WHO Surgical Site Infection Prevention Guidelines

Web Appendix 3

Summary of a systematic review on decolonization with mupirocin ointment with or without chlorhexidine gluconate body wash for the prevention of *Staphylococcus aureus* infection in nasal carriers undergoing surgery

1. Introduction

Staphylococcus aureus is the leading health care-associated pathogen in hospitals worldwide. Infections with *S. aureus* are associated with substantial morbidity and mortality and this trend is increasing due to the widespread dissemination of methicillin-resistant *S. aureus* (MRSA) [1]. Staphylococcal infections occur regularly in hospitalized patients and may have severe consequences, including postoperative wound infections, nosocomial pneumonia and catheter-related bacteraemia [2-6]. A recent study of over 7 million hospital admissions in the United States of America (USA) estimated that the annual national impact was 2.7 million additional hospital days, US$ 9.5 billion excess costs and at least 12 000 in-patient deaths [7]. The consequences of these infections are thus immense, both for the patient and the health care system, and it is essential to implement effective prevention strategies.

Traditionally, the control of *S. aureus* has focused on preventing cross-transmission between patients [8]. However, it has been shown repeatedly that a large proportion of nosocomial *S. aureus* infections (approximately 80% after surgery) originate from the patients' own flora [4,9,10]. Nasal carriage of *S. aureus* is now considered a well-defined risk factor for subsequent infection in various groups of patients [3,11].

Mupirocin nasal ointment (applied two times daily for 5 days) is an effective, safe and relatively low-cost treatment for the eradication of carriage. Mupirocin can be used for the eradication of both methicillin-sensitive *S. aureus* (MSSA) and MRSA, although mupirocin resistance has been reported [12]. Several interventional studies have attempted to reduce the infection rates by eradicating nasal carriage [3]. Recently, rapid molecular diagnostics that can detect nasal carriage of *S. aureus* within hours rather than days have become available [13,14], thus enabling the pre-emptive treatment of carriers when appropriate.

The surgical site infection (SSI) prevention guideline published by the Society for Healthcare Epidemiology of America (SHEA)/Infectious Diseases Society of America (IDSA) [15] recommends to screen for *S. aureus* and decolonize surgical patients for high-risk procedures. Some SSI prevention bundles, such as the one issued by the US Institute of Health Improvement [16], recommend to screen for *S. aureus* and decolonize prior to surgery, if positive. However, these recommendations are not based upon systematic reviews of the literature and meta-analysis or a rigorous evaluation of the quality of the available evidence.

2. PICO question

Is mupirocin nasal ointment in combination with or without a chlorhexidine gluconate (CHG) body wash effective in reducing the number of *S. aureus* infections in nasal carriers undergoing surgery?

- **P**opulation: patients of any age with nasal carriage of *S. aureus* (either methicillin-resistant or -susceptible) identified by microbiological culture techniques and undergoing a surgical procedure
- **I**ntervention: preoperative intranasal mupirocin ointment (in combination with or without a CHG body wash)
- **C**omparator: placebo or no treatment
- **O**utcome: *S. aureus* infection rate (overall health care-associated infections and SSI), SSI-attributable mortality

3. Methods

The following databases were searched: Medline (Ovid); Excerpta Medica Database (EMBASE/Ovid); Cumulative Index to Nursing and Allied Health Literature (CINAHL); the Cochrane Library, the Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Wounds Group Specialized Register; and WHO regional medical databases. The upper time limit for the review was 25 January 2016 with no time limit to the past. There were no language restrictions. A comprehensive list of search terms was used, including Medical Subject Headings (MeSH) (Appendix 1).

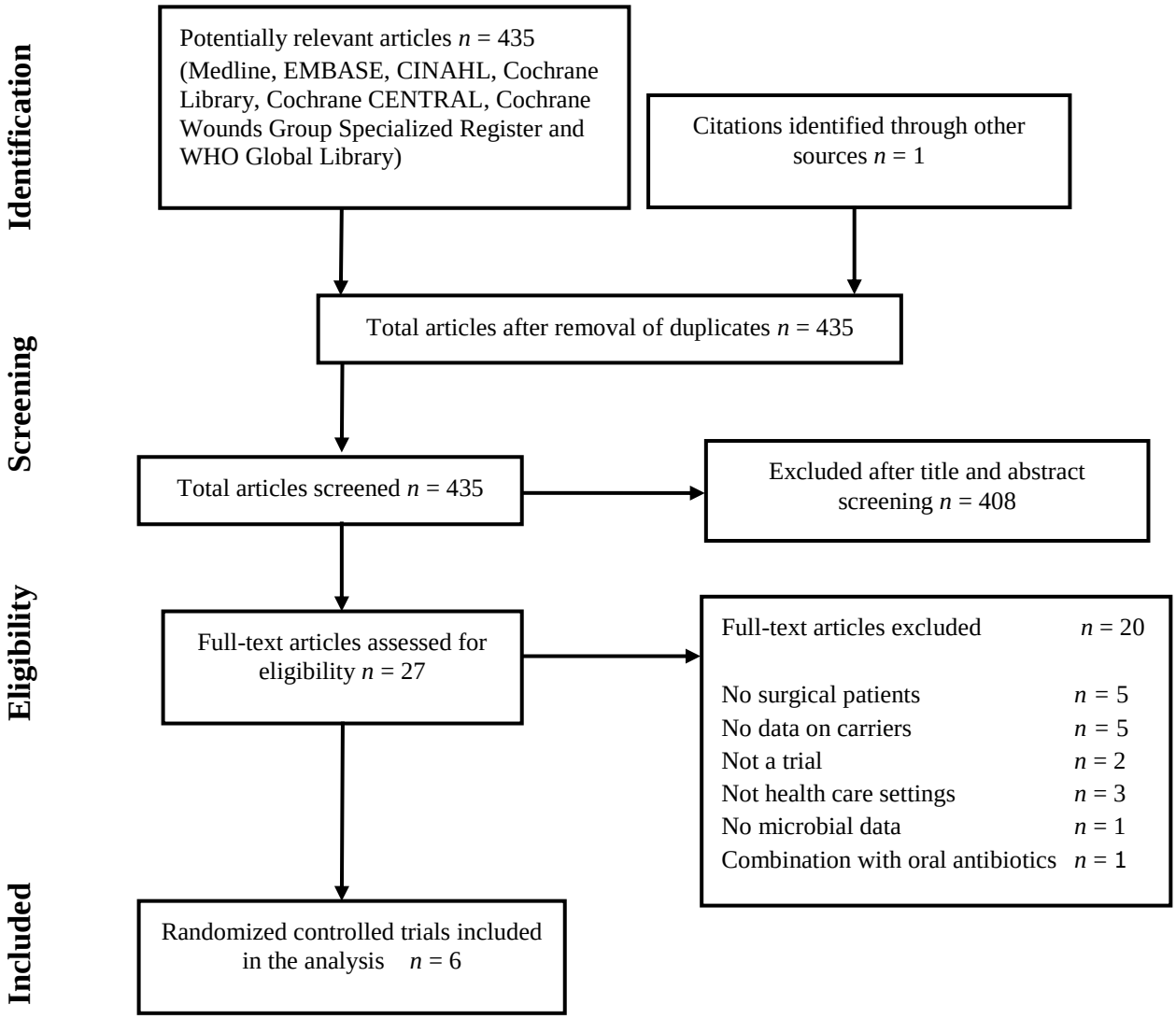
Two independent reviewers screened titles and abstracts of retrieved references for potentially relevant studies. The full text of all potentially eligible articles was obtained and then reviewed independently by two authors for eligibility based on inclusion criteria. Duplicate studies were excluded.

The two authors extracted data in a predefined evidence table (Appendix 2) and critically appraised the retrieved studies using the Cochrane Collaboration tool to assess the risk of bias of randomized controlled studies (RCTs) [17] (Appendix 3). Any disagreements were resolved through discussion or after consultation with the senior author, when necessary.

Meta-analyses of available comparisons were performed using Review Manager version 5.3 as appropriate [18] (Appendix 4). Adjusted odds ratios (OR) and mean difference with 95% confidence intervals (CI) were extracted and pooled for each comparison with a random effects model. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology [19] (GRADE Pro software) [20] was used to assess the quality of the body of retrieved evidence (Appendix 5).

4. Study selection

Flow chart of the study selection process



5. Summary of findings and quality of the evidence

A total of 6 RCTs [21-26] were identified with an SSI outcome comparing mupirocin ointment given intranasally to *S. aureus* carriers preoperatively in combination with or without chlorhexidine gluconate (CHG) soap *vs*. placebo or no treatment. Some studies included both *S. aureus* nasal carriers and non-carriers [22,23,25], but data for carriers only were extracted for this review. The mupirocin concentration was 2% in all trials. However, the frequency of daily application and the duration of treatment varied among studies. In 2 of the included 6 studies [21,26], CHG 4% soap was used for full body wash in combination with the mupirocin nasal ointment. In one study [24], CHG 2% soap body wash was used as a standard preoperative clinical practice.Studies focused on adult patients and no study was available in the paediatric population. The number of included patients and the type of surgical procedure varied among studies. Five trials [22-26] described patients undergoing cardiac, orthopaedic, general, gynaecological, neurological or Mohs micrographic surgery. One [21] included both surgical (cardiac, vascular, orthopaedic, gastrointestinal or general surgery) and non-surgical patients (internal medicine). For the analyses, non-surgical patients were excluded. Study characteristics are presented in Appendix 2.

According to the included studies, the following comparisons were made:

1. Mupirocin in combination with or without CHG body wash *vs.* placebo/no treatment with the outcome of:
    a. overall health care-associated *S. aureus* infections
    b. health care-associated SSI caused by *S. aureus*

The results of the meta-analyses based on these comparisons are presented in Appendix 4.

1a. Five of the 6 RCTs compared mupirocin nasal ointment in combination with or without CHG soap to placebo or no treatment with the outcome of overall health care-associated *S. aureus* infections. Two trials [21,25] showed a significant effect of mupirocin in combination with or without CHG body wash on reducing the *S. aureus* infection rate, whereas the remaining trials [22-24] found no significance between the mupirocin/CHG and control groups (Appendices 2 and 4). Reported *S. aureus* infections included SSI, bacteraemia, respiratory tract, skin and urinary tract infections.

Meta-analysis of the 5 studies showed that the use of mupirocin 2% ointment in combination with or without CHG body wash in surgical patients with nasal *S. aureus* carriage has significant benefit when compared to placebo/no treatment on the reduction of the overall health care-associated *S. aureus* infection rate (OR: 0.48; 95% CI: 0.32–0.71).

The quality of the evidence for this comparison was moderate due to imprecision (Appendix 5).

1b. All 6 RCTs reported on the outcome of health care-associated SSI caused by *S. aureus*., One trial [21] showed a significant effect of mupirocin in combination with or without CHG body wash on the reduction of the *S. aureus* SSI rate, whereas the remaining studies [22-26]

found no significant difference in the SSI rate between the mupirocin/CHG and control groups.

Meta-analysis of the 6 studies showed that the use of mupirocin 2% ointment in combination with or without CHG body wash in surgical patients with nasal *S. aureus* carriage has significant benefit in reducing the SSI rate with *S. aureus* (OR: 0.46; 95% CI: 0.31–0.69) when compared to placebo/no treatment.

The quality of the evidence for this comparison was moderate due to imprecision (Appendix 5).

In meta-regression analysis, there was no evidence that the effect differed between different types of surgery (*P*=0.986).

In conclusion, the retrieved evidence can be summarized as follows.

1a. Overall, a moderate quality of evidence shows that the use of mupirocin 2% ointment in combination with or without CHG body wash in surgical patients with nasal *S. aureus* carriage has significant benefit when compared to placebo/no treatment in reducing the overall health care-associated *S. aureus* infection rate.

1b. Overall, a moderate quality of evidence shows that the use of mupirocin 2% ointment in combination with or without CHG body wash in surgical patients with nasal *S. aureus* carriage has significant benefit when compared to placebo/no treatment in reducing the SSI rate with *S. aureus*.

Four of the 6 studies [21,23-25] were high quality, randomized, double-blind, placebo-controlled trials. The remaining 2 studies [22,26] were not placebo-controlled. However, the results show the same reduction in *S. aureus* infections with or without the inclusion of the 2 studies of lesser quality. The included studies did not assess screening for *S. aureus* as part of the intervention and they did not investigate the role of screening in this context.

6. Other factors considered in the review of studies

The systematic review team identified the following other factors to be considered.

Potential harms

A point of concern is the development of mupirocin resistance [27]. In facilities where mupirocin is used, monitoring of antimicrobial resistance is recommended [28-30]. The available evidence [23-25] and additional studies [31,32] showed no trend towards an increasing prevalence of mupirocin resistance following the short-term use of mupirocin in surgical patients. However, there is evidence that the increased short-term use of mupirocin leads to an increase of resistance to mupirocin and other antibiotics [33]. Given the logistic challenge, some hospitals prefer to treat all patients with mupirocin instead of known carriers only. However, this "treat-all" strategy is associated with a high rate of unnecessary and thus unethical treatment that increases the likelihood of the development of resistance [34,35].

Patient population

Although several types of surgery were included in the analyses, most patients were undergoing cardiothoracic or orthopaedic surgery. In one study, a reduction of the SSI rate was found for both groups, but statistical significance was only found in the cardiothoracic group [21]. Cost-effectiveness was statistically significant in both groups [36]. For clean surgery, one-year mortality was decreased in the treatment group compared to the placebo group [37]. In conclusion, there is strong evidence for the effectiveness of the perioperative use of mupirocin 2% ointment in combination with or without CHG body wash in cardiothoracic patients with known nasal carriage of *S. aureus* and strong indications in orthopaedic surgery. If feasible, a "screen-and-treat" strategy can be used effectively for surgery where *S. aureus* infections occur frequently and represent a devastating outcome, for example, in nasal carriers who are receiving a cardiac device or other high-risk patients.

Resource use

The use of mupirocin was shown to be cost-effective in 2 separate studies, including the "screen-and-treat" strategy for *S. aureus* [21,36]. Hospital costs were on average € 1911 lower per patient treated with mupirocin and CHG soap than costs in the non-treatment arm, that is, € 8602 vs. € 10 513, respectively (P=0.01). Subgroup analysis showed that cardiothoracic patients treated with mupirocin and CHG who were nasal carriers of *S. aureus* cost € 2841 less (€ 9628 vs. € 12 469, respectively; P=0.006) than non-treated patients. Similarly, orthopaedic carriers cost € 955 less than non-treated patients (€ 6097 vs. € 7052; P=0.05) [36].

Feasibility and equity

A "screen-and-treat" strategy may be a challenge to implement because of its logistics. The nasal sample must be taken and analyzed before surgery and the patient must receive at least one dose of mupirocin before surgery (procedure used by Bode and colleagues 2010) [21]. Ideally, screening must be performed in the outpatient clinic to ensure that nasal *S. aureus* carriers can start treatment at home. This is feasible for elective surgery, but in the case of acute surgery, screening must be performed as soon as possible after admission as the time between admission and surgery is now very short.

7. Key uncertainties and future research priorities

The systematic review team identified the following key uncertainties and future research priorities.

We do not expect other RCTs to study this topic in the near future as it is considered unethical not to treat these patients when a large multicentre double-blind RCT [21] has found that there is a strong effect in the overall group.

In the future, it is probable that other products will be tested. For example, a povidone-iodine solution was recently tested in an open-label trial [38] and reported a similar effect to mupirocin.

However, the quality of this study was low. Good quality RCTs are needed to test other options than mupirocin.

APPENDICES

Appendix 1: Search terms

Medline (via Ovid)

1 exp mupirocin/
2 mupirocin.mp.
3 bactroban.mp.
4 centany.mp.
5 eismycin.mp.
6 plasimine.mp.
7 pseudomonic acid.mp.
8 or/1-7
9 exp *Staphylococcus aureus*/
10 exp *Staphylococcal infections*/
11 staphylococ$.mp.
12 *S aureus*.mp.
13 or/9-12
14 8 and 13

EMBASE (via OVID)

1 exp mupirocin/
2 exp pseudomonic acid/
3 (mupirocin or bactroban or centany or eismycin or plasimine or pseudomonic acid).mp.
4 or/1-3
5 exp *Staphylococcus aureus*/
6 exp *Staphylococcus infection*/
7 staphylococ$.mp.
8 *S aureus*.mp.
9 or/5-8
10 (nasal or naso$).mp.
11 and/4,9-10

CINAHL

S9 S3 and S8
S8 S4 or S5 or S6 or S7
S7 TI *S aureus* or AB *S aureus*
S6 TI staphylococ* or AB staphylococ
S5 (MH "staphylococcal infections+")
S4 (MH "*Staphylococcus aureus*")
S3 S1 or S2
S2 TI (mupirocin or bactroban or centany or eismycin or plasimine or pseudomonic acid) or AB (mupirocin or bactroban or centany or eismycin or plasimine or pseudomonic acid)
S1 (MH "mupirocin")

Cochrane Library, Cochrane CENTRAL,
Cochrane Wounds Group Specialized Register

#1 MeSH descriptor mupirocin explode all trees
#2 mupirocin
#3 bactroban
#4 centany
#5 eismycin
#6 plasimine
#7 pseudomonic acid
#8 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)
#9 MeSH descriptor *Staphylococcus aureus* explode all trees
#10 MeSH descriptor staphylococcal infections explode all trees
#11 staphylococ*
#12 "*S aureus*"
#13 (#9 OR #10 OR #11 OR #12)
#14 (#8 AND #13)

WHO Global Library

1 mupirocin
2 bactroban
3 centany
4 eismycin
5 plasimine
6 pseudomonic acid
7 (1 OR 2 OR 3 OR 4 OR 5 OR 6)
8 staphylococ
9 *aureus*
10 (8 OR 9)
11 (7 AND 10)

Appendix 2: Evidence table

Study, year	Type of surgery	Population	Infection Criteria	Intervention	Control	Timing	Outcome
Bode, 2010 [21]	General, cardiothoracic, orthopaedic, vascular and gastrointestinal.	Nasal *S. aureus* carriers.	CDC	Mupirocin 2% nasal ointment (Bactroban®, GlaxoSmithKline, Brentford, UK) in combination with CHG soap, 40 mg per mL (Hibiscrub®, Mölnlycke, Göteborg, Sweden) for a total body wash.	Placebo nasal ointment and placebo body wash.	Two times daily for 5 days perioperatively, with at least one dose before surgery.	All health care-associated *S. aureus* infection I: 16/441 (3.6%) C: 31/367 (8.4%) *S. aureus* SSI I: 11/441 (2.5%) C: 29/367 (7.9%)
Garcia, 2003 [22]	Cardiothoracic.	Both nasal *S. aureus* carriers and non-carriers.	CDC	Mupirocin 2% nasal ointment (Bactroban®).	No treatment.	Two times daily for 5 days preoperatively.	Identical numbers for all health care-associated *S. aureus* infection and *S. aureus* SSI I: 1/31 (3.2%) C: 3/34 (8.8%)
Kalmeijer, 2002 [23]	Orthopaedic (elective first operation or revision + prosthetic implant material).	Both nasal *S. aureus* carriers and non-carriers.	CDC	Mupirocin 2.15% nasal ointment (GlaxoSmithKline; lot 550150/96G04).	Placebo.	Two times daily from the day of hospital admission (day before surgery) until the day of surgery.	Identical numbers for all health care-associated *S. aureus* infection and *S. aureus* SSI I: 2/95 (2.1%) C: 5/86 (5.8%)
Konvalinka, 2006 [24]	Elective cardiac.	Nasal *S. aureus* carriers.	CDC	Mupirocin 2% nasal ointment (CHG 2% soap/body wash as standard care).	Placebo (CHG 2% soap/body wash as standard care).	Two times daily for 7 days preoperatively.	Identical numbers for all health care-associated *S. aureus* infection and *S. aureus* SSI

							I: 5/130 (3.8%) C: 4/127 (3.1%)
Perl, 2002 [25]	General, gynaecological, neurological and cardiothoracic.	Both nasal *S. aureus* carriers and non-carriers.	CDC	Mupirocin 2% nasal ointment.	Placebo.	Two times daily for 5 days preoperatively.	All health care-associated *S. aureus* infection I: 17/430 (4.0%) C: 34/439 (7.7%) *S. aureus* SSI I: 16/432 (3.7%) C: 26/439 (5.9%)
Tai, 2013 [26]	Mohs micrographic.	Nasal *S. aureus* carriers.	CDC	Mupirocin 2% nasal ointment in combination with CHG 4% body wash.	No treatment.	Two times daily for 5 days preoperatively.	No data about all health care-associated *S. aureus* infection *S. aureus* SSI I: 4/102 (3.9%) C: 11/101 (10.9%)

CDC: Centers for Disease Control and Prevention; I: intervention; C: control; CHG: chlorhexidine gluconate; SSI: surgical site infection.

Appendix 3: Risk of bias assessment of the included studies

RCT, author , year, reference	Sequence generation	Allocation concealment	Participants blinded	Care providers blinded	Outcome assessors blinded	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Bode, 2010 [21]	Low	Low	Low	Low	Low	Low	Low	-
Garcia, 2003 [22]	Unclear	Unclear	High	High	High	Unclear	Unclear	-
Kalmeijer, 2002 [23]	Low	Low	Low	Low	Low	Low	Low	-
Konvalinka, 2006 [24]	Low	Low	Low	Low	Low	Low	Low	-
Perl, 2002 [25]	Unclear	Unclear	Low	Low	Low	Low	Low	-
Tai, 2013 [26]	Unclear	Unclear	High	High	High	Unclear	Unclear	-

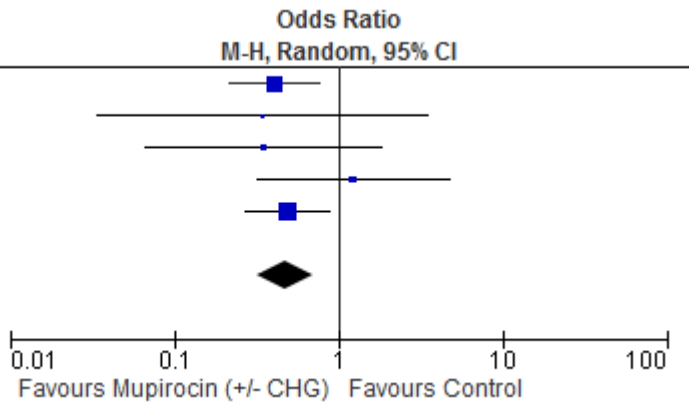
RCT: randomized controlled trial.

Appendix 4: Meta-analyses

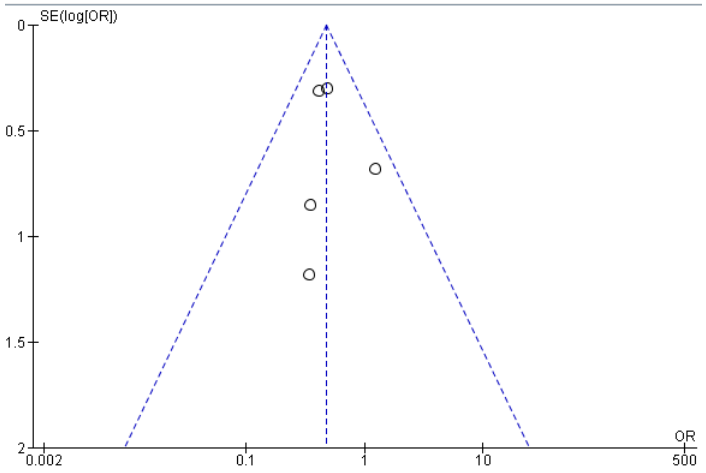
Comparison 1a: Mupirocin vs. placebo/no treatment, overall health care-associated *S. aureus* infection outcome

Study or Subgroup	Mupirocin (+/- CHG) Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Bode 2010	16	441	31	367	40.0%	0.41 [0.22, 0.76]
Garcia 2003	1	31	3	34	2.9%	0.34 [0.03, 3.50]
Kalmeijer 2002	2	95	5	86	5.5%	0.35 [0.07, 1.84]
Konvalinka 2006	5	130	4	127	8.6%	1.23 [0.32, 4.69]
Perl 2002	17	430	34	439	43.0%	0.49 [0.27, 0.89]
Total (95% CI)		**1127**		**1053**	**100.0%**	**0.48 [0.32, 0.71]**
Total events	41		77			

Heterogeneity: Tau² = 0.00; Chi² = 2.39, df = 4 (P = 0.66); I² = 0%
Test for overall effect: Z = 3.68 (P = 0.0002)



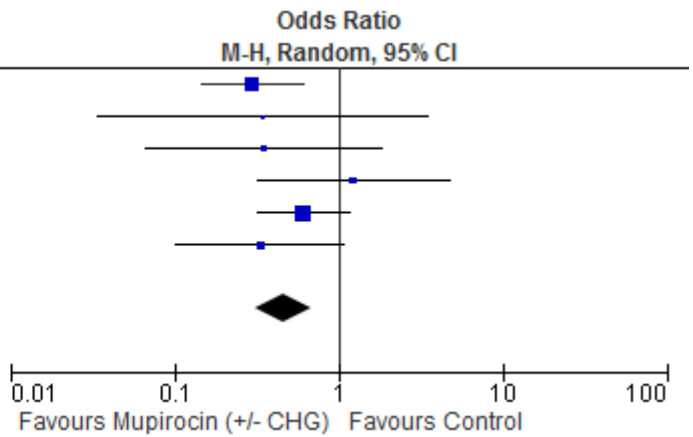
Funnel plot 1a: Mupirocin vs. placebo/no treatment



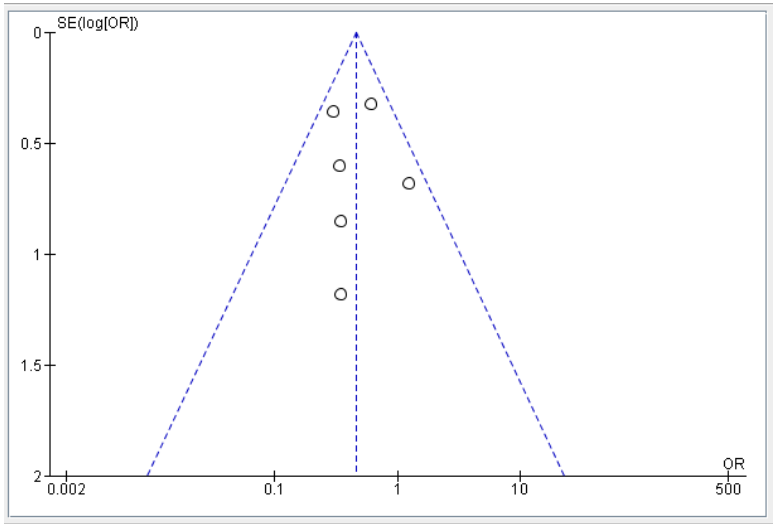
Comparison 1b: Mupirocin vs. placebo/no treatment, health care-associated SSI caused by *S. aureus* outcome

Study or Subgroup	Mupirocin (+/- CHG) Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Bode 2010	11	441	29	367	31.7%	0.30 [0.15, 0.61]
Garcia 2003	1	31	3	34	3.0%	0.34 [0.03, 3.50]
Kalmeijer 2002	2	95	5	86	5.7%	0.35 [0.07, 1.84]
Konvalinka 2006	5	130	4	127	8.9%	1.23 [0.32, 4.69]
Perl 2002	16	432	26	439	39.2%	0.61 [0.32, 1.16]
Tai 2013	4	102	11	101	11.5%	0.33 [0.10, 1.09]
Total (95% CI)		**1231**		**1154**	**100.0%**	**0.46 [0.31, 0.69]**
Total events	39		78			

Heterogeneity: Tau² = 0.00; Chi² = 4.73, df = 5 (P = 0.45); I² = 0%
Test for overall effect: Z = 3.81 (P = 0.0001)



Funnel plot 1b: Mupirocin vs. placebo/no treatment



M-H: Mantel-Haenszel (test); CI: confidence interval

Appendix 5. GRADE tables

Comparisons 1a and b: Mupirocin nasal ointment for the prevention of *S. aureus* infection in nasal carriers undergoing surgery

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mupirocin nasal ointment	Control	Relative (95% CI)	Absolute	
Overall health care-associated *S. aureus* infection											
5	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	41/1127 (3.6%)	77/1053 (7.3%)	OR: 0.48 (0.32-0.71)	37 fewer per 1000 (from 20 fewer to 49 fewer)	⊕⊕⊕O MODERATE
Health care-associated *S. aureus* SSI											
6	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	39/1231 (3.2%)	78/1154 (6.8%)	OR: 0.46 (0.31-0.69)	36 fewer per 1000 (from 21 fewer to 46 fewer)	⊕⊕⊕O MODERATE

[1] Optimal information size not met

RCT: randomized controlled trial; CI: confidence interval; OR: odds ratio; SSI: surgical site infection.

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