Topical antibiotics for preventing surgical site infection in wounds healing by primary intention (Protocol)

Heal CF, van Driel ML, Lepper PD, Banks JL

This is a reprint of a Cochrane protocol, prepared and maintained by The Cochrane Collaboration and published in The Cochrane Library 2014, Issue 12

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Topical antibiotics for preventing surgical site infection in wounds healing by primary intention (Protocol)

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Topical antibiotics for preventing surgical site infection in wounds healing by primary intention

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Editorial group: Cochrane Wounds Group.

Citation: Heal CF, van Driel ML, Lepper PD, Banks JL. Topical antibiotics for preventing surgical site infection in wounds healing by primary intention. Cochrane Database of Systematic Reviews 2014, Issue 12. Art. No.: CD011426. DOI: 10.1002/14651858.CD011426.

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To determine if the application of topical antibiotics to wounds healing by primary intention reduces the incidence of surgical site infection.

BACKGROUND

Description of the condition

Many surgical procedures are conducted each year. The majority of these procedures result in wounds that heal by primary intention, which means that the wound edges are approximated using sutures, staples, clips or glue. In wounds healing by secondary intention, the edges are not approximated and the wound heals by granulation, re-epithelialisation and contraction. Most wounds heal without complications but surgical site infections can occur after surgery in the site where the surgery took place. Most wound infections are caused by contamination during surgery with the patient’s own micro-organisms (Kulayalat 2007). They may be superficial and self-limiting, involving the skin only, or they may be deeper and life-threatening. Surgical site infection is classified by the Centers for Disease Control (CDC) as superficial incisional, deep incisional and organ/space infections (CDC 2014; Mangram 1999).

Surgical site infections account for up to 20 per cent of all of healthcare-associated infections (Magill 2014). At least five per cent of patients who have a surgical procedure will go on to develop a surgical site infection, highlighting the importance of good prevention, detection and management (NICE 2008). Superficial surgical site infections can delay healing, impair cosmetic outcome and potentially cause other morbidity, such as deeper infections, as well as potentially increasing costs, and the consumption of healthcare resources (Bratzler 2004).

In order to understand surgical site infection, it is first important to understand the classification of surgical wounds. Surgical wounds are traditionally classified into different categories, and infection rates vary by category. This classification is important in order to predict postoperative infection rates and thus aid the decision to prescribe postoperative antibiotics, whether oral or topical (Table 1).

- Clean (class 1): Noninfective operative wounds in which no
inflammation is encountered, with no involvement of respiratory, alimentary, genitourinary tract and oropharyngeal cavity. Additionally, these wounds must be the result of elective procedures, closed by primary intention and drained with closed drainage system if required.

- Clean/contaminated (class 2): Operative wounds in which either the respiratory, alimentary, or genitourinary tract is entered under controlled conditions and with only minor contamination. This category specifically includes wounds as a result of operations involving the biliary tract, appendix, and oropharynx, provided no evidence of infection or a major break in sterile technique is encountered.

- Contaminated (class 3): Fresh, accidental wounds, resulting from operations with major breaks in sterile technique or gross spillage from the gastrointestinal tract, and incisions in which acute, nonpurulent inflammation is encountered. This category includes traumatic lacerations.

- Dirty (class 4): Old traumatic wounds with retained devitalised tissue and those that involve existing clinical infection or perforated viscera. Organisms causing postoperative infection are likely to be present in the operative field before the operation.

In a general surgical setting the acceptable rate of infection following clean surgery (class 1) is less than 5% (Cruse 1980; Culver 1991; Mangram 1999). In contrast, clean contaminated wounds (class 2) have a risk of infection of less than 10%. Therefore, in a general surgical setting, oral antibiotic prophylaxis of surgical wounds is usually considered optional for clean procedures, and reserved for certain at risk patients or high risk procedures (Brazier 2004). If guidelines for prophylaxis after general surgery are extrapolated to a dermatological surgery setting, then most dermatological procedures, which are considered to be class 1 clean surgery, should not require prophylaxis, and most guidelines reflect this (Maragh 2005; Messingham 2005; Wright 2008). However, as in general surgery, even within cohorts with a low overall risk of infection, some procedures may be at higher risk and infection rates may be greater than 5% in these high risk groups. Although limited guidelines exist for the use of oral antibiotics as infection prophylaxis, there are no guidelines for the use of topical antibiotics after general and dermatological surgery.

There is no universal agreement on the definition of wound infection. A systematic review identified 41 different definitions, and 13 grading scales for surgical site infections, the majority of which had not been validated (Bruce 2001). The most widely accepted description for dermatologic surgical site infection, however, is based on the 1992 US CDC classification, in which infection must occur within 30 days of surgery and involve skin or deep tissue at the incision site (Mangram 1999).

In addition, one of the following must apply:
1. purulent discharge from the incisional wound;
2. organisms are isolated on culture of aseptically obtained wound fluid or tissue;
3. one or more of the following is present: pain, tenderness, localised swelling, redness, heat, or the surgeon has deliberately re-opened wound (unless culture of the incision is negative);
4. the treating doctor diagnoses a superficial incisional surgical site infection. Stitch abscesses are not defined as infection.

Although this definition has limitations, it is the most widely implemented standard definition of wound infection, and is the closest to a gold standard available. Even when using guidelines, the diagnosis of infection is still subjective and there may be inter- and intra-observer variation.

**Description of the intervention**

The most common method of application of topical antibiotic is in the form of an ointment. Other possible delivery methods include cream, lotion, solution, gel, tincture, foam, paste, powder, and impregnated dressings. An ointment base classically contains 80% oil and 20% water, and therefore is more occlusive and will drive the medication into the skin more rapidly than a solution or cream base; thus ointments are an optimal delivery method for topical antibiotics. The only data available on the frequency of topical antibiotic use on wounds is a survey of plastic surgeons in the UK which revealed that 66% used chloramphenicol eye ointment in their practice, mainly as prophylaxis against infection (Erel 1999). Other uses for antibiotic ointment include the treatment of secondarily infected wounds (Leyden 1987), otitis externa, treatment of secondarily infected eczema and the treatment of impetigo (AEG 2010). Antibiotic ointments may also have a role in accelerating wound healing in both acute and chronic situations (Berger 2000; Eaglstein 1980; Geronemus 1979). Adverse effects may include allergic contact dermatitis (Blondeel 1978; Leyden 1979; Marks 1998), anaphylaxis (Saryan 1998), and the theoretical possibility of antibiotic resistance (Bradley 1995; Fukuda 2002; Miller 1996). There are several different types of antibiotic ointments used in clinical practice, and the preferred choice varies per country (Table 2). The most frequently used are Chloromycetin, Neosporin and Bactroban. Chloromycetin ointment consists of 10 mg/g of chloramphenicol, in plastibase 30 W and liquid paraffin (Pfizer 2014). Neosporin ointment is also known as triple antibiotic ointment in the USA. Each gram of Neosporin ointment contains polymixin B sulfate 5000 units, neomycin sulfate 5 mg and bacitracin zinc 400 units in a paraffin ointment base. Bactroban ointment contains mupirocin, a naturally occurring antibiotic. Many of these topical antibiotic agents contain antibiotics that are not recommended for systemic use due to serious adverse effects. The risk of serious effects is considered low with topical use, thus they are safe for use in this form (Kasten 1999).

Neosporin ointment has been available over-the-counter in the USA since the 1970s, while it has been confined to a prescription medication in Australia. It ceased to be available in Australia in October 2006, because of non availability of an ingredient.
How the intervention might work

The role of topical antibiotics is to reduce the microbial contaminant exposure following the surgical procedure. A surgeon may choose to use a topical antibiotic on a wound by considering the likelihood of infection and weighing up the risks and benefits of treatment. There is a lack of evidence in the literature regarding the efficacy of antibiotic ointment in preventing wound infection. Topical antibiotics have a number of mechanisms of action. Chloramphenicol is a bacteriostatic broad spectrum antibiotic that exerts an effect by inhibiting protein synthesis of the bacteria and interfering with transfer of activated amino acids to ribosomes. Neomycin has moderate gram-negative action through inhibition of protein synthesis. Mupirocin is active against gram-positive aerobic bacteria by inhibiting bacterial protein synthesis (HCN 2014). Antibiotics differ from antiseptics as they selectively target specific organisms, whereas antiseptics non selectively destroy or inhibit the growth of organisms (McDonnell 1999).

Why it is important to do this review

The question of whether topical antibiotics are useful in the prevention of infections in wounds healing by primary intention is particularly relevant in primary care. Rationalising the use of antibiotics is important to minimise the impact on antibiotic resistance in the community. Despite the theoretical risk of antibiotic resistance, only mupirocin has been shown to contribute to an emerging resistance pattern when used in vitro (Bradley 1995; Miller 1996). The evidence for use of topical antibiotics is conflicting and therefore a systematic review of trials will be important to guide clinical practice. In some countries, such as the USA, topical antibiotics are available over-the-counter, whereas in others they are only available when prescribed by a doctor. The efficacy of this treatment is therefore important to consumers as well as health practitioners. Better information on its efficacy could assist in rationalising use and contribute to controlling development of antibiotic resistance in the community.

OBJECTIVES

To determine if the application of topical antibiotics to wounds healing by primary intention reduces the incidence of surgical site infection.

METHODS

Criteria for considering studies for this review

Types of studies

We will include trials reported as randomised controlled trials (RCTs), or quasi-RCTs with a parallel group design. We will include trials published as abstracts if sufficient data are available. We will also include unpublished RCTs if sufficient data are available. We will accept trials with paired designs (one wound treated with topical antibiotic, and the other treated without topical antibiotic, at different sites in the same patient).

Types of participants

We will include:

- people of any age, gender or country of origin who have undergone surgical procedures where healing of the surgical wound was planned by primary intention, i.e. where wounds have edges approximated with sutures, staples, clips or glue;
- any surgical setting, including dermatology outpatients or inpatients, emergency department, general surgery and primary care;
- all wound classes; and
- mixed populations (if the data allows the results from the relevant population to be extracted).

We will exclude:

- studies including people with wounds that are already infected (secondarily infected wounds), i.e. we will not include antibiotics for treating rather than preventing wound infection;
- wounds healing by secondary intention; and
- instances where there has been antibiotic irrigation or washout of wounds, subcutaneous infiltration of the antibiotic, or any topical treatment applied prior to closure by primary intention.

Types of interventions

The intervention will be topical antibiotics. This will include ointment, cream, lotion, solution, gel, tincture, foam, paste, powder, and impregnated dressings. We will not include silver or antiseptics in our definition of topical antibiotics. The topical antibiotic must be applied after the wound is closed by primary intention, therefore we will not include antibiotic irrigation or washouts, subcutaneous infiltration of the antibiotic or any topical treatment applied prior to closure by primary intention. We will not include antibiotic-coated sutures. We will exclude patients on concomitant systemic antibiotics. We will include single application post-operatively, or multiple applications in the postoperative period. We will record dosage of antibiotic if this information is available. The topical antibiotic may be applied with or without a dressing. The comparison group will be placebo - which might contain the vehicle of the topical antibiotic - oral antibiotic, alternative topical antibiotic, topical antiseptic or no treatment. We will not consider the comparator groups to be homogenous for the purposes of data synthesis.
Types of outcome measures
We will not consider outcomes in eligibility criteria. We will consider secondary outcomes with and without validated scales.

Primary outcomes
- Superficial surgical site infection, as defined by the CDC definition of surgical site infection. In this definition infection must occur within 30 days of the procedure, therefore this time point will be used as a cut-off for this primary outcome measure. We will also accept the trial authors’ definitions of infection.
- Proportion of patients with any adverse effect within 30 days of the procedure. Adverse effects will be allergic contact dermatitis, anaphylaxis, or infections with patterns of antibiotic resistance.

Secondary outcomes
- Wound healing: time-to-healing or proportion of wounds healed at the end of the trial.
- Patient satisfaction measured within six months of the procedure.
- Health-related quality of life at 30 days and three months.
- Financial cost for each infection prevented (number needed to treat) This calculation will be made by using the NNT to calculate the financial cost of prescribing topical prophylactic antibiotics to a number of patients in order to prevent a single wound infection.

Search methods for identification of studies

Electronic searches
We will search the following electronic databases to identify reports of relevant RCTs:
- Cochrane Wounds Group Specialised Register;
- The Cochrane Central Registrar of controlled trials (CENTRAL) (The Cochrane Library, latest Issue);
- OvidMEDLINE (1946 to present);
- OvidMEDLINE (In-Process & Other Non-Indexed Citations, present);
- Ovid EMBASE (1974 to present);
- EBSCO CINAHL (1982 to present).

We will use the following provisional search strategy in the Cochrane Central Register of Controlled Trials (CENTRAL):
#1 MeSH descriptor: [Antibiotic Prophylaxis] this term only
#2 MeSH descriptor: [Anti-Bacterial Agents] explode all trees
#3 MeSH descriptor: [Ointments] this term only
#4 MeSH descriptor: [Skin Cream] this term only
#5 MeSH descriptor: [Administration, Topical] explode all trees

#6 #1 or #2
#7 #5 and #6
#8 (topical near/5 antibiotic*):ti,ab,kw
#9 (mupirocin or bactroban or bacitracin or "polymixin B" or neomycin or erythromycin or chloramphenicol or chloromycetin or chloroguanidinium or neosporin):ti,ab,kw
#10 (antibiotic* near/5 (foam* or tincature* or gel or gels or solution* or lotion* or cream*)):ti,ab,kw
#11 (antibiotic* near/5 (powder* or liquid* or drop* or spray* or paste* or ointment*)):ti,ab,kw
#12 ((antibiotic* or impregnat*) near/5 dressing*):ti,ab,kw
#13 #3 or #4 or #7 or #8 or #9 or #10 or #11 or #12
#14 MeSH descriptor: [Surgical Wound Infection] explode all trees
#15 MeSH descriptor: [Surgical Wound Dehiscence] this term only
#16 (surg* near/5 infect*):ti,ab,kw
#17 (surg* near/5 wound*):ti,ab,kw
#18 (surg* near/5 site*):ti,ab,kw
#19 (surg* near/5 incision*):ti,ab,kw
#20 (surg* near/5 dehisc*):ti,ab,kw
#21 (wound* near/5 dehisc*):ti,ab,kw
#22 (wound* near/5 infect*):ti,ab,kw
#23 (wound* near/5 disrupt*):ti,ab,kw
#24 wound next complication*:ti,ab,kw
#25 #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24
#26 #13 and #25

We will adapt this strategy to search Ovid MEDLINE Appendix 1, Ovid EMBASE Appendix 2 and EBSCO CINAHL Appendix 3.
We will combine 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 will combine the EMBASE search with the Ovid EMBASE filter developed by the UK Cochrane Centre (Lefebvre 2011). We will combine the CINAHL searches with the trial filters developed by the Scottish Intercollegiate Guidelines Network SIGN 2011). We will not restrict studies with respect to language, date of publication or study setting.

We will search the following clinical trials registries:
- ClinicalTrials.gov (http://www.clinicaltrials.gov/);
- WHO International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/Default.aspx);
- EU Clinical Trials Register (https://www.clinicaltrialregister.eu/).

Searching other resources
We will search the bibliographies of all retrieved and relevant publications identified by these strategies for additional eligible trials.
While we will not perform handsearches for this review, they are conducted by the Cochrane Wounds Group in order to inform the
Wounds Group Specialised Register, which we will search. We will contact manufacturers and pharmaceutical companies regarding studies for inclusion.

Data collection and analysis

We will follow guidelines given by the Cochrane Handbook for Systematic Reviews of Interventions (Deeks 2011) and the Cochrane Wounds Group.

Selection of studies

Two review authors (CH and PL) will independently screen the studies identified by the literature search. These review authors will analyse the titles and abstracts of all citations found through the search strategy described above. They will obtain a copy of the full article for each citation reporting a potentially eligible trial. Independently, the two review authors will apply the eligibility criteria; any discrepancies will be resolved by consensus discussion with the third review author (MVD). Where necessary and possible, additional information will be sought from the principal investigator of the trial concerned. We will justify, in the final report, any exclusion of a potentially eligible trial from the review.

Data extraction and management

Two review authors (CH and PL) will independently extract data. We will summarise data using a pre designed data extraction form. We will pilot the data extraction tool. Data from trials published in duplicate will be included only once. One review author will extract the data (CH) and a second (PL) will check the data for accuracy. Any discrepancy will be resolved by discussion or in consultation with a third review author (MVD).

We will extract the following data:

- Source (study ID);
- Eligibility (confirm eligibility for review);
- Characteristics of the trial (date of study, setting, location of care, country, source of funding);
- Methods (study design, sequence generation, allocation sequence concealment, blinding, other concerns about bias);
- Participants (number, diagnostic criteria, age, sex, co morbidities, class of wound);
- Intervention (type of topical antibiotic, delivery vehicle, dose, frequency of application, co interventions);
- Comparative intervention (placebo ointment, alternative antibiotic ointment, no treatment control);
- For each outcome of interest: outcome definition, unit of measurement, for scales upper and lower limit;
- Primary outcomes (definition of surgical site infection, unit of measurement);
- Secondary outcomes (outcome definition and unit of measurement);
- Results (number of participants allocated to each intervention group, sample size, missing participants, summary data - e.g. 2x2 data for dichotomous data, means and standard deviations for continuous data, estimate of effect with confidence intervals and P value, subgroup analysis);
- Key conclusions of study authors.

Assessment of risk of bias in included studies

Two review authors (CH and PL) will independently assess each included study. Assessment will be undertaken using the Cochrane Collaboration’s tool for assessing risk of bias (Higgins 2011). The ‘Risk of bias’ tool considers the domains of:

- sequence generation;
- allocation concealment;
- blinding of participants and personnel;
- blinding of outcome assessment;
- incomplete outcome data;
- freedom from selective reporting; and
- other potential bias.

We acknowledge that there is no accepted definition of what constitutes a trial at high risk of bias, therefore we will set a threshold so that trials assessed as at risk for any one of the following essential elements of risk of bias - random number generation, allocation concealment and assessor blinding - will be considered to be at high risk of bias. Also, if missing outcome data are unequally distributed over the intervention arms we will discuss this, consider the study at high risk of bias, and perform intention to treat analysis.

We will complete a ‘Risk of bias’ table for each eligible study. We will combine these data into a ‘Risk of bias’ summary figure.

Measures of treatment effect

The primary outcome is dichotomous (wound infection or no wound infection) and will be measured using risk ratio as the effect measure, with 95% confidence interval. We will use mean difference with standard deviation and 95% confidence interval to analyse continuous variables (patient satisfaction) using the same scales. Where different scales are used to assess continuous outcomes, we will use standardised mean difference with standard deviation in the analysis (Deeks 2011). Time-to-healing is a form of time-to-event data, more correctly analysed using survival methods which can account for censoring (i.e. just for the time that people were observed, so it takes account of when they dropped out); it is inappropriate to report and analyse time-to-wound healing as if it were a continuous variable unless everyone healed and there was no loss to follow-up.

Unit of analysis issues
The unit of analysis in trials is most likely to be the patient recruited into the trial. It is possible that cluster randomised trial designs will be encountered, for example randomisation by surgeon, or by operating list, or by general practice surgery or hospital. We will analyse such trials based on allocation, using summary values for each cluster, allowing the clusters to become the individuals and analyse them as such. We will use analysis from the trials that adjust for clustering. If there are trials that do not adjust for clustering, we will attempt to adjust the analysis for correlation. This may be done through a number of methods, ideally based on a direct estimate of the required effect measure as stated in Deeks 2011. We will use the generic inverse variance method in Review Manager 5 (RevMan 2014) to pool data from cluster randomised trials (Deeks 2011).

If there are three arms in a study, where two of the arms are clinically similar for the purposes of the review, we will combine arms to create a single pair-wise comparison. Where we cannot combine arms and we include multiple arms in the same analysis, we will divide the control group(s) between the two arms for the purpose of comparison. In order to avoid unit of analysis error when measurement occurs at multiple time points, we will only pool data from one time point that is closest to the other included studies.

Dealing with missing data

If the results of a RCT have been published, but information on the outcome of interest is not reported, we will attempt, whenever possible, to contact the trial authors for the missing information. If continuous data are not presented as mean and standard deviation, we will attempt, whenever possible, to contact the trial authors for the information in this format. If the data are not available, we will attempt to impute the missing standard deviation by borrowing from similar studies or we will calculate the standard deviation from P values, t values, confidence intervals or standard errors, whichever is available. We will follow the methods described in the Cochrane Handbook for Systematic Reviews of Interventions (Deeks 2011). In the completed review, we will report all efforts made to obtain additional information.

Excluding participants from the analysis after randomisation, or ignoring participants lost to follow-up can, in effect, undo the process of randomisation, and thus potentially introduce bias into the trial. Therefore, where possible, all analyses will be by intention-to-treat (Hollis 1999). If participants were allocated to one intervention (for example, antibiotic ointment), but after randomisation underwent a different intervention (for example, placebo ointment), they will be analysed according to their randomisation allocation.

If the results for dichotomous variables are not reported in some participants, we will base our analysis on both a worst possible outcome (for example, wound infection occurred in all non reported cases), and a best possible outcome (for example, wound infection did not occur in any non reported cases). Where participants are excluded from analysis without good cause we will conduct a sensitivity analysis to determine any effect of attrition bias.

Assessment of heterogeneity

We will explore the presence or absence of heterogeneity using visual inspection of forest plots. If there is no apparent face value heterogeneity (e.g. clearly different populations or types of wounds, different category of control group) we will perform a Chi$^2$ test with significance set at P value 0.10. We will also calculate the I$^2$ statistic (Deeks 2011). This explores the proportion of variability caused by heterogeneity rather than by chance. Thresholds for the interpretation of the I$^2$ statistic can be misleading. A rough guide to interpretation will be:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity; and
- 75% to 100%: considerable heterogeneity.

When interpreting and exploring the I$^2$ statistic, we will take factors such as clinical and methodological heterogeneity - in particular the placebo treatment used - along with whether the heterogeneity is in the magnitude of effect or in the direction of effect, into account, particularly where ranges overlap (Deeks 2011). We will explore this further in subgroup analyses. If heterogeneity is very high (> 75%), we will not pool these studies; we will explore the impact of heterogeneity on the overall outcome with a sensitivity analysis (see Sensitivity analysis).

Assessment of reporting biases

We will compare the reported outcomes with those stated in the published protocol of the studies, if available, or in the methods section of the published report, and also those listed in clinical trials registries as both primary and secondary outcomes (for example http://www.clinicaltrials.gov/). If sufficient studies are identified (a minimum of 10), we will assess the risk of publication bias by creating a funnel plot using software within Review Manager 5 (RevMan 2014), using visual inspection and statistical tests for asymmetry.

Data synthesis

One review author (CH) will enter quantitative data into Review Manager 5 (RevMan 2014), and a second (PL) will check the data. We will calculate summary estimates of treatment effect (with 95% confidence interval) for each outcome and every comparison. For continuous outcomes, we will present the pooled mean difference with the standard deviation as a measure of the spread. For dichotomous outcomes, we will calculate the risk ratio as the effect measure, with 95% confidence interval. We will also calculate the
absolute risk difference, that will allow us to calculate the number needed to treat. We will meta-analyse the results of clinically homogeneous studies using Review Manager 5 (RevMan 2014). We will conduct meta-analyses using a random-effects model. If insufficient data are available for meta-analyses, we will present a narrative synthesis of the outcome across the included studies. We will present all results in 'Summary of findings' tables, and rate the quality of evidence using the GRADE system (see below) (Schünemann 2011a).

**Subgroup analysis and investigation of heterogeneity**

If there are sufficient trials of adequate size it may be possible to conduct subgroup analyses. We plan to conduct subgroup analyses for:
- class 1 versus class 2 versus class 3 wounds;
- dermatological versus general surgery;
- class of antibiotic used;
- single application versus multiple applications; and
- no treatment control versus placebo ointment control.

We will look at results and heterogeneity within subgroups. If there are only two subgroups we will investigate if the confidence intervals overlap, and we will perform statistical tests of subgroup comparison.

**Sensitivity analysis**

We will perform a sensitivity analysis to assess the impact of heterogeneity on the overall estimate of effect by first pooling all studies, and subsequently removing the outlier studies that seem to be contributing to the statistical heterogeneity. We will also perform sensitivity analysis to assess the impact of risk of bias on the overall effect measure. We will compare the outcomes of these analyses and describe the implications for the conclusion of the review. We plan to remove studies at high risk of bias in order to assess the effect of this on the result.

**Summary of findings tables**

We will present the main results of the review in 'Summary of findings' tables. These tables present key information concerning the quality of the evidence, the magnitude of the effects of the interventions examined, and the sum of the available data for the main outcomes (Schünemann 2011a). The 'Summary of findings' tables also include an overall grading of the evidence related to each of the main outcomes using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach. The GRADE approach defines the quality of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the true quantity of specific interest. The quality of a body of evidence involves consideration of within-trial risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias (Schünemann 2011b).

We plan to present the following outcomes in the 'Summary of findings' tables:
- superficial surgical site infection;
- adverse events;
- time-to-complete wound healing, or proportion of wounds healed during the trial period.

**ACKNOWLEDGEMENTS**

James Cook University College of Medicine and Dentistry. Mr Stephen Anderson, Librarian, James Cook University, Townsville.

Cochrane Wounds Group peer reviewers; Kurinchi Gurusamy, Mark Corbett, Elmer Villanueva, Zubir Ahmed, Roy Buffery and Janet Yarrow.

Copy Editor Clare Dooley.

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Bruce 2001

CDC 2014

Cruse 1980

Calver 1991

Deeks 2011

Eaglstein 1980

Erel 1999

Fukuda 2002

Geronemus 1979

HCN 2014

Higgins 2011

Hollis 1999

Kasten 1999

Kulaylat 2007

Lefebvre 2011

Leyden 1979

Leyden 1987

Magill 2014

Mangram 1999

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Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
Maragh 2005

Marks 1998

McDonnell 1999

Messingham 2005

Miller 1996

NICE 2008

Pfizer 2014

Schünemann 2011a

Schünemann 2011b

SIGN 2011

Wright 2008

* Indicates the major publication for the study

### ADDITIONAL TABLES

#### Table 1. Table 1: Wound classification

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<tr>
<td>Class 1/Clean</td>
<td>Noncontaminated wound</td>
<td>5%</td>
<td>Sterile minor skin excision</td>
</tr>
<tr>
<td>Class 2/Clean Contaminated</td>
<td>Operative wound in respiratory, alimentary, genitourinary tract, minor break in aseptic technique</td>
<td>10%</td>
<td>Biliary tract, appendix, vagina, oropharynx</td>
</tr>
<tr>
<td>Class 3/Contaminated</td>
<td>Open, fresh, accidental wound, acute nonpurulent inflammation, gross spillage from gas-</td>
<td>20% to 30%</td>
<td>Open cardiac massage, gross spillage from gastrointestinal tract</td>
</tr>
</tbody>
</table>
Table 1.  Table 1: Wound classification  

| Class 4/ Dirty-Infected | Purulent inflammation, Gross contamination with foreign bodies, penetrating trauma > 4 hours old, devitalised tissue | 30% to 40% | Old traumatic wound, abscess |

Table 2.  Table 2: Topical antibiotics

<table>
<thead>
<tr>
<th>Ointment</th>
<th>Trade name, availability</th>
<th>Mode of activity</th>
<th>Range of activity</th>
<th>Main use</th>
<th>Side effects/additional considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mupirocin</td>
<td>Bactroban</td>
<td>Inhibitor of bacterial protein synthesis</td>
<td>Gram +ve organisms, especially <em>Staphylococcus aureus</em></td>
<td>Impetigo, elimination of <em>Staphylococcus aureus</em> from anterior nares</td>
<td>Anaphylaxis reported</td>
</tr>
<tr>
<td>Bacitracin</td>
<td>Ingredient of triple antibiotic ointment</td>
<td>Interferes with bacterial cell wall synthesis</td>
<td>Gram +ve organisms</td>
<td>Impetigo, furunculosis, pyodermas</td>
<td>Cross-sensitisation with neomycin</td>
</tr>
<tr>
<td>Polymixin B</td>
<td>Available singly, combined with bacitracin or in triple antibiotic ointment</td>
<td>Disrupts bacterial cell membrane and increases cell permeability</td>
<td>Gram -ve organisms, including <em>Pseudomonas aeruginosa</em>, <em>Enterbacter</em> and <em>Escherichia Coli</em></td>
<td>Bacterial conjunctivitis</td>
<td>Limited spectrum of activity</td>
</tr>
<tr>
<td>Neomycin</td>
<td>Available alone, or as ingredient of triple antibiotic ointment</td>
<td>Interferes with bacterial cell wall synthesis</td>
<td>Aerobic +ve and gram -ve bacilli</td>
<td>Prevention of infection in superficial abrasions, cuts or burns</td>
<td>Allergic contact dermatitis</td>
</tr>
<tr>
<td>Polymixin B, neomycin and bacitracin</td>
<td>Triple antibiotic ointment</td>
<td>Combination of mechanisms</td>
<td>Range of gram +ve and gram -ve organisms</td>
<td>Prevention of infection in superficial abrasions, cuts or burns</td>
<td>Allergic contact dermatitis</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Eryacne</td>
<td>Inhibitor of bacterial protein synthesis</td>
<td>Gram +ve cocci</td>
<td>Acne</td>
<td>Low incidence of sensitisation</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>Chlormycetin or Chlorsig</td>
<td>Disrupts bacterial cell membrane</td>
<td>Wide range of gram +ve and gram -ve organisms</td>
<td>Bacterial conjunctivitis</td>
<td>Aplastic anaemia</td>
</tr>
</tbody>
</table>

Topical antibiotics for preventing surgical site infection in wounds healing by primary intention (Protocol)  
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Appendix 1. MEDLINE search strategy

1 Antibiotic Prophylaxis/
2 exp Anti-Bacterial Agents/
3 Ointments/
4 Skin Cream/
5 exp Administration, Topical/
6 1 or 2
7 5 and 6
8 (topical adj5 antibiotic*).tw.
9 (mupirocin or bactroban or bacitracin or polymixin B or neomycin or erythromycin or chloramphenicol or chloramycetin or chlorsig or neosporin).tw.
10 (antibiotic* adj5 (foam* or tincture* or gel or gels or solution* or lotion* or cream*)).tw.
11 (antibiotic* adj5 (powder* or liquid* or drop* or spray* or paste* or ointment*)).tw.
12 ((antibiotic* or impregnat*) adj5 dressing*).tw.
13 3 or 4 or 7 or 8 or 9 or 10 or 11 or 12
14 Surgical Wound Infection/
15 Surgical Wound Dehiscence/
16 (surg* adj5 infect*).tw.
17 (surg* adj5 wound*).tw.
18 (surg* adj5 site*).tw.
19 (surg* adj5 incision*).tw.
20 (surg* adj5 dehisc*).tw.
21 (wound* adj5 dehisc*).tw.
22 (wound* adj5 infect*).tw.
23 (wound* adj5 disrupt*).tw.
24 wound complication*.tw.
25 or/14-24
26 13 and 25
27 randomized controlled trial.pt.
28 controlled clinical trial.pt.
29 randomi?ed.ab.
30 placebo.ab.
31 clinical trials as topic.sh.
32 randomly.ab.
33 trial.ti.
34 or/27-33
35 exp animals/ not humans.sh.
36 34 not 35
37 26 and 36
Appendix 2. EMBASE search strategy

1 antibiotic prophylaxis/
2 exp antibiotic agent/
3 exp ointment/
4 skin cream/
5 exp topical drug administration/
6 1 or 2
7 5 and 6
8 (topical adj5 antibiotic*).tw.
9 (mupirocin or bactroban or bacitracin or polymixin B or neomycin or erythromycin or chloramphenicol or chloromycetin or chlorsig or neosporin).tw.
10 (antibiotic* adj5 (foam* or tincture* or gel or gels or solution* or lotion* or cream*)).tw.
11 (antibiotic* adj5 (powder* or liquid* or drop* or spray* or paste* or ointment*)).tw.
12 ((antibiotic* or impregnat*) adj5 dressing*).tw.
13 3 or 4 or 7 or 8 or 9 or 10 or 11 or 12
14 surgical infection/
15 wound dehiscence/
16 (surg* adj5 infect*).tw.
17 (surg* adj5 wound*).tw.
18 (surg* adj5 site*).tw.
19 (surg* adj5 incision*).tw.
20 (surg* adj5 dehisc*).tw.
21 (wound* adj5 dehisc*).tw.
22 (wound* adj5 infect*).tw.
23 (wound* adj5 disrupt*).tw.
24 wound complication*.tw.
25 or/14-24
26 13 and 25
27 Randomized controlled trials/
28 Single-Blind Method/
29 Double-Blind Method/
30 Crossover Procedure/
31 (random$ or factorial$ or crossover$ or cross over$ or cross-over$ or placebo$ or assign$ or allocat$ or volunteer$).ti,ab.
32 (doubl$ adj blind$).ti,ab.
33 (sing$ adj blind$).ti,ab.
34 or/27-33
35 exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/
36 human/ or human cell/
37 and/35-36
38 35 not 37
39 34 not 38
40 26 and 39
Appendix 3. CINAHL search strategy

S39 S26 AND S38
S38 S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37
S37 MH "Quantitative Studies"
S36 TI placebo* or AB placebo*
S35 MH "Placebos"
S34 TI random* allocat* or AB random* allocat*
S33 MH "Random Assignment"
S32 TI random?ed control* trial* or AB random?ed control* trial*
S31 AB ( singl* or doubl* or trebl* or tripl*) and AB ( blind* or mask* )
S30 TI ( singl* or doubl* or trebl* or tripl* ) and TI ( blind* or mask* )
S29 TI clinic* N1 trial* or AB clinic* N1 trial*
S28 PT Clinical trial
S27 MH "Clinical Trials+"
S26 S13 AND S25
S25 S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24
S24 TI wound N1 complication* OR AB wound N1 complication*
S23 TI wound* N5 disrupt* OR AB wound* N5 disrupt*
S22 TI wound* N5 infect* OR AB wound* N5 infect*
S21 TI wound* N5 dehisc* OR AB wound* N5 dehisc*
S20 TI surg* N5 dehisc* OR AB surg* N5 dehisc*
S19 TI surg* N5 incision* OR AB surg* N5 incision*
S18 TI surg* N5 site* OR AB surg* N5 site*
S17 TI surg* N5 wound* OR AB surg* N5 wound*
S16 TI surg* N5 infect* OR AB surg* N5 infect*
S15 (MH "Surgical Wound Dehiscence")
S14 (MH "Surgical Wound Infection")
S13 S3 OR S4 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12
S12 TI (antibiotic* or impregnat*) N5 dressing* OR AB (antibiotic* or impregnat*) N5 dressing*
S11 TI (antibiotic* N5 (powder* or liquid* or drop* or spray* or paste* or ointment*)) OR AB (antibiotic* N5 (powder* or liquid* or drop* or spray* or paste* or ointment*))
S10 TI (antibiotic* N5 (foam* or tincture* or gel or gels or solution* or lotion* or cream*)) OR AB (antibiotic* N5 (foam* or tincture* or gel or gels or solution* or lotion* or cream*))
S9 TI (mupirocin or bacitracin or "polymixin B" or neomycin or erythromycin or chloramphenicol or chloramycin or chlorsig or neosporin) OR AB (mupirocin or bacitracin or "polymixin B" or neomycin or erythromycin or chloramphenicol or chloramycin or chlorsig or neosporin)
S8 TI topical N5 antibiotic* OR AB topical N5 antibiotic*
S7 S5 AND S6
S6 S1 OR S2
S5 (MH "Administration, Topical+")
S4 (MH "Creams") OR (MH "Powders")
S3 (MH "Ointments")
S2 (MH "Antibiotics+")
S1 (MH "Antibiotic Prophylaxis")
CONTRIBUTIONS OF AUTHORS

CH conceived the question, developed, co-ordinated and edited the protocol, and is guarantor of the protocol.

PL contributed to the writing and editing of the protocol.

MVD contributed to the writing and editing of the protocol.

JB contributed to the writing and editing of the protocol.

Contributions of editorial base:

Kurinchi Gurusamy, Editor: advised on methodology, interpretation and protocol content. Approved the final protocol prior to submission.

Sally Bell-Syer: coordinated the editorial process. Advised on methodology, interpretation and content. Edited the protocol.

Amanda Briant: designed the search strategy and edited the search methods section.

DECLARATIONS OF INTEREST

Clare Heal - none declared.

Mieke van Driel - none declared.

Phoebe Lepper - none declared.

Jennifer Banks - none declared.

SOURCES OF SUPPORT

Internal sources

- James Cook University College of Medicine and Dentistry, Australia.
- Mr Stephen Anderson, Librarian, James Cook University, Townsville, Australia.

External sources

- The National Institute of Health Research is the sole funder of the Cochrane Wounds Group, UK.