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## Chapter 4.1

# Mupirocin ointment for preventing *Staphylococcus aureus* infections in carriers

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# Abstract

## Background

*Staphylococcus aureus* (*S. aureus*) is the leading nosocomial (hospital acquired) pathogen in hospitals throughout the world. Traditionally, control of *S. aureus* has been focused on preventing cross-infection between patients, however, it has been shown repeatedly that a large proportion of nosocomial *S. aureus* infections originate from the patient's own flora. Nasal carriage of *S. aureus* is now considered a well defined risk factor for subsequent infection in various groups of patients. Local antibiotic treatment with mupirocin ointment is often used to eradicate nasal *S. aureus*.

## Objectives

To determine whether the use of mupirocin nasal ointment in patients with identified *S. aureus* nasal carriage reduced *S. aureus* infection rates.

## Search methods

We searched the Cochrane Wounds Group Specialised Register (May 2008), the Cochrane Central Register of Controlled Trials (CENTRAL, Issue 2 2008), MEDLINE (1950 to May 2008), EMBASE (1980 to May 2008) and CINAHL (1982 to May 2008). To identify unpublished trials, abstract books from major scientific meetings (ICAAC, ESCMID and SHEA) were handsearched, researchers and manufacturers of mupirocin were contacted and other electronic databases were searched (SIGLE, ASLIB Index, mRCT, USA Clinical Trials).

## Selection criteria

Randomised controlled trials (RCTs) comparing nasal mupirocin with no treatment or placebo or alternative nasal treatment in the prevention of *S. aureus* infections in nasal *S. aureus* carriers were included.

## Data collection and analysis

Titles, abstracts and full-text articles of studies retrieved from the search process were independently assessed by two authors for inclusion. From included studies a data extraction form was made and the quality of the trial was assessed. The primary outcome was the *S. aureus* infection rate (any site). Secondary outcomes were time to infection, mortality, adverse events and infection rate caused by micro-organisms other than *S. aureus*.

## Results

Nine RCTs involving 3396 participants met the inclusion criteria. Patient populations varied and several types of nosocomial *S. aureus* infection were described including bacteraemia, exit-site infections, peritonitis, respiratory tract infections, skin infections, surgical site infections (SSI) and urinary tract infections. After pooling the eight studies that compared mupirocin with placebo or with no treatment, there was a statistically significant reduction in the rate of *S. aureus* infection associated with intranasal mupirocin (RR 0.55, 95% CI 0.43–0.70).

A planned subgroup analysis of surgical trials demonstrated a significant reduction in the rate of nosocomial *S. aureus* infection rate associated with mupirocin use (RR 0.55, 95% CI 0.34 to 0.89) however this effect disappeared if the analysis only included surgical site infections caused by *S. aureus* (RR 0.63, 95% CI 0.38–1.04), possibly due to a lack of power. The infection rate caused by micro-organisms other than *S. aureus* was significantly higher in patients treated with mupirocin compared with control patients (RR 1.38, 95% CI 1.11–1.72).

## Authors' conclusions

In people who are nasal carriers of *S. aureus*, the use of mupirocin ointment results in a statistically significant reduction in *S. aureus* infections.

## Background

*Staphylococcus aureus* (*S. aureus*) is the leading nosocomial (hospital acquired) pathogen in hospitals throughout the world. Infection with *S. aureus* is associated with substantial morbidity and mortality - a trend that is increasing due to the widespread dissemination of meticillin-resistant *S. aureus* (MRSA).<sup>1</sup> MRSA is not more pathogenic (disease-causing) than *S. aureus*, but therapy is more problematic.

Staphylococcal infections occur regularly in hospitalised patients and can have severe consequences including postoperative wound infections, nosocomial pneumonia, and catheter-related bacteraemia (bacteria in the blood that can cause disease, e.g. endocarditis, elsewhere in the body).<sup>2-6</sup> A recent study of over seven million hospital admissions in the US estimated that 0.8% of all patients suffered from infection with *S. aureus*, corresponding to a total of nearly 300,000 patients in US hospitals in 2003. After controlling for confounders the annual impact in the US was estimated to be 2.7 million additional days in hospital, US\$9.5 billion excess costs, and at least 12,000

in-patient deaths.<sup>7</sup> Since the consequences of these infections are immense, effective prevention strategies are essential.

Traditionally, control of *S. aureus* has been focused on preventing cross-infection between patients, however, it has been shown repeatedly that a large proportion of nosocomial *S. aureus* infections originate from patients' own flora (non-pathogenic bacteria normally present on the patient).<sup>3,8-10</sup> Nasal carriage (presence in the nose) of *S. aureus* is now considered a well defined risk factor for subsequent infection in various groups of patients, including those on dialysis; with cirrhosis of the liver; undergoing surgery; and with intravascular devices or in intensive care.<sup>4,11</sup>

Three approaches to the elimination of *S. aureus* carriage are available: local application of antibiotics or antiseptics; administration of systemic antibiotics; and the harnessing of bacterial interference through active culture of a minimally-pathogenic strain of *S. aureus* (bacterial interference is the term given to the effect that different micro-organisms can have on each other when they are present simultaneously). This interference can result in partial or complete inhibition of one micro-organism - desired in this case - though sometimes activity may be increased. The first strategy, namely local application of antibiotics or antiseptics is the most common, for example mupirocin nasal ointment, applied twice daily for five days, is particularly highly used. Mupirocin can be used for the eradication of both meticillin sensitive and meticillin resistant *S. aureus*, although MRSA resistance for mupirocin has been shown.<sup>12</sup>

## Objectives

To determine whether mupirocin nasal ointment reduces rates of *S. aureus* infection in patients who are nasal carriers of *S. aureus*.

## Methods

### Criteria for considering studies for this review

#### Types of studies

Randomised controlled trials (RCTs) irrespective of language or publication status.

#### Types of participants

Studies of nasal carriers (identified by microbiological culture) of *S. aureus* (both meticillin-resistant and meticillin-sensitive) that are using hospital services (either

as inpatient or outpatient) were included. We included studies of patients from any population, gender and age.

### Types of interventions

Trials in which participants were randomly allocated intranasal mupirocin ointment or an alternative were included. Eligible control group treatments were placebo, no treatment or alternative topical treatment. We excluded studies that had systemic antibiotics or active colonisation as a comparator.

### Types of outcome measures

#### Primary outcomes

*S. aureus* infection rate - determined according to well-defined criteria (for example Centres for Disease Control (CDC) guidelines). The infection rate consists of the number of infected patients per study group. Infection caused by both meticillin-resistant and meticillin-sensitive *S. aureus* was included.

#### Secondary outcomes

Where reported, the following outcomes were recorded:

1. Time to infection.
2. Mortality.
3. Adverse events.
4. Infection rate caused by other micro-organisms than *S. aureus*

### Search methods for identification of studies

#### Electronic searches

We systematically searched the following electronic databases for relevant trial reports: Cochrane Wounds Group Specialised Register (Searched 28/5/08);

The Cochrane Central Register of Controlled Trials (CENTRAL, Issue 2 2008); Ovid MEDLINE (1950 to May Week 2 2008);

Ovid EMBASE (1980 to 2008 Week 21);

Ovid CINAHL (1982 to May Week 4 2008)

#### Search strategy for CENTRAL:

#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)

The Ovid MEDLINE search was combined with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision); Ovid format and the EMBASE and CINAHL searches were combined with the trial filters developed by the Scottish Intercollegiate Guidelines Network.<sup>13,14</sup>

Searches for unpublished trials and unfinished studies were conducted in: The System for Information on Grey Literature (SIGLE) Index to Theses (ASLIB Index) mRCT (<http://www.controlled-trials.com/mrct/>) ClinicalTrials.gov

No language or date restrictions were applied

## Searching other resources

Citation lists from the identified studies were searched. The authors, who are experts in this field with a long standing interest in this subject, searched their personal archives, including the abstracts from the following major scientific meetings from 1995 to 2007:

Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) European Society of Clinical Microbiology and Infectious Diseases (ESCMID) The Society for Healthcare Epidemiology of America (SHEA)

Unpublished trials and unfinished studies were identified by contacting researchers and the manufacturer of mupirocin (GlaxoSmithKline BV, Zeist, The Netherlands).

## Data collection and analysis

### Selection of studies

Titles and abstracts of studies retrieved by the search were independently assessed by two review authors (JK, MvR) for their eligibility for inclusion in the review. Studies that were clearly ineligible were discarded. Full versions of all potentially relevant studies were obtained and independently assessed for inclusion by two review authors. Disagreements were resolved by discussion or by reference to a third review author (MB). When more than one published report of a trial existed, all publications were considered

and maximal data were extracted however, only a single set of data was used in any meta-analysis. If data were missing from reports, then attempts were made to contact the study authors to obtain the missing information.

## Data extraction and management

Types of information and data extracted included the following:

1. Study authors.
2. Year of publication.
3. Country where study performed.
4. Study design (RCT).
5. Patient population.
6. Baseline characteristics of participants per treatment group (gender, age, and prevalence of co-morbidity such as diabetes).
7. Length, dose and timing of mupirocin treatment.
8. Methods used for identifying micro-organisms.
9. Criteria used for identifying infections / definition of infection used.
10. Withdrawals (per group with numbers and reasons).
11. Numbers of *S. aureus* nasal carriers in mupirocin and placebo treated patients.
12. Number of nosocomial *S. aureus* infections among mupirocin and placebo treated patients.
13. Healthcare setting.
14. Adverse events.

## Assessment of risk of bias in included studies

The quality of the included studies was assessed independently by JK and MvR without blinding to authorship or journal using the criteria described below. The results of the validity criteria were summarised in a table and taken into account in the conclusions and discussion.

### Quality checklist

All included trials were assessed for quality using a quality checklist that considered the following points:

#### 1. Allocation concealment

Trials were awarded the following grades for allocation concealment:

A = Adequate: a randomisation method described that would not allow an investigator/participant to know or influence an intervention group before an eligible participant entered the study.



B = Unclear: trial states that it is 'randomised', but no information on the method used is available.

C = Inadequate: inadequate method of randomisation used, such as alternate medical record numbers or unsealed envelopes; or any information in the study that indicated that investigators or participants could influence the intervention group.

## 2. Blinding

The following points were graded as 'yes' for present, 'no' for absent, and 'not stated' if the relevant information is not stated in the trial report:

- a. Blinding of investigators.
- b. Blinding of participants.
- c. Blinding of outcome assessor.
- d. Blinding of data analysis.

The above was considered not to have been blinded if the treatment group can be identified in > 20% of participants because of any side effects of the treatment.

## 3. Intention-to-treat analysis:

This evaluated whether participants were analysed in the groups to which they were originally randomised, and was graded as:

Yes - specifically stated by authors that intention-to-treat analysis was undertaken, and this was confirmed on study assessment.

Yes - not specifically stated, but confirmed on study assessment.

No - not reported, and lack of intention-to-treat analysis confirmed on study assessment. (Patients who were randomised were not included in the analysis because they did not receive the study intervention, they withdrew from the study or were not included because of protocol violation)

No - stated, but not confirmed upon study assessment

Not stated

## 4. Completeness of follow up

Percentage of participants excluded or lost to follow up was recorded.

## Data synthesis

Primary and secondary outcomes of the studies were analysed for each study individually, and, where appropriate combined across studies.

Infection rates and mortality were expressed as relative risk (RR) with 95% confidence intervals (CI). In the first instance, data from all studies were pooled in a forest plot using the random-effects model. Levels of heterogeneity were analysed using the chi-square test and the  $I^2$  statistic.<sup>15,16</sup> Values of  $I^2$  over 50% indicate a substantial level

of heterogeneity. If heterogeneity over 50% was detected the studies were presented in a narrative summary. It was planned to analyse time to event data as hazard ratios, pooling where appropriate.

#### Subgroup analysis and investigation of heterogeneity

Subgroup analyses were planned where obvious differences existed between the included study groups; these differences might have existed in the following variables: age, healthcare setting (for example surgical compared with non surgical), or length, timing, and dose of treatment. The performed subgroup analyses were based on healthcare setting, i.e. subgroup analyses were performed for surgical patients and for dialysis patients. No other subgroup analyses were performed because no obvious differences existed in age, or length, timing, and dose of treatment.

## Results

### Description of studies

#### Results of the search

The search resulted in 217 hits. 193 of these were excluded after reading the abstracts. Full-text assessment of 24 potentially eligible papers identified 9 eligible RCTs reported in 10 publications (see Characteristics of included studies).<sup>17-26</sup> Twelve papers did not meet the inclusion criteria (see Characteristics of excluded studies).<sup>27-38</sup>

#### Included studies

Nine RCTs were included in this review.

#### Patient populations

The nine included trials described different patient populations.<sup>17-26</sup> Four trials<sup>18,20,21,24</sup> described surgical patients (cardiac, orthopaedic, general, gynaecological or neurological surgery), three trials described dialysis patients<sup>17,22,23</sup> (two trials of continuous ambulatory peritoneal dialysis<sup>22,23</sup> (CAPD) and one haemodialysis<sup>17</sup>), one trial non surgical patients<sup>26</sup> and one trial confined itself to people colonised with MRSA<sup>19</sup>. The mean age of patients treated with mupirocin varied from 50.7 years to 82.0 years.<sup>19,24</sup> In the control group the mean age ranged between 48.0 and 74.0 years.<sup>19,23</sup> Seven studies reported that no statistically significant differences existed between the patient characteristics at baseline, i.e. age, sex and underlying disease, between the treatment and control group.<sup>17-20,22,23,26</sup> Konvalinka found COPD was more prevalent in the mupirocin group ( $p < 0.01$ ) and Perl noted that patients receiving placebo were more likely to have

had a renal disease ( $p=0.04$ ).<sup>21,24</sup> The number of included patients varied significantly between the included studies (Characteristics of included studies), i.e. Pérez-Fontan included 11 patients in the mupirocin treatment group, while Wertheim included 793 patients in this group. Garcia, Kalmeijer and Perl included both *S. aureus* nasal carriers and non-carriers.<sup>28,20,24</sup> Data for carriers only were extracted for this review. The other trials included carriers only.

In total, 1690 patients with nasal carriage were treated with mupirocin and 1706 patients were allocation to control groups, i.e. they received placebo, no treatment or nasal neomycin.

## Interventions

In all 9 trials mupirocin ointment was given intranasally to *S. aureus* carriers. In the surgical trials patients received mupirocin pre-operatively.<sup>18,20,21,24</sup> In seven trials control patients were treated with a placebo.<sup>17,19,20,21,22,24,26</sup> Garcia gave the control group no treatment. Pérez-Fontan compared mupirocin with nasal neomycin. The application of mupirocin varied from twice daily for 5 days in surgical patients to thrice daily for two weeks and subsequent three times weekly for a total of nine months in hemodialysis patients and twice daily for 5 days and every four weeks for a maximum of 18 months in CAPD patients.

## Outcomes

The primary outcome of *S. aureus* infection rate was reported in all nine papers. The secondary outcomes reported varied between the papers. Time to infection was described in one paper.<sup>26</sup> Mortality was described in five papers.<sup>17,21,22,24,26</sup> Six papers described the adverse events<sup>17,21-24,26</sup> and the infection rate caused by other micro-organisms than *S. aureus* was described in four papers<sup>21-24</sup>.

## Excluded studies

Twelve papers did not meet the inclusion criteria (Characteristics of excluded studies). The main reasons for exclusion were that the research described was not an RCT; that the study evaluated skin rather than nasal mupirocin, that the study reported elimination rather than infection data or that the intervention involved a combination of several interventions.

## Risk of bias in included studies

The methodological quality of the included studies varied from high to low quality. Seven out of nine studies were double-blind RCTs<sup>17,19-22,24,26</sup>; and in four out of these all other quality indicators, i.e. blinding, intention-to-treat, description of loss of follow-up, were also met<sup>20,21,24,26</sup>. These four studies were classified as studies of high quality. Although

not specified in the protocol we judged studies to be of high quality if they concealed allocation, undertook blinding and an ITT analysis. Two out of nine studies were of low quality.<sup>18,23</sup> Although not specified in the protocol we judged studies to be of low quality if they did not conceal allocation or if the method of allocation was unclear, no blinding was achieved or reported and an ITT analysis was not reported or confirmed. The allocation concealment of Garcia was inadequate because they used consecutive numbers, patients with even numbers were allocated to the treatment group and patients with odd numbers were control patients. In this study no placebo was used, so the study was not double-blind. A sensitivity analysis removing the unblinded study of Garcia was undertaken, although this was not pre specified in the protocol. Pérez-Fontan did not describe any blinding. This trial was analysed separately for all outcomes because they compared mupirocin with neomycin ointment, whilst all the other studies compared mupirocin with placebo or no treatment. Seven of nine studies performed an a priori sample size calculation based on the estimated infection rate in the control group and the aimed reduction rate in the treatment group (Figures 1 and 2).<sup>18-22,24,26</sup>

## Effects of interventions

In total, 1690 patients with nasal carriage were treated with mupirocin and 1706 patients were control patients, i.e. they received placebo, no treatment or nasal neomycin.

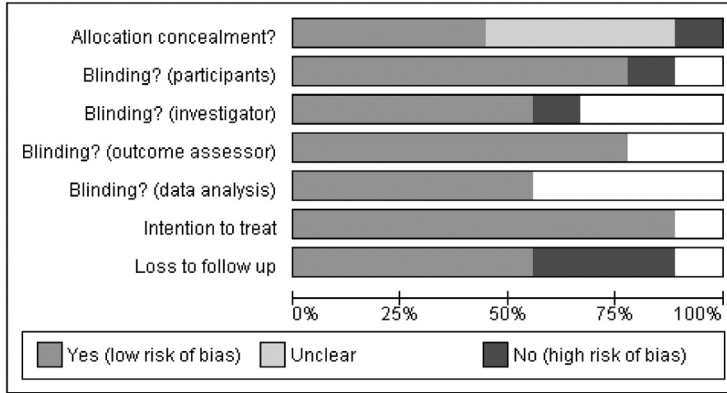
### Comparison 1: Mupirocin compared with placebo or no treatment

Primary outcome *S. aureus* infection rate (8 RCTs, 3374 participants)

In seven studies<sup>17,19-22,24,26</sup> control patients were treated with placebo and in one study control patients did not receive any treatment<sup>18</sup>. Harbarth reported the infection rate caused by meticillin-resistant *S. aureus*, while the other studies reported the overall *S. aureus* infection rate caused by both meticillin-sensitive and meticillin-resistant *S. aureus*.

Looking at individual study results, two trials<sup>22,24</sup> showed a significant effect of mupirocin on reducing the *S. aureus* infection rate, whilst the remaining trials found no significant difference between mupirocin and control. Pooling the eight studies ( $I^2 = 3\%$ ) demonstrated a statistically significant reduction in *S. aureus* infection rate associated with mupirocin (RR 0.55, 95% CI 0.43–0.70, fixed-effect) (Analysis 1.1). Whilst there was little or no statistical heterogeneity in this analysis, the trials included diverse patient populations comprising surgical patients, non-surgical patients and both haemodialysis and CAPD patients. This diversity of patient populations was also demonstrated in the range of types of *S. aureus* infections reported (bacteraemia, exit-site infections, episodes of peritonitis, respiratory tract infections, skin infections, surgical site infections (SSI) and urinary tract infections).

Pooling together only those studies which were judged to be of high quality<sup>20,21,24,26</sup>, (i.e. studies meeting all quality criteria), also demonstrated a statistically significant



**Figure 1.** Methodological quality graph: review authors' judgements about each methodological quality item presented across all included studies.

	Allocation concealment?	Blinding? (participants)	Blinding? (investigator)	Blinding? (outcome assessor)	Blinding? (data analysis)	Intention to treat	Loss to follow up
Boelaert 1989	?	+		+		+	+
Garcia 2003	-	-	-			+	+
Harbarth 1999	?	+	+	+	+	+	-
Kalmeijer 2002	+	+	+	+	+	+	-
Konvalinka 2006	+	+	+	+	+	+	-
Mup Study Group 1996	?	+		+		+	+
Perl 2002	+	+	+	+	+	+	+
Pérez-Fontan 1992	?						
Wertheim 2004b	+	+	+	+	+	+	+

**Figure 2.** Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

reduction in *S. aureus* infection rate associated with mupirocin (RR 0.69, 95% CI 0.47–1.00, fixed-effect) (Analysis 1.2).

We pre-specified in the protocol our plans to investigate whether there were differential effects of mupirocin in different groups, particularly surgical and non-surgical patients. Four trials were confined to surgical patients and involved 686 patients in the treatment and 686 in the control group.<sup>18,20,21,24</sup> These trials were pooled ( $I^2 = 0\%$ , fixed-effect) and showed a statistically significant reduction of the nosocomial *S. aureus* rate (RR 0.55, 95% CI 0.34–0.88) (Analysis 2.1). This significant reduction was not affected by the exclusion of the low quality, non-blinded study<sup>18</sup> (RR 0.56, 95% CI 0.34–0.91) (Analysis 2.2).

When the analysis was confined to the outcome of *S. aureus* surgical site infection (this analysis was not pre-specified and therefore can only be described as exploratory) there was no longer a statistically significant effect of mupirocin however the comparison probably lacks statistical power (4 trials, 688 patients treated with mupirocin, 686 control patients, RR 0.63, 95% CI 0.38–1.04) (Analysis 2.3).

A further subgroup analysis in dialysis patients (which was not pre-specified in the protocol and can only be regarded as exploratory) 2 trials<sup>17,22</sup> (n = 151 mupirocin, 151 control) showed a statistically significant reduction in the overall *S. aureus* infection rate associated with mupirocin (fixed-effect,  $I^2 = 0\%$ , RR 0.44, 95% CI 0.32–0.62) (Analysis 3.1).

## Comparison 2: Mupirocin compared with neomycin

Primary outcome *S. aureus* infection rate (1 RCT, 22 participants)

Pérez-Fontan compared mupirocin with topical neomycin.<sup>23</sup> During the study period one catheter-related infection was caused by *S. aureus* in the mupirocin group (n=12) and two *S. aureus* infections were identified in the neomycin group (n=10); one case of peritonitis and one case of catheter-related infection. There was no statistically significant difference in rates of *S. aureus* infection between these two treatment groups, however this study was underpowered to detect anything other than extremely large treatment effects (RR 0.42, 95% CI 0.04–3.95) (Analysis 4.1).

## Comparisons 1 and 2: Secondary outcomes

Time to infection

Wertheim described the median time between treatment and development of *S. aureus* infection.<sup>26</sup> Analysis of time to infection of patients from the intention-to-treat analysis showed no difference between the groups (mupirocin: 25 days, placebo: 12 days,  $p=0.28$  in Mann-Whitney test). This result should be treated with caution as the authors did not undertake an appropriate analysis for time to event-type data (i.e. log-rank test or Cox proportional hazards regression model).

### Mortality

Five trials reported mortality.<sup>17,21,22,24,26</sup> However, Perl reported mortality in both carriers and non-carriers, separate data on carriers were not available, so this study was not included in the mortality analysis. There was no statistically significant difference in mortality between treated and untreated carriers (RR 0.91, 95% CI 0.64–1.31) (Analysis 5.1). Only one study described whether mortality was from any cause or due to an infection.<sup>21</sup> In the placebo group two of the five deaths were from an infection, i.e. one death was related to a surgical site infection caused by *S. aureus* and one to pneumonia escalating to multi-organ failure. None of the four deaths in the mupirocin group were due to infections. Perl stated that no deaths were attributed to mupirocin therapy.

### Adverse Events

Six studies reported data about adverse events due to mupirocin.<sup>17,21-24,26</sup> Boelaert and Konvalinka reported that no side effects occurred in any of the 35 and 257 participants, respectively.<sup>17,21</sup> Pérez-Fontan described slight nasal pruritus and an unpleasant smell immediately after administration of mupirocin (number of patients was not described).<sup>23</sup> In the trial of the Mupirocin Study Group side effects were infrequent and mild, being equally common in treatment and placebo groups, and only a few patients were unable to tolerate the ointment (number of patients was not described).<sup>22</sup> Perl reported the number of adverse events in both carriers and non-carriers.<sup>24</sup> Data for carriers only were not available. 97 of the 2012 patients in the mupirocin group (4.8%) and 96 of the 2018 patients in the placebo group (4.8%) showed side effects such as rhinorrhea and itching at the application site. Five patients (one treated with mupirocin and four with placebo) withdrew from the study because of adverse events such as nasal burning, nasal bleeding, and headache. Perl stated that no deaths were attributed to mupirocin therapy. Wertheim mentioned 4 patients with an itching or burning sensation of the nose, of which 2 patients received mupirocin (n=793) and 2 placebo (n=809). No serious adverse events were observed or reported.

### Infection rate caused by micro-organisms other than *S. aureus*

Four studies described the infection rate caused by micro-organisms other than *S. aureus*.<sup>21-24</sup> Data from the Mup Study Group, Perl and Konvalinka were pooled.<sup>21,22,24</sup> Pérez-Fontan was analysed separately because the control group was treated with neomycin.<sup>23</sup>

Pooling three trials showed significantly more infections caused by other micro-organisms in the mupirocin group (RR 1.38, 95% CI 1.11–1.72) (Analysis 6.1).<sup>21,22,24</sup> These infections were caused by both gram-positive and gram-negative micro-organisms, i.e. *CNS*, *Streptococcus pneumoniae*, *Enterobacter cloacae*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*. There was no difference between both treatment groups

in prevalence of gram-positive or gram-negative micro-organisms (RR 0.88, 95% CI 0.55–1.41 and RR 1.65, 95% CI 0.78–3.47) (Analysis 6.2; Analysis 6.3).

Pérez-Fontan found that 7 of the 8 infections in the mupirocin group (n=12) were caused by other micro-organisms compared with 3 of the 5 infections in the neomycin group (n=10) (RR 1.33, 95% CI 0.64–2.79) (Analysis 7.1).<sup>23</sup>

## Discussion

### Reduction of *S. aureus* infections by application of mupirocin

Previously, several reviews in this area have been performed but these included both carriers and non-carriers of *S. aureus*.<sup>39-42</sup> Strippoli evaluated the use of different antimicrobial approaches to prevent peritonitis in peritoneal dialysis patients.<sup>41</sup> Nasal mupirocin compared with placebo significantly reduced the exit-site and tunnel infection rate but not peritonitis rate. Kallen found no significant effect of mupirocin on the surgical site infection rate after general surgery.<sup>39</sup> However, in non general surgery (cardiothoracic surgery, orthopedic surgery, neurosurgery) a significant reduction was found. In contrast, Trautmann concluded that mupirocin prophylaxis did not reduce the *S. aureus* surgical site infection rate in patients undergoing orthopedic, gastrointestinal, and cardiothoracic surgery. Laupland reported that prophylactic treatment of patients with intranasal mupirocin in large trials did not lead to a significant reduction in the overall rate of infections.<sup>40</sup> However, subgroup analyses and several small studies revealed lower rates of *S. aureus* infection among selected populations of patients with nasal carriage treated with mupirocin. Our review is the first one that included nasal *S. aureus* carriers only. Nasal mupirocin ointment reduced the overall *S. aureus* infection rate in nasal carriers. This analysis included surgical patients, non surgical patients and dialysis patients. Subgroup analysis revealed a significant effect in dialysis patients and surgical patients. When the surgical site infections were analysed as primary outcome in surgical patients, no statistically significant effect was found.

### Secondary outcomes

Wertheim did not find a significant difference in number of infections between non surgical patients treated with mupirocin or placebo, but they reported a significantly longer time to infection in the per-protocol analysis of patients treated with mupirocin (p=0.02). So, possibly mupirocin protects patients from getting infected for the first period after treatment. However, this outcome was only reported in one study and no significance was found in their intention-to-treat analysis, although they did not use the correct statistical analysis.



The mortality between mupirocin and control groups was not significantly different and no serious adverse events were mentioned. Analysis of the infection rate caused by micro-organisms other than *S. aureus* showed significant more infections caused by other micro-organisms in the mupirocin group (RR 1.38, 95% CI 1.11–1.72). It is possible that infections with other micro-organisms replace the infections caused by *S. aureus*. Maybe by reducing the *S. aureus* carriage, it makes someone more susceptible to other micro-organisms. More research in this field is required.

### Development of resistance

Up till now routine use of mupirocin has not been applied in many hospitals, mainly because due to concern about the development of mupirocin resistance and the absence of convincing evidence that mupirocin reduces the infection rate. Resistance has been observed when mupirocin was used for prolonged periods, especially when it was used as a skin ointment.<sup>43</sup> However, Fawley observed no trend towards increasing prevalence of mupirocin resistance during a 4-year study period with mupirocin use in surgical patients.<sup>44</sup> In our review, five studies reported that no development of resistance to mupirocin in the isolated *S. aureus* strains was found during the study period.<sup>17,20,21,23,26</sup> During the 4-year study Perl found 6 of the 1021 tested *S. aureus* isolates were resistant to mupirocin.<sup>24</sup> In the study of Harbarth 4 strains acquired low-level mupirocin resistance during mupirocin therapy.<sup>19</sup> The Mup Study Group showed that low-level and high-level resistance occurred in both groups, but there was no evidence that treatment with mupirocin resulted in colonisation with resistant *S. aureus*.<sup>22</sup> It can be concluded that mupirocin resistance will not be a problem after short-term intranasal use in surgical or dialysis patients.

### Endogenous infections

Mupirocin is applied to prevent patients infecting themselves with endogenous bacteria and therefore, although this was not prespecified in the protocol, it is interesting to know how many of the infections were caused by the endogenous strain. Included studies mentioned that in about 80% of the infections the *S. aureus* strain isolated from the nares was identical to that isolated from the infected site.<sup>17,24,26</sup> They did not describe the number of endogenous infections in the mupirocin and placebo groups separately, so it was impossible to analyse the difference in the number of endogenous infections between both groups. Probably, in both the mupirocin and control group there will be a comparable number of infections caused by strains from the environment, for example from the health care workers in the operation room, while a higher number of endogenous infections is expected to be found in the control group. Kalmeijer described fewer endogenous infections in the mupirocin group, but this was not statistically significant (RR 0.19, 95% CI 0.02–1.62). However, in this analysis both carriers and

non-carriers were included. When patients treated with mupirocin develop an infection with the nose strain, it can be assumed that mupirocin treatment failed. Nasal carriage is eliminated in about 80% of patients treated with mupirocin and 30% in those treated with placebo.<sup>20,21,24</sup> The number of endogenous infections was not prespecified in our protocol, but should be considered in future studies/reviews.

## Limits

There are several limitations of the included studies and the review. The quality of the studies varied from high to low quality, i.e. only four of the nine included studies were studies of high quality.<sup>20,21,24,26</sup> Second, the primary outcomes were reported by all studies, but there was limited information for some of the secondary outcomes, i.e. time to infection was described in one of the nine included studies<sup>26</sup>, mortality in 5 studies<sup>17,21,22,24,26</sup>, adverse events in 6 studies<sup>17,21-24,26</sup> and the infection rate caused by other micro-organisms than *S. aureus* in 4 studies<sup>21-24</sup>. Third, the possibility of publication bias was not assessed in the review. It is likely that studies without a significant reduction of the infection rate are harder to publish than studies with a significant effect. Fourth, although no statistical heterogeneity was found, a lot of clinical heterogeneity existed between patient populations of the included studies. Furthermore, we assessed the *S. aureus* infection rate as primary outcome, i.e. both meticillin-susceptible and meticillin-resistant *S. aureus* infections were included. Only one study assessed the number of meticillin-resistant infections<sup>19</sup>, so no subgroup analysis could be performed to study the effect of mupirocin on the infection rate caused by meticillin-resistant *S. aureus* in patients with nasal carriage of this variant of *S. aureus*.

## Authors' conclusions

### Implications for practice

Up till now routine use of mupirocin has not been applied in many hospitals, mainly due to concern about the development of mupirocin resistance and the absence of convincing evidence that mupirocin reduces the infection rate. Short-term use of intranasal mupirocin ointment does not seem to be associated with resistance. Intranasal mupirocin should be considered for use in proven nasal carriers of *S. aureus* in hospitalised surgical, dialysis and non surgical patient groups at risk of infection.

### Implications for research

This review shows that the effectiveness of mupirocin is related to carriers only. Recent technological advances in rapid diagnostics have provided the ability to detect nasal carriage of *S. aureus* within hours rather than days, which makes it possible to treat

nasal carriers rapidly.<sup>45,46</sup> At the moment, rapid tests that can discriminate MRSA from MSSA are being evaluated. Application of these tests will result in timely, appropriate prescription of anti microbials (both local and systemic).

## Acknowledgements

The authors would like to thank the Cochrane Wounds Group Editors (David Margolis, Joan Webster and Gill Worthy) and referees (Allen Holloway, David Leaper, Barbara Postle, Rachel Richardson, Mark Rodgers and Jack Tweed) and copy editor (Elizabeth Royle) for their comments on the protocol and the review.

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### Other published versions of this review

- van Rijen MML, Bonten M, Wenzel RP, Kluytmans JAJW. Intranasal mupirocin for reduction of *Staphylococcus aureus* infections in surgical patients with nasal carriage: A systematic review. *J Antimicrob Chemother* 2008; 61(2):254-61.

# Characteristics of studies

## Characteristics of included studies

### Boelaert 1989

<b>Methods</b>	Double-blind, randomised controlled trial
<b>Participants</b>	Hemodialysis patients. All carriers. Mupirocin: 17. Placebo: 18. No significant difference between both groups.
<b>Interventions</b>	Mupirocin or placebo. Thrice daily for 2 weeks and subsequent 3 times weekly for a total of 9 months.
<b>Outcomes</b>	S. aureus infection rate Mortality Adverse events

### Risk of bias table

Item	Judgement	Description
Allocation concealment?	Unclear	B - Unclear
Blinding? (participants)	Yes	
Blinding? (investigator)	Unclear	
Blinding? (outcome assessor)	Yes	
Blinding? (data analysis)	Unclear	
Intention to treat	Yes	not reported but confirmed
Loss to follow up	Yes	Mupirocin:41 Placebo:17

### Garcia 2003

<b>Methods</b>	Randomised, prospective trial
<b>Participants</b>	Cardiothoracic patients. Both carriers and non-carriers. Mupirocin: 31 carriers, Placebo: 34 carriers. No significant difference between both groups.
<b>Interventions</b>	Mupirocin twice daily for 5 days. Controls received no treatment.
<b>Outcomes</b>	S. aureus infection rate.

### Risk of bias table

Item	Judgement	Description
Allocation concealment?	No	C - Inadequate
Blinding? (participants)	No	
Blinding? (investigator)	No	
Blinding? (outcome assessor)	Unclear	
Blinding? (data analysis)	Unclear	
Intention to treat	Yes	not reported but confirmed by author
Loss to follow up	Yes	Mupirocin:13 Control:15



## Harbarth 1999

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<b>Methods</b>	Double-blind, randomised controlled trial
<b>Participants</b>	Patients colonised with MRSA. Mupirocin: 48 Placebo: 50. No significant difference between both groups.
<b>Interventions</b>	Mupirocin or placebo. Twice daily for 5 days.
<b>Outcomes</b>	S. aureus infection rate.

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### Risk of bias table

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<b>Item</b>	<b>Judgement</b>	<b>Description</b>
Allocation concealment?	Unclear	B - Unclear
Blinding? (participants)	Yes	
Blinding? (investigator)	Yes	
Blinding? (outcome assessor)	Yes	
Blinding? (data analysis)	Yes	
Intention to treat	Yes	reported and confirmed
Loss to follow up	No	

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## Kalmeijer 2002

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<b>Methods</b>	Double-blind, randomised controlled trial
<b>Participants</b>	Orthopedic surgery patients. Both carriers and non-carriers. Mupirocin: 95 carriers. Placebo: 86 carriers. No significant difference between both groups.
<b>Interventions</b>	Mupirocin or placebo. Twice daily from the day of admission (day before surgery) to the hospital until the day of surgery.
<b>Outcomes</b>	S. aureus infection rate.

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### Risk of bias table

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<b>Item</b>	<b>Judgement</b>	<b>Description</b>
Allocation concealment?	Yes	A - Adequate
Blinding? (participants)	Yes	
Blinding? (investigator)	Yes	
Blinding? (outcome assessor)	Yes	
Blinding? (data analysis)	Yes	
Intention to treat	Yes	reported and confirmed
Loss to follow up	No	

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## Konvalinka 2006

<b>Methods</b>	Double-blind, randomised controlled trial
<b>Participants</b>	Elective cardiac surgery patients. All carriers. Mupirocin: 130. Placebo: 127. Only COPD was more prevalent in the mupirocin group ( $p < 0.01$ )
<b>Interventions</b>	Mupirocin or placebo. Twice daily for 7 days, before surgery.
<b>Outcomes</b>	<i>S. aureus</i> infection rate. Mortality. Adverse events. Infection rate caused by other micro-organisms than <i>S. aureus</i> .

### Risk of bias table

Item	Judgement	Description
Allocation concealment?	Yes	A - Adequate
Blinding? (participants)	Yes	
Blinding? (investigator)	Yes	
Blinding? (outcome assessor)	Yes	
Blinding? (data analysis)	Yes	
Intention to treat	Yes	reported and confirmed
Loss to follow up	No	

## Mup Study Group 1996

<b>Methods</b>	Double-blind, randomised controlled trial
<b>Participants</b>	CAPD patients. All carriers. Mupirocin: 134. Placebo: 133. No significant difference between both groups.
<b>Interventions</b>	Mupirocin or placebo. Twice daily for 5 days every 4 weeks, for maximal 18 months.
<b>Outcomes</b>	<i>S. aureus</i> infection rate. Mortality. Adverse events. Infection rate caused by other micro-organisms than <i>S. aureus</i> .
<b>Notes</b>	This study was sponsored by the manufacturers of mupirocin (SmithKline Beecham, Baxter Health Care)

### Risk of bias table

Item	Judgement	Description
Allocation concealment?	Unclear	B - Unclear
Blinding? (participants)	Yes	
Blinding? (investigator)	Unclear	
Blinding? (outcome assessor)	Yes	
Blinding? (data analysis)	Unclear	
Intention to treat	Yes	reported and confirmed
Loss to follow up	Yes	Mupirocin:1 Placebo:1

## Perl 2002

<b>Methods</b>	Double-blind, randomised controlled trial
<b>Participants</b>	General, gynaecologic, neurologic and cardiothoracic. patients. Both carriers and non-carriers. Mupirocin: 430 carriers. Placebo: 439 carriers. Patients that received placebo were more likely to have had renal disease (p=0.04).
<b>Interventions</b>	Mupirocin or placebo. Twice daily for up to 5 days, before the operation.
<b>Outcomes</b>	S. aureus infection rate. Mortality. Adverse events. Infection rate caused by other micro-organisms than S. aureus.

### Risk of bias table

Item	Judgement	Description
Allocation concealment?	Yes	A - Adequate
Blinding? (participants)	Yes	
Blinding? (investigator)	Yes	
Blinding? (outcome assessor)	Yes	
Blinding? (data analysis)	Yes	
Intention to treat	Yes	reported and confirmed
Loss to follow up	Yes	Mupirocin 10.4 Placebo 13.2

## Pérez-Fontan 1992

<b>Methods</b>	Randomised, prospective trial.
<b>Participants</b>	CAPD patients. All carriers. Mupirocin: 11. Neomycin: 8. No significant difference between both groups.
<b>Interventions</b>	Mupirocin or Neomycin. Mupirocin thrice daily for 7 days. Neomycin sulphate thrice daily for 7 days.
<b>Outcomes</b>	S. aureus infection rate. Adverse events. Infection rate caused by other micro-organisms than S. aureus.

### Risk of bias table

Item	Judgement	Description
Allocation concealment?	Unclear	B - Unclear
Blinding? (participants)	Unclear	
Blinding? (investigator)	Unclear	
Blinding? (outcome assessor)	Unclear	
Blinding? (data analysis)	Unclear	
Intention to treat	Unclear	
Loss to follow up	Unclear	

## Wertheim 2004b

<b>Methods</b>	Double-blind, randomised controlled trial
<b>Participants</b>	Nonsurgical patients. All carriers. Mupirocin: 793. Placebo: 809. No significant difference between both groups.
<b>Interventions</b>	Mupirocin or placebo. Twice daily for 5 days, started 1 to 3 days after admission.
<b>Outcomes</b>	<i>S. aureus</i> infection rate. Time to infection. Mortality. Adverse events.

### Risk of bias table

Item	Judgement	Description
Allocation concealment?	Yes	A - Adequate
Blinding? (participants)	Yes	
Blinding? (investigator)	Yes	
Blinding? (outcome assessor)	Yes	
Blinding? (data analysis)	Yes	
Intention to treat	Yes	reported and confirmed
Loss to follow up	Yes	Mupirocin: 9.7 Placebo:8.3

## Characteristics of excluded studies

### Critchley 2006

**Reason for exclusion:** Not a trial.

### Di Filippo 1999

**Reason for exclusion:** No data about carriers. Author could not be contacted for additional information.

### Klaus 2002

**Reason for exclusion:** This was an abstract on the 5th European Peritoneal Dialysis Meeting in Brussels, Belgium, 4-7 May 2002. Family members of CAPD patients with nasal carriage were treated with mupirocin or placebo. It is unclear whether patients with nasal carriage were treated with mupirocin and how many carriers in both treatment groups (mupirocin/placebo) developed an infection caused by *S. aureus*. This abstract has not resulted in a paper yet and the author could not be contacted for additional information.

### Leigh 1993

**Reason for exclusion:** Not health-care related.

### Martin 1999

**Reason for exclusion:** No description of infections. Only data about eradication.

### Mody 2003

**Reason for exclusion:** Not health-care related.

## Niwa 1999

**Reason for exclusion:** No data about carriers. Author could not be contacted for additional information.

## Raz 1996

**Reason for exclusion:** Not health-care related.

## Simor 2007

**Reason for exclusion:** Combination of mupirocin treatment with oral antibiotics.

## Sit 2007

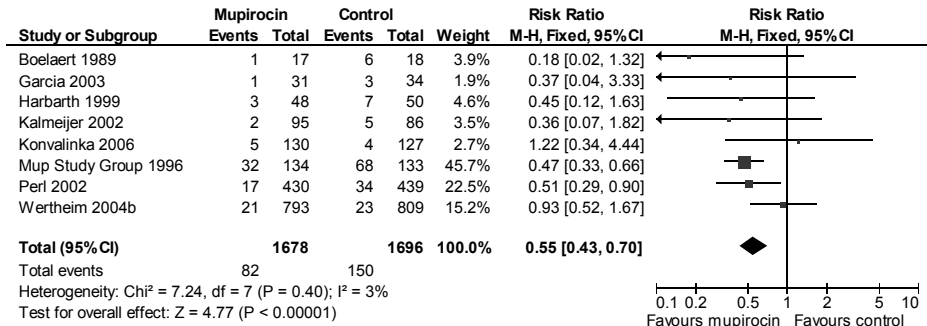
**Reason for exclusion:** No data about carriers. Author contacted for additional information.

## Suzuki 2003

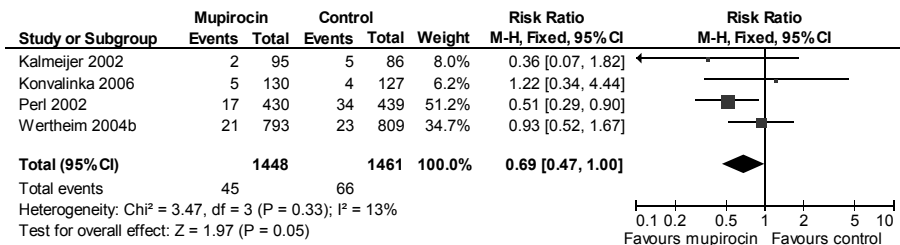
**Reason for exclusion:** No data about carriers. Author contacted for additional information, but no reply was received.

## Wasielewski 2003

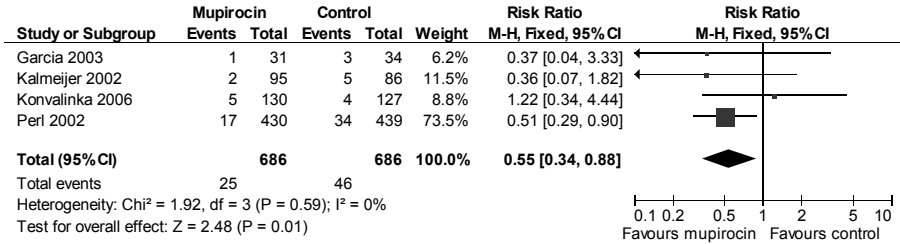
**Reason for exclusion:** Not a trial. Describes the results of the trial by Perl et al.



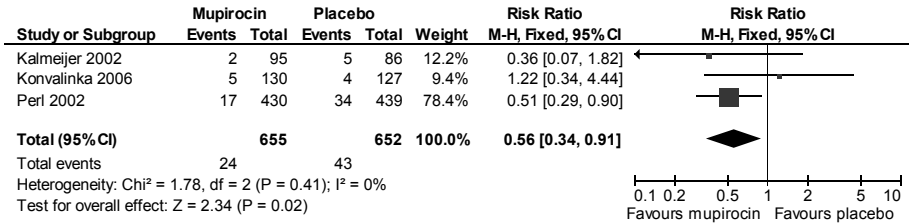
**Figure 1.1.** Nosocomial *S. aureus* infections among patients with *S. aureus* nasal carriage.



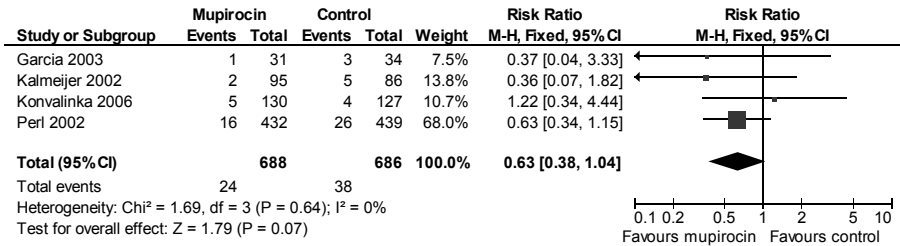
**Figure 1.2.** Nosocomial *S. aureus* infections among patients with *S. aureus* nasal carriage (High quality studies).



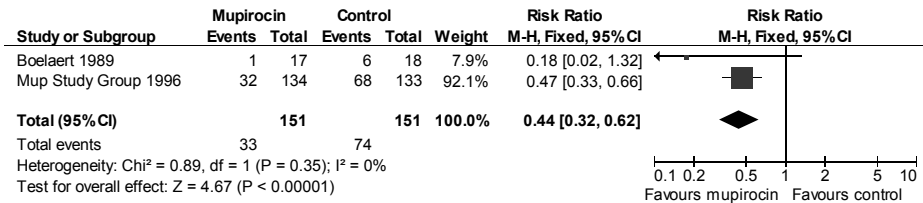
**Figure 2.1.** Nosocomial *S. aureus* infections among surgical patients with *S. aureus* nasal carriage.



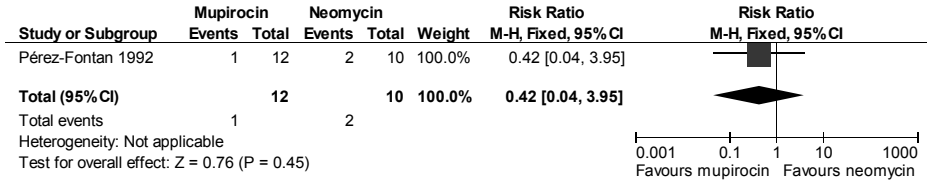
**Figure 2.2.** Nosocomial *S. aureus* infections among surgical patients with *S. aureus* nasal carriage (High quality studies).



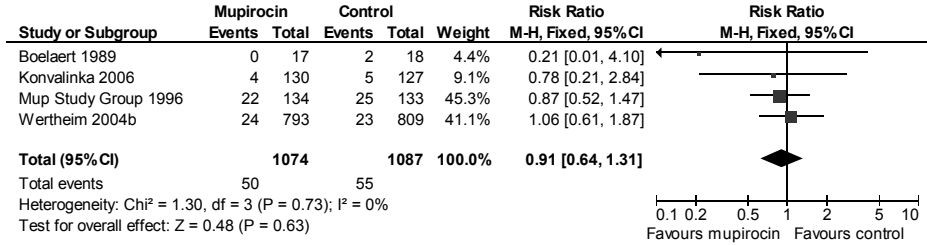
**Figure 2.3.** Nosocomial *S. aureus* surgical site infection.



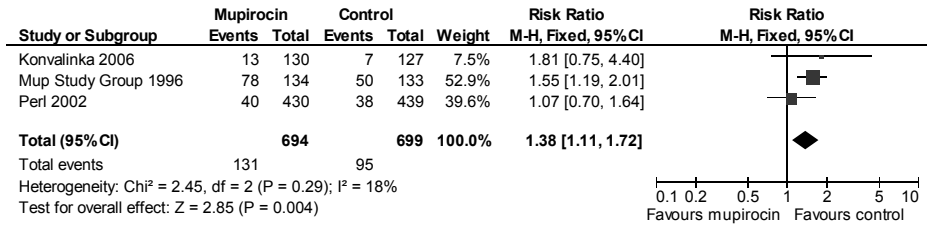
**Figure 3.1.** Nosocomial *S. aureus* infections among dialysis patients with *S. aureus* nasal carriage.



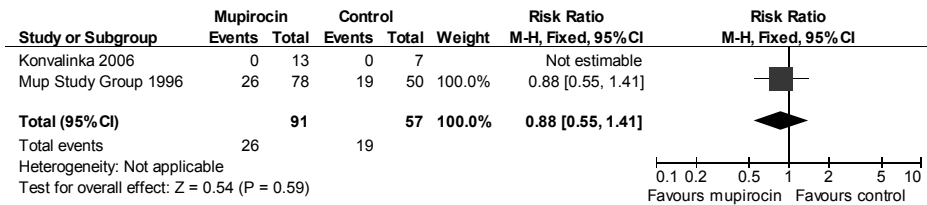
**Figure 4.1.** Nosocomial *S. aureus* infections among CAPD patients: a comparison of mupirocin to neomycin.



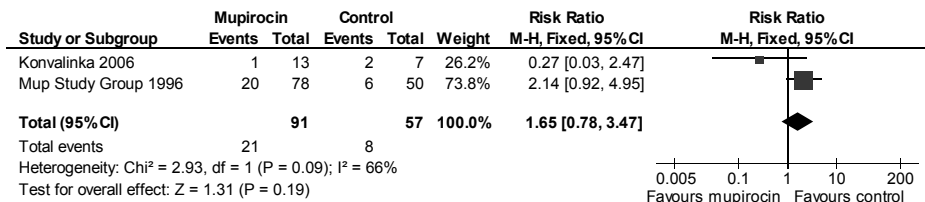
**Figure 5.1.** Mortality among patients with *S. aureus* nasal carriage



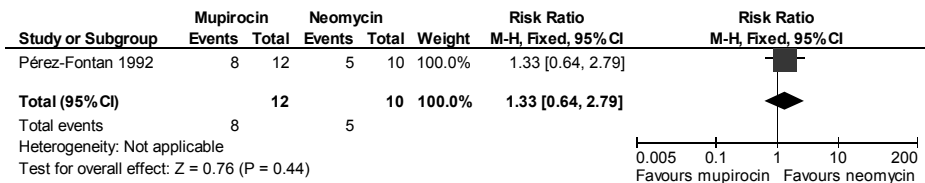
**Figure 6.1.** Infection rate caused by other micro-organisms than *S. aureus*.



**Figure 6.2.** Infection rate caused by other gram-positive micro-organisms than *S. aureus*.



**Figure 6.3.** Infection rate caused by gram-negative micro-organisms.



**Figure 7.1.** Infection rate caused by other micro-organisms than *S. aureus*: a comparison of mupirocin to neomycin.