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

DOI:
10.1002/14651858.CD012462.

Document Version
Final published version

Cochrane Library

Cochrane Database of Systematic Reviews

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

Liu Z, Norman G, Iheozor-Ejiofor Z, Wong JKF, Crosbie EJ, Wilson P

Liu Z, Norman G, Iheozor-Ejiofor Z, Wong JKF, Crosbie EJ, Wilson P.
Nasal decontamination for the prevention of surgical site infection in Staphylococcus aureus carriers.
Cochrane Database of Systematic Reviews 2016, Issue 12. Art. No.: CD012462.
DOI: 10.1002/14651858.CD012462.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Protocol]

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

Zhenmi Liu[1], Gill Norman[1], Zipporah Iheozor-Ejiofor[1], Jason KF Wong[2], Emma J Crosbie[3], Peter Wilson[4]

[1]Division of Nursing, Midwifery & Social Work, School of Health Sciences, Faculty of Biology, Medicine & Health, University of Manchester, Manchester, UK. [2]Plastic and Reconstructive Surgery, University Hospital South Manchester, Manchester, UK. [3]Institute of Cancer Sciences, Division of Molecular and Clinical Cancer Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK. [4]Clinical Microbiology and Virology, University College London Hospitals NHS Foundation Trust, London, UK

Contact address: Zhenmi Liu, Division of Nursing, Midwifery & Social Work, School of Health Sciences, Faculty of Biology, Medicine & Health, University of Manchester, Jean McFarlane Building, Oxford Road, Manchester, M13 9PL, UK. zhenmi.liu@manchester.ac.uk, liuzhenmi1983@Hotmail.com.

Editorial group: Cochrane Wounds Group.
Publication status and date: New, published in Issue 12, 2016.

Citation: Liu Z, Norman G, Iheozor-Ejiofor Z, Wong JKF, Crosbie EJ, Wilson P. Nasal decontamination for the prevention of surgical site infection in *Staphylococcus aureus* carriers. *Cochrane Database of Systematic Reviews* 2016, Issue 12. Art. No.: CD012462. DOI: 10.1002/14651858.CD012462.

ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

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

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 cause delayed wound healing, increased hospital stays, 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 2016). 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). 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 similar 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 Western healthcare settings, SSI was the leading cause of hospital-acquired infection in a systematic review of studies in low- and middle-income 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 Centres 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 4.

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 contamination of a surgical incision with micro-organisms from the patient's own body (endogenous bacteria) during surgery. Infection caused by micro-organisms from an outside source following surgery is less common (NICE 2008). *Staphylococcus aureus* (*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. 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). 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).

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 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 frequently 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 two 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 -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 will be available. In some areas of surgical practice this may substantially affect the evidence base. A previous Cochrane Review (Van Rijen 2008a) 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. Another publication by the same authors (Van Rijen 2008b) also focused on mupirocin as an intervention and included only trials in surgical patients who were *S aureus* carriers. 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 will directly address and update the evidence base for nasal decontamination in this group for the prevention of SSI and associated morbidity and mortality. It will also include any intervention used for nasal decontamination in *S aureus* carriers scheduled to undergo surgery, and will not be 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 will examine sensitive and resistant *S aureus* SSIs separately in this review, which will allow us 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, treated in any setting.

METHODS

Criteria for considering studies for this review

Types of studies

We will include all published and unpublished randomised controlled trials (RCTs) irrespective of language of report. This will include cluster-randomised trials. We will 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 are included in the study (alternation)).

Types of participants

People of any age undergoing surgery who are nasal carriers of *S aureus*. Surgery is 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 will include studies including either or both adults and children who are 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 will be included. We will exclude studies including mixed population (both carriers and non carriers).

Types of interventions

We will include studies where the type or schedule of nasal decontamination is the only systematic difference between study arms. This review will therefore include comparisons of nasal decontamination procedures with each other and/or placebo and/or treatment as usual or no intervention. We anticipate that we may 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 are expected, for example, antimicrobial skin preparation, however these co-interventions must be delivered similarly to all comparison groups as this review aims to determine the effect of nasal decontamination specifically.

Types of outcome measures

We list primary and secondary outcome measures below. If a trial is otherwise eligible (correct study design, population, and intervention/comparator) but does not report a listed outcome, then we will contact the study authors, where possible, in order to establish whether a relevant outcome was measured but not reported. However, we do not plan to exclude otherwise eligible studies solely on the basis of reported outcomes.

Where possible, we anticipate grouping outcomes by the following time points, review authors' judgement will be used as to whether statistical pooling within these time categories is appropriate:

- Short-term: 30 days
- Medium-term: 30 days to 12 months
- Long-term: more than 12 months.

We will report 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 is different from latest time point available).

Primary outcomes

The primary outcomes for this review will be SSI and adverse events.

Occurrence of postoperative SSI - the proportion of people who develop SSIs, as defined by the Centers for Disease Control and Prevention (CDC) (Mangram 1999) or by the study authors. We will not differentiate between superficial and deep-incisional infection. The SSI outcome is measured in participants who were scheduled to undergo surgery. Whatever the organism implicated in the SSI we will extract 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 will be 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 develop infections, as defined by study authors. The infection outcome is 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 will 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 have developed the search strategy in consultation with Cochrane Wound's Information Specialist.

Electronic searches

We will search the following electronic databases for randomised controlled trials:

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

The draft search strategy for CENTRAL is presented in Appendix 1. We will adapt this strategy to search Ovid MEDLINE, Ovid Embase, and EBSCO CINAHL Plus. We will combine the Ovid MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision) (Lefebvre 2011). We will combine the Embase search with the Ovid Embase randomised trials filter terms developed by the UK Cochrane Centre (Lefebvre 2011). We will combine the CINAHL searches with the randomised trials filter terms developed by the Scottish Intercollegiate Guidelines Network (SIGN 2015). We will not impose any restrictions with respect to language, date of publication, or study setting.

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

Data collection and analysis

Selection of studies

Two review authors (ZL and GN) will independently assess the titles and abstracts of the citations retrieved by the searches for relevance. After this initial assessment, we will obtain full-text copies of all studies considered to be potentially relevant. Two review authors (ZL and GN) will independently check the full papers for eligibility; disagreements will be resolved by discussion and, where required, the input of a third review author (ZI). Where required and possible, we will contact study authors where the eligibility of a study is unclear. We will record all reasons for exclusion of studies for which we have obtained full copies. We will complete a PRISMA flowchart to summarise this process (Liberati 2009). Where studies have been reported in multiple publications/reports, we will obtain all publications. Data extraction will be performed at the level of the study rather than the report.

Data extraction and management

We will extract and summarise details of the eligible studies using a data extraction sheet. Two review authors (ZL and GN) will extract data independently and will resolve disagreements by discussion, drawing on a third review author (ZI) where required. Where data are missing from reports, we will attempt to contact the study authors to obtain this information. Where a study with more than two intervention arms is included, we will only extract data from intervention and control groups that meet the eligibility criteria. We will extract the following data, where possible, by treatment group for the prespecified interventions and outcomes in this review. We will collect 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) will independently assess 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 will resolve 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 will record issues with unit of analysis, for example, where a cluster trial has been undertaken but analysed at the individual level in the study report (Appendix 2). We will assess blinding and completeness of outcome data for each of the review outcomes separately. We will present our assessment of risk of bias using two 'Risk of bias' summary figures; one that is a summary of bias for each item across all studies, and a second that shows a cross-tabulation of each trial by all of the risk of bias items.

For trials using cluster-randomisation, we will also consider the risk of bias considering: 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 will calculate the risk ratio (RR) with 95% confidence intervals (CIs). For continuous outcomes we will use the mean difference (MD) with 95% CIs, if all trials use the same or a similar assessment scale. If trials use different assessment scales, we will use 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) (RevMan 2014).

We will record where a cluster-randomised trial has been conducted, but incorrectly analysed. We will record this as part of the 'Risk of bias' assessment. If possible, we will approximate 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 intra cluster (or intra class) correlation coefficient (ICC).

If we cannot analyse the study data correctly, we will extract and present outcome data but 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 are missing data that we think should be included in the analyses, we will contact relevant study authors to request whether these data are available.

Where data remain missing for the proportion of participants with SSI, we will assume 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 will conduct a completed case analysis as a sensitivity analysis and will also explore alternative scenarios using different assumptions about missing cases.

For continuous variables, such as length of hospital stay, and for all secondary outcomes, we will present available data from the study reports/study authors, but we do not plan to impute missing data. Where measures of variance are missing, we will calculate these wherever possible. If calculation is not possible, we will contact study authors. Where these measures of variation are not available, we will exclude the study from any relevant meta-analyses that we conduct.

Assessment of heterogeneity

Assessment of heterogeneity can be a complex, multifaceted process. Firstly, we will consider 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 will supplement this assessment of clinical and methodological heterogeneity by information regarding statistical heterogeneity, assessed using the Chi² test (we will consider 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 will be assessed, the overall assessment of heterogeneity will assess these measures in combination with the methodological and clinical assessment of heterogeneity. See Data synthesis for further information about how we will deal 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 plan to present funnel plots for meta-analyses comprising 10 RCTs or more using RevMan 5 (RevMan 2014).

Data synthesis

We will combine 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 will consider clinical and methodological heterogeneity, and undertake pooling when studies appear 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 will be to use the random-effects model. We will only use a fixed-effect approach when clinical heterogeneity is thought to be minimal, and statistical heterogeneity is not statistically significant for the Chi^2 value and 0% for the I^2 assessment (Kontopantelis 2013). We will adopt this approach as it is 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 is thought to be acceptable, or of interest, we may meta-analyse even when statistical heterogeneity is high, but we will attempt to interpret the causes behind this heterogeneity, and will consider using meta-regression for that purpose, if possible (Thompson 1999).

We will present data using forest plots, where possible. For dichotomous outcomes, we will present the summary estimate as a RR with 95% CI. Where continuous outcomes are measured in the same way across studies, we plan to present a pooled MD with 95% CI; we plan to pool SMD estimates where studies measure the same outcome, but use different scales.

We will obtain pooled estimates of treatment effect using RevMan 5 software (RevMan 2014).

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

We will present the main results of the review in 'Summary of findings' tables. These tables present key information concerning the quality of the evidence, the magnitude of the effects of the interventions examined, and the sum of the available data for the main outcomes (Schünemann 2011a). The 'Summary of findings' tables also include an overall grading of the evidence related to each of the main outcomes using the GRADE approach. The GRADE approach defines the quality of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the true quantity of specific interest. The quality of a body of evidence involves consideration of within-trial risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates, and risk of publication bias (Schünemann 2011b). We plan to present the following 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 will 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 will downgrade only when studies have been classed at high risk of bias for one or more domains. We will not downgrade for unclear risk of bias assessments. In assessing the precision of effect estimates for SSI we will follow GRADE guidance (GRADE 2013) and calculate an optimal information size (OIS) using conventional sample size calculation methods. We will use the OIS, along with the size of 95% CIs in terms of whether they spanned estimates of benefit and harm, to assess for downgrading. We will calculate the OIS based on GRADE guidance of using a relative risk reduction of between 20% and 30%. The OIS will be summarised but should not be treated as optimal sample sizes for any future research - within a GRADE assessment the OIS is used to assess the stability of CIs rather than being used to assess the appropriateness of a sample size to detect a difference per se.

We will also follow GRADE guidance and downgrade twice for imprecision when there are very few events, and CIs around effects included both appreciable benefit and appreciable harm.

Subgroup analysis and investigation of heterogeneity

Where feasible, we will explore the effects of interventions in children (aged under 18) and adults separately. If a sufficient number of studies are identified we will additionally explore the effects of interventions as follows:

- emergency versus elective surgery;
- open versus laparoscopic surgery; and
- according to classification of the infection risk of surgery (HICPAC 1999).

Where possible, we plan to perform sensitivity analyses to explore the effect of the following

- Studies at high risk of bias for any domain compared with other studies with no domain classed at high risk of bias.

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

ACKNOWLEDGEMENTS

The authors are grateful to the following peer reviewers: Kurinchi Gurusamy (editor); Alexis Llewellyn, Brian Hong and Helen Castledine.

The authors would like to thank Ursula Gonthier for proof-reading this protocol and Denise Mitchell for copy editing it.

REFERENCES

Additional references

Allegranzi 2010
Allegranzi B, Nejad SB, Combescure C, Graafmans W, Attar H, Donaldson L, et al. Burden of endemic health-care-associated infection in developing countries: systematic review and meta-analysis. *Lancet* 2010;**377**(9761):228–41.

Anderson 2008
Anderson DJ, Chen LF, Schmader KE, Sexton DJ, Choi Y, Link K, et al. Poor functional status as a risk factor for surgical site infection due to methicillin-resistant staphylococcus aureus. *Infection Control and Hospital Epidemiology* 2008;**29**(9):832–9.

Astagneau 2009
Astagneau P, L'Hériteau F, Daniel F, Parneix P, Venier AG, Malavaud S, et al. ISO-RAISIN Steering Group. Reducing surgical site infection incidence through a network: results from the French ISO-RAISIN surveillance system. *Journal of Hospital Infection* 2009;**72**(2):127–34.

Awad 2012
Awad SS. Adherence to surgical care improvement project measures and post-operative surgical site infections. *Surgical Infections* 2012;**13**(2):234–7.

Bebko 2015
Bebko SP, Green DM, Awad SS. Effect of a preoperative decontamination protocol on surgical site infections in patients undergoing elective orthopedic surgery with hardware implantation. *JAMA Surgery* 2015;**150**(5):390–5.

Bode 2010
Bode GM, Kluytmans JA, Wertheim HF, Bogaers D, Vandenbroucke-Grauls CM, Roosendaal R, et al. Preventing surgical-site infections in nasal carriers of Staphylococcus aureus. *New England Journal of Medicine* 2010;**362**:9–17.

British National Formulary 2016
British Medical Association, Royal Pharmaceutical Society. Naseptin® (Alliance). www.evidence.nhs.uk/formulary/bnf/current/12-ear-nose-and-oropharynx/122-drugs-acting-on-the-nose/1223-nasal-preparations-for-infection/nasal-staphylococci/naseptin (accessed 19 September 2016).

Brown 2014
Brown B, Tanner J, Padley W. This wound has spoiled everything: emotional capital and the experience of surgical site infections. *Sociology of Health and Illness* 2014;**36**(8):1171–87.

Bruce 2001
Bruce J, Russell EM, Mollison J, Krukowski ZH. The measurement and monitoring of surgical adverse events. *Health Technology Assessment* 2001;**5**(22):1–194.

Campoccia 2013
Campoccia D, Montanaro L, Arciola CR. A review of the clinical implications of anti-infective biomaterials and infection-resistant surfaces. *Biomaterials* 2013;**34**:8018–29.

CDC 2016
Centers for Disease Control (CDC). Surgical Site Infection (SSI) Event. Procedure-associated Module SSI 2016: www.cdc.gov/nhsn/PDFs/pscmanual/9pscssicurrent.pdf.

Chemaly 2010
Chemaly RF, Hachem RY, Husni RN, Bahna B, Abou Rjaili G, Waked A, et al. Characteristics and outcomes of methicillin resistant staphylococcus aureus surgical-site infections in patients with cancer: a case-control study. *Annals of Surgical Oncology* 2010;**17**:1499–1506.

Coates 2009
Coates T, Bax R, Coates A. Nasal decolonization of Staphylococcus aureus with mupirocin: strengths, weaknesses and future prospects. *Journal of Antimicrobial Chemotherapy* 2009;**64**:9-15.

de Lissovoy 2009
de Lissovoy G, Fraeman K, Hutchins V, Murphy D, Song D, Vaughn BB. Surgical site infection: incidence

and impact on hospital utilization and treatment costs. *American Journal of Infection Control* 2009;**37**(5):387–97.

Deeks 2011
Deeks JJ, Higgins JPT, Altman DG. Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT, Green S (editors) Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Edwards 2008
Edwards C, Counsell A, Boulton C, Moran CG. Early infection after hip fracture surgery: risk factors, costs and outcome. *Journal of Bone and Joint Surgery British Edition* 2008;**90**:770–7.

Gibbons 2011
Gibbons C, Bruce J, Carpenter J, Wilson AP, Wilson J, Pearson A, et al. Identification of risk factors by systematic review and development of risk-adjusted models for surgical site infection. *Health Technology Assessment* 2011;**15**(30): 1–156.

GRADE 2013
Schünemann H, Broż ek J, Guyatt G, Oxman A, GRADE working group. GRADE Handbook. gdt.guidelinedevelopment.org/central_prod/_design/client/handbook/handbook.html (accessed 5 August 2016).

Hibbard 2002
Hibbard JS, Mulbery GK, Brady AR. A clinical study comparing the skin antisepsis and safety of chloraprep, 70% isopropylalcohol and 2% aqueous chlorhexidine. *Journal of Infusion Nursing* 2002;**25**(4):244–9.

HICPAC 1999
Hospital Infection Control Practices Advisory Committee (HICPAC). Guideline for prevention of surgical site infection 1999. *Infection Control and Hospital Epidemiology* 1999;**20**(4):259.

Higgins 2003
Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**: 557–60.

Higgins 2011a
Higgins JPT, Altman DG, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Higgins 2011b
Higgins JPT, Deeks JJ, Altman DG (editors). Chapter 16: Special topics in statistics. In: Higgins JPT, Green S (editors) Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org. The Cochrane Collaboration. Available from www.cochrane–handbook.org..

Hoffrage 2000
Hoffrage U, Lindsey S, Hertwig R, Gigerenzer G. Medicine: communicating statistical information. *Science* 2000;**290** (5500):2261–2.

Kontopantelis 2012
Kontopantelis E, Reeves D. Performance of statistical methods for meta-analysis when true study effects are non-normally distributed. *Statistical Methods Methodology Research* 2012;**21**:409–26.

Kontopantelis 2013
Kontopantelis E, Springate DA, Reeves D. A re-analysis of the Cochrane Library data: the dangers of unobserved heterogeneity in meta-analysis. *PLoS One* 2013;**8**(7): e69930.

Korol 2013
Korol E, Johnston K, Waser N, Sifakis F, Jafri HS, Lo M, et al. A systematic review of risk factors associated with surgical site infections among surgical patients. *PLoS ONE* 2013;**8**(12):e83743.

Leaper 2015
Leaper D, Tanner J, Kiernan M, Assadian O, Edmiston C. Surgical site infection: poor compliance with guidelines and care bundles. *International Wound Journal* 2015;**12**(3): 357–62.

Leekha 2011
Leekha S, Terrell CL, Edson RS. General principles of antimicrobial therapy. *Mayo Clinic Proceedings* 2011;**86**(2): 156-67.

Lefebvre 2011
Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JPT, Green S (editors) Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org. The Cochrane Collaboration, 2011. Available from www.cochrane–handbook.org.

Levy 2013
Levy PY, Ollivier M, Drancourt M, Raoult D, Argenson JN. Relation between nasal carriage of Staphylococcus aureus and surgical site infection in orthopedic surgery: the role of nasal contamination. A systematic literature review and meta-analysis. *Orthopaedics and Traumatology: Surgery and Research* 2013;**99**:645–51.

Liberati 2009
Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *BMJ* 2009;**339**:b2700.

Macpherson 2004
Macpherson G (editor). *Black's Student Medical Dictionary*. London: A&C Black Publishers Limited, 2004.

Mangram 1999
Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. Guideline for prevention of surgical site infection.

Infection Control and Hospital Epidemiology 1999;**20**(4): 247–78.

NICE 2008
National Institute for Health and Care Excellence (NICE). Prevention and treatment of surgical site infection. Clinical guideline [CG74]. October 2008. www.nice.org.uk/Guidance/cg74 (accessed 19 September 2016).

Nouwen 2006
Nouwen J, Schouten J, Schneebergen P, et al. Staphylococcus aureus carriage patterns and the risk of infections associated with continuous peritoneal dialysis. *Journal of Clinical Microbiology* 2006;**44**:2233-6.

Owens 2008
Owens CD, Stoessel K. Surgical site infections: epidemiology, microbiology and prevention. *Journal of Hospital Infection* 2008;**70**(S2):3–10.

Patel 2009
Patel JB, Gorwitz RJ, Jernigan JA. Mupirocin resistance. *Clinical Infectious Diseases* 2009;**49**(6):935–41.

Peacock 2001
Peacock SJ, de Silva I, Lowy FD. What determines nasal carriage of Staphylococcus aureus?. *Trends in Microbiology* 2001;**9**(12):605–10.

Plowman 2000
Plowman R, Graves N, Griffin M. The Socio-economic Burden of Hospital Acquired Infection. London: Public Health Services Laboratory 2000.

Public Health England 2014
Public Health England. Surveillance of surgical site infections in NHS hospitals in England: 2013 to 2014. www.gov.uk/government/uploads/system/uploads/attachment_data/file/386927/SSI_report_2013_14_final__3_.pdf (accessed 1 July 2016).

RevMan 2014 [Computer program]
Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Schünemann 2011a
Schünemann HJ, Oxman AD, Higgins JPT, Vist GE, Glasziou P, Guyatt GH. Chapter 11: Presenting results and 'Summary of findings' tables. In: Higgins JPT, Green S (editors) Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org. The Cochrane Collaboration, 2011. Available from www.cochrane–handbook.org.

Schünemann 2011b
Schünemann HJ, Oxman AD, Higgins JPT, Deeks JJ, Glasziou P, Guyatt GH. Chapter 12: Interpreting results and drawing conclusions. In: Higgins JPT, Green S (editors) Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org. The Cochrane Collaboration, 2011. Available from www.cochrane–handbook.org.

SIGN 2015
Scottish Intercollegiate Guidelines Network (SIGN). Search filters. www.sign.ac.uk/methodology/filters.html#random (accessed 10 July 2016).

Smyth 2008
Smyth ETM, McIlvenny G, Enstone JE, Emmerson AM, Humphreys H, Fitzpatrick F, et al. Four Country Healthcare Associated Infection Prevalence Survey 2006: overview of the results. *Journal of Hospital Infection* 2008;**69**:230–48.

Spann 2004
Spann CT, Taylor SC, Weinberg JM. Topical antimicrobial agents in dermatology. *Clinics in Dermatology* 2004;**50**(7): 407-21.

Sterne 2011
Sterne JAC, Egger M, Moher D. Chapter 10: Addressing reporting biases. In: Higgins JPT, Green S (editors) Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org. The Cochrane Collaboration, 2011. Available from www.cochrane–handbook.org.

Thompson 1999
Thompson SG, Sharp SJ. Explaining heterogeneity in meta-analysis: a comparison of methods. *Statistics in Medicine* 1999;**18**:2693–708.

Van Rijen 2008a
Van Rijen M, Bonten M, Wenzel R, Kluytmans J. Mupirocin ointment for preventing Staphylococcus aureus infections in nasal carriers. *Cochrane Database of Systematic Reviews* 2008, Issue 4. [DOI: 10.1002/14651858.CD006216.pub2]

Van Rijen 2008b
Van Rijen MML, Bonten M, Wenzel RP, Kluytmans J. Intranasal mupirocin for reduction of Staphylococcus aureus infections in surgical patients with nasal carriage: a systematic review. *Journal of Antimicrobial Chemotherapy* 2008;**61**(2):254–61.

von Eiff 2001
von Eiff C, Becker K, Machka K, Stammer H, Peters G. Nasal carriage as a source of Staphylococcus aureus bacteremia. *The New England Journal of Medicine* 2001; **344**:11–16.

Webster 2015
Webster J, Osborne S. Preoperative bathing or showering with skin antiseptics to prevent surgical site infection. *Cochrane Database of Systematic Reviews* 2015, Issue 2. [DOI: 10.1002/14651858.CD004985.pub5]

Wertheim 2004
Wertheim HFL, Vos MC, Ott A, Van Belkum A, Voss A, Kluytmans JA, et al. Risk and outcome of nosocomial Staphylococcus aureus bacteraemia in nasal carriers versus non-carriers. *Lancet* 2004;**364**:703-5.

Wertheim 2005
Wertheim HFL, Melles DC, Vos MC, Van Leeuwen W, Van Belkum A, Verbrugh HA, et al. The role of nasal carriage in Staphylococcus aureus infections. *The Lancet. Infectious Diseases* 2005;**5**:751-62.
* *Indicates the major publication for the study*

APPENDICES

Appendix 1. The Cochrane Central Register of Controlled Trials (CENTRAL) provisional search strategy

#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

Appendix 2. 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 3. 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.

Appendix 4. 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

CONTRIBUTIONS OF AUTHORS

Zhenmi Liu: developed the protocol; coordinated the protocol development; produced the first draft of the protocol; contributed to writing and editing the protocol; made an intellectual contribution to the protocol; advised on the protocol; approved the final version of the protocol prior to submission; and is a guarantor of the protocol.

Gill Norman: developed the protocol; coordinated the protocol development; contributed to writing and editing the protocol; made an intellectual contribution to the protocol; advised on the protocol; approved the final version of the protocol prior to submission; and is a guarantor of the protocol.

Zipporah Iheozor-Ejiofor: advised on the protocol.

Jason Wong: made an intellectual contribution to the protocol; advised on the protocol; and approved the final version of the protocol prior to submission.

Emma Crosbie: made an intellectual contribution to the protocol; advised on the protocol; and approved the final version of the protocol prior to submission.

Peter Wilson: made an intellectual contribution to the protocol; advised on the protocol; and approved the final version of the protocol prior to submission.

Contributions of the editorial base

Nicky Cullum (Editor): edited the protocol; advised on methodology interpretation and protocol content; approved the final protocol prior to submission.
Gill Rizzello (Managing Editor): co-ordinated the editorial process; advised on content; edited the protocol.
Reetu Child (Information Specialist): designed the search strategy and edited the search methods section.

DECLARATIONS OF INTEREST

Zhenmi Liu: My employment at the University of Manchester is supported by a grant from National Institute for Health Research (NIHR), UK (NIHR Systematic Review Fellowships).

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

Zipporah Iheozor-Ejiofor: Nothing to declare.

Jason Wong: Nothing to declare.

Emma 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 have a number of non-commercial grants for research in the area of transmission of infection. I was part funded by the UCLH/UCL Comprehensive Biomedical Centre with funding from the Department of Health's NIHR Biomedical Research Centres.

SOURCES OF SUPPORT

Internal sources

- Division of Nursing, Midwifery & Social Work, School of Health Sciences, Faculty of Biology, Medicine & Health, University of Manchester, Manchester, UK.

External sources

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

This project was supported by the National Institute for Health Research, via Cochrane Infrastructure and Cochrane Programme Grant funding (NIHR Cochrane Programme Grant 13/89/08 - High Priority Cochrane Reviews in Wound Prevention and Treatment) to Cochrane Wounds. The views and opinions expressed herein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, National Health Service or the Department of Health.