National Institute for Health and Care Excellence

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Surgical site infection: prevention and treatment

Evidence reviews for effectiveness of nasal decontamination in prevention of surgical site infection

NICE guideline CG74

Evidence reviews

[Month Year]

Draft for Consultation

These evidence reviews were developed by NICE Guideline Updates Team

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Effectiveness of nasal decolonisation in the prevention of surgical site infection

Review question

Does the use of nasal decolonisation to eliminate *Staphylococcus aureus* (alone or in combination with other interventions) affect the rate of surgical site infection?

Two further sub-questions were answered in the update:

- What is the contribution to clinical effectiveness of the timing of nasal decolonisation for the prevention of surgical site infection?
- What is the cost-effectiveness of different nasal decolonisation interventions for the prevention of surgical site infection caused by *S. aureus*?

Introduction

Staphylococcus aureus (S. aureus) is the most common cause of surgical site infections (SSIs) in all types of surgery. Topical antimicrobial agents which are active against *S. aureus* can be utilised to decolonise patients prior to surgery.

The 2008 NICE guideline on the prevention and treatment of surgical site infection recommended against the use of nasal decontamination with topical antimicrobial agents for the elimination *S. aureus* to reduce the risk of surgical site infection. This decision was driven by the evidence which demonstrated that mupirocin or chlorhexidine nasal decontamination did not reduce the overall rate of SSI.

The topic was reviewed in 2017 by NICE's surveillance team and new evidence was identified which examined the use of nasal decolonisation for the elimination of *S. aureus*, and thus prompted a partial update of guideline. This review aims to determine the clinical and cost effectiveness of nasal decolonisation using topical antimicrobial agents for the prevention of SSIs with or without the combined use of chlorhexidine body wash or glycopeptide prophylaxis. Timing of nasal decolonisation for the prevention of SSI will also be examined.

This review identified studies that fulfilled the conditions specified in PICO table. For full details of the review protocol, see appendix A.

Table 1 PICO: Does the use of nasal decolonisation to eliminate Staphylococcus aureus (alone or in combination with other interventions) affect the rate of surgical site infection?

Population	People of any age undergoing any surgery, including minimally invasive surgery (arthroscopic, thoracoscopic and laparoscopic surgery)
Interventions	The usage and timing of the following treatments in combination with or without a chlorhexidine body wash or glycopeptide prophylaxis: • Intranasal mupirocin • Nasal Povidone-Iodine solution • Chlorhexidine nasal gel • Chlorhexidine and neomycin cream (Naseptin) • Octenisan nasal gel

Comparator	• Placebo • No decolonisation • Different nasal decolonisation procedures
Outcomes	• Surgical site infections (superficial, deep and organ/space SSI) including MRSA and MSSA SSI defined using appropriate criteria such as CDC SSI criteria. (Including SSIs up to 30 days and 1 year). • Other types of nosocomial infections • Mortality post-surgery • Length of hospital stay • Postoperative antibiotic use • Hospital readmission • Infectious complications such as septicaemia or septic shock • Adverse events: ○ Antimicrobial resistance

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual (2014). The review protocol for this review question is in appendix A. Methods specific to this review question are described in the review protocol in appendix B.

Declarations of interest were recorded according to NICE's 2018 conflicts of interest policy.

A search strategy was used to identify all studies that examined the effectiveness of different antimicrobial agents (outlined in Table 1) which are used for nasal decolonisation prior to surgery to reduce the risk of SSIs. Randomised control trials (RCTs) and systematic reviews of RCTs were considered for inclusion. The review protocol also specified that in the event of less than 5 RCTs being identified, quasi-randomised trials would also be considered for inclusion.

Studies were also excluded if they:

- Included patients undergoing a surgical procedure that does not involve a visible incision and therefore does not result in the presence of a conventional surgical wound
- Were not in English
- Were not full reports of the study (for example, published only as an abstract)

The studies included in this review examined different populations, types of surgery and timing of nasal decolonisation. The evidence statements produced reflect these differences.

According to the Centres for Disease Control and Prevention (CDC) a SSI is defined as an infection occurring within 30 days after operation. A deep SSI is defined as an infection which occurs within 30 days after the operation if no implant is left in place, or within 1 year if implant is placed. Therefore SSI within 30 days and 1 year were prioritised in this review.

Follow-up of SSI varied among the studies that were included in the review. Where possible sub-group analyses was conducted based on follow-up period (for example at 30 days after surgery and within 8 weeks of surgery) and this information was incorporated into the evidence statements.

Clinical evidence

Included studies

From a database of 835 studies, 70 studies were identified as being potentially relevant. Following full text review of the 70 studies, 9 RCTs were included which examined the following interventions:

- mupirocin versus placebo nasal ointment
- mupirocin versus no nasal decolonisation
- mupirocin versus 5% povidone iodine
- mupirocin in combination with chlorhexidine body wash versus no treatment (no nasal decolonisation or body wash)
- mupirocin in combination with chlorhexidine body wash versus placebo (placebo ointment in combination with placebo soap)
- nasal chlorhexidine versus placebo.

No studies of relevant study design were identified which examined the effectiveness of chlorhexidine and neomycin cream or octenisan nasal gel. No studies were identified which compared the timing of nasal decolonisation.

The included studies explored a number of different outcomes. Data on overall SSI (irrespective of pathogen) and *S. aureus* SSI was extracted. Where possible, data on superficial, deep and organ space occupying SSI was extracted. Data on methicillin-resistant *Staphylococcus aureus* (MRSA) and Methicillin-sensitive *Staphylococcus aureus* (MSSA) specific SSI was also extracted.

Studies included in this review also examined a number of different surgeries. However, sufficient evidence was not identified to conduct sub-group analyses based on wound classification, elective surgery or emergency surgery.

Comparative evidence was not identified in terms of antimicrobial resistance. However the information presented in the studies was discussed with the committee and added to the rational and impact section.

For the search strategy, see appendix C. For clinical evidence study selection flowchart, see appendix D.

Excluded studies

List of papers excluded at full text, with reasons, is given in Appendix K.

Summary of clinical studies included in the evidence review

The included studies are summarised in Table 2 below. See appendix E for full evidence tables.

Table 2 Summary table of included studies

Short Title	Title	Study Details	Intervention	Comparator	Outcomes
Bode (2010)	Preventing surgical-site infections in nasal carriers of Staphylococcus aureus	• **Study location** Rotterdam, The Netherlands. • **Study setting** 3 university hospitals. • **Study dates** October 2005 to	• 2% mupirocin ointment and chlorhexidine body wash	• Placebo (placebo ointment in combination with placebo soap)	• S. aureus SSI • S. aureus superficial SSI • S. aureus deep SSI • S. aureus nosocomial infections

Short Title	Title	Study Details	Intervention	Comparator	Outcomes
		June 2007 • **Duration of follow-up** until 6 weeks after discharge. • **Sources of funding** Supported by grants from ZonMw, MoInlycke Healthcare, GlaxoSmithKline, Roche, bioMerieux, and 3M			
Kalmeijer (2002)	Surgical site infections in orthopedic surgery: the effect of mupirocin nasal ointment in a double-blind, randomized, placebo-controlled study	• **Study location** The Netherlands • **Study setting** Department of Orthopedic Surgery • **Study dates** January 1997 to July 1999 • **Duration of follow-up** 1 month after surgery • **Sources of funding** Mupirocin ointment and the ingredients for placebo were provided by GlaxoSmithKline.	• 2.15% mupirocin ointment	• Placebo nasal ointment	• Overall SSI • Overall superficial SSI • Overall deep SSI • S. aureus SSI • Length of hospital stay • Hospital readmission
Konvalinka (2006)	Impact of treating Staphylococcus aureus nasal carriers on wound infections in cardiac surgery	• **Study location** Ontario, Canada • **Study setting** Hospital setting • **Study dates** March 1997 and March 2003. • **Duration of follow-up** 8 weeks • **Sources of funding** The Cardiovascular Surgery Research Grant and St Michael's Hospital Foundation Grant.	• 2% mupirocin ointment	• Placebo ointment	• Overall SSI • Overall superficial SSI • Overall deep SSI. • S. aureus SSI • Mortality

Short Title	Title	Study Details	Intervention	Comparator	Outcomes
Perl (2002)	Intranasal mupirocin to prevent postoperative Staphylococcus aureus infections	• **Study location** Iowa, USA • **Study setting** University of Iowa Hospitals and Clinics and the Veterans Affairs Medical Centre • **Study dates** April 1995 to December 1998 • **Duration of follow-up** 30 days • **Sources of funding** Research grant from GlaxoSmithKline	• 2% mupirocin ointment	• Placebo	• Overall SSI • S. aureus SSI • Overall nosocomial infections • S. aureus nosocomial infections
Phillips (2014)	Preventing surgical site infections: a randomized, open-label trial of nasal mupirocin ointment and nasal povidone-iodine solution	• **Study location** New York, USA • **Study setting** Not specified • **Study dates** March 2011 to March 2012 • **Duration of follow-up** 3 months • **Sources of funding** 3M Corporation, the manufacturer of the nasal povidone-iodine solution, provided financial support.	• 2% mupirocin ointment	• Different nasal decolonisation procedures: Povidone iodine 5% solution	• Overall deep SSI • S. aureus deep SSI • MRSA deep SSI • MSSA deep SSI
Segers (2006)	Prevention of nosocomial infection in cardiac surgery by decontamination of the nasopharynx and oropharynx with chlorhexidine gluconate: a randomized controlled trial	• **Study location** Amsterdam, The Netherlands. • **Study setting** Community Hospital • **Study dates** August 1st 2003 to September 1st 2005 • **Duration of follow-up** 30 days • **Sources of funding** No funding. All materials were provided by the local hospital	• 0.12% chlorhexidine gluconate solution	• Placebo	• Overall SSI • Overall deep SSI • S. aureus SSI • Overall nosocomial infections • Nosocomial infection: Lower respiratory tract infection • Nosocomial infection: Urinary tract infection • Nosocomial infection: Bacteraemia • 30- day mortality post-

Short Title	Title	Study Details	Intervention	Comparator	Outcomes
		pharmacy.			surgery • Length of hospital stay • Hospital readmission
Sousa (2016)	Preoperative Staphylococcus aureus Screening/Decolonization Protocol Before Total Joint Arthroplasty-Results of a Small Prospective Randomized Trial	• **Study location** Portugal • **Study setting** Department of Orthopaedics • **Study dates** January 2010 and December 2012 • **Duration of follow-up** 1 year after surgery. • **Sources of funding** Not specified	• 2% mupirocin ointment and chlorhexidine body wash	• No treatment (no nasal decolonisation or body wash)	• Overall deep SSI • S. aureus deep SSI
Suzuki (2003)	Randomized clinical trial of preoperative intranasal mupirocin to reduce surgical-site infection after digestive surgery	• **Study location** Japan • **Study setting** University hospital • **Study dates** June 1998 and December 2000 • **Duration of follow-up** 30 days • **Sources of funding** Not reported	• 2% mupirocin ointment	• No nasal decolonisation	• Overall SSI • Overall superficial SSI • Overall deep SSI • S. aureus SSI • Overall nosocomial infections
Tai (2013)	Nasal carriage of Staphylococcus aureus in patients undergoing Mohs micrographic surgery is an important risk factor for postoperative surgical site infection: a prospective randomised study	• **Study location** Australia • **Study setting** Surgery and Dermatology Centre. • **Study dates** 1st April to 31st October 2011 • **Duration of follow-up** All patients were followed up in the postoperative period for signs of clinical infection. Duration is not specified. • **Sources of funding** Not specified.	• 2% mupirocin ointment and chlorhexidine body wash	• No treatment (no nasal decolonisation or body wash)	• S. aureus SSI • MRSA SSI • MSSA SSI

Quality assessment of clinical studies included in the evidence review

All studies included in the review were RCTs. The quality of the evidence was initially graded as high. A number of studies demonstrated unclear blinding of participants and personnel however the studies were not downgraded in this domain as the outcome measures were objective. Studies were mainly downgraded for unclear random sequence generation, allocation concealment, blinding of outcome assessment or for the conduction of 'as treated' analysis as opposed to intention to treat.

Studies included in the review classified infections using the Centres for Disease Control and Prevention (CDC) SSI criteria as well as the Nosocomial Infection Surveillance System definitions. The follow–up period within studies also ranged from 30 days to 1 year. Studies which did not specify the criteria used to classify infections or follow-up period were downgraded for serious indirectness.

One study was also downgraded for indirectness for the use of chlorhexidine as a mouth wash as well as a nasal gel. See appendix G for full GRADE tables, and appendix F for forest plots in situations where data have been meta-analysed.

Economic evidence

Included studies

A literature search was conducted to identify cost–utility analyses comparing nasal decolonisation interventions. Nasal decolonisation may be conditional on the results of a diagnostic test to support decision-making in some settings, and so studies that evaluated 'screen and treat' strategies were included. Standard health economic filters were applied to a clinical search, returning a total of 536 citations. Following review of all titles and abstracts, 25 studies were identified as being potentially relevant to this decision problem, and were ordered for full review. After reviewing the full texts, 3 studies were included as economic evidence for nasal decolonisation.

Excluded studies

Studies that were excluded upon full review are listed in Appendix K, including the primary reason for exclusion.

Summary of studies included in the economic evidence review

A summary of each of the 3 studies included as economic evidence is provided below. Full economic evidence tables for each study are provided in Appendix I. A summary economic evidence profile is provided in Appendix J.

Courville et al. (2012)

Courville et al. (2012) developed a 1-year decision-tree model to evaluate the cost-effectiveness of preoperative nasal mupirocin, given for 5 days, to prevent SSI in people undergoing total hip or knee arthroplasty in the US. The comparators were: (1) preoperative screening cultures for all patients and treat those positive for *S. aureus*; (2) treat everybody without screening; and (3) do not provide any screening or treatment. Clinical inputs were sourced from a systematic literature review, with an SSI relative risk of 0.61 with mupirocin in *S. aureus* carriers (26% prevalence). Screening sensitivity and specificity were 0.52 and 0.85, respectively. The authors assumed that an SSI required a full hip or knee revision procedure. An SSI reduced a person's quality of life utility value by 20%.

The 'treat all' mupirocin strategy was found to dominate the restricted treatment strategies in both the hip and knee arthroplasty populations, providing a small gain in quality-adjusted life-years (QALYs) per patient (0.0002 to 0.0005) and lower overall costs (saving £151 to £205) over 1 year. Treating all patients continued to dominate in the majority of univariate sensitivity analyses, unless the cost of SSI revision surgery was low (close to that of the primary arthroplasty procedure), or if the SSI relative risk with mupirocin is 0.99. In this latter scenario the 'no treatment' strategy becomes dominant, though it lies outside the range of values that the authors identified in the literature (0.10 to 0.64). The screening strategy was not found to be cost effective in any alternative scenario.

Wassenberg et al. (2011)

Wassenberg et al. (2011) evaluated the cost-effectiveness of preoperative nasal mupirocin with chlorhexidine soap, given for 5 days, to prevent deep SSI in people undergoing joint implant or cardiac surgery in the Netherlands. The comparators were: (1) do not provide any screening or treatment; (2) screen all patients with rapid PCR and culture, and treat those positive for *S. aureus*; and (3) treat everybody with mupirocin, without screening. Screening was modelled as being highly effective, with sensitivity of 0.97 and specificity of 0.99. Records from 1 hospital during the period 2001 to 2010 were reviewed to quantify hospital costs and mortality associated with a deep SSI, with data from 53 SSIs out of approximately 1,200 procedures per year. Life-expectancy was discounted by 3% per year, but SSI costs were all incurred within 1 year of the primary procedure. The deep SSI relative risk of mupirocin was 0.21 in *S. aureus* carriers (18% prevalence) (Bode et al., 2010).

The 'treat all' mupirocin strategy was found to dominate both restricted treatment strategies. Treating all patients produces an additional 0.010 discounted life-years per patient compared with the screen and treat strategy, and 0.024 more than the no treatment strategy. The total cost saving is estimated to be £41 and £114 per patient, over the screening and no treatment strategies respectively. Sensitivity analysis showed that the 'treat all' strategy, without screening, remained cost-saving if the SSI relative risk with mupirocin was worse than the base-case estimate (0.60 instead of 0.21).

Young & Winston (2006)

The US modelling analysis by Young & Winston (2006) was included in the original guideline. The 90-day decision-tree model compared preoperative mupirocin in elective surgery (cardiothoracic, neurologic, gynaecologic and general), given for 5 days according to the following strategies: (1) screen with nasal culture and treat screen-positive individuals; (2) treat all patients without screening; and (3) do not provide any screening or treatment. Clinical inputs were sourced from a systematic literature review, using RCTs where available. The SSI relative risk with mupirocin was 0.49 in *S. aureus* (23% prevalence). Screening appears to have been assumed to be 100% accurate. Direct healthcare costs were sourced from the literature review where possible, otherwise Medicare charges were used. Patient productivity loss costs were included, however they are likely to have been an inconsequential component of total costs.

The 'screen and treat' mupirocin strategy was found to dominate both of the other strategies. It prevented 86 SSIs and 2 deaths per 10,000 patients compared with no treatment, and treating all patient was not more effective at reducing the incidence of SSI. Its total cost saving compared with the 'treat all' strategy is estimated to be $14 (£10) per patient, or $8 (£6) per patient if only hospital costs are included, due to avoiding unnecessary treatment costs. One-way sensitivity analysis found that

mupirocin efficacy was the only parameter likely to influence cost-effectiveness results; an SSI relative risk with mupirocin of 0.92 makes the 'treat all' strategy incur higher costs than 'no treatment', with a cost per life-year gained of $389,782 (£277,000).

Economic model

The committee advised that the cost effectiveness of nasal decontamination of *S. aureus* is an area of uncertainty, and that any recommendations may have a significant impact on NHS practice. This question was therefore prioritised for new economic modelling

Model methods

A decision-tree model was developed, adopting a very similar structure to the model developed for the initial guideline. The model captures the short-term decision about whether to use nasal decontamination. At model entry a patient has just undergone a surgical procedure, from which they are subject to a risk of SSI and mortality. For the purpose of this decision problem, the model focuses on SSIs caused by *S. aureus.* After the perioperative period, the model applies age-related life expectancy to surviving patients. In this way, the full impact of any SSI-related mortality on health gains are captured. The model takes a patient perspective for outcomes and an NHS and PSS perspective for costs, in line with the NICE manual for guideline development (NICE 2014). Long-term outcomes are discounted at a rate of 3.5% per year.

The model includes 3 comparators: universal decolonisation using mupirocin; decolonisation with mupirocin in people who are screened positive for nasal carriage of *S. aureus;* and no decolonisation at all (standard care only). Standard care is assumed to capture general infection control measures, such as a chlorhexidine body wash. Mupirocin is the only active intervention included, as this was the focus of almost the entire body of clinical evidence. The screen-and-treat strategy was included as the committee felt that the decision to use nasal decontamination of *S. aureus* is intrinsically linked with knowledge about whether the person is a carrier of *S. aureus* or not.

Baseline *S. aureus* SSI rates were obtained from 2 UK sources: a surveillance study in an English hospital in the base-case analysis (Jenks et al., 2014), and a national registry (PHE, 2017) in a scenario analysis. The committee expressed a strong preference for the hospital study, advising that its higher SSI rates (5.1% overall, compared with 1.3%) are more representative of outcomes in current practice and their own experiences. Furthermore, the committee felt that the PHE data was 'opt-in' and therefore likely suffered from systematic under reporting. In this study, 33% of SSIs were caused by *S. aureus,* compared with 11% in the PHE data. These data are used to inform baseline *S. aureus* SSI rates without nasal decontamination, for 17 different types of surgery as well as a pooled 'all surgery' cohort. As the screening strategy will provide information about whether a person is a *S. aureus* carrier or non-carrier, it is necessary to adjust the baseline infection rate to reflect this distinction, as the Jenks and PHE data are in general surgical populations composed of some carriers and some non-carriers. To do so, we used RCT control-arm data to obtain odds ratios for *S. aureus* SSI incidence in carriers and non-carriers compared with the general surgical population (2.4 and 0.6 respectively; Kalmeijer et al., 2006; Perl et al., 2002).

Treatment effects were informed by pooling the 5 mupirocin RCTs identified in the clinical review that report *S. aureus* SSI rates in carriers, comparing mupirocin with

placebo or no nasal decontamination (Bode et al., 2010; Kalmeijer et al., 2002; Konvalinka et al., 2006; Perl et al., 2002; Tai et al., 2013). The mupirocin pooled odds ratio was found to be 0.47 (0.31 to 0.70) in a fixed-effect analysis, and 0.47 (0.30–0.73) in a random-effects analysis. Excluding an RCT in the highly-specialised Mohs surgery setting (Tai et al., 2013) and another that was unclear about its use of a chlorhexidine wash on the control arm (Kalmeijer et al., 2006) had little impact on these odds ratios (0.50 and 0.53). The mupirocin odds ratios were applied in the model to treated *S. aureus* carriers, whose prevalence was set to 25% of the surgical population, informed by a UK observational study (den Heijer et al., 2013). On the universal mupirocin model arm, non-carriers treated with mupirocin were assumed to experience no treatment effect on their risk of *S. aureus* SSI. On the screening arm, only correctly-identified carriers (true-positive results) received the treatment effect. A full diagnostic accuracy literature search was not conducted for this review; therefore the inputs used in the model for the initial guideline were used for these data. In the base-case analysis, a nasal swab and culture with sensitivity of 0.68 and specificity of 0.95 was applied. A scenario analysis applied the superior, but more expensive, polymerase chain reaction (PCR) test (sensitivity 0.98, specificity >0.99).

Resource use inputs include the cost associated with intervention: mupirocin (£4.24; NHS Drug Tariff VIIIA, May 2018) and screening (£10–29 including nurse time; guideline committee and original guideline model). The committee advised that mupirocin is self-administered by the person due to undergo surgery; therefore no administration cost was applied. For SSI costs, data on excess bed days attributable to an SSI across different types of surgery was obtained from the English hospital study (Jenks et al., 2014), and was costed using NHS reference costs 2016–17. The average SSI cost is £3,123, ranging from £823 to £9,056.

Recent evidence suggests there might not be a significant mortality effect attributable to SSI (Badia et al., 2017); however, the committee felt that such an effect is very likely to exist, but that it is difficult to quantify. We estimated a mortality odds ratio associated with SSI vs. no SSI of 1.5 (0.8 to 4.1), based on the UK SSI surveillance data used in the original guideline model (Coello et al., 2005). This was applied to baseline mortality rates by surgery type, from the PHE (2017) data, to estimate separate mortality rates in people who experience an SSI and those who do not. People who survive are assumed to experience typical, age-related life expectancy and quality of life after the surgical period, informed by UK population norms (ONS, 2017; Kind et al., 1999). The impact of an infection on quality of life is informed by a UK EQ-5D study in people undergoing laparotomy (Pinkney et al., 2013), which found that people will an SSI report a bigger utility loss at 7 days (-35% vs. -33%) and 30 days (-17% vs. -6%). We linearly interpolated that it will take people who have an SSI 22 additional days to fully recover to baseline quality of life, compared with 6 additional days for people who do not have an SSI. These effects are applied as a one-off QALY loss.

Model results

Base-case model results, across all types of surgery for a cohort aged 70 and 42% male (PHE, 2017), suggest that universal nasal decolonisation of *S. aureus* with mupirocin is cost effective, dominating both the screen-and-treat and no treatment strategies (Table). It produces the highest number of QALYs as it ensures that all *S. aureus* carriers receive nasal decontamination, and there is no negative health effect caused by treating non-carriers. The cost of treating everybody is more than offset by not screening people and reducing the incidence of SSI. Probabilistic sensitivity analysis from 1,000 model runs indicates that universal mupirocin has a 99.6% probability of being cost-effective when QALYs are valued at £20,000 each.

Providing nasal decontamination only to people who screen positive for *S. aureus* has a 0% probability of being optimal. One-way sensitivity analysis showed that results are sensitive to baseline *S. aureus* SSI rates; if much lower infection rates are used, from the PHE (2017) registry, universal mupirocin is no longer cost-effective compared with providing no nasal decontamination (Figure 1). No other individual model parameter or setting – for example, reducing mupirocin efficacy to its 95% confidence interval limit (odds ratio: 0.70), or assuming that mupirocin requires nurse-led administration – affects the base case model result.

Table 3: Base case cost-effectiveness model results

Strategy	Total cost	Total QALYs	Incremental cost	Incremental QALYs	ICER
Universal mupirocin	£43	8.9233			
Mupirocin if screened positive	£55	8.9232	£12	-0.0001	Dominated by universal mupirocin
Standard care only	£56	8.9229	£13	-0.0003	Dominated by universal mupirocin

Key: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

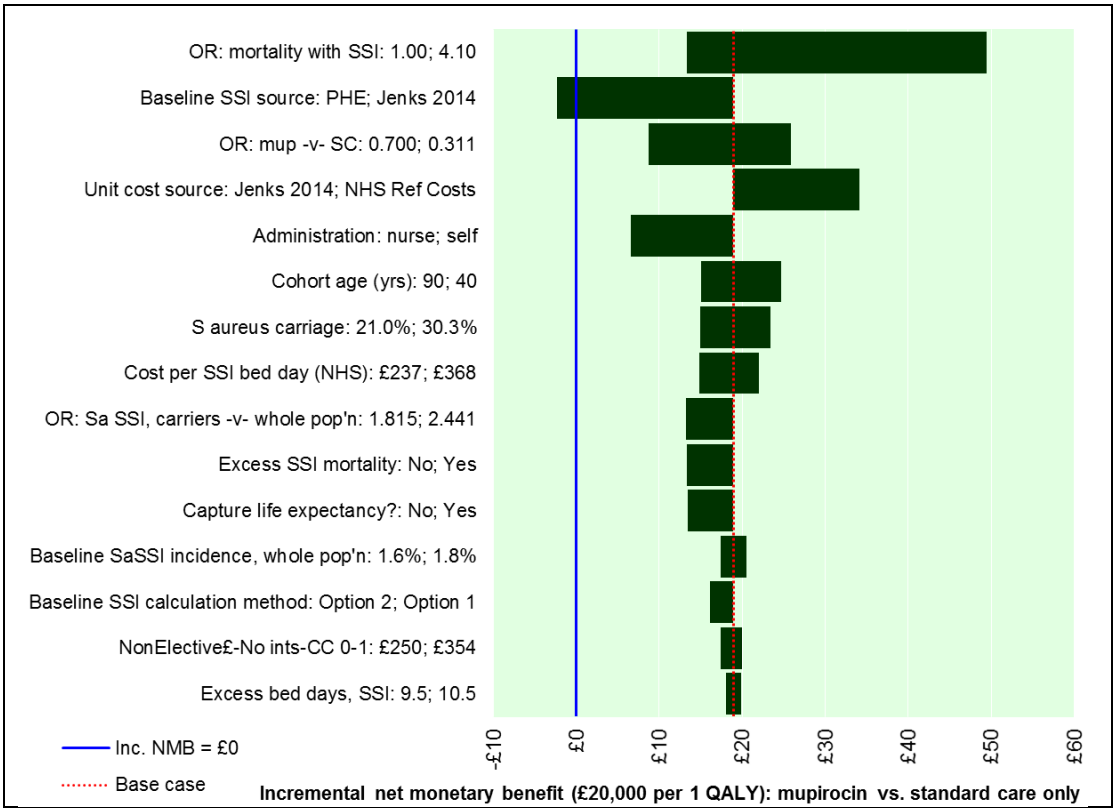

Figure 1: One-way sensitivity analysis

In subgroup analysis, the basecase result was found to be largely consistent across different types of surgery. The only specialties in which universal mupirocin was not the dominant strategy were breast surgery (ICER vs. standard care: £849 per QALY gained) and cranial surgery (ICER vs. standard care: £13,089 per QALY gained). The respective probabilities of its ICER being

£20,000 or better are 76% and 65%. This probability is 67% in spinal surgery, though mupirocin was dominant in the deterministic result. Across all other types of surgery the probability of mupirocin being cost-effective, when a QALY is valued at £20,000, is 89% or higher.

Evidence statements

The format of the evidence statements is explained in the methods in appendix B. Evidence statements were also stratified by population.

Clinical evidence

Evidence identified in the review explored a number of different surgeries and timing of decolonisation. Where possible, evidence statements were constructed to reflect these characteristics. Evidence statements were stratified based on different populations.

Mupirocin versus placebo

Outcomes in whole population undergoing surgery

- Low quality evidence from 2 RCTs, including 4,478 people could not differentiate overall SSI at 30 days between people who received mupirocin and those who received placebo before undergoing surgery.

- Low to very low quality evidence from 1 RCT, including 614 people could not differentiate the following outcomes between people who received mupirocin a day before orthopaedic surgery and those who received placebo:
    - Overall Superficial SSI at 30 days
    - Overall Deep SSI at 30 days
    - Hospital readmission
    - Mean hospital stay

- Low quality evidence from 2 RCTs, including 4,400 people could not differentiate *S. aureus* SSI at 30 days between people who received mupirocin and those who received placebo before undergoing surgery.

- Moderate quality evidence from 1 RCT, including 3,864 people could not differentiate overall nosocomial infections defined as bloodstream, respiratory tract, catheter and surgical site infections within 30 days between people who received mupirocin 5 days before surgery and those who received placebo.

- Low quality evidence from 1 RCT, including 3,370 people could not differentiate *S. aureus* nosocomial infections defined as bloodstream, respiratory tract, catheter and surgical site infections within 30 days between people who received mupirocin 5 days before surgery and those who received placebo.

Outcomes in *S. aureus* carriers undergoing surgery

- Low quality evidence from 1 RCT, including 869 *S. aureus* carriers, indicated that people who received mupirocin 5 days before surgery had a lower incidence of *S. aureus* nosocomial infections at 30 days after surgery compared to those who received placebo.

- Very low quality from evidence from 2 RCTs, including 1,148 *S. aureus* carriers could not differentiate overall SSI between people who received mupirocin compared to those who received placebo before surgery.
    - Low quality evidence from 1 RCT could not differentiate overall SSI at 30 days
    - Low quality evidence from 1 RCT could not differentiate overall SSI within 8 weeks of surgery.

- Low quality evidence from 1 RCT, including 257 *S. aureus* carriers could not differentiate the following outcomes between people who received mupirocin 7 days before cardiac surgery and those who received placebo:
    - Overall superficial SSI within 8 weeks of surgery
    - Overall deep SSI within 8 weeks of surgery
    - Overall deep space occupying SSI within 8 weeks of surgery
    - Mortality within 8 weeks of surgery.

- Low quality evidence from 1 RCT, including 891 *S. aureus* carriers could not differentiate overall nosocomial infections defined as bloodstream, respiratory tract, catheter and surgical site infections within 30 days between people who received mupirocin 5 days before surgery and those who received placebo.

- Moderate quality evidence from 3 RCTs, including 1,318 *S. aureus* carriers could not differentiate *S. aureus* SSI between people who received mupirocin and those who received placebo before undergoing surgery.
    - Very low quality evidence from 2 RCTs could not differentiate *S. aureus* SSI at 30 days
    - Low quality evidence from 1 RCT could not differentiate *S. aureus* SSI within 8 weeks of surgery

Mupirocin versus no nasal decolonisation

Outcomes in whole population undergoing surgery

- Moderate to low quality evidence from 1 RCT, including 395 people could not differentiate the following outcomes between people who received mupirocin 3 days before digestive surgery and those who received no nasal decolonisation:
    - Overall SSI at 30 days
    - Overall superficial SSI at 30 days
    - Overall deep SSI at 30 days
    - S. aureus SSI at 30 days
    - Overall nosocomial infections at 30 days.

Mupirocin versus 5% povidone iodine

In whole population

Low to very low quality evidence from 1 RCT, including 1,697 people could not differentiate the following outcomes between people who received mupirocin 5 days before arthroplasty or spine fusion surgery and those who received 5% povidone iodine:

- Overall deep SSI within 3 months of surgery
- *S. aureus* deep SSI within 3 months of surgery

- MRSA deep SSI within 3 months of surgery
- MSSA deep SSI within 3 months of surgery.

Mupirocin in combination with chlorhexidine body wash versus no treatment

Outcomes in *S. aureus* carriers undergoing surgery

Low quality evidence from 1 RCT, including 203 *S. aureus* carriers indicated that people who received mupirocin in combination with chlorhexidine body wash 5 days before Mohs surgery had lower incidence of MSSA SSI during the postoperative phase compared to people who received no nasal decolonisation and body wash. However, very low quality evidence, could not differentiate the following outcomes between the two groups:

- S. aureus SSI during postoperative period
- MRSA SSI during postoperative period

- Very low quality evidence from 1 RCT, including 228 *S. aureus* carriers could not differentiate the following outcome after primary total hip or knee arthroplasty between people who received mupirocin in combination with chlorhexidine body wash at least a week before surgery and those who received no nasal decolonisation and body wash:
  - Overall deep SSI at 1 year
  - S. aureus deep SSI at 1 year

Mupirocin in combination with chlorhexidine body wash versus placebo

Outcomes in *S. aureus* carriers undergoing surgery

- High quality evidence from 1 RCT, including 808 *S. aureus* carriers indicated that people who received mupirocin in combination with chlorhexidine body wash 5 days before surgery had lower incidence of the following outcomes compared to those who received placebo:
  - *S. aureus* SSI until 6 weeks after discharge
  - *S. aureus* deep SSI until 6 weeks after discharge
  - *S. aureus* nosocomial infections until 6 weeks after discharge.

  However, moderate to low quality evidence, could not differentiate the following outcomes between the two groups:

  - *S. aureus* superficial SSI until 6 weeks after discharge
  - Mortality until 6 weeks after discharge
  - Mortality in *S. aureus* carriers with infection until 6 weeks after discharge.

Chlorhexidine versus placebo

Outcomes in whole population undergoing surgery

- Moderate to low quality evidence from 1 RCT, including 954 people indicated that people who received chlorhexidine up to 4 times a day before cardiothoracic surgery had lower incidence of the following outcomes compared to those who received placebo:
  - Overall deep SSI at 30 days
  - Overall nosocomial infections at 30 days

- Lower respiratory tract infection (LRTI) at 30 days
- Mean hospital stay.

However, low to very low quality evidence, could not differentiate the following outcomes between the two groups:

- Overall SSI at 30 days
- S. aureus SSI at 30 days
- Urinary tract infection (UTI) at 30 days
- Bacteraemia at 30 days
- Mortality at 30 days
- Hospital readmission.

Economic evidence

- Three partially applicable economic evaluations with potentially serious limitations compared providing a 5-day course of preoperative intranasal mupirocin, to all patients and to patients screened positive for *S. aureus*, in various surgical settings, with providing no nasal decolonisation. Two studies found the universal treatment strategy to be more effective and cost-saving compared with the other options, while 1 study found the screen-and-treat strategy to be dominant. Conclusions were largely robust to one-way sensitivity analysis.
- A directly applicable economic model with minor limitations compared the use of mupirocin nasal ointment in all surgical patients with its use only in patients screened positive for *S. aureus* and with no nasal decolonisation. It found that universal mupirocin dominates other strategies in most types of surgery. Its ICER is better than £20,000 per QALY gained in all types, with likelihoods ranging from 65% to 100%. Results are sensitive to the baseline incidence of SSI; mupirocin is less likely to be cost effective if the underlying risk of SSI is very low.

Recommendations

A1. Consider nasal mupirocin in combination with a chlorhexidine body wash before procedures in which *Staphylococcus aureus* is a likely cause of a surgical site infection.

A2. Maintain surveillance on antimicrobial resistance associated with the use of mupirocin. For information on antimicrobial stewardship programmes see the NICE guideline on antimicrobial stewardship: systems and processes for effective antimicrobial medicine use.

Research recommendations

1. What is the clinical effectiveness of nasal decolonisation using mupirocin in combination with a chlorhexidine body wash in the whole population?
2. What is the contribution to clinical effectiveness of the timing of nasal decolonisation and body wash for the prevention of surgical site infection?
3. Is the use of chlorhexidine body wash associated with increased antimicrobial resistance?
4. What is the effectiveness of decolonisation using alternative interventions in combination with nasal decolonisation in the prevention of surgical site infections, in people who present with contraindication to chlorhexidine?

Rationale and impact

Why the committee made the recommendations

Evidence was identified that examined the use of mupirocin alone and mupirocin in combination with a chlorhexidine body wash. Mupirocin alone was effective in reducing *Staphylococcus aureus* infections caught in hospital in people who were identified as carriers of *S. aureus*. However, mupirocin did not reduce surgical site infections in all people having surgery.

The evidence also showed that people identified as carriers of *S. aureus* who used nasal mupirocin in combination with a chlorhexidine body wash before surgery had fewer surgical site infections caused by *S. aureus* (including deep infections, methicillin-sensitive infections and infections caught in hospital) than those who did not have the intervention. However, the evidence was very limited and only covered *S. aureus* carriers.

Economic studies favoured the use of mupirocin alone. However the studies were not UK-based and could not be applied to NHS practice (for example, because of the high cost of treating surgical site infections in US studies). An economic model based on UK data demonstrated that, compared with no treatment, using mupirocin with a chlorhexidine body wash before all operations was an efficient use of resources in most specialist surgeries. However, there was less certainty of cost effectiveness for surgery with a low risk of surgical site infections caused by S. aureus.

But due to limited evidence, the committee were unable to make strong recommendations on nasal decolonisation before surgery and agreed that it should not be offered to all people having surgery. The committee applied their clinical understanding and experience of current practice, and recommended that nasal mupirocin with chlorhexidine body wash should be considered before procedures that have an increased risk of surgical site infection caused by S. aureus, for which there would be the most benefit. The committee were aware that the recommendation does not fully reflect the clinical and economic analysis but agreed that any new recommendations should reflect current practice.

The recommendation does not define which procedures are associated with a higher risk, but the committee agreed that centres will be aware of these procedures, which include cardiac and orthopaedic surgery. Furthermore, the recommendation does not state timing of nasal decolonisation due to lack of evidence. But the committee were aware that mupirocin and chlorhexidine bundle can be given 2 days prior to surgery to 3 days after surgery.

The committee also took into consideration the potential side effects of mupirocin, such as a burning sensation and local reactions, and cautions for the use of chlorhexidine solution in people with existing skin conditions and in preterm newborn babies.

There was a lack of evidence on antimicrobial resistance associated with the use of mupirocin and chlorhexidine body wash. The committee agreed that it would be helpful to encourage service providers to maintain surveillance on antimicrobial resistance associated with the use of mupirocin. This would allow any increase in resistance to be captured.

The committee developed a research recommendation on the effectiveness of nasal mupirocin with chlorhexidine body wash across all surgical procedures to help determine whether this should be extended to all people having surgery.

Antimicrobial resistance associated with the use of chlorhexidine body wash was also identified by the committee as an important area of research.

Impact of the recommendations on practice

There is considerable variability in practice. In some decolonisation is always offered before certain types of surgery, for example, before orthopaedic surgery. In other centres decolonisation is offered only to people who are identified as methicillin-resistant S. aureus (MRSA) or methicillin-sensitive S. aureus (MSSA) carriers.

The new recommendation better reflects current practice and allow centres more flexibility to change practice and consider decolonisation for people who are likely to benefit the most. The recommendation may reduce surgical site infections in people having surgery with a high risk of infection, such as cardiac surgery.

Maintenance of surveillance systems assessing antimicrobial resistance associated with the use of mupirocin will reinforce good practice.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee identified SSI including superficial SSI, deep SSI and organ space SSI as outcomes of interests. Studies included in the review captured SSI at different follow up periods. Based on the CDC definition of SSIs, the committee identified outcomes at 30 days and 1 year to be important.

The quality of the evidence

Overall, the committee noted that the studies included in the review were of low to moderate quality. None of the studies included were conducted in the UK. Much of the studies provided old evidence with new evidence only being identified for the bundled use of intranasal mupirocin and chlorhexidine body wash.

One study [Bode 2010] provided high quality evidence which demonstrated a significant difference in the incidence of *S. aureus* SSI, *S. aureus* deep SSI and *S. aureus* nosocomial infections in *S. aureus* carriers who received intranasal mupirocin with chlorhexidine body wash, 4 days before surgery. However, the committee noted limitations with this data set. Firstly, while some studies [Kalmeijer 2002 and Perl 2002] included data on both whole population and carrier population, Bode 2010 only included patients identified as high risk through real-time PCR (polymerase chain reaction).

Furthermore, the committee raised concerns about the classification of SSIs in this study. While the study states that CDC definitions were used to classify SSIs, the study only reported superficial and deep SSI. The study also only reported significant findings with regards for deep SSI. The committee noted that in some surgery types, for example colorectal surgery both superficial SSI and deep SSI occur. This study did include people undergoing gastrointestinal surgery, however it did not specify if any people underwent colorectal surgery specifically. The committee concluded that the study may have based on the occurrence of deep SSI as opposed to looking at both superficial and deep SSIs.

Additionally Bode 2010 only reported data on infections caused by *S. aureus*. While *S. aureus* is one of the most common microorganism associated with surgical site

infections, infections can also be caused by other microorganisms such as *Staphylococcus epidermidis* (*S. epidermidis*). Similar to Bode 2010, Perl 2002 and Tai 2013 did not report data on infections caused by *S. epidermidis*. Konvalinka 2006, Philips 2014 and Sousa 2016 all reported infections caused by other microorganisms such as *Pseudomonas aeruginosa* but did not specifically report data on infections caused by *S. epidermidis.* Suzuki 2003 did report that infections were caused by *S. epidermidis* along with *S. aureus*. While the focus of this review was on surgical site infections caused by *S. aureus,* information on infections caused by other microorganisms can also be useful.

A number of different surgeries were explored in this review, including cardiac surgery, orthopaedic surgery and knee arthroplasty. One study was identified [Tai 2013] which included people undergoing Mohs surgery, which is a procedure used to treat skin cancer. While this study did demonstrate significant reduction in incidence of MSSA SSI, the committee identified this study to have a small sample size. Furthermore, the committee also noted that Mohs surgery is a niche procedure.

One study [Segers 2006] was identified which examined the effectiveness of chlorhexidine gluconate. It should be noted that while this study identified a significant reduction in the incidence of overall deep SSI, overall nosocomial infections, lower respiratory tract infection and mean hospital stay, patients were administered chlorhexidine in the form of a gel for nasal application as well as an oral rinse. Due to the use of the intervention as an oral rinse, this study was downgraded for indirectness.

Benefits and harms

Surgical site infections are associated with increased costs and poor patient outcomes. The consequence of SSIs varies between different surgical procedures and events can be detrimental in high-risk surgeries such as cardiac surgery. In such high risk surgeries, consequences associated with SSIs are a major concern. Studies included in this review included people undergoing a number of different surgeries, including cardiac surgery.

The evidence base showed that the combined use of mupirocin with the use of chlorhexidine body wash did reduce the incidence of *S. aureus* SSI and deep SSI. Keeping in mind the consequences associated with SSIs, particularly in vulnerable people undergoing high risk surgeries, the committee noted the importance of decolonisation among these patients to provide protection against endogenous pathogens.

Due to the effectiveness of the combined use of mupirocin and chlorhexidine body wash in reducing *S. aureus* SSI the committee recommended for the combined use of mupirocin and chlorhexidine wash for nasal and whole body decolonisation during surgeries in which the risk of *S. aureus* SSI is high. The current recommendations do not explicitly outline which surgeries should be considered as high risk. However, healthcare professionals should be aware of high risk surgeries within their Trusts and the consequences associated with SSIs with these surgical procedures.

The committee also identified mupirocin to the effective against *Staphylococcus epidermidis* (*S. epidermidis*), which is also associated with surgical site infections. This suggests that the use of mupirocin could potentially provide protection against other endogenous pathogens. However, it should be noted that the focus of this question was on *S. aureus* due to which evidence on *S. epidermidis* was not identified.

Topical use of mupirocin has been associated with side effects such as burning sensation and local reactions, however the frequency of side effects is not known. Caution should also be taken when using mupirocin on pregnant women and people with moderate or severe renal impairment. It was also noted that chlorhexidine should not be used on people with existing skin conditions and in people who present chlorhexidine sensitivity. There is also a potential risk of severe chemical injuries associated with the use of chlorhexidine solution in preterm neonates.

The committee acknowledged these adverse events and noted that that caution must be taken when considering using of chlorhexidine body wash in patients presenting with contraindications. The committee also identified alternative interventions such as octenisan and polyhexanide that could be utilised instead of chlorhexidine. However, it should be noted that only studies examining the combined use of mupirocin and chlorhexidine body wash were identified. Due to this, no recommendations can be made on other nasal decolonisation protocols. Therefore, the committee identified this as an area which requires further research and made a research recommendation to reflect this.

In this review, antimicrobial resistance was identified as an important outcome as the committee identified resistance as a potential harm associated with the use of mupirocin and chlorhexidine body wash. No comparative data was identified, however three studies were identified which examined antimicrobial resistance. Perl 2002, which compared mupirocin with placebo, conducted in vitro susceptibility tests. The study found that 6 out of 1021 *S. aureus* isolates obtained from 6 patients, were resistant to mupirocin. Furthermore, the study reported that only 4 isolates were identified that were resistant to mupirocin, three of which were obtained from patients who were not treated with mupirocin.

Two further studies [Kalmeijer 2002 and Konvalinka 2006] were identified which also compared mupirocin with placebo. Both studies did not report tests which were conducted to ascertain resistance, but Kalmeijer concluded that none of *S. aureus* isolates were susceptible to mupirocin, while Konvalinka reported that none of the isolates from either nasal or wound culture were methicillin resistant. The committee noted that all three studies were based outside of the UK where antimicrobial resistance rates and policies were different. Therefore, this evidence was not identified are being compelling enough to stop the use of mupirocin for nasal decolonisation.

The committee also acknowledged that despite the extensive use of mupirocin over the last decade, resistance has not emerged. There is also active surveillance being conducted in the UK to capture resistance associated with the use of mupirocin. As the new recommendation allows healthcare professionals to consider the use of mupirocin, the committee noted that it is important that this surveillance is maintained to ensure any increase in resistance is registered. Therefore the committee made a recommendation for the maintenance antimicrobial resistance associated with mupirocin.

Furthermore, no evidence was identified which examined the antimicrobial resistance associated with the use of chlorhexidine body wash. The committee highlighted that a surveillance system has not been established to capture the increase in resistance associated with the use of chlorhexidine body wash. As the new recommendations allow healthcare professionals to consider the use of chlorhexidine body wash, the committee identified antimicrobial resistance associated with chlorhexidine as an important area of research. Therefore a research recommendation was developed to allow the establishment of a surveillance registry to examine the increase in resistance associated with the use of chlorhexidine.

The committee further noted that the combined used of mupirocin and chlorhexidine should only be considered when necessary and use should be based on MRSA and MSSA infection rates. Furthermore, as Trusts apply different dosage and duration of decolonisation in line with their own policies, existing decolonisation protocols should be taken into consideration when considering using the use of mupirocin and chlorhexidine body wash.

It should be acknowledged that the new recommendation does not support the use of mupirocin as part of standard care given to all patients but instead only administered to people who are undergoing procedures in which risk of *S. aureus* SSI is high. Considering the concerns with antimicrobial resistance, it is important that use of mupirocin and chlorhexidine body wash does not exceed recommended amount and prolonged and repetitive use is not advised.

Cost effectiveness and resource use

The committee discussed the cost-effectiveness evidence for nasal decolonisation of *S. aureus.* It was noted that the 3 published studies included all found in favour of nasal decolonisation with mupirocin; however, all 3 were non-UK studies, limiting their applicability to NHS practice. It was agreed that this is particularly important for the estimated costs of treating an SSI, which are likely to be very high in the US studies. The committee agreed that the additional cost attributable to an SSI is likely to be much lower in the NHS. The committee discussed whether the Young & Winston (2006) study provides evidence that a strategy of screening people for *S. aureus,* and treating only those screen positive, is cost effective compared with giving mupirocin to all patients. It was noted that the study applied 100% diagnostic accuracy of screening, such that there is no health loss associated with failing to identify *S. aureus* carriers, and that this is therefore not strong evidence with which to recommend a strategy of nasal decolonisation only in *S. aureus* carriers.

The committee went on to discuss the economic model developed for this guideline, adopting a UK perspective, with resource use and cost inputs from directly relevant data-sources. It agreed that the resource use data, and the use of a UK EQ-5D study to inform the quality of life impact of SSI, made this analysis more applicable to the decision problem than the published studies. The committee agreed that the model should include a 'screen-and-treat' strategy, as knowledge about whether the person is a carrier of *S. aureus* will directly influence the decision regarding whether to provide nasal decolonisation of *S. aureus*.

The committee discussed the most appropriate way to characterise baseline SSI rates in the model, aware that the 2 main data-sources report disparate SSI rates. It heard that the PHE (2017) data suggest a relatively low underlying risk of SSI, compared with a considerably higher risk of SSI from the English hospital surveillance study (Jenks et al., 2014). The committee also saw that European registry data appear to suggest SSI incidence rates closer to the PHE data than the Jenks et al. (2014) data. However, the committee expressed a strong preference for using the hospital surveillance data to inform baseline SSI risk, advising that these values are much more representative of clinical experience. The committee highlighted evidence in abdominal surgery trial control arms – which benefit from extensive trial follow-up – suggesting the SSI rate is over 20%, and so the Jenks data might still underestimate baseline SSI incidence (though being more accurate than the PHE data). It also advised that the PHE data are likely to be subject to high degree of selection bias, as hospitals need to opt in to provide data, and that the data are dominated by low-risk surgeries, such as hip and knee prostheses (together comprising 62% of all surgical episodes reported). It advised that a thorough hospital

surveillance study is more likely to capture all SSIs across surgical specialties, and that this benefit of the Jenks study offsets its smaller sample size.

The committee reviewed the cost-effectiveness results from the new model, noting that universal nasal mupirocin – alongside standard infection control, including a chlorhexidine body wash – is highly likely to be an efficient use of resources in most surgical specialties. These results would have been even more strongly in favour of universal mupirocin if, based on committee experience, baseline SSI rates are higher than those reported in the Jenks et al. (2014) hospital surveillance data. In this respect the model results may in fact be conservative estimates of the cost effectiveness of mupirocin. The committee noted that the base-case result was largely robust to one-way sensitivity analysis and scenario analysis, including extreme values of *S. aureus* carriage prevalence. The only parameter of influence was the use of lower baseline SSI rates, from the PHE (2017) registry, instead of the hospital surveillance study. As noted above, the committee felt that the PHE values significantly underestimate the incidence of SSI, and that the Jenks et al. (2014) are likely to be more representative of current NHS outcomes.

The committee discussed whether it is plausible that a universal nasal decolonisation strategy would always provide the highest number of QALYs. The committee accepted that this was plausible, after agreeing that nasal mupirocin is not associated with important negative side effects, and screening measures are subject to imperfect sensitivity.

The committee discussed the results presented by type of surgery, observing that in 15 out of 17 specialties universal mupirocin remained dominant, consistent with the base-case 'all surgery' population. Mupirocin did not have an ICER worse than £20,000 per QALY gained in any of the 17 surgical subgroups. The most uncertain results were in cranial and spinal surgery, with 65% and 67% probabilities of mupirocin being cost effective respectively, due to their low underlying SSI risk and, in the case of cranial surgery, a low estimated additional resource use associated with SSI. The committee advised that, based on clinical experience, nasal decolonisation is sometimes currently used in breast surgery practice, which would make the baseline SSI incidence in breast surgery lower than if no nasal decolonisation were used. This may mean the non-dominant mupirocin ICER in breast surgery (£849 per QALY gained) is a conservative estimate. The committee also noted that the screen-and-treat strategy is very unlikely to be the optimal choice, even if the superior PCR test is used. This is consistent with the 2 published economic evaluations that assumed imperfect diagnostic accuracy.

The committee discussed the relative effectiveness evidence used in the model, which came from 5 pooled mupirocin RCTs which reported *S. aureus* SSI rates in *S. aureus* carriers. The committee advised that Mohs surgery is a highly specialised setting that is less representative of general surgical practice. It saw that excluding this trial (Tai et al., 2013) from the pooled measure of effect did not influence cost-effectiveness conclusions. The committee noted that most of the clinical evidence included in this review, which had been separated in different ways, did not indicate a significant benefit associated with mupirocin, and agreed that this warrants a cautious approach to interpreting model results. Given this, the committee recommended that nasal decolonisation with mupirocin is considered, alongside a chlorhexidine body wash, replacing a previous recommendation advising against its use.

Other factors the committee took into account

The secondary aim in this evidence review was to examine the timing of nasal decolonisation for the prevention of SSI. The committee noted that typically, mupirocin and chlorhexidine bundle is given 2 days prior to surgery to 3 days after surgery. However no evidence was identified which explored timing of nasal decolonisation. Furthermore, timing of nasal decolonisation in the included studies ranged from five days before surgery to the day before surgery. Due to the lack of evidence, the committee were unable to comment on when mupirocin and chlorhexidine body wash should be administered. The committee did identify this as an important area which required further research as timing of decolonisation can vary and made a research recommendation to reflect this. Furthermore, as repetitive and prolonged use of antibiotics and antiseptics is not advised when taking into consideration antimicrobial resistance, understanding timing of decolonisation is crucial.

In this review evidence on people who had been identified as *S. aureus* carriers through screening and the whole population (in whom screening was not conducted) was identified. However, studies examining the combined use of mupirocin with chlorhexidine body wash only included people who had been identified as *S. aureus* carriers through screening. Due to the lack of information on the whole population, the committee identified this as an important area of further research.

The committee further noted that studies included in the review did not provide data on children. Due to the lack of evidence in this population, specific recommendations could not be made for this population group. Additionally, the committee identified risks associated with the use of chlorhexidine in preterm neonates. As data on alternative body washes was not identified, no recommendations could be made, however the committee identified this as an important area for research and made a research recommendation to examine the effectiveness of other nasal decolonisation protocols.

The committee also discussed that as decolonisation with mupirocin and chlorhexidine takes place prior to surgery, people may be required to self-administer the treatment. While some manufacturers may provide a guide to aid people with the procedure, people with learning disabilities, English as their second language or the elderly who live alone may find the application of the intervention difficult. However, it was noted that in some centres, people may be invited to the centres a day before surgery to assist in washing. Chlorohexidine wipes are also available however these are more expensive so their use is subject to funding with some NHS trusts being unable to fund their use.

Appendices

Appendix A – Review protocols

Review protocol for the effectiveness of nasal decolonisation in the prevention of surgical site infection

ID	Field	Content
0.	PROSPERO registration number	Review was not registered on PROSPERO as review was completed and presented to the committee prior to protocol sign off.
1.	Review title	RQ 1 The effectiveness of nasal decolonisation in the prevention of surgical site infection?
2.	Review question	Does the use nasal decolonisation to eliminate *Staphylococcus aureus* (alone or in combination with other interventions) affect the rate of surgical site infection?
3.	Objective	• To determine the clinical effectiveness of nasal d decolonisation using topical antimicrobial agents for the prevention of SSI with or without the combined use of body wash or glycopeptide prophylaxis. • To examine the timing of nasal decolonisation for the prevention of SSI.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Cumulated Index to Nursing and Allied Health Literature (CINAHL) • Database of Abstracts of Reviews of Effectiveness (DARE) • Embase

		• MEDLINE/MEDLINE in Process • NHS EED Searches will be restricted by: • No date limit applied • English language • Human studies Other searches: • Reference searching • Inclusion lists of systematic reviews Full search strategies for all databases will be published in the final review.
5.	Condition or domain being studied	Surgical site infection is a type of health-care associated infection in which a wound infection occurs after an invasive procedure. Surgical site infections have been shown to compose up to 20% of all of healthcare-associated infections. At least 5% of patients undergoing a surgical procedure develop a surgical site infection.
6.	Population	Inclusion: People of any age undergoing any surgery, including minimally invasive surgery (arthroscopic, thoracoscopic and laparoscopic surgery) Exclusion: Patients undergoing a surgical procedure that does not involve a visible incision, and therefore does not result in the presence of a conventional surgical wound.

7.	Intervention/Exposure/Test	The usage and timing of the following treatments in combination with or without a chlorhexidine body wash or glycopeptide prophylaxis: • Intranasal mupirocin • Nasal Povidone-Iodine solution • Chlorhexidine nasal gel • Chlorhexidine and neomycin cream (Naseptin) • Octenisan nasal gel
8.	Comparator/Reference standard/Confounding factors	• Placebo • No decolonisation • Different nasal decolonisation procedures
9.	Types of study to be included	• RCTs • Systematic reviews of RCTs If less than five RCTs identified, quasi randomised trials will be used
10.	Other exclusion criteria	• Conference abstracts and non-published studies will be excluded from the review. • Non-English language publications
11.	Context	Surgical site infection: prevention and treatment was published in October 2008. This guideline includes recommendations on information for patients and carers, the preoperative phase, the intraoperative phase and the post-operative phase.

		The guideline underwent regular surveillance at 3, 6 and 8 years following publication. During the 8 year surveillance process new evidence on the choice of preoperative skin antiseptics was identified. This warranted an update of this review question.
12.	Primary outcomes (critical outcomes)	• Surgical site infections (superficial, deep and organ/space SSI) including MRSA and MSSA SSI defined using appropriate criteria such as CDC SSI criteria. (Including SSIs up to 30 days and 1 year). • Other types of nosocomial infections • Mortality post-surgery • Length of hospital stay • Postoperative antibiotic use • Hospital readmission • Infectious complications such as septicaemia or septic shock • Adverse events: ○ Antimicrobial resistance
13.	Secondary outcomes (important outcomes)	• People of any age undergoing any surgery who are nasal carriers of *S.aureus* identified by an appropriate screening method • Types of surgery (including cardiac and prosthetic surgery) • Elective surgery • Emergency surgery • Timing of nasal decolonisation
14.	Data extraction (selection and coding)	See Appendix B

15.	Risk of bias (quality) assessment	See Appendix B
16.	Strategy for data synthesis	See Appendix B
17.	Analysis of sub-groups	• Type of surgery (including cardiac and orthopaedic surgery) • Wound classification (clean, clean-contaminated, contaminated, dirty) • Elective surgery • Emergency surgery
18.	Type and method of review	☒ Intervention ☐ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)
19.	Language	English
20.	Country	England

21.	Anticipated or actual start date	March 2018		
22.	Anticipated completion date	April 2019		
23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
		Preliminary searches	☑	☑
		Piloting of the study selection process	☑	☑
		Formal screening of search results against eligibility criteria	☑	☑
		Data extraction	☑	☑
		Risk of bias (quality) assessment	☑	☑

		Data analysis	☑	☑
24.	Named contact	**5a. Named contact** Guideline Updates Team **5b Named contact e-mail** SSI@nice.org.uk **5c Named contact address** NICE Guideline Updates Team Centre for Guidelines NICE 10 Spring Gardens London, SW1A 2BU **5d Named contact phone number** +44 (0) 300 323 0410 **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE) and NICE Guideline Updates Team		
25.	Review team members	From the Centre for Guidelines: • Caroline Mulvihill, Guideline Lead • Shreya Shukla, Technical Analyst		

		• Jamie Elvidge, Health Economist • Sarah Glover, Information Specialist
26.	Funding sources/sponsor	This systematic review is being completed by the Centre for Guidelines which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are: Chair: Damien Longson Members: • Melanie Burden, Infection Control Nurse • Pamela Carroll, Theatre Practitioner • Annie Hitchman, Patient/ carer • Peter Jenks, Microbiologist • David Leaper, Surgeon • Thomas Pinkney, Surgeon • Melissa Rochon, Infection Control Nurse • Giovanni Satta, Microbiologist

		• David Saunders, Anaesthetist • Nigel Westwood, Patient/ carer
29.	Other registration details	
30.	Reference/URL for published protocol	
31.	Dissemination plans	The reviewers and guideline committee work with NICE's communications team to disseminate and promote awareness of the guideline at the time of publication and afterwards. Members from the NICE communications team discuss with the reviewers and the committee opportunities for promoting the guideline. Committee members may be asked to take part in such activities. With help from the guideline committee and the developer, they identify how to reach relevant audiences for the guideline, including people using services, carers, the public, practitioners and providers. NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE. NICE may also use other means of raising awareness of the guideline – for example, newsletters, websites, training programmes, conferences, implementation workshops, NICE field team support and other speaking engagements. Some of these may be suggested by guideline committee members (particularly members affiliated to organisations for people using services and carer organisations). Each

		guideline is different and activities for raising awareness will vary depending on the type and content of the guideline.
32.	Keywords	Intervention, nasal decontamination, surgical site infections, invasive surgery, superficial SSI, deep SSI, deep organ space SSI, intranasal mupirocin, nasal povidone-iodine solution, chlorhexidine, neomycin cream, naseptin
33.	Details of existing review of same topic by same authors	N/ A – this is a new review
34.	Current review status	☐ Ongoing ☒ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35..	Additional information	
36.	Details of final publication	www.nice.org.uk

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Appendix B- Methods

Priority screening

The reviews undertaken for this guideline all made use of the priority screening functionality with the EPPI-reviewer systematic reviewing software. This uses a machine learning algorithm (specifically, an SGD classifier) to take information on features (1, 2 and 3 word blocks) in the titles and abstract of papers marked as being 'includes' or 'excludes' during the title and abstract screening process, and re-orders the remaining records from most likely to least likely to be an include, based on that algorithm. This re-ordering of the remaining records occurs every time 25 additional records have been screened.

As an additional check to ensure this approach did not miss relevant studies, the included studies lists of included systematic reviews were searched to identify any papers not identified through the primary search.

Quality assessment

Individual systematic reviews were quality assessed using the ROBIS tool, with each classified into one of the following three groups:

- High quality – It is unlikely that additional relevant and important data would be identified from primary studies compared to that reported in the review, and unlikely that any relevant and important studies have been missed by the review.
- Moderate quality – It is possible that additional relevant and important data would be identified from primary studies compared to that reported in the review, but unlikely that any relevant and important studies have been missed by the review.
- Low quality – It is possible that relevant and important studies have been missed by the review.

Each individual systematic review was also classified into one of three groups for its applicability as a source of data, based on how closely the review matches the specified review protocol in the guideline. Studies were rated as follows:

- Fully applicable – The identified review fully covers the review protocol in the guideline.
- Partially applicable – The identified review fully covers a discrete subsection of the review protocol in the guideline.
- Not applicable – The identified review, despite including studies relevant to the review question, does not fully cover any discrete subsection of the review protocol in the guideline.

Using systematic reviews as a source of data

If systematic reviews were identified as being sufficiently applicable and high quality, and were identified sufficiently early in the review process (for example, from the surveillance review or early in the database search), they were used as the primary source of data, rather than extracting information from primary studies. The extent to which this was done depended on the quality and applicability of the review, as defined in Table 4. When systematic reviews were used as a source of primary data, any unpublished or additional data included in the review which is not in the primary studies was also included. Data from these systematic reviews was then quality assessed and presented in GRADE tables as described below, in the same way as if data had been extracted from primary studies. In questions where data was extracted from both systematic reviews and primary studies, these

were cross-referenced to ensure none of the data had been double counted through this process.

Table 4: Criteria for using systematic reviews as a source of data

Quality	Applicability	Use of systematic review
High	Fully applicable	Data from the published systematic review were used instead of undertaking a new literature search or data analysis. Searches were only done to cover the period of time since the search date of the review.
High	Partially applicable	Data from the published systematic review were used instead of undertaking a new literature search and data analysis for the relevant subsection of the protocol. For this section, searches were only done to cover the period of time since the search date of the review. For other sections not covered by the systematic review, searches were undertaken as normal.
Moderate	Fully applicable	Details of included studies were used instead of undertaking a new literature search. Full-text papers of included studies were still retrieved for the purposes of data analysis. Searches were only done to cover the period of time since the search date of the review.
Moderate	Partially applicable	Details of included studies were used instead of undertaking a new literature search for the relevant subsection of the protocol. For this section, searches were only done to cover the period of time since the search date of the review. For other sections not covered by the systematic review, searches were undertaken as normal.

Evidence of effectiveness of interventions

Quality assessment

Individual RCTs were quality assessed using the Cochrane Risk of Bias Tool. Other study were quality assessed using the ROBINS-I tool. Each individual study was classified into one of the following three groups:

- Low risk of bias – The true effect size for the study is likely to be close to the estimated effect size.
- Moderate risk of bias – There is a possibility the true effect size for the study is substantially different to the estimated effect size.
- High risk of bias – It is likely the true effect size for the study is substantially different to the estimated effect size.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, intervention, comparator and/or outcomes in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, intervention, comparator and/or outcomes.
- Partially indirect – Important deviations from the protocol in one of the population, intervention, comparator and/or outcomes.
- Indirect – Important deviations from the protocol in at least two of the following areas: population, intervention, comparator and/or outcomes.

Methods for combining intervention evidence

Meta-analyses of interventional data were conducted with reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011).

Where different studies presented continuous data measuring the same outcome but using different numerical scales (e.g. a 0-10 and a 0-100 visual analogue scale), these outcomes were all converted to the same scale before meta-analysis was conducted on the mean differences. Where outcomes measured the same underlying construct but used different instruments/metrics, data were analysed using standardised mean differences (Hedges' g).

A pooled relative risk was calculated for dichotomous outcomes (using the Mantel–Haenszel method). Both relative and absolute risks were presented, with absolute risks calculated by applying the relative risk to the pooled risk in the comparator arm of the meta-analysis.

Fixed- and random-effects models (der Simonian and Laird) were fitted where appropriate, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models were the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model were clearly not met, even after appropriate pre-specified subgroup analyses were conducted, random-effects results are presented. Fixed-effects models were deemed to be inappropriate if one or both of the following conditions was met:

- Significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. This decision was made and recorded before any data analysis was undertaken.
- The presence of significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$.

In any meta-analyses where some (but not all) of the data came from studies at high risk of bias, a sensitivity analysis was conducted, excluding those studies from the analysis. Results from both the full and restricted meta-analyses are reported. Similarly, in any meta-analyses where some (but not all) of the data came from indirect studies, a sensitivity analysis was conducted, excluding those studies from the analysis.

Meta-analyses were performed in Cochrane Review Manager v5.3.

Minimal clinically important differences (MIDs)

The Core Outcome Measures in Effectiveness Trials (COMET) database was searched to identify published minimal clinically important difference thresholds relevant to this guideline. Identified MIDs were assessed to ensure they had been developed and validated in a methodologically rigorous way, and were applicable to the populations, interventions and outcomes specified in this guideline. In addition, the Guideline Committee were asked to prospectively specify any outcomes where they felt a consensus MID could be defined from their experience. In particular, any questions looking to evaluate non-inferiority (that one treatment is not meaningfully worse than another) required an MID to be defined to act as a non-inferiority margin.

No MIDs were identified. Therefore, a default MID interval for dichotomous outcomes of 0.8 to 1.25 was used.

When decisions were made in situations where MIDs were not available, the 'Evidence to Recommendations' section of that review should make explicit the committee's view of the expected clinical importance and relevance of the findings. In particular, this includes

consideration of whether the whole effect of a treatment (which may be felt across multiple independent outcome domains) would be likely to be clinically meaningful, rather than simply whether each individual sub outcome might be meaningful in isolation.

GRADE for pairwise meta-analyses of interventional evidence

GRADE was used to assess the quality of evidence for the selected outcomes as specified in 'Developing NICE guidelines: the manual (2014)'. Data from all study designs was initially rated as high quality and the quality of the evidence for each outcome was downgraded or not from this initial point, based on the criteria given in Table 5.

Table 5: Rationale for downgrading quality of evidence for intervention studies

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies at high and low risk of bias.
Indirectness	Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between direct and indirect studies.
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the I^2 statistic. N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study. Not serious: If the I^2 was less than 33.3%, the outcome was not downgraded. Serious: If the I^2 was between 33.3% and 66.7%, the outcome was downgraded one level. Very serious: If the I^2 was greater than 66.7%, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies with the smallest and largest effect sizes.
Imprecision	If an MID other than the line of no effect was defined for the outcome, the outcome was downgraded once if the 95% confidence interval for the effect size crossed one line of the MID, and twice if it crosses both lines of the MID. If the line of no effect was defined as an MID for the outcome, it was downgraded once if the 95% confidence interval for the effect size crossed the

GRADE criteria	Reasons for downgrading quality
	line of no effect (i.e. the outcome was not statistically significant), and twice if the sample size of the study was sufficiently small that it is not plausible any realistic effect size could have been detected. For continuous outcomes, study was downgraded 1 level for non-significant results. Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios.

The quality of evidence for each outcome was upgraded if any of the following three conditions were met:

- Data from non-randomised studies showing an effect size sufficiently large that it cannot be explained by confounding alone.
- Data showing a dose-response gradient.
- Data where all plausible residual confounding is likely to increase our confidence in the effect estimate.

Publication bias

Publication bias was assessed in two ways. First, if evidence of conducted but unpublished studies was identified during the review (e.g. conference abstracts, trial protocols or trial records without accompanying published data), available information on these unpublished studies was reported as part of the review. Secondly, where 10 or more studies were included as part of a single meta-analysis, a funnel plot was produced to graphically assess the potential for publication bias.

Evidence statements

Evidence statements for pairwise intervention data are classified in to one of four categories:

- Situations where the data are only consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is 'statistically significant'), and the magnitude of that effect is most likely to meet or exceed the MID (i.e. the point estimate is not in the zone of equivalence). In such cases, we state that the evidence showed that there is an effect.
- Situations where the data are only consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is 'statistically significant'), but the magnitude of that effect is most likely to be less than the MID (i.e. the point estimate is in the zone of equivalence). In such cases, we state that the evidence could not demonstrate a meaningful difference.
- Situations where the data are consistent, at a 95% confidence level, with an effect in either direction (i.e. one that is not 'statistically significant') but the confidence limits are smaller than the MIDs in both directions. In such cases, we state that the evidence demonstrates that there is no difference.
- In all other cases, we state that the evidence could not differentiate between the comparators.

For outcomes without a defined MID or where the MID is set as the line of no effect, evidence statements are divided into 2 groups as follows:

- We state that the evidence showed that there is an effect if the 95% CI does not cross the line of no effect.
- The evidence could not differentiate between comparators if the 95% CI crosses the line of no effect.

Health economics

Literature reviews seeking to identify published cost–utility analyses of relevance to the issues under consideration were conducted for all questions. In each case, the search undertaken for the clinical review was modified, retaining population and intervention descriptors, but removing any study-design filter and adding a filter designed to identify relevant health economic analyses. In assessing studies for inclusion, population, intervention and comparator, criteria were always identical to those used in the parallel clinical search; only cost–utility analyses were included. Economic evidence profiles, including critical appraisal according to the Guidelines manual, were completed for included studies.

Economic studies identified through a systematic search of the literature are appraised using a methodology checklist designed for economic evaluations (NICE guidelines manual; 2014). This checklist is not intended to judge the quality of a study per se, but to determine whether an existing economic evaluation is useful to inform the decision-making of the committee for a specific topic within the guideline.

There are 2 parts of the appraisal process. The first step is to assess applicability (that is, the relevance of the study to the specific guideline topic and the NICE reference case); evaluations are categorised according to the criteria in Table 1.

Table 1 Applicability criteria

Level	Explanation
Directly applicable	The study meets all applicability criteria, or fails to meet one or more applicability criteria but this is unlikely to change the conclusions about cost effectiveness
Partially applicable	The study fails to meet one or more applicability criteria, and this could change the conclusions about cost effectiveness
Not applicable	The study fails to meet one or more applicability criteria, and this is likely to change the conclusions about cost effectiveness. These studies are excluded from further consideration

In the second step, only those studies deemed directly or partially applicable are further assessed for limitations (that is, methodological quality); see categorisation criteria in Table 2.

Table 2 Methodological criteria

Level	Explanation
Minor limitations	Meets all quality criteria, or fails to meet one or more quality criteria but this is unlikely to change the conclusions about cost effectiveness
Potentially serious limitations	Fails to meet one or more quality criteria and this could change the conclusions about cost effectiveness

Level	Explanation
Very serious limitations	Fails to meet one or more quality criteria and this is highly likely to change the conclusions about cost effectiveness. Such studies should usually be excluded from further consideration

Studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly applicable UK analysis was available, then other less relevant studies may not have been included. Where selective exclusions were made on this basis, this is noted in the relevant section.

Where relevant, a summary of the main findings from the systematic search, review and appraisal of economic evidence is presented in an economic evidence profile alongside the clinical evidence.

Appendix C – Literature search strategies

Sources searched to identify the clinical evidence:

Databases	Date searched	Version/files
Cochrane Central Register of Controlled Trials (CENTRAL)	15/03/2018	Issue 2 of 12, February 2018
Cochrane Database of Systematic Reviews (CDSR)	15/03/2018	Issue 3 of 12, March 2018
Database of Abstracts of Reviews of Effect (DARE)	15/03/2018	Issue 2 of 4, April 2015
Embase (Ovid)	15/03/2018	1974 to 2018 March 14
MEDLINE (Ovid)	15/03/2018	1946 to Present with Daily Update
MEDLINE In-Process (Ovid)	15/03/2018	1974 to 2018 March 14
CINAHL with full text (EBSCO)	15/03/2018	-
PubMed	15/03/2018	-
MHRA	15/03/2018	-

The MEDLINE search strategy is presented below. This was translated for use in all of the other databases listed. The aim of the search was to identify evidence for the clinical question being asked. Randomised Controlled Trial and Systematic Review filters were used to identify the study designs specified in the Review Protocol.

1 Surgical Wound Infection/
2 Wound Infection/
3 SURGICAL WOUND DEHISCENCE/
4 ((wound? or incision* or suture*) adj4 (infect* or sepsis or septic* or dehiscen* or site* or contaminat* or disrupt* or ruptur* or separat*)).tw.
5 (SSI or SSIs or SSTI or SSTIs).tw.
6 or/1-5
7 exp Specialties, Surgical/
8 exp Surgical Procedures, Operative/
9 surgery.fs.
10 (surger* or surgical* or operat* or procedure* or postop* or post-op* or post op* or postsurg* or post-surg* or post surg* or presurg* or pre-surg* or pre surg* or preop* or pre-op* or pre op*).tw.
11 exp Minimally Invasive Surgical Procedures/
12 (arthroscop* or laparoscop* or thoracoscop* or endoscop*).tw.
13 Infection Control/
14 (infection adj4 control).tw.

15 Postoperative Complications/
16 Preoperative care/
17 or/7-16
18 Staphylococcal Infections/
19 exp Staphylococcus aureus/
20 (staph* adj4 aureus).tw.
21 (MRSA or MSSA).tw.
22 (methicillin adj4 resistant adj4 staph*).tw.
23 “s aureus”.tw.
24 Gram-positive Bacterial Infections/
25 ((gram-positive adj4 bacterial adj4 infection*) or (gram adj4 positive adj4 bacterial adj4 infection*)).tw.
26 Cross Infection/
27 (cross adj4 infection*).tw.
28 ((health adj4 care adj4 associated adj4 infection*) or (healthcare adj4 associated adj4 infection*)).tw.
29 (hospital adj4 infection*).tw.
30 nosocomial*.tw.
31 exp Sepsis/
32 (blood adj4 poisoning*).tw.
33 (sepsis or septic* or pyaemi* or pyohemi*).tw.
34 or/18-33
35 17 and 34
36 6 or 35
37 exp Anti-Infective Agents, Local/
38 Chlorhexidine/
39 chlorhexidine.tw.
40 (naseptin or novalsan or tubulicid or “sebidan a” or mk 412a or mk-412a or mk412a).tw. (44)
41 (acriflex or bacticlens or bactigras or “cx powder” or cepton or chlorasept or chlorohex or clorhexitulle or corsodyl or curasept or dispray or eczmol or elgydium or hibidil or hibiscrub or hibitane or hydrex or periochip or perioguard or rotersept or savlon or serotulle or spotoway or sterexidine or steripod or gluconate or uniscrub or unisept or “uriflex c” or phiso-med or CB12 or cetriclens or chloraprep or Clearasil or covonia or cyteal or dermol or eludril or germolene or germoloid* or hibi or hibicet or hibisol or instillagel or medi-swab or medi-wipe or mycil or nystaform* or quinoderm or savloclens or savlodil or sterets or steriwipe or tisept or torbetol or travasept or tri-ac or xylocaine).tw.
42 Mupirocin/
43 (mupirocin* or bactroban).tw.
44 Povidone-Iodine/
45 ((povidone adj4 iodine) or povidone-iodine).tw.
46 ((povidine adj4 iodine) or povidine-iodine).tw.
47 (PVP-I or PVPI or PVP I or PVP-iodine or PVPiodine or pvp iodine or polyvinylpyrrolidoneiodine* or polyvinylpyrrolidone-iodine* or polyvinylpyrrolidone iodine*).tw.
48 (alphadine* or betadine* or betaisodona or betasept or “brush off” or “cold sore lotion” or disadine* or inadine or pharmadine* or povidine* or “savlon dry” or videne or codella).tw. (530)
49 (octenisan or octenide or octenidine or octeniderm or “win 41464” or “win 41464 2”).tw. (168)
50 Decontamination/
51 decontaminat*.tw.
52 decoloni*.tw.

53 or/37-52
54 36 and 53
55 exp glycopeptides/
56 (glycopeptide* or glucopeptide* or macroglycopeptide* or bleomycin* or peptidoglycan* or ristocetin* or teicoplanin* or vancomycin*).tw.
57 55 or 56
58 exp Antibiotic Prophylaxis/
59 (antibiotic adj4 (prophyla* or premedicat*)).tw.
60 58 or 59
61 36 and 57 and 60
62 54 or 61
63 Nasal Cavity/
64 Nasal Mucosa/
65 Nasopharynx/
66 exp Oropharynx/
67 nares.tw.
68 nasal.tw.
69 (nose or noses).tw.
70 oropharyn*.tw.
71 nasopharyn*.tw. (28630)
72 pharyn*.tw. (34295)
73 mouth.tw. (54514)
74 Mouth/ (19975)
75 (oral or orally).tw.
76 Mouthwashes/
77 (mouthwash* or mouthrins*).tw.
78 Administration, Intranasal/
79 (intranasal* or intra nasal* or intra-nasal*).tw.
80 or/63-79
81 62 and 80
82 animals/ not humans/
83 81 not 82
84 limit 83 to i English language
85 Randomized Controlled Trial.pt.
86 Controlled Clinical Trial.pt.
87 Clinical Trial.pt.
88 exp Clinical Trials as Topic/
89 Placebos/
90 Random Allocation/
91 Double-Blind Method/
92 Single-Blind Method/
93 Cross-Over Studies/
94 ((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw.
95 (random$ adj3 allocat$).tw.
96 placebo$.tw.
97 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw.
98 (crossover$ or (cross adj over$)).tw.
99 or/85-98
100 Meta-Analysis.pt.
101 Network Meta-Analysis/
102 Meta-Analysis as Topic/
103 Review.pt.

104 exp Review Literature as Topic/
105 (metaanaly$ or metanaly$ or (meta adj3 analy$)).tw.
106 (review$ or overview$).ti.
107 (systematic$ adj5 (review$ or overview$)).tw.
108 ((quantitative$ or qualitative$) adj5 (review$ or overview$)).tw.
109 ((studies or trial$) adj2 (review$ or overview$)).tw.
110 (integrat$ adj3 (research or review$ or literature)).tw.
111 (pool$ adj2 (analy$ or data)).tw.
112 (handsearch$ or (hand adj3 search$)).tw.
113 (manual$ adj3 search$).tw.
114 or/100-113
115 99 or 114
116 84 and 115

Economic evaluations and quality of life data

Search filters to retrieve economic evaluations and quality of life papers were appended to the strategy listed above to identify relevant evidence. The MEDLINE economic evaluations and quality of life search filters are presented below. They were translated for use in MEDLINE in Process, Embase, The Cochrane Library, CINAHL and Econlit databases.

Sources searched to identify economic evaluations:

Databases	Date searched
Embase (Ovid)	15/03/2018
MEDLINE (Ovid)	15/03/2018
MEDLINE In-Process (Ovid)	15/03/2018
EconLit (Ovid)	15/03/2018
NHS Economic Evaluation Database (NHS EED) (legacy database)	15/03/2018
Health Technology Assessment (HTA Database)	15/03/2018
CINAHL Plus with Fulltext (EBSCO)	16/03/2018

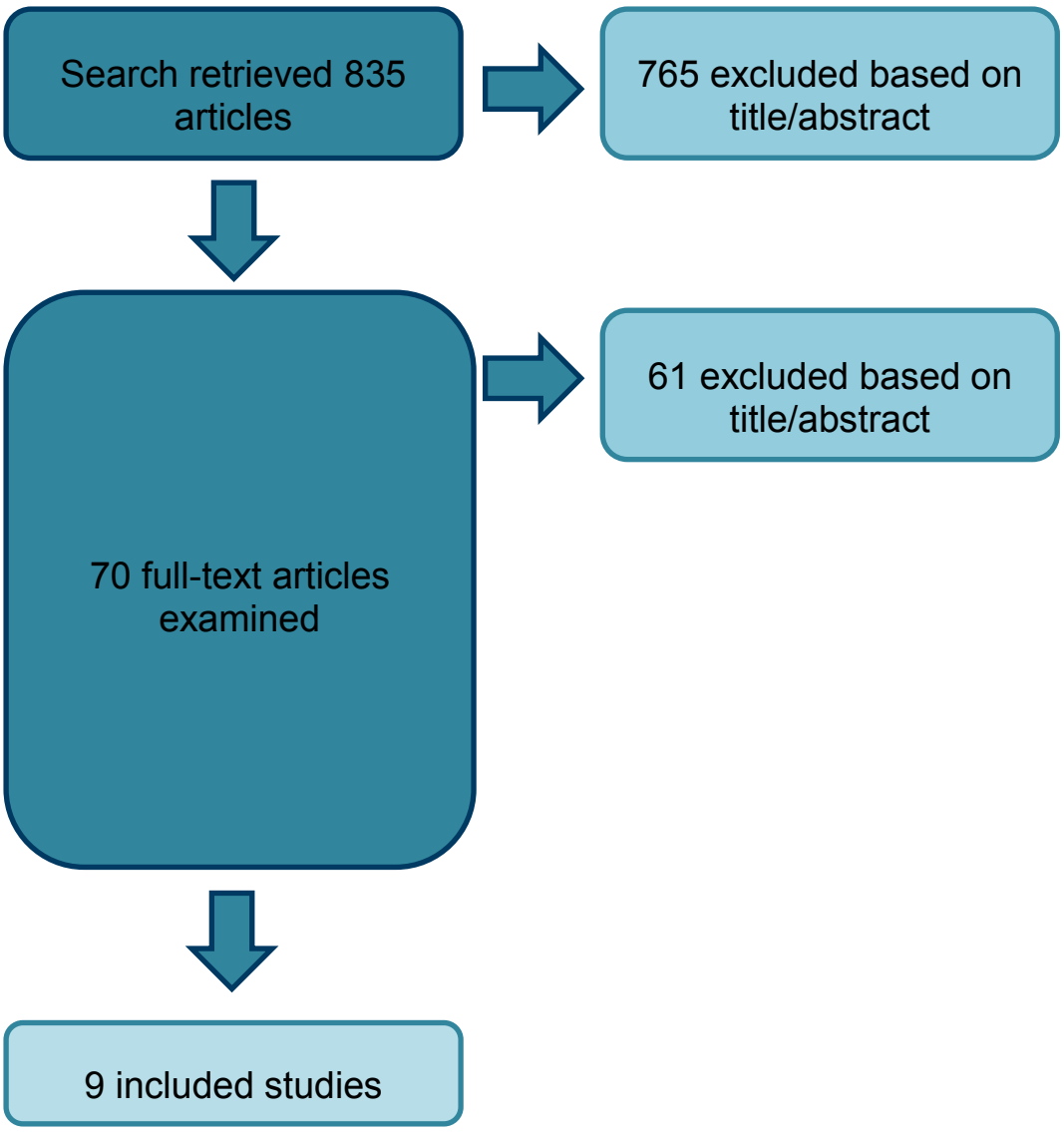
<u>Economic evaluations</u>

1. Economics/
2. exp "Costs and Cost Analysis"/
3. Economics, Dental/
4. exp Economics, Hospital/
5. exp Economics, Medical/
6. Economics, Nursing/
7. Economics, Pharmaceutical/
8. Budgets/
9. exp Models, Economic/
10. Markov Chains/
11. Monte Carlo Method/
12. Decision Trees/
13. econom$.tw.
14. cba.tw.
15. cea.tw.
16. cua.tw.
17. markov$.tw.
18. (monte adj carlo).tw.
19. (decision adj3 (tree$ or analys$)).tw.
20. (cost or costs or costing$ or costly or costed).tw.
21. (price$ or pricing$).tw.
22. budget$.tw.
23. expenditure$.tw.
24. (value adj3 (money or monetary)).tw.
25. (pharmacoeconomic$ or (pharmaco adj economic$)).tw.
26. or/1-25

Quality of Life
1. "Quality of Life"/
2. quality of life.tw.
3. "Value of Life"/
4. Quality-Adjusted Life Years/
5. quality adjusted life.tw.
6. (qaly$ or qald$ or qale$ or qtime$).tw.
7. disability adjusted life.tw.
8. daly$.tw.
9. Health Status Indicators/
10. (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
11. (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
12. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
13. (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
14. (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
15. (euroqol or euro qol or eq5d or eq 5d).tw.
16. (qol or hql or hqol or hrqol).tw.
17. (hye or hyes).tw.
18. health$ year$ equivalent$.tw.
19. utilit$.tw.

20. (hui or hui1 or hui2 or hui3).tw.
21. disutili$.tw.
22. rosser.tw.
23. quality of wellbeing.tw.
24. quality of well-being.tw.
25. qwb.tw.
26. willingness to pay.tw.
27. standard gamble$.tw.
28. time trade off.tw.
29. time tradeoff.tw.
30. tto.tw.
31. or/1-30

Appendix D – Clinical evidence study selection



Appendix E – Clinical evidence tables

E.1 Bode (2010)

Item	Bode (2010)
Title	Preventing surgical-site infections in nasal carriers of Staphylococcus aureus
Study Details	**Study type** • Randomised controlled trial Double blind, placebo-controlled, multicentre trial. • **Study location** Rotterdam, The Netherlands. • **Study setting** 3 university hospitals. • **Study dates** October 2005 to June 2007 • **Duration of follow-up** until 6 weeks after discharge. • **Sources of funding** Supported by grants from ZonMw, Molnlycke Healthcare, GlaxoSmithKline, Roche, bioMerieux, and 3M **Inclusion criteria** • Patients screened for nasal carriage of S. aureus either immediately on admission or during the week before admission. • Patient would remain hospitalised for at least 4 days in one of the participating departments. • Nasal carriage of S. aureus determined by real-time PCR and the ability to start intervention within 24 hours after the patients' admission to the ward. Patients were from internal medicine, cardiothoracic surgery, vascular surgery, orthopaedics, gastrointestinal surgery, or general surgery) **Exclusion criteria** • Aged less than 18 years. • Presence of active infection with S. aureus at the time of randomisation, known allergy to mupirocin or chlorhexidine, pregnancy, breast-feeding, use of mupirocin in the preceding 4 weeks, and the presence of a nasal foreign body.

Item	Bode (2010)
	• **Sample size** 917 (includes non-surgical patients) **Sample characteristics** • **Split between study groups** Intervention: 504 Comparator: 413 • **Loss to follow-up** 1 patient withdrew consent in treatment group. • **% female** Intervention: 34.30% Comparator: 39.20% • **Mean age (SD)** Intervention: 61.8 (13.9) Comparator: 62.8 (13.3) • **Diabetes (%)** intervention: 22.3% Comparator: 17.2%
Interventions	• 2% mupirocin ointment and chlorhexidine body wash Mupirocin ointment 2% (Bactroban, GlaxoSmithKline) in combination with chlorhexidine gluconate soap, 40 mg per millilitre. Nasal ointment was applied twice daily, and the soap wash used daily for a total-body wash. The duration of the study treatment was 5 days, irrespective of the timing of any interventions. Patients received antibiotic therapy.
Comparator	• Placebo Placebo ointment in combination with placebo soap. Placebo soap and ointment were identical to the active treatment except for the active ingredients. Nasal ointment was applied twice daily, and the soap was used daily for a total-body wash. The duration of the study treatment was 5 days, irrespective of the timing of any interventions. Patients received additional antibiotics.
Outcome measure(s)	• **S. aureus SSI** Until 6 weeks after discharge according to Centres for Disease Control and prevention (CDC)-criteria. Patients were monitored for hospital-acquired S. aureus infection by means of microbiological cultures. Attending physicians were encouraged to obtain culture samples if infection was suspected. • **S. aureus superficial SSI** Until 6 weeks after discharge according to Centres for Disease Control and prevention (CDC)-criteria. Patients were monitored for hospital-acquired S. aureus infection by means of microbiological cultures. Attending physicians were encouraged to obtain culture

Item	Bode (2010)
	samples if infection was suspected. **• S. aureus deep SSI** Until 6 weeks after discharge according to Centres for Disease Control and prevention (CDC)-criteria. Patients were monitored for hospital-acquired S. aureus infection by means of microbiological cultures. Attending physicians were encouraged to obtain culture samples if infection was suspected. **• S. aureus nosocomial infections** Until 6 weeks after discharge according to Centres for Disease Control and prevention (CDC)-criteria. **• Mortality**
Risk of Bias and Directness	**Random sequence generation** • Low risk of bias **Allocation concealment** • Low risk of bias **Blinding of participants and personnel** • Low risk of bias **Blinding of outcome assessment** • Low risk of bias **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Low **Directness** • Directly applicable

E.2 Kalmeijer (2002)

Item	Kalmeijer (2002)
Title	Surgical site infections in orthopaedic surgery: the effect of mupirocin nasal ointment in a double-blind, randomized, placebo-controlled study
Study details	**Study type** • Randomised controlled trial

Item	Kalmeijer (2002)
	Randomised, double-blind, placebo-controlled clinical trial • **Study location** The Netherlands • **Study setting** Department of Orthopaedic Surgery • **Study dates** January 1997 to July 1999 • **Duration of follow-up** 1 month after surgery • **Sources of funding** Mupirocin ointment and the ingredients for placebo were provided by GlaxoSmithKline. **Inclusion criteria** • All patients undergoing elective orthopaedic surgery during which prosthetic implant material was used (i.e. hip, knee, or back surgery). •Patients undergoing a revision operation of the same type **Exclusion criteria** •Patient with an active infection at the moment of inclusion and those who had received antibiotic treatment in the previous 24 hours. • **Sample size** 614 **Sample characteristics** • **Split between study groups** Intervention: 315 Comparator: 299 • **Loss to follow-up** 43 patients underwent surgery that did not involve the use of prosthetic material. • **%female** Intervention: 67% Comparator: 65.6%

Item	Kalmeijer (2002)
	• **Mean age (SD)** Intervention: 62.9 (13.6) Comparator: 62.7 (10.6) • **Body Mass Index (SD)** Intervention: 27.0 (4.2) Comparator: 27.2 (4.3) • **Diabetes (%)** Insulin dependent diabetes Intervention: 1% Comparator: 0.3%
Interventions	• 2.15% mupirocin ointment Mupirocin nasal ointment containing 2.15% weight/weight mupirocin calcium in a soft, white ointment bases consisting of paraffin and a mixture of glycerine esters. Patients were administered to the hospital the day before surgery was performed. A nasal swab was done of both nares from culture. Thereafter, therapy with mupirocin nasal ointment was administered. Ointment was applied twice daily. Before surgery, ≥2 doses of nasal ointment were administered. Cefamandole was given as perioperative antibiotic prophylaxis to all patients.
Comparator	• Placebo Placebo ointment was produced in the hospital pharmacy from paraffin and Softisan, according to GlaxoSmithKline protocol. Ointment was applied twice daily. Before surgery, ≥2 doses of nasal ointment were administered. Cefamandole was given as perioperative antibiotic prophylaxis to all patients.
Outcome measure(s)	• **Overall SSI** 30 days SSI diagnosed according to standard criteria developed by CDC. The medical records of all patients were studied. After discharge from the hospital, follow up studies were performed over the phone by use of a standardised questionnaire that was based on the CDC criteria. Patients were asked whether they had experienced any of the following symptoms; purulent drainage from the incision, pain and tenderness, and redness or heat; in addition, they were asked whether an antibiotic had been prescribed and whether a specimen of the wound had been obtained for culture. It one of the answers indicated an infection, the patient was seen at the outpatient department by an orthopaedic surgeon for further evaluation. (Reported in whole population) • **Overall superficial SSI** 30 days SSI diagnosed according to standard criteria developed by CDC. The medical records of all patients were studied. After discharge from the hospital, follow up studies were performed over the phone by use of a standardised questionnaire that was based on the CDC criteria. Patients were asked whether they had experienced any of the following symptoms; purulent drainage from the incision, pain and tenderness, and redness or heat; in addition, they were asked whether an antibiotic had been prescribed and whether a specimen of the wound had been obtained for culture. It one of the answers indicated an infection, the patient was seen at the outpatient department by an orthopaedic surgeon for further evaluation. (Reported in whole population)

Item	Kalmeijer (2002)
	• **Overall deep SSI** 30 days SSI diagnosed according to standard criteria developed by CDC. The medical records of all patients were studied. After discharge from the hospital, follow up studies were performed over the phone by use of a standardised questionnaire that was based on the CDC criteria. Patients were asked whether they had experienced any of the following symptoms; purulent drainage from the incision, pain and tenderness, and redness or heat; in addition, they were asked whether an antibiotic had been prescribed and whether a specimen of the wound had been obtained for culture. It one of the answers indicated an infection, the patient was seen at the outpatient department by an orthopaedic surgeon for further evaluation. (Reported in whole population) • **S. aureus SSI** 30 days SSI diagnosed according to standard criteria developed by CDC. The medical records of all patients were studied. After discharge from the hospital, follow up studies were performed over the phone by use of a standardised questionnaire that was based on the CDC criteria. Patients were asked whether they had experienced any of the following symptoms; purulent drainage from the incision, pain and tenderness, and redness or heat; in addition, they were asked whether an antibiotic had been prescribed and whether a specimen of the wound had been obtained for culture. It one of the answers indicated an infection, the patient was seen at the outpatient department by an orthopaedic surgeon for further evaluation. (Reported in whole population and *S. aureus* carriers) • **Length of hospital stay** (Reported in whole population) • **Hospital readmission** (Reported in whole population) • **Antimicrobial resistance**
Risk of Bias and Directness	**Random sequence generation** • Low risk of bias **Allocation concealment** • Low risk of bias **Blinding of participants and personnel** • Low risk of bias **Blinding of outcome assessment** • Low risk of bias **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias (Whole population) • High risk of bias (In *S. aureus* carriers) **Other sources of bias** • Low risk of bias **Overall risk of bias** • Low (Whole population)

Item	Kalmeijer (2002)
	• Moderate (In *S. aureus* carriers) **Directness** • Directly applicable

E.3 Konvalinka (2006)

Item	Konvalinka (2006)
Title	Impact of treating Staphylococcus aureus nasal carriers on wound infections in cardiac surgery
Study details	**Study type** • Randomised controlled trial double-blind, randomised, placebo-controlled trial. **• Study location** Ontario, Canada **• Study setting** Hospital setting **• Study dates** March 1997 and March 2003. **• Duration of follow-up** 8 weeks **• Sources of funding** The Cardiovascular Surgery Research Grant and St Michael's Hospital Foundation Grant. **Inclusion criteria** • Patients undergoing elective open-heart surgery, who were screened for S. aureus nasal carriage two weeks before surgery (nasal cultures also obtained again at admission just prior to surgery). **Exclusion criteria** • None reported **• Sample size** 257

Item	Konvalinka (2006)
	Sample characteristics **• Split between study groups** Intervention: 130 Comparator: 127 **• Loss to follow-up** Not reported. **• %female** Intervention: 14.60% Comparator: 14.20% **• Mean age (SD)** Intervention: 62.5(10.8) Comparator: 62.5(10.5) **• Body Mass Index (SD)** Intervention: 28.7(4.6) Comparator: 29.4(4.0) **• Diabetes (%)** Intervention: 28.5% Comparator: 28.3%
Interventions	• 2% mupirocin ointment Administered intranasally with a Q-tip cotton applicator to the vestibule of both nares, twice daily for 7 days before surgery. Standard pre-operative clinical practice was also followed which included a full shower or bath with chlorhexidine antiseptic soap 12h pre-operatively, surgical site cleansing and administration of routine antibiotic prophylaxis starting just before surgery.
Comparator	• Placebo Identical appearing placebo applied intranasally with a Q-tip cotton applicator to the vestibule of both nares, twice daily for 7 days before surgery. Standard pre-operative clinical practice was also followed which included a full shower or bath with chlorhexidine antiseptic soap 12h pre-operatively, surgical site cleansing and administration of routine antibiotic prophylaxis starting just before surgery.
Outcome measure(s)	**• Overall SSI** Wound infections were classified according to the Nosocomial infection Surveillance System definitions (A SSI defined by the occurrence of one of the following within 8 weeks of surgery, 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 surgery site was infected as corroborated by one or more of the listed criteria). **• Overall superficial SSI** Wound infections were classified according to the Nosocomial infection Surveillance System definitions.

Item	Konvalinka (2006)
	• Overall deep SSI Wound infections were classified according to the Nosocomial infection Surveillance System definitions. **• S. aureus SSI** Wound infections were classified according to the Nosocomial infection Surveillance System definitions. **• Mortality** **• Antimicrobial resistance**
Risk of Bias and Directness	**Random sequence generation** • Low risk of bias **Allocation concealment** • Low risk of bias **Blinding of participants and personnel** • Low risk of bias **Blinding of outcome assessment** • Low risk of bias **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias. **Overall risk of bias** • Low **Directness** • Directly applicable

E.4 Perl (2002)

Item	Perl (2002)
Title	Intranasal mupirocin to prevent postoperative Staphylococcus aureus infections
Study details	**Study type** • Randomised controlled trial Randomised, double-blind, placebo-controlled clinical trial **• Study location**

Item	Perl (2002)
	Iowa, USA • **Study setting** University of Iowa Hospitals and Clinics and the Veterans Affairs Medical Centre • **Study dates** April 1995 to December 1998 • **Duration of follow-up** 30 days • **Sources of funding** Research grant from GlaxoSmithKline **Inclusion criteria** • Adults who underwent elective and nonemergency cardiothoracic, general, oncologic, gynaecologic or neurologic surgical procedures. • Patients with S. aureus nasal carriage. **Exclusion criteria** • Patients who were allergic to mupirocin or glycerin ester. • Patients who were pregnant or breast-feeding. • Patients who were participating in another clinical trial. • Patients who had had S. aureus infections within the previous month. • Patients who had documented disruption of the nasal and facial bones. • Patients who were only having permanent central catheters inserted. • **Sample size** 3864 **Sample characteristics** **• Split between study groups** Intervention Group: 1933 Intervention Group (carriers): 444 Comparator Group: 1931 Comparator Group (carriers): 447 **• Loss to follow-up** 313/3864 **• %female**

Item	Perl (2002)
	Total Population: Intervention: 49.90% Comparator:47.40% Carriers: Intervention: 47.50% Comparator: 45% • **Mean age (SD)** Total Population: Intervention: 53.8 (16.3) Comparator: 54.2 (16.5) Carriers: Intervention: 50.7 (16.1) Comparator: 52.0 (17.4) • **Body Mass Index (SD)** Total Population : Intervention: 28.9 (7.8) Comparator: 29.0 (7.9) Carriers: Intervention: 29.6 (8.5) Comparator: 29.9 (8.8) • **Diabetes (%)** Total Population: Intervention: 15.9 % Comparator: 16.7% Carriers: Intervention: 14.7% Comparator: 15.9%
Interventions	• 2% mupirocin ointment Cotton swabs used to apply mupirocin to the interior of each anterior nares twice daily for up to 5 days before the operative procedure.

Item	Perl (2002)
	Surgeons followed standard clinical practice and used prophylactic antimicrobial regimens when appropriate. Patients who had undergone cardiac procedures showered with chlorhexidine the night before and the morning of the procedure.
Comparator	• Placebo Cotton swabs used to apply placebo to the interior of each anterior nares twice daily for up to 5 days before the operative procedure. Surgeons followed standard clinical practice and used prophylactic antimicrobial regimens when appropriate. Patients who had undergone cardiac procedures showered with chlorhexidine the night before and the morning of the procedure.
Outcome measure(s)	**• Overall SSI** 30 days SSI diagnosed according to standard criteria developed by CDC Study personnel examined hospitalised patients and reviewed their medical records every three to five days and telephoned discharged patients weekly during the follow-up period to determine whether the patients had signs or symptoms of infection. Patients who had signs of infection were asked to telephone the study personnel immediately. Three physicians who were unaware of the patients' treatment assignments reviewed the records of all patients with S. aureus infections at surgical sites to ensure that the criteria for infection were met. Cultures were obtained from surgical sites when signs and symptoms of infection were observed. **• S. aureus SSI** 30 day SSI diagnosed according to standard criteria developed by CDC. **• Overall nosocomial infections** 30 days Group includes infections of the bloodstream, respiratory tract, catheter and surgical site infection **• S. aureus nosocomial infections** 30 days Group includes infections of the bloodstream, respiratory tract, catheter and surgical site infection. **• Antimicrobial resistance** In vitro susceptibility of the isolates to oxacillin was determined by disk-diffusion testing, performed according to methods specified by the National Committee for Clinical Laboratory Standards. Susceptibility to mupirocin was determined with the E test (AB Biodisk), according to the manufacturer's instructions. An organism was considered resistant to mupirocin if the minimal inhibitory concentration exceeded 4µg per millilitre.
Risk of Bias and Directness	**Random sequence generation** • Unclear risk of bias Insufficient information provided. **Allocation concealment** • Unclear risk of bias Insufficient information provided. **Blinding of participants and personnel** • Unclear risk of bias Unclear if study personnel were blinded. *However, as outcomes were objective measures, study was not downgraded in this domain.* **Blinding of outcome assessment**

Item	Perl (2002)
	• Unclear risk of bias Unclear if study personnel were blinded. **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Moderate Unclear random sequence generation, allocation concealment and blinding of outcome assessment. **Directness** • Directly applicable

E.5 Philips (2014)

Item	Phillips (2014)
Title	Preventing surgical site infections: a randomized, open-label trial of nasal mupirocin ointment and nasal povidone-iodine solution
Study details	**Study type** • Randomised controlled trial • **Study location** New York, USA • **Study setting** Not specified • **Study dates** March 2011 to March 2012 • **Duration of follow-up** 3 months • **Sources of funding** 3M Corporation, the manufacturer of the nasal povidone-iodine solution, provided financial support.

Item	Phillips (2014)
	Inclusion criteria • Subjects at least 18 years old who presented to the pre-surgical assessment clinic to primary or revision arthroplasty and spine fusion surgery. **Exclusion criteria** • Pregnancy, breastfeeding, allergy to mupirocin or povidone iodine, interval from pre surgical assessment clinic visit to surgery of less than 7 days and an infectious indication for surgery. Need for nasal intubation. • **Sample size** 1697 **Sample characteristics** • **Split between study groups** Intervention: 855 Comparator: 842 • **Loss to follow-up** Not reported. • **%female** Intervention: 61% Comparator: 59% • **Mean Age (range)** Intervention: 62.4 (19.2-93.2) Comparator: 61.8 (19.1-92.4) • **Median Body Mass Index (range)** Intervention: 29.5 (14.9-58.9) Comparator: 29.5 (12.0-57.3) • **Diabetes (%)** Intervention: 13% Comparator: 12%
Interventions	• 2% mupirocin ointment Applied to each nostril for the 5 days prior to surgery. Treatment combined with application of six 2% chlorhexidine wipes on specific body surfaces from chin to toe the evening prior and morning of surgery. Subjects also received routine antimicrobial prophylaxis, surgical site preparation and surgical draping.

Item	Phillips (2014)
Comparator	• Different nasal decontamination procedures: Povidone iodine 5% solution Two 30 second applications into each nostril (4 applications in total) within 2 hours of surgical incision. Treatment combined with application of six 2% chlorhexidine wipes on specific body surfaces from chin to toe the evening prior and morning of surgery. Subjects also received routine antimicrobial prophylaxis, surgical site preparation and surgical draping.
Outcome measure(s)	**• Overall deep SSI** SSI diagnosed according to standard criteria developed by CDC and Prevention's National Healthcare Safety Network case definitions. Potential SSI were identified by review of microbiology reports, hospital readmissions, if a report was received from another healthcare facility (as mandated by New York State Department of Health regulations) and during Infection Prevention and Control (IPC) rounds on inpatient units. IPC practitioners reviewing the records were blinded to study participation and receipt of study treatment, potential cases were discussed at a group meeting to ensure consistent application of the SSI case definition. **• S. aureus deep SSI** SSI diagnosed according to standard criteria developed by CDC. **• MRSA deep SSI** SSI diagnosed according to standard criteria developed by CDC. **• MSSA deep SSI** SSI diagnosed according to standard criteria developed by CDC
Risk of Bias and Directness	**Random sequence generation** • Unclear risk of bias Insufficient information provided. **Allocation concealment** • Unclear risk of bias Insufficient information provided. **Blinding of participants and personnel** • High risk of bias Study is open label. *However, as outcomes were objective measures, study was not downgraded in this domain.* **Blinding of outcome assessment** • Low risk of bias **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Unclear risk of bias Insufficient information provided.

Item	Phillips (2014)
	Overall risk of bias • Moderate Unclear random sequence generation and allocation concealment. **Directness** • Directly applicable

E.6 Segers (2006)

Item	Segers (2006)
Title	Prevention of nosocomial infection in cardiac surgery by decontamination of the nasopharynx and oropharynx with chlorhexidine gluconate: a randomized controlled trial
Study details	**Study type** • Randomised controlled trial Randomised, double-blind, placebo-controlled trial. • **Study location** Amsterdam, The Netherlands. • **Study setting** Community Hospital • **Study dates** August 1st 2003 to September 1st 2005 • **Duration of follow-up** 30 days • **Sources of funding** No funding. All materials were provided by the local hospital pharmacy. **Inclusion criteria** • All patients older than 18 years who were scheduled to undergo sternotomy for cardiothoracic surgery. **Exclusion criteria** • Patients undergoing emergency procedures.

Item	Segers (2006)
	• Patients with preoperative infection, preoperative use of antimicrobials, or both. • Hypersensitivity to chlorhexidine gluconate. • Absence of written informed consent. • Treatment with an alternative prophylactic regimen like selective decontamination of the digestive tract. • Patients who were hospitalised less than 1 day before their surgery were not included in the study. • **Sample size** 991 **Sample characteristics** **• Split between study groups** Intervention : 485 Comparator : 469 **• Loss to follow-up** Intervention : 6 discontinued treatment Comparator : 9 discontinued treatment **• %female** Intervention : 25.4% Comparator : 28.4% **• Mean age (SD)** Intervention : 65.3 (10.4) Comparator : 66.4 (9.9) **• Body Mass Index (SD)** Intervention : 27.3 (11.0) Comparator: 26.8 (3.8) **• Diabetes (%)** Intervention : 19.0% Comparator : 19.8%
Interventions	• 0.12% chlorhexidine gluconate solution 0.12% chlorhexidine gluconate solution was used as an oral rinse and as a nasal gel for nasal application. The nose ointment was applied 4 times a day in both nostrils. The protocol was continued until the nasogastric tube was removed, usually the day after surgery. All patients were treated according to the local open heart protocol, including antibiotic prophylaxis.

Item	Segers (2006)
Comparator	• Placebo Placebo was identical to experimental drug in terms of colour, taste and smell. The oropharyngeal solution was used as a mouth rinse and applied to buccal, pharyngeal, gingival and tooth surfaces for 30 seconds 4 times daily. The nose ointment was applied 4 times a day in both nostrils.
Outcome measure(s)	**• Overall SSI** Diagnosis according to the criteria developed by CDC. Follow-up was completed by contacting and visiting the referring cardiology departments. Medical records of all patients were reviewed. Culture results were provided by the departments of medical microbiology in the hospitals and in referring hospitals. **• Overall deep SSI** Diagnosis according to the criteria developed by CDC. Deep SSI was defined as a wound defect in which infection is present beneath the subcutaneous layers. **• S. aureus SSI** Diagnosis according to the criteria developed by CDC. **• Overall nosocomial infections** Diagnosis according to the criteria developed by CDC. **• Nosocomial infection: Lower respiratory tract infection** Any LRTI occurring during hospital stay or within 48 hours after discharge were considered an infection related to surgical procedure. **• Nosocomial infection: Urinary tract infection** **• Nosocomial infection: Bacteraemia** **• 30- day mortality post-surgery** **• Length of hospital stay** **• Hospital readmission**
Risk of Bias and Directness	**Random sequence generation** • Low risk of bias **Allocation concealment** • Low risk of bias **Blinding of participants and personnel** • Low risk of bias **Blinding of outcome assessment** • Low risk of bias **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias

Item	Segers (2006)
	Other sources of bias • Low risk of bias **Overall risk of bias** • Low **Directness** • Partially directly applicable Chlorhexidine also used as an oral rinse.

E.7 Sousa (2016)

Item	Sousa (2016)
Title	Preoperative Staphylococcus aureus Screening/Decolonization Protocol Before Total Joint Arthroplasty-Results of a Small Prospective Randomized Trial
Study details	**Study type** • Randomised controlled trial **• Study location** Portugal **• Study setting** Department of Orthopaedics **• Study dates** January 2010 and December 2012 **• Duration of follow-up** 1 year after surgery. **• Sources of funding** Not reported. **Inclusion criteria** • Patients undergoing elective primary total hip (THA) or knee arthroplasty (TKA). • Patients identified as S. aureus carriers. **Exclusion criteria**

Item	Sousa (2016)
	• None reported • **Sample size** 1028 **Sample characteristics** **• Split between study groups** 228 *S. aureus* carriers randomised. Intervention: 113 Comparator: 115 **• Loss to follow-up** No patients lost to follow-up after 1 year.
Interventions	• 2% mupirocin ointment and chlorhexidine body wash Carriers were reconvened at least 1 week before surgery and educated about the rationale for the decolonisation protocol. Patients were instructed to apply a 2% mupirocin nasal ointment twice daily to both nares and to bathe with chlorhexidine soap daily for 5 days. All patients received prophylactic perioperative antibiotics.
Comparator	• No treatment Patients received no nasal decontamination or body wash. All patients received prophylactic perioperative antibiotics.
Outcome measure(s)	**• Overall deep SSI** Prosthetic joint infection (PJI) at 1 year follow-up. CDC definition of implant-related SSI used. Definitive diagnosis of PJI was made when at least 2 intraoperative microbiological samples grew the same organism or only 1 positive sample in the presence of a sinus tract, elevated serum erythrocyte sedimentation rate/ C reactive protein, or elevated serum synovial leukocyte count or neutrophil percentage in accordance with a recently proposed definition. **• S. aureus deep SSI** Prosthetic joint infection at 1 year follow-up. CDC definition of implant-related SSI used.
Risk of Bias and Directness	**Random sequence generation** • Low risk of bias **Allocation concealment** • Unclear risk of bias Insufficient information provided. **Blinding of participants and personnel** • Unclear risk of bias Insufficient information provided. *However, as outcomes were objective measures, study was not downgraded in this domain.* **Blinding of outcome assessment**

Item	Sousa (2016)
	• Unclear risk of bias Insufficient information provided. **Incomplete outcome data** • High risk of bias Intention-to-treat analysis not conducted. **Selective reporting** • Low risk of bias **Other sources of bias** • Unclear risk of bias Insufficient information provided. Unable to assess baseline imbalances between intervention arms. **Overall risk of bias** • High Unclear allocation concealment and blinding of outcome assessment. Furthermore, intention to treat analysis not conducted. **Directness** • Directly applicable

E.8 Suzuki (2003)

Item	Suzuki (2003)
Title	Randomized clinical trial of preoperative intranasal mupirocin to reduce surgical-site infection after digestive surgery
Study details	**Study type** • Randomised controlled trial • **Study location** Japan • **Study setting** University hospital • **Study dates** June 1998 and December 2000 • **Duration of follow-up** 30 days • **Sources of funding** Not reported

Item	Suzuki (2003)
	Inclusion criteria • Consecutive patients who underwent abdominal digestive surgery **Exclusion criteria** • Patients undergoing colorectal and laparoscopic procedures. • **Sample size** 395 **Sample characteristics** • **Split between study groups** Intervention: 193 Comparator: 202 • **Loss to follow-up** Not reported. • **%female** Intervention: 34% Comparator: 33% • **Mean age (SD)** Intervention: 63 (12) Comparator: 62 (13) • **Diabetes (%)** Intervention: 34% Comparator: 42%
Interventions	• 2% mupirocin ointment Patients in the treated group were given 30 mg mupirocin calcium hydrate (Bactroban; SmithKline and Beecham Pharmaceuticals, Tokyo, Japan) via Q-tip swab to each nostril three times a day on each of the three days before operation. All patients had an antiseptic shower with chlorhexidine wither the evening before, or on the morning of the surgery. Prophylactic intravenous antibiotics were started during operation, followed by the same regimen every 12h for 4-5 days after surgery.
Comparator	• No nasal decontamination All patients had an antiseptic shower with chlorhexidine wither the evening before, or on the morning of the surgery. Prophylactic intravenous antibiotics were started during operation, followed by the same regimen every 12h for 4-5 days after surgery.

Item	Suzuki (2003)
Outcome measure(s)	• **Overall SSI** SSI diagnosed according to standard criteria developed by CDC. The diagnosis of infective complications were made by a trained infection team consisting of digestive surgeons and radiologists with an assessor blinded technique. • **Overall superficial SSI** SSI diagnosed according to standard criteria developed by CDC. • **Overall deep SSI** SSI diagnosed according to standard criteria developed by CDC. • **S. aureus SSI** SSI diagnosed according to standard criteria developed by CDC. • **Overall nosocomial infections** Defined as the presence of patchy bronchopenumonic infiltrates or consolidation on chest radiography, with at least one clinical symptom (fever, productive cough, pleuritic chest pain or dyspnoea), and was confirmed by a positive sputum culture. All pneumonias were diagnosed within 14 days after surgery.
Risk of Bias and Directness	**Random sequence generation** • Unclear risk of bias Insufficient information provided. **Allocation concealment** • Low risk of bias **Blinding of participants and personnel** • Low risk of bias Insufficient information provided. However, study was not downgraded for this domain. **Blinding of outcome assessment** • Low risk of bias **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Low **Directness** • Directly applicable

E.9 Tai (2013)

Item	Tai (2013)
Title	Nasal carriage of Staphylococcus aureus in patients undergoing Mohs micrographic surgery is an important risk factor for postoperative surgical site infection: a prospective randomised study
Study details	**Study type** • Randomised controlled trial • **Study location** Australia • **Study setting** Surgery and Dermatology Centre. • **Study dates** 1st April to 31st October 2011 • **Duration of follow-up** All patients were followed up in the postoperative period for signs of clinical infection. Duration is not specified. • **Sources of funding** Not specified. **Inclusion criteria** • Patients presenting for assessment for MMS. • Patients with positive nasal cultures of S. aureus. **Exclusion criteria** • Patients receiving systemic antibiotics preoperatively. • Patients in whom the reconstructions were to be performed elsewhere (for example, by an oculoplastic surgeon). • **Sample size** 787 Mohs surgeries **Sample characteristics** • **Split between study groups** 203 patients test positive for S. aureus Intervention: 102 Comparator: 101 • **Loss to follow-up**

Item	Tai (2013)
	Not specified. • **%female** Intervention: 35% Comparator: 35% • **Mean age (SD)** Intervention: 64 (SD not specified) Comparator: 67 (SD not specified)
Interventions	• 2% mupirocin ointment and chlorhexidine body wash Patients with positive nasal cultures for S. aureus randomised to intervention group underwent a decolonisation protocol consisting of twice daily intranasal mupirocin ointment and once daily face and full body wash with chlorhexidine gluconate 4% aqueous solution for 5 days per-operatively. No prophylactic antibiotics were used.
Comparator	• No treatment Patients with positive nasal cultures for S. aureus randomised to control group received no treatment (nasal decontamination or body wash). No prophylactic antibiotics were used.
Outcome measure(s)	• **S. aureus SSI** SSI diagnosed only if clinical signs of infection (for example erythema, induration, tenderness or purulent discharge) occurred in the context of a positive culture on wound swab. Not clear if CDC definition was used. • **MRSA SSI** SSI diagnosed only if clinical signs of infection (for example erythema, induration, tenderness or purulent discharge) occurred in the context of a positive culture on wound swab. Not clear if CDC definition was used. • **MSSA SSI** SSI diagnosed only if clinical signs of infection (for example erythema, induration, tenderness or purulent discharge) occurred in the context of a positive culture on wound swab. Not clear if CDC definition was used.
Risk of Bias and Directness	**Random sequence generation** • Unclear risk of bias Insufficient information provided. **Allocation concealment** • Unclear risk of bias Insufficient information provided. **Blinding of participants and personnel** • Unclear risk of bias Insufficient information provided. *However, as outcomes were objective measures, study was not downgraded in this domain.* **Blinding of outcome assessment**

Item	Tai (2013)
	• Unclear risk of bias Insufficient information provided. **Incomplete outcome data** • Unclear risk of bias Loss to follow up not specified. **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Moderate Unclear random sequence generation, allocation concealment and blinding of outcome assessment. **Directness** • Partially directly applicable Unclear if CDC SSI definition was used. Follow-up not specified.

Appendix F – Forest plots

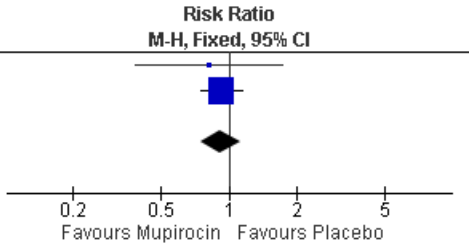
F.1 Mupirocin versus placebo

Outcomes in whole population

Overall SSI

Study or Subgroup	Mupirocin Events	Mupirocin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kalmeijer 2002 a	12	315	14	299	8.0%	0.81 [0.38, 1.73]
Perl 2002 a	152	1933	164	1931	92.0%	0.93 [0.75, 1.14]
Total (95% CI)		**2248**		**2230**	**100.0%**	**0.92 [0.75, 1.12]**
Total events	164		178			

Heterogeneity: Chi² = 0.10, df = 1 (P = 0.75); I² = 0%
Test for overall effect: Z = 0.84 (P = 0.40)

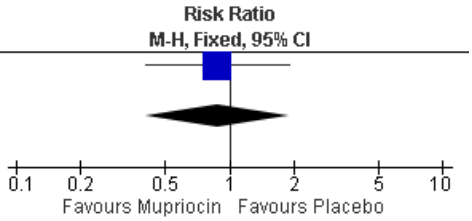


Follow up: 30 days

Overall superficial SSI

Study or Subgroup	Mupirocin Events	Mupirocin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kalmeijer 2002 a	12	315	13	299	100.0%	0.88 [0.41, 1.89]
Total (95% CI)		**315**		**299**	**100.0%**	**0.88 [0.41, 1.89]**
Total events	12		13			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.34 (P = 0.74)

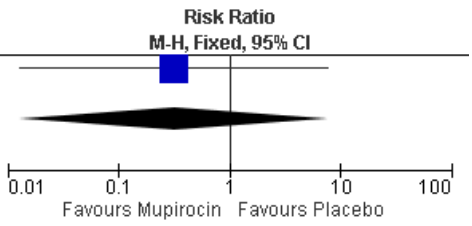


Follow up: 30 days

Overall deep SSI

Study or Subgroup	Mupirocin Events	Mupirocin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kalmeijer 2002 a	0	315	1	299	100.0%	0.32 [0.01, 7.74]
Total (95% CI)		**315**		**299**	**100.0%**	**0.32 [0.01, 7.74]**
Total events	0		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.71 (P = 0.48)

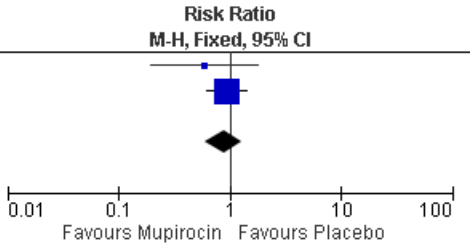


Follow up: 30 days

S. aureus SSI

Study or Subgroup	Mupirocin Events	Mupirocin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kalmeijer 2002 a	5	315	8	299	15.1%	0.59 [0.20, 1.79]
Perl 2002 a	43	1892	46	1894	84.9%	0.94 [0.62, 1.41]
Total (95% CI)		**2207**		**2193**	**100.0%**	**0.88 [0.60, 1.30]**
Total events	48		54			

Heterogeneity: Chi² = 0.57, df = 1 (P = 0.45); I² = 0%
Test for overall effect: Z = 0.63 (P = 0.53)

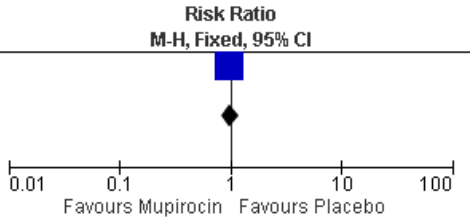


Follow up: 30 days

Overall nosocomial infections

Study or Subgroup	Mupirocin Events	Mupirocin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Perl 2002 a	218	1933	220	1931	100.0%	0.99 [0.83, 1.18]
Total (95% CI)		**1933**		**1931**	**100.0%**	**0.99 [0.83, 1.18]**
Total events	218		220			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.11 (P = 0.91)

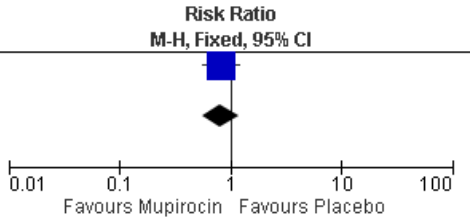


Follow up: 30 days

S. aureus nosocomial infections

Study or Subgroup	Mupirocin Events	Mupirocin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Perl 2002 a	45	1884	55	1886	100.0%	0.82 [0.56, 1.21]
Total (95% CI)		**1884**		**1886**	**100.0%**	**0.82 [0.56, 1.21]**
Total events	45		55			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.01 (P = 0.31)

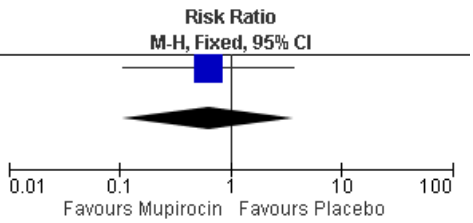


Follow up: 30 days

Hospital readmission

Study or Subgroup	Mupirocin Events	Mupirocin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kalmeijer 2002 a	2	315	3	299	100.0%	0.63 [0.11, 3.76]
Total (95% CI)		**315**		**299**	**100.0%**	**0.63 [0.11, 3.76]**
Total events	2		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.50 (P = 0.61)

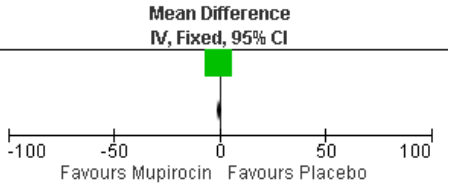


Follow up: 30 days

Mean hospital stay

Study or Subgroup	Mupirocin Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Kalmeijer 2002 a	14.7	7.3	315	15	6.3	299	100.0%	-0.30 [-1.38, 0.78]
Total (95% CI)			**315**			**299**	**100.0%**	**-0.30 [-1.38, 0.78]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.55 (P = 0.59)



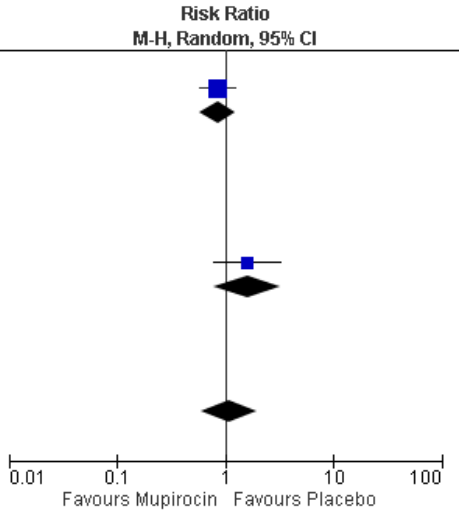
Follow up: 30 days

Outcomes in *S. aureus* Carriers

Overall SSI

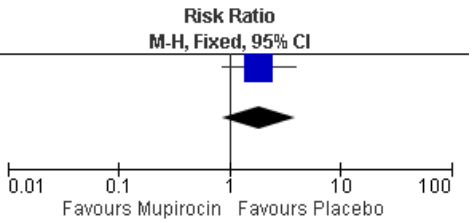
Study or Subgroup	Mupirocin Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 At 30 days						
Perl 2002 b	44	444	52	447	61.8%	0.85 [0.58, 1.24]
Subtotal (95% CI)		**444**		**447**	**61.8%**	**0.85 [0.58, 1.24]**
Total events	44		52			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.83 (P = 0.41)						
1.2.2 Within 8 weeks of surgery						
Konvalinka 2006	18	130	11	127	38.2%	1.60 [0.79, 3.25]
Subtotal (95% CI)		**130**		**127**	**38.2%**	**1.60 [0.79, 3.25]**
Total events	18		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.30 (P = 0.19)						
Total (95% CI)		**574**		**574**	**100.0%**	**1.08 [0.59, 1.97]**
Total events	62		63			

Heterogeneity: Tau² = 0.11; Chi² = 2.35, df = 1 (P = 0.12); I² = 58%
Test for overall effect: Z = 0.26 (P = 0.79)
Test for subgroup differences: Chi² = 2.35, df = 1 (P = 0.13), I² = 57.5%



Overall superficial SSI

Study or Subgroup	Mupirocin Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Konvalinka 2006	17	130	9	127	100.0%	1.85 [0.85, 3.99]
Total (95% CI)		**130**		**127**	**100.0%**	**1.85 [0.85, 3.99]**
Total events	17		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.56 (P = 0.12)						

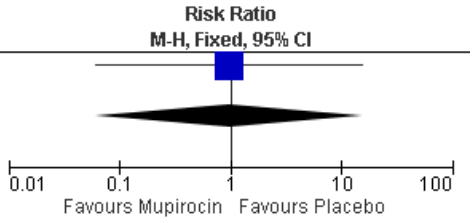


Follow up: Within 8 weeks

Overall deep SSI

Study or Subgroup	Mupirocin Events	Mupirocin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Konvalinka 2006	1	130	1	127	100.0%	0.98 [0.06, 15.45]
Total (95% CI)		**130**		**127**	**100.0%**	**0.98 [0.06, 15.45]**
Total events	1		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.02 (P = 0.99)

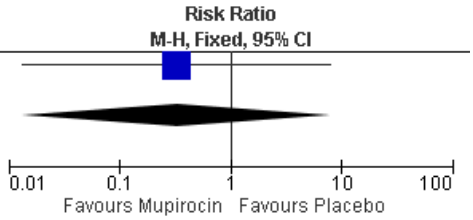


Follow up: Within 8 weeks

Overall deep space occupying SSI

Study or Subgroup	Mupirocin Events	Mupirocin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Konvalinka 2006	0	130	1	127	100.0%	0.33 [0.01, 7.92]
Total (95% CI)		**130**		**127**	**100.0%**	**0.33 [0.01, 7.92]**
Total events	0		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.69 (P = 0.49)

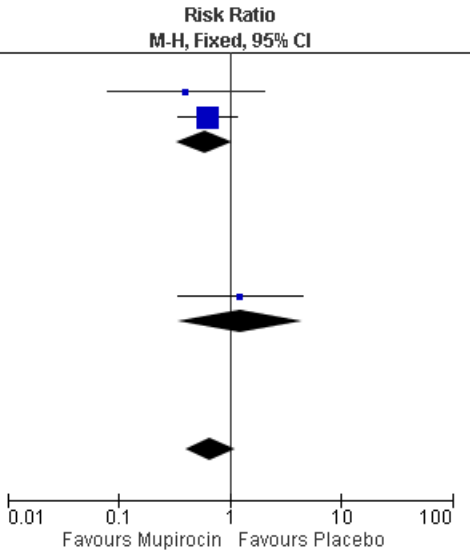


Follow up: Within 8 weeks

S. aureus SSI

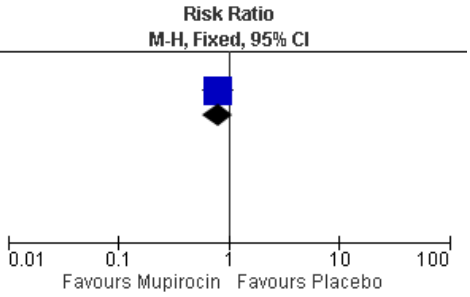
Study or Subgroup	Mupirocin Events	Mupirocin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.15.1 At 30 days						
Kalmeijer 2002 b	2	95	5	95	14.4%	0.40 [0.08, 2.01]
Perl 2002 b	16	432	26	439	74.0%	0.63 [0.34, 1.15]
Subtotal (95% CI)		**527**		**534**	**88.4%**	**0.59 [0.33, 1.04]**
Total events	18		31			
1.15.2 Within 8 weeks of surgery						
Konvalinka 2006	5	130	4	127	11.6%	1.22 [0.34, 4.44]
Subtotal (95% CI)		**130**		**127**	**11.6%**	**1.22 [0.34, 4.44]**
Total events	5		4			
Total (95% CI)		**657**		**661**	**100.0%**	**0.66 [0.40, 1.11]**
Total events	23		35			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.30 (P = 0.76)
Heterogeneity: Chi² = 1.27, df = 2 (P = 0.53); I² = 0%
Test for overall effect: Z = 1.57 (P = 0.12)
Test for subgroup differences: Chi² = 1.03, df = 1 (P = 0.31), I² = 2.6%



Overall nosocomial infections

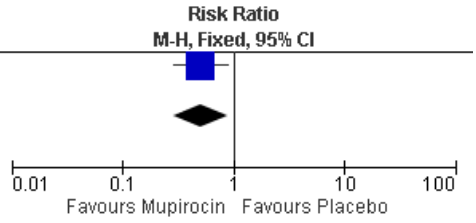
Study or Subgroup	Mupirocin Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.13.1 At 30 days						
Perl 2002 b	57	444	72	447	100.0%	0.80 [0.58, 1.10]
Subtotal (95% CI)		**444**		**447**	**100.0%**	**0.80 [0.58, 1.10]**
Total events	57		72			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.38 (P = 0.17)						



Test for subgroup differences: Not applicable

S. aureus nosocomial infections

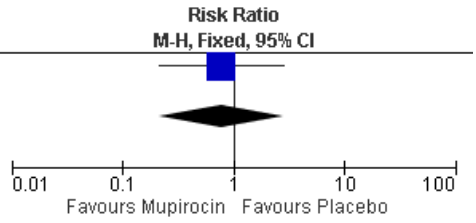
Study or Subgroup	Mupirocin Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Perl 2002 b	17	430	34	439	100.0%	0.51 [0.29, 0.90]
Total (95% CI)		**430**		**439**	**100.0%**	**0.51 [0.29, 0.90]**
Total events	17		34			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.33 (P = 0.02)						



Follow up: 30 days

Mortality

Study or Subgroup	Mupirocin Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Konvalinka 2006	4	130	5	127	100.0%	0.78 [0.21, 2.84]
Total (95% CI)		**130**		**127**	**100.0%**	**0.78 [0.21, 2.84]**
Total events	4		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.37 (P = 0.71)						

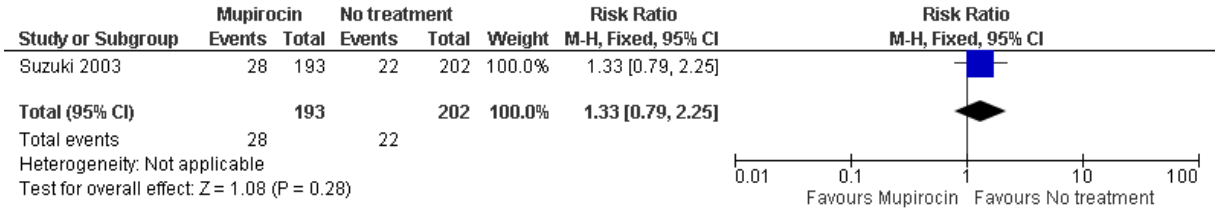


Follow up: Within 8 weeks

F.2 Mupirocin versus no nasal decontamination

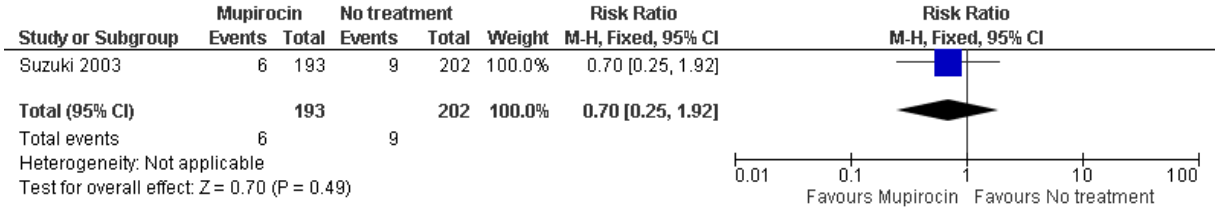
Outcomes in whole population

Overall SSI



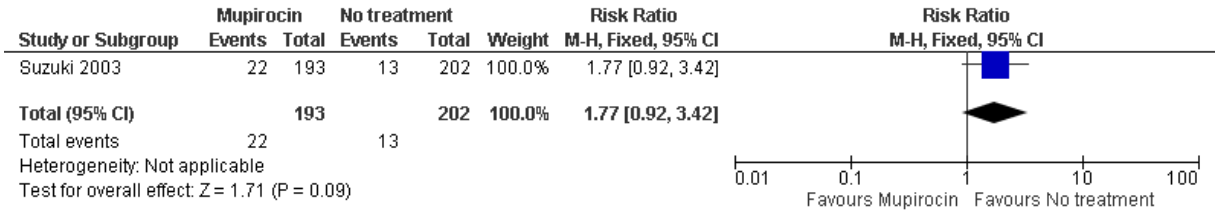
Follow up: 30 days

Overall superficial SSI



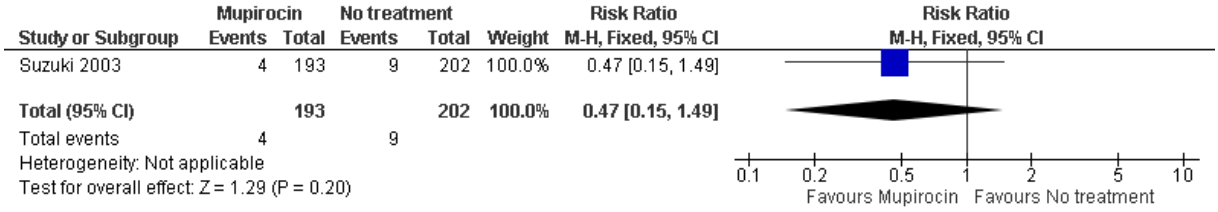
Follow up: 30 days

Overall deep SSI



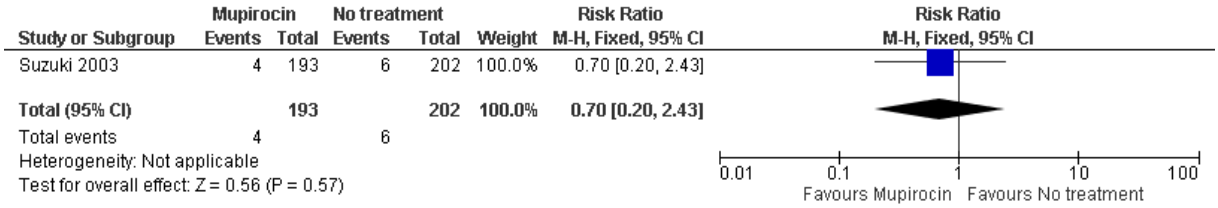
Follow up: 30 days

S. aureus SSI



Follow up: 30 days

Overall nosocomial infections

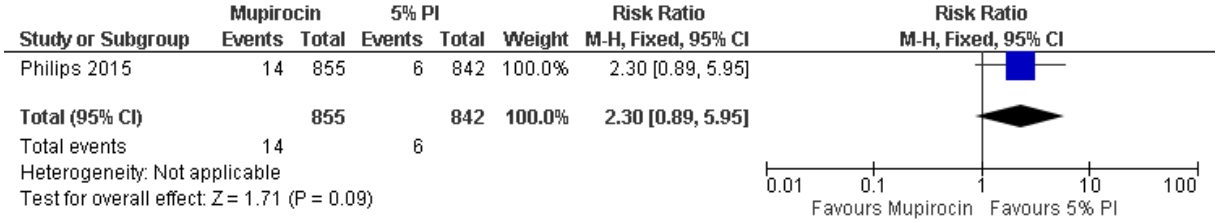


Follow up: 30 days

F.3 Mupirocin versus 5% Povidone Iodine

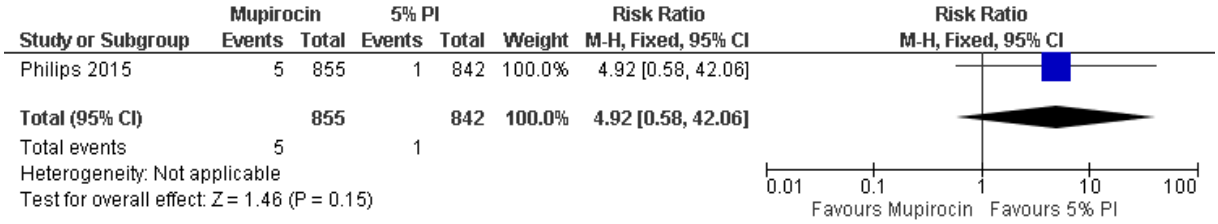
Outcomes in whole population

Overall deep SSI



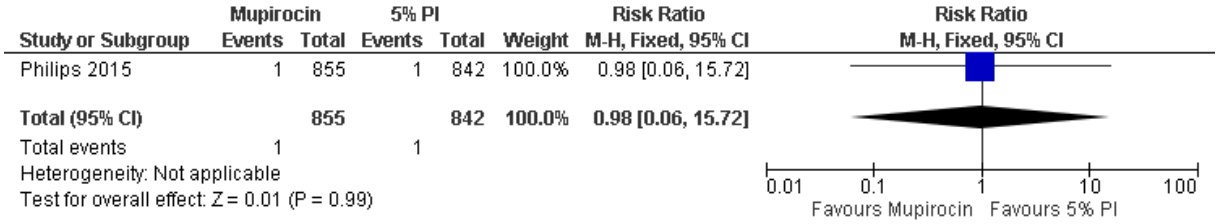
Follow up: within 3 months

S. aureus deep SSI



Follow up: within 3 months

MRSA deep SSI

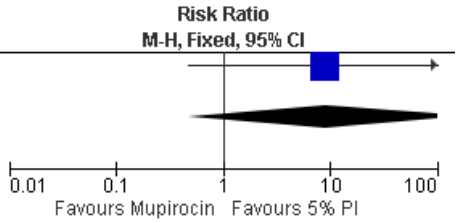


Follow up: within 3 months

MSSA deep SSI

Study or Subgroup	Mupirocin Events	Mupirocin Total	5% PI Events	5% PI Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Philips 2015	4	855	0	842	100.0%	8.86 [0.48, 164.37]
Total (95% CI)		**855**		**842**	**100.0%**	**8.86 [0.48, 164.37]**
Total events	4		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.46 (P = 0.14)



Follow up: within 3 month

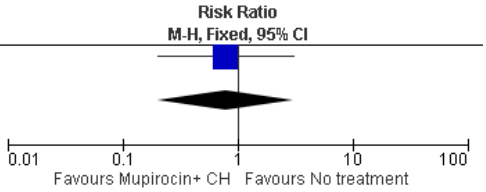
F.4 Mupirocin + CH wash versus no treatment

S. aureus carriers

Overall deep SSI (PJI)

Study or Subgroup	Mupirocin + CH wash Events	Mupirocin + CH wash Total	No treatment Events	No treatment Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Sousa 2016	3	89	6	139	100.0%	0.78 [0.20, 3.04]
Total (95% CI)		**89**		**139**	**100.0%**	**0.78 [0.20, 3.04]**
Total events	3		6			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.36 (P = 0.72)

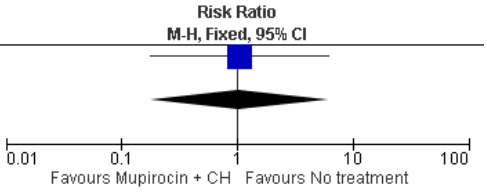


Follow up: at 1 year

S. aureus deep SSI (PJI)

Study or Subgroup	Mupirocin + CH wash Events	Mupirocin + CH wash Total	No treatment Events	No treatment Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Sousa 2016	2	89	3	139	100.0%	1.04 [0.18, 6.11]
Total (95% CI)		**89**		**139**	**100.0%**	**1.04 [0.18, 6.11]**
Total events	2		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.04 (P = 0.96)

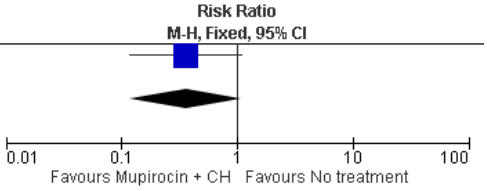


Follow up: at 1 year

S. aureus SSI

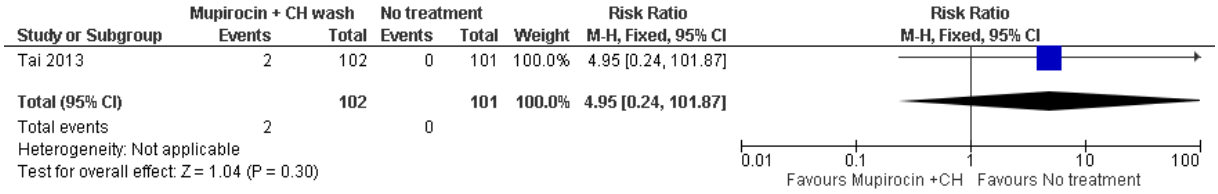
Study or Subgroup	Mupirocin + CH wash Events	Mupirocin + CH wash Total	No treatment Events	No treatment Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Tai 2013	4	102	11	101	100.0%	0.36 [0.12, 1.09]
Total (95% CI)		**102**		**101**	**100.0%**	**0.36 [0.12, 1.09]**
Total events	4		11			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.80 (P = 0.07)



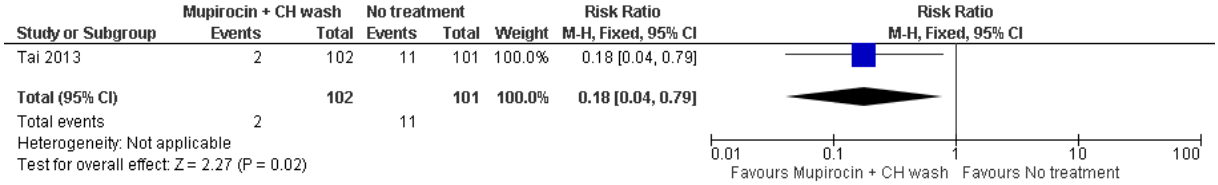
Follow up: postoperative period

MRSA SSI



Follow up: postoperative period

MSSA SSI

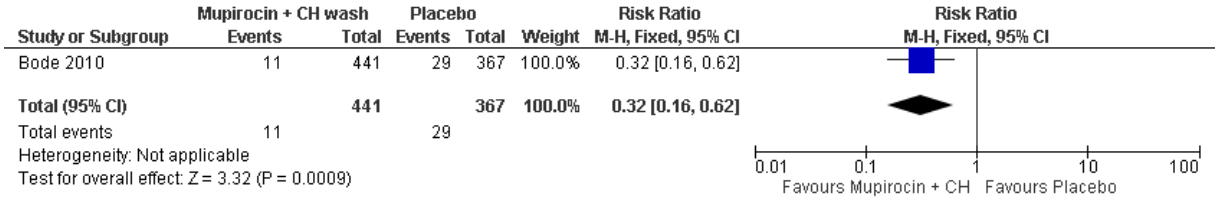


Follow up: postoperative period

F.5 Mupirocin + CH wash versus placebo

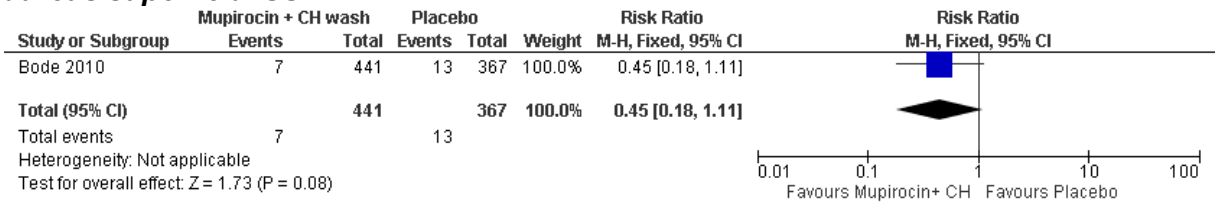
S. aureus carriers

S. aureus SSI



Follow up: until 6 weeks after discharge

S. aureus superficial SSI

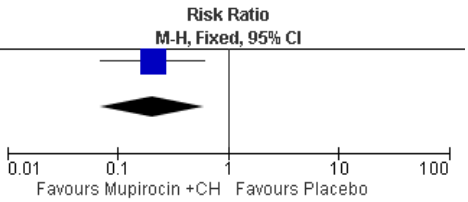


Follow up: until 6 weeks after discharge

S. aureus deep SSI

Study or Subgroup	Mupirocin + CH wash Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bode 2010	4	441	16	367	100.0%	0.21 [0.07, 0.62]
Total (95% CI)		**441**		**367**	**100.0%**	**0.21 [0.07, 0.62]**
Total events	4		16			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.83 (P = 0.005)

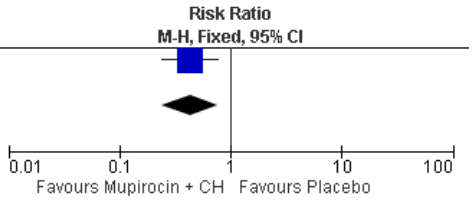


Follow up: until 6 weeks after discharge

S. aureus nosocomial infections

Study or Subgroup	Mupirocin + CH wash Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bode 2010	16	441	31	367	100.0%	0.43 [0.24, 0.77]
Total (95% CI)		**441**		**367**	**100.0%**	**0.43 [0.24, 0.77]**
Total events	16		31			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.82 (P = 0.005)

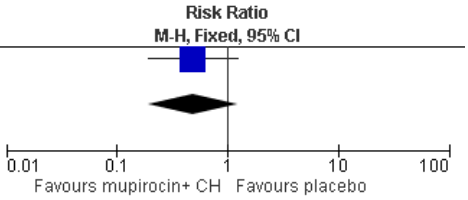


Follow up: until 6 weeks after discharge

Mortality

Study or Subgroup	Mupirocin + CH wash Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bode 2010	7	441	12	367	100.0%	0.49 [0.19, 1.22]
Total (95% CI)		**441**		**367**	**100.0%**	**0.49 [0.19, 1.22]**
Total events	7		12			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.54 (P = 0.12)

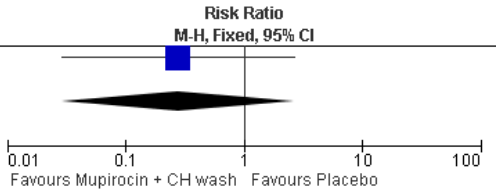


Follow up: until 6 weeks after discharge

Mortality in carriers with S. aureus infections

Study or Subgroup	Mupirocin + CH wash Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bode 2010	1	441	3	367	100.0%	0.28 [0.03, 2.66]
Total (95% CI)		**441**		**367**	**100.0%**	**0.28 [0.03, 2.66]**
Total events	1		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.11 (P = 0.27)



Follow up: until 6 weeks after discharge

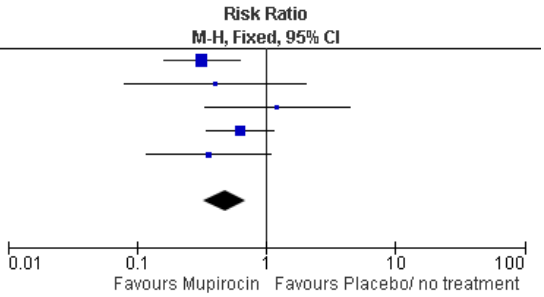
F.6 Mupirocin (with or without CH was) versus all non-active interventions

S. aureus carriers

S. aureus SSI

Study or Subgroup	Mupirocin Events	Mupirocin Total	Placebo/ no treatment Events	Placebo/ no treatment Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bode 2010	11	441	29	367	40.8%	0.32 [0.16, 0.62]
Kalmeijer 2002 b	2	95	5	95	6.4%	0.40 [0.08, 2.01]
Konvalinka 2006	5	130	4	127	5.2%	1.22 [0.34, 4.44]
Perl 2002 b	16	432	26	439	33.3%	0.63 [0.34, 1.15]
Tai 2013	4	102	11	101	14.3%	0.36 [0.12, 1.09]
Total (95% CI)		**1200**		**1129**	**100.0%**	**0.48 [0.33, 0.70]**
Total events	38		75			

Heterogeneity: Chi² = 4.50, df = 4 (P = 0.34); I² = 11%
Test for overall effect: Z = 3.81 (P = 0.0001)



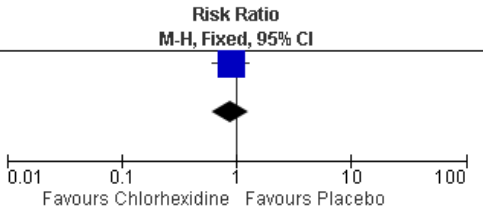
F.7 Chlorhexidine + CH wash versus placebo

Whole population

Overall SSI

Study or Subgroup	Chlorhexidine Events	Chlorhexidine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Segers 2006	48	485	52	469	100.0%	0.89 [0.62, 1.29]
Total (95% CI)		**485**		**469**	**100.0%**	**0.89 [0.62, 1.29]**
Total events	48		52			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.60 (P = 0.55)

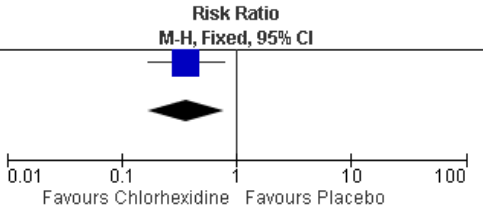


Follow up: at 30 days

Overall deep SSI

Study or Subgroup	Chlorhexidine Events	Chlorhexidine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Segers 2006	9	485	24	469	100.0%	0.36 [0.17, 0.77]
Total (95% CI)		**485**		**469**	**100.0%**	**0.36 [0.17, 0.77]**
Total events	9		24			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.63 (P = 0.008)

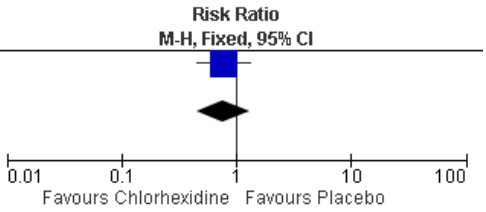


Follow up: at 30 days

S. aureus SSI

Study or Subgroup	Chlorhexidine Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Segers 2006	23	485	29	469	100.0%	0.77 [0.45, 1.31]
Total (95% CI)		**485**		**469**	**100.0%**	**0.77 [0.45, 1.31]**
Total events	23		29			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.98 (P = 0.33)

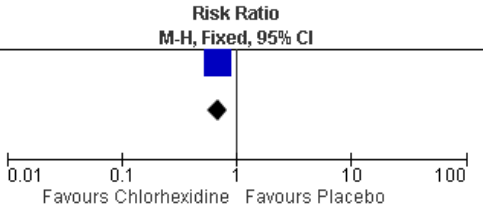


Follow up: at 30 days

Overall nosocomial infection

Study or Subgroup	Chlorhexidine Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Segers 2006	116	485	164	469	100.0%	0.68 [0.56, 0.84]
Total (95% CI)		**485**		**469**	**100.0%**	**0.68 [0.56, 0.84]**
Total events	116		164			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.70 (P = 0.0002)

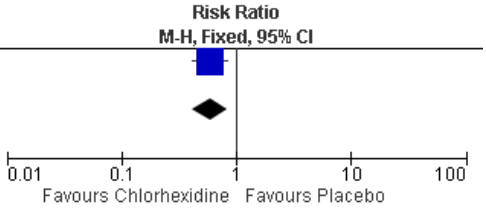


Follow up: at 30 days

Nosocomial infection: Lower respiratory tract infection (LRTI)

Study or Subgroup	Chlorhexidine Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Segers 2006	45	485	74	469	100.0%	0.59 [0.42, 0.83]
Total (95% CI)		**485**		**469**	**100.0%**	**0.59 [0.42, 0.83]**
Total events	45		74			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.99 (P = 0.003)

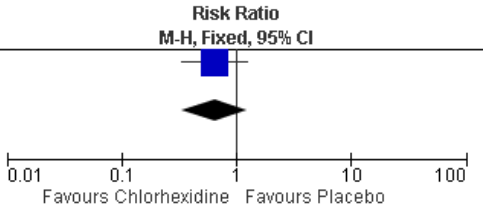


Follow up: at 30 days

Nosocomial infection: urinary tract infection (UTI)

Study or Subgroup	Chlorhexidine Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Segers 2006	14	485	21	469	100.0%	0.64 [0.33, 1.25]
Total (95% CI)		**485**		**469**	**100.0%**	**0.64 [0.33, 1.25]**
Total events	14		21			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.30 (P = 0.20)

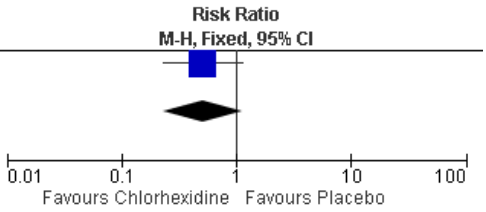


Follow up: at 30 days

Nosocomial infection: bacteraemia

Study or Subgroup	Chlorhexidine Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Segers 2006	9	485	17	469	100.0%	0.51 [0.23, 1.14]
Total (95% CI)		**485**		**469**	**100.0%**	**0.51 [0.23, 1.14]**
Total events	9		17			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.64 (P = 0.10)

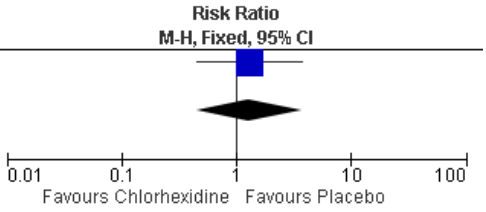


Follow up: at 30 days

Mortality

Study or Subgroup	Chlorhexidine Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Segers 2006	8	485	6	469	100.0%	1.29 [0.45, 3.69]
Total (95% CI)		**485**		**469**	**100.0%**	**1.29 [0.45, 3.69]**
Total events	8		6			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.47 (P = 0.64)

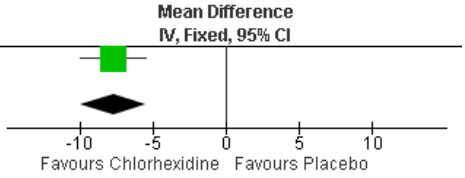


Follow up: at 30 day

Mean hospital stay

Study or Subgroup	Chlorhexidine Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Segers 2006	14.4	13.8	485	22.1	21	469	100.0%	-7.70 [-9.96, -5.44]
Total (95% CI)			**485**			**469**	**100.0%**	**-7.70 [-9.96, -5.44]**

Heterogeneity: Not applicable
Test for overall effect: Z = 6.67 (P < 0.00001)

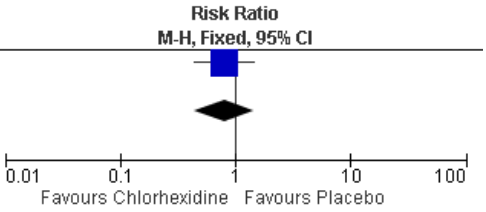


Follow up: at 30 days

Hospital readmission

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Segers 2006	19	485	23	469	100.0%	0.80 [0.44, 1.45]
Total (95% CI)		**485**		**469**	**100.0%**	**0.80 [0.44, 1.45]**
Total events	19		23			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.74 (P = 0.46)



Follow up: at 30 days

Appendix G – GRADE tables

G.1 Mupirocin versus placebo

Outcomes in whole population

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Overall SSI – RR <1 favours mupirocin										
2 Perl 2002 Kalmeijer 2002	RCT	4478	RR 0.92 (95% CI 0.75, 1.12)	8 per 100 people	7 per 100 people (6, 9)	Serious[1]	Not serious	Not serious	Serious[2]	Low
Overall superficial SSI - RR <1 favours mupirocin										
1 Kalmeijer 2002	RCT	614	RR 0.88 (95% CI 0.41, 1.89)	4 per 100 people	4 per 100 people (6,8)	Not serious	Not serious	NA[3]	Very Serious[4]	Low
Overall deep SSI - RR <1 favours mupirocin										
1 Kalmeijer 2002	RCT	614	RR 0.32 (95% CI 0.01, 7.74)	3 per 100 people	3 per 100 people (0, 26)**	Serious[5]	Not serious	NA[3]	Very Serious[4]	Very low
S. aureus SSI - RR <1 favours mupirocin										
2 Perl 2002 Kalmeijer 2002	RCT	4400	RR 0.88 (95% CI 0.60, 1.30)	2 per 100 people	2 per 100 people (2,19)	Serious[1]	Not serious	Not serious	Very Serious[4]	Very low
Overall nosocomial infections (bloodstream, respiratory tract, catheter and surgical site) - RR <1 favours mupirocin										
1 Perl 2002	RCT	3864	RR 0.99 (95% CI 0.83, 1.18)	11 per 100 people	11 per 100 people (9, 13)	Serious[5]	Not serious	NA[3]	Not serious	Moderate
S. aureus nosocomial infections at 30 days (bloodstream, respiratory tract, catheter and surgical site) - RR <1 favours mupirocin										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1 Perl 2002	RCT	3770	RR 0.82 (95% CI 0.56, 1.21)	3 per 100 people	2 per 100 people (2,4)	Serious[5]	Not serious	NA[3]	Serious[2]	Low
Hospital Readmission – RR< 1 favours mupirocin										
1 Kalmeijer 2002	RCT	614	RR 0.63 (95% CI 0.11, 3.76)	1 per 100 people	1 per 100 people (0, 4)	Not serious	Not serious	NA[3]	Very Serious[4]	Low
Mean hospital stay– effect size below 0 favours mupirocin										
1 Kalmeijer 2002	RCT	614	MD -0.30 (95% CI -1.38, 0.78)	-	-	Not serious	Not serious	NA[3]	Serious[6]	Moderate

1. Greater than 33.3% of the weight in the meta-analysis came from a study at moderate risk of bias. Downgrade 1 level for serious risk of bias.
2. 95% confidence interval crosses one end of a defined MID interval (0.8, 1.25). Downgrade 1 level.
3. Inconsistency not applicable
4. 95% confidence interval crosses both ends of a defined MID interval (0.8, 1.25). Downgrade 2 levels.
5. Study demonstrated unclear random sequence generation, allocation concealment and blinding of outcome assessment. Downgrade 1 level for serious risk of bias.
6. Non-significant result. Downgrade 1 level.

* Derived by taking the overall number of event/ total number of participants and multiplying by 100

** Derived by taking the overall number of event/ total number of participants and multiplying by 1000

Outcomes in S. aureus carriers

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Overall SSI - RR <1 favours mupirocin										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
2 Perl 2002 Konvalinka 2006	RCT	1148	RR 1.08 (95% CI 0.59, 1.97)	11 per 100 people	12 per 100 people (6, 22)	Serious[1]	Not serious	Serious[2]	Very Serious[3]	Very Low
Overall SSI at 30 days - RR <1 favours mupirocin										
1 Perl 2002	RCT	891	RR 0.85 (95% CI 0.58, 1.24)	12 per 100 people	10 per 100 people (7, 14)	Serious[4]	Not serious	NA[5]	Serious[6]	Low
Overall SSI within 8 weeks of surgery - RR <1 favours mupirocin										
1 Konvalinka 2006	RCT	257	RR 1.60 (95% CI 0.79, 3.25)	9 per 100 people	14 per 100 people (7, 28)	Not serious	Not serious	NA[5]	Very Serious[3]	Low
Overall superficial SSI - RR <1 favours mupirocin										
1 Konvalinka 2006	RCT	257	RR 1.85 (95% CI 0.85, 3.99)	7 per 100 people	13 per 100 people (6, 28)	Not serious	Not serious	NA[5]	Serious[6]	Moderate
Overall deep SSI - RR <1 favours mupirocin										
1 Konvalinka 2006	RCT	257	RR 0.98 (95% CI 0.06, 15.45)	1 per 100 people	1 per 100 people (0, 12)	Not serious	Not serious	NA[5]	Very Serious[3]	Low
Overall deep space occupying SSI - RR <1 favours mupirocin										
1 Konvalinka 2006	RCT	257	RR 0.33 (95% CI 0.01, 7.92)	1 per 100 people	0 per 100 people (0, 6)	Not serious	Not serious	NA[5]	Very Serious[3]	Low
S. aureus SSI - RR <1 favours mupirocin										
3 Perl 2002 Kalmeijer 2002	RCT	1318	RR 0.66 (95% CI 0.40, 1.11)	5 per 100 people	3 per 100 people (2, 6)	Serious[1]	Not serious	Not serious	Serious[6]	Low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Konvalinka 2006										
S. aureus SSI at 30 days- RR <1 favours mupirocin										
2 Perl 2002 Kalmeijer 2002	RCT	1,061	RR 0.59 (95% CI: 0.33, 1.04)	6 per 100 people	3 per 100 people (2,6)	Serious[1]	Not serious	Not serious	Serious[6]	Very low
S. aureus SSI within 8 weeks of surgery- RR <1 favours mupirocin										
1 Konvalinka 2006	RCT	257	RR 1.22 (95% CI: 0.34, 4.44)	3 per 100 people	4 per 100 people (1,14)	Not serious	Not serious	NA[5]	Very Serious[3]	Low
Overall nosocomial infections (bloodstream, respiratory tract, catheter and surgical site) - RR <1 favours mupirocin										
1 Perl 2002	RCT	891	RR 0.80 (95% CI 0.58, 1.10)	16 per 100 people	13 per 100 people (9, 18)	Serious[4]	Not serious	NA[5]	Serious[6]	Low
S. aureus nosocomial infections (bloodstream, respiratory tract, catheter and surgical site) - RR <1 favours mupirocin										
1 Perl 2002	RCT	869	RR 0.51 (95% CI 0.29, 0.90)	8 per 100 people	4 per 100 people (2, 7)	Serious[4]	Not serious	NA[5]	Serious[6]	Low
Mortality - RR< 1 favours mupirocin										
1 Konvalinka 2006	RCT	257	RR 0.78 (95% CI 0.21, 2.84)	4 per 100 people	3 per 100 people (1, 11)	Not serious	Not serious	NA[5]	Very Serious[3]	Low

1. Greater than 33.3% of the weight in the meta-analysis came from a study at moderate risk of bias. Downgrade 1 level for serious risk of bias.
2. The I^2 was between 33.3% and 66.7%, the outcome was downgraded one level.
3. 95% confidence interval crosses both ends of a defined MID interval (0.8, 1.25). Downgrade 2 levels.
4. Study demonstrated unclear random sequence generation, allocation concealment and blinding of outcome assessment. Downgrade 1 level for serious risk of bias.

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
5. Inconsistency not applicable 6. 95% confidence interval crosses one end of a defined MID interval (0.8, 1.25). Downgrade 1 level. * Derived by taking the overall number of event/ total number of participants and multiplying by 100										

G.2 Mupirocin versus no nasal decontamination

Outcomes in whole population

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Overall SSI – RR <1 favours mupirocin										
1 Suzuki 2003	RCT	395	RR 1.33 (95% CI: 0.79, 2.25)	11 per 100 people	14 per 100 people (9, 25)	Not serious	Not serious	NA[1]	Very serious [2]	Low
Overall superficial SSI– RR <1 favours mupirocin										
1 Suzuki 2003	RCT	395	RR 0.70 (95% CI: 0.25, 1.92)	4 per 100 people	3 per 100 people (1, 3)	Not serious	Not serious	NA[1]	Very serious [2]	Low
Overall deep SSI– RR <1 favours mupirocin										
1 Suzuki 2003	RCT	395	RR 1.77 (95% CI: 0.92, 3.42)	6 per 100 people	11 per 100 people (6, 22)	Not serious	Not serious	NA[1]	Serious [3]	Moderate
S. aureus SSI - RR <1 favours mupirocin										
1 Suzuki 2003	RCT	395	RR 0.47 (95% CI: 0.15, 1.49)	4 per 100 people	2 per 100 people (1, 7)	Not serious	Not serious	NA[1]	Very serious [2]	Low
Overall nosocomial infections - RR <1 favours mupirocin										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1 Suzuki 2003	RCT	395	RR 0.70 (95% CI: 0.20, 2.43)	3 per 100 people	2 per 100 people (0, 6)	Not serious	Not serious	NA[1]	Very serious [2]	Low

1. Inconsistency not applicable
2. 95% confidence interval crosses both ends of a defined MID interval (0.8, 1.25). Downgrade 2 levels.
3. 95% confidence interval crosses one end of a defined MID interval (0.8, 1.25). Downgrade 1 level.

* Derived by taking the overall number of event/ total number of participants and multiplying by 100

G.3 Mupirocin versus 5% povidone iodine

Outcomes in whole population

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Overall deep SSI– RR <1 favours mupirocin										
1 Philips 2014	RCT	1697	RR 2.30 (95% CI: 0.89, 5.95)	1 per 100 people	2 per 100 people (1,4)	Serious [1]	Not serious	NA[2]	Serious[3]	Low
S. aureus deep SSI – RR <1 favours mupirocin										
1 Philips 2014	RCT	1697	RR 4.92 (95% CI: 0.58, 42.06)	0 per 100 people	1 per 100 people (0, 5)	Serious [1]	Not serious	NA[2]	Very Serious[4]	Very Low
MRSA deep SSI – RR <1 favours mupirocin										
1 Philips 2014	RCT	1697	RR 0.98 (95% CI: 0.06, 15.72)	1 in 100 people	1 in 100 people (0, 19)**	Serious [1]	Not serious	NA[2]	Very Serious[4]	Very Low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
MSSA deep SSI - RR <1 favours mupirocin										
1 Philips 2014	RCT	1697	RR 8.86 (95% CI: 0.48, 164.37)	Not calculable[5]	Not calculable[5]	Serious [1]	Not serious	NA[2]	Very Serious[4]	Very Low

1. Study demonstrated unclear random sequence generation, allocation concealment and blinding of outcome assessment. Downgrade 1 level for serious risk of bias.
2. Inconsistency not applicable
3. 95% confidence interval crosses one end of a defined MID interval (0.8, 1.25). Downgrade 1 level.
4. 95% confidence interval crosses both ends of a defined MID interval (0.8, 1.25). Downgrade 2 levels.
5. The absolute risk was not calculable as there were no events in the control arm.

* Derived by taking the overall number of event/ total number of participants and multiplying by 100

** Derived by taking the overall number of event/ total number of participants and multiplying by 1000

G.4 Mupirocin and chlorhexidine body wash vs No nasal decontamination

Outcomes in S. aureus carriers

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Overall deep SSI (PJI) – RR <1 favours mupirocin										
1 Sousa 2016	RCT	228	RR 0.78 (95% CI: 0.20, 3.04)	4 per 100 people	3 per 100 people (1, 15)	Very Serious[1]	Not serious	NA[2]	Very serious[3]	Very low
S. aureus deep SSI (PJI) – RR <1 favours mupirocin										
1	RCT	228	RR 1.04 (95% CI: 0.18, 6.11)	3 per 100 people	3 per 100 people (0, 17)	Very Serious[1]	Not serious	NA[2]	Very serious[3]	Very low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Sousa 2016										
S. aureus SSI during postoperative period in S. aureus carriers – RR <1 favours mupirocin										
1 Tai 2013	RCT	203	RR 0.36 (95% CI: 0.12, 1.09)	11 per 100 people	4 per 100 people (1, 12)	Serious[4]	Serious[5]	NA[2]	Serious[6]	Very low
MRSA SSI - RR <1 favours mupirocin										
1 Tai 2013	RCT	203	RR 4.95 (95% CI: 0.24, 101.87)	Not calculable[7]	Not calculable[7]	Serious[4]	Serious[5]	NA[2]	Very serious[3]	Very Low
MSSA SSI - RR <1 favours mupirocin										
1 Tai 2013	RCT	203	RR 0.18 (95% CI: 0.04, 0.79)	11 per 100 people	2 per 100 (0, 9)	Serious[4]	Serious[5]	NA[2]	Not serious	Low

1. Downgrade 2 levels for very serious risk of bias due unclear allocation concealment and blinding of outcome assessment. Furthermore, intention to treat analysis not conducted.
2. Inconsistency not applicable
3. 95% confidence interval crosses both ends of a defined MID interval (0.8, 1.25). Downgrade 2 levels.
4. Downgrade 1 level for serious risk of bias due to unclear random sequence generation, allocation concealment and blinding of outcome assessment.
5. Follow-up of SSI and criteria used to define SSI was not specified. Downgrade 1 level.
6. 95% confidence interval crosses one end of a defined MID interval (0.8, 1.25). Downgrade 1 level.
7. The absolute risk was not calculable as there were no events in the control arm.

* Derived by taking the overall number of event/ total number of participants and multiplying by 100

G.5 Mupirocin and chlorhexidine body wash vs placebo

Outcomes in S. aureus carriers

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
S. aureus SSI– RR <1 favours mupirocin										
1 Bode 2010	RCT	808 surgical patients	RR 0.32 (95% CI: 0.16, 0.62)	8 per 100 people	3 per 100 people (1, 5)	Not serious	Not serious	NA[1]	Not serious	High
S. aureus superficial SSI– RR <1 favours mupirocin										
1 Bode 2010	RCT	808 surgical patients	RR 0.45 (95% CI: 0.18, 1.11)	4 per 100 people	2 per 100 people (1, 4)	Not serious	Not serious	NA[1]	Serious[2]	Moderate
S. aureus deep SSI – RR <1 favours mupirocin										
1 Bode 2010	RCT	808 surgical patients	RR 0.21 (95% CI: 0.07, 0.62)	4 per 100 people	1 per 100 people (0, 3)	Not serious	Not serious	NA[1]	Not serious	High
S. aureus nosocomial infections - RR <1 favours mupirocin										
1 Bode 2010	RCT	808 surgical patients	RR 0.43 (95% CI: 0.24, 0.77)	8 per 100 people	4 per 100 people (2, 7)	Not serious	Not serious	NA[1]	Not serious	High
Mortality - RR <1 favours mupirocin										
1 Bode 2010	RCT	808 surgical patients	RR 0.49 (955 CI: 0.19, 1.22)	3 per 100 people	2 per 100 people (1, 6)	Not serious	Not serious	NA[1]	Serious[2]	Moderate
Mortality in S. aureus carriers with infection - RR <1 favours mupirocin										
1 Bode 2010	RCT	808 surgical patients	RR 0.28 (95% CI: 0.03, 2.66)	1 per 100 people	0 per 100 people (0, 2)	Not serious	Not serious	NA[1]	Very serious[3]	Low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1. Inconsistency not applicable 2. 95% confidence interval crosses one end of a defined MID interval (0.8, 1.25). Downgrade 1 level. 3. 95% confidence interval crosses both ends of a defined MID interval (0.8, 1.25). Downgrade 2 levels. * Derived by taking the overall number of event/ total number of participants and multiplying by 100										

G.6 Mupirocin (with or without chlorhexidine body wash) vs all non-active interventions

Following meta-analysis was conducted to support the economic evaluation.

Outcomes in S. aureus carriers

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
S. aureus SSI– RR <1 favours mupirocin										
5 Bode 2010 Kalmeijer 2002 Konvalinka 2006 Perl 2002 Tai 2013	RCT	2329	RR 0.48 (95% CI: 0.33, 0.70)	7 per 100 people	3 per 100 people (2,5)	Serious[1]	Not serious	Not serious	Not serious	Moderate
1. Greater than 33.3% of the weight in the meta-analysis came from a study at moderate risk of bias. Downgrade 1 level for serious risk of bias. * Derived by taking the overall number of event/ total number of participants and multiplying by 100										

G.7 Chlorhexidine vs. placebo

In whole population

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Overall SSI– RR <1 favours chlorhexidine										
1 Segers 2006	RCT	954	RR 0.89 (95% CI 0.62, 1.29)	11 per 100 people	10 per 100 people (7, 14)	Not serious	Serious[1]	NA[2]	Very Serious [3]	Very low
Overall deep SSI– RR <1 favours chlorhexidine										
1 Segers 2006	RCT	954	RR 0.36 (95% CI 0.17, 0.77)	5 per 100 people	2 per 100 people (1, 4)	Not serious	Serious[1]	NA[2]	Not serious	Moderate
S. aureus SSI– RR <1 favours chlorhexidine										
1 Segers 2006	RCT	954	RR 0.77 (95% CI 0.45, 1.31)	6 per 100 people	5 per 100 people (3, 8)	Not serious	Serious[1]	NA[2]	Very Serious [3]	Very low
Overall nosocomial infections (lower respiratory tract infection, urinary tract infection, bacteraemia and SSI) - RR <1 favours chlorhexidine										
1 Segers 2006	RCT	954	RR 0.68 (95% CI 0.56, 0.84)	35 per 100 people	24 per 100 people (20, 29)	Not serious	Serious[1]	NA[2]	Serious[4]	Low
Nosocomial infection : LRTI - RR <1 favours chlorhexidine										
1 Segers 2006	RCT	954	RR 0.59 (95% CI 0.42, 0.83)	16 per 100 people	9 per 100 people (7, 13)	Not serious	Serious[1]	NA[2]	Serious[4]	Low
Nosocomial infection : UTI - RR <1 favours chlorhexidine										
1 Segers 2006	RCT	954	RR 0.64 (95% CI 0.33, 1.25)	4 per 100 people	3 per 100 people (1, 6)	Not serious	Serious[1]	NA[2]	Very Serious [3]	Very Low
Nosocomial infection : bacteraemia - RR <1 favours chlorhexidine										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1 Segers 2006	RCT	954	RR 0.51 (95% CI 0.23, 1.14)	4 per 100 people	2 per 100 people (1, 4)	Not serious	Serious[1]	NA[2]	Serious[4]	Low
Mortality - RR <1 favours chlorhexidine										
1 Segers 2006	RCT	954	RR 1.29 (95% CI 0.45, 3.76)	1 per 100 people	2 per 100 people 91, 5)	Not serious	Serious[1]	NA[2]	Very Serious [3]	Very Low
Mean hospital Stay– effect size below 0 favours chlorhexidine										
1 Segers 2006	RCT	954	MD -7.70 (95% CI -9.96, -5.44)	-	-	Not serious	Serious[1]	NA[2]	Not serious	Moderate
Hospital Readmission – RR< 1 favours chlorhexidine										
1 Segers 2006	RCT	954	RR 0.80 (95% CI 0.44, 1.45)	5 per 100 people	4 per 100 people (2, 7)	Not serious	Serious[1]	NA[2]	Very Serious [3]	Very Low

1. Downgrade 1 level for serious indirectness. In the study chlorhexidine was used as a nasal gel and mouthwash.
2. Inconsistency not applicable.
3. 95% confidence interval crosses both ends of a defined MID interval (0.8, 1.25). Downgrade 2 levels.
4. 95% confidence interval crosses one end of a defined MID interval (0.8, 1.25). Downgrade 1 level.

* Derived by taking the overall number of event/ total number of participants and multiplying by 100

Appendix H – Economic evidence tables

Study, Population, Country and Quality	Data Sources	Other Comments	Incremental (no treatment as reference) [1]			Conclusions	Uncertainty
			Cost [2]	Effect (QALYs)	ICER		
Courville et al., (2012) Economic model comparing nasal mupirocin, with & without screening, and no intervention in hip and knee arthroplasty patients. US. **Partially applicable** [a, b] **Potentially serious limitations** [c, d]	Effects: Systematic literature review. Mupirocin SSI RR in carriers: 0.61 (26% prevalence). Costs: Direct health care costs from US orthopaedic literature and previous economic evaluation of mupirocin. Utilities: Baseline utilities from US study, derived using Quality of Well-being Scale. Incidence of SSI assumed to reduce utility by 20%.	1-year decision tree model. Incidence of SSI assumed to require full hip or knee revision procedure. Study also included a 'screen and treat' strategy.	Hip **Screen & treat** -$213 (-£151) **Treat all** -$35 (-£25) Knee **Screen & treat** -$233 (-£166) **Treat all** -$56 (-£40)	**Screen & treat** +0.0002 **Treat all** +0.0003 **Screen & treat** +0.0002 **Treat all** +0.0002	**Treat all dominates** **Treat all dominates**	'Treating all patients who undergo total joint arthroplasty with a 5-day course of preoperative mupirocin is cost-effective when implemented to prevent deep SSI.'	One-way sensitivity analysis showed treating all patients typically continued to dominate the 'no treatment' strategy. This was not the case if: • The cost of SSI revision surgery is much lower (close to that of the primary arthroplasty procedure) • Mupirocin is much less effective at preventing SSI (RR = 0.99).
Key: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; RR, relative risk.							
Note: (1) Fully incremental analysis. (2) Costs in 2005 US dollars converted to British pounds using HMRC exchange rate as at April 2018: £1 = $1.4065.							
Applicability: (a) US setting. (b) QALYs were not derived using EQ-5D utility values. **Quality:** (c) No probabilistic sensitivity analysis presented. (d) No direct quality of life value for SSI.							

Study, Population, Country and Quality	Data Sources	Other Comments	Incremental (no treatment as reference) [1]			Conclusions	Uncertainty
			Cost [2]	Effect	ICER		
Wassenberg et al., (2011) Economic evaluation comparing nasal mupirocin plus chlorhexidine soap, with and without PCR screening, and no intervention in joint implant and cardiac surgery patients. Netherlands. **Partially applicable** [a, b] **Potentially serious limitations** [c, d, e]	Effects: Baseline data and SSI mortality from 1 hospital. Mupirocin deep SSI RR in carriers from 1 RCT: 0.21 (18% prevalence). Costs: Direct hospital costs of SSI from 1 hospital (n=53). National pharmaceutical prices and nurse-time (5 minutes) costs used for mupirocin and its administration. Utilities: Not a cost–utility analysis, however results suggest that treatment is the dominant strategy.	Life-expectancy estimated based on 10 years of data collection (2001-2010), discounted by 3% per year. All costs incurred within 1 year (no discounting).	**Screen & treat** -€48 (-£42) **Treat all** -€131 (-£114)	**Screen & treat** +0.014 LYs (7 deep SSIs & 1 death avoided per 1,000) **Treat all** +0.010 LYs(4 deep SSIs & 0.9 deaths avoided per 1,000)	**Treat all dominates**	'Treating all patients without screening is the dominant strategy, resulting on most health gains and largest savings. The benefits … outweigh the future risks of reduced effectiveness due to widespread resistance to antiseptics and mupirocin.'	One-way sensitivity analysis showed the base-case results to be robust, for example treating all patients remained dominant if the effectiveness of mupirocin at preventing SSI was reduced (RR = 0.60).
Key: ICER, incremental cost-effectiveness ratio; LY, life year; RCT, randomised controlled trial; RR, relative risk.							
Note: (1) Fully incremental analysis. (2) Costs in 2009 euros converted to British pounds using HMRC exchange rate as at April 2018: £1 = €1.1465.							
Applicability: (a) Netherlands setting. (b) Discount rate of 3%. **Quality:** (c) No probabilistic sensitivity analysis presented. (d) Cost and life-expectancy data from 1 hospital (n=53 and n=37 respectively). (e) Potential conflict of interest.							

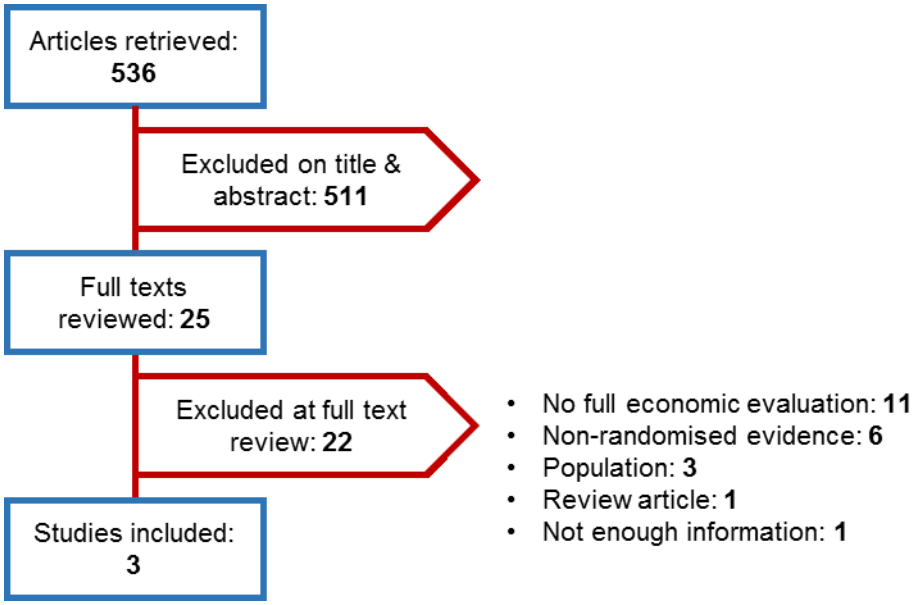
Study, Population, Country and Quality	Data Sources	Other Comments	Incremental (no treatment as reference) [1]			Conclusions	Uncertainty
			Cost [2]	Effect	ICER		
Young & Winston (2006) Economic evaluation comparing nasal mupirocin with no intervention in elective	Effects: Systematic literature review. Mupirocin SSI RR in carriers: 0.49 (23% prevalence).	90-day decision tree model (no discounting).	**Treat all** -$102 (-£72)	**Treat all** 86 deep SSIs & 2 deaths avoided per 10,000 patients.	**Screen & treat dominates**	'We found the use of mupirocin before surgery to be cost saving in a target population who underwent a	Treating people screened positive with mupirocin remained dominant and cost saving if only hospital costs were included.

Study, Population, Country and Quality	Data Sources	Other Comments	Incremental (no treatment as reference) [1]			Conclusions	Uncertainty
			Cost [2]	Effect	ICER		
surgery patients (cardiothoracic, neurologic, gynaecologic, general). US. **Partially applicable** [a, b] **Potentially serious limitations** [c, d]	Costs: Direct health care costs sourced from the systematic review, supplemented with charge costs where necessary. Productivity loss costs included. Utilities: Not a cost–utility analysis, however results suggest that treatment is the dominant strategy.	Screening assumed to have perfect diagnostic accuracy. Productivity losses included but unlikely to have a bearing on model conclusions.	**Screen & treat** -$14 (-£8)	**Screen & treat** Equal to above		broad range of surgical procedures. Prevention of relatively few infections provides substantial monetary savings.'	One-way sensitivity analysis showed base-case results to be robust to parameter uncertainty. The 'treat all' strategy became cost-bearing only if mupirocin was significantly less effective (SSI RR=0.92).
Key: ICER, incremental cost-effectiveness ratio; RR, relative risk.							
Note: (1) Fully incremental analysis. (2) Costs in 2003 US dollars converted to British pounds using HMRC exchange rate as at April 2018: £1 = $1.4065.							
Applicability: (a) US setting. (b) Productivity loss costs included (societal analysis). **Quality:** (c) No probabilistic sensitivity analysis presented. (d) Medicare costs (charges) used for some resource use items, rather than actual service provision costs.							

Study, Population, Country and Quality	Data Sources	Other Comments	Incremental (no treatment as reference) [1]			Conclusions	Uncertainty
			Cost	Effect (QALYs)	ICER		
NICE economic model developed for this review Economic evaluation comparing nasal mupirocin, either universal or are positive screening, with no intervention, in all surgical patients UK.	Effects: 5 RCTs identified through a systematic literature review. Mupirocin *S. aureus* SSI OR in carriers: 0.47 (25% prevalence). Costs: Direct SSI resource use sourced from an English hospital SSI surveillance study.	Lifetime decision tree model. Surviving patients experience age-related UK quality-adjusted life-expectancy, discounted by 3.5% per year. Baseline *S. aureus* SSI rates from English hospital SSI surveillance study, based on committee advice.	**Treat all** -£13 **Screen & treat** -£12	**Treat all** +0.0003 **Screen & treat** +0.0001	**Treat all dominates**	Universal nasal decontamination with mupirocin is highly likely to have an ICER of £20,000 or better, compared with both a screen-and-treat strategy and a strategy of no nasal decontamination.	The ICER for universal mupirocin was £20,000 or better in 99.6% of PSA model runs. In subgroup analysis, its ICER was better than £20,000 per QALY gained in all types of surgery; in 15 out of 17 its deterministic ICER remained dominant. In 14 out of 17 its probability of being optimal was 89% or

Study, Population, Country and Quality	Data Sources	Other Comments	Incremental (no treatment as reference) [1]			Conclusions	Uncertainty
			Cost	Effect (QALYs)	ICER		
Directly applicable **Minor limitations** [a, b]	All unit costs from UK sources. Utilities: EQ-5D study following laparotomy in people who experienced SSI and people who did not experience SSI. Linear interpolation of recovery to baseline: 52 days with SSI; 35 days without SSI.	Alternative source: PHE registry. *S. aureus* SSI incidence: carriers vs. general cohort, OR = 2.4; non-carriers vs, general cohort, OR = 0.6. No treatment effect in non-carriers. Risk of death due to SSI, OR = 1.5 (derived from original CG74 model data).					higher. In breast, cranial and spinal surgery, the probability was between 65% and 76%. One-way sensitivity analysis and scenario analysis showed baseline results to be largely robust. The only parameter of influence was baseline SSI incidence. If baseline SSI risk is very low, treatment with mupirocin is less likely to be cost-effective.
Key: ICER, incremental cost-effectiveness ratio; OR, odds ratio.							
Note: (1) Fully incremental analysis.							
Applicability: Directly applicable. **Quality:** (a) Cohort age data, and excess bed days associated with SSI, informed by median values (means estimated using medians, ranges and 95% confidence intervals, where reported). (b) Assumption that the proportion of SSIs caused by *S. aureus* (33% in base case analysis) is consistent across types of surgery.							

Appendix I – Economic evidence study selection



Appendix J – Excluded studies

Clinical studies

Short Title	Title	Reason for Exclusion
Alexandrou (2008)	Pre-Operative Reduction of Nasal and Conjunctival Bacterial Flora With the Use of Mupirocin Nasal Ointment: a Comparison of 3 vs. 5 Day Administration of Mupirocin	• Conference abstract
Anderson (2015)	Efficacy of skin and nasal povidone-iodine preparation against mupirocin-resistant methicillin-resistant Staphylococcus aureus and S. aureus within the anterior nares	• Study does not contain any of the outcomes of interest
Bebko (2015)	Effect of a preoperative decontamination protocol on surgical site infections in patients undergoing elective orthopaedic surgery with hardware implantation	• Not a relevant study design. Retrospective review.
Bryan (2013)	Preventing deep wound infection after coronary artery bypass grafting: A review	• Review article but not a systematic review
Bryce (2014)	Nasal photodisinfection and chlorhexidine wipes decrease surgical site infections: a historical control study and propensity analysis	• Study does not contain any relevant interventions Study examined intranasal photodisinfection therapy.
Casewell (1986)	Elimination of nasal carriage of Staphylococcus aureus with mupirocin ('pseudomonic acid') - A controlled trial	• Does not contain a population of interest Study included non-surgical patients.
Chen (2013)	Preoperative decolonization effective at reducing staphylococcal colonization in total joint arthroplasty patients	• Study does not contain any of the outcomes of interest
Cimochowski (2001)	Intranasal mupirocin reduces sternal wound infection after open heart surgery in diabetics and nondiabetics	• Not a relevant study design Before and after study.
Dupeyron (2002)	A clinical trial of mupirocin in the eradication of methicillin-resistant Staphylococcus aureus nasal carriage in a digestive disease unit	• Not a relevant study design. Before and after study,
Egozi (2015)	Nasal carriage of Staphylococcus aureus in patients undergoing caesarean section and surgical site infection: a prospective randomized trial	• Conference abstract

Short Title	Title	Reason for Exclusion
Fritz (2013)	Mupirocin and chlorhexidine resistance in Staphylococcus aureus in patients with community-onset skin and soft tissue infections	• Does not contain a population of interest Study includes people with skin and soft tissue infections.
García (2003)	Use of nasal mupirocin for Staphylococcus aureus: effect on nasal carriers and nosocomial infections	• Study not reported in English
George (2016)	Effectiveness of Decolonization With Chlorhexidine and Mupirocin in Reducing Surgical Site Infections: A Systematic Review	• Systematic review did not contain new relevant papers
Gernaat-van (1998)	Prophylactic mupirocin could reduce orthopaedic wound infections. 1,044 patients treated with mupirocin compared with 1,260 historical controls	• Not a relevant study design Before and after study.
Glotzbec'er (2013)	What's the evidence? Systematic literature review of risk factors and preventive strategies for surgical site infection following paediatric spine surgery	• Study not relevant to RQ Study examined risk factors.
Harold (2017)	Multifaceted aseptic protocol decreases surgical site infections following hip arthroplasty	• Not a relevant study design. Retrospective review.
Horiuchi (2006)	Nasopharyngeal decolonization of methicillin-resistant Staphylococcus aureus can reduce PEG peristomal wound infection	• Does not contain a population of interest Study did not contain patients undergoing surgery.
Hudson (1994)	The efficacy of intranasal mupirocin in the prevention of staphylococcal infections: a review of recent experience	• Review article but not a systematic review
Jabbour (2010)	Does nasal decontamination reduce the incidence of infections after cardiac surgery?	• Study not reported in English
Kallen (2005)	Perioperative intranasal mupirocin for the prevention of surgical-site infections: systematic review of the literature and meta-analysis	• Systematic review did not contain new relevant papers
Kawana (1999)	A trial of povidone-iodine (PVP-I) nasal inhalation and gargling to remove potentially pathogenic bacteria colonized in the pharynx	• Study not reported in English
Kluytmans (1996)	Reduction of surgical-site infections in cardiothoracic surgery by elimination of nasal carriage of Staphylococcus aureus	• Not a relevant study design Before and after study.

Short Title	Title	Reason for Exclusion
Krueger (2002)	Influence of combined intravenous and topical antibiotic prophylaxis on the incidence of infections, organ dysfunctions, and mortality in critically III surgical patients: A prospective, stratified, randomized, double-blind, placebo-controlled clinical trial	• Study does not contain any relevant interventions Study examined the use of antibiotic prophylaxis only.
Laupland (2003)	Treatment of Staphylococcus aureus Colonization and Prophylaxis for Infection with Topical Intranasal Mupirocin: An Evidence-Based Review	• Review article but not a systematic review
Lefebvre (2017)	Staphylococcus aureus screening and decolonization reduces the risk of surgical site infections in patients undergoing deep brain stimulation surgery	• Not a relevant study design Before and after study.
Levy (2013)	Relation between nasal carriage of Staphylococcus aureus and surgical site infection in orthopaedic surgery: the role of nasal contamination. A systematic literature review and meta-analysis	• Systematic review did not contain new relevant papers
Liu (2017)	Nasal decontamination for the prevention of surgical site infection in Staphylococcus aureus carriers	• Systematic review did not contain new relevant papers No new studies identified. Included one study which examined an intervention which was not of interest.
Ma (2017)	Systematic review of a patient care bundle in reducing staphylococcal infections in cardiac and orthopaedic surgery	• Systematic review did not contain new relevant papers
Maiocco (2007)	Decontamination of the nasopharynx and oropharynx with chlorhexidine reduced nosocomial infections in cardiac surgery	• Not a relevant study design. Commentary on Segers 2006 study.
Martorell (2004)	Surgical site infections in cardiac surgery: An 11-year perspective	• Not a relevant study design. Retrospective review.
Mehta (2013)	Dose-ranging study to assess the application of intranasal 2% mupirocin calcium ointment to eradicate Staphylococcus aureus nasal colonization	• Study does not contain any of the outcomes of interest
Mehtar (1998)	New strategies for the use of mupirocin for the prevention of serious infection	• Review article but not a systematic review
Mody (2003)	Mupirocin-Based Decolonization of Staphylococcus aureus Carriers in Residents of 2 Long-Term Care	• Study not relevant to RQ

Short Title	Title	Reason for Exclusion
	Facilities: A Randomized, Double-Blind, Placebo-Controlled Trial	Study did not contain surgical patients.
Moon (2010)	Reducing hospital-associated infections in Staphylococcus aureus carriers	• Not a relevant study design. Summary of Bode 2010 study.
Moreira (2007)	Efficacy of a program of prevention and control for methicillin-resistant staphylococcus aureus Infections in an intensive-care unit	• Study not relevant to RQ Prospective cohort study which included patients hospitalised in ICU.
Nardi (2001)	Reduction in gram-positive pneumonia and antibiotic consumption following the use of a SDD protocol including nasal and oral mupirocin	• Does not contain a population of interest Study carried out in an intensive care unit.
Perl (2003)	Prevention of Staphylococcus aureus infections among surgical patients: beyond traditional perioperative prophylaxis	• Review article but not a systematic review
Reiser (2017)	Effect of pre-operative octenidine nasal ointment and showering on surgical site infections in patients undergoing cardiac surgery	• Not a relevant study design Before and after study.
Rezapoor (2017)	Povidone-Iodine-Based Solutions for Decolonization of Nasal Staphylococcus aureus: A Randomized, Prospective, Placebo-Controlled Study	• Study does not contain any of the outcomes of interest
Ridenour (2007)	Selective use of intranasal mupirocin and chlorhexidine bathing and the incidence of methicillin-resistant Staphylococcus aureus colonization and infection among intensive care unit patients	• Does not contain a population of interest Non-surgical patients included.
Ro (2008)	Methicillin-resistant Staphylococcus aureus colonization: a review of the literature on prevention and eradication	• Does not contain a population of interest Systematic review did not focus on surgical patients.
Rohr (2003)	Methicillin-resistant Staphylococcus aureus whole-body decolonization among hospitalized patients with variable site colonization by using mupirocin in combination with octenidine dihydrochloride	• Not a relevant study design. Before and after study.
Sadigursky (2017)	Prophylaxis with nasal decolonization in patients submitted to total knee and hip arthroplasty: systematic review and meta-analysis	• Systematic review did not match review protocol Systematic review only included observational studies.

Short Title	Title	Reason for Exclusion
Schora (2014)	Impact of Detection, Education, Research and Decolonization without Isolation in Long-term care (DERAIL) on methicillin-resistant Staphylococcus aureus colonization and transmission at 3 long-term care facilities	• Study does not contain any relevant interventions Study focused on a strategy which involved active surveillance using nasal swabs samples, decolonisation of carriers on intervention units, hand hygiene instruction, and enhanced cleaning of the environment.
Schweizer (2012)	Surgical site infections and their prevention	• Review article but not a systematic review
Schweizer (2013)	Effectiveness of a bundled intervention of decolonization and prophylaxis to decrease Gram positive surgical site infections after cardiac or orthopaedic surgery: systematic review and meta-analysis	• Systematic review did not contain new relevant papers
Schweizer (2015)	Association of a bundled intervention with surgical site infections among patients undergoing cardiac, hip, or knee surgery	• Not a relevant study design Before and after study.
Segers (2008)	Prevention of nosocomial infections after cardiac surgery by decontamination of the nasopharynx and oropharynx with chlorhexidine; a prospective, randomised study	• Study not reported in English
Shrem (2016)	Pre-caesarean Staphylococcus aureus nasal screening and decolonization: a prospective randomized controlled trial	• Not a relevant study design Quasi randomised trial.
Shuman (2012)	Preoperative topical antimicrobial decolonization in head and neck surgery	• Not a relevant study design Quasi-randomised trial.
Singh (2006)	Impact of an aggressive infection control strategy on endemic Staphylococcus aureus infection in liver transplant recipients	• Not a relevant study design Before and after study.
Sporer (2016)	Methicillin-Resistant and Methicillin-Sensitive Staphylococcus aureus Screening and Decolonization to Reduce Surgical Site Infection in Elective Total Joint Arthroplasty	• Not a relevant study design. Before and after study.
Tai (2012)	A prospective randomised study of Staphylococcus aureus nasal carriage as a major risk factor for infection in Mohs micrographic surgery	• Conference abstract
Thompson (2013)	Decreasing methicillin-resistant Staphylococcus aureus surgical site	• Not a relevant study design

Short Title	Title	Reason for Exclusion
	infections with chlorhexidine and mupirocin	Before and after study.
Trautmann (2008)	Intranasal mupirocin prophylaxis in elective surgery. A review of published studies	• Systematic review did not contain new relevant papers
van Rijen (2008)	New approaches to prevention of staphylococcal infection in surgery	• Review article but not a systematic review
van Rijen (2008)	Intranasal mupirocin for reduction of Staphylococcus aureus infections in surgical patients with nasal carriage: a systematic review	• Systematic review did not contain new relevant papers
van Rijen (2008)	Mupirocin ointment for preventing Staphylococcus aureus infections in nasal carriers	• Systematic review did not match review protocol Included studies which examined surgical and non-surgical patients.
Verhoeven (2014)	Detection and clinical relevance of Staphylococcus aureus nasal carriage: an update	• Review article but not a systematic review
Yano (2000)	Preoperative intranasal mupirocin ointment significantly reduces postoperative infection with Staphylococcus aureus in patients undergoing upper gastrointestinal surgery	• Not a relevant study design Before and after study.
Yu (2011)	Relationship between nasal colonization of Staphylococcus aureus and nosocomial infection after cardiac surgery	• Study not reported in English

Economic studies

Study	Full title	Primary reason for exclusion
Bebko 2015	Bebko SP (2015). Effect of a preoperative decontamination protocol on surgical site infections in patients undergoing elective orthopedic surgery with hardware implantation. *JAMA Surg,* 150 (5): 390.	Not a full economic evaluation
Bilici 2016	Bilici S, Durna YM, Yigit O, et al. (2016). The effect of mupirocin- and fusidic acid-nasal packings, place after septoplasty, on the nasal bacterial profile. *Allergy Rhinol,* 7 (4): e207-12.	Not a full economic evaluation
Cimochowski 2001	Cimochowsky GE, Harostock MD, Brown R, et al. (2001). Intranasal mupirocin reduces sternal wound infection after open heart surgery in diabetics and nondiabetics. *Ann Thorac Surg,* 71 (5): 1572-9.	Based on non-randomised evidence

Study	Full title	Primary reason for exclusion
Cunha 2011	Cunha BA, Thekkel V, Schoch P, et al. (2011). Clinical and cost ineffectiveness of preoperative screening for methicillin-resistant Staphylococcus aureus and intranasal mupirocin in preventing methicillin-resistant S aureus infections in cardiothoracic surgery. *Am J Infect Control,* 39 (3): 243-6.	Based on non-randomised evidence
Davey 1998	Davey P (1998). Eradication of nasal carriage of Staphylococcus aureus – is it cost-effective? *J Hosp Infect,* 40: S31-7.	Review article, no additional CUAs
Gurusamy 2015	Gurusamy KS. Koti R, Wilson P, Davidson BR. (2015). Antibiotic prophylaxis for the prevention of methicillin-resistant Staphylococcus aureus (MRSA) related complications in surgical patients. *Cochrane database of systematic reviews,* 8.	Not a full economic evaluation
Hetem 2016	Hetem DJ, Bootsma MCJ, Bonten MJM (2016). Prevention of surgical site infections: decontamination with mupirocin based on preoperative screening for Staphylococcus aureus carriers or universal decontamination? *Clin Infect Dis,* 62 (5): 631-6.	Not a full economic evaluation
Huang 2014	Huang SS, Septimus E, Avery TR, et al. (2014). Cost savings of universal decolonization to prevent intensive care unit infection: implications of the REDUCE MRSA trial. *Inf Control Hosp Epidemiol,* 35: S23-31.	Population (general ICU)
Kerbel 2018	Kerbel YE, Sunkerneni AR, Kirchner GJ, et al. (2018). The cost-effectiveness of preoperative Staphylococcus aureus screening and decolonization in total joint arthroplasty. *J Arthroplasty,* Epub ahead of print.	Not a full economic evaluation
Lee 2011	Lee YJ, Chen JZ, Lin HC, et al. (2011). Impact of active screening for methicillin-resistant Staphylococcus aureus (MRSA) and decolonization on MRSA infection, mortality and medical cost: a quasi-experimental study in surgical intensive care unit. *Critical Care,* 19: 143.	Based on non-randomised evidence
Liu 2017	Liu Z, Norman G, Iheofor-Ejiofor Z, et al. (2017). Nasal decontamination for the prevention of surgical site infection in Satphylococcus aureus carriers. *Cochrane dataset of systematic reviews,* 5.	Not a full economic evaluation
Peng 2017	Peng HM, Wang LC, Zhai JL, et al. (2017). Effectiveness of preoperative decolonization with nasal povidone iodine in Chinese patients undergoing elective orthopedic surgery: a prospective cross-sectional study. *Brazilian J Medical Biological Res,* 51 (2): e6736.	Not a full economic evaluation
Piraino 2000	Piraino B (2000). Staphylococcus aureus infections in dialysis patients: focus on prevention. *ASAIO Journal,* 46 (5): S13-27.	Not a full economic evaluation
Shreshta 2003	Shrestha NK, Shermock KM, Gordon SM, et al. (2003). Predictive value and cost-effectiveness analysis of a rapid polymerase chain reaction for preoperative detection of nasal carriage of Staphylococcus aureus. *Inf Control Hosp Epidemiol,* 24 (5): 327-33.	Not a full economic evaluation
Stambough 2017	Stambough JB, Nam D, Warren DK, et al. (2017). Decreased hospital costs and surgical site infection incidence with a universal decolonization protocol in primary total joint arthroplasty. *J Arthroplasty,* 32: 728-34.	Based on non-randomised evidence
Rao 2008	Rao N, Cannella B, Crossett LS, et al. (2008). A preoperative decolonization protocol for Staphylococcus	Based on non-randomised evidence

Study	Full title	Primary reason for exclusion
	aureus prevents orthopaedic infections. *Clin Orthop Relat Res,* 466: 1343-8.	
Rieser 2018	Rieser GR, Moskal JT. (2018). Cost efficacy of methicillin-resistant Staphylococcus aureus decolonization with intranasal povidone-iodine. *J Arthroplasty,* Epub ahead of print. .	Not a full economic evaluation
Rowbotham 2011	Rowbotham JV, Graves N, Cookson BD, et al. (2011). Screening, isolation, and decolonisation strategies in the control of meticillin resistant Staphylococcus aureus in intensive care units: cost effectiveness evaluation. *BMJ,* 343 (7827): d5694.	Population (general ICU)
Torres 2016	Torres EG, Lindmair-Snell JM, Langan JW, Burnikel BG (2016). Is preoperative nasal povidone-iodine as efficient and cost-effective as standard methicillin-resistant Staphylococcus aureus screening protocol in total joint arthroplasty? *J Arthroplasty,* 31 (1): 215-8.	Based on non-randomised evidence
Vandenbergh 1996	VandenBergh MFQ, klutymans JAJW, van Hout BA, et al. (1996). Cost-effectiveness of perioperative mupirocin nasal ointment in cardiothoracic surgery. *Inf Control Hosp Epidemiol,* 17 (12): 786-92.	Based on non-randomised evidence
Williams 2017	Williams DM, Miller AO, Henry MW, et al. (2017). Cost-effectiveness of staphylococcus aureus decolonization strategies in high-risk total joint arthroplasty patients. *J Arthroplasty,* 32 (9): S91-6.	Insufficient information provided
Ziakas 2015	Ziakas PD, Zacharioudakis IM, Zervou FN, Mylonakis E. Methicillin-resistant Staphylococcus aureus prevention strategies in the ICU: a clinical decision analysis. *Crit Care Med,* 43 (2): 382-93.	Population (general ICU)

Appendix K – Research recommendations

1. What is the clinical effectiveness of nasal decolonisation using mupirocin in combination with a chlorhexidine body wash in the whole population?

Three studies were identified which examined the clinical effectiveness of nasal decolonisation using mupirocin in combination with a chlorhexidine body wash. Out of the three studies, one study demonstrated a significant reduction in *S. aureus* SSI (including deep and superficial SSI) and *S. aureus* nosocomial infections. However, these studies only included people who were identified as *S. aureus* carriers. Therefore, no information was identified with regards to the effectiveness of this bundled intervention in the whole population.

Further research is needed using a robust study design such as a health technology assessment to explore the clinical effectiveness of mupirocin with chlorhexidine in the whole population. Studies should also explore the effectiveness of the bundle intervention in different surgical procedures. Studies should be UK based. Research in this area is essential to inform future updates of key recommendations in this guidance which in turn can help improve patient outcomes.

PICO	**Population:** People of any age undergoing any surgery, including minimally invasive surgery (arthroscopic, thoracoscopic and laparoscopic surgery) **Interventions:** • Intranasal mupirocin • Intranasal mupirocin with chlorhexidine body wash **Comparator:** • Placebo • Other decolonisation protocols • No treatment **Outcomes:** • Surgical site infections (superficial, deep and organ/space SSI), including MRSA and MSSA SSI • Other types of nosocomial infections • Infectious complications such as septicaemia or septic shock • Adverse events such as: antimicrobial resistance (measured using recognised method e.g. PCR)
Current evidence base	8 RCTs of low power
Study design	Randomised controlled trial
Other comments	This surveillance registry should be maintained within UK settings, should take into consideration different surgical procedures and should contain an adequate sample size.

2. What is the contribution to clinical effectiveness of the timing of nasal decolonisation and body wash for the prevention of surgical site infection?

The timing of decolonisation in the studies included in this review ranged from a day before surgery to five days before surgery, however no studies were identified which compared different timings and duration of decolonisation. Therefore no recommendations could be made around when decolonisation should be initiated. Further research is needed using a robust study design to explore the clinical effectiveness of the timing of nasal decolonisation. Studies should be UK based and should consider different surgical procedures. Research in this area is essential to inform future updates of key recommendations in this guidance.

PICO	**Population:** People of any age undergoing any surgery, including minimally invasive surgery (arthroscopic, thoracoscopic and laparoscopic surgery) **Interventions:** Following interventions given at different times prior to surgery: • Intranasal mupirocin • Intranasal mupirocin with body wash or wipes (e.g. chlorhexidine) **Comparator:** • Different timing of nasal decolonisation compared to each other **Outcomes:** other Outcomes**es:** • Surgical site infections (superficial, deep and organ/space SSI), including MRSA and MSSA SSI • Other types of nosocomial infections • Infectious complications such as septicaemia or septic shock • Adverse events such as: antimicrobial resistance (measured using recognised method e.g. PCR)
Current evidence base	No randomised controlled trials were identified.
Study design	Randomised controlled trial
Other comments	This surveillance registry should be maintained within UK settings, should take into consideration different surgical procedures and should contain an adequate sample size.

3. Is the use of chlorhexidine body wash associated with increased antimicrobial resistance?

In this review, no extractable data was identified on antimicrobial resistance associated with the use of mupirocin. Furthermore, no evidence was identified on the antimicrobial resistance associated with the use of chlorhexidine body wash. Currently, antimicrobial susceptibility associated with the use of mupirocin is measured as part of surveillance, however a similar database has not been established for the use of chlorhexidine. Therefore, surveillance of antimicrobial susceptibility is also needed to examine any increase in resistance. Research in this area is essential to inform future updates of key recommendations in this guidance which in turn can help improve patient outcomes.

PICO	**Population:** People of any age undergoing any surgery, including minimally invasive surgery (arthroscopic, thoracoscopic and laparoscopic surgery) **Interventions:** • Chlorhexidine body wash **Outcomes: Outcomes:** • Antimicrobial resistance measured using in vitro studies which utilise dilution method, PCR or any other recognised method to ascertain resistance.
Current evidence base	No studies were identified.
Study design	Surveillance registry
Other comments	This surveillance registry should be maintained within UK settings and should take into consideration different surgical procedures.

4. What is the effectiveness of decolonisation using alternative interventions in combination with nasal decolonisation in the prevention of surgical site infections, in people who present with contraindication to chlorhexidine?

In the review, evidence was identified on the effectiveness of the bundled use of mupirocin and chlorhexidine body wash in the prevention of surgical site infection. However, it was identified that in some instances use of chlorhexidine may not be appropriate, such as when a person is sensitive to chlorhexidine. Therefore, further research is needed using a robust study design, to identify alternative interventions for decolonisation. These studies should be conducted in the UK and should take into consideration different surgical procedures. Research in this area can effective intervention to be identified for people presenting with contraindications. This can help improve patient outcomes.

PICO	**Population:** People of any age undergoing any surgery, including minimally invasive surgery (arthroscopic, thoracoscopic and laparoscopic surgery) **Interventions:** **Nasal decolonisation in combination with body wash using alternative interventions such as:** • Octenisan • Polyhexanide **Comparator:** • Placebo • No decolonisation • Different nasal decolonisation protocols **Outcomes:** • Surgical site infections (superficial, deep and organ/space SSI), including MRSA and MSSA SSI • Other types of nosocomial infections • Infectious complications such as septicaemia or septic shock • Adverse events such as: antimicrobial resistance
Current evidence base	No studies were identified.
Study design	Randomised controlled trial
Other comments	This surveillance registry should be maintained within UK settings, should take into consideration different surgical procedures and should contain an adequate sample size.

Appendix L - References

Included studies

Bode Lonneke G. M, Kluytmans Jan A. J. W, Wertheim Heiman F. L, Bogaers Diana, Vandenbroucke-Grauls Christina M. J. E, Roosendaal Robert, Troelstra Annet, Box Adrienne T. A, Voss Andreas, van der Tweel , Ingeborg , van Belkum , Alex , Verbrugh Henri A, and Vos Margreet C (2010) Preventing surgical-site infections in nasal carriers of Staphylococcus aureus. The New England journal of medicine 362(1), 9-17

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Konvalinka A, Errett L, and Fong I W (2006) Impact of treating Staphylococcus aureus nasal carriers on wound infections in cardiac surgery. The Journal of hospital infection 64(2), 162-8

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Phillips Michael, Rosenberg Andrew, Shopsin Bo, Cuff Germaine, Skeete Faith, Foti Alycia, Kraemer Kandy, Inglima Kenneth, Press Robert, and Bosco Joseph (2014) Preventing surgical site infections: a randomized, open-label trial of nasal mupirocin ointment and nasal povidone-iodine solution. Infection control and hospital epidemiology 35(7), 826-32

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