the baseline incidence of SSI was lower than that expected when the sample size was calculated. Some authors inappropriately reported topical antibiotics to be ineffective, rather than acknowledging that their study was underpowered.

In the existing published literature there was one editorial[30], two literature reviews[31,32] and three systematic reviews[33–35] that, in all but one case, concluded that there was little evidence for the efficacy of topical antibiotics to prevent SSI, particularly after dermatological surgery. One study[35] pooled data from four studies comparing topical antibiotics with petroleum/paraffin for dermatological procedures, and favoured topical antibiotics (pooled odds ratio 0·71, 95 per cent c.i. 0·42 to 0·19). Guidelines[2,14] recommend that antibiotic prophylaxis, not limited to topical antibiotics, is not required for clean minor surgical procedures. National Institute for Health and Care Excellence (NICE) guidelines also state: 'do not use topical antibiotics in wounds healing by primary intention to reduce the risk of surgical site infection'[2]. The present review has contributed additional evidence, although practice must be guided by clinical judgement of risks and benefits.

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Supporting information

Additional supporting information may be found online in the supporting information tab for this article:

Fig. S1 Forest plot comparing the risk of allergic contact dermatitis with topical antibiotics *versus* no topical antibiotic (Word document)

Fig. S2 Forest plot comparing the risk of allergic contact dermatitis with topical antibiotics *versus* antiseptics (Word document)