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Prophylactic antibiotics to prevent surgical site infection after breast cancer surgery (Review)

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[Intervention Review]

Prophylactic antibiotics to prevent surgical site infection after breast cancer surgery

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ABSTRACT

Background

Surgery has been used as part of breast cancer treatment for centuries; however any surgical procedure has the potential risk of infection. Infection rates for surgical treatment of breast cancer are documented at between 3% and 15%, higher than average for a clean surgical procedure. Pre- and perioperative antibiotics have been found to be useful in lowering infection rates in other surgical groups, yet there is no consensus on the use of prophylactic antibiotics for breast cancer surgery. This is an update of a Cochrane Review first published in 2005 and last updated in 2014.

Objectives

To determine the effects of prophylactic (pre- or perioperative) antibiotics on the incidence of surgical site infection (SSI) after breast cancer surgery.

Search methods

For this fourth update, in August 2018 we searched the Cochrane Wounds Specialised Register; the Cochrane Central Register of Controlled Trials (CENTRAL); Ovid MEDLINE (including In-Process & Other Non-Indexed Citations); Ovid Embase; and EBSCO CINAHL Plus. We also searched clinical trials registries for ongoing and unpublished studies, and scanned reference lists of relevant included studies as well as reviews, meta-analyses and health technology reports to identify additional studies. There were no restrictions with respect to language, date of publication or study setting.

Selection criteria

We included randomised controlled trials of pre- and perioperative antibiotics for patients undergoing surgery for breast cancer. Primary outcomes were rates of surgical site infection (SSI) and adverse reactions.

Data collection and analysis

Three review authors independently examined the title and abstracts of all studies identified by the search strategy, then assessed study quality and extracted data from those that met the inclusion criteria. We contacted study authors to obtain missing information. We evaluated the certainty of evidence using the GRADE approach. We used standard methodological procedures expected by Cochrane.

Main results

A total of 11 randomised controlled trials (2867 participants) were included in the review. No new studies were identified in this update. All studies included breast cancer patients and were based in the hospital setting. Ten studies evaluated preoperative antibiotic compared

with no antibiotic or placebo. One study evaluated perioperative antibiotic compared with placebo or no antibiotic. Pooling of the results demonstrated that prophylactic antibiotics administered preoperatively probably reduce the incidence of SSI for patients undergoing breast cancer surgery without reconstruction (pooled risk ratio (RR) 0.67, 95% confidence interval (CI) 0.53 to 0.85; moderate certainty evidence). Anticipated absolute effects were calculated for the outcome incidence of SSI; 105 per 1000 for the none or placebo group and 71 per 1000 (95% CI 56 to 89) for the preoperative antibiotic prophylaxis group. Analysis of the single study comparing perioperative antibiotic with no antibiotic was inconclusive for incidence of SSI (RR 0.11, 95% CI 0.01 to 1.95; very low certainty evidence). No studies presented separate data for patients who underwent reconstructive surgery at the time of removal of the breast tumour.

Secondary outcomes were not consistently included in the studies investigating preoperative antibiotic prophylaxis. It is very uncertain whether there is a difference in incidence of adverse events between the treatment and no treatment or placebo groups (10 studies, 2818 participants); very low certainty evidence downgraded one level for serious risk of bias, one level for serious inconsistency and one level for serious imprecision. It is unclear whether there is a difference in time to onset of infection between the treatment and no treatment or placebo groups (4 studies, 1450 participants); low certainty evidence downgraded one level for serious risk of bias and one level for serious inconsistency. It is unclear whether there is a difference in rates of readmission to hospital between the treatment and placebo groups (3 studies, 784 participants); low certainty evidence downgraded one level for serious inconsistency and one level for serious risk of bias. It is unclear whether there is a difference in cost of care between the treatment and no treatment or placebo groups (2 studies, 510 participants); low certainty evidence downgraded one level for serious risk of bias and one level for serious inconsistency. No analysable secondary outcome data were reported for the single study evaluating perioperative antibiotics.

Authors' conclusions

Prophylactic antibiotics administered preoperatively probably reduce the risk of SSI in patients undergoing surgery for breast cancer. However, it is very uncertain whether there is an effect on incidence of adverse events. Furthermore, the effects on time to onset of infection, readmission to hospital and cost of care remain unclear. Further studies are required to establish the best protocols for clinical practice.

PLAIN LANGUAGE SUMMARY

Do antibiotics prevent surgical site infection after breast cancer surgery?

What was the aim of this review?
The aim of this review was to determine whether giving people antibiotics before or during an operation is effective for preventing surgical site infection (SSI) following breast cancer surgery. Researchers from Cochrane collected and analysed all relevant studies (randomised controlled trials) to answer this question and found 11 relevant studies. Randomised controlled trials are medical studies where people are chosen at random to receive different treatments. This type of trial provides the most reliable health evidence.

Key messages
There is moderate certainty evidence that antibiotics given before an operation probably reduce the risk of SSI in patients having surgery for breast cancer. We cannot be certain whether antibiotics given during an operation reduce the risk of developing an SSI, as the available evidence is of very low certainty.

What was studied in this review?
Breast cancer is the most common cancer affecting women and the leading cause of cancer death in women. Surgical removal of all or part of the breast is a common treatment for people diagnosed with breast cancer. However, an infection of the surgical wound is often a complication of the surgery, affecting up to 15% of patients. Having an SSI may require a longer stay in hospital or a repeat operation. Taking antibiotics prior to the operation or during the operation aims to reduce the risk of developing an infection in the surgical wound.

What are the main results of the review?
In August 2018 we searched for randomised controlled trials that investigated whether antibiotics given to people before or during surgery for breast cancer prevent an infection of the surgical site (SSI). This is an update of an existing review and no new relevant studies were found in the most recent search. We analysed the results of 11 studies with 2867 participants. Ten studies looked at giving antibiotics to patients prior to the surgery compared with not giving antibiotics or giving placebo. One study compared giving antibiotics perioperatively (between induction of anaesthetic and the patient leaving the recovery room) to not giving antibiotics. The results showed us that giving antibiotics before surgery probably reduced the risk of developing surgical site infection in patients undergoing breast cancer surgery with moderate certainty. No conclusions can be made from the results of the single study comparing perioperative antibiotics to no antibiotics as the evidence is of very low certainty. It is very uncertain whether there is an effect on incidence of adverse events. Furthermore, the effects on time to onset of infection, readmission to hospital and cost of care remain unclear. The review is not able to establish which antibiotic is most appropriate.

How up to date is this review?
We searched for studies that had been published up to August 2018.

Summary of findings for the main comparison. Preoperative antibiotics compared with placebo or no antibiotic for breast cancer surgery

Preoperative antibiotics compared with placebo or no antibiotic for breast cancer surgery

Patient or population: breast cancer surgery
Setting: hospital
Intervention: preoperative antibiotics
Comparison: none or placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with none or placebo	Risk with Preoperative antibiotics				
Wound infections Proportion of wound infections Follow-up: 5-42 days	Study population 105 per 1,000	71 per 1,000 (56 to 89)	RR 0.67 (0.53 to 0.85)	2823 (10 RCTs)	⊕⊕⊕⊖ Moderate [1]	Pooled meta-analysis of included studies suggests that preoperative antibiotic prophylaxis probably reduces incidence of SSI with moderate certainty.
Adverse reactions to treatment Proportion of participants with adverse reactions to treatment Follow-up: 5-42 days	No pooled analysis was possible. All ten studies reported adverse reactions and in eight studies no adverse reactions attributable to treatment were identified. In Gupta 2000 reported 41 adverse events (23%) in the treatment group and 33 (18%) in the control group, but no details were reported on type of adverse events. Amland 1995 reported 4 events (2.3%) in the treatment group and 5 events (3.0%) in the placebo group. In the treatment group 2 gastrointestinal events, 1 skin rash and 1 other adverse reaction was reported. In the placebo group 2 gastrointestinal events, 2 skin rashes and 1 other event was reported.		-	2818 (10 RCTs)	⊕⊖⊖⊖ Very low [2 3 4]	It is very uncertain whether there is a difference in incidence of adverse events between the treatment and no treatment or placebo groups.
Time to onset of infection Mean time to onset of infection	No pooled analysis was possible. Two studies (Gupta 2000; Platt 1990) documented similar mean times to onset of infection: 12 and 11 days in the intervention group and 11 and 10 days in the control group respectively. Wagman 1990 documented mean time of onset of infection of 17.7 days in the intervention group and 9.6 days in the control group. Gulluoglu 2013 stated that the time to onset of infection was similar in both the control and intervention group.		-	1450 (4 RCTs)	⊕⊕⊖⊖ Low [5 6]	It is unclear whether there is a difference in time to onset of infection between the treatment and no treatment or placebo groups.

Follow-up: 10-42 days					
Readmission to hospital Proportion of patients readmitted to hospital Follow-up: 28-42 days	No pooled analysis was possible. Three studies (Bold 1998; Gulluoglu 2013; Platt 1990) reported readmission rates following treatment. In one study (Gulluoglu 2013) no patients required readmission to hospital. In the other two studies, due to heterogeneity (I^2 = 70.8%) we did not pool results. Bold 1998 reported lower readmission rates in those treated with prophylactic antibiotics and Platt 1990 found no difference in readmission rates.	-	784 (3 RCTs)	⊕⊕⊖⊖ Low [3 5]	It is unclear whether there is a difference in rates of readmission to hospital between the treatment and placebo groups.
Cost of care Heterogenous cost calculation methodology Follow-up: 28-30 days	No pooled analysis was possible. Two studies (Bold 1998; Gulluoglu 2013) reported the cost of care. Bold 1998 found that the average cost per patient was USD 49.80 in the antibiotic prophylaxis group and USD 364.87 in the control group. Gulluoglu 2013. reported that the control group had a considerably higher cost (USD 20.26) when compared with the treatment group (USD 8.48).	-	510 (2 RCTs)	⊕⊕⊖⊖ Low [5 6]	It is unclear whether there is a difference in cost of care between the treatment and no treatment or placebo groups.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1] Downgraded 1 level: serious imprecision (all but one confidence intervals crosses line of no effect).
[2] Downgraded 1 level: serious risk of bias (two studies with one or more domains assessed as high risk of bias and considered to lower confidence in estimate of effect).
[3] Downgraded 1 level: serious inconsistency: included studies had considerably high statistical heterogeneity precluding pooling of data.
[4] Downgraded 1 level: serious imprecision due to few events.
[5] Downgraded 1 level: serious risk of bias as one study with one or more domains assessed as high risk of bias and considered to lower confidence in the estimate of effect.
[6] Downgraded 1 level: serious inconsistency preventing pooling of data.

Summary of findings 2. Perioperative antibiotics compared with placebo or no antibiotic for breast cancer surgery

Perioperative antibiotics compared with placebo or no antibiotic for breast cancer surgery

Patient or population: breast cancer surgery
Setting: hospital
Intervention: perioperative antibiotics compared with no antibiotic
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with Perioperative antibiotics compared with no antibiotic				
Wound infection Proportion of wound infections Follow-up: 6 months	Study population 182 per 1,000	20 per 1,000 (2 to 355)	RR 0.11 (0.01 to 1.95)	44 (1 RCT)	⊕⊖⊖⊖ Very low [1,2]	It is very uncertain whether there is a difference in incidence of SSI between the treatment and no treatment or placebo groups.
Adverse reactions to treatment	No data reported					
Time to onset of infection	No data reported					
Readmission to hospital	No analysable data reported					
Cost of care	No data reported					

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1] Downgraded 2 levels: very serious risk of bias as majority of domains evaluated as high risk of bias and considered to substantially lower confidence in estimate of effect.

2 Downgraded 2 levels: very serious imprecision (large confidence interval crossing line of no effect, few events and did not meet optimal information size criterion).

BACKGROUND

Description of the condition

Breast cancer is the second most common cancer in the world; it is the most common cancer affecting women; and it is the leading cause of cancer death in women (GCO 2018). Surgery for removal of breast cancer has been common practice for centuries (Donegan 1995); it is normally used as part of a multi-faceted approach to care with the aim of curing the patient of their cancer in early-stage tumours or prolonging life for others (NICE 2002). Surgical intervention ranges from removing the breast and associated axillary lymph nodes, to lumpectomy with or without sentinel node biopsy (Harris 2004). Whilst the risk of breast cancer for men is only 1%, treatment for men is very similar to that for women (Harris 2004). As with all surgical procedures, breast cancer surgery runs the risk of complications. One such risk is postoperative surgical site infection (SSI), even though breast cancer surgery is considered a 'clean surgical procedure'. Clean surgical procedures, as defined by Haley 1985, are those which have a low risk of bacterial contamination during the surgery. Some women have immediate breast reconstruction; however this group of patients has a higher risk of SSI (Spauwen 2000).

Despite internationally recognised infection control guidelines (Mangram 1999), the incidence of SSI in those being treated for breast cancer is thought to range between 3% (Lefebvre 2000) and 15% (Witt 2003). This is a higher incidence of infection than the 3.4% SSI rate associated with other clean surgical techniques (Vazquez-Aragon 2003). A recent review found that women who had been treated for breast cancer and who had immediate reconstruction had an SSI rate of between 0% and 53%, whilst non-cancer patients undergoing the same reconstructive surgery had an average rate of 2.5% (Pittet 2005). There are several factors that are documented as increasing the risk of infection for surgical patients generally. These include patient risk factors, for example diabetes, obesity and smoking (Haley 1985; Mangram 1999); surgical technique, for example aseptic technique (Ritter 1988); and type of surgery, for example whether the wound is contaminated (Gruendemann 2001). In addition, surgery for breast cancer has several risk factors that make this patient group more susceptible to infection, including use of chemotherapy prior to surgery (neo-adjuvant chemotherapy); technique of diagnostic biopsy; re-operation for recurrence or to achieve better tumour margins; and reconstructive surgery with implants and seroma accumulation and drainage (Morris 1988; Tran 2003). Infection may lead to considerable morbidity for the patient, delay in adjuvant treatment, such as radiotherapy, and increased cost of care if the patient requires supplementary treatment due to infection (Coello 1993).

Description of the intervention

Pre- or perioperative antibiotics are used as pharmacological prophylaxis for SSI, which may occur as a complication of surgical procedures. They are used as a preventative measure when there is no known infection. We considered studies in which the use of antibiotics was the only systematic treatment difference between comparison groups.

How the intervention might work

The administration of antibiotics to prevent infection is termed 'antibiotic prophylaxis'. Prophylaxis works by improving tissue defence mechanisms and promoting normal immune responses after an episode of trauma such as that of surgery (Ayeleke 2017). Multiple classes of antibiotic can be used for prophylaxis and these work in differing ways. The most commonly used antibiotics are bactericidal, meaning they kill the bacteria, rather than preventing further growth.

Why it is important to do this review

Pre- and perioperative antibiotics have been shown to reduce the risk of postoperative infection in several patient groups (the term 'perioperative' refers to administration between induction of anaesthetic and the patient leaving the recovery room) (Ayeleke 2017; Gruendemann 2001; SIGN 2014). In colorectal surgery antibiotic prophylaxis has been found to reduce long- and short-term morbidity, decrease length of hospital stay and lower the overall cost of care (SIGN 2014). However, the use of prophylactic antibiotics in preventing infection is still a controversial issue and their routine use is not common in breast cancer surgery. Some feel that a clean surgical procedure should not require prophylactic antibiotics (Sheridan 1994); others suggest that the use of pre- or perioperative antibiotics merely masks the symptoms of infection until after the patient is discharged (Wagman 1990). In addition increased antibiotic use may lead to antibiotic resistance (Davies 2013) and adverse effects such as clostridium difficile infection that causes gastro-intestinal problems (SIGN 2014). This review aims to identify the best available evidence regarding the effectiveness of pre- or perioperative antibiotics in reducing the incidence of postoperative infections in patients undergoing breast cancer surgery.

OBJECTIVES

To determine the effects of prophylactic antibiotics (pre- or perioperative) on surgical site infection (SSI) after breast cancer surgery.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and controlled clinical trials (where patients were allocated by quasi-random methods such as alternation, case record numbers or days of the week).

Types of participants

People with breast cancer undergoing breast surgery with or without immediate reconstruction as part of their treatment.

We included studies that involved mixed patient groups (i.e. cancer and non-cancer, other surgeries or breast implants not as part of cancer treatment) as long as it was possible to extract separate data for those undergoing surgery primarily to treat breast cancer.

Types of interventions

Any pre- or perioperative antibiotics used as prophylaxis where there was no known infection and where the use of antibiotics was the only systematic treatment difference between comparison groups.

We only included trials of one antibiotic compared with another if there was a control or placebo arm, as benefit from prophylactic antibiotics has not yet been established in this patient group.

Definitions of key terms are as follows.

- 'Antibiotic regimen' describes the characteristics of the antibiotic treatment (i.e. type of antibiotic, route, dose, number of doses and timing of administration).
- 'Preoperative antibiotic prophylaxis' is antibiotic therapy given within 24 hours prior to surgery, solely for prophylaxis (i.e. not for an infection that is already suspected).
- 'Perioperative antibiotic prophylaxis' is antibiotic therapy administered between commencement of induction of surgery and the patient leaving the recovery room.

Comparisons of interest were:

- preoperative antibiotic compared with no antibiotic or placebo;
- perioperative antibiotics compared with no antibiotic or placebo;
- head-to-head comparisons of antibiotics.

Types of outcome measures

Primary outcomes

- Incidence of postsurgical breast surgical site (wound) infection (SSI)*. Where possible, this should be reported as the number of participants in each group with a clinically significant infection. Research demonstrates that 98% of acute SSIs related to non-implant breast surgery occur within 28 days (Mitchell 1999). However, where there is surgical re-construction, guidelines recommend that this time is increased to one year post surgery (Mangram 1999). Therefore we included all studies that presented data on acute SSI within one year of surgery. A sensitivity analysis was conducted on studies with outlying follow-up periods and risk of bias to assess whether they had a significant impact on pooled data.
- Adverse reactions (e.g. anaphylaxis, gastro-intestinal or skin rash).

*Surgical site infection: ideally this should be defined using outcomes from a validated assessment tool such as ASEPSIS (Wilson 1986) which are based on CDC definitions (Mangram 1999).

Secondary outcomes

- Death
- Delay in adjuvant cancer treatment because of breast wound infection
- Time to wound healing
- Time to infection
- Readmission to hospital
- Cost of care (should be a comparison between the treatment and control group)

Search methods for identification of studies

Electronic searches

For the fourth update of this review we revised the search strategies and searched the following electronic databases to identify reports of relevant clinical trials.

- Cochrane Wounds Specialised Register (searched 17 August 2018);
- Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 7) via the Cochrane Register of Studies (CRS-Web) (searched 17 August 2018);
- Ovid MEDLINE including In-Process & Other Non-Indexed Citations (1946 to 17 August 2018);
- Ovid Embase (1974 to 17 August 2018);
- EBSCO CINAHL Plus (Cumulative Index to Nursing and Allied Health Literature; 1937 to 17 August 2018).

The search strategies for the Cochrane Wounds Specialised Register, CENTRAL, Ovid MEDLINE, Ovid Embase and EBSCO CINAHL Plus can be found in Appendix 1. We combined the Ovid MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision) (Lefebvre 2011). We combined the Embase search with the Ovid Embase filter developed by the UK Cochrane Centre (Lefebvre 2011). We combined the CINAHL Plus searches with the trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN 2018). There were no restrictions with respect to language, date of publication or study setting.

We also searched the following clinical trials registries.

- ClinicalTrials.gov (www.clinicaltrials.gov) (searched 17 August 2018)
- World Health Organization (WHO) International Clinical Trials Registry Platform (www.who.int/trialsearch) (searched 17 August 2018).

Search strategies for clinical trial registries can be found in Appendix 1.

Details of the search strategies used for the previous version of the review are given in Jones 2014.

Searching other resources

In addition, we screened references in all articles found by the above search strategy for further studies. We contacted experts in the field and interest groups to try and obtain access to unpublished or ongoing work. We followed up conference proceedings and grey literature that was considered to be potentially eligible for inclusion by both authors by contacting the study authors for further information.

Data collection and analysis

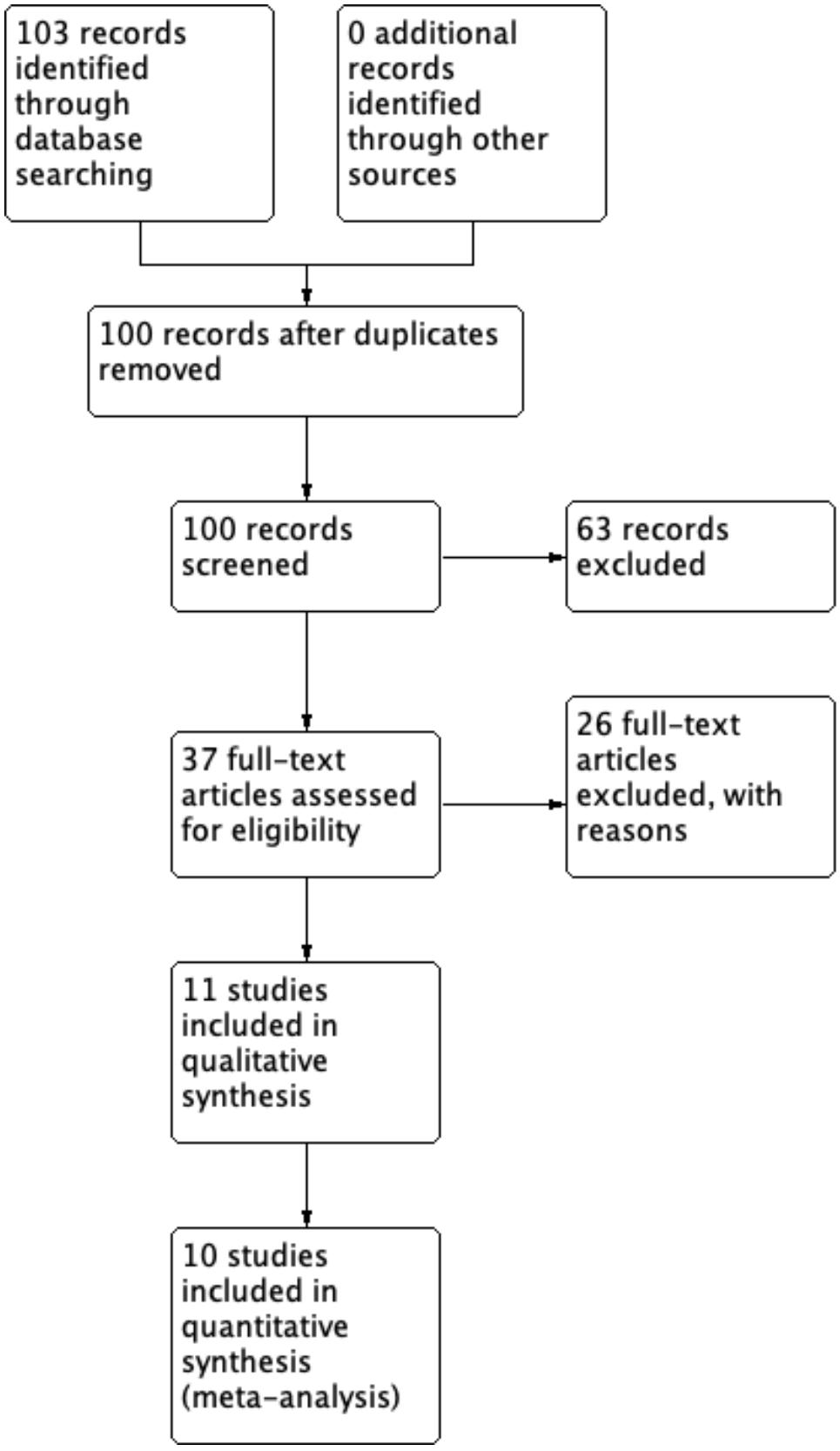
We undertook data collection and analysis according to the methods set out in the original protocol for this review (Cunningham 2005).

Selection of studies

Two review authors independently examined the title and abstract of citations identified by the search. We obtained all reports of potentially eligible trials as full-text articles and two review authors independently applied the inclusion criteria, resolving disagreements by discussion. Where we identified studies with multiple publications, we only included the study once in the review and extracted/collated all relevant data. Figure 1

summarises our study selection process in a PRISMA flowchart (Liberati 2009).

Figure 1. Study flow diagram.



Data extraction and management

Two review authors independently extracted trial data using a specifically designed data extraction tool. We extracted data on study risk of bias (as defined below), antibiotic intervention (i.e. drug name, dose route, duration of treatment), setting, source of funding, length of follow-up and outcomes.

Assessment of risk of bias in included studies

Two review authors independently assessed each included study using the Cochrane tool for assessing risk of bias (Higgins 2011). This tool addresses six specific domains, namely sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other issues (e.g. extreme baseline imbalance) (see Appendix 2 for details of criteria on which the judgement was based). We assessed blinding and completeness of outcome data for each outcome separately. We completed a 'Risk of bias' table for each eligible study. We discussed any disagreement amongst all review authors to achieve a consensus. We presented assessment of risk of bias using a 'Risk of bias' summary figure, which presents all of the judgements in a cross-tabulation of study by entry. This display of internal validity indicates the weight the reader may give the results of each study. We linked the Cochrane tool ratings to the GRADE assessment of risk of bias in accordance with the GRADE handbook guidance (GRADE 2013).

Measures of treatment effect

Where possible for each trial we calculated the risk ratio (RR) of infection and 95% confidence interval (95% CI), such that an RR of greater than one indicates a higher risk of infection in the first group named. We reported continuous data (i.e. number of days to infection), where possible, as mean difference (MD) with 95% CI.

Unit of analysis issues

We treated study participants as the unit of analysis when studies randomised at the study participant level and measured outcomes at the surgical wound level, whereby the number of SSIs identified appeared equal to the number of participants affected (e.g. one SSI per person). In all of the studies in our review the study participant was the unit of randomisation and the unit of analysis.

We did not identify any cluster randomised controlled trials in this review and plan to follow the guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* to conduct an appropriate analysis in future updates(Higgins 2011).

Dealing with missing data

Missing data is common and this absence introduces a potential source of bias into clinical trials. For outcome data we addressed this by stratifying missing data into high- and low-risk categories based on the likely impact on analysis (Incomplete outcome data (attrition bias)). We made efforts to obtain missing data by contacting study authors. Where authors did not respond and where data remained missing for analysis we assumed that randomised participants were not included in an analysis for that outcome (i.e. they were considered in the denominator but not the numerator).

Assessment of heterogeneity

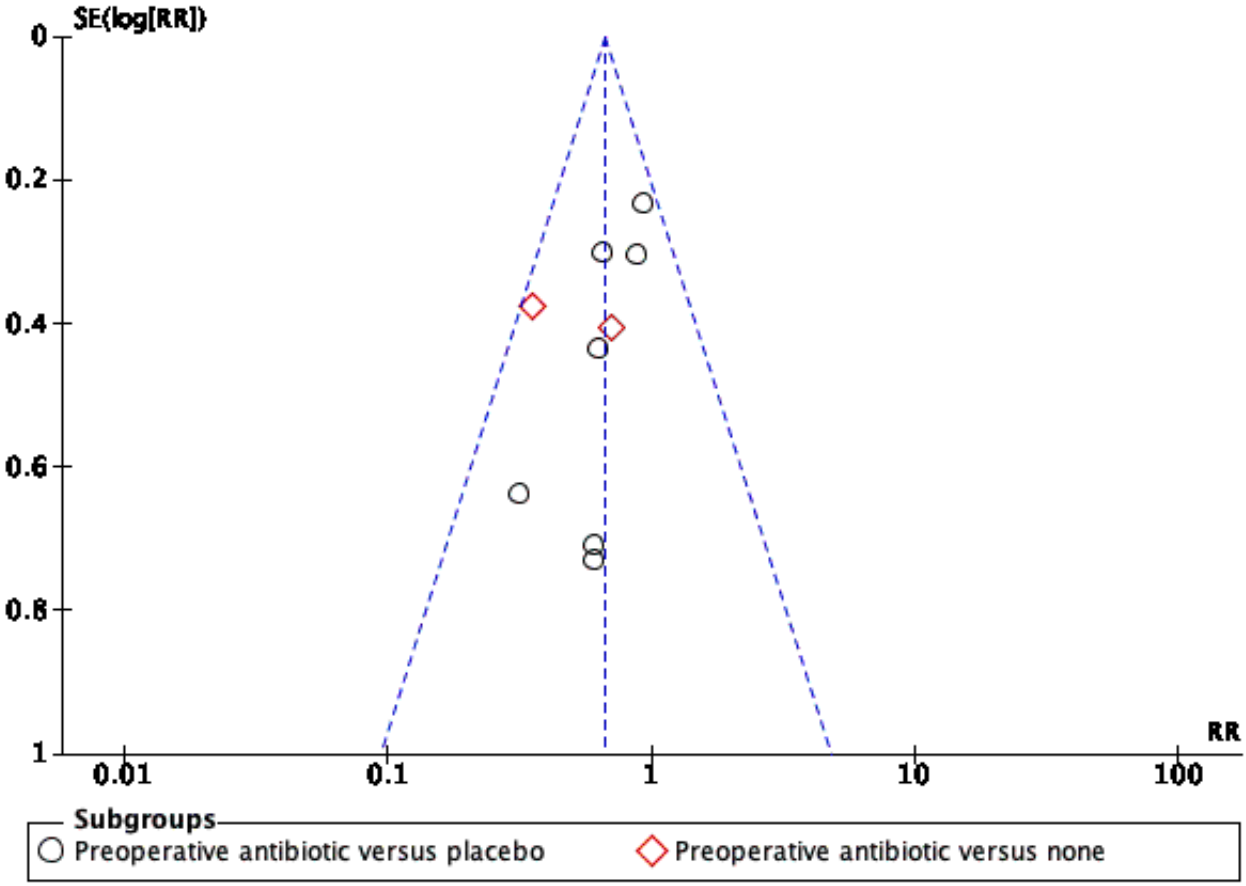
We considered clinical and methodological heterogeneity as the degree to which the included studies varied in terms of participant, intervention, outcome and characteristics such as length of follow-up. We supplemented this assessment of clinical and methodological heterogeneity with information regarding statistical heterogeneity in conjunction with the I^2 measure (Higgins 2003). This examines the percentage of total variation across studies due to heterogeneity rather than chance.

In general values of I^2 over 50% indicate a high level of heterogeneity. In the absence of clinical heterogeneity and in the presence of statistical heterogeneity (I^2 over 50%), we envisaged using a random-effects model; however, we did not plan to pool studies where heterogeneity was very high (I^2 over 75%). In the event, as there was no clinical or statistical heterogeneity we used a fixed-effect model.

Assessment of reporting biases

Reporting biases occur when the dissemination of research findings is influenced by the results. Positive and statistically significant results are more likely to be published. All of the studies in this review are published and a symmetrical funnel plot indicates that there may not be publication bias (Figure 2).

Figure 2. Funnel plot of comparison: 1 Preoperative antibiotics versus none or placebo, outcome: 1.1 Wound infections.



There are multiple factors at play, which mean that reporting bias cannot be excluded on this basis alone. Due to the low number of studies included in the trial we elected to omit statistical analysis and use only visual inspection of the funnel plot symmetry, as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Data synthesis

Methods of synthesising the studies were dependent on trial quality, design and heterogeneity. We explored both clinical and statistical heterogeneity. In the absence of clinical and statistical heterogeneity we applied a fixed-effect model to pool data using Cochrane Review Manager 5 (RevMan) software (Review Manager 2014). We presented pooled data on forest plots where possible. Where synthesis was inappropriate we have presented a narrative overview. We pooled data regardless of length of follow-up in the individual studies. Follow-up did vary in included studies and we discuss this in the narrative synthesis.

Subgroup analysis and investigation of heterogeneity

As patients undergoing reoperation, reconstruction with or without implants and patients receiving neo-adjuvant chemotherapy are documented as having a higher risk of infection (Tran 2003), we planned to conduct a prespecified subgroup analysis of each of these factors where there were sufficient data available. The proposed subgroups were:

- patients undergoing immediate reconstruction without implants (i.e. TRAM flap);
- patients undergoing immediate reconstruction with implants (i.e. silicone or saline); and
- patients who have received chemotherapy (excluding hormone treatment) prior to surgery.

There were not enough discrete data available in the studies identified in this fourth update to facilitate these subgroup analyses.

Sensitivity analysis

Since there is evidence that the quality of allocation concealment particularly affects the result of studies (Schulz 1995), we examined the effect of excluding studies judged to have inadequate allocation concealment in a prespecified sensitivity analysis. We additionally examined the effect of excluding studies with high risk of bias in one or more domains in pooled analyses. This was not planned in the original review protocol.

'Summary of findings' tables and GRADE assessment of the certainty of evidence

We present the main results of the review in 'Summary of findings' tables (Schünemann 2011b). These present the results of our GRADE assessment of quality of evidence in addition to the magnitude of effects of the pooled interventions.

For our outcomes we graded the quality of the evidence using the GRADE approach. The GRADE approach involves the consideration of domains including risk of bias, inconsistency, indirectness and imprecision to assess the quality of the evidence (Schünemann 2011a). It is a systematic and transparent method for determining to what extent the estimate of effect or association is likely to represent the true quantity of interest. The GRADE handbook was used as guidance for evaluating the evidence, and for downgrading when indicated (GRADE 2013). The 'Summary of findings' tables were created using the GRADEpro GDT software and imported into RevMan software (GRADEpro GDT). Two reviewers independently evaluated the evidence according to the GRADE approach and in the case of differences in evaluation they consulted a third reviewer to determine the final outcome.

Outcomes were evaluated and downgraded using GRADE guidance for the aforementioned domains. For the 'risk of bias' GRADE domain we downgraded the evidence when an included study for the outcome considered was evaluated as being at high risk of bias and judiciously considered to lower confidence in the estimate of effect as per GRADE handbook guidance. We did not downgrade evidence for unclear 'risk of bias'. For the 'imprecision' GRADE domain we downgraded evidence based on when there were few events, optimal information size was not met and if the confidence interval crossed the line of no appreciable effect. The optimal information size for dichotomous outcomes was set at 200 patients from power calculations by Gupta 2000 and Bold 1998. For continuous outcomes we considered downgrading for imprecision with sample sizes less than 400 as per GRADE guidance.

We present the GRADE assessment of the following primary outcomes and secondary outcomes in 'Summary of findings for the main comparison' and 'Summary of findings 2'. We include both pooled and non-pooled data with further narrative analysis in the review text.

- Wound infections
- Adverse reactions to treatment
- Time to onset of infection
- Readmission to hospital
- Cost of care

RESULTS

Description of studies

Results of the search

See Figure 1. We identified no new studies for inclusion in this fourth update; and we found four more studies to exclude (Lewin 2015; Phillips 2016; Ruiz-Tovar 2013; Yang 2017). In total 11 studies met the inclusion criteria for this version of the review (Amland 1995; Bold 1998; Cabaluna 2012; Chow 2000; Gulluoglu 2013; Gupta 2000; Hall 2006; Paajanen 2009; Platt 1990; Wagman 1990; Yetim 2010). One study met the inclusion criteria based on a published abstract of conference proceedings but as we could not obtain full data we will investigate its inclusion in the next update (Prudencio 2017). We identified one study in conference proceedings but could not obtain an abstract; it is therefore awaiting classification for the next update (Kumar 2005). We could not obtain one study via the British Library so it is also awaiting classification (Exner 1992; see Characteristics of studies awaiting classification table). We did not identify any ongoing studies in trial registries.

Characteristics of included studies; Characteristics of excluded studies.

Included studies

Participants

Of the 11 studies, eight included women only (Bold 1998; Cabaluna 2012; Chow 2000; Gulluoglu 2013; Gupta 2000; Paajanen 2009; Wagman 1990; Yetim 2010); one comprised almost entirely women (Hall 2006); and two may have contained male and female breast surgery participants, although this could not be established from the data presented in the report or by contacting the authors (Amland 1995; Platt 1990). All of these studies included breast cancer patients as one of multiple patient groups being analysed. The studies were conducted between 1990 and 2013. Study sizes ranged between 44 and 618 (Yetim 2010 and Hall 2006 respectively). In total 2867 participants were included for meta-analysis, 1439 in treatment arms and 1428 in control arms. These studies were conducted in hospital settings, were single-centre trials and were conducted in eight different countries. Country of origin for studies were: Australia (Hall 2006), Norway (Amland 1995), USA (Bold 1998; Platt 1990; Wagman 1990), Japan (Chow 2000), Finland (Paajanen 2009), the Philippines (Cabaluna 2012), Turkey (Gulluoglu 2013; Yetim 2010), and the United Kingdom (Gupta 2000). All included studies had been published.

Types of surgery

Types of participants included patients undergoing plastic surgery (Amland 1995), herniorrhaphy or breast surgery (Platt 1990), axillary lymph node dissection for breast cancer (Bold 1998), and primary, non-reconstructive surgery for breast cancer (Cabaluna 2012; Gulluoglu 2013; Gupta 2000; Hall 2006; Wagman 1990). One study was designed to look at inflammatory rather than infective episodes; however discrete data on infection rates were presented and therefore the study was eligible for inclusion (Chow 2000). Two studies looked at axillary lymph node dissection as part of breast cancer treatment (Bold 1998; Gulluoglu 2013). One study looked at core needle biopsy and primary, non-reconstructive surgery for breast cancer (Paajanen 2009). The four remaining studies looked solely at breast cancer patients receiving primary, non-reconstructive surgery for breast cancer (Cabaluna 2012; Gupta 2000; Wagman 1990; Yetim 2010).

Length of follow-up

Length of follow-up from surgery ranged from five days (Chow 2000) to six months (Yetim 2010). One study followed up patients between 10 and 14 days post discharge, but did not document the length of hospital stay for these patients (Gupta 2000).

Source of funding

Three studies stated that they were sponsored by a pharmaceutical company (Amland 1995; Bold 1998; Platt 1990; Pfizer AS, SmithKline

Beecham and Smith Kline & French Laboratories, respectively). One study was funded by the American Cancer Society (Wagman 1990); and another by the Finnish Cultural Foundation (Paajanen 2009). The source of funding was not reported in the other studies.

Antibiotics used

The antibiotics evaluated included:

- azithromycin, single dose decided according to body weight, taken 8 p.m. the night before surgery (Amland 1995);
- oral clarithromycin (500 mg) for 10 doses (Chow 2000);
- intravenous Augmentin (1.2 g) (Gupta 2000);
- a single dose of intravenous flucloxacillin (2 g) (Hall 2006);
- cefazolin (six doses) (Wagman 1990);
- a single dose of intravenous dicloxacillin (1 g) (Paajanen 2009);
- a single dose of cefonicid (1 g) (Bold 1998; Platt 1990);
- a single dose of intravenous cefazolin (1 g) (Cabaluna 2012);
- a single dose of intravenous ampicillin-sulbactam (1 g) (Gulluoglu 2013);
- collagen plus gentamycin sulphate (200 mg) inserted under the surgical wound prior to surgical closure (Yetim 2010).

Five studies were very similar in terms of length of follow-up, choice of antibiotic and type of surgery undertaken (Bold 1998; Cabaluna 2012; Gulluoglu 2013; Platt 1990; Wagman 1990). All studies had similar inclusion and exclusion criteria.

Immediate reconstruction with or without implants

We identified no eligible studies evaluating prophylactic antibiotics for reconstructive surgery (with or without implants). Whilst three studies included patients undergoing reconstructive surgery, we excluded the studies following scrutiny (Amland 1995; Baker 2000; Franchelli 1994). It was not clear in two studies that the patients had undergone surgery as part of breast cancer treatment (Amland 1995; Franchelli 1994); whilst one study was excluded because the research was addressing the needs of dental patients with existing implants (Baker 2000).

Neo-adjuvant chemotherapy

Two studies included patients who had received neo-adjuvant chemotherapy (Bold 1998; Platt 1990).

Excluded studies

We excluded a total of 26 studies for the following reasons: eight did not include breast cancer patients or included a combination of breast cancer patients and non-breast cancer patients; 14 studies were not RCTs or quasi RCTs; three studies did not include a placebo or no treatment arm; and one did not measure the incidence of surgical site infection (see Characteristics of excluded studies table).

Risk of bias in included studies

See 'Risk of bias' summary figure (Figure 3) and 'Risk of bias' graph (Figure 4). We judged studies to be at overall unclear or high risk of bias if they were described as unclear or at high risk of bias in the majority of the domains.

Figure 3. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

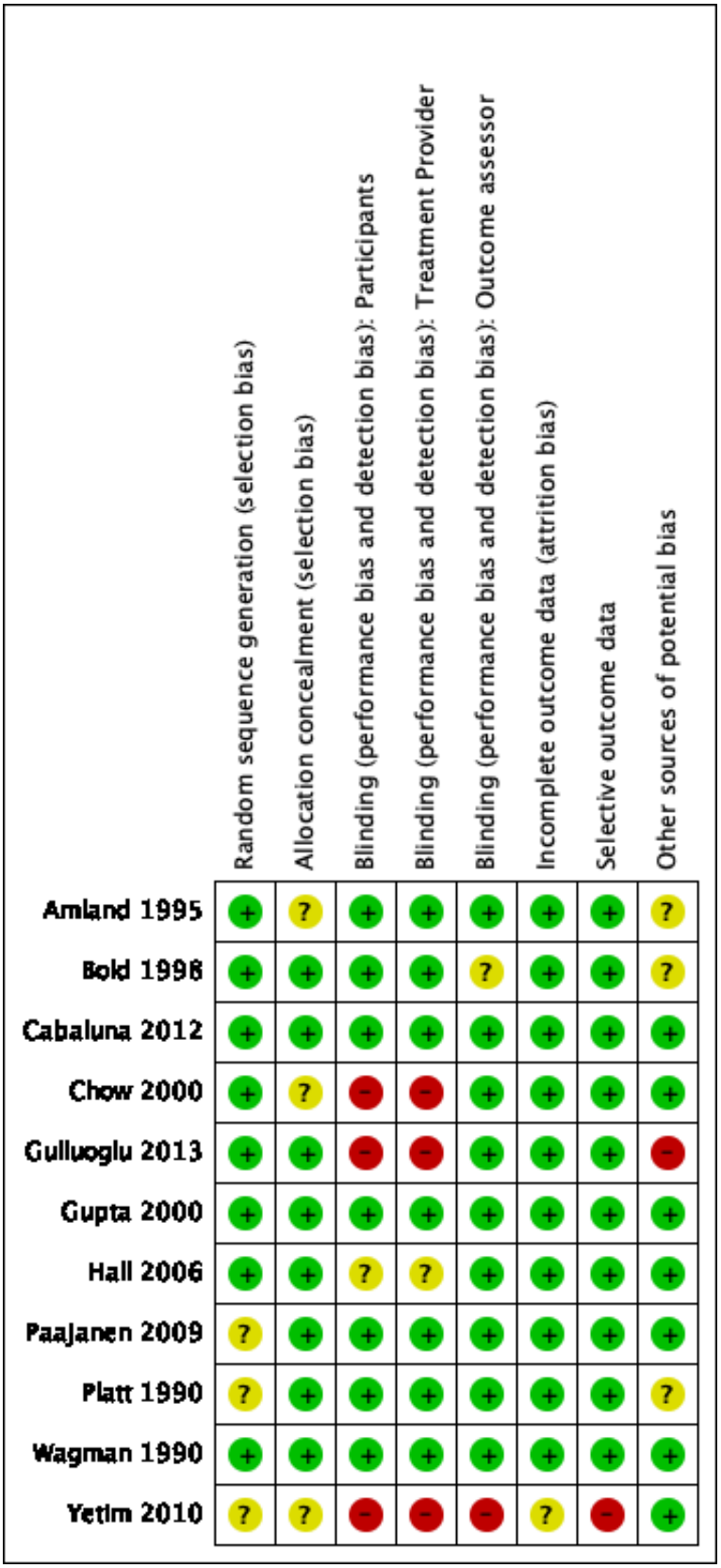
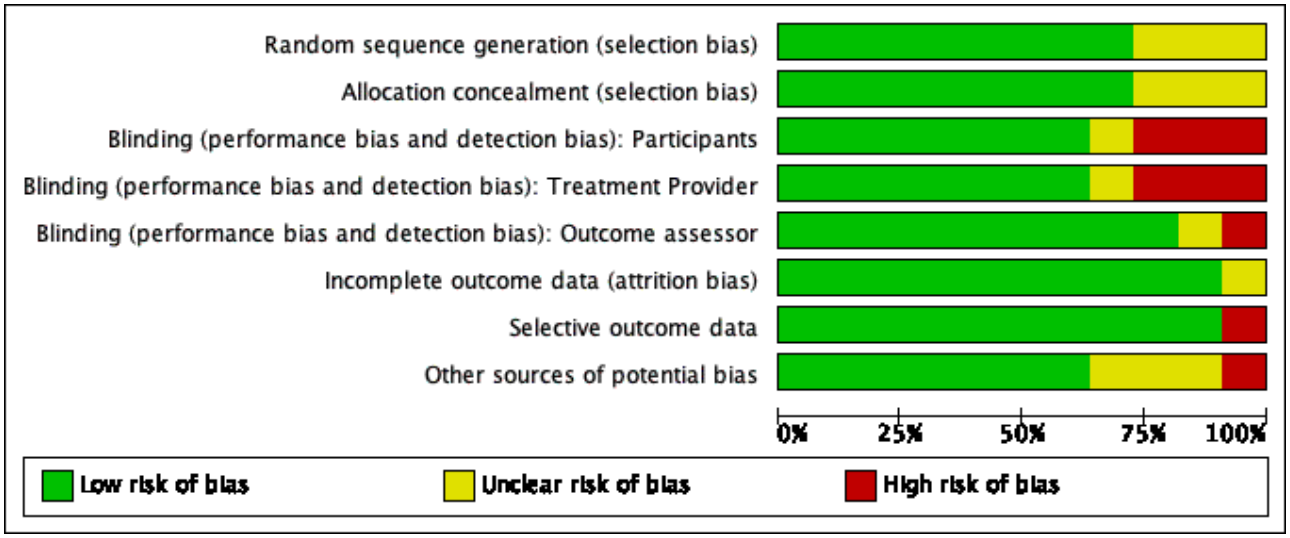


Figure 4. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Sequence generation

Eleven studies were described as RCTs, but only eight adequately generated the randomisation sequence by reporting the use of computer-generated numbers or sequences of blocks of 10 and were at low risk of bias for this domain (Amland 1995; Bold 1998; Cabaluna 2012; Chow 2000; Gulluoglu 2013; Gupta 2000; Hall 2006; Wagman 1990). We classified three studies at unclear risk of bias as the authors failed to report the method by which randomisation sequence was generated (Paajanen 2009; Platt 1990; Yetim 2010).

Allocation concealment

Adequate allocation concealment was described for eight studies and they were therefore at low risk of bias (Bold 1998; Cabaluna 2012; Gulluoglu 2013; Gupta 2000; Hall 2006; Paajanen 2009; Platt 1990; Wagman 1990). Three of these studies used the hospital pharmacy to generate the allocation for participants (Bold 1998; Platt 1990; Wagman 1990). One study stated that consecutive patients were allocated to group by a computer program but the method of allocation was not described (Chow 2000); and two studies used sealed, opaque, sequentially numbered envelopes (Gupta 2000; Hall 2006). One study reported the use of both hospital pharmacy as well as sealed, opaque, sequentially numbered envelopes (Paajanen 2009). In the remaining three studies the method of allocation concealment was not described and therefore we classified them at unclear risk of bias (Amland 1995; Chow 2000; Yetim 2010).

Blinding

Blinding (participants and treatment providers – all outcomes)

Adequate blinding of participants and treatment providers was clearly reported in seven trials and therefore these were at low risk of bias (Amland 1995; Bold 1998; Cabaluna 2012; Gupta 2000; Paajanen 2009; Platt 1990; Wagman 1990). We classified three trials as having inadequate blinding of both participants and treatment providers mainly because the control groups were not blinded as they were not given any treatment (Chow 2000; Gulluoglu 2013; Yetim 2010). Whilst blinding was not specifically reported by Hall 2006 the antibiotic was administered after the induction of anaesthesia; therefore it is possible that blinding was adequate but as there was no statement by the study authors we judged this to be at unclear risk of bias.

Blinding (outcome assessors – all outcomes)

Nine studies described adequate blinding of outcome assessors and these were at low risk of measurement bias. All antibiotic compared with placebo studies stated that the key physician was unaware of patient allocation until data collection was complete (Amland 1995; Cabaluna 2012; Chow 2000; Gulluoglu 2013; Gupta 2000; Hall 2006; Paajanen 2009; Platt 1990; Wagman 1990). In one study it remained unclear if the outcome assessors were adequately blinded (Bold 1998); and in another it was judged that the nature of the collagen implants under the wound site would prevent blinding of the outcome assessors (Yetim 2010).

Incomplete outcome data

In 10 studies we judged the loss to follow-up to be low, with similar numbers of participants lost in both control and treatment groups and valid reasons given (Amland 1995; Bold 1998; Cabaluna 2012; Chow 2000; Gulluoglu 2013; Gupta 2000; Hall 2006; Paajanen 2009; Platt 1990; Wagman 1990). We judged one study to be at unclear risk for this domain because the authors stated that patients would be followed up for six months post surgery, but only reported data at seven days (Yetim 2010).

We judged six studies to have undertaken an intention-to-treat (ITT) analysis either because they explicitly reported this or because there were no dropouts from the study and the numbers of participants in the groups analysed at the final follow-up of the study were the same as those randomised at the outset (Amland 1995; Cabaluna 2012; Gulluoglu 2013; Gupta 2000; Hall 2006; Paajanen 2009). ITT analysis was not reported in the other five studies (Bold 1998; Chow 2000; Platt 1990; Wagman 1990; Yetim 2010).

Selective reporting

The study protocols were not available but all the important outcome measures stated in the Methods section were reported in the results and therefore we judged this domain to be at low risk of bias for all studies except one. It is unclear why follow up data at 6 months were not included in the published study and we have therefore judged it to be at high risk of bias for selective reporting (Yetim 2010).

Other potential sources of bias

We judged seven trials to be at low risk of bias for this domain because there was no imbalance in the baseline characteristics and the studies appeared free from other forms of bias (Cabaluna 2012; Chow 2000; Gupta 2000; Hall 2006; Paajanen 2009; Wagman 1990; Yetim 2010). In three of the remaining studies there was some funding reported from pharmaceutical companies but the extent of industry involvement was unclear and we have judged there to be an unclear risk of bias (Amland 1995; Bold 1998; Platt 1990). One study highlighted a difference in the baseline characteristics, stating that patients in the control group had considerably more frequent open surgical biopsies than those in the prophylaxis group; as a result we judged this study at high risk of bias for this domain (Gulluoglu 2013).

Effects of interventions

See: **Summary of findings for the main comparison** Preoperative antibiotics compared with placebo or no antibiotic for breast cancer surgery; **Summary of findings 2** Perioperative antibiotics compared with placebo or no antibiotic for breast cancer surgery

See: Summary of findings for the main comparison; Summary of findings 2.

Comparison 1: preoperative antibiotics compared with placebo or no antibiotic (10 trials, 2823 participants)

Seven studies compared preoperative antibiotics with placebo (Amland 1995; Bold 1998; Cabaluna 2012; Gupta 2000; Paajanen 2009; Platt 1990; Wagman 1990). Three studies compared preoperative antibiotics with no treatment (Chow 2000; Hall 2006; Gulluoglu 2013).

Incidence of postoperative wound infection

All 10 trials recorded incidence of wound infection as an outcome. Results are presented as risk ratio (RR), where the risk ratio is the risk of infection in the intervention group divided by the risk of infection in the control group. A risk ratio of less than one indicates fewer infections in the intervention group. Two studies compared cefonicid with placebo (Bold 1998; Platt 1990), one compared azithromycin with placebo (Amland 1995), one compared Augmentin with placebo (Gupta 2000), two compared cefazolin with placebo (Cabaluna 2012; Wagman 1990), one compared flucloxacillin with no treatment (Hall 2006), one compared ampicillin-sulbactam with no treatment (Gulluoglu 2013), one compared dicloxacillin with placebo (Paajanen 2009), and one compared clarithromycin with no treatment (Chow 2000).

We pooled all the trials using a fixed-effect model as there was no clinical or statistical evidence of heterogeneity ($I^2 = 0\%$). The pooled risk ratio shows that giving preoperative antibiotics probably reduces the risk of wound infection after breast cancer surgery (RR 0.67, 95% CI 0.53 to 0.85) (Analysis 1.1). This is moderate certainty evidence downgraded one level for imprecision, as all but one of the confidence intervals crossed the line of no effect.

We carried out a sensitivity analysis to exclude Chow 2000, as this study had short follow-up, only compared antibiotic with no antibiotic and reported inflammation rather than infection as its primary outcome. The sensitivity analysis demonstrated no effect from removing Chow 2000 from the pooled analysis. Additionally, we carried out a sensitivity analysis to exclude Gulluoglu 2013 due to one or more domains being assessed as at high risk of bias in order to determine whether this met our criteria for downgrading by reducing our confidence in the estimate of effect. The sensitivity analysis demonstrated no effect from removing Gulluoglu 2013 from the pooled analysis. Since there is evidence that the quality of allocation concealment influences study results (Schulz 1995), we examined the effect of excluding studies judged to have inadequate allocation concealment in a prespecified sensitivity analysis. We judged two studies to have unclear allocation concealment (Amland 1995; Chow 2000). Removing these studies from the meta-analysis resulted in a pooled RR of 0.67 (95% CI 0.52 to 0.85) which was still in favour of prophylactic antibiotics. Finally, we examined the effect of excluding all three studies (Amland 1995; Chow 2000; Gulluoglu 2013) from the meta-analysis which resulted in a pooled RR of 0.74 (95% CI 0.57 to 0.96) which was still in favour of prophylactic antibiotics.

One study documented infection rates in those who received neo-adjuvant chemotherapy (Bold 1998); there was no difference between the groups treated with cefonicid compared with the placebo group (RR 0.21, 95% CI 0.01 to 4.12) (Analysis 1.2). Another study provided details of the number of patients who had previously received chemotherapy but did not report separate data on infection rates for these patients (Platt 1990).

Adverse reactions to treatment

Ten studies reported whether adverse events did or did not occur (please refer to other data tables for 'Adverse effects from antibiotics' under Data and analyses '1 Preoperative antibiotics versus none or placebo') (Amland 1995; Bold 1998; Cabaluna 2012; Chow 2000; Gulluoglu 2013; Gupta 2000; Hall 2006; Paajanen 2009; Platt 1990; Wagman 1990) (Analysis 1.4). Eight studies reported there were no adverse events (Bold 1998; Cabaluna 2012; Chow 2000; Gulluoglu 2013; Hall 2006; Paajanen 2009; Platt 1990; Wagman 1990). Two studies reported adverse events (Amland 1995; Gupta 2000). Gupta 2000 reported 41 adverse events (23%) in the treatment group and 33 (18%) in the control group, but no details were reported on type of adverse events. Although we contacted authors for clarification about the nature of these events, they did not reply. Amland 1995 reported four events (2.3%) in the treatment group and five events (3.0%) in the placebo group. In the treatment group two gastrointestinal events, one skin rash and one other adverse reaction were reported. In the placebo group two gastrointestinal events, two skin rashes and one other event were reported. One study made no mention of adverse events in the study report (Yetim 2010). It is very uncertain whether there is a difference in incidence of adverse events between the treatment and no treatment or placebo groups. We downgraded the evidence three levels and assessed the evidence as very low certainty overall. We downgraded one level for serious risk of bias (two studies with one or more domains assessed as at high risk of bias and considered to lower confidence in estimate of effect).

We downgraded one level for serious inconsistency as the included studies had considerably high statistical heterogeneity for this outcome (I^2 = 84.9%) precluding pooling of data. We downgraded one level for serious imprecision due to few events.

Death

No studies presented information on deaths.

Delay in adjuvant cancer treatment caused by SSI

No studies presented information on delays in adjuvant cancer treatments due to SSI.

Time to wound healing

No studies presented information on time to wound healing.

Time to onset of infection

Four studies reported time to onset of infection (Analysis 1.5). Gupta 2000, Platt 1990 and Wagman 1990 presented a mean time to infection whereas Gulluoglu 2013 presented the data without a measure of variance and therefore we have not combined this in a meta-analysis. It is unclear whether there is a difference in time to onset of infection between the treatment and no treatment or placebo groups. The overall certainty of the evidence is low, downgraded one level for serious risk of bias (one study with one or more domains assessed as at high risk of bias and considered to lower confidence in the estimate of effect) and one level for serious inconsistency preventing pooling of data. Two studies documented similar mean times to onset of infection: 12 and 11 days in the intervention group and 11 and 10 days in the control group respectively (Gupta 2000; Platt 1990). Wagman 1990 documented mean time of onset of infection of 17.7 days in the intervention group and 9.6 days in the control group. Gulluoglu 2013 stated that the time to onset of infection was similar in both the control and intervention group. The study provided a table of data with a range of onset of infection times. The majority of infections (62%) were detected between three and seven days postoperatively.

Readmission to hospital

Three studies reported readmission rates following treatment (Bold 1998; Gulluoglu 2013; Platt 1990). In one study no patients required readmission to hospital (Gulluoglu 2013). In the other two studies, due to statistical heterogeneity (I^2 = 70.8%) we did not pool results. One study reported lower readmission rates in those treated with prophylactic antibiotics (RR 0.11, 95% CI 0.01 to 0.88) (Analysis 1.6) and a shorter duration of readmission (placebo group 5.9 days, prophylaxis group 3.0 days) (Bold 1998); the other study found no reduction in readmission rates (RR 1.0, 95% CI 0.29 to 3.42) (Platt 1990) (Analysis 1.6). It is, therefore, unclear whether there is a difference in rates of readmission to hospital between the treatment and placebo groups. The overall certainty of the evidence is low, downgraded one level for serious inconsistency due to statistical heterogeneity and one level for serious risk of bias (one study with one or more domains assessed as at high risk of bias and considered to lower confidence in the estimate of effect).

Cost of care

Two studies reported the cost of care (Bold 1998; Gulluoglu 2013) (Analysis 1.3). In one study the cost did not include the cost of operation or associated stay in hospital, but the cost of any additional care or medications (i.e. antibiotic prophylaxis, postoperative antibiotics or wound care) was calculated (Bold 1998). Study authors found that the average cost per patient was USD 49.80 in the antibiotic prophylaxis group and USD 364.87 in the control group. The majority of this cost difference was accounted for in patients readmitted to hospital for wound complications. In the other study little detail is given regarding what the cost included (Gulluoglu 2013). The report states "SSI-related treatment cost" was calculated. The study reported that the control group had a considerably higher cost (USD 20.26) when compared with the treatment group (USD 8.48). It is unclear whether there is a difference in cost of care between the treatment and no treatment or placebo groups. The overall certainty of the evidence is low, downgraded one level for serious risk of bias (one study with one or more domains assessed as high risk of bias and considered to lower confidence in the estimate of effect) and one level for serious inconsistency (heterogenous calculation methodology).

Comparison 2: perioperative antibiotics compared with placebo or no antibiotic (one trial, 44 participants)

One study compared perioperative antibiotics with no antibiotic (Yetim 2010).

Incidence of postoperative wound infection

This small study which is at overall high risk of bias presented wound infection as an outcome. The study compared gentamycin-infused collagen (Gentacoll) inserted perioperatively with no antibiotic. There were no infections in the antibiotic-treated group compared with four infections in the control group. Whilst the study authors stated this to be in favour of the antibiotic group, this was not replicated in our analysis (RR 0.11, 95% CI 0.01 to 1.95) (Analysis 2.1). It is very uncertain whether there is a difference in incidence of SSI between the treatment and no treatment or placebo groups. The evidence was downgraded two levels for very serious risk of bias as the majority of domains were evaluated as at high risk of bias and were considered to substantially lower confidence in estimate of effect. The evidence was downgraded two levels for very serious imprecision (large confidence interval crossing the line of no effect, few events and did not meet optimal information size criterion). The overall certainty of the evidence is very low.

Adverse reactions to treatment

The study did not report any adverse reactions to treatment.

Deaths

The study did not report any information on deaths.

Delay in adjuvant cancer treatment caused by SSI

The study did not report any information on delays in adjuvant cancer treatment caused by SSI.

Time to onset of infection

The study did not report any information on the time to onset of infection.

Readmission to hospital

The study reported that two participants in the control group had to be readmitted for parenteral antibiotics as a result of wound infection. No participants in the antibiotic group were readmitted.

Cost of care

The study did not report the cost of care.

DISCUSSION

Summary of main results

This review finds that preoperative antibiotics probably reduce the risk of SSI in people undergoing surgery for breast cancer when compared with placebo or no treatment with moderate certainty. Of the 10 studies that reported data on adverse events, only one found an increase of events in the intervention group; however detailed information about the nature of the adverse events was not given and adverse events were generally poorly reported across the included studies. In addition data for some of the outcomes, including deaths, delays in adjuvant cancer treatments, cost and readmissions, were reported by few of the included studies. We found one study that evaluated perioperative antibiotics compared with no antibiotic: the evidence from this small study was evaluated as very low certainty and no conclusions can be made. We found no studies evaluating antibiotics for breast reconstruction at the time of the initial surgery.

Overall completeness and applicability of evidence

We found only 11 studies with a total of 2867 participants — not many considering the number of people affected globally by breast cancer. Whilst it is encouraging that we evaluated some of the evidence as moderate quality it is possible that the numbers are not adequate to evaluate fully the risks and benefits of antibiotic prophylaxis for breast cancer surgery. In addition we had to exclude some trials that included people having immediate breast reconstruction as we were unable to obtain discrete data specifically for breast cancer patients.

Whilst we made every effort to obtain unpublished data, all the included studies had been published. We assessed publication bias using a funnel plot; due to the small number of studies, however, we elected to omit statistical analysis of funnel plot asymmetry. Visual inspection of the funnel plot did not suggest publication bias.

This review did not discriminate between the choice of antimicrobial agent used in each study, and we assumed the agents evaluated to be appropriate for the likely pathogens causing SSI in breast cancer surgery; further studies are required to evaluate the comparative efficacy of different agents. The vast majority of studies we identified administered the antimicrobial agent preoperatively. Other recent research has recommended that antibiotic prophylaxis should generally be administered as a single dose preoperatively in order to maximise benefit and minimise adverse effects from treatment (SIGN 2014).

Quality of the evidence

We assessed certainty of evidence, downgrading where necessary, according to GRADE 2013 guidelines. In general the included trials were at low risk of bias for the main domains of sequence generation and allocation concealment. Amland 1995, Chow 2000 and Yetim 2010 had unclear allocation concealment but excluding these studies from the analysis made little difference to the result. One study had a follow-up of only five days (Chow 2000). As the average time to onset of infection in the other included studies ranged between 11 and 17.7 days it might have been appropriate to specify in the protocol a minimum follow-up time. However, excluding data from this study made no difference to the overall outcomes. Gulluoglu 2013 had one or more domains with high of bias, however, removing the study from the pooled analysis did little to change the overall outcome thus we did not downgrade the evidence for risk of bias in the main preoperative antibiotics comparison. We were unable to ascertain whether the risk of bias affected our confidence in estimate of effect for the other outcomes without pooled data and downgraded the evidence one level on this basis. We judged the evidence from one study which compared perioperative antibiotics with no antibiotic to be at very high risk of bias overall due to a failure of blinding, insufficient information given regarding selection bias and possible selective reporting (Yetim 2010). Pooling of data was only possible with one outcome and we downgraded other outcomes with evidence of inconsistency by one level for statistical or clinical heterogeneity.

Overall, there are sufficient data from this review to suggest with moderate certainty that preoperative antibiotic prophylaxis probably reduces surgical site infections in those undergoing non-reconstructive breast cancer surgery. However further research would be required to establish the best protocols for practice.

Potential biases in the review process

We grouped the results of the main analysis by comparator (placebo or nothing) in the main analysis of 10 studies. This may introduce bias although (with reference to a Cochrane Review analysing the issue) it is unlikely to be clinically significant (Hróbjartsson 2010).

Agreements and disagreements with other studies or reviews

We found one systematic review and meta-analysis on the effects of antibiotic prophylaxis for breast cancer surgery which also concluded that prophylactic antibiotics reduce SSIs (Tejirian 2006). Another systematic review also considered non-breast-cancer patients and concluded that prophylactic antibiotics reduce the incidence of SSIs (Sajid 2012). A meta-analysis of antibiotic prophylaxis in breast reduction surgery concluded that preoperative antibiotics prevent SSIs but it did not include breast cancer patients (Shortt 2014). Two non-systematic reviews did not draw any firm conclusions (D'Amico 2001; Hall 2000). Similar systematic reviews in other types of clean surgery are scarce and have produced varied results (Gillespie 2010; Sanchez-Manuel 2012).

AUTHORS' CONCLUSIONS

Implications for practice

Preoperative prophylactic antibiotics probably reduce the risk of an SSI in people undergoing breast cancer surgery. However, it is very uncertain whether there is an effect on incidence of adverse events. Furthermore, the effects on time to onset of infection, readmission to hospital and cost of care remain unclear. More studies are required to establish the best protocols for clinical practice.

Implications for research

Further large, high-quality randomised controlled trials are needed to establish the most effective prophylactic antibiotic protocols. Analysis of secondary outcomes, such as adverse events, delays

in adjuvant cancer treatments and costs of care, would aid the development of well-considered and useful protocols and standards for practice. In addition trials need to evaluate the use of antibiotics in women undergoing immediate breast reconstruction.

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Authors of previous versions of the review

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Amland 1995

Methods	RCT: randomisation via computer-generated blocks of 10 Loss to follow-up: < 20% Intention-to-treat: unclear Power calculation: unclear as not stated by the author Reliable primary outcome: done
Participants	Male and female. Age 6 years or above. Admitted for plastic surgery and able to give informed consent. Trial exclusion criteria: intolerance to trial drug, terminal illness or immunosuppression, serious underlying disease, pregnant or breast feeding, received antibiotics in the 2 weeks prior to surgery, malabsorption illnesses, receiving carbamazepine or cyclosporins, renal or hepatic impairment, history of mental illness Total breast excision participants: 76 Study included breast reconstruction and implants, which have not been included in this analysis as the author could not be contacted to find out if reconstruction was secondary to cancer treatment.
Interventions	I) Azithromycin – single dose. Dose according to body weight. Dose taken 8 p.m. the night before surgery (n = 42) C) Placebo used but no details provided (n = 34)
Outcomes	Infection rates Adverse effects
Notes	Length of follow-up: 30 days Funding organisation: not stated Country of origin: Norway

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomisation was performed in blocks of 10 patients using a randomised chart" Comment: computer-generated blocks of 10. Method of generating the random schedule reported.
Allocation concealment (selection bias)	Unclear risk	Comment: not reported
Blinding (performance bias and detection bias) Participants	Low risk	Comment: reported as placebo-controlled, double-blind study (no further detail given)
Blinding (performance bias and detection bias) Treatment Provider	Low risk	Comment: reported as placebo-controlled, double-blind study (no further detail given)

Amland 1995 *(Continued)*

Blinding (performance bias and detection bias) Outcome assessor	Low risk	Quote: “Blinding was maintained until every patient had completed follow-up and all diagnosis of wound infection had been made”. Comment: the wound was assessed “by the physician” using a “specifically designed wound assessment chart”. It was judged that the physician undertaking the wound assessment was likely blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: “the inclusion of these patients in the final analysis after the intention to treat principle did not alter the end result significantly." Comment: only 1 patient was lost to follow-up (placebo group)
Selective outcome data	Low risk	Comment: the study protocol was not available, however, the Results section clearly reports the incidence of wound infection using a prespecified scoring system. The study states “there were 8 wound infections in the azithromycin group and 32 in the placebo group.”
Other sources of potential bias	Unclear risk	Comment: in the acknowledgements the authors state “the present work was supported by Pfizer AS.” This is a pharmaceutical company. However, the study appears to be free of any other source of bias.

Bold 1998

Methods	RCT: randomisation using computer-generated blocks Loss to follow-up: < 20% Intention-to-treat: unclear Power calculation: unclear, stated as under-powered Clear definition of infection
Participants	All female; 18 years old or above undergoing axillary lymph node dissection Excluded if: there was history of allergy to cephalosporin, aspirin use within 5 days, recent antibiotic use or infection, pregnancy or breast feeding, wound infection from surgery in the past 4 weeks, hepatic or renal impairment, diabetes, inflammatory breast cancer, concomitant isolated limb perfusion or those undergoing immediate breast reconstruction Total number of patients randomised = 200 22 excluded after randomisation Of these, 141 were confirmed breast cancer patients
Interventions	I) Cefonicid 1 g, intravenously 60 minutes prior to operation (n = 88) C) Placebo used was normal saline as per antibiotic regime (n = 90)
Outcomes	Infection rates Re-hospitalisation rates Cost of care Adverse events
Notes	Length of follow-up: 4 weeks post surgery Funded by SmithKline Beecham Country of origin: USA

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “Randomisation was accomplished with a computer-generated block randomisation table”.

Bold 1998 *(Continued)*

		Comment: computer-generated blocks used. Method of generating the random schedule reported.
Allocation concealment (selection bias)	Low risk	Comment: hospital pharmacy performed randomisation and provided placebo or antibiotic in identical IV bags
Blinding (performance bias and detection bias) Participants	Low risk	Quote: "Blinding of antibiotic administration was accomplished through the hospital pharmacy." The authors go on to state "[pharmacy] provided the placebo or cefonicid in identical intravenous bags". Comment: participants likely blinded
Blinding (performance bias and detection bias) Treatment Provider	Low risk	Quote: "Blinding of antibiotic administration was accomplished through the hospital pharmacy." The authors go on to state "[pharmacy] provided the placebo or cefonicid in identical intravenous bags". Comment: treatment provider likely blinded
Blinding (performance bias and detection bias) Outcome assessor	Unclear risk	Quote: "patients were followed up in an outpatient clinic and monitored for signs of symptoms of infection." The authors go on to say "a research nurse also contacted the patient and referring physician for wound follow up for 4 weeks after surgery" Comment: no comment is made as to whether the assessors remained blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Twenty-two patients were excluded from the analysis because of protocol violations". 10 were from the placebo group and 12 from the treatment group. This left 90 patients in the placebo group and 88 patients in the cefonicid group. Comment: the reasons for exclusion seem valid and are unlikely to introduce bias; overall the loss to follow-up was less than 20%
Selective outcome data	Low risk	Quote: in the introduction to the study the authors state "the study was undertaken to determine whether a single dose of cephalosporin could decrease the incidence of post operative wound infection". They go on to state "the results would be subject to a cost benefit analysis". Comment: the results clearly document the incidence of wound infection in table II as well as a cost benefit analysis in table III
Other sources of potential bias	Unclear risk	Comment: the paper states "the study was sponsored in part by a grant from SmithKline Beecham". This is a pharmaceutical company. However, the study appears to be free of any other source of bias.

Cabaluna 2012

Methods	RCT: randomisation sequence generated by computer Loss to follow-up: < 20% Intention-to-treat: not stated, no patients excluded from the analysis Power calculation: not stated Clear definition of infection: done; predefined clinical indicators
Participants	All females aged between 18 and 80 with histologically diagnosed breast cancer who were scheduled for MRM Total number: 254 No patients excluded after randomisation

Cabaluna 2012 *(Continued)*

	Exclusion criteria: males, recurrent breast cancer, previous radiotherapy, patients with diabetes or severe malnutrition, patients receiving steroids, patients planned for immediate reconstruction, patients who had had antibiotics in the last week, patients with allergy to cephalosporins, patients with existing local infection
Interventions	I) Cefazolin 1 g given intravenously at the time of anaesthesia C) Normal saline 10 ml
Outcomes	Primary outcome: incidence of surgical site infection (SSI) within 30 days of MRM Secondary outcomes: presence of haematoma and seroma
Notes	Length of follow-up: 30 days post surgery Source of funding: not stated Country of origin: the Philippines

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomised with a computer-generated randomization list" Comment: computer-generated randomisation lists were used. Method of generating the random schedule reported.
Allocation concealment (selection bias)	Low risk	Quote: "The table of random numbers was only available to a single nurse research assistant, who was responsible for preparing the treatment and placebo solutions". Comment: allocation concealment achieved using a research nurse
Blinding (performance bias and detection bias) Participants	Low risk	Quote: "A nurse research assistant prepared the antibiotic and placebo solutions. Patient, surgeon, anesthesiologist and all other reporting room staff were blinded as to treatment allocation". Comment: participants likely blinded
Blinding (performance bias and detection bias) Treatment Provider	Low risk	Quote: "A nurse research assistant prepared the antibiotic and placebo solutions. Patient, surgeon, anesthesiologist and all other reporting room staff were blinded as to treatment allocation". Comment: treatment provider likely blinded
Blinding (performance bias and detection bias) Outcome assessor	Low risk	Quote: "the outcome evaluator was blinded as to what study arm the patient belonged to". Comment: outcome assessor likely blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "No patent withdrew from the study". Comment: low risk of attrition bias
Selective outcome data	Low risk	Quote: "the primary outcome was occurrence of SSI within 30 days of MRM" Comment: the authors state the primary outcome of the study was occurrence of surgical site infection (SSI). The authors clearly state the definition of a SSI and report the incidence of SSIs in the Results section.

Cabaluna 2012 *(Continued)*

Other sources of potential bias	Low risk	Comment: the study appears to be free of other sources of bias

Chow 2000

Methods	RCT: computer-generated sequence Loss to follow-up: < 20% Intention-to-treat: not done Power calculation: unclear Clear definition of infection: unclear; addressed inflammation rather than infection.
Participants	All females diagnosed with breast cancer and undergoing mastectomy Total patients randomised: 56 with 2 being excluded after randomisation Excluded if: pregnant, diabetic, hepatic or renal impairment, myasthenia gravis, tendency to bleeding, immunosuppression or antibiotics within the preceding 2 weeks
Interventions	I) Clarithromycin 500 mg orally first dose commenced the day prior to surgery (n = 28). Treatment continued twice daily for 3 days post surgery. C) Control group received no placebo (n = 24)
Outcomes	Inflammatory responses Infection rates Flap necrosis (stated as minor in both groups) Pain Range of movement
Notes	Length of follow-up 5 days post surgery Country of origin: Japan

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “consecutive patients (except those excluded) were enrolled and randomised into two groups by computer”. Comment: randomised into 2 groups by computer. Method of generating the random schedule reported
Allocation concealment (selection bias)	Unclear risk	Comment: no further information is given on the randomisation process
Blinding (performance bias and detection bias) Participants	High risk	Quote: "Patients in the study group were given oral clarithromycin. Patients in the control group did not receive any clarithromycin.” Comment: control group received no treatment
Blinding (performance bias and detection bias) Treatment Provider	High risk	Quote: "Patients in the study group were given oral clarithromycin. Patients in the control group did not receive any clarithromycin.” Comment: control group received no treatment
Blinding (performance bias and detection bias) Outcome assessor	Low risk	Quote: “All surgeons and medical staff responsible for assessing the outcome were unaware of the randomisation results because separate prescription sheets were given for the clarithromycin prescription”.

Chow 2000 *(Continued)*

		Comment: blinding of outcome assessor achieved
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: “fifty six patients with breast cancer were recruited for the randomised trial. Two patients in the control group dropped out due to refusal of venepuncture.” Comment: the number lost to follow-up is low and the reason was valid
Selective outcome data	Low risk	Comment: the study protocol was not available; however, the outcomes of this study included postoperative wound infection as well as evidence of the systemic inflammatory response syndrome. This was documented in the introduction to the study and in the outcomes. The results discuss the changes in several inflammatory markers and the results of blood culture tests. The authors state “no patient developed a wound infection”.
Other sources of potential bias	Low risk	Quote: "There were no significant differences between the two groups in terms of age, area of dissection, blood loss, operation time, and the amount of parenteral fluid administered during the perioperative period". Comment: there was no imbalance in the baseline characteristics and the study seems to be free from other forms of bias

Gulluoglu 2013

Methods	RCT: randomisation sequence generated by computer Loss to follow-up: < 20% Intention-to-treat: done, 3 patients excluded from the analysis Power calculation: done and adequately powered Clear definition of infection: done; predefined clinical indicators
Participants	All females with primary non-recurrent operable breast cancer Total number: 369 3 excluded after randomisation Exclusion criteria: males, ductal carcinoma in situ, locally advanced, metastatic or bilateral breast cancer, patients having neoadjuvant chemotherapy, patients undergoing immediate reconstruction, patients with an allergy to beta-lactam or cephalosporin antibiotics, patients with diabetes mellitus, renal disease, Cushing's disease, HIV, additional cancers, blood count abnormalities, immunosuppression, or history of antibiotics in the last month.
Interventions	I) Ampicillin-sulbactam (Ampisid) by intravenous bolus at the time of anaesthesia C) No intervention
Outcomes	Primary outcome: incidence of surgical site infection (SSI) in patients with a BMI over 25 Secondary outcomes: incidence of SSI in patients with a BMI under 25, time to SSI development, culture results, adverse reactions, cost
Notes	Length of follow up: 30 days post surgery Source of funding: not stated Country of origin: Turkey
Risk of bias	

Gulluoglu 2013 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Allocation of patients was done by simple randomization using a computer-generated table of random numbers". Comment: computer-generated randomization lists were used. Method of generating the random schedule reported.
Allocation concealment (selection bias)	Low risk	Quote: "Allocations were concealed from patients and observers. The computer generated randomization list was prepared by an investigator with no involvement in the trial". Comment: allocation concealment achieved using a research assistant
Blinding (performance bias and detection bias) Participants	High risk	Quote: "Patients in the prophylaxis group received 1 g ampicillin-sulbactam by intravenous bolus injection. Those in the control group received no intervention". Comment: control group received no treatment
Blinding (performance bias and detection bias) Treatment Provider	High risk	Quote: "Patients in the prophylaxis group received 1 g ampicillin-sulbactam by intravenous bolus injection. Those in the control group received no intervention". Comment: control group received no treatment
Blinding (performance bias and detection bias) Outcome assessor	Low risk	Quote: "Wounds were inspected before their discharge and examined by caregivers blinded to the allocation". Comment: outcome assessor likely blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Three patients were excluded from the primary analysis because they underwent a second surgery within 1 month: 2 in the prophylaxis group and 1 in the control group". "Data from the randomised patients were analyzed on an intention-to-treat basis". Comment: small number of losses to follow-up, with a legitimate reason
Selective outcome data	Low risk	Comment: primary outcome measure clearly stated on page 38 (SSI incidence). This is reported clearly as the first outcome in the results.
Other sources of potential bias	High risk	Quote: "patients in the control group had significantly more open surgical biopsies than those in the prophylaxis group (16% vs 6%)". Comment: this could potentially be a source of bias as patients who had an open surgical biopsy may be more likely to have an infection

Gupta 2000

Methods	RCT: randomisation sequence generated by computer Loss to follow-up: < 20% Intention-to-treat: not done, 6 patients excluded from the analysis Power calculation: done, but under-powered Clear definition of infection: done; predefined clinical indicators
Participants	All female; 18 years of age or above Total number: 357 44 excluded after randomisation

Gupta 2000 *(Continued)*

	Exclusion criteria: known penicillin allergy, infection within 72 hours' pre-surgery, pregnant, on other antibiotics or with hepatic or renal impairment Treatment group: 177 Placebo group: 180 Diagnosis of breast cancer. Receiving mastectomy or wide local excision with or without axillary
Interventions	I) Augmentin 1.2 g intravenous. Single dose. Given perioperatively (after induction but before first incision) C) Placebo: normal saline as per treatment regime
Outcomes	Infection rate Adverse events Time to wound healing
Notes	Follow-up for 10 to 14 days post discharge Funding not stated Country of origin: UK

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomised to receive the antibiotic or placebo (20 ml 0.9% sterile saline) by reference to a computer generated list". Comment: computer-generated list used. Method of generating the random schedule reported.
Allocation concealment (selection bias)	Low risk	Quote: "The randomization list was generated by computer. The randomization codes were kept in sealed envelopes. Codes were sequentially allocated to randomised patients. Neither the patient nor any of the staff involved with this study were aware of the allocation of treatment until after the study had been completed." Comment: sealed, opaque, sequentially-numbered envelopes
Blinding (performance bias and detection bias) Participants	Low risk	Quote: "Patients were randomised to receive the antibiotic or placebo (20 ml 0.9% sterile saline)." The administration of antibiotic is then described "Where the study agent was administered the anaesthetist was instructed to reconstitute the antibiotic from vials of sterile powder. It was then administered to the patients as a single intravenous bolus injection through a peripherally placed 22 gauge intravenous cannula, shortly after the induction of anaesthesia". Finally the authors state "neither the patient nor any of the staff involved with this study were aware of the allocation of treatment until after the study had been completed". Comment: the study is described as "a prospective, randomised, observer blind, placebo-controlled study". Participants were blinded.
Blinding (performance bias and detection bias) Treatment Provider	Low risk	Quote: "Patients were randomised to receive the antibiotic or placebo (20 ml 0.9% sterile saline)." The administration of antibiotic is then described "Where the study agent was administered the anaesthetist was instructed to reconstitute the antibiotic from vials of sterile powder. It was then administered to the patients as a single intravenous bolus injection through a peripherally placed 22 gauge intravenous cannula, shortly after the induction of anaesthesia". Finally the authors state "neither the patient nor any of the staff involved with this study were aware of the allocation of treatment until after the study had been completed".

Gupta 2000 *(Continued)*

		Comment: healthcare providers blinded. The anaesthetist was not blinded but took no further part in the study.
Blinding (performance bias and detection bias) Outcome assessor	Low risk	Quote: “At no time until the breaking of the code was the investigator made aware of whether the active agent or the placebo was administered, so making this study ‘observer blind’”. Comment: outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: “Protocol violations resulted in six patients being excluded from the intention-to-treat group”. Table 1 shows that 357 patients were randomised and screened and 351 patients were "valid for efficacy analysis". The table also states that 313 patients "completed study". No information is given on these 44 patients who did not complete the study. Comment: 3 patients were lost from each group for the efficacy analysis, but the study reports that an intention-to-treat analysis was undertaken on 351 patients
Selective outcome data	Low risk	Quote: "The primary end point was the incidence of wound infection. Secondary endpoints included febrile morbidity, duration of post-operative hospital stay, delay in progressing to chemotherapy radiotherapy or surgical cosmesis due to wound infection and the incidence of chest or urinary infection, septicaemia or other infections". Comment: in the results the incidence of wound infections are clearly shown in table 6. The number of secondary endpoints is also documented.
Other sources of potential bias	Low risk	Comment: the study appears to be free of other sources of bias

Hall 2006

Methods	RCT: computer-generated random numbers arranged into blocks of 10 Intention-to-treat analysis: done Power calculation: done Reliable primary outcome: done No loss to follow-up
Participants	618 (616 women and 2 men). Scheduled for non-reconstructive breast surgery. Excluded if penicillin hypersensitivity, reconstructive surgery, warfarin therapy, antibiotics within 72 hours, phenytoin therapy or existing infection. Only 2 patients (1 in each group) had received preoperative chemotherapy
Interventions	I) Single IV dose of 2 g flucloxacillin administered over at least 5 minutes immediately after the induction of general anaesthesia C) No treatment
Outcomes	Infection rates Adverse effects Cellulitis Wound scores
Notes	Follow-up: 42 days Country of origin: Australia
Risk of bias	

Hall 2006 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were allocated to a group using computer-generated random numbers arranged into blocks with a cell size of 10". Comment: computer-generated list used. Method of generating the random schedule reported.
Allocation concealment (selection bias)	Low risk	Quote: "Concealment was achieved by placing the group allocation into opaque, serially numbered envelopes that were monitored to detect breaches of the randomisation protocol". Comment: allocation concealment achieved
Blinding (performance bias and detection bias) Participants	Unclear risk	Comment: the study had no placebo for the control group; however, the authors state "Patients in the study group received flucloxacillin 2 g administered intravenously, over at least 5 min, immediately after the induction of general anaesthesia". As the antibiotic was given after the induction of anaesthesia by an anaesthetist it may be assumed that participants were blinded but this was not reported in the study
Blinding (performance bias and detection bias) Treatment Provider	Unclear risk	Comment: the study had no placebo for the control group; however, the authors state "Patients in the study group received flucloxacillin 2 g administered intravenously, over at least 5 min, immediately after the induction of general anaesthesia". As the antibiotic was given after the induction of anaesthesia by an anaesthetist it may be assumed that treatment personnel was blinded but this was not reported in the study
Blinding (performance bias and detection bias) Outcome assessor	Low risk	Quote: "All assessments [of wound infection] were performed without any knowledge of the patient's allocated group" Comment: outcome assessors blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: Figure 3 shows 618 patients randomised to either control or flucloxacillin. All patients were followed up at 42 days. There was no loss to follow-up.
Selective outcome data	Low risk	Quote: "Wound infection was the primary endpoint. It was defined as either the discharge of pus, or a serous discharge containing pathogenic organisms. Wounds were also evaluated using a previously validated scoring system". In the results the authors clearly document the incidence of wound infection "Both groups had a similar rate of postoperative wound infection: ten of 311 (3.2 per cent) in the flucloxacillin group and 14 of 307 (4.6 per cent) in the control group." Comment: the study protocol was not available but the important outcome measures stated in the Methods section are reported in the results
Other sources of potential bias	Low risk	Comment: the study appears to be free of other sources of bias

Paajanen 2009

Methods	RCT: method of randomisation not reported

Paajanen 2009 *(Continued)*

	No loss to follow-up Intention-to-treat analysis: done as all the participants were analysed in the groups to which they were randomised Power calculation: unclear as not stated by the author Reliable primary outcome: done Clear definition of infection: done
Participants	All females patients undergoing non-reconstructive breast cancer surgery between years 2004 and 2007 were included Total number: 292 Exclusion criteria: patients with lack of consent, penicillin hypersensitivity, logistic failure Treatment group: 144 Control group: 148 Diagnosis of breast cancer. Confirmed preoperatively by mammographic stereotactic or ultra-sound-guided core needle biopsy.
Interventions	I) Intravenous 1 g of dicloxacillin in a 100 ml bottle. Single dose 30 minutes before surgery. C) Placebo infusion of 100 ml of saline
Outcomes	Infection rates
Notes	Follow-up: 30 days Country of origin: Finland

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: “The patients were randomised to receive either an intravenous single dose of 1 g of dicloxacillin in a 100 ml or a placebo infusion of 100 ml of saline 30 min prior to surgery.” Comment: method of generating the random schedule not reported
Allocation concealment (selection bias)	Low risk	Quote: “The hospital pharmacy generated allocation using sealed opaque sequentially numbered envelopes.” Comment: allocation concealed using sealed, opaque, sequentially numbered envelopes
Blinding (performance bias and detection bias) Participants	Low risk	Quote: “The research group including the operating surgeon, research nurses, other medical staff, and study participants, were blinded to the participant’s allocation.” Comment: participants were blinded adequately
Blinding (performance bias and detection bias) Treatment Provider	Low risk	Quote: “The research group including the operating surgeon, research nurses, other medical staff, and study participants, were blinded to the participant’s allocation.” Comment: healthcare providers were blinded adequately
Blinding (performance bias and detection bias) Outcome assessor	Low risk	Quote: “All assessments were performed without knowledge of the patient’s assigned group.” Comment: outcome assessors were blinded adequately

Paajanen 2009 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there was no loss to follow-up. Table 3 depicts that all the randomised participants were analysed in the group to which they were allocated.
Selective outcome data	Low risk	Quote: the authors state that SSI was the primary endpoint. A clear definition of infection is documented. The results state "The rate of postoperative SSI was 5.6% (8/144) in the dicloxacillin group and 8.8% (13/148) in the placebo group." Comment: the study protocol was not available but the important outcome measures stated in the Methods section are reported in the results.
Other sources of potential bias	Low risk	Quote: "The patient characteristics and risk factors for SSI were similar in the antibiotic prophylaxis and placebo groups." Comment: there was no imbalance in the baseline characteristics and the study seems to be free from other forms of bias

Platt 1990

Methods	RCT; randomisation via blocks of 10 Loss to follow-up: < 20% Intention-to-treat: unclear Power calculation: adequate for the study as a whole, but may be under-powered for the breast group Clear definition of infection: done
Participants	Included male and female patients aged 18 or above having mastectomy, lumpectomy, excisional breast biopsy, axillary node clearance or reduction mammoplasty. Included are those who speak English, lived within 35 miles of the hospital, have no recognised infection at the time of surgery, recent antibiotic use or known allergy to beta-lactam antibiotics. Total number of participants: 606 18 years old or over
Interventions	I) Cefonicid 1 g intravenous. Within 90 minutes pre-surgery (n = 303). Dose regime: single dose. C) Placebo was a mixture of glycerin, mannitol and riboflavin given as per the treatment regime
Outcomes	Infection rate Adverse reaction to treatment Time to onset of infection Associated morbidity from wound infection Economic evaluation Other infective episodes
Notes	Length of follow-up: 4 to 6 weeks Sponsored by Smith, Kline & French Laboratories Country of origin: USA

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were randomly assigned separately in blocks of 10 to receive cefonicid or placebo." Comment: method of generating the random schedule not reported

Platt 1990 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: "treatment codes were not known by anyone at the participating centres unless the sealed opaque label attached to each vial was opened." They go on to state "investigators were required to return these labels intact." Comment: allocation concealment achieved
Blinding (performance bias and detection bias) Participants	Low risk	Quote: study described as a "Randomised, double-blind trial". "Cefonicid and placebo were supplied in identical numbered vials. The authors state "treatment codes were not known by anyone at the participating centres unless the sealed opaque label attached to each vial was opened." They go on to state "investigators were required to return these labels intact". Comment: participants were blinded adequately
Blinding (performance bias and detection bias) Treatment Provider	Low risk	Quote: study described as a "Randomised, double-blind trial". "Cefonicid and placebo were supplied in identical numbered vials. The authors state "treatment codes were not known by anyone at the participating centres unless the sealed opaque label attached to each vial was opened." They go on to state "investigators were required to return these labels intact". Comment: treatment providers were blinded adequately
Blinding (performance bias and detection bias) Outcome assessor	Low risk	Quote: "drug assignments were not known during any follow up evaluations, including non scheduled visits for suspected wound infection." They repeat this in the surveillance of wound infection paragraph: "all investigators were unaware of the treatment codes until the last evaluation was completed." Comment: automated data processing and analyses in laboratory. Outcome assessor blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: table 1 documents numbers of and reasons for exclusion of patients from analysis after randomisation. 50 patients from the treatment group and 51 from the control group were excluded. Similar reasons for exclusion were documented for both groups. No separate exclusion data are given for the breast cancer patients. Overall the loss to follow-up was less than 20% and therefore judged to be adequate
Selective outcome data	Low risk	Comment: the study protocol was not available; however, the incidence of wound infection was the primary outcome measure. The authors document the definition of a wound infection clearly. The results are displayed in table 4. They are separated for breast surgery versus hernia surgery.
Other sources of potential bias	Unclear risk	Comment: the paper states "the study was supported by a grant from Smith, Kline & French laboratories". This is a pharmaceutical company. However, the study appears to be free of any other source of bias.

Wagman 1990

Methods	RCT: random numbers table generated by Department of Biostatistics Loss to follow-up: < 20% Intention-to-treat: unclear Power calculation: unclear Clear definition of infection: done; predefined clinical indicators
Participants	All breast cancer surgery except re-construction Excluded were those with a history of allergy to the study antibiotic or receiving other antibiotics

Wagman 1990 *(Continued)*

	Total number of participants: 118
Interventions	I) Cefazolin 25 mg per kg. Intravenous. First dose within 30 minutes pre-surgery. Dose regime: 6 doses at 6-hour intervals (n = 59). C) Placebo: normal saline bolus as per the treatment regime (n = 59)
Outcomes	Infection rates Adverse events Time to onset of infection Effect of length of surgery Effect of pre-surgery biopsy
Notes	Length of follow-up: 30 days postoperative Country of origin: USA Sponsored by the American Cancer Society Career Development Award

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “Randomisation was performed in the Pharmacy using a table of random numbers generated by the Department of Biostatistics”. Comment: random number tables used. Method of generating the random schedule reported.
Allocation concealment (selection bias)	Low risk	Quote: “Randomisation was performed in the Pharmacy using a table of random numbers generated by the Department of Biostatistics”. Comment: central allocation, i.e. pharmacy-controlled
Blinding (performance bias and detection bias) Participants	Low risk	Quote: “The patient, surgeon and Infection Control office had no knowledge of the patient assignments”. Comment: blinding of participants done
Blinding (performance bias and detection bias) Treatment Provider	Low risk	Quote: “The patient, surgeon and Infection Control office had no knowledge of the patient assignments”. Comment: blinding of treatment providers done
Blinding (performance bias and detection bias) Outcome assessor	Low risk	Quote: “The patient, surgeon and Infection Control office had no knowledge of the patient assignments. The code was broken after initial data evaluation”. Comment: blinding of outcome assessors done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Nine patients were excluded from the study after randomisation (one patient did not undergo surgical treatment, one underwent biopsy only, five patients failed to receive a complete course of antibiotics and two had antibiotics for another reason)". Comment: the number lost to follow-up is low and the reasons were valid
Selective outcome data	Low risk	Comment: the study protocol was not available but the important outcome measures stated in the Methods section are reported in the results
Other sources of potential bias	Low risk	Comment: the study appears to be free of other sources of bias.

Yetim 2010

Methods	RCT: patients were randomly allocated into 1 of 2 groups No loss to follow-up Intention-to-treat analysis: done as all the participants were analysed in the groups to which they were randomised Power calculation: not done Reliable primary outcome: done
Participants	All female patients who were diagnosed with breast cancer and underwent modified radical mastectomy with axillary dissection between June 2006 and June 2009 were included Exclusion criteria: patients with inflammatory breast cancer who had neoadjuvant radiotherapy, chronic diseases, e.g. diabetes, immune suppression, were excluded Treatment group: 22 Control group: 22
Interventions	I) Gentacoll applied to the axillary area and under the flap before closure of the surgical wound. 2 pieces of Gentacoll were used in each area. Gentacoll is 10 cm × 10 cm × 0.5 cm collagen from equine tendons with 200 mg gentamycin sulphate. C) No Gentacoll
Outcomes	Wound infection Seroma formation Drain removal time Total drainage volumes Duration of hospital stay
Notes	Length of follow-up: 6 months Country of origin: Turkey

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: “patients were randomly allocated in to one of two groups”. Comment: no further information regarding randomisation is given
Allocation concealment (selection bias)	Unclear risk	Comment: no information is given regarding the concealment of randomisation
Blinding (performance bias and detection bias) Participants	High risk	Quote: “Group I underwent modified radical mastectomy during which Gentacoll was applied to the axiliary area and under the flap area of the breast before closure of the surgical wound. Two pieces of Gentacoll were used for each area, each comprising 10 × 10 × 0.5 cm collagen plus gentamycin sulphate (200 mg). Group II underwent modified radical mastectomy without the application of Gentacoll.”

Yetim 2010 *(Continued)*

		Comment: it is not clear whether the participants were blinded in the study; however, they may have been aware of four 10 cm × 10 cm × 0.5 cm pieces of collagen placed under the skin and were therefore unable to be blinded
Blinding (performance bias and detection bias) Treatment Provider	High risk	Quote: "Group I underwent modified radical mastectomy during which Gentacoll was applied to the axiliary area and under the flap area of the breast before closure of the surgical wound. Two pieces of Gentacoll were used for each area, each comprising 10 × 10 × 0.5 cm collagen plus gentamycin sulphate (200 mg). Group II underwent modified radical mastectomy without the application of Gentacoll." Comment: as the surgeons were responsible for applying the Gentacoll they could not be blinded in the study
Blinding (performance bias and detection bias) Outcome assessor	High risk	Quote: "patients were followed up 7 days after discharge from hospital and at 1, 3 and 6 months after surgery" Comment: no information is given as to who performed the follow-up and whether or not they were blinded. At follow-up wound infection and seroma formation was assessed as well as drain information and duration of hospital stay. It could be considered that the healthcare professional assessing for wound infection would be able to see if collagen implants had been inserted.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there was no loss to follow-up documented in the study. 44 patients were enrolled and randomised and the results tables give follow-up data for all 44 participants. However, the authors state that patients would be followed up for 6 months post surgery but the only information given in the paper is for the first 7 days. This has been evaluated as high risk of bias for selective reporting.
Selective outcome data	High risk	Comment: the study protocol was not available; however, wound infection, seroma formation, drain removal time, total drainage volumes and duration of hospital stay were recorded and displayed in results tables 2 and 3. As it is unclear why outcome data for the full 6 month follow up period has not been included the published st has been evaluated as high risk of bias for selective reporting.
Other sources of potential bias	Low risk	Comment: the study appears to be free from other sources of bias

C: control
I: intervention
IV: intravenous
MRM: modified radical mastectomy
RCT: randomised controlled trial

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Baker 2000	This study was from the perspective of dentists managing risk in patients undergoing dental work who were at risk of remote infection due to implants, not infection risk as an acute surgical complication
Bertin 1998	Not an RCT or quasi-RCT
Boyd 1981	Not an RCT – retrospective analysis

Study	Reason for exclusion
D'Amico 2001	Not an RCT
Erfle 2002	Not an RCT or quasi-RCT
Esposito 2006	Study includes hernia repair and breast cancer surgery. Unable to separate data for breast patients.
Franchelli 1994	Although the data were on reconstructive surgery, the paper did not state being secondary to breast cancer treatment. It also did not state whether the surgery was immediate or delayed reconstruction.
Hall 2000	Not an RCT
LeRoy 1991	Not an RCT
Lewin 2015	Excluded as no breast cancer patients are in the study. It is a study involving breast reduction patients.
Lewis 1995	Excluded as unable to obtain separate data for breast patients despite writing to the author.
Morimoto 1998	Excluded as this study was comparing antibiotic dose and regime rather than antibiotic versus placebo/none.
Penel 2004	Not an RCT or quasi-RCT
Penel 2007	Not an RCT or quasi-RCT
Phillips 2016	Excluded as there was no placebo or control. This is a comparison of 2 antibiotic regimes.
Platt 1992	Not an RCT or quasi-RCT
Platt 1993	This is a meta-analysis of Platt 1990 and Platt 1992. The latter was not an RCT; and the former is an included study in this systematic review.
Ruiz-Tovar 2013	Study of microbial contamination of drain fluid
Sanguinetti 2009	Removal of benign lesions included in study. No separate data was obtainable for breast cancer patients.
Sasaki 1988	Excluded as not an RCT following translation. No comparison made.
Serletti 1994	Addressed reduction mammoplasty. Surgery not cancer-related.
Shamilov 1991	Not an RCT or quasi-RCT
Spicher 2003	Found not to be an RCT following translation. The article analyses the authors' experience of implementing guidelines for using antibiotics with patients undergoing reconstructive surgery.
Sultan 1989	No separate data were obtainable for breast patients
Thomas 1999	Addresses long-acting versus short-acting antibiotic comparison rather than antibiotic versus none or placebo
Yang 2017	Not an RCT or quasi-RCT. Retrospective study design.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Exner 1992

Methods	'Prospective open trial'. Unclear randomisation. Unclear blinding.
Participants	21 female patients undergoing breast surgery
Interventions	Treatment group: 400 mg intravenous Teicoplanin Control group: Unclear
Outcomes	Teicoplanin levels in wound exudate were found to be high Teicoplanin levels in fat, breast tissue and wound exudate exceeded the MIC90 for target bacterial strains Teicoplanin was well tolerated
Notes	Requested from British Library and currently unavailable

Kumar 2005

Methods	RCT: unknown method of randomisation
Participants	Unknown
Interventions	Antibiotic therapy Warming
Outcomes	Unknown
Notes	Conference proceeding. No abstract available. Awaiting classification.

Prudencio 2017

Methods	RCT : unknown method of randomisation. Patients randomly allocated to 1 of 2 groups Double blinded Placebo controlled No details regarding intention-to-treat analysis, loss to follow-up or power calculation available
Participants	124 patients undergoing breast cancer surgery Patients undergoing breast reconstruction were excluded Treatment group: 62 Control group: 62
Interventions	Treatment group: received 2 g of pre-operative intravenous cefazolin Control group: received 0.9% sodium chloride intravenously

Prudencio 2017 *(Continued)*

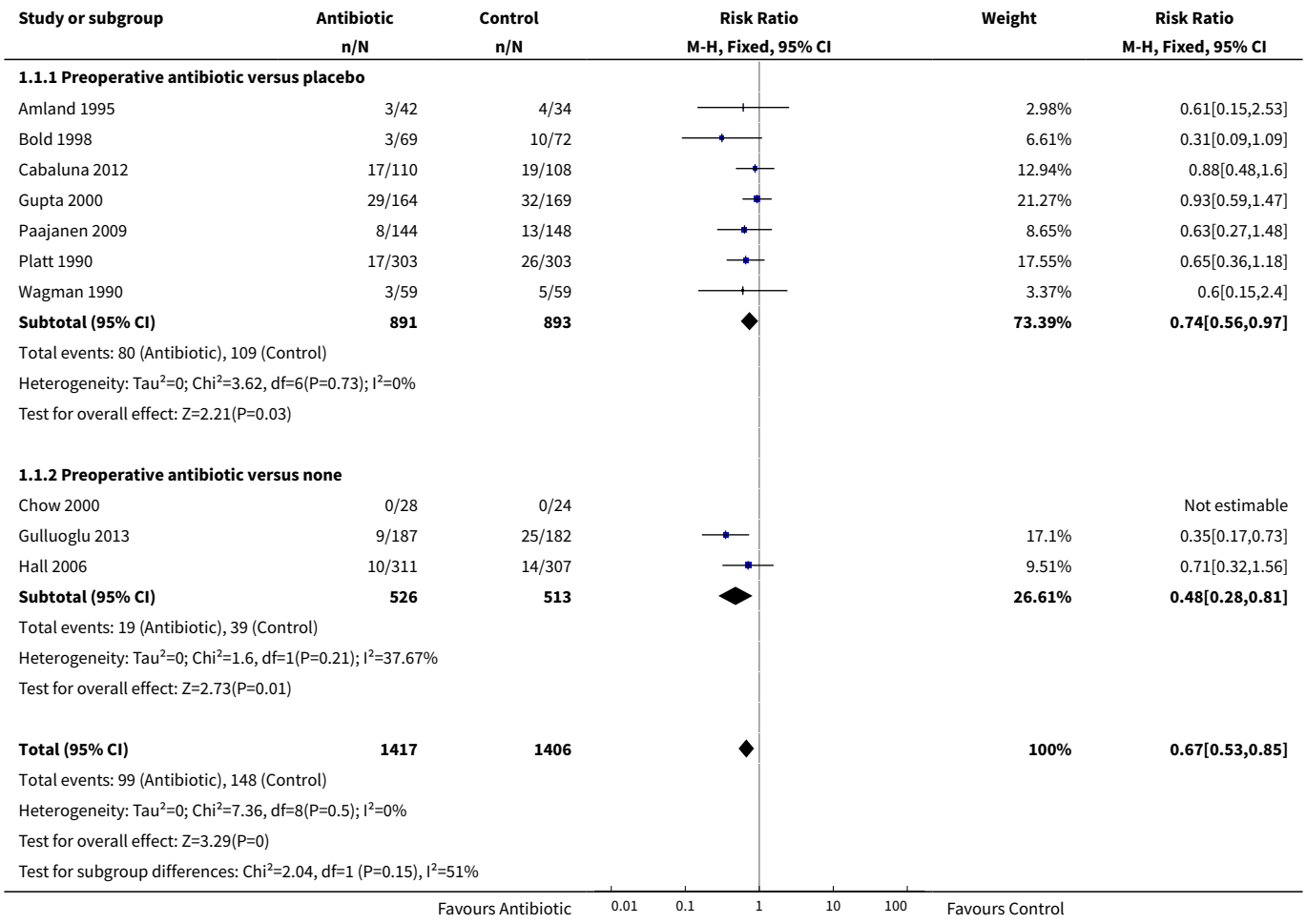
Outcomes	1 patient in the control group developed SSI No patients in the treatment group developed SSI SSI rate: 0.0008% No statistical difference between group Conclusion: supports a minimal need for antibiotics
Notes	Abstract published. No full paper published at time of review. We made efforts to contact study authors but no unpublished data could be acquired.

DATA AND ANALYSES

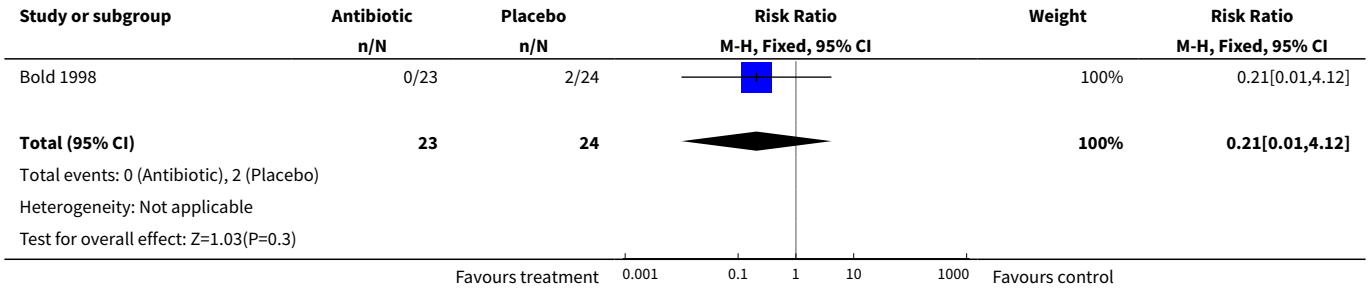
Comparison 1. Preoperative antibiotics compared with placebo or no antibiotic

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Wound infections	10	2823	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.53, 0.85]
1.1 Preoperative antibiotic versus placebo	7	1784	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.56, 0.97]
1.2 Preoperative antibiotic versus none	3	1039	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.28, 0.81]
2 Infection rates in those who received neo-adjuvant chemo	1	47	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.01, 4.12]
3 Cost of care			Other data	No numeric data
4 Adverse effects from antibiotics			Other data	No numeric data
4.1 Preoperative antibiotics versus placebo			Other data	No numeric data
4.2 Preoperative antibiotics versus none			Other data	No numeric data
5 Time to onset of infection			Other data	No numeric data
5.1 Preoperative antibiotic versus placebo			Other data	No numeric data
6 Readmission to hospital	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Preoperative antibiotics versus placebo	2	784	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.04, 3.49]

Analysis 1.1. Comparison 1 Preoperative antibiotics compared with placebo or no antibiotic, Outcome 1 Wound infections.



Analysis 1.2. Comparison 1 Preoperative antibiotics compared with placebo or no antibiotic, Outcome 2 Infection rates in those who received neo-adjuvant chemo.



Analysis 1.3. Comparison 1 Preoperative antibiotics compared with placebo or no antibiotic, Outcome 3 Cost of care.

	Cost of care		
Study	**Antibiotic**	**Placebo**	**Cost calculation**
Bold 1998	Total cost in the treatment group: USD 4382.57 Average per patient: USD 49.80	Total cost in the placebo group: USD 32,838.16 Average per patient: USD 364.87	Treatment costs were calculated from: cost of prophylaxis administration, charges for outpatient treatment and charges for inpatient treatment.
Gulluoglu 2013	Average SSI related treatment cost: USD 8.48	Average SSI related treatment cost: USD 20.26	Little information is given regarding what is included in the SSI (surgical site infection) treatment cost.

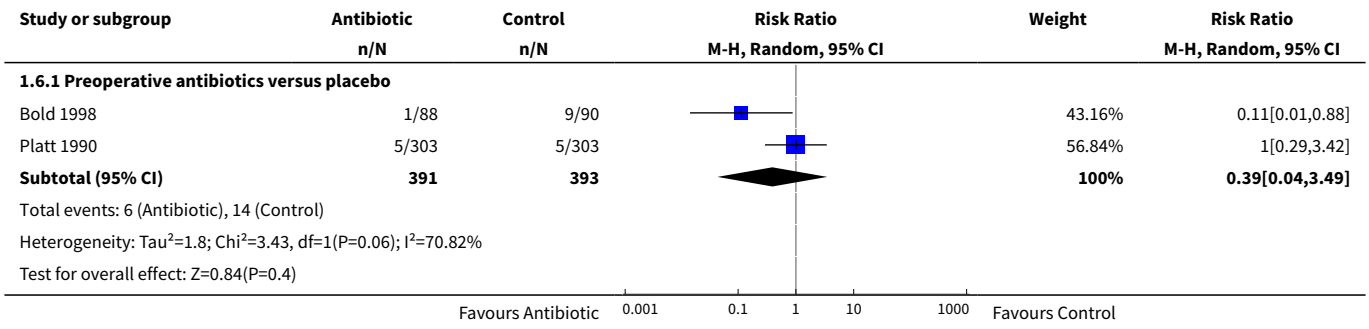
Analysis 1.4. Comparison 1 Preoperative antibiotics compared with placebo or no antibiotic, Outcome 4 Adverse effects from antibiotics.

	Adverse effects from antibiotics	
Study	**Antibiotic**	**Control**
Preoperative antibiotics versus placebo		
Amland 1995	Side effects considered by the investigator to be related to treatment were recorded in 4 of the 171 patients receiving the antibiotic (2.3%) 2 GI; 1 skin rash; 1 other	Side effects considered by the investigator to be related to treatment were present in 5 of the control group (3.0%) 2 GI; 2 skin rash; 1 other
Bold 1998	Stated as: "no patient suffered a complication related to the antibiotic administration"	None recorded
Cabaluna 2012	Stated as: "None of the women included in the study developed hypersensitivity to cefazolin"	None recorded
Gupta 2000	41 adverse events noted, details not provided as to whether these were per patient or per event	33 adverse events noted, details not provided as to whether these were per patient or per event
Paajanen 2009	None recorded	None recorded
Platt 1990	None recorded	None recorded
Wagman 1990	Stated as: "no untoward reactions"	Stated as: "no untoward reactions"
Preoperative antibiotics versus none		
Chow 2000	No adverse events recorded	No adverse events recorded
Gulluoglu 2013	Stated as "No adverse reaction was observed in patients who received antibiotics"	
Hall 2006	Stated as 'no side effects observed' from the flucloxacillin	None recorded

Analysis 1.5. Comparison 1 Preoperative antibiotics compared with placebo or no antibiotic, Outcome 5 Time to onset of infection.

	Time to onset of infection	
Study	**Antibiotic**	**Control**
Preoperative antibiotic versus placebo		
Gulluoglu 2013	0 infections between 0 and 2 days, 6 (67%) infections detected between 3 and 7 days, 2 (22%) infections detected between 8 and 14 days, 1 (11%) infection detected between 15 and 30 days, no infections detected beyond 30 days	1 (4%) infection detected between 0 and 2 days,15 (60%) infections detected between 3 and 7 days, 7 (28%) infections detected between 8 and 14 days, 2 (8%) infections detected between 15 and 30 days, no infections detected beyond 30 days
Gupta 2000	Mean time to onset of infection 12 days	Mean time to onset of infection 11 days
Platt 1990	Mean time to onset of infection 11 days	Mean time to onset of infection 10 days
Wagman 1990	Mean time to onset of infection 17.7 days	Mean time to onset of infection 9.6 days

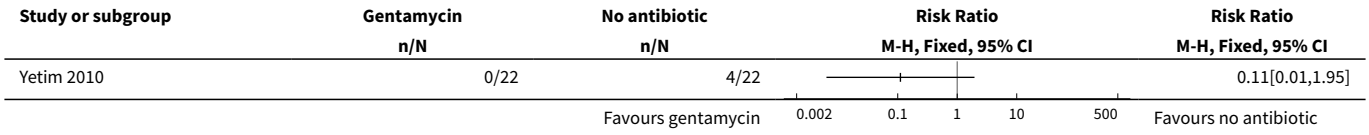
Analysis 1.6. Comparison 1 Preoperative antibiotics compared with placebo or no antibiotic, Outcome 6 Readmission to hospital.



Comparison 2. Perioperative antibiotics compared with placebo or no antibiotic

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Wound infection	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2 Perioperative antibiotics compared with placebo or no antibiotic, Outcome 1 Wound infection.



APPENDICES

Appendix 1. Search strategy

Cochrane Wounds Specialised Register

1 MESH DESCRIPTOR Surgical Wound Infection EXPLODE ALL AND INREGISTER

2 MESH DESCRIPTOR Surgical Wound Dehiscence EXPLODE ALL AND INREGISTER

3 (surg* near5 infect*) AND INREGISTER

4 (surg* near5 wound*) AND INREGISTER

5 (surg* near5 site*) AND INREGISTER

6 (surg* near5 incision*) AND INREGISTER

7 (surg* near5 dehisc*) AND INREGISTER

8 (wound* near5 dehisc*) AND INREGISTER

9 (wound* near5 infect*) AND INREGISTER

10 (wound* near5 disrupt*) AND INREGISTER

11 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 AND INREGISTER

12 MESH DESCRIPTOR Breast Neoplasms EXPLODE ALL AND INREGISTER

13 ((breast next cancer*) near5 surg*) AND INREGISTER

14 ((breast next neoplasm*) near5 surg*) AND INREGISTER

15 ((breast next carcinoma*) near5 surg*) AND INREGISTER

16 MESH DESCRIPTOR Mastectomy EXPLODE ALL AND INREGISTER

17 MESH DESCRIPTOR Mammaplasty EXPLODE ALL AND INREGISTER

18 mastectom* AND INREGISTER

19 mammaplasty AND INREGISTER

20 MESH DESCRIPTOR Breast EXPLODE ALL WITH QUALIFIER SU AND INREGISTER

21 #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 AND INREGISTER

22 MESH DESCRIPTOR Anti-Bacterial Agents EXPLODE ALL AND INREGISTER

23 (antibiotic* or clindamycin or cefuroxime or cefuroxim or ceftazidime or ofloxacin or levofloxacin or azithromycin or sulbactam or ampicillin or mezlocillin or oxacillin or vancomycin or tobramycin or ciprofloxacin or clarithromycin or gentamycin) AND INREGISTER

24 #22 OR #23 AND INREGISTER

25 #11 AND #21 AND #24 AND INREGISTER

The Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies (CRS-Web)

1 MESH DESCRIPTOR Surgical Wound Infection EXPLODE ALL AND CENTRAL:TARGET

2 MESH DESCRIPTOR Surgical Wound Dehiscence EXPLODE ALL AND CENTRAL:TARGET

3 (surg* near5 infect*) AND CENTRAL:TARGET

4 (surg* near5 wound*) AND CENTRAL:TARGET

5 (surg* near5 site*) AND CENTRAL:TARGET

6 (surg* near5 incision*) AND CENTRAL:TARGET

7 (surg* near5 dehisc*) AND CENTRAL:TARGET

8 (wound* near5 dehisc*) AND CENTRAL:TARGET

9 (wound* near5 infection*) AND CENTRAL:TARGET

10 (wound* near5 disrupt*) AND CENTRAL:TARGET

11 (wound next complication*) AND CENTRAL:TARGET

12 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11

13 MESH DESCRIPTOR Breast Neoplasms EXPLODE ALL AND CENTRAL:TARGET

14 ((breast next cancer*) near5 surg*) AND CENTRAL:TARGET

15 ((breast next neoplasm*) near5 surg*) AND CENTRAL:TARGET

16 ((breast next carcinoma*) near5 surg*) AND CENTRAL:TARGET

17 MESH DESCRIPTOR Mastectomy EXPLODE ALL AND CENTRAL:TARGET

18 MESH DESCRIPTOR Mammaplasty EXPLODE ALL AND CENTRAL:TARGET

19 mastectom* AND CENTRAL:TARGET

20 mammaplast* AND CENTRAL:TARGET

21 MESH DESCRIPTOR Breast EXPLODE ALL WITH QUALIFIER SU AND CENTRAL:TARGET

22 #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21

23 MESH DESCRIPTOR Anti-Bacterial Agents EXPLODE ALL AND CENTRAL:TARGET

24 (antibiotic* or clindamycin or cefuroxime or cefuroxim or ceftazidime or ofloxacin or levofloxacin or azithromycin or sulbactam or ampicillin or mezlocillin or oxacillin or vancomycin or tobramycin or ciprofloxacin or clarithromycin or gentamycin) AND CENTRAL:TARGET

25 #23 OR #24

26 #25 AND #12 AND #22

Ovid MEDLINE

1 exp Surgical Wound Infection/

2 exp Surgical Wound Dehiscence/

3 (surg* adj5 infect*).tw.

4 (surg* adj5 wound*).tw.

5 (surg* adj5 site*).tw.

6 (surg* adj5 incision*).tw.

7 (surg* adj5 dehisc*).tw.

8 (wound* adj5 dehisc*).tw.

9 (wound* adj5 infect*).tw.

10 (wound* adj5 disrupt*).tw.

11 wound complication*.tw.

12 or/1-11

13 exp Breast Neoplasms/su [Surgery]

14 (breast cancer* adj5 surg*).tw.

15 (breast neoplasm* adj5 surg*).tw.

16 (breast carcinoma* adj5 surg*).tw.

17 exp Mastectomy/

18 exp Mammaplasty/

19 (mastectomy or mammaplasty).tw.

20 exp Breast/su [Surgery]

21 or/13-20

22 exp Anti-Bacterial Agents/

23 (antibiotic* or clindamycin or cefuroxime or cefuroxim or ceftazidime or ofloxacin or levofloxacin or azithromycin or sulbactam or ampicillin or mezlocillin or oxacillin or vancomycin or tobramycin or ciprofloxacin or clarithromycin or gentamycin).tw.

24 22 or 23

25 12 and 21 and 24

26 randomised controlled trial.pt.

27 controlled clinical trial.pt.

28 randomi?ed.ab.

29 placebo.ab.

30 clinical trials as topic.sh.

31 randomly.ab.

32 trial.ti.

33 or/26-32

34 exp animals/ not humans.sh.

35 33 not 34

36 25 and 35

Ovid Embase

1 exp surgical infection/

2 exp wound dehiscence/

3 (surg* adj5 infect*).tw.

4 (surg* adj5 wound*).tw.

5 (surg* adj5 site*).tw.

6 (surg* adj5 incision*).tw.

7 (surg* adj5 dehisc*).tw.

8 (wound* adj5 dehisc*).tw.

9 (wound* adj5 infect*).tw.

10 (wound* adj5 disrupt*).tw.

11 wound complication*.tw.

12 or/1-11

13 exp Breast Tumor/su [Surgery]

14 (breast cancer* adj5 surg*).tw.

15 (breast neoplasm* adj5 surg*).tw.

16 (breast carcinoma* adj5 surg*).tw.

17 exp mastectomy/

18 exp breast reconstruction/

19 (mastectomy or mammaplasty).tw.

20 exp Breast Surgery/

21 or/13-20

22 exp antibiotic agent/

23 (antibiotic* or clindamycin or cefuroxime or cefuroxim or ceftazidime or ofloxacin or levofloxacin or azithromycin or sulbactam or ampicillin or mezlocillin or oxacillin or vancomycin or tobramycin or ciprofloxacin or clarithromycin or gentamycin).tw.

24 or/22-23

25 12 and 21 and 24

26 Randomized controlled trials/

27 Single-Blind Method/

28 Double-Blind Method/

29 Crossover Procedure/

30 (random* or factorial* or crossover* or cross over* or cross-over* or placebo* or assign* or allocat* or volunteer*).ti,ab.

31 (doubl* adj blind*).ti,ab.

32 (singl* adj blind*).ti,ab.

33 or/26-32

34 exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/

35 human/ or human cell/

36 and/34-35

37 34 not 36

38 33 not 37

39 25 and 38

EBSCO CINAHL Plus

S38 S24 AND S37

S37 S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36

S36 TI allocat* random* or AB allocat* random*

S35 MH "Quantitative Studies"

S34 TI placebo* or AB placebo*

S33 MH "Placebos"

S32 TI random* allocat* or AB random* allocat*

S31 MH "Random Assignment"

S30 TI randomi?ed control* trial* or AB randomi?ed control* trial*

S29 AB (singl* or doubl* or trebl* or tripl*) and AB (blind* or mask*)

S28 TI (singl* or doubl* or trebl* or tripl*) and TI (blind* or mask*)

S27 TI clinic* N1 trial* or AB clinic* N1 trial*

S26 PT Clinical trial

S25 MH "Clinical Trials+"

S24 S12 AND S20 AND S23

S23 S21 OR S22

S22 TI (antibiotic* or clindamycin or cefuroxime or cefuroxim or ceftazidime or ofloxacin or levofloxacin or azithromycin orsulbactam or ampicillin or mezlocillin or oxacillin or vancomycin or tobramycin or ciprofloxacin OR clarithromycin OR gentamycin) OR AB (antibiotic* or clindamycin or cefuroxime or cefuroxim or ceftazidime or ofloxacin or levofloxacin or azithromycin orsulbactam or ampicillin or mezlocillin or oxacillin or vancomycin or tobramycin or ciprofloxacin OR clarithromycin OR gentam ycin)

S21 (MH "Antibiotics+")

S20 S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19

S19 (MH "Breast+/SU")

S18 TI (mastectom* OR mammaplasty) OR AB (mastectom* OR mammaplasty)

S17 (MH "Mastectomy+")

S16 TI ((breast carcinoma*) N5 surg*) OR AB ((breast carcinoma*) N5 surg*)

S15 TI ((breast neoplasm*) N5 surg*) OR AB ((breast neoplasm*) N5 surg*)

S14 TI ((breast cancer*) N5 surg*) OR AB ((breast cancer*) N5 surg*)

S13 (MH "Breast Neoplasms+/SU")

S12 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11

S11 TI wound complication* OR AB wound complication*

S10 TI wound* N5 disrupt* OR AB wound* N5 disrupt*

S9 TI wound* N5 infect* OR AB wound* N5 infect*

S8 TI wound* N5 dehisc* OR AB wound* N5 dehisc*

S7 TI surg* N5 dehisc* OR AB surg* N5 dehisc*

S6 TI surg* N5 incision* OR AB surg* N5 incision*

S5 TI surg* N5 site* OR AB surg* N5 site*

S4 TI surg* N5 wound* OR AB surg* N5 wound*

S3 TI surg* N5 infect* OR AB surg* N5 infect*

S2 (MH "Surgical Wound Dehiscence")

S1 (MH "Surgical Wound Infection")

US National Institutes of Health Ongoing Trials Register (ClinicalTrials.gov)

antibiotic* OR clindamycin OR cefuroxime OR cefuroxim OR ceftazidime OR ofloxacin OR levofloxacin OR azithromycin OR sulbactam OR ampicillin OR mezlocillin OR oxacillin OR vancomycin OR tobramycin OR ciprofloxacin OR clarithromycin OR gentamycin | Breast Cancer

antibiotic* OR clindamycin OR cefuroxime OR cefuroxim OR ceftazidime OR ofloxacin OR levofloxacin OR azithromycin OR sulbactam OR ampicillin OR mezlocillin OR oxacillin OR vancomycin OR tobramycin OR ciprofloxacin OR clarithromycin OR gentamycin | Breast Neoplasms

antibiotic* OR clindamycin OR cefuroxime OR cefuroxim OR ceftazidime OR ofloxacin OR levofloxacin OR azithromycin OR sulbactam OR ampicillin OR mezlocillin OR oxacillin OR vancomycin OR tobramycin OR ciprofloxacin OR clarithromycin OR gentamycin | Breast Carcinoma in Situ

antibiotic* OR clindamycin OR cefuroxime OR cefuroxim OR ceftazidime OR ofloxacin OR levofloxacin OR azithromycin OR sulbactam OR ampicillin OR mezlocillin OR oxacillin OR vancomycin OR tobramycin OR ciprofloxacin OR clarithromycin OR gentamycin | Breast Adenocarcinoma

antibiotic* OR clindamycin OR cefuroxime OR cefuroxim OR ceftazidime OR ofloxacin OR levofloxacin OR azithromycin OR sulbactam OR ampicillin OR mezlocillin OR oxacillin OR vancomycin OR tobramycin OR ciprofloxacin OR clarithromycin OR gentamycin | mastectomy

antibiotic* OR clindamycin OR cefuroxime OR cefuroxim OR ceftazidime OR ofloxacin OR levofloxacin OR azithromycin OR sulbactam OR ampicillin OR mezlocillin OR oxacillin OR vancomycin OR tobramycin OR ciprofloxacin OR clarithromycin OR gentamycin | mammaplasty

antibiotic* OR clindamycin OR cefuroxime OR cefuroxim OR ceftazidime OR ofloxacin OR levofloxacin OR azithromycin OR sulbactam OR ampicillin OR mezlocillin OR oxacillin OR vancomycin OR tobramycin OR ciprofloxacin OR clarithromycin OR gentamycin | breast AND surgery

World Health Organization International Clinical Trials Registry Platform

breast AND cancer [Title] AND antibiotic* OR clindamycin OR cefuroxime OR cefuroxim OR ceftazidime OR ofloxacin OR levofloxacin OR azithromycin OR sulbactam OR ampicillin OR mezlocillin OR oxacillin OR vancomycin OR tobramycin OR ciprofloxacin OR clarithromycin OR gentamycin [Interventions]

breast AND cancer [Condition] AND antibiotic* OR clindamycin OR cefuroxime OR cefuroxim OR ceftazidime OR ofloxacin OR levofloxacin OR azithromycin OR sulbactam OR ampicillin OR mezlocillin OR oxacillin OR vancomycin OR tobramycin OR ciprofloxacin OR clarithromycin OR gentamycin [Interventions]

breast AND neoplasm* [Title] AND antibiotic* OR clindamycin OR cefuroxime OR cefuroxim OR ceftazidime OR ofloxacin OR levofloxacin OR azithromycin OR sulbactam OR ampicillin OR mezlocillin OR oxacillin OR vancomycin OR tobramycin OR ciprofloxacin OR clarithromycin OR gentamycin [Interventions]

breast AND neoplasm* [Condition] AND antibiotic* OR clindamycin OR cefuroxime OR cefuroxim OR ceftazidime OR ofloxacin OR levofloxacin OR azithromycin OR sulbactam OR ampicillin OR mezlocillin OR oxacillin OR vancomycin OR tobramycin OR ciprofloxacin OR clarithromycin OR gentamycin [Interventions]

mastectomy OR mammaplasty [Title] AND antibiotic* OR clindamycin OR cefuroxime OR cefuroxim OR ceftazidime OR ofloxacin OR levofloxacin OR azithromycin OR sulbactam OR ampicillin OR mezlocillin OR oxacillin OR vancomycin OR tobramycin OR ciprofloxacin OR clarithromycin OR gentamycin [Interventions]

mastectomy OR mammaplasty [Condition] AND antibiotic* OR clindamycin OR cefuroxime OR cefuroxim OR ceftazidime OR ofloxacin OR levofloxacin OR azithromycin OR sulbactam OR ampicillin OR mezlocillin OR oxacillin OR vancomycin OR tobramycin OR ciprofloxacin OR clarithromycin OR gentamycin [Interventions]

breast AND surgery [Title] AND antibiotic* OR clindamycin OR cefuroxime OR cefuroxim OR ceftazidime OR ofloxacin OR levofloxacin OR azithromycin OR sulbactam OR ampicillin OR mezlocillin OR oxacillin OR vancomycin OR tobramycin OR ciprofloxacin OR clarithromycin OR gentamycin [Interventions]

breast AND surgery [Condition] AND antibiotic* OR clindamycin OR cefuroxime OR cefuroxim OR ceftazidime OR ofloxacin OR levofloxacin OR azithromycin OR sulbactam OR ampicillin OR mezlocillin OR oxacillin OR vancomycin OR tobramycin OR ciprofloxacin OR clarithromycin OR gentamycin [Interventions]

Appendix 2. Cochrane tool for assessing risk of bias

1. Was the allocation sequence randomly generated?

Low risk of bias

The investigators describe a random component in the sequence generation process such as: referring to a random number table; using a computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots.

High risk of bias

The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example: sequence generated by odd or even date of birth; sequence generated by some rule based on date (or day) of admission; sequence generated by some rule based on hospital or clinic record number.

Unclear

Insufficient information about the sequence generation process provided to permit a judgement of low or high risk of bias.

2. Was the treatment allocation adequately concealed?

Low risk of bias

Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: central allocation (including telephone, web-based and pharmacy-controlled randomisation); sequentially-numbered drug containers of identical appearance; sequentially-numbered, opaque, sealed envelopes.

High risk of bias

Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: use of an open random allocation schedule (e.g. a list of random numbers); assignment envelopes without appropriate safeguards (e.g. envelopes were unsealed, non-opaque, or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.

Unclear

Insufficient information provided to permit a judgement of low or high risk of bias. This is usually the case if the method of concealment is not described, or not described in sufficient detail to allow a definite judgement, for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.

3. Blinding - was knowledge of the allocated interventions adequately prevented during the study?

Low risk of bias

Any one of the following:

- No blinding, but the review authors judge that the outcome and the outcome measurement are not likely to be influenced by lack of blinding.
- Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
- Either participants or some key study personnel were not blinded, but outcome assessment was blinded and the non-blinding of others unlikely to introduce bias.

High risk of bias

Any one of the following.

- No blinding or incomplete blinding, and the outcome or outcome measurement is likely to be influenced by lack of blinding.
- Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken.
- Either participants or some key study personnel were not blinded, and the non-blinding of others likely to introduce bias.

Unclear

Either of the following.

- Insufficient information to permit judgement of low or high risk of bias.
- The study did not address this outcome.

4. Were incomplete outcome data adequately addressed?

Low risk of bias

Any one of the following.

- No missing outcome data.
- Reasons for missing outcome data are unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias).
- Missing outcome data are balanced in numbers across intervention groups, with similar reasons for missing data across groups.
- For dichotomous outcome data, the proportion of missing outcomes compared with the observed event risk is not enough to have a clinically relevant impact on the intervention effect estimate.
- For continuous outcome data, a plausible effect size (difference in means or standardised difference in means) among missing outcomes is not enough to have a clinically relevant impact on the observed effect size.
- Missing data have been imputed using appropriate methods.

High risk of bias

Any one of the following.

- Reason for missing outcome data are likely to be related to the true outcome, with either an imbalance in numbers or reasons for missing data across intervention groups.
- For dichotomous outcome data, the proportion of missing outcomes compared with the observed event risk is enough to induce clinically relevant bias in the intervention effect estimate.
- For continuous outcome data, a plausible effect size (difference in means or standardised difference in means) among missing outcomes is enough to induce a clinically relevant bias in the observed effect size.
- 'As-treated' analysis done with a substantial departure of the intervention received from that assigned at randomisation.

- Potentially inappropriate application of simple imputation.

Unclear

Either of the following.

- Insufficient reporting of attrition/exclusions to permit a judgement of low or high risk of bias (e.g. number randomised not stated, no reasons for missing data provided).
- The study did not address this outcome.

5. Are reports of the study free of suggestion of selective outcome reporting?

Low risk of bias

Either of the following.

- The study protocol is available and all of the study's prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the prespecified way.
- The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were prespecified (convincing text of this nature may be uncommon).

High risk of bias

Any one of the following.

- Not all of the study's prespecified primary outcomes have been reported.
- One or more primary outcomes is/are reported using measurements, analysis methods, or subsets of the data (e.g. subscales) that were not prespecified.
- One or more reported primary outcomes was/were not prespecified (unless clear justification for their reporting is provided, such as an unexpected adverse effect).
- One or more outcomes of interest in the review is/are reported incompletely so that they cannot be entered in a meta-analysis.
- The study report fails to include results for a key outcome that would be expected to have been reported for such a study.

Unclear

Insufficient information provided to permit a judgement of low or high risk of bias. It is likely that the majority of studies will fall into this category.

6. Other sources of potential bias

Low risk of bias

The study appears to be free of other sources of bias.

High risk of bias

There is at least one important risk of bias. For example, the study:

- had a potential source of bias related to the specific study design used; or
- has been claimed to have been fraudulent; or
- had some other problem.

Unclear

There may be a risk of bias, but there is either:

- insufficient information to assess whether an important risk of bias exists; or
- insufficient rationale or evidence that an identified problem will introduce bias.

WHAT'S NEW

Date	Event	Description
13 June 2019	New citation required but conclusions have not changed	Updated. Conclusions not changed.

Date	Event	Description
17 August 2018	New search has been performed	New search, no new studies included and four studies newly excluded (Lewin 2015; Phillips 2016; Ruiz-Tovar 2013; Yang 2017). GRADE assessment of evidence added to the review.
17 August 2018	New search has been performed	Additional review author added, text updated.

HISTORY

Protocol first published: Issue 2, 2005
Review first published: Issue 2, 2006

Date	Event	Description
4 March 2014	New citation required but conclusions have not changed	Third update, conclusions remain unchanged.
4 March 2013	New search has been performed	New search, two further studies included (Cabaluna 2012; Gulluoglu 2013) and five studies excluded.
23 September 2011	New citation required but conclusions have not changed	New authors added to the review
31 August 2011	New search has been performed	Second update, new searches, two studies added (Paajanen 2009; Yetim 2010), two studies excluded (Esposito 2006; Sanguinetti 2009).
11 August 2009	Amended	Contact details updated.
24 October 2008	New search has been performed	One new trial added. Conclusions unchanged.
28 July 2008	Amended	Converted to new review format.
18 December 2005	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Michael Gallagher: designed and coordinated this review update; screened records for eligibility; undertook GRADE assessment of the quality of the evidence; updated the review text; approved the final review update prior to publication and is guarantor of the review update.

Daniel Jones: contributed to the second and took the lead for the third update of this review. For this update he screened records for eligibility, undertook GRADE assessment of the quality of the evidence; updated the review text and approved the final review update prior to publication.

Sophie Bell-Syer: contributed to the second, third and fourth update of this review. For this update she screened records for eligibility; updated the review text and approved the final review update prior to publication.

Contributions of editorial base

Gill Norman (Editor): edited the updated review, advised on methodology, interpretation and review content; approved this review update prior to submission.

Nicky Cullum (Coordinating Editor): edited the previous versions of the review, advised on methodology, interpretation and review content; approved the previous versions of the review prior to submission.

Gill Rizzello: coordinated the editorial process for this update; advised on interpretation and content; edited this review update.

Ruth Foxlee (Information Specialist) designed the search strategy. Naomi Shaw and Sophie Bishop (Information Specialists) ran the searches and edited the search methods sections for this update.

Ursula Gonthier and Tom Patterson (Editorial Assistants): edited the Plain Language Summary and references sections of this update.

DECLARATIONS OF INTEREST

Michael Gallagher: none known.

Daniel Jones: none known.

Sophie Bell-Syer: none known.

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Internal sources

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- Department of Health Sciences, University of York, York, UK.

External sources

- National Institute for Health Research (NIHR), UK.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In this fourth update we undertook a GRADE assessment of the evidence to reflect current Cochrane Review methodology. Additionally, we incorporated a new search of trial registries as per Cochrane editorial guidance. In the fourth update of the review we additionally carried out a sensitivity analysis to assess the effects of excluding data from one study (Gulluoglu 2013) as this study had one or more domains with high risk of bias. This sensitivity analysis was not prespecified in the protocol for this review.

In the third update of this review we carried out a sensitivity analysis to assess the effects of excluding the data from one study (Chow 2000), as this study had short follow-up, only compared antibiotics with no antibiotic and reported inflammation rather than infection as its primary outcome. This sensitivity analysis was not prespecified in the protocol for this review. We had planned subgroup analyses evaluating breast reconstruction patients; however, there were not adequate data available to proceed.

INDEX TERMS

Medical Subject Headings (MeSH)

*Antibiotic Prophylaxis; Breast Neoplasms [*surgery]; Mastectomy; Preoperative Care [methods]; Randomized Controlled Trials as Topic; Surgical Wound Infection [*prevention & control]; Wound Healing

MeSH check words

Female; Humans