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Nasal decontamination for the prevention of surgical site infection in Staphylococcus aureus carriers (Review)

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[Intervention Review]

Nasal decontamination for the prevention of surgical site infection in *Staphylococcus aureus* carriers

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ABSTRACT

Background

Surgical site infection rates in the month following surgery vary from 1% to 5%. Due to the large number of surgical procedures conducted annually, the costs of these surgical site infections (SSIs) can be considerable in financial and social terms. Nasal decontamination using antibiotics or antiseptics is performed to reduce the risk of SSIs by preventing organisms from the nasal cavity being transferred to the skin where a surgical incision will be made. *Staphylococcus aureus* (*S aureus)* colonises the nasal cavity and skin of carriers and can cause infection in open or unhealed surgical wounds. *S aureus* is the leading nosocomial (hospital-acquired) pathogen in hospitals worldwide. The potential effectiveness of nasal decontamination of *S aureus* is thought to be dependent on both the antibiotic/antiseptic used and the dose of application; however, it is unclear whether nasal decontamination actually reduces postoperative wound infection in *S aureus* carriers.

Objectives

To assess the effects of nasal decontamination on preventing surgical site infections (SSIs) in people who are *S aureus* carriers undergoing surgery.

Search methods

In September 2016 we searched the Cochrane Wounds Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL) (the Cochrane Library), Ovid MEDLINE, Ovid MEDLINE (In-Process & Other Non-Indexed Citations), Ovid Embase, and EBSCO CINAHL Plus. We also searched three clinical trial registries and the references of included studies and relevant systematic reviews. There were no restrictions based on language, date of publication or study setting.

Selection criteria

Randomised controlled trials (RCTs) which enrolled *S aureus* carriers with any type of surgery and assessed the use of nasal decontamination with antiseptic/antibiotic properties were included in the review.

Data collection and analysis

Two review authors independently performed study selection, data extraction, risk of bias assessment and GRADE assessment.

Main results

We located two studies (291 participants) for inclusion in this review. The trials were clinically heterogeneous with differences in duration of follow-up, and nasal decontamination regimens. One study compared mupirocin (2% contained in a base of polyethylene glycol 400 and polyethylene glycol 3350) with a placebo in elective cardiac surgery patients; and one study compared Anerdian (iodine 0.45% to 0.57% (W/V), chlorhexidine acetate 0.09% to 0.11% (W/V)) with no treatment also in cardiac surgery patients. The trials reported limited outcome data on SSI, adverse events and secondary outcomes (e.g. *S aureus* SSI, mortality).

Mupirocin compared with placebo

This study found no clear difference in SSI risk following use of mupirocin compared with placebo (1 trial, 257 participants); risk ratio (RR) 1.60, 95% confidence interval (CI) 0.79 to 3.25 based on 18/130 events in the mupirocin group and 11/127 in the control group; low-certainty evidence (downgraded twice due to imprecision).

Anerdian compared with no treatment

It is uncertain whether there is a difference in SSI risk following treatment with Anerdian compared with no treatment (1 trial, 34 participants); RR 0.89, 95% CI 0.06 to 13.08 based on 1/18 events in the Anerdian group and 1/16 in the control group; very low certainty evidence (downgraded twice due to imprecision and once due to risk of bias).

Authors' conclusions

There is currently limited rigorous RCT evidence available regarding the clinical effectiveness of nasal decontamination in the prevention of SSI. This limitation is specific to the focused question our review addresses, looking at nasal decontamination as a single intervention in participants undergoing surgery who are known *S aureus* carriers. We were only able to identify two studies that met the inclusion criteria for this review and one of these was very small and poorly reported. The potential benefits and harms of using decontamination for the prevention of SSI in this group of people remain uncertain.

PLAIN LANGUAGE SUMMARY

Nasal decontamination (cleaning the nose with anti-bacterial products) for the prevention of surgical site infection in people carrying *S aureus*

Review question

We reviewed the evidence about whether nasal decontamination (cleaning the nose with anti-bacterial products) is effective and safe for preventing surgical site infection (SSI) in people carrying *Staphylococcus aureus* (*S aureus*) bacteria.

Background

If bacteria get into a wound site during surgery, this can result in a wound infection commonly called an SSI. SSIs are one of the most common forms of healthcare-associated infections, with around 1 in 20 surgical patients developing an SSI in hospital. This proportion rises when people go home. SSIs can result in delayed wound healing, increased hospital stays, increased use of antibiotics, unnecessary pain and, in extreme cases, death, so their prevention is a key aim for health services. People who are carrying bacteria such as *S aureus* are especially vulnerable to wound infections. These bacteria can be carried in the nose, and then transferred to a surgical wound. People who are having surgery can have a nasal swab to test for bacteria, and their noses can be cleaned with anti-bacterial products (antibiotics and antiseptics) before the operation. This can help reduce the growth of bacteria. We wanted to find out if this nasal decontamination is effective in reducing SSIs, and whether people had any adverse reactions to this treatment, such as skin irritation.

Study characteristics

In September 2016 we searched for randomised controlled trials (RCTs) involving nasal decontamination for preventing SSI. We included two studies with 291 participants, all adults undergoing cardiac surgery. The anti-bacterial products used for cleaning the nose were mupirocin (antibiotic cream) and Anerdian (disinfectant solution).

Key results

It is unclear whether nasal decontamination makes a difference to the rate of SSI in people carrying *S aureus* bacteria. *S aureus* SSI was reported in only one trial and the results do not allow us to be certain about differences in infection rates. Some participants in the Anerdian study reported side effects such as itching around the nose, but these were not serious. Mortality was low where reported (one death was directly related to *S aureus* infection).

Quality of the evidence

The two studies we found did not have many participants and the results were inconclusive. The Anerdian study report did not provide information about how the trial was conducted and this makes it difficult to be sure if it was at risk of bias. The mupirocin study was of better quality and at low risk of bias; but the small number of participants and limited effects affect the quality of the results. Evidence of the potential benefits and harms of using nasal decontamination for the prevention of SSI is currently of low to very low certainty. Larger, better-reported RCTs are needed to assess the clinical effectiveness of this treatment.

This plain language summary is up to date as of September 2016.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Mupirocin compared with placebo for the prevention of surgical site infection in *Staphylococcus aureus* carriers

Patient or population: *S aureus* carriers undergoing cardiac surgery
Setting: hospital
Intervention: mupirocin
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with mupirocin				
SSI Follow-up: eight weeks	Study population		RR 1.60 (0.79 to 3.25)	257 (1 study)	⊕⊕◯◯ LOW[1]	There is no clear difference in the incidence of SSI in participants treated with mupirocin compared with those treated with placebo
	87 per 1000	139 per 1000 (68 to 281)				
	Risk difference: 52 more SSIs per 1000 with mupirocin treatment compared with placebo (21 fewer to 194 more)					
S aureus SSI	Study population		RR 1.22 (0.34 to 4.44)	257 (1 study)	⊕⊕◯◯ LOW[1]	There is no clear difference as the estimate is imprecise with wide confidence intervals which include both possible benefits and harms
	31 per 1000	38 per 1000 (11 to 140)				
	Risk difference: 7 more S aureus SSIs per 1000 with mupirocin treatment compared with placebo (31 fewer to 73 more)					
Mortality	Study population		RR 0.78 (0.21 to 2.84)	257 (1 study)	⊕⊕◯◯ LOW[1]	It is unclear whether there is a difference in the number of participants with *S aureus* SSI between mupirocin

						and placebo. None of the deaths in the mupirocin group were attributable to an infection, whereas one death in the placebo group was directly related to *S aureus* infection.
	39 per 1000	31 per 1000 (8 to 112)				
	Risk difference: 8 more deaths per 1000 with mupirocin treatment compared with placebo (20 fewer to 109 more)					
Adverse events	Not estimable	Not estimable	Not estimable	257 (1 study)	n/a	No events were reported and therefore no evaluation was possible

*__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

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: 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 quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low quality: 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 twice for imprecision due to small numbers of events and wide confidence intervals which include the possibility of both benefit and harm for the intervention.

BACKGROUND

Description of the condition

The complications associated with surgical wounds are an important, yet underestimated, burden to patient care. Over the years this burden has been reduced through the advent of aseptic surgery, clean air operating, preoperative bathing, antimicrobial prophylaxis, and minimally invasive surgery (Owens 2008). However, surgery inevitably carries a risk of infection as it involves cutting through the skin, the body's first defence against infection (Campoccia 2013). The ideal scenario at the end of any surgical procedure is that the wound can be closed and the site remains clean. However, surgical wound infections remain a major cause of patient morbidity and occasionally mortality. The development of a surgical site infection (SSI) is an important avoidable consequence of interventional surgery and deserves to be better understood. How harmful microbes become established at the surgical site, and their impact on wound healing, remain poorly understood. The techniques used in current clinical care therefore need strong supporting evidence to establish whether they minimise SSI.

SSIs occur following an invasive surgical procedure (NICE 2008), and can cause delayed wound healing, increased hospital stay, increased use of antibiotics, and unnecessary pain. They can lead to a need for reoperation and can cause mortality (Awad 2012; Brown 2014; Plowman 2000). SSI is associated with a mortality rate of 3%, and 75% of SSI-associated deaths are directly attributable to the SSI (CDC 2017). SSIs can be extremely costly to treat as well: it has been estimated that people with SSIs require, on average, an additional hospital stay of 6.5 days, and that hospital costs are doubled. When extrapolated to all acute hospitals in England, it is estimated that the annual cost is approximately GBP 1 billion (Plowman 2000). Recent figures from the UK suggest that SSIs lead to a median increased hospital stay of 10 days (95% CI 7 to 13 days) per patient with an associated median additional cost attributed to SSI of GBP 5239 (95% CI GBP 4622 to 6719) (Jenks 2014). The UK National Institute for Health and Care Excellence (NICE) identified that an SSI increased the costs of surgery by two to five times (NICE 2008).

A 2006 prevalence survey in the UK National Health Service (NHS) indicated that approximately 8% of all patients (5743/75,694 patients over a four-month period) admitted to hospital suffer healthcare-associated infections, with 15% of these infections being SSIs (Smyth 2008). In the UK around 2% to 5% of surgical patients develop an SSI (NICE 2008; Public Health England 2014), though this percentage varies greatly depending on the circumstances. A US study found SSI incidence of 1% based on over 750,000 episodes of surgical hospitalisation, and a French study found a similarly low SSI rate (Astagneau 2009; de Lissovoy 2009). However such values are known to underestimate the levels of SSI by not considering those that develop after discharge from hospital (Bruce 2001; Gibbons 2011; Leaper 2015). Most SSIs present within the first 30 days following a procedure (NICE 2008). While more data are available for developed healthcare settings, SSI was the leading cause of hospital-acquired infection in a systematic review of studies in developing countries (Allegranzi 2010).

There are many recognised risk factors for SSI. These include length of hospital stay, obesity, patient co morbidities, duration and complexity of surgery, and degree of wound contamination (Anderson 2008; Chemaly 2010; Edwards 2008; Korol 2013). The US Centers for Disease Control and Prevention classified surgical procedures and their resulting surgical wounds by their likely level of contamination (HICPAC 1999), which is summarised in Appendix 1.

The risk of developing a SSI is related to the wound's potential for contamination. Many micro-organisms can cause contamination, and most SSIs are caused by micro-organisms from the patient's own body (endogenous bacteria). Infection caused by micro-organisms from an outside source (exogenous bacteria) following surgery is less common (NICE 2008). *S aureus* is the leading nosocomial (hospital-acquired) pathogen in hospitals worldwide (Van Rijen 2008a). Staphylococcal infections can have severe consequences including postoperative wound infections, nosocomial pneumonia, and catheter-related bacteraemia (bacteria in the blood that can cause disease elsewhere in the body, such as the lining of the heart (endocarditis) (Van Rijen 2008a). Since the consequences of these infections can be extremely serious, effective prevention strategies need to be established. More than 80% of *S aureus*-related infections are caused by bacteria carried by patients themselves (von Eiff 2001; Wertheim 2004). *S aureus* colonises the skin and mucous membranes of human beings and the nose is the most common site for *S aureus* (Wertheim 2005). The presence of *S aureus* in the nose is now considered a well-defined risk factor for subsequent infection. To date, evidence shows that rates of infection are higher in carriers than in non-carriers: people with large numbers of *S aureus* microbes in their nose have a risk of health care-associated infection that is three to six times higher than non-carriers and low-level carriers in some specific population groups (Bode 2010; Coates 2009; Nouwen 2006). Individuals are usually infected with their own carriage isolate and the temporary eradication of carriage following the use of topical mupirocin has been shown to reduce nosocomial infection (Peacock 2001).

Description of the intervention

The high additional costs and risks associated with SSI have led to the adoption of strategies to reduce its incidence. The first step in the management of SSIs is prevention. A well-recognised method for clearing the nose of *S aureus* bacteria is the use of antiseptics applied in or around the nose; for example, mupirocin ointment applied twice daily to the nose for five days before an operation (Van Rijen 2008a). This type of nasal decontamination is fre-

quently combined with whole-body bathing or showering with skin antiseptic immediately before surgery, designed to prevent SSIs by removing as many bacteria as possible from the patient's skin. Chlorhexidine or a triclosan preparation is usually used for this purpose, and there is evidence that the numbers of bacteria on the skin are reduced when these skin washes are applied (Webster 2015). Whilst this review focuses on the preoperative application of antibiotics or antiseptics to the nose in order to eliminate *S aureus* bacteria and reduce the risk of SSI, it should be borne in mind that the combination of this method with other whole-body cleaning techniques makes it difficult to isolate the effectiveness of nasal decontamination alone (Patel 2009).

How the intervention might work

Antimicrobial treatments are applied topically (to the surface of the skin) to destroy potentially harmful bacteria. Most of these treatments belong to one of the two following major groups.

- **Antibiotics** inhibit DNA/protein synthesis in bacteria or disrupt the bacterial cell wall, therefore they are widely used to destroy or inhibit the growth of micro-organisms (Macpherson 2004). These chemicals are produced either naturally (by a micro-organism), or synthetically. They are relatively nontoxic, but their effectiveness can be reduced as bacteria become resistant to them. An example of a commonly-used antibiotic is mupirocin. Mupirocin is highly effective against aerobic gram-positive cocci (*S aureus, S epidermidis*, and β-haemolytic streptococci), and some gram-negative cocci but allows microbes that do not cause disease to survive (Spann 2004). Mupirocin ointment is one of the most commonly-used popular antibiotics in clinical practice. Mupirocin (Bactroban, Beecham Laboratories) is currently formulated as a 2% ointment in a water-miscible polyethylene glycol base. It has often been used to eradicate microbes because of its microbiological effectiveness, safety and low cost (Van Rijen 2008a).
- **Antiseptics** can kill micro-organisms (bacteriocidal) or slow their growth (bacteriostatic). Compared with antibiotics, antiseptics often target a wide range of microbes and can reduce the presence of other micro-organisms such as viruses and fungi (Macpherson 2004). Antiseptics usually work without damaging certain living tissues, therefore they can be used on intact skin and on some open wounds to kill or inhibit micro-organisms. Examples of commonly-used antiseptics are povidone-iodine and chlorhexidine. As the problem of bacterial resistance has led to antibiotics being used more sparingly, alternative methods for cleansing the nose are being evaluated. Povidone-iodine (PI) is an antiseptic with potential benefits for intranasal decolonisation because it has a broad activity against gram-positive and gram-negative bacteria (Bebko 2015). Chlorhexidine is an antiseptic thought to be effective against a wide range of gram-positive and gram-negative bacteria, lipophilic viruses and yeasts (Hibbard 2002). Depending on its concentration, it can kill bacteria or inhibit their growth. Chlorhexidine kills bacteria by disrupting the cell membrane. In topical applications, it is shown to have the unique ability to bind to the proteins present in human tissues such as skin and mucous membranes with limited absorption throughout the body. Protein-bound chlorhexidine releases slowly leading to prolonged activity (Leekha 2011). Naseptin Nasal Cream is currently formulated with chlorhexidine dihydrochloride (0.1%) and used commonly to eradicate nasal infection with, and carriage of, staphylococci (British National Formulary 2016).

These are examples of agents used for nasal decontamination; this list is not intended to be exhaustive.

Why it is important to do this review

Rationalising the use of antibiotics is important to minimise the impact of antibiotic resistance. The National Institute for Health and Care Excellence (NICE) guidelines reviewed evidence from five randomised controlled trials (RCTs) which included both carriers and non-carriers. The nasal decontamination, which was delivered with other co-interventions, was not the only difference between groups. NICE concluded that the use of nasal decontamination could not be recommended to reduce the risk of SSIs (NICE 2008). The research used to inform this guideline is now almost 10 years old, making it likely that a number of additional trials would be available. In some areas of surgical practice this may substantially affect the evidence base. A previous Cochrane Review only looked at one intervention for nasal decontamination (mupirocin) and participants were not restricted to those undergoing surgery; both inpatients and outpatients were included and SSI was only examined as a subgroup of all infections (Van Rijen 2008a). Another publication by the same authors also focused on mupirocin as an intervention and included only trials in surgical patients who were *S aureus* carriers (Van Rijen 2008b). The analyses in this patient group showed a benefit for the intervention over no intervention in terms of SSI. A recent review paper including both RCTs and non-RCTs also identified the need for more evidence on several of the questions in this review (Levy 2013). Other previous reviews have included participants not known to be *S aureus* carriers and also participants who were not scheduled for surgery. No recent fully systematic review has evaluated the evidence for nasal decontamination in identified *S aureus* carriers undergoing surgery. This review directly addresses and updates the evidence base for nasal decontamination in this group for the prevention of SSI and associated morbidity and mortality. It includes any intervention used for nasal decontamination in *S aureus* carriers scheduled to undergo surgery, and is not restricted to the use of mupirocin. It is important to consider alternatives to mupirocin, as all prophylactic antibiotic use must be weighed against considerations of increasing antibiotic resistance. We attempted to examine sensitive and resistant *S aureus* SSIs separately

in this review, in order to consider whether resistance may be affected (see Secondary outcomes).

OBJECTIVES

To assess the effects of nasal decontamination on preventing surgical site infections (SSIs) in people who are *S aureus* carriers undergoing surgery.

METHODS

Criteria for considering studies for this review

Types of studies

We included all published and unpublished randomised controlled trials (RCTs) irrespective of language of report. This included cluster-randomised trials. We did not include quasi-randomised trials (i.e. trials where the method of allocating participants to different forms of care is not truly random, for example allocation by date of birth, day of the week, medical record number, month of the year, or the order in which participants were included in the study (alternation)).

Types of participants

People of any age undergoing surgery who were nasal carriers of *S aureus*. Surgery was defined as a procedure involving: (1) an incision being made into the skin forming an open wound; or (2) an operative procedure to treat an existing traumatic wound/injury. We included studies including either or both adults and children who were nasal carriers of *S aureus,* identified by nasal culture identification or polymerase chain reaction (PCR) assay or any other appropriate/valid methods. Studies of participants treated in any setting were included. We excluded studies including mixed population (both carriers and non-carriers).

Types of interventions

We planned to include studies where the type or schedule of nasal decontamination was the only systematic difference between study arms. This review therefore aimed to include comparisons of nasal decontamination procedures with each other and/or placebo and/or treatment as usual or no intervention. We anticipated that we could include studies evaluating the following types of comparisons:

- comparisons of a nasal decontamination intervention compared with no intervention or with placebo;
- comparisons of different nasal decontamination interventions;
- comparisons of different schedules, timings, or doses of the same nasal decontamination compared with the same topical antibiotics applied in an alternative schedule/timing/dose.

All of these types of comparison could potentially include nasal decontamination used as part of a bundle of interventions aimed at SSI reduction as well as a single intervention. Co-interventions designed to reduce SSI were expected, for example antimicrobial skin preparation; however these co-interventions had to be delivered similarly to all comparison groups as this review aimed to determine the effect of nasal decontamination specifically.

Types of outcome measures

We list primary and secondary outcome measures below. If a trial was otherwise eligible (correct study design, population, and intervention/comparator) but did not report a listed outcome, then we contacted the study authors, where possible, in order to establish whether a relevant outcome was measured but not reported. However, we did not plan to exclude otherwise eligible studies solely on the basis of reported outcomes.
Where possible, we anticipated grouping outcomes by the following time points. Review authors' judgement was used as to whether statistical pooling within these time categories was appropriate:

- short term: 30 days;
- medium term: 30 days to 12 months;
- long term: more than 12 months.

We reported all outcome measures at the latest time point available (assumed to be length of follow-up if not specified) and the time point specified in the methods as being of primary interest (if this was different to the latest time point available).

Primary outcomes

The primary outcomes for this review were SSI and adverse events.
Occurrence of postoperative SSI: the proportion of people who developed SSIs, as defined by the Centers for Disease Control and Prevention (CDC) (Mangram 1999); or by the study authors. We did not differentiate between superficial and deep-incisional infection. The SSI outcome was measured in participants who were scheduled to undergo surgery. Whatever the organism implicated in the SSI we extracted any data on antibiotic resistance.
Adverse events (e.g. burning localised to the area of application; itching, erythema, stinging and dryness localised to the area of application; cutaneous sensitisation reactions to mupirocin or the ointment base). These were included where reported as total number of individuals with adverse events in each intervention group.

Secondary outcomes

- *S aureus* SSI - see above specifications.
- Other nosocomial infections caused by meticillin-sensitive *Staphylococcus aureus* (MSSA) and meticillin-resistant *Staphylococcus aureus* (MRSA) (analysed separately): the proportion of participants who developed infections, as defined by study authors. The infection outcome was measured in participants who were scheduled to undergo surgery.
- 30-day mortality/in-hospital mortality.
- Resource use (including measurements of resource use such as length of hospital stay and re-operation/intervention and length of absence from work/time to return to work), where reported as means/medians/proportions with appropriate measures of variance.
- Cost (both direct and indirect costs), where reported as means with appropriate measures of variance.
- Health-related quality of life (measured using a standardised generic questionnaire such as EQ-5D, SF-36, SF-12 or SF-6). We did not include ad hoc measures of quality of life that were not likely to be validated and would not be common to multiple trials.

Search methods for identification of studies

We developed the search strategy in consultation with the Cochrane Wounds Information Specialist.

Electronic searches

We searched the following electronic databases to identify reports of randomised controlled trials.

- Cochrane Wounds Specialised Register (searched 26 September 2016);
- Cochrane Central Register of Controlled Trials (CENTRAL; *The Cochrane Library* 2016, Issue 8) (searched 26 September 2016);
- Ovid MEDLINE (including In-Process & Other Non-Indexed Citations, MEDLINE Daily and Epub Ahead of Print) (1946 to 26 September 2016);
- Ovid Embase (1974 to 26 September 2016);
- EBSCO CINAHL Plus (1937 to 26 September 2016).

The search strategies for CENTRAL, Ovid MEDLINE, Ovid Embase and EBSCO CINAHL Plus can be found in Appendix 2. 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 randomised trials filter terms developed by the UK Cochrane Centre (Lefebvre 2011). We combined the CINAHL searches with the randomised trials filter terms developed by the Scottish Intercollegiate Guidelines Network (SIGN 2015). We imposed no restrictions with respect to language, date of publication, or study setting.

We also searched the following clinical trial registries for ongoing and unpublished studies:

- ClinicalTrials.gov (www.clinicaltrials.gov/);
- the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/Default.aspx);
- the European Union (EU) Clinical Trials Register (www.clinicaltrialsregister.eu).

Searching other resources

We tried to identify other potentially eligible trials or ancillary publications by searching the reference lists of retrieved included trials as well as relevant systematic reviews, guidelines, meta-analyses, and health-technology assessment reports.

Data collection and analysis

The approach was previously detailed in the protocol for this review (Liu 2016).

Selection of studies

Two review authors (ZL and GN) independently assessed the titles and abstracts of the citations retrieved by the searches for relevance. After this initial assessment, we obtained full-text copies of all studies considered to be potentially relevant. Two review authors (ZL and GN) independently checked the full papers for eligibility; they resolved disagreements by discussion and, where required, the input of a third review author (ZI). Where required and possible, we contacted study authors when the eligibility of a study was unclear. We recorded all reasons for exclusion of studies for which we obtained full copies. We completed a PRISMA flowchart to summarise this process (Liberati 2009).

Where studies were reported in multiple publications/reports, we obtained all publications. We tried to include all relevant outcome data from these multiple publications. We performed data extraction at the level of the study rather than the report.

Data extraction and management

We extracted and summarised details of the eligible studies using a data extraction sheet. Two review authors (ZL and GN) extracted data independently and resolved disagreements by discussion, drawing on a third review author (ZI) where required. Where data were missing from reports, we attempted to contact the study authors to obtain this information. Where a study with more than two intervention arms was included, we only extracted data from intervention and control groups that met the eligibility criteria.

We extracted the following data, where possible, by treatment group for the prespecified interventions and outcomes in this review. We collected outcome data for relevant time points, as described in Types of outcome measures.

- Country of origin.
- Type of wound and surgery.
- Unit of randomisation (e.g. participant or wound).
- Unit of analysis (e.g. participant or wound).
- Trial design (e.g. parallel; cluster).
- Number of participants randomised to each trial arm.
- Eligibility criteria and key baseline participant data, including type of scheduled surgery.
- Details of treatment regimen received by each group.
- Duration of treatment.
- Details of any co-interventions.
- Primary and secondary outcome(s) (with definitions and time points).
- Outcome data for primary and secondary outcomes (by group).
- Duration of follow-up.
- Number of withdrawals (by group).
- Publication status of study.
- Source of funding for trial.

Assessment of risk of bias in included studies

Two review authors (ZL and GN) independently assessed included studies using the Cochrane approach for assessing risk of bias as detailed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). We resolved disagreements through discussion or by consulting a third review author (ZI). The Cochrane tool for assessing risk of bias addresses specific domains: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete data, selective outcome reporting, and other issues. In this review we recorded unit of analysis issues, for example where a cluster trial was undertaken but analysed at the individual level in the study report (Appendix 2). We assessed blinding and completeness of outcome data for each of the review outcomes separately. We presented our assessment of risk of bias using two 'Risk of bias' summary figures; one that was a summary of bias for each item across all studies, and a second that showed a cross-tabulation of each trial by all of the risk of bias items.

For trials using cluster-randomisation, we also considered the risk of bias with regard to recruitment bias, baseline imbalance, loss of clusters, incorrect analysis, and comparability with individually randomised trials (Higgins 2011b; Appendix 3).

Measures of treatment effect

For dichotomous outcomes, we calculated the risk ratio (RR) with 95% confidence intervals (CIs). For continuous outcomes we used the mean difference (MD) with 95% CIs, if all trials used the same or a similar assessment scale. If trials used different assessment scales, we used the standardised mean difference (SMD) with 95% CIs.

Risk of binary outcomes, absolute risk reductions, risk difference and number needed to treat for an additional beneficial/harmful outcome (NNTB/NNTH) are absolute measures. Hoffrage 2000 suggests that physicians' inferences about statistical outcomes are more appropriate when they deal with 'natural frequencies' - that is, whole numbers of people, both treated and untreated - than when effects are presented as percentages. This evidence provides the rationale for presenting absolute risks in 'Summary of findings' tables as numbers of people with events per 1000 people receiving the intervention.

Unit of analysis issues

Where a cluster trial has been conducted and correctly analysed, effect estimates and their standard errors may be meta-analysed using the generic inverse-variance method in Review Manager 5 (RevMan 5) (Review Manager 2014).

We recorded where a cluster-randomised trial was conducted, but incorrectly analysed. We recorded this as part of the 'Risk of bias' assessment. If possible, we approximated the correct analyses based on guidance from the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b), using information on:

- the number of clusters (or groups) randomised to each intervention group; or the average (mean) size of each cluster;
- the outcome data ignoring the cluster design for the total number of individuals (for example, number or proportion of individuals with events, or means and standard deviations); and
- an estimate of the intracluster (or intraclass) correlation coefficient (ICC).

If we could not analyse the study data correctly, we extracted and presented outcome data but did not analyse it further.

Dealing with missing data

It is common to have data missing from trial reports. Excluding participants post-randomisation from the analysis or ignoring those participants who are lost to follow-up compromises the randomisation, and potentially introduces bias into the trial. Where there were missing data that we thought should be included in the analyses, we contacted relevant study authors to request whether these data were available.

Where data remained missing for the proportion of participants with SSI, we assumed that if randomised participants were not included in the results section of the paper, they did not have an SSI (i.e. in the analysis, missing participants would be considered in the denominator but not the numerator). If appropriate, we conducted a completed case analysis as a sensitivity analysis and also explored alternative scenarios using different assumptions about missing cases.

For continuous variables, such as length of hospital stay, and for all secondary outcomes, we presented available data from the study reports/study authors, but we did not plan to impute missing data. Where measures of variance were missing, we calculated these wherever possible. If calculation was not possible, we contacted study authors. Where these measures of variation were not available, we excluded the study from any relevant meta-analyses that we conducted.

Assessment of heterogeneity

Assessment of heterogeneity can be a complex, multifaceted process. Firstly, we considered clinical and methodological heterogeneity: that is, the degree to which the included studies vary in terms of participant, intervention, outcome, and characteristics such as duration of follow-up. We supplemented this assessment of clinical and methodological heterogeneity with information regarding statistical heterogeneity, assessed using the Chi^2 test (we considered a significance level of $P < 0.10$ to indicate statistically significant heterogeneity) in conjunction with the I^2 measure (Higgins 2003). I^2 examines the percentage of total variation across RCTs that is due to heterogeneity rather than chance (Higgins 2003). In general, I^2 values of 30% or more may represent moderate heterogeneity (Higgins 2003), and values of 75% or more indicate considerable heterogeneity (Deeks 2011). However, these figures are only a guide, and it has been recognised that statistical tests and metrics may miss important heterogeneity. Thus, whilst these were assessed, the overall assessment of heterogeneity assessed these measures in combination with the methodological and clinical assessment of heterogeneity. See Data synthesis for further information about how we dealt with potential heterogeneity in the data analyses.

Assessment of reporting biases

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results. Publication bias is one of a number of possible causes of 'small-study effects', that is, a tendency for estimates of the intervention effect to be more beneficial in smaller RCTs. Funnel plots allow a visual assessment of whether small-study effects may be present in a meta-analysis. A funnel plot is a simple scatter plot of the intervention effect estimates from individual RCTs against some measure of each trial's size or precision (Sterne 2011). We had planned to present funnel plots for meta-analyses comprising 10 RCTs or more using RevMan 5 (Review Manager 2014).

Data synthesis

We combined details of included studies in a narrative review according to type of comparator, where appropriate by type of surgical wound, and then by outcomes and time period. We considered clinical and methodological heterogeneity, and undertook pooling when studies appeared appropriately similar in terms of wound type, intervention type, duration of follow-up, and outcome type. In terms of meta-analytical approach, our default approach was to use the random-effects model. We only used a fixed-effect approach when clinical heterogeneity was thought to be minimal, and statistical heterogeneity was not statistically significant for the Chi^2 value and 0% for the I^2 measure (Kontopantelis 2013). We adopted this approach as it was recognised that statistical assessments can miss potentially important between-study heterogeneity in small samples, hence the preference for the more conservative random-effects model (Kontopantelis 2012). Where clinical heterogeneity was thought to be acceptable, or of interest, we planned to consider meta-analysis even when statistical heterogeneity was high, alongside attempts to interpret the causes behind this heterogeneity, and use of meta-regression, if possible (Thompson 1999). We presented data using forest plots, where possible. For dichotomous outcomes, we presented the summary estimate as a RR with 95% CI. Where continuous outcomes were measured in the same way across studies, we presented a pooled MD with 95% CI; we pooled SMD estimates where studies measured the same outcome, but used different scales.

We obtained pooled estimates of treatment effect using RevMan 5 software (Review Manager 2014).

'Summary of findings' tables and assessment of the quality of the evidence using the GRADE approach

We present the main results of the review in 'Summary of findings for the main comparison' and 'Summary of findings 2'. 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 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 presented the following primary outcomes in the 'Summary of findings' tables:

- SSI events
- number of nosocomial infections caused by MSSA and MRSA separately
- adverse events
- mortality.

For relevant outcomes reported for comparisons not listed above we present GRADE assessments narratively within the Results section without a 'Summary of findings' table.

In terms of the GRADE assessment, when making decisions for the risk of bias domain, we downgraded only when studies were classed at high risk of bias for one or more domains. We did not downgrade for unclear risk of bias assessments. In assessing the precision of effect estimates, we also followed GRADE guidance (GRADE 2013); we assessed the size of confidence intervals, downgrading twice for imprecision when there were very few events and CIs around effects included both appreciable benefit and appreciable harm.

Subgroup analysis and investigation of heterogeneity

If feasible, we had planned to explore the effects of interventions in children (aged under 18) and adults separately. If a sufficient number of studies were identified we had also planned to explore the effects of :

- emergency versus elective surgery;
- open versus laparoscopic surgery;
- different classifications of the infection risk of surgery (HICPAC 1999).

However, due to an insufficient number of included studies no sub-group analyses were conducted.

We also planned to perform sensitivity analyses to explore the effect of studies at high risk of bias for any domain compared with other studies with no domain classed at high risk of bias, however due to an insufficient number of included studies these were not conducted.

Elements of this Methods section are based on the standard Cochrane Wounds protocol template.

RESULTS

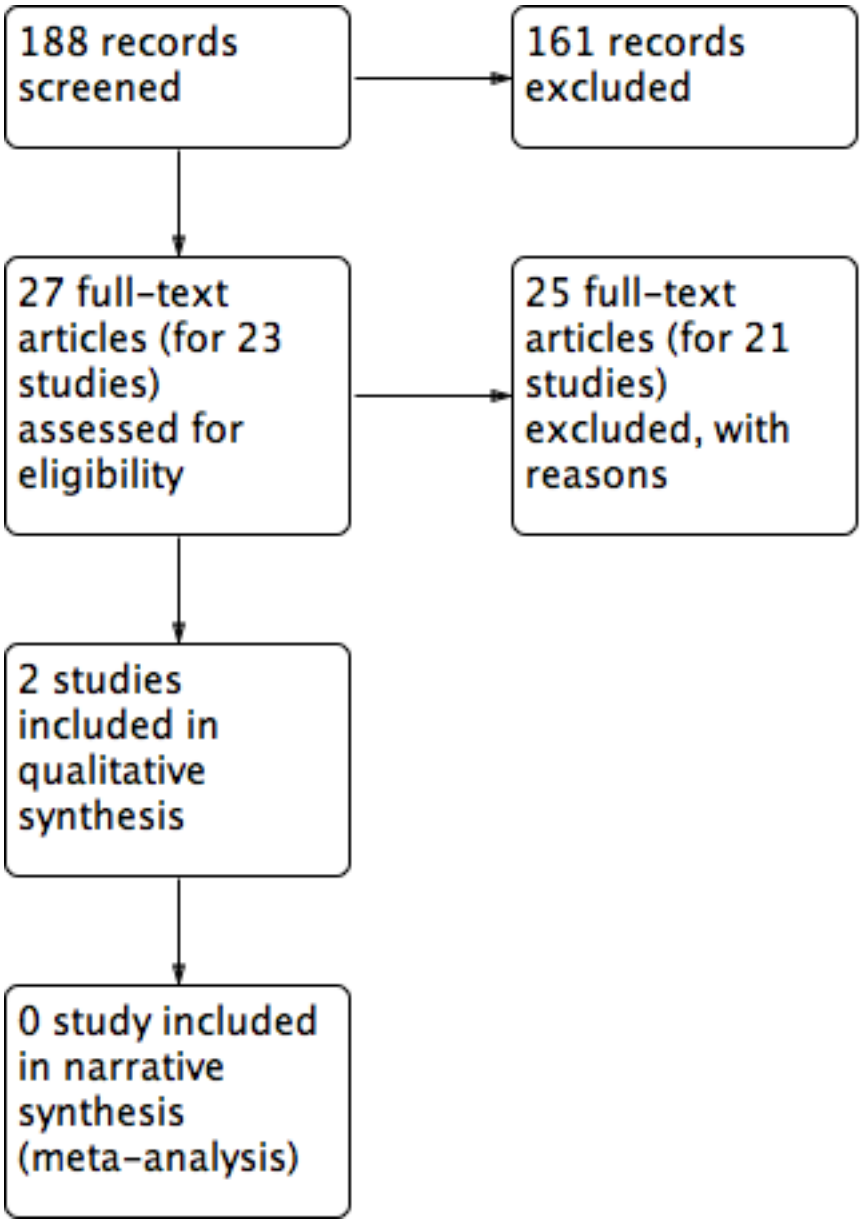
Description of studies

See Characteristics of included studies; Characteristics of excluded studies

Results of the search

The search yielded 188 citations which were screened for potential eligibility. Of these, 23 trials (from 27 publications) were obtained as full-text for a more detailed assessment. We included only two of these studies in this review and excluded the remaining 21 studies (Figure 1).

Figure 1. Study flow diagram.



Included studies

This review includes two 2-arm RCTs collectively containing 297 participants.

The first study contained 257 participants (Konvalinka 2006). The study, conducted in a hospital in Canada, had 8 weeks' follow-up. Konvalinka 2006 recruited *S aureus* nasal carriers undergoing cardiac surgery and compared 2% mupirocin with a placebo. Both study arms were also treated with standard pre-operative clinical practice (included a full shower or bath pre-operatively and administration of routine antibiotic prophylaxis starting just before surgery) and participants were followed up for two months. Konvalinka 2006 also reported the definition of SSI as follows: the presence of exudate from the wound; the edges of the wound were erythematous beyond 2 cm margin; the wound culture yielded a pathogen with signs of inflammation; or a physician stated in the medical record that the surgical site was infected as corroborated by one or more of the listed criteria.

Yu 2011, the second included study, randomised 34 *S aureus* nasal carriers undergoing elective cardiac surgery in one Cardiology Department of a Chinese hospital, and had an unclear follow-up time. Yu 2011 evaluated the use of Anerdian, which contained 0.45% to 0.57% (W/V) iodine and 0.09% to 0.11% (W/V) chlorhexidine acetate, compared with no treatment. Due to the limited information reported in Yu 2011, we attempted to contact the authors, this has so far been unsuccessful as we have been unable to locate correct contact information.

Excluded studies

We excluded 21 studies reported in 25 records after appraisal as full-texts (see Characteristics of excluded studies). Many of these full-texts were obtained because the initial record contained so little information we were initially unsure about eligibility (e.g. not sure whether it was a 'carriers only' study or mixed population). Studies were excluded for the following reasons:

- the study was not truly an RCT (1 study: Shrem 2016);
- no relevant outcome data were available (1 study: Mehta 2013);
- nasal decontamination was not the only systematic difference between study groups: examples of additional treatments were chlorhexidine body wash; tea tree oil body wash; and rinsing of oropharynx with chlorhexidine gluconate (11 studies: Bode 2010; Caelli 2000; Dryden 2004; Golan 2010; Moon 2010; Rijen 2012; Segers 2006; Shuman 2012; Sousa 2016; Tai 2013; Vinciullo 2014);
- mixed population, not only carriers (8 studies: Andenaes 1996; Anonymous 2004; Garcia 2003; Harbarth 2000; Jabbour 2010; Kalmeijer 2002; Perl 2002; Phillips 2014).

Risk of bias in included studies

See Figure 2; Figure 3

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

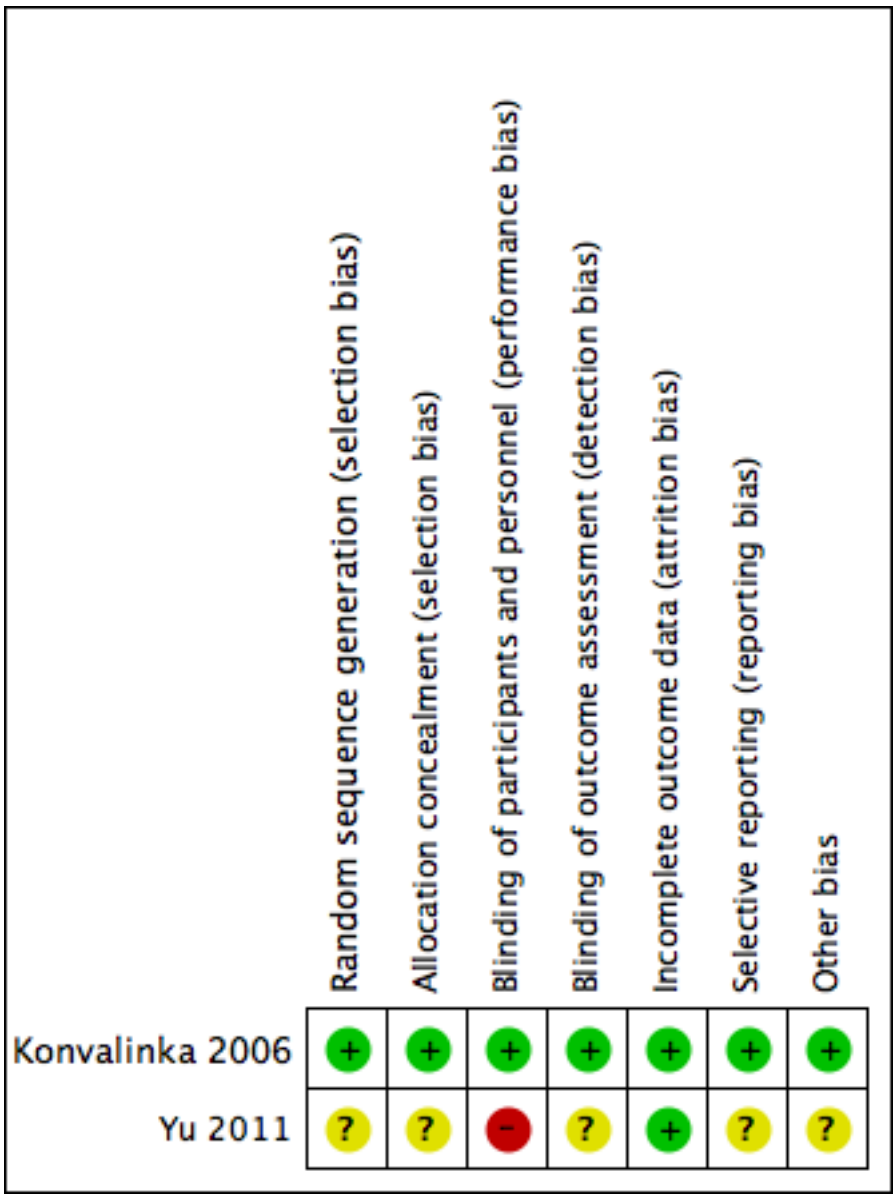
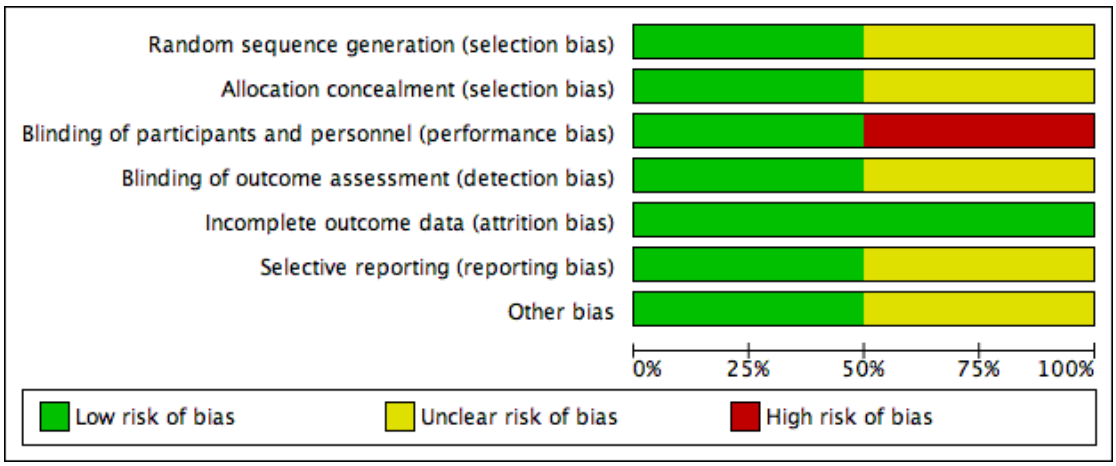


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Overall, Yu 2011 was at high risk for performance bias. The Konvalinka 2006 trial was deemed to be at low risk of bias.

Allocation

We classed Yu 2011 as being at unclear risk of bias, as the trialists reported no information about methods used to generate the randomisation sequence or allocation procedure. Konvalinka 2006 was classed at low risk of bias as the randomisation numbers were computer generated and the code was only available to research pharmacists.

Blinding

Blinded outcome assessment is important in wound care studies for outcomes that have a subjective element to their assessment like SSI. The risk of bias associated with outcome assessment was rated as unclear in Yu 2011 as there was no information to confidently classify the studies as at high or low risk of bias; meanwhile, blinding of patients and investigators was judged to have not been done as the control group did not receive any placebo. Konvalinka 2006 was classed at low risk of bias for this domain as it was stated that "an identical-appearing placebo [was] administered intranasally" and "blinding was maintained until after analysis by the pharmacist".

Incomplete outcome data

We judged both trials to be at low risk of bias for the domain of incomplete outcome data. Konvalinka 2006 conducted the analysis on the basis of the intention-to-treat approach. Yu 2011 was classed at low risk of bias.

Selective reporting

We judged Konvalinka 2006 to be at low risk of bias for the domain of selective reporting, as the trial report suggested that all outcome data collected were reported. Yu 2011 was classed at unclear risk of bias.

Other potential sources of bias

Konvalinka 2006 was classed at low risk of bias as methodology was reported sufficiently well. Yu 2011 was classed at unclear risk of bias as it was not clear what methods had been used to calculate SSI data; the follow-up time was also unclear.

Effects of interventions

See: **Summary of findings for the main comparison** Mupirocin compared with placebo for the prevention of surgical site infection in Staphylococcus aureus carriers; **Summary of findings 2** Anerdian compared with no treatment for the prevention of surgical site infection in Staphylococcus aureus carriers

Comparison 1: mupirocin compared with placebo (one study; 257 participants)

Summary of findings for the main comparison.

One study was included in this comparison (Konvalinka 2006). It allocated people undergoing elective cardiac surgery to treatment with either nasal decontamination using mupirocin (2% contained in a base of polyethylene glycol 400 and polyethylene glycol 3350) or placebo. Both arms received the same co-intervention: standard pre-operative clinical practice included a full shower or bath with chlorhexidine antiseptic soap 12 hours pre-operatively, surgical site cleansing pre-operatively, and administration of routine antibiotic prophylaxis starting just before surgery. The follow-up time was 8 weeks (medium term follow-up).

Primary outcome: SSI

Konvalinka 2006: this study found no clear difference in SSI risk following use of mupirocin compared with placebo: RR 1.60, 95% CI 0.79 to 3.25 based on 18/130 (7 sternal and 11 leg) events in the mupirocin group and 11/127 (6 sternal and 5 leg) in the control group (Analysis 1.1). We considered this to be low-certainty evidence due to imprecision (downgraded twice due to small numbers of events and wide confidence intervals which include the possibility of both benefit and harm for the intervention).

Primary outcome: adverse events

Konvalinka 2006 reported information on adverse effects, noting that no adverse reactions were reported for either mupirocin or placebo. No GRADE assessment was possible.

Secondary outcomes: *S aureus* SSI

Konvalinka 2006 found no clear difference in the risk of *S aureus* SSIs following treatment with mupirocin compared with placebo : RR 1.22, 95% CI 0.34 to 4.44 based on 5/130 events in the mupirocin group and 4/127 in the control group (Analysis 1.2). We considered this to be low-certainty evidence due to imprecision (downgraded twice).

Secondary outcomes: mortality

This study found no clear difference in the risk of mortality in the mupirocin group compared with the placebo group: RR 0.78 95% CI 0.21 to 2.84 based on 4/130 events in the mupirocin group and 5/127 in the control group (Analysis 1.3). We considered this to be low-certainty evidence due to imprecision (downgraded twice). None of the four deaths in the mupirocin group were attributable to an infection, whereas one of the five deaths in the placebo group was considered by the study authors to be directly related to *S aureus* infection, and one death was a result of pneumonia escalating to multi-organ failure.

No data on other review outcomes were available for this comparison.

Comparison 1 Summary: mupirocin compared with placebo

It is unclear whether mupirocin used as a nasal decontaminant makes any difference in preventing subsequent SSI and mortality amongst *S aureus* carriers (low-certainty evidence).

Comparison 2: Anerdian compared with no treatment (one study; 34 participants)

Summary of findings 2

One study was included in this comparison (Yu 2011). This study allocated people undergoing elective cardiac surgery to treatment with either nasal decontamination using Anerdian (iodine 0.45% to 0.57% (W/V), chlorhexidine acetate 0.09% to 0.11% (W/V)) or no treatment. Both arms received the same co-intervention: second or third generation cephalosporin during the perioperative period to three days after surgery. The follow-up time was unclear.

Primary outcome: SSI

Yu 2011: it is uncertain whether there was a difference in the risk of SSIs following treatment with Anerdian compared with no treatment : RR 0.89, 95% CI 0.06 to 13.08 based on 1/18 events in the Anerdian group and 1/16 in the control group (Analysis 2.1). We considered these data to be very low certainty evidence due to imprecision (downgraded twice) and high risk of bias (downgraded once).

Primary outcome: adverse events

It was not clear how adverse event data had been collected. The study summarised data on side effects of the use of Anerdian. Ten events of dry skin and itch and two events of nasal mucosa bleeding were reported in the treatment group. It was not clear that this was the total number of participants with events. We have not analysed data further. No GRADE assessment was possible.

No data on other review outcomes were available.

Comparison 2 Summary: Anerdian compared with no treatment

We are uncertain whether Anerdian reduces subsequent SSI rate amongst *S aureus* carriers as the certainty of the evidence has been assessed as very low. No data on other outcomes were available.

'Summary of findings' tables

We have included two 'Summary of findings' tables which give an overview of the volume and quality of the evidence (Summary of findings for the main comparison; Summary of findings 2).

Subgroup analysis

We did not perform any subgroup analyses, as only one trial was included for each comparison.

ADDITIONAL SUMMARY OF FINDINGS [Explanation]

Anerdian compared with no treatment for the prevention of surgical site infection in *Staphylococcus aureus* carriers

Patient or population: *S aureus* carriers undergoing cardiac surgery
Setting: Hospital
Intervention: Anerdian
Comparison: no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with no treatment	Risk with Anerdian				
SSI Follow-up unclear	Study population		RR 0.89 (0.06 to 13.08)	34 (1 study)	⊕◯◯◯ VERY LOW[2,3]	Very small numbers of participants and effects and very wide CIs which span benefit and harm so it is uncertain whether there is a difference between Anerdian and no treatment
	63 per 1000	56 per 1000 (4 to 818)				
	Risk difference: 7 fewer SSI per 1000 with Anerdian treatment compared with no treatment (59 fewer to 755 more)					
Adverse events	Not estimable	Side-effects (dryness and itch n = 10; and nasal mucosa bleeding n = 2)	n/a	34 (1 study)	n/a	Not clear that this is total number of participants with an event - no analysable data so no assessment

*__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

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: 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 quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[2] Downgraded twice for imprecision and once for high risk of performance bias in the single trial.
[3] Downgraded once for risk of bias

DISCUSSION

Summary of main results

We included two RCTs with a total of 291 randomised participants (Konvalinka 2006; Yu 2011). Each study assessed a different nasal decontamination treatment compared with no active treatment. There was therefore evidence for two comparisons: mupirocin versus placebo (one study, 257 participants; 8 weeks of follow-up time (Konvalinka 2006)); and Anerdian versus no intervention (one study, 34 participants; unclear follow-up time (Yu 2011)).

Mupirocin versus placebo

For the primary outcome of SSI it was unclear from available evidence whether there was a difference in incidence of either SSI or *S aureus*-specific SSI between participants treated with mupirocin compared with those given placebo. It was also unclear whether there was a difference in mortality between the groups (also low-certainty evidence). There were no adverse events reported. The low-certainty evidence was downgraded twice due to imprecision.

Anerdian versus no treatment

There was very low certainty evidence for the primary outcome of SSI for the comparison of Anerdian with no treatment: it is uncertain whether there was a difference between the treatment groups. The single study was at high risk of performance bias and was also very small, with low event rates and, as such, was underpowered (Yu 2011). The data reported were limited and there was no clear definition of SSI. Adverse event reporting was unclear: the data did not clearly represent the total number of participants with an event. The very low certainty evidence was downgraded once for risk of performance bias and twice for imprecision.

All the evidence was low or very low certainty. This was primarily a consequence of imprecision as a result of small sample sizes and low event rates.

Overall completeness and applicability of evidence

Only cardiac surgery (contamination class 1) was represented in the two included RCTs. Both trials reported reduction of SSIs as an objective. Where SSI was reported the process used to define infection was not given in one trial, nor was it clear over what follow-up period data collection took place (Yu 2011). The two studies reported limited outcome data, including for the primary outcome of adverse events. *S aureus* SSI and mortality were reported in one study (Konvalinka 2006). Outcomes for other patient-important outcomes such as quality of life were not reported. The other secondary outcomes of this review (other nosocomial infections caused by MSSA and MRSA, resource use and cost) were not addressed either.

The included studies were also small (or very small) in terms of number of participants and outcome events, which meant they were underpowered. Paradoxically the small, underpowered nature of studies means that as well as being at risk of type 2 errors (that is, missing important differences), they are at increased risk of type I errors as statistically significant findings are more likely to be spurious (Button 2010), although this was not the case in the trials included in this review. Overall, the sub-optimal methodological reporting, the small sample size and the limited quality of outcome data collection mean that the current evidence base is incomplete and of limited value to decision makers.

Quality of the evidence

RCTs need to be adequately powered so that they are able to detect treatment effects of a specified size, if they exist. This means that sample size calculations should be used to help estimate the number of people that should be recruited to a trial. Additionally trials should have an adequate follow-up period so that there is enough time in which important outcome events, such as complete wound healing, can occur. Both trials included in this review were small (or very small), and the follow-up period of one study was uncertain (Yu 2011).

This results in a limited evidence base, with further problems in quality caused by the reporting of limited outcomes. SSI, *S aureus* SSI, and mortality as well as adverse events, constitute potentially important outcomes. Such outcomes should be collected rigorously with a clear methodology. Ultimately, there were few studies that could be considered for inclusion in the review, and the two studies included presented limited outcome data.

Rigorous RCTs in wound care are feasible - they should follow good practice conduct and reporting guidelines e.g. CONSORT (Schulz 2010). Key areas of good practice are: the robust generation of a randomisation sequence, for example computer generated, robust allocation concealment, for example the use of a telephone randomisation service; and blinded outcome assessment, where possible. All this information should be clearly stated in the study report as all trial authors should now anticipate the inclusion of their trials in systematic reviews. Additionally, studies should clearly report how the collection of adverse event data was planned and how this process was standardised for both treatment arms. In terms of analysis, where possible, data from all participants should be included: that is an intention-to-treat analysis should be conducted, and measures of variation such as the standard deviation or standard error should be presented around measures where appropriate. Steps should be taken during the trial to prevent missing data as far as possible.

Potential biases in the review process

We attempted to overcome potential publication bias through rigorous searching. In this review we considered as much evidence as it was possible to obtain, including studies that were not published in English language journals. Three articles were identified in languages other than English and required translations. One of these studies was subsequently included in the review and was published in Chinese (Yu 2011). We therefore believe that language bias is unlikely to have been present. Konvalinka 2006 reported non-industry funding sources while funding sources were not reported by Yu 2011; with only two studies it is difficult to determine an impact of funding sources.

Agreements and disagreements with other studies or reviews

A systematic review of mupirocin for preventing *S aureus* infections in nasal carriers was published in 2008 (Van Rijen 2008a), which was mainly aimed to determine whether mupirocin reduced nosocomial *S aureus* infections. Van Rijen 2008a includes 10 studies and reports that the use of mupirocin ointment in people who are nasal carriers results in a statistically significant reduction in *S aureus* infection. Van Rijen 2008a and our review both include Konvalinka 2006 in a comparison of mupirocin versus placebo for *S aureus* SSIs (as a subgroup analysis in Van Rijen 2008a). The trials included in the Van Rijen 2008a review and this Cochrane review were not identical. Unlike this review, Van Rijen 2008a focused on nasal decontamination using mupirocin only. Van Rijen 2008a also included other trials which are excluded from this Cochrane review because the participants were not all scheduled to undergo surgery or because nasal decontamination was one of multiple interventions and was not the only systematic treatment difference between groups.

Broader inclusion criteria were also used for the reviews underpinning guidance by the UK National Institute for Health and Clinical Excellence (NICE) and by the World Health Organization (WHO) (NICE 2008; WHO 2016). Both these sets of guidance therefore included more trials than our review and came to differing conclusions as to the value of nasal decontamination.

Neither of the reviews which underpin current guidance included the small Chinese language study which we identified but, like Van Rijen 2008a, both included trial which employed nasal decontamination as part of a bundle of interventions (that is nasal decontamination was not the only systematic difference between groups). The review by WHO 2016 included trials which also used chlorhexidine gluconate body washes or soaps in only the mupirocin ointment arm, employing placebo soap or no treatment in the comparison group; these were large trials which will have contributed considerable weight to the analysis. Additionally this WHO review differed further from our review in that it did not limit inclusion to only known carriers of *S aureus,* and also included at least one trial in which not all participants underwent surgery.

Including trials with participants with and without *S aureus,* or those who were not scheduled for surgery, means that the data represent a more heterogenous patient population, rather than exploring the effect of identifying and treating surgical patients who are *S aureus* carriers and who may be assumed to be the only population who would benefit from the intervention of nasal decontamination for the prevention of (*S aureus*) SSI.

Where nasal decontamination is employed in conjunction with other antimicrobial measures, such as bathing or showering with antiseptic agents, it is rarely possible to be sure whether any difference in outcome measure - including SSI - is attributable to the nasal decontamination (either wholly or in part). By evaluating nasal decontamination as the only systematic difference between the groups, our review has sought to assess this association specifically. The sparseness of the evidence base evaluating the impact of nasal decontamination in this way means that we are not clear what these effects are. The contribution of our review may be considered alongside reviews of the other individual interventions commonly included in these infection control care bundles (Webster 2015).

To the best of our knowledge our review is the only review which examines the effectiveness of nasal decontamination using any agent, focuses on the effectiveness of nasal decontamination as a single strategy (rather than as a component in a bundle of interventions), and restricts treatment to known carriers of *S aureus* who are scheduled to undergo surgery. The results of our review therefore differ from those of the other reviews discussed, which have adopted broader approaches to the question but may not have isolated the effectiveness of nasal decontamination in surgical populations. With a more recent search, our review has contributed additional evidence to this treatment policy: that the effectiveness of nasal decontamination in *S aureus* carriers for the prevention of SSI is unclear, though practice must be guided by clinical judgement of risks and benefits.

AUTHORS' CONCLUSIONS

Implications for practice

This review found insufficient or low-certainty evidence for an effect of nasal decontamination alone on rates of SSIs. This comprehensive review of RCT evidence highlights the current uncertainty regarding the effectiveness of nasal decontamination as a prevention for SSI in *S aureus* carriers. It is important to note that one trial out of two in this review was very small and at high or unclear risk of bias across most domains. Given these uncertainties, practitioners' choice of treatment for surgical wounds may be informed by the costs and potential side effects when choosing between alternatives.

Implications for research

SSIs following surgery are an important issue given the large number of people undergoing surgery annually world-wide; and preoperative nasal decontamination is widely undertaken in an attempt to reduce rates of SSIs (Peacock 2001; Van Rijen 2008a). However, there are only two RCTs included in this review, presenting data from fewer than 300 participants. The low or very low certainty of the evidence for each of the comparisons evaluated means that the effectiveness of each of the interventions assessed is unclear. This is a consequence of single trials with small sample sizes resulting in very serious imprecision for both comparisons and of additional high risk of bias in the comparison of Anerdian versus no intervention. The evidence for the effectiveness of methods of nasal decontamination of *S aureus* carriers as a single intervention for the prevention of SSI is therefore insufficient to support decision making.

If further trials are undertaken they should attempt to measure the impact of nasal decontamination as a single intervention on SSIs in order to isolate the impact of this intervention from other measures. Investigators should also adhere to a recognised definition of SSI, which includes a 30-day follow-up. Trials should be conducted with adequate sample sizes based on a priori sample size calculations and take account of any data cross-over or clustering. Future trials might address important clinical questions - these should be prioritised in conjunction with patients, health professionals and policy makers. Any future trials should be considered alongside concerns about increasing antibiotic resistance, and increases in single- and multi-drug resistance in *S aureus* in particular. All trial designs for research assessing prophylactic use of antibiotics should consider potential harms as well as benefits of the intervention and these should include the issue of resistance.

Current trials report very limited data on secondary outcomes. Outcomes which were not assessed by our included studies in the time frames defined by our protocol included quality of life, resource use and cost. Where it is a priority for patients, carers and health professionals, further research to evaluate the clinical and cost effectiveness of nasal decontamination is warranted. Large and robust RCTs are likely to be the most appropriate study design. Undertaking such studies represents an investment in terms of research costs as well as the opportunity cost of health professionals, and patient time. Thus, any future research must follow good practice guidelines for design, implementation and reporting so that the data produced provide maximum use to patients, health professionals and policy makers. Outcomes such as adverse events, antibiotic resistance and resource use may have an important role in influencing decision making regarding the use of different preoperative decontamination products and thus should be assessed.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Konvalinka 2006

Methods	2-arm RCT. Setting: one hospital in Canada. Only carriers randomised. Follow-up time: 8 weeks (via telephone twice monthly) with GPs and participants
Participants	263 elective cardiac surgery patients (valve replacement; CABG surgery; blood product transfusion and re-exploration) Only colonised patients were enrolled (all carriers). Mupirocin: 130. Placebo: 127. (ITT analysed numbers). Only COPD was more prevalent in the mupirocin group (P < 0.01) Age: mupirocin: 62.5 ± 10.8; placebo: 62.5 ± 10.5. Inclusion criteria: participants undergoing elective open-heart surgery who screened positive for nasal carriage of *S aureus* 2 weeks before surgery. Exclusion criteria: not reported. No Surgical wound classification statement - judged as "clean".
Interventions	Mupirocin or placebo. Twice daily for 7 days, before surgery Group 1: mupirocin 2% contained in a base of polyethylene glycol 400 and polyethylene glycol 3350; twice daily for seven days before surgery (n = 130) Group 2: base of polyethylene glycol 400 and polyethylene glycol 3350 - an identical-appearing placebo administered intranasally (the base only) (n = 127) Co-interventions: standard pre-operative clinical practice included a full shower or bath with chlorhexidine antiseptic soap (2%) 12 hours pre-operatively, surgical site cleansing with 4% chlorhexidine solution with 4% isopropyl alcohol pre-operatively, and administration of routine antibiotic prophylaxis starting just before surgery. Antibiotic prophylaxis consisted of cefazolin 1 g every 8 hours (or clindamycin in those with penicillin allergy) for 24 hours
Outcomes	**Primary outcome** SSI - defined by author as: the presence of exudate from the wound, the edges of the wound were erythematous beyond 2 cm margin, the wound culture yielded a pathogen with signs of inflammation, or a physician stated in the medical record that the surgical site was infected as corroborated by one or more of the listed criteria Mupirocin group: n = 18 (13.8%) Control group: n = 11 (8.6%) Adverse events: no adverse effects were reported for either mupirocin or placebo **Secondary outcomes** *S aureus* SSI: • Mupirocin group: n = 5 (3.8%). • Control group: n = 4 (3.2%). Mortality: • mupirocin group: n = 4. • Control group: n = 5 (one death was directly related to *S aureus* infection).

Konvalinka 2006 (*Continued*)

Notes	Not company funded. Funded by The Cardiovascular Surgery Research Grant and St. Michael's Hospital Foundation Grant

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomisation numbers were computer generated with a 1:1 ratio for mupirocin and placebo." Comment: the study reported use of computer-generated sequence
Allocation concealment (selection bias)	Low risk	Quote: "The randomisation numbers were computer generated with a 1:1 ratio for mupirocin and placebo, and code was available to research pharmacist." Comment: allocation concealed using a pharmacist who carried the randomisation code
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Patients were randomised to receive either 2% mupirocin ointment or an identical-appearing placebo administered intranasally". "All patients were treated equally, as the research assistant was unaware of the randomisation assignment." Comment: blinding of patients and investigators was judged to have been done as the placebo group received an ointment of identical appearance. Also, all patients were treated equally as the research assistant was also blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Blinding was maintained until after analysis by the pharmacist, who divided the treatment groups into A and B." Comment: outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "The remaining 263 were randomised to mupirocin or placebo. Of these, five were excluded from analysis due to cancellation of surgery." "Of the 257 patients included in the intention-to-treat analysis, 130 received mupirocin and 127 received placebo." "One patient was excluded from the intention-to-treat analysis alone, as it was not clear to which treatment he was

Konvalinka 2006 (*Continued*)

		randomised; he used mupirocin on his own initiative. - otherwise the numbers don't add up" Comment: the reason for exclusion was given and ITT analysis was done on all participants who underwent surgery
Selective reporting (reporting bias)	Low risk	Comment: outcomes were properly specified in the Methods section and outcome fully described in results analysis, therefore low risk judgement given
Other bias	Low risk	No evidence of other sources of bias and sufficiently well reported

Yu 2011

Methods	2-arm RCT. Setting: Cardiology department in one hospital in China. Nasal bacterial cultures were performed by taking swabs on admission Cardiac surgery patients with SA colonization were randomly divided into the decolonization group and control group (test and then randomise carrier) Duration of treatment of decolonization was 6 days.
Participants	34 SA carriers who were undergoing cardiac surgery (coronary artery bypass grafting and heart valve replacement); taken from screened population (age range 19 to 86 years; mean 58.4 ± 15.3) Inclusion criteria: at least 18 years old, elective cardiac surgery Exclusion criteria: emergency surgery; uncontrolled infection before surgery; die within 48 hours after surgery No Surgical wound classification statement - judged as "clean".
Interventions	Decolonization group: treated with Anerdian III (iodine 0.45% to 0.57% (W/V), chlorhexidine acetate 0.09% to 0.11% (W/V)) applied in nares 3 days before surgery and 3 days after surgery, four times a day in both nasal cavities (n = 18) Control group: none (n = 16). Co-intervention: both groups received the second or third generation cephalosporin during perioperative period to 3 days after surgery
Outcomes	**Primary outcome** SSI (not defined by authors). Anerdian/placebo: 1/18 vs. 1/16 Adverse events: side-effects of treatment only in Anerdian group (Dry and itch n = 10; and nasal mucosa bleeding n = 2) (not clear that this is total number of participants with event - not further analysed) **Secondary outcomes** None.

Yu 2011 (*Continued*)

Notes	The follow-up period was not reported. Source of funding was not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients with SA colonization were randomly divided into decolonization group and control group." Comment: method of randomisation not stated.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: blinding of patients and investigators was judged to have not been done as the control group did not receive any placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"All participants in Decolonization group completed the treatment." Comment: adequate evidence to award low risk judgement - 100% follow-up implied based on the numbers in each group
Selective reporting (reporting bias)	Unclear risk	No details.
Other bias	Unclear risk	No details.

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

Study	Reason for exclusion
Andenaes 1996	Mixed population.
Anonymous 2004	Wrong patient population.
Bode 2010	Nasal decontamination procedure not the only difference between the groups
Caelli 2000	Nasal decontamination procedure not the only difference between the groups

(*Continued*)

Dryden 2004	Nasal decontamination procedure not the only difference between the groups
Garcia 2003	Mixed population.
Golan 2010	Nasal decontamination procedure not the only difference between the groups
Harbarth 2000	Wrong patient population.
Jabbour 2010	Mixed population.
Kalmeijer 2002	Mixed population.
Mehta 2013	No outcomes.
Moon 2010	Nasal decontamination procedure not the only difference between the groups
Perl 2002	Mixed population.
Phillips 2014	Mixed population.
Rijen 2012	Nasal decontamination procedure not the only difference between the groups
Segers 2006	Nasal decontamination procedure not the only difference between the groups
Shrem 2016	Wrong study design - not a truly RCT.
Shuman 2012	Nasal decontamination procedure not the only difference between the groups
Sousa 2016	Nasal decontamination procedure not the only difference between the groups
Tai 2013	Nasal decontamination procedure not the only difference between the groups
Vinciullo 2014	Nasal decontamination procedure not the only difference between the groups

DATA AND ANALYSES

Comparison 1. Mupirocin compared with placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SSI	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 S. aureus SSI	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Mortality	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 2. Anerdian compared with no treatment

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

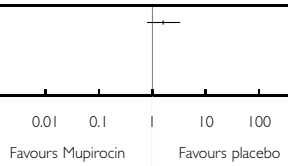
Analysis 1.1. Comparison 1 Mupirocin compared with placebo, Outcome 1 SSI.

Review: Nasal decontamination for the prevention of surgical site infection in *Staphylococcus aureus* carriers

Comparison: 1 Mupirocin compared with placebo

Outcome: 1 SSI

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Konvalinka 2006	18/130	11/127		1.60 [0.79, 3.25]



Analysis 1.2. Comparison 1 Mupirocin compared with placebo, Outcome 2 S. aureus SSI.

Review: Nasal decontamination for the prevention of surgical site infection in *Staphylococcus aureus* carriers

Comparison: 1 Mupirocin compared with placebo

Outcome: 2 S. aureus SSI

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Konvalinka 2006	5/130	4/127		1.22 [0.34, 4.44]

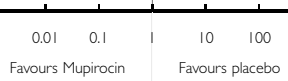
Analysis 1.3. Comparison 1 Mupirocin compared with placebo, Outcome 3 Mortality.

Review: Nasal decontamination for the prevention of surgical site infection in *Staphylococcus aureus* carriers

Comparison: 1 Mupirocin compared with placebo

Outcome: 3 Mortality

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Konvalinka 2006	4/130	5/127		0.78 [0.21, 2.84]

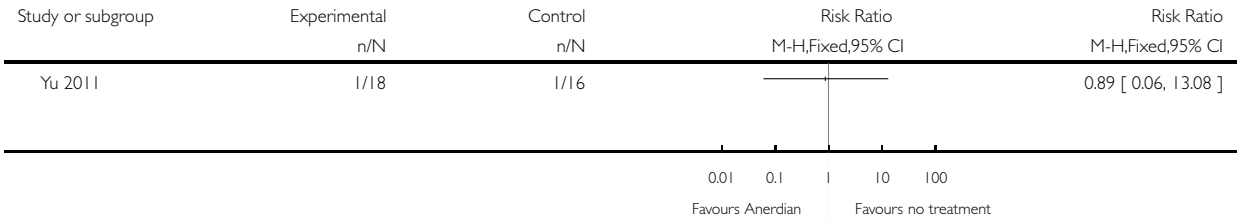


Analysis 2.1. Comparison 2 Anerdian compared with no treatment, Outcome 1 SSI.

Review: Nasal decontamination for the prevention of surgical site infection in *Staphylococcus aureus* carriers

Comparison: 2 Anerdian compared with no treatment

Outcome: 1 SSI



APPENDICES

Appendix 1. HICPAC surgical wound classification

Clean (Class 1): noninfective operative wounds in which no inflammation is encountered, with no involvement of respiratory*, gastrointestinal*, genitourinary tract*, and oropharyngeal cavity*.

Clean-contaminated (Class 2): operative wounds in which either the respiratory*, gastrointestinal*, 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.

Glossary

biliary tract - liver, gall bladder and bile ducts
controlled conditions - within a sterile operating theatre
gastrointestinal tract - digestive system
genitourinary tract - bladder and reproductive system
gross spillage - bowel contents leaking into the wound
nonpurulent - free from pus
operative field - area around the wound
oropharyngeal cavity - mouth and throat
oropharynx - back of the mouth
perforated viscera - an opening in the stomach or bowel
respiratory tract - airways
retained devitalised tissue - dead skin/muscle cells that remain in a wound

sterile technique - methods to decrease the likelihood of SSI such as use of sterile instruments, drapes, surgical masks and hand washing
traumatic lacerations - cut or tear caused by an object e.g. bullet wound

Appendix 2. Search strategies

The Cochrane Central Register of Controlled Clinical Trials (CENTRAL)
#1 MeSH descriptor: [Nose] explode all trees
#2 (nose* or nas* or rhin*):ti,ab,kw
#3 {or #1-#2}
#4 MeSH descriptor: [Staphylococcal Infections] explode all trees
#5 MeSH descriptor: [Staphylococcus aureus] explode all trees
#6 (staphylococ* or "S aureus"):ti,ab,kw
#7 {or #4-#6}
#8 {and #3, #7}
#9 MeSH descriptor: [Anti-Infective Agents] explode all trees
#10 MeSH descriptor: [Antibiotic Prophylaxis] explode all trees
#11 MeSH descriptor: [Mupirocin] explode all trees
#12 MeSH descriptor: [Chlorhexidine] explode all trees
#13 MeSH descriptor: [Povidone-Iodine] explode all trees
#14 MeSH descriptor: [Administration, Intranasal] explode all trees
#15 MeSH descriptor: [Decontamination] explode all trees
#16 (antibiotic* or antimicrobial* or antibacterial* or antiseptic*):ti,ab,kw
#17 (Mupirocin or Chlorhexidine or Povidone-Iodine or bactroban or centany or eismycin or plasimine or "pseudomonic acid" or Naseptin or CHG):ti,ab,kw
#18 (intranasal* or decontamin* or decoloni*):ti,ab,kw
#19 {or #9-#18}
#20 MeSH descriptor: [Surgical Wound Infection] explode all trees
#21 MeSH descriptor: [Surgical Wound Dehiscence] explode all trees
#22 MeSH descriptor: [Cross Infection] explode all trees
#23 (surg* near/5 infect*):ti,ab,kw
#24 (surg* near/5 wound*):ti,ab,kw
#25 (surg* near/5 site*):ti,ab,kw
#26 (surg* near/5 incision*):ti,ab,kw
#27 (surg* near/5 dehisc*):ti,ab,kw
#28 (wound* near/5 dehisc*):ti,ab,kw
#29 (wound* near/5 infect*):ti,ab,kw
#30 (wound* near/5 disrupt*):ti,ab,kw
#31 (wound next complication*):ti,ab,kw
#32 (cross near/5 infect*):ti,ab,kw
#33 SSI:ti,ab,kw
#34 {or #20-#33}
#35 {and #8, #19, #34} in Trials
Ovid MEDLINE
1 exp Nose/
2 (nose* or nas* or rhin*).mp.
3 or/1-2
4 exp Staphylococcal Infections/
5 exp Staphylococcus aureus/
6 staphylococ*.mp.
7 S aureus.mp.
8 or/4-7
9 and/3,8

10 exp Anti-Infective Agents/
11 exp Antibiotic Prophylaxis/
12 exp Mupirocin/
13 exp Chlorhexidine/
14 exp Povidone-Iodine/
15 exp Administration, Intranasal/
16 exp Decontamination/
17 (antibiotic* or antimicrobial* or antibacterial* or antiseptic*).mp.
18 (Mupirocin or Chlorhexidine or Povidone-Iodine or bactroban or centany or eismycin or plasimine or pseudomonic acid or Naseptin or CHG).mp.
19 (intranasal* or decontamin* or decoloni*).mp.
20 or/10-19
21 exp Surgical Wound Infection/
22 exp Surgical Wound Dehiscence/
23 exp Cross Infection/
24 (surg* adj5 infect*).mp.
25 (surg* adj5 wound*).mp.
26 (surg* adj5 site*).mp.
27 (surg* adj5 incision*).mp.
28 (surg* adj5 dehisc*).mp.
29 (wound* adj5 dehisc*).mp.
30 (wound* adj5 infect*).mp.
31 (wound* adj5 disrupt*).mp.
32 wound complication*.mp.
33 (cross adj5 infect*).mp.
34 SSI.mp.
35 or/21-34
36 and/9,20,35
37 randomized controlled trial.pt.
38 controlled clinical trial.pt.
39 randomi?ed.ab.
40 placebo.ab.
41 clinical trials as topic.sh.
42 randomly.ab.
43 trial.ti.
44 or/37-43
45 exp animals/ not humans.sh.
46 44 not 45
47 and/36,46

Ovid Embase

1 exp nose/
2 (nose* or nas* or rhin*).mp.
3 or/1-2
4 exp Staphylococcus infection/
5 exp Staphylococcus aureus/
6 staphylococ*.mp.
7 S aureus.mp.
8 or/4-7
9 and/3,8
10 exp antiinfective agent/
11 exp antibiotic prophylaxis/
12 exp intranasal drug administration/
13 (antibiotic* or antimicrobial* or antibacterial* or antiseptic*).mp.

14 (Mupirocin or Chlorhexidine or Povidone-Iodine or bactroban or centany or eismycin or plasimine or pseudomonic acid or Naseptin or CHG).mp.
15 (intranasal* or decontamin* or decoloni*).mp.
16 or/10-15
17 exp surgical infection/
18 exp wound dehiscence/
19 exp cross infection/
20 (surg* adj5 infect*).mp.
21 (surg* adj5 wound*).mp.
22 (surg* adj5 site*).mp.
23 (surg* adj5 incision*).mp.
24 (surg* adj5 dehisc*).mp.
25 (wound* adj5 dehisc*).mp.
26 (wound* adj5 infect*).mp.
27 (wound* adj5 disrupt*).mp.
28 wound complication*.mp.
29 (cross adj5 infect*).mp.
30 SSI.mp.
31 or/17-30
32 and/9,16,31
33 Randomized controlled trials/
34 Single-Blind Method/
35 Double-Blind Method/
36 Crossover Procedure/
37 (random* or factorial* or crossover* or cross over* or cross-over* or placebo* or assign* or allocat* or volunteer*).ti,ab.
38 (doubl* adj blind*).ti,ab.
39 (singl* adj blind*).ti,ab.
40 or/33-39
41 exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/
42 human/ or human cell/
43 and/41-42
44 41 not 43
45 40 not 44
46 and/32,45

EBSCO CINAHL Plus

S46 S32 AND S45
S45 S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44
S44 TI allocat* random* or AB allocat* random*
S43 MH "Quantitative Studies"
S42 TI placebo* or AB placebo*
S41 MH "Placebos"
S40 TI random* allocat* or AB random* allocat*
S39 MH "Random Assignment"
S38 TI randomi?ed control* trial* or AB randomi?ed control* trial*
S37 AB (singl* or doubl* or trebl* or tripl*) and AB (blind* or mask*)
S36 TI (singl* or doubl* or trebl* or tripl*) and TI (blind* or mask*)
S35 TI clinic* N1 trial* or AB clinic* N1 trial*
S34 PT Clinical trial
S33 MH "Clinical Trials+"
S32 S9 AND S16 AND S31
S31 S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30
S30 TX SSI
S29 TX (cross N5 infect*)

S28 TX wound complication*
S27 TX (wound* N5 disrupt*)
S26 TX (wound* N5 infect*)
S25 TX (wound* N5 dehisc*)
S24 TX (surg* N5 dehisc*)
S23 TX (surg* N5 incision*)
S22TX (surg* N5 site*)
S21TX (surg* N5 wound*)
S20 TX (surg* N5 infect*)
S19 (MH "Cross Infection+")
S18 (MH "Surgical Wound Dehiscence")
S17 (MH "Surgical Wound Infection")
S16 S10 OR S11 OR S12 OR S13 OR S14 OR S15
S15 TX (intranasal* or decontamin* or decoloni*)
S14 TX (Mupirocin or Chlorhexidine or Povidone-Iodine or bactroban or centany or eismycin or plasimine or pseudomonic acid or Naseptin or CHG)
S13 TX (antibiotic* or antimicrobial* or antibacterial* or antiseptic*)
S12 (MH "Administration, Intranasal")
S11 (MH "Antibiotic Prophylaxis")
S10 (MH "Antiinfective Agents+")
S9 S3 AND S8
S8 S4 OR S5 OR S6 OR S7
S7 TX S aureus
S6 TX staphylococ*
S5 (MH "Staphylococcus Aureus+")
S4 (MH "Staphylococcal Infections+")
S3 S1 OR S2
S2 TX (nose* or nas* or rhin*)
S1 (MH "Nose+")

Appendix 3. Risk of bias assessment (individually randomised controlled trials)

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 to permit 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 to permit 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 unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias).
- Missing outcome data 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 observed event risk not enough to have a clinically relevant impact on the intervention effect estimate.
- For continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes not enough to have a clinically relevant impact on 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 likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups.
- For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate.
- For continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size.
- 'As-treated' analysis done with 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 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 are reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not prespecified.
- One or more reported primary outcomes 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 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 to permit 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.

Appendix 4. Risk of bias assessment (cluster-randomised controlled trials)

In cluster-randomised trials, particular biases to consider include: (i) recruitment bias; (ii) baseline imbalance; (iii) loss of clusters; (iv) incorrect analysis; and (v) comparability with individually randomised trials.

(i) Recruitment bias can occur when individuals are recruited to the trial after the clusters have been randomised, as the knowledge of whether each cluster is an 'intervention' or 'control' cluster could affect the types of participants recruited.

(ii) Cluster-randomised trials often randomise all clusters at once, so lack of concealment of an allocation sequence should not usually be an issue. However, because small numbers of clusters are randomised, there is a possibility of chance baseline imbalance between the randomised groups, in terms of either the clusters or the individuals. Although not a form of bias as such, the risk of baseline differences can be reduced by using stratified or pair-matched randomisation of clusters. Reporting of the baseline comparability of clusters, or statistical adjustment for baseline characteristics, can help reduce concern about the effects of baseline imbalance.

(iii) Occasionally, complete clusters are lost from a trial, and have to be omitted from the analysis. Just as for missing outcome data in individually randomised trials, this may lead to bias. In addition, missing outcomes for individuals within clusters may also lead to a risk of bias in cluster-randomised trials.

(iv) Many cluster-randomised trials are analysed by incorrect statistical methods, not taking the clustering into account. Such analyses create a 'unit of analysis error' and produce over-precise results (the standard error of the estimated intervention effect is too small) and P values that are too small. They do not lead to biased estimates of effect. However, if they remain uncorrected, they will receive too much weight in a meta-analysis.

(v) In a meta-analysis including both cluster and individually randomised trials, or including cluster-randomised trials with different types of clusters, possible differences between the intervention effects being estimated need to be considered. For example, in a vaccine trial of infectious diseases, a vaccine applied to all individuals in a community would be expected to be more effective than if the vaccine was applied to only half of the people. Another example is provided by a Cochrane review of hip protectors. The cluster trials showed large positive effect, whereas individually randomised trials did not show any clear benefit. One possibility is that there was a 'herd effect' in the cluster-randomised trials (which were often performed in nursing homes, where compliance with using the protectors may have been enhanced). In general, such 'contamination' would lead to underestimates of effect. Thus, if an intervention effect is still demonstrated despite contamination in those trials that were not cluster-randomised, a confident conclusion about the presence of an effect can be drawn. However, the size of the effect is likely to be underestimated. Contamination and 'herd effects' may be different for different types of cluster.

CONTRIBUTIONS OF AUTHORS

Zhenmi Liu: conceived, designed and coordinated the review; extracted data; checked the quality of data extraction; analysed and interpreted data; undertook and checked quality assessment; performed statistical analysis; checked the quality of the statistical analysis; produced the first draft of the review; contributed to writing and editing the review; made an intellectual contribution to the review; approved the final review prior to submission; performed translations and is a guarantor of the review.

Gill Norman: coordinated the review; checked the quality of data extraction; checked quality assessment; checked the quality of the statistical analysis; contributed to writing or editing the review; made an intellectual contribution to the review; approved the final review prior to submission and advised on the review.

Zipporah Iheozor-Ejiofor: advised on the review.

Jason Wong: contributed to writing or editing the review; made an intellectual contribution to the review; approved the final review prior to submission and advised on the review.

Emma Crosbie: made an intellectual contribution to the review and approved the final review prior to submission.

Peter Wilson: made an intellectual contribution to the review and approved the final review prior to submission.

Contributions of the editorial base

Nicky Cullum (Editor): Edited the protocol; advised on methodology interpretation and content; approved the final protocol prior to submission.
Jo Dumville (Editor): Edited the review; advised on methodology interpretation and content; approved the final review prior to submission.
Gill Rizzello (Managing Editor): co-ordinated the editorial process; advised on content; edited the review.
Naomi Shaw and Reetu Child (Information Specialists); designed the search strategy, ran the searches and edited the search methods section.
Ursula Gonthier (Editorial Assistant): edited the Plain Language Summary and the reference section. Advised on response to copy edit comments.

DECLARATIONS OF INTEREST

Zhenmi Liu: my employment at the University of Manchester is funded by the NIHR (NIHR Research Methods Programme Systematic Review Fellowship NIHR-RMFI-2015-06-52).

Gill Norman: my employment at the University of Manchester is funded by the NIHR and focuses on high priority Cochrane reviews in the prevention and treatment of wounds.

Zipporah Iheozor-Ejiofor: none known.

Jason KF Wong: none known.

Emma J Crosbie: I am a Scientific Editor for BJOG. I have received funding from an NIHR Clinician Scientist Award, the HTA, Wellbeing of Women/the Wellcome Trust and Central Manchester University Hospitals NHS Foundation Trust. I am an employee of the University of Manchester.

Peter Wilson: I am a consultant microbiologist in the NHS advising on antibiotic use and I advise some private hospitals on infection control. I am a member of a clinical trial drug safety monitoring board for a monoclonal antibody. I have been an expert witness in infection related cases. I hold a number of non-commercial grants for research in the area of transmission of infection. I am part funded by the UCLH/UCL Comprehensive Biomedical Centre with funding from the Department of Health's NIHR Biomedical Research Centres.

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- National Institute for Health Research, UK.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We clarified that we would not include studies in which a mixed population (including *S aureus* carriers and no carriers) were all randomised to nasal decontamination treatment schedules or placebo/no treatment, but would only include studies in which only carriers were randomised.

We planned to calculated the OIS based on GRADE guidance of using a relative risk reduction of between 20% and 30%, however this was not conducted and we revised the methods to downgrade based on the size of the confidence intervals and a qualitative assessment of the number of events. This decision was made prior to the conduct of the review and will not have introduced any bias into the review.

INDEX TERMS

Medical Subject Headings (MeSH)

*Cardiac Surgical Procedures; Anti-Bacterial Agents [*therapeutic use]; Anti-Infective Agents, Local [*therapeutic use]; Carrier State [*drug therapy]; Chlorhexidine [therapeutic use]; Drug Combinations; Iodine [therapeutic use]; Mupirocin [therapeutic use]; Nose [*microbiology]; Randomized Controlled Trials as Topic; Staphylococcal Infections [*drug therapy; mortality]; Staphylococcus aureus; Surgical Wound Infection [*prevention & control]

MeSH check words

Humans