Systematic Review of Surgical Site Infections

in Cardiac and Orthopaedic Surgery

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Background

This project provides the Health Quality and Safety Commission New Zealand (the Commission) with a systematic literature review and meta-analysis on interventions aimed at reducing Gram-positive surgical site infections (SSIs) in orthopaedic and cardiac surgeries. While SSIs due to *Staphylococcus aureus* are the Commission's prime interest, the review has also included other Gram-positive organisms. We built on the Schweizer et al.[1] meta-analysis (the base reference) provided by Commission by identifying appropriate literature published between January 2011 and December 2015. The methods and reporting has been aligned with those used in the base reference, with particular emphasis given to the direction and feedback provided by the Commission.

Introduction

Surgical site infections (SSIs) are the second most common cause of nosocomial infection. SSIs are associated with prolonged hospital stay and increased re-hospitalisation and mortality rates, as well as additional healthcare costs.[2] Patient-related outcomes, such as quality of life, are also negatively impacted by SSIs due to delayed healing, discomfort, loss of productivity and an increased need for additional medical interventions, such as surgery.

In the Australian and New Zealand healthcare systems, between 2-13% of hospitalised patients can expect a healthcare-acquired infection, of which 20% were SSIs.[3, 4] In Australia, healthcare-acquired infection impacts 180,000 patients and accounts for 2 million bed days each year. The costs associated with these incidents are significant; in 2003, the cost of nosocomial infection to the New Zealand healthcare system was estimated at NZ$85.26 million,[5] and the costs associated with only 126 SSIs in one Australian state were recently reported to be in excess of AU$5 million.[6]

SSIs following cardiac and orthopaedic surgery are of particular interest and like many SSIs are thought to be preventable.[1] Sternal wound infections, arising from open-heart surgery, occur infrequently, in approximately 1-4% of patients, but are associated with severe outcomes, including 15 to 40% mortality.[7, 8] SSIs following

total joint replacement procedures are also uncommon (1 to 3%) but can have devastating consequences.

It is thought a large proportion of SSIs arise from contamination with the patient's own bacterial flora (from skin, mucous membranes and the gastrointestinal tract).[1] The most commonly isolated pathogens in SSIs are *Staphylococcus aureus*.[9] As such, the most frequently used antimicrobial agents for surgical prophylaxis are cefazolin, cefuroxime and cefamandole due to their activity against these Gram-positive organisms, their safety profile and low cost.[9] The recent emergence of methicillin-resistant *S. aureus* (MRSA) has resulted in an increased use of alternative antibiotics, in particular vancomycin.[9]

In order to reduce the risk of SSIs, a number of interventions are used in current clinical practice, and there is a drive for these to become applied in a more consistent manner. Standard practice includes antibiotic prophylaxis with β-lactam or alternative agent, provided as a single dose in the hour preceding the operation. In New Zealand, the Health Quality and Safety Commission launched the Surgical Site Infection Improvement (SSII) Programme in 2012.[10] Delivered by the Auckland and Canterbury District Health Boards, this programme was the first national quality improvement initiative implemented to provide a consistent, evidence-based approach to collecting and reporting high-quality data about SSIs.[10] The aim of the programme is to promote and encourage a culture of change and guidance on practice to reduce SSIs.[10]

Specifically, the Programme encourages a combination of interventions regarding SSI prevention; namely correct use of surgical antimicrobial prophylaxis and use of an alcohol-based pre-operative skin antiseptic. The SSII Programme's Implementation Manual for orthopaedic and cardiac surgery describes optimal surgical antimicrobial prophylaxis by correct antimicrobial agent, dose and timing of administration. The first choice antibiotic is ≥ 2g of cefazolin (≥ 1.5g cefuroxime is also acceptable); given in a single dose 0-60 minutes before knife to skin.[11] The Manual states clindamycin or vancomycin should be reserved as alternative agents in β-lactam allergy, and for vancomycin to be added to cefazolin prophylaxis in patients with MRSA.[11] The

recommended preoperative skin antisepsis preparation should be with an alcohol (≥ 70%) based solution containing either chlorhexidine gluconate or povidone-iodine.

Currently, some hospitals also use an anti-staphylococcal bundle to reduce SSIs. The bundle consist of nasal and/or skin decolonisation where topical applications of ointment such as mupirocin are used with or without body washes or wipes, often chlorhexidine, before admission to theatre.[12, 13] Although the effectiveness of this bundled approach has been tested in a number of trials and a systematic review,[1] some of the published results have been inconsistent and the overall impact of these measures is still unclear.

In this review, we define "a bundle" to be pre-theatre prophylactic nasal and/or skin decolonisation, in addition to standard care. The aim of this systematic review is to expand the evidence base of an earlier systematic review,[1] to assess the effectiveness of bundled prophylaxis in preventing SSI with Gram-positive bacteria among patients undergoing cardiac operations or total joint replacement procedures. The results will inform whether the bundled interventions should be adopted in addition to standard SSI prevention protocolsin these procedures.

Methods

The review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. [14]

Literature sources and search strategies

Three bibliographic databases, PubMed, Embase and the Cochrane Library of Systematic Reviews were searched from inception to June 2016. Comprehensive search strategies were utilised to identify all relevant published literature in line with the Population-Intervention-Comparator-Outcome (PICO criteria). Medical Subject Headings (MeSH) terms were used in PubMed and Cochrane Library of Systematic Reviews searches, and EmTree terms were used for Embase searches. Free keywords, wildcards, and their combinations were used to search titles and abstracts. Search strategies for PubMed and Embase are provided in Appendix II. All citations were

retrieved to EndNote X7.1 management software (Thomson Reuters, Philadelphia, USA) for study screening. The search logic illustrating the search process is shown in Figure.a 1.

PICO criteria

PICO criteria (Table.a 1) were defined *a priori*.

Regarding the Population, the review focused on patients of all ages (including paediatric patients) receiving elective cardiac or orthopaedic surgery Cardiac surgeries excluded cardiothoracic procedures with thoracotomy or sternotomy involving only surgery of lungs. Studies including patients who underwent other surgeries, depending on the proportion of patients, were included on a case-by-case basis.

Population: Studies that reported patients of all ages (including paediatric patients) receiving elective cardiac (with sternotomy) or orthopaedic surgeries (arthroplasty).

The intervention is a "treatment bundle", defined as preoperative nasal decolonisation and/or extended skin decolonisation. Antibiotic regimens can be varied where any route of administration, except topical and intra-wound application of antibiotics, any β-lactam with or without glycopeptide, or glycopeptide alone, regardless of timing, any duration or dosage were deemed appropriate. Nasal decolonisation with any agent was considered appropriate. Skin decolonisation can include pre-theatre body washing, wiping or preparation with any appropriate agent.

The intervention is a prophylaxis bundle, defined as the use of prophylaxis antibiotics and nasal and/or extended skin decolonisation.

The comparator was placebo or standard care, however defined. This may include prophylaxis antibiotic mono-therapy such as β-lactam or glycopeptide.

The primary outcome was SSI, whether reported as SSIs (pathogens not otherwise specified), infections caused by *S. aureus*, MRSA or MSSA (methicillin-susceptible *S. aureus*) subgroups were reported separately where possible. Secondary outcomes include infections by coagulase-negative-staphylococci, and complications.

Studies using another bundle as the comparator were included but discussed

separately. Comparisons of drug administration route, timing, duration, and dosage (antibiotics or decolonisation) were excluded. Other study inclusion and exclusion criteria were:

Inclusion criteria:

- Human clinical studies;
- English language;
- Systematic reviews and randomised control trials (RCTs);
- Comparative cohort studies.

Exclusion criteria:

- All literature with an evidence level lower than Level IIIB, including case series, case reports, conference abstracts, articles with an abstract only, letters, editorials, communications, non-human studies, *in vitro* or laboratory studies;
- Pathogen eradication studies with no reporting of SSIs.

Study selection

The process of study selection for this review went through four phases. First, all identified reference citations were retrieved and imported into a single Endnote database, and duplicates were removed. Second, studies were reviewed by title and abstract and excluded if they did not meet the selection criteria (NM, DRT), and reasons for exclusion were noted. Third, all remaining studies were examined in full-text (NM). Conflicts were resolved by discussion (NM, AM, SR, NG, ALC). Finally, studies were included to address the research questions if they met the PICO and the study eligibility criteria. An independent researcher (DF) underwent a separate check to ensure no studies were missed during this process. The process of study selection is summarised in a PRISMA chart.

Data extraction of the included studies

Data extraction was undertaken by one researcher (NM) and checked by another (ALC, DRT). Any discrepancy of the extracted data was resolved through discussion. Only data were extracted, including data presented in tables, graphs, figures, or if

numerical data could be accurately extrapolated. A standardised extraction template designed *a priori* was used. Information in the template included baseline characteristics, pre-surgical bacteria screening, and the timing, duration, dosage, and administration routes of any intervention. Descriptive statistics were extracted or calculated for all safety and effectiveness outcomes in individual studies.

Extraction of data was undertaken for study information including authors, years of publication, places (countries), study designs and surgical procedures performed. Pre-surgical *S. aureus* screening methods and carrier status of any interested pathogen were also extracted where possible. We devoted particular attention to whether or not screening results made any difference to patient eligibility or treatment applied in any study. Interventions and comparators were extracted and broken down by nasal and skin decolonisation and antibiotic protocols. Specifically, antibiotics (including β-lactam and/or glycopeptide) and decolonisation protocols with information of initiation timing, duration, dosage, and administration routes were targeted during the extraction.

Patient inclusion and exclusion criteria of each study were extracted. Detail of patient eligibility was particularly examined by the type of surgery patients received (emergency/elective), surgical procedures performed, and length of retrospective data when historical controls were used in non-randomised studies. Patient characteristics were extracted by age, gender, body mass index and comorbidities. The length of follow-up was extracted for RCTs.

It is important to acknowledge that not all data in the included publications can be used directly for the purpose of evidence synthesis, in particular for meta-analyses. Data extraction was exhaustive, including sourcing online appendices, data regeneration and contacting the corresponding authors. It was noted when data re-generation was required from the published values or provided by sources other than the published articles.

Evidence quality appraisal

Included RCTs were assessed using the Cochrane Risk of Bias tool.[15] Data was reported using a risk of bias graph for individual studies and a summary figure for all

studies using Review Manager (RevMan) (Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration). The Downs and Black scoring system was used to assess the quality of comparative cohort studies.[16] Summary scales for reporting, external validity, internal validity-bias, and internal validity-confounding and statistical power were reported. Quality appraisal was undertaken by one reviewer (NM) and checked by a second (DRT, ALC, DF), and any disagreement was resolved through discussion.

Evidence synthesis and statistical analyses

The outcome of general SSIs (all cause), and infections caused by *S. aureus*, MRSA and MSSA, as well as coagulase-negative staphylococci were meta-analysed. RCTs and observational studies were analysed separately. When a study investigated both cardiac and orthopaedic surgeries, the study was split into two sub-studies and grouped into the corresponding subgroups depending on data availability. SSIs caused by different pathogens (all cause), *S. aureus*, MRSA, and MSSA) were also analysed separately when data were available.

As all data were patient counts. Relative risks and associated 95% confidence intervals were used for pooling due to improved interpretability in a clinical context. Random-effect models were used due to diversity in treatment regimens. Prediction intervals and I squared values were used to describe heterogeneity. Restricted maximum likelihood methods were used for the random-effect model. Forest plots were generated to illustrate the meta-analyses results. R 3.3.1 and the package "metafor" were utilised to conduct all meta-analyses.[17]

Sensitivity analyses were performed to investigate influential studies. Trim and fill methods were used to detect publication bias and funnel plots were generated.

Results

The literature search identified 7,178 published articles across all databases. In total six systematic reviews were identified, including the 2013 report by Schweizer et al.[1] Four RCTs and 11 observational studies published before 31 January 2012 were

identified through hand searching of the existing systematic reviews. We independently reviewed 2,724 articles published from 1 January 2011. One-hundred and eighteen studies were examined by full text and two RCTs and eight observational studies were found to be eligible for inclusion (new studies). All excluded studies were noted with the reason for exclusion falling into any one of the eleven categories. In total, six RCTs and 19 observational studies formed the evidence base of this review. The PRISMA flow chart illustrating study selection is shown in Figure.a 2. Detail of treatment bundles was extracted and tabulated in Table.a 2.

Randomised controlled trials

Six RCTs, comprising 4,213 patients, assessed the bundled intervention for SSI prevention. Five of the RCTs contributed data to meta-analyses. The remaining RCT was a comparison of two bundles and was not included in the meta-analyses.[18] Two studies[18, 19] were identified as new studies published later than 2011, which were not included in any of the systematic reviews. The other four studies[20-23] were included through hand searching of systematic reviews.

Study characteristics

The two new RCTs were formally extracted and assessed for study information (PICO criteria and patient characteristics) and study quality. An overview of the study and patient characteristics is given in Table.a 3 and Table.a 4 respectively. Extracted data from the four studies identified by a previous systematic review can be sourced from the online appendix.[1] All patients were adults. Two of the RCTs[22, 23] included cardiac surgery patients, and three included orthopaedic surgery patients.[19, 21, 23] Patient baseline characteristics were reported by all RCTs. The orthopaedic study by Phillips et al. [18] included 315 spinal surgery patients in a total patient population of 1,697. The study by Bode et al.,[20] which had both cardiothoracic and orthopaedic data reported, was split into two sub-studies for the purpose of meta-analyses. All surgeries were elective procedures although two RCTs[20, 22] did not report this information. Screening for *S. aureus* carrier status was conducted in all six RCTs. Nasal culture was utilised for screening in all studies apart from one, which used the polymerase chain reaction (PCR) method.[20] Three RCTs[19, 20, 22] used screening results

to determine patient eligibility and only included *S. aureus* positive patients. The length of follow-up ranged from four weeks to 12 months, by means of telephone interviews or hospital visits.

Treatment and its comparison

All RCTs were bundled studies where the intervention involved nasal and/or extended skin decolonisation and prophylaxis antibiotics. However, treatment regimens for antibiotics and nasal and/or decolonisation varied across studies, by choice of drug and dosage. β-lactam prophylaxis was used in all studies. Clindamycin was used on penicillin-allergic patients in three studies[18, 21, 22] and vancomycin was used on patients with positive screening or history of MRSA in three studies.[18-20] With varied frequency and duration of application, mupirocin was the main nasal decolonisation agent used for the intervention in five RCTs, with chlorhexidine gluconate gel used in one RCT.[23] There are also variations in the skin decolonisation measure. Three RCTs prescribed patients with chlorhexidine soap[19, 20, 22] in the intervention arm to shower with before surgeries (days varied) and one study[18] applied whole body wipes with chlorhexidine the evening before surgery. Except for one RCT which compared mupirocin with povidone-iodine for nasal decolonisation,[18] the other five studies were all placebo-controlled where sham ointment and/or soaps were used in the placebo arms.

Quality appraisal

Quality appraisal of the included RCTs was only performed on two of the new ones using the Cochrane Risk of Bias Tool. The quality of RCTs identified by previous systematic reviews through pearling was assessed by a systematic review published in 2013.[1] The overall quality of the RCTs was from medium to high (Figure.a 5). The two new studies were not blinded for patients and did not have all the data reported. The four old studies, however, were all blinded studies.

Effectiveness outcomes

Infections were as defined by National Healthcare Safety Network (NHSN) Centre for Disease Control and Prevention (CDC) in four RCTs.[18-20, 23] Five RCTs[18, 19, 21-23] reported both non-pathogen specific and *S. aureus* SSIs and two studies[18, 23] also reported SSIs

caused by MRSA. In addition, Phillips et al.[18] also reported SSIs related to MRSA, MSSA and coagulase-negative staphylococcus. Meta-analysis was performed on non-pathogen specific and *S. aureus* SSIs data with surgical type as the subgroup where appropriate. As Bode et al.[20] investigated both cardiac and orthopaedic surgeries, the study was split into the corresponding groups in the analysis. For non-pathogen specified SSIs, four RCTs contributed to the meta-analysis (Figure 1). Two studies were of *S. aureus* population only. The result showed equivalence in SSI prevention comparing bundled treatment to placebo with a high degree of consistency (RR = 0.91, 95% CI = (0.72, 1.30), I^2 = 0%). Due to the limited number of RCTs in each surgical category, subgroup analysis was not performed.

Figure 1   All-cause SSIs, RCTs
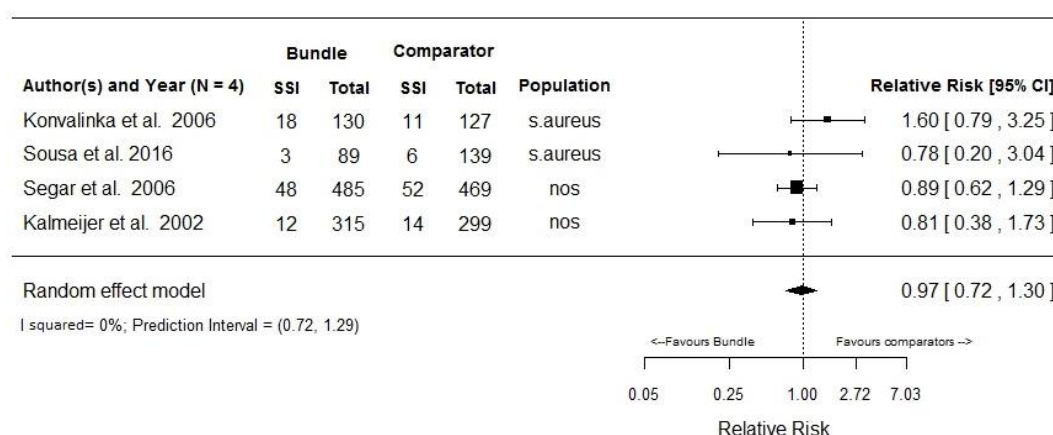
Author(s) and Year (N = 4)	Bundle SSI	Bundle Total	Comparator SSI	Comparator Total	Population	Relative Risk [95% CI]
Konvalinka et al. 2006	18	130	11	127	s.aureus	1.60 [0.79 , 3.25]
Sousa et al. 2016	3	89	6	139	s.aureus	0.78 [0.20 , 3.04]
Segar et al. 2006	48	485	52	469	nos	0.89 [0.62 , 1.29]
Kalmeijer et al. 2002	12	315	14	299	nos	0.81 [0.38 , 1.73]
Random effect model						0.97 [0.72 , 1.30]

I squared= 0%; Prediction Interval = (0.72, 1.29)

<--Favours Bundle   Favours comparators -->

0.05   0.25   1.00   2.72   7.03

Relative Risk

Notes: CI = confidence interval; SSI = surgical site infection; RCT = randomised controlled trial.

Results of meta-analyses on *S. aureus* SSIs were based on data from five RCTs, with data for cardiac and orthopaedic surgeries available from Bode et al. 2010 (Figure 2). The overall result showed a 41% improvement (RR = 0.59, 95% CI = (0.33, 1.06), I^2 = 32.72%) in avoiding *S. aureus* SSIs when using the bundled treatment compared to placebo. However, the bundled treatment was not statistically better than placebo, and the analysis showed increased statistical heterogeneity (prediction interval = (0.22, 1.59)). A trend of improved effectiveness of the bundled treatment in *S. aureus* SSIs could be observed, attributable to the inclusion of Bode et al.[20] study.
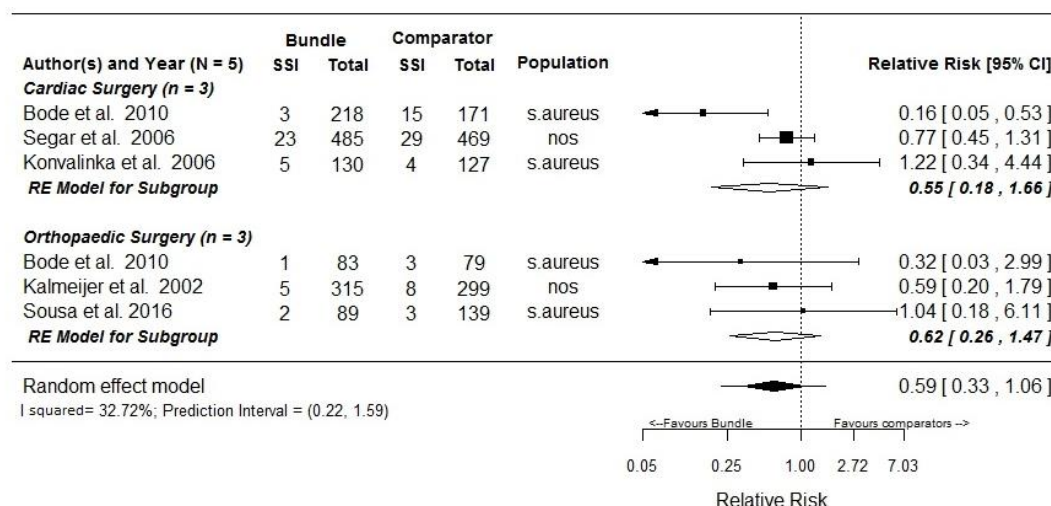
Figure 2   S. aureus SSIs, RCTs

Notes: CI = confidence interval; SSI = surgical site infection; RCT = randomised controlled trial.

The RCT by Phillips et al.[18] compared two nasal decolonisation protocols and concluded that povidone-iodine could be an effective alternative to mupirocin. Relative risks were not evaluated. Phillips et al. reported significant differences between mupirocin and povidone-iodine decolonisation in per-protocol (PP) analysis (p = 0.06, 0.03) but not in intent-to-treat (ITT) analysis (p = 0.1, 0.2), for both non-specific and *S. aureus* SSIs respectively. No statistically significant difference was identified for any of these SSIs between arms with no relative risk reported.

Observational studies

Nineteen observational studies, comprising 128,632 patients, were included in this review. All studies contributed to the meta-analyses. Eight new studies were deemed eligible.

Study characteristics

Data extraction and quality assessment were performed only on the eight new studies. An overview of the study and patient characteristics is summarised in Table.a 5 and Table.a 6. Nine of the included studies[7, 24-31] included cardiac patients and the other nine[32-40] included orthopaedic patients; the remaining study included both populations. Two cardiac studies [28, 31] were on paediatric patients and the remaining

were all adults. MRSA screening was performed in 14 studies. Four utilised PCR[24, 33, 36, 41] and nine performed culture methods[27-30, 32, 35, 37, 39, 41] to identify positive carriers. The study by Schweizer et al.[41] reported both PCR and culture methods and the other two studies[25, 38] did not report screening methods. Two studies[35, 39] only included *S. aureus* patients in their studies based on the screening result.

Treatment and comparison

All observational studies explicitly reported the use of β-lactam as the baseline surgical prophylactic antibiotic except for Bebko et al.[37] who adopted prevention measures based on the Surgical Care Improvement Project[42] with no specific detail provided. Clindamycin was reported as the alternative agent for β-lactam allergy.[25, 30, 35, 39] Vancomycin was reported as the main drug for patients with MRSA-positive status or history,[28, 33, 41] or some β-lactam contraindications as well.[29, 35] Two studies reported the use of vancomycin but were not clear on the regimen[26, 27] and Schweizer et al.[41] used both β-lactam and vancomycin to MRSA-positive patients.

Decolonisation protocols for observational studies were more varied than RCTs. Mupirocin (2% ointment) was used variously by 18 studies,[7, 24-36, 38-41] and povidone-iodine was used in two studies as the decolonisation agent.[37, 38] When screening was performed, in some studies decolonisation was only applied to positive *S. aureus* carriers only. Specifically, mupirocin was applied to MRSA positive patients in two studies,[36, 38] to both MRSA and MSSA carrier patients in one study,[41] and to *S. aureus* carriers in one study.[39] In addition, two studies utilised a discontinuation protocol of decolonisation where mupirocin was initially applied to all (including comparator) patients and then stopped when screening returned with negative results for MRSA[24, 38] or *S. aureus.*[27] Skin decolonisation and mouthwash were also applied in some studies. Chlorhexidine was prescribed to patients in the form of soaps for showing [25, 26, 29-33, 36, 41] or wipes for skin cleansing.[37] The study by Wilcox et al.[40] prescribed triclosan soaps instead of chlorhexidine to patients for showering. Mouthwash using chlorhexidine was applied to patients in only one study.[37]

Historical controls were reported by 15[7, 24, 26-29, 31-34, 36-38, 40, 41] observational studies and they were often controlled for a period of time before an implementation of

infection prevention programs. Few studies reported the exact constituents of their control programs. Concurrent controls were reported by four studies.[25, 30, 35, 39] Where both historical and concurrent controls were reported, only concurrent control data contributed to the meta-analysis.

Effectiveness outcomes

SSIs were reported in all the included studies. The NHSN definition of SSIs was adopted by 14 studies.[7, 25, 27-30, 32-34, 36, 37, 39-41] Non-pathogen specific SSIs, *S. aureus* SSIs, SSIs due to MRSA and MSSA, and coagulase-negative staphylococcal SSIs were reported by the included observational studies. Meta-analyses were performed on all five types of SSIs where possible. Schweizer et al.[41] reported all *S. aureus* SSIs and the other two studies[38, 40] only reported MRSA SSIs. The all-cause SSI meta-analysis was performed on all observational studies using all available data. Where appropriate, subgroup analyses were based on surgical types (cardiac or orthopaedic). Schweizer et al. included both cardiac and orthopaedic patients on non-pathogen specific and *S. aureus* SSI; therefore data was split and allocated to the corresponding subgroups as two sub-studies.[41]

Figure 3   All cause SSI by surgical groups, observational studies

| Author(s) and Year (N = 20)	Bundle		Comparator		Relative Risk [95% CI]
Orthopaedic Surgery (n = 10)	SSI	Total	SSI	Total	
Hadley et al. 2010	21	1644	6	414	0.88 [0.36 , 2.17]
Baratz et al. 2015	27	3434	33	3080	0.73 [0.44 , 1.22]
Gernaat-van der Sluis et al. 1998	14	1044	34	1260	0.50 [0.27 , 0.92]
Schweizer et al. 2015	17	11059	66	20642	0.48 [0.28 , 0.82]
Rao et al. 2011	17	1440	20	741	0.44 [0.23 , 0.83]
Kim et al. 2010	13	7019	24	5293	0.41 [0.21 , 0.80]
Bebko et al. 2015	4	365	13	344	0.29 [0.10 , 0.88]
Sankar et al. 2005	0	231	1	164	0.24 [0.01 , 5.78]
Price et al. 2008	0	43	2	43	0.20 [0.01 , 4.05]
Wilcox et al. 2003	2	1135	7	420	0.11 [0.02 , 0.51]
RE Model for Subgroup					**0.50 [0.39 , 0.64]**
Cardiac Surgery (n = 10)					
Schweizer et al. 2015	13	3257	35	7576	0.86 [0.46 , 1.63]
Jog et al. 2008	17	765	23	697	0.67 [0.36 , 1.25]
Kohler et al. 2015	37	646	81	945	0.67 [0.46 , 0.97]
Martorell et al. 2004	12	469	19	466	0.63 [0.31 , 1.28]
Nicholson et al. 2006	12	1077	18	954	0.59 [0.29 , 1.22]
Katayanagi 2015	7	101	12	73	0.42 [0.17 , 1.02]
Walsh et al. 2011	20	2496	59	2766	0.38 [0.23 , 0.62]
Cimochowski et al. 2001	8	854	27	992	0.34 [0.16 , 0.75]
Kluytmans et al. 1996	11	752	6	116	0.28 [0.11 , 0.75]
Adler et al. 2012	16	971	23	310	0.22 [0.12 , 0.41]
RE Model for Subgroup					**0.49 [0.37 , 0.64]**
Random effect model					0.49 [0.41 , 0.59]

I squared = 46.86%; Prediction Interval = (0.31, 0.78)

<--Favours Bundle   Favours comparators -->

0.05   0.25   1.00   2.72   7.03

Relative Risk

Notes: CI = confidence interval; SSI = surgical site infection; RCT = randomised controlled trial.
Data of Price et al. 2008 and Wilcox et al. 2003 were MRSA SSI only.

The meta-analysis of all 19 included observational studies found a significant decrease in risk of non-pathogen specific SSIs when comparing the bundled treatment to a comparator (RR = 0.49, 95% CI = (0.41, 0.59), I^2 = 46.86%) (Figure 3). Results of cardiac and orthopaedic subgroups were similar to the overall results (RR = 0.50 and 0.49 respectively). The prediction interval showed statistical significance in favour of the bundle treatment.

Figure 4   S. aureus SSIs for observational studies
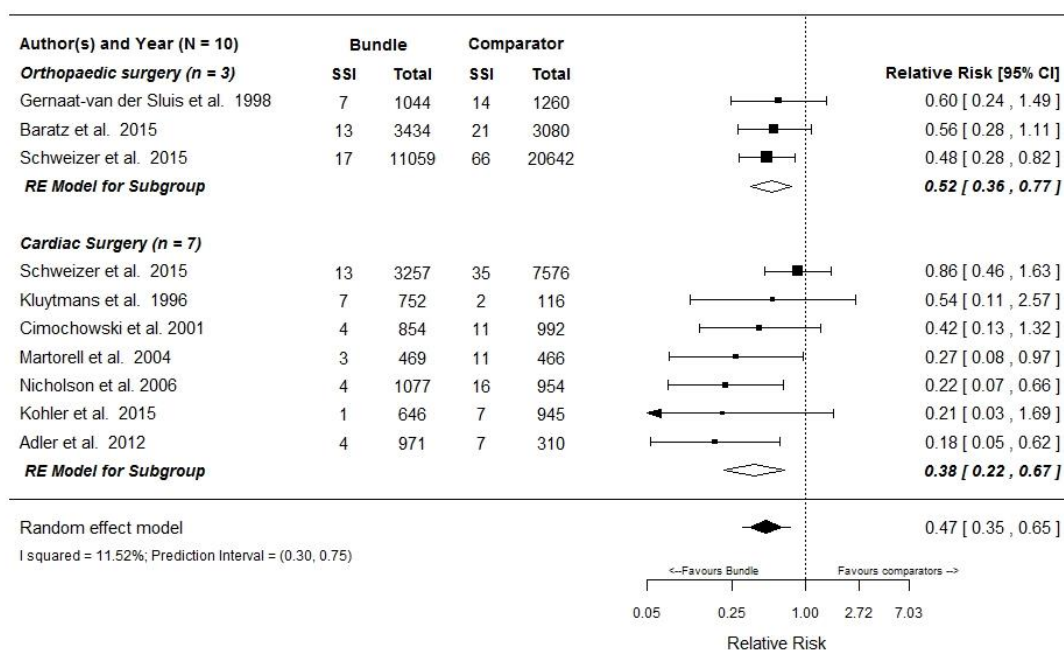
Notes: CI = confidence interval; SSI = surgical site infection.

Ten studies contributed to the meta-analysis of *S. aureus* SSIs (Figure 4). Compared to non-specific SSIs, the benefit of bundle was similar for *S. aureus* SSIs although with less heterogeneity (RR = 0.47, 95% CI = (0.35, 0.65), I^2 = 11.52%). The bundled treatment was more effective in preventing *S. aureus* SSIs in cardiac surgery with a risk reduction of 62% (RR = 0.38, 95% CI (0.22, 0.67)).

MRSA and MSSA SSIs were also significantly reduced by the bundled treatment (Table 1). In fact, MRSA SSIs were decreased most effectively by the bundle in cardiac surgery (n=4, RR = 0.19, 95% CI = (0.05, 0.67)) with greater heterogeneity.

Table 1   Summary table for all meta-analyses of all observational studies

	Non-pathogen specific SSIs	S. aureus SSIs	MRSA SSIs	MSSA SSIs
Cardiac surgery	n = 10 RR = 0.49 95% CI = (0.37, 0.64) I^2 = 46.98%	n = 7 RR = 0.49 95% CI = (0.22, 0.67) I^2 = 38.22%	n = 4 RR = 0.19 95% CI = (0.05, 0.67) I^2 = 50.72%	n = 2 RR = 0.55 95% CI = (0.07, 4.43) I^2 = 54.86%
Orthopaedic surgery	n = 10 RR = 0.49 95% CI = (0.37, 0.64) I^2 =0.00%	n = 3 RR = 0.52 95% CI = (0.36, 0.77) I^2 = 0.00%	n = 7 RR = 0.48 95% CI = (0.33, 0.71) I^2 = 28.84	n = 4 RR = 0.50 95% CI = (0.34, 0.73) I^2 = 24.08%
Overall	N = 19 RR = 0.49 95% CI = (0.41, 0.59) I^2 = 46.86%	N = 9 RR = 0.47 95% CI = (0.35, 0.65) I^2 = 11.52%	N = 11 RR = 0.28 95% CI = (0.16, 0.48) I^2 = 40.59%	N = 6 RR = 0.52 95% CI = (0.35, 0.80) I^2 = 0.00%

Notes: RR = relative risk; CI = confidence interval; SSI = surgical site infection; SSI = surgical site infection; MRSA = methicillin-resistance staphylococcus aureus; MSSA = methicillin-sensitive staphylococcus aureus.

A meta-analysis was also performed on coagulase-negative staphylococcal SSIs in six observational studies.[7, 24, 25, 30, 31, 33] The result showed that coagulase-negative staphylococcal SSI was not significantly affected by using bundled treatment (n = 6, RR = 0.68, 95% CI = (0.29, 1.56), I^2 = 64.01%, analysis not shown) with a high level of heterogeneity. Therefore, the effectiveness of the bundle on coagulase-negative staphylococcal SSIs is uncertain.

Quality assessment

The included studies published later than 2011 were assessed for their quality using Downs and Black quality appraisal tool (Table.a 7). The quality of studies published before 2011 were assessed and reported by a systematic review.[1] The overall level of bias was from medium to high, with a score ranging from 11 to 19 out of 26 and had an average score of 14.75. The quality of reporting was medium, given 15 out of 19 studies involved historical controls with no clear specifications of what controlled measures were undertaken exactly. All studies were excellent regarding external validity but less robust regarding internal validity. As expected, all included observational studies were rated as low concerning confounding biases, due to the

absence of randomisation or blinding, or the lack of confounding adjustment. Sample sizes of the observational studies were much larger than in the RCTs, with over half the studies reporting a power calculation.

Sensitivity analyses and publication bias

Sensitivity analyses were performed to identify influential studies on all meta-analyses performed. No study was outstanding. Therefore, no study was removed. Accumulative meta-analyses were also performed against years of publication, and no particular trend was observed. Funnel plots were generated to detect publication biases. Only *S. aureus* related SSIs by RCTs and observational studies were tested. Both funnel plots were visibly symmetrical, indicating no substantial biases. A "trim and fill" method was applied to impute potential missing studies. Results of imputed meta-analyses were very similar to original results (Figure.a 3 and Figure.a 4). Therefore, there is no substantial publication bias in this systematic review.

Discussion

Surgical site infection can be a serious complication after surgery that affects patient well-being, prolongs hospital stay, increases surgical mortality and morbidity, and imposes huge financial burden on health systems.[43-47] While SSIs remain difficult to eradicate, studies continue to tackle the issue. The data are complex and diverse, with each study having a slightly different scope. Among the systematic reviews identified by this study, three studies had inconclusive results with regard to the effectiveness of antibiotics or nasal decolonisation in reducing SSIs.[43, 48, 49] This current systematic review can be considered the most comprehensive to date, including studies published over 20 years. In addition, the dedicated meta-analyses investigated the effectiveness of the bundled treatment of SSIs for both orthopaedic and cardiac surgery caused by various pathogens. We have taken a pragmatic approach in this review regarding study selection and evidence synthesis. Systematic reviews were used to identify studies published prior to 2011. We also consulted with clinical experts on study eligibility and decisions on inclusions. Data from studies predating 2011 were extracted independently. These data were combined with

studies identified by the literature search executed for this review. Evidence synthesis was inclusive with all studies incorporated into meta-analyses when appropriate. We found that the bundled treatment was significantly more effective than standard care for cardiac or orthopaedic surgeries in observational studies, especially for *S. aureus* related infections. On the other hand, the bundled intervention in RCTs showed a protective trend in of *S. aureus* SSIs without achieving statistical significance. The varied outcome between RCTs and observational studies likely reflected a complex yet important insight of the application of the bundled intervention in clinical practice which is reflected in the observational data but less so in the bounds of a formally implemented clinical trial.

The specific elements that constitute a bundled treatment are open to interpretation. For the purposes of this review we defined "a bundled treatment" to be the addition of pre-theatre nasal and/or skin decolonisation to standard care, including for example the use of prophylactic antibiotics. However, this definition of "bundle" is not universally adopted. One of six systematic reviews[1] used the term "bundle" to compare with standard care, although neither "bundle" nor "standard care" were clearly specified. Bundled interventions, as a generic term, have been utilised by studies external to this review, although generally with different meanings across different clinical settings.[8, 50-52]

While the meta-analyses were in favour of the bundled treatment in observational studies, the results from RCTs did not achieve statistical significance. Three of the included RCTs stated no reduction in SSIs rate when using nasal decolonisation.[19, 21, 22] This variation between RCTs and observational studies was also observed in previous systematic reviews.[1, 12, 48] We noticed that nasal decolonisation and surgical antibiotic prophylaxis in the RCTs were more likely to be consistently administered in this strictly controlled environment. It is clear that prophylaxis antibiotics do have protective effects against SSIs. Since all included studies used antibiotics in treatment and comparator arms, the added effect of SSI control by the bundle may be masked due to partial or complete *S. aureus* suppression by antibiotics. In contrast, we observed that the majority of the observational studies reported a treatment standardisation process, which included optimised antibiotic regimens[7, 29, 31, 34, 53] and

improved compliance in nasal decolonisation.[18, 42, 50, 54, 55] While the observational studies demonstrated greater effectiveness, they are more vulnerable to biases, or confounding factors, although are more likely to reflect real-life clinical practice.

Nasal carriage of *S. aureus* is a well-established risk factor for SSIs after major surgeries.[48, 56, 57] Many studies in this review performed pre-surgical *S. aureus* screening to determine the carrier status of the patients. Treatment plans were then customised according to the screening results. Although the impact of *S. aureus* screening was not a research question of this review, the issue introduced a level of uncertainty. In some studies, patients with a negative result were not treated with nasal decolonisation or under a different antibiotic regimen. In our review, an intent-to-treat (ITT) analysis was applied wherever possible. Patients who missed treatment due to the negative screening result may have skewed the overall results. It is also noted that it is impossible to screen every single patient, especially in emergency settings, and the sensitivity of the screening is dependent on the method used, i.e. PCR or culture. Nevertheless, previous systematic reviews have already established the effectiveness of the intervention based on pre-surgery screening in preventing SSIs.[43, 46, 58] The choice between combining screening with a personalised treatment regimen versus universal application of a decolonisation intervention to reduce the occurrence of SSIs will depend on local factors, e.g. how the patient's clinical pathway is organised and regional antimicrobial susceptibility profiles.

The review was undertaken in the context of the New Zealand SSII Program. Two recent local clinical guidelines on SSIs for cardiac and orthopaedic surgeries were identified, published by the Health Quality and Safety Commission, Ministry of Health, New Zealand.[59, 60] The guidelines recommend cefazolin as the first-line antibiotic with vancomycin or clindamycin reserved for patients with β-lactam allergy. It is recommended vancomycin should be added to cefazolin for known MRSA carriers. Skin preparation, by applying alcohol-based antiseptic solutions, containing chlorhexidine gluconate or povidone-iodine before incision, is also recommended. These recommendations are consistent with most of the standard care regimens described in the included studies. In Australia, the Australian Guidelines for the Prevention and Control of Infections in Healthcare, published in

2010, recommend the use of prophylaxis antibiotics, yet without providing any regimen detail. A recent review article identified that in Australia prophylaxis antibiotic use was not based on any an overarching guideline or standard and many patients were receiving prophylaxis unnecessarily.[61] In terms of decolonisation, *S. aureus* screening, nasal decolonisation with mupirocin, and body wash using chlorhexidine were recognised by the Australian Guideline as an effective measure for cardiac and orthopaedic surgeries although no direction is provided regarding the implementation of these interventions in hospitals.

This current systematic review has some limitations. A number of studies were excluded from the analysis, e.g. studies on minor orthopaedic surgeries,[57, 62, 63] and studies dedicated to shoulder surgery.[64, 65] Certain groups of specialised surgeries were also excluded such as spinal surgeries, maxillofacial surgeries, or cardiac device implantation procedures with small incisions. Further research is encouraged to investigate how SSI can be effectively reduced for those procedures. Regarding meta-analysis of all-cause SSIs, we have assumed that SSIs in cardiac and orthopaedic surgeries were caused by Gram-positive bacteria based on the regimen of antibiotics. This assumption may have overestimated the pooled effectiveness of the treatment effect. Moreover, the possible confounding factors in observational studies and any adjustments were not investigated in this review. Great diversity was observed regarding study designs, treatments in both study arms or outcome reporting within and across studies. Due to the nature of observational studies and lack of detail in historical controls, confounding adjustments were difficult to perform. Also, part of the study selection was based on hand searching bibliographies of systematic reviews. Due to the subtle differences in PICO between this review and others, it is possible that relevant studies published before 2011 may have been missed. However, based on the very low heterogeneity and narrow prediction intervals of the meta-analyses, it is unlikely that any other studies either existing, or published in the future, would have substantially impacted our results.

Conclusion

The evidence base for a prophylaxis bundle intervention for surgical site infection is

complex and diverse. With an appropriate and standardised bundle of prophylactic antibiotics, nasal and skin decolonisation, SSIs in orthopaedic and cardiac surgeries can be effectively reduced, especially for *S. aureus* related SSIs. However, further research should focus on how the combination of pre-surgical screening and prophylaxis bundle can work together in reducing the infection rate.

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Appendix I   Figures and Tables

Figures

Figure.a 1   Search logic
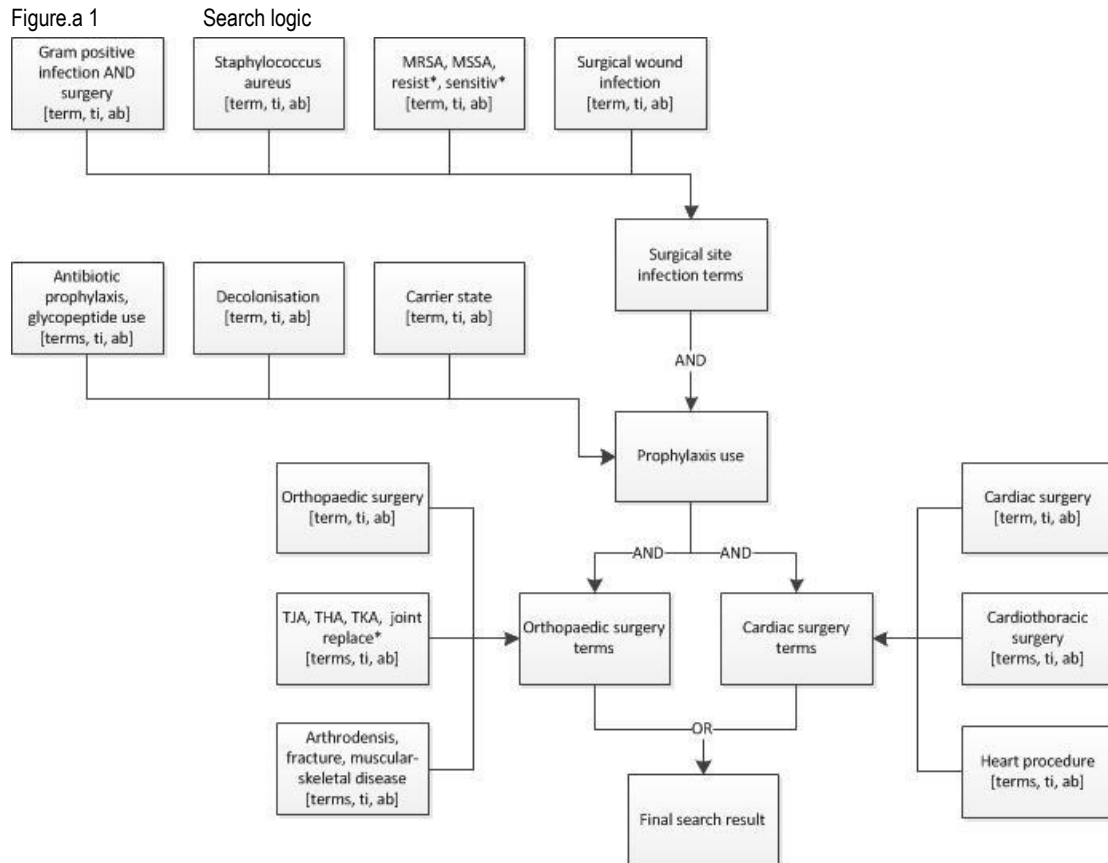
Figure.a 2   PRISMA chart for study selection

Figure.a 3   Publication bias for RCTs
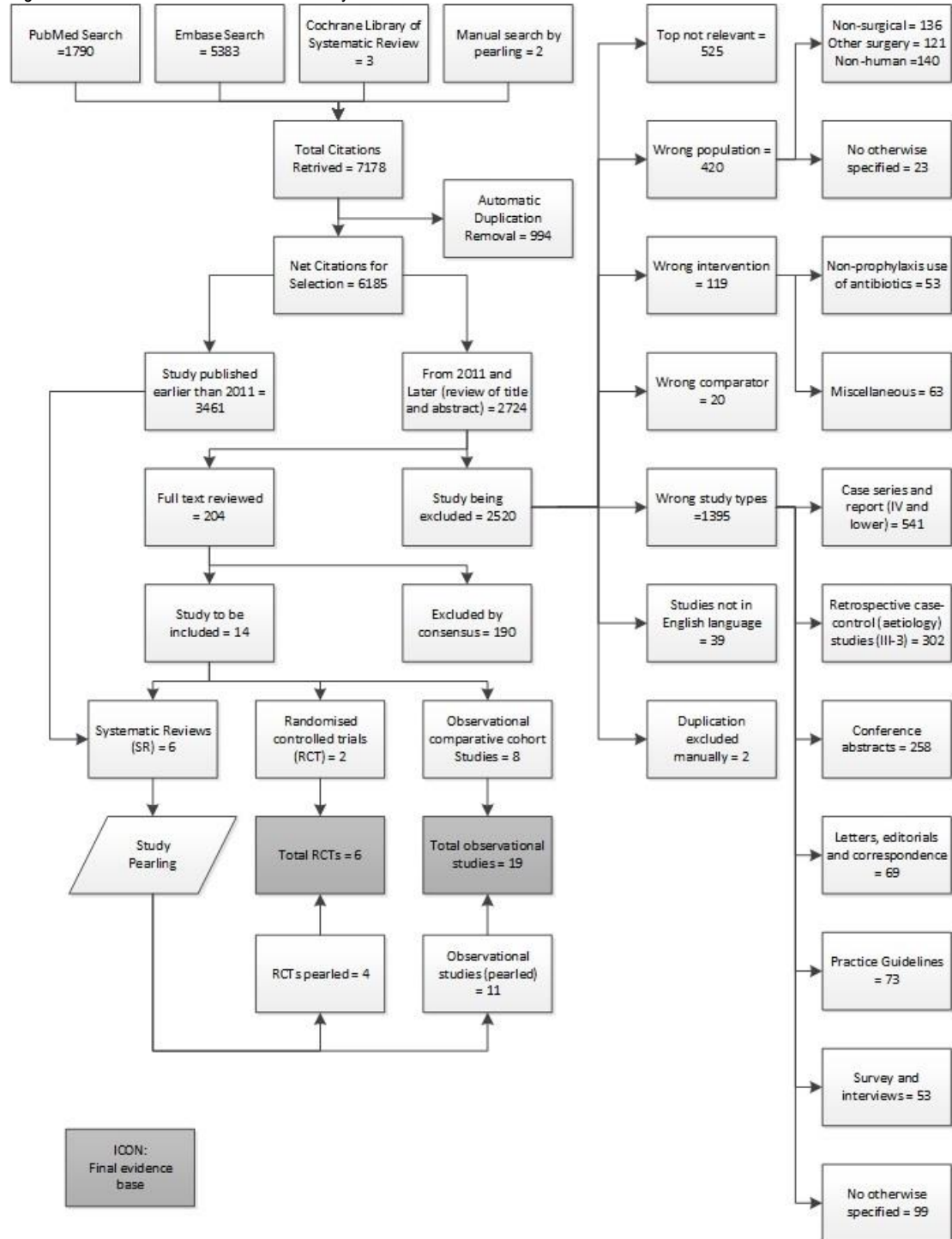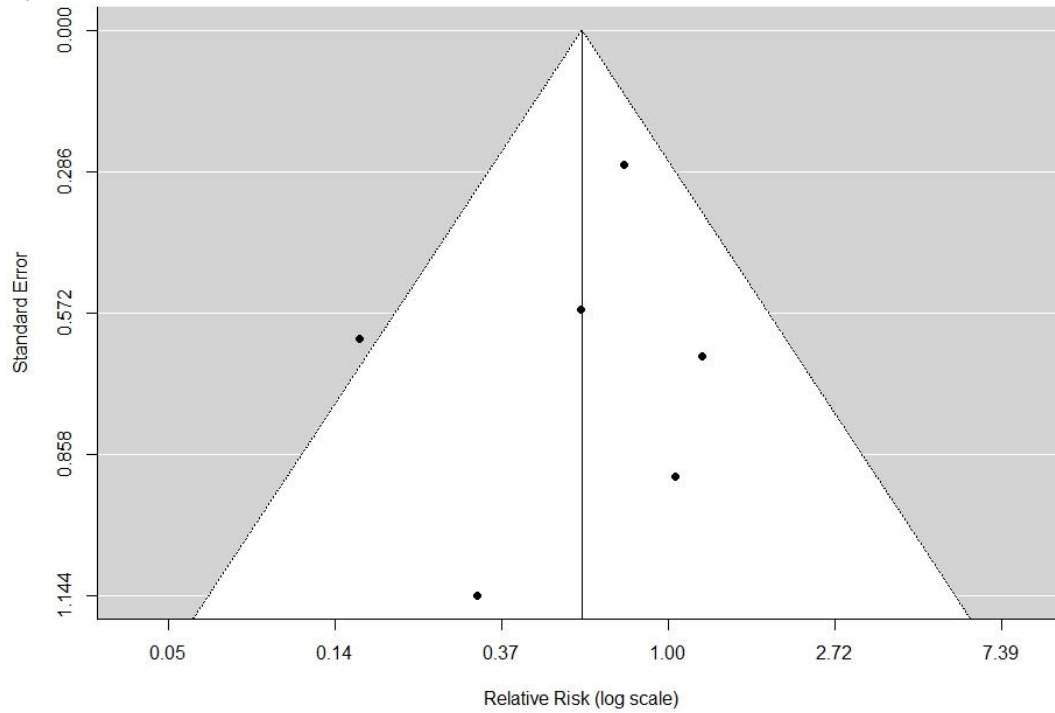

Note: the trim and fill method was applied with no imputed data needed for RCT meta-analysis.

Figure.a 4   Publication bias for observational studies with trim and fill method
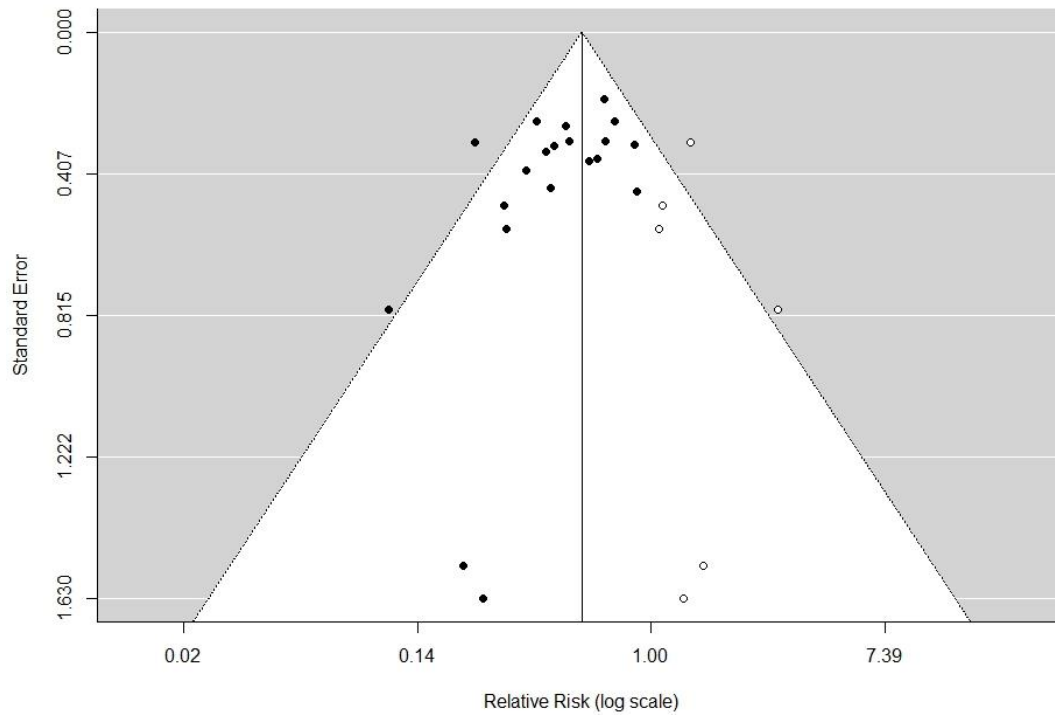
Note: the trim and fill method was applied. Open markers represent the filled data compensating for publication bias. The imputed data showed consistent result with the original meta-analysis.

Figure.a 5a   Risk of bias for all RCTs

Figure.a 5b   Risk of bias summary for RCTs

Tables

Table.a 1 PICO criteria

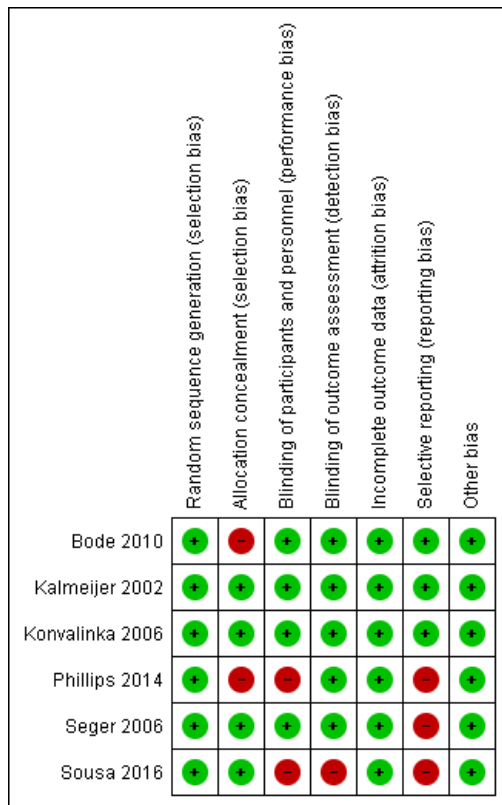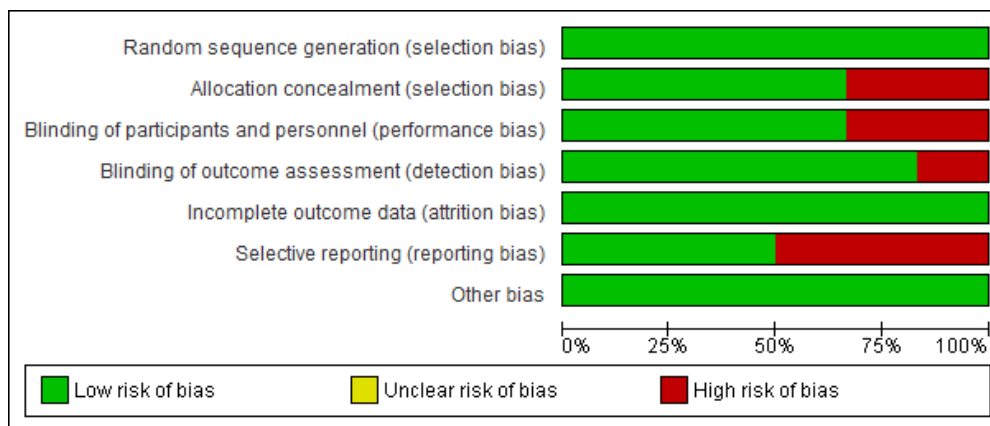|	Inclusion	Exclusion
Population	Surgical patients, including paediatric patients: • Undergoing open cardiac or elective orthopaedic surgeries (total knee or hip arthroplasty); • At risk of having surgical site infection by Gram positive bacteria (by MRSA and MSSA).	• Thoracotomy or sternotomy involving lungs only; • Specialised orthopaedic procedures or procedures involving orthopaedic surgeons and surgeons from other specialties (e.g. spinal or maxillofacial surgeries); • Patients receiving other orthopaedic surgeries (e.g. wrists, elbow, foot and ankle, emergency).
Intervention	Any one or combination of interventions of: • Standard antibiotic regimen; • Nasal and skin decolonisation.	• Topical application of antibiotics (e.g. intrawound powder application of vancomycin); • Non-glycopeptide prophylactic antibiotics alone without decolonisation (e.g. β-lactam or aminoglycoside only).
Comparator	Patients treated with standard care, including antibiotic prophylaxis mono-therapy: • For RCTs, placebos are a valid comparator; • For prospective observational studies, the comparator need to be specified; • For observational studies using historical controls, any non-standardised approaches are considered as valid comparators.	• Comparison between non-glycopeptide antibiotics without bundling with one or more decolonisation measures; • A comparison of dosage, timing or duration comparisons of only one particular type of antibiotic.
Outcomes	Primary outcomes: • Surgical infection rate by type of bacteria (MRSA, MSSA SSIs; Gram-negative SSIs, other SSIs). Secondary outcomes: • Length of stay; • Readmission; • Intervention-related adverse events.	• Aetiology (risk factors) of surgical site infection other than interventions /comparator (e.g. patients baseline characteristics or healthcare personnel-related factors); • Post-intervention carrier status.

Table notes: MRSA = methicillin-resistance staphylococcus aureus; MSSA = methicillin-sensitive staphylococcus aureus; RCT = randomised control trial; SSI = surgical site infections.

Table.a 2 Protocols of treatment bundles for all studies

Study Study Types	Nasal decolonisation		Skin decolonisation		Additional antiseptic measures
	Agent	Application protocol	Agent	Application protocol	
RCTs					
Bode et al. 2010 RCT	*[Intervention]* Mupirocin (2%) *[Comparator]* Placebo	*[Intervention]* Before surgery: twice a day for 5 days *[Comparator]* Placebo	*[Intervention]* Chlorhexidine soap (40mg/mL) shower *[Comparator]* Placebo	*[Intervention]* Before surgery: once a day for 5 days *[Comparator]* Placebo	
Kalmeijer et al. 2002 RCT	*[Intervention]* Mupirocin (2.15%) *[Comparator]* Placebo	*[Intervention]* Before surgery: twice a day for 1 day *[Comparator]* Placebo	*[Intervention]* No skin decolonisation	*[Intervention]* No skin decolonisation	
Konvalinka et al. 2006 RCT	*[Intervention]* Mupirocin (2%) *[Comparator]* Placebo	*[Intervention]* Before surgery: twice a day for 7 days *[Comparator]* Placebo	*[All patients]* Chlorhexidine soap (2%) and Chlorhexidine wipe at site (4%) in isopropyl alcohol (4%) before knife-to-skin	*[All patients]* Before surgery: 12 hours on the day of surgery	
Phillips et al. 2014 RCT	*[Intervention]* Mupirocin (2%) *[Comparator]* Povidone iodine (5%)	*[Intervention]* Before surgery: 5 days prior to surgery *[Comparator]* On day of surgery: 30 second application within 2 hours of surgery	*[All patients]* Chlorhexidine (2%) whole body wipe	*[All patients]* On the day of surgery	
Segers et al. 2006 RCT	*[Intervention]* Chlorhexidine (0.12%) 10mL *[Comparator]* Placebo	*[Intervention]* Before surgery: 4 times a day up to the day of surgery *[Comparator]* Placebo	*[All patients]* Chlorhexidine soap (40mg/mL) shower	*[All patients]* Before surgery: one day	*[All patients]* Oral rinse with CHG (0.12%) 30 seconds 4 times a day Hair removal with clippers
Sousa et al. 2016 RCT	*[Intervention]* Mupirocin (2%) *[Comparator]* No decolonisation	*[Intervention]* Before surgery: twice a day, 5 days before surgery *[Comparator]* No decolonisation	*[Intervention]* Chlorhexidine soap	*[Intervention]* Before surgery: 5 days	

Study Study Types	Nasal decolonisation		Skin decolonisation		Additional antiseptic measures
	Agent	Application protocol	Agent	Application protocol	
Observational studies					
Adler et al. 2012 Observational study	*[Intervention]* Mupirocin	*[Intervention]* Before surgery: twice a day for 5 days	*[Intervention]* Chlorhexidine gluconate shower; 2% CHG/70% isopropyl alcohol skin preparation	*[Intervention]* Before surgery: once a day for 2 days, skin preparation before knife-to-skin	
Baratz et al. 2015 Observational study	*[Intervention]* Mupirocin (2%)	*[Intervention]* Before surgery: twice a day for 5 days	*[Intervention]* Chlorhexidine (4%) soap;	*[Intervention]* Before surgery: daily for 5 days including day of surgery	
Bebko et al. 2015 Observational study	*[Intervention]* Povidone iodine (5%)	*[Intervention]* On the day of surgery in the morning	*[Intervention]* Chlorhexidine (2%) soap;	*[Intervention]* Before surgery: once the night before the day of surgery	*[Intervention]* Oral rinse with chlorhexidine (0.12%) once the night before surgery
Cimochowski et al. 2011 Observational study	*[Intervention]* Mupirocin	*[Intervention]* Before surgery: twice on the night before and the morning; After surgery: continued for 5 days	*[Intervention]* No skin decolonisation	*[Intervention]* No skin decolonisation	
Gernaat-van der Sluis 1998 Observational study	*[Intervention]* Mupirocin	*[Intervention]* Before surgery: twice on the day before; On the day of surgery: once in the morning	*[Intervention]* No skin decolonisation	*[Intervention]* No skin decolonisation	
Harley et al. 2010 Observational study	*[Intervention]* Mupirocin (2%)	*[Intervention]* Before surgery: for 5 days (frequency unknown)	*[Intervention]* Chlorhexidine (2%) soap;	*[Intervention]* Before surgery: for 5 day (frequency unknown)	
Jog et al. 2008 Observational study	*[Intervention]* Mupirocin (2%)	*[Intervention]* Before surgery: 3 times daily Continued after surgery until culture returns negative for MRSA	*[Intervention]* Triclosan (2%)	*[Intervention]* Before surgery: 3 times daily Continued after surgery until culture returns negative for MRSA	
Katayanagi 2015 Observational study	*[Intervention]* Mupirocin	*[Intervention]* On the day of surgery: immediately before and last for 2 days after surgery	*[Intervention]* No skin decolonisation	*[Intervention]* No skin decolonisation	
Kim et al. 2010 Observational study	*[Intervention]* Mupirocin (2%)	*[Intervention]* Before surgery: twice a day for 5 days	*[Intervention]* Chlorhexidine (2%) soap;	*[Intervention]* Before surgery: once daily for 5 day	

Study Study Types	Nasal decolonisation		Skin decolonisation		Additional antiseptic measures
	Agent	Application protocol	Agent	Application protocol	
Kluytmans et al. 1996 Observational study	*[Intervention]* Mupirocin	*[Intervention]* One day before surgery and last for 5 days until discharge	*[All patients]* Chlorhexidine or povidone iodine soap;	*[All patients]* Detail not provided	
Kohler et al. 2015	*[Intervention]* Mupirocin	*[Intervention]* Before surgery: twice a day for minimum 5 days	*[Intervention]* Chlorhexidine (4%) soap;	*[Intervention]* Before surgery: once a day for minimum 4 days	*[Intervention]* Octenidine hydrochloride impregnated washing gloves were used instead for bedridden patients
Martorell et al. 2004 Observational study	*[Intervention]* Mupirocin	*[Intervention]* Before surgery: 3 days	*[Intervention]* Chlorhexidine showering	*[Intervention]* Before surgery: 3 days	
Nicholson et al. 2006 Observational study	*[Intervention]* Mupirocin	*[Intervention]* Before surgery: twice a day until the culture result is available	*[Intervention]* No skin decolonisation	*[Intervention]* No skin decolonisation	
Price et al. 2008 Observational study	*[Intervention]* Mupirocin (2%)	*[Intervention]* Before surgery: no less than 6 doses	*[Intervention]* No skin decolonisation	*[Intervention]* No skin decolonisation	
Rao et al. 2011 Observational study	*[Intervention]* Mupirocin	*[Intervention]* Before surgery: twice a day for 5 days	*[Intervention]* Chlorhexidine soap;	*[Intervention]* Before surgery: daily for 5 days including day of surgery	
Sankar et al. 2005 Observational study	*[Intervention]* Mupirocin or povidone iodine	*[Intervention]* Before surgery: until culture returns negative for MRSA	*[Intervention]* Agent unknown	*[Intervention]* One week prior to hospital admission	
Schweizer et al 2015 Observational	*[Intervention]* Mupirocin	*[Intervention]* Before surgery: twice a day for minimum 5 days	*[Intervention]* Chlorhexidine bath;	*[Intervention]* Before surgery: once daily for 5 day of surgery	
Walsh et al. 2011 Observational study	*[Intervention]* Mupirocin	*[Intervention]* One day before surgery and last for 5 days until discharge (exclude emergency cases)	*[Intervention]* No skin decolonisation	*[Intervention]* No skin decolonisation	

Study Study Types	Nasal decolonisation		Skin decolonisation		Additional antiseptic measures
	Agent	Application protocol	Agent	Application protocol	
Wilcox et al. 2003 Observational study	*[Intervention]* Mupirocin	*[Intervention]* Before surgery: once on the day before surgery; After surgery: continue for 4 days	*[Intervention]* Triclosan (2%)	*[Intervention]* Before surgery: the day or night before	

Table.a 3   Study characteristics of RCTs (new studies)

Author Year Country	Design	Surgery	Baseline				Intervention		Comparator		Outcome	
			Screening for Staphylococcus aureus	Baseline antibiotics	Baseline decolonization	Pre-operative MRSA/MSSA outcome	Decolonization method	Antibiotic prophylaxis	Decolonization method	Antibiotic prophylaxis	First outcome	Second outcome
Phillips et al. 2014 USA	RCT single centre	Arthroplasty (hip, knee, shoulder and their revision surgeries) and spinal surgery (spinal fusion)	Nasal culture was performed for identification of *S. aureus*. The test of the nasal isolates was not reported.	Cefazolin 1 g; clindamycin 600 mg for β-lactam allergy subjects; vancomycin 1 g for MRSA positive subjects	Six 2% chlorhexidine wipes on specific body surfaces from chin to toes the evening prior and morning of surgery	[I]: MSSA = 137, MRSA = 25, *S. aureus* = 162; [C]: MSSA = 130, MRSA = 21, *S. aureus* = 151;	Mupirocin 2% ointment specifically formulated for use on intranasal mucosal surfaces into each nostril for the 5 days prior to surgery	The same as the baseline	A two 30 second applications of povidone iodine 5% solution formulated as a nasal antiseptic into each nostril (4 applications total) within 2 hours of surgical incision	The same as the baseline	Surgical site infection within the 3 months	NR
Sousa et al. 2016 Portugal	RCT single centre	Total Joint Arthroplasty, including THA and TKA	Nares swabbing 2 to 4 weeks before surgery	Cefazolin 2 g administered 30 to 60 minutes before surgery followed by 1 g every 8 hours for 24 hours	NR	MRSA = 8; Detailed breakdown for MRSA/MSSA between [I] and [C] are not available.	2% mupirocin nasal ointment twice a day both nares; bathe with chlorhexidine soap daily for 5 days before surgery	Baseline antibiotics and vancomycin 1 g, 60 min before surgery followed by 1 g every 12 hours for 24 hours	No decolonisation	Baseline antibiotics and vancomycin 1 g, 60 min before surgery followed by 1 g every 12 hours for 24 hours	The overall rate of SSI including all pathogens within first year post surgery	Infections involving *S. aureus* bacteria only

Notes: ITT = Intent-to-treat analysis; PP = per protocol analysis; BMI = body mass index; Notes: [I] = intervention; [C] = comparator; NR = not reported; nos = not otherwise specified; SD = standard deviation; CI = confidence interval; SSI = surgical site infection; ASA = American Society of Anaesthesiologists; RCT = randomised controlled trial; s.aureus = staphylococcus aureus; RR = relative risk; CI = confidence interval; SSI = surgical site infection; SSI = surgical site infection; s.aureus = staphylococcus aureus; MRSA = methicillin-resistance staphylococcus aureus; MSSA = methicillin-sensitive staphylococcus aureus.

Table.a 4   Patients characteristics for RCTs (new studies)

Author Year Country	Design	Inclusion criteria	Exclusion criteria	Patients enrolled	Patients included (ITT)	Patient completed (PP)	[I] Gender (ITT) [M/F]	[C] Gender (ITT) [M/F]	[I] Age (ITT)	[C] Age (ITT)	[I] BMI (ITT)	[C] BMI (ITT)	[I] Co-morbidities (ITT)	[C] Co-morbidities (ITT)	Patient loss	Length of follow-up
Phillips et al. 2014 USA	RCT Single centre	At least 18 years old who presented to the pre-surgical assessment clinic prior to primary or revision arthroplasty and spine fusion surgery	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 (typically for cervical spine surgery)	1874	1874	1539	332 /523	343 /499	Median = 42.4, Range = 19.2, 93.2	Median = 61.8, Range = 19.1, 92.4	Median = 29.5, Range = 14.9, 58.9	Median = 29.5, Range = 12.0, 57.3	Diabetes mellitus = 110 (13%) Rheumatoid arthritis = 36 (4.2%)	Diabetes mellitus = 104 (12%) Rheumatoid arthritis = 36 (4.3%)	335	Up to 3 months
Sousa et al. 2016 Portugal	RCT Single centre	Patients receiving elective primary arthroplasty (THA or TKA) between 1/2010 and 12/2012 regardless of preoperative diagnosis	NR	1305	1028	1028	78 /150	236 /564	64.5, Range = 23, 91	67.1, Range = 21, 92	NR	NR	Obesity (BMI>30) = 76 (33.3%) Diabetes = 50 (21.9%) Inflammatory arthritis = 15 (6.6%) ASA>3 = 65 (28.5%)	Obesity (BMI>30) = 287 (35.9%) Diabetes = 164 (20.5%) Inflammatory arthritis = 20 (2.5%) ASA>3 = 206 (25.8%)	0	Up to 3 months

Notes: ITT = Intent-to-treat analysis; PP = per protocol analysis; BMI = body mass index; Notes: [I] = intervention; [C] = comparator; NR = not reported; nos = not otherwise specified; SD = standard deviation; CI = confidence interval; SSI = surgical site infection; ASA = American Society of Anaesthesiologists; RCT = randomised controlled trial; s.aureus = staphylococcus aureus; RR = relative risk; CI = confidence interval; SSI = surgical site infection; SSI = surgical site infection; s.aureus = staphylococcus aureus; MRSA = methicillin-resistance staphylococcus aureus; MSSA = methicillin-sensitive staphylococcus aureus.

Table.a 5   Study characteristics of observational studies (new studies)

Author Year Country	Design	Surgery	Screening method	Screening results	[I] Decolonization method	[I] Antibiotic prophylaxis	[C] Decolonization method	[C] Antibiotic prophylaxis	First outcome	Second outcome
Adler et al. 2012 USA	Respective cohort	Cardiovascular surgery with median sternotomy	NR	NR	Mupirocin to nares twice daily for 5 days prior to surgery, bathing with chlorhexidine gluconate from neck down for 2 nights prior to the day of surgery	Cefazolin 20mg/kg pre-op within 5 minutes before incision and repeated every 3 hours (6 if neonates) give or take 30 minutes during surgery; clindamycin 10mg/kg pre-op within 15 minutes before incision and repeated every 3 hours (6 if term neonates and 12 for pre-term neonates) minutes during surgery; vancomycin 15mg/kg pre-op within 90–120 minutes before incision and repeated every 6 hours (12 hours for neonates) give or take 30 minutes during surgery for patients with contraindication or known MRSA/MSSA	Povidone-iodine for skin preparation	Non-standardised antibiotic prophylaxis	A population-level assessment of the SSI rate over time	A multivariable analysis of risk of SSI using patient-level data
Baratz et al. 2015 USA	Retrospective cohort	Elective total joint arthroplasty	[I] Screened for MRSA and MSSA by PCR	[I] MRSA=158; MSSA=486;	Carriers of MSSA and MRSA provided intranasal 2% mupirocin ointment (twice daily 5 days) and daily skin cleansing with 4% chlorhexidine soap (5 days)	Cefazolin pre- and two post-operative at 8-hour intervals, MRSA carrier and patient allergic to beta-lactam received vancomycin, intraoperative and one dose 12-hours post-op	NR	NR	Effectiveness of the 2-week decolonisation protocol	Risk of infection

Author Year Country	Design	Surgery	Screening method	Screening results	[I] Decolonization method	[I] Antibiotic prophylaxis	[C] Decolonization method	[C] Antibiotic prophylaxis	First outcome	Second outcome
Bebko et al. 2015 USA	Prospective cohort	Elective orthopaedic surgery with hardware implantation	Testing for MRSA nasal colonization status was performed for patients whoever admitted for more than 24 hours as per the hospital-wide screening of all admitted patients	[I]: MRSA = 5/225; [C]: MRSA = 14/244	consisting of the application of both chlorhexidine washcloths, 2%, and oral rinse, 0.12% (both once, the night before surgery), along with an intranasal povidone-iodine solution, 5% (once, the morning before surgery)	Regimen recommended by Surgical Care Improvement Program	NR	NR	Rate of SSIs within a 30 day follow-up among patients undergoing elective orthopaedic surgery with hardware implants	NR
Katayanagi 2015 Japan	Retrospective cohort	Open heart surgery	Nasal swabbing and culture for MRSA carrier	NR	Mupirocin ointment for nasal cavity for MRSA positive patients	Vancomycin for positive patients (immediately before surgery until 2 days after surgery), and reducing durations of general prophylactic antibiotics	NR	Standard antibiotic regimens	Incidence of wound infection	Incidence of mediastinitis
Kohler et al. 2015 Switzerland	Prospective cohort	Cardiac surgery by sternotomy including coronary artery bypass grafts and valve repairs; heart transplant and pacemaker surgery excluded	Not routinely performed	Not reported	A twice daily application of mupirocin ointment in both nares and a once daily whole body washing or showering using a liquid soap with chlorhexidine digluconate 4%; octenidine hydrochloride impregnated washing gloves were used instead for bedridden patients	Cefuroxim, clindamycin and other antibiotics were used, detail not reported	no treatment	Cefuroxim, clindamycin and other antibiotics were used, detail not reported	SSI rates based on standardized prospective surveillance protocol, adjusting for potential confounding factors in a quasi-experimental study	SSI cases in terms of infection depth and spectrum of causative pathogens

Author Year Country	Design	Surgery	Screening method	Screening results	[I] Decolonization method	[I] Antibiotic prophylaxis	[C] Decolonization method	[C] Antibiotic prophylaxis	First outcome	Second outcome
Rao et al. 2011 USA	Retrospective cohort	Elective orthopaedic surgery (Total joint arthroplasty)	Nasal swabbing and culture for *S. aureus*, MRSA and MSSA	[I] *S. aureus* positive = 321/1285	Mupirocin nasal ointment twice daily; bathe with CHG for 5 days immediately before the scheduled surgery	Cefazolin 2g administered 30-60 min before surgery followed by 1g every 8 hours for 24 hours. MRSA history/penicillin allergic patients receiving vancomycin 1g 60 minutes before surgery followed by 1g per 12 hours for 1 day.	NR	Standard antibiotic regimens with the intervention	Surgical site infections in *S. aureus* carriers	Surgical site infections in all patients
Schweizer et al. 2015 USA	Prospective cohort	Scheduled, urgent, or emergent primary hip or knee arthroplasty, primary cardiac surgery through a median sternotomy incision	Nares swabbing during clinic visits 10-14 days, but no more than 30 days before the operations Culture	[I]: MRSA=367, MSSA=1455, unknown = 4905, *S. aureus* neg = 6400;	Patients with positive screening tests for either MRSA or MSSA applied mupirocin intranasally twice daily and bathed with chlorhexidine gluconate once daily for up to 5 days immediately before their operations	Noncarriers and MSSA carriers received either cefazolin or cefuroxime for perioperative prophylaxis, whereas MRSA carriers received both cefazolin or cefuroxime and vancomycin	Patients having elective procedures to baths with chlorhexidine gluconate 1 day before the surgery; mupirocin was used but not all centres	Vancomycin applied to some patients with variation in application criteria	Rates of *S. aureus* either antimicrobial susceptible or resistant isolates deep incisional and organ space SSIs	Length of hospital stay (LOS), readmissions, and rates of Gram-positive SSIs
Walsh et al. 2011 USA	Prospective cohort	Cardiovascular surgery with median sternotomy incision	Nasal culture for MRSA	NR	Mupirocin nasal ointment applied regardless of carrier status to the anterior nares 1 day (emergency) or for 5 days	Vancomycin for S aureus carriers	Skin prep with chlorhexidine alcohol	Vancomycin for S aureus carriers	Surgical site infection rate after implementation of the MRSA intervention program	NR

Notes: [I] = intervention; [C] = comparator; NR = not reported; nos = not otherwise specified; BMI = body mass index; SD = standard deviation; CI = confidence interval; SSI = surgical site infection; ASA = American Society of Anaesthesiologists; RCT = randomised controlled trial; s.aureus = staphylococcus aureus; RR = relative risk; CI = confidence interval; SSI = surgical site infection; SSI = surgical site infection; s.aureus = staphylococcus aureus; MRSA = methicillin-resistance staphylococcus aureus; MSSA = methicillin-sensitive staphylococcus aureus.

Table.a 6   Patients characteristics of observational studies (new studies)

Author Year Country	Design	Inclusion criteria	Exclusion criteria	Patients enrolled	Patients included	[I] Gender [M/F]	[C] Gender [M/F]	[I] Mean age	[C] Mean age	[I] Mean BMI	[C] Mean BMI	[I] Co-morbidities	[C] Co-morbidities	Length of follow-up
Adler et al. 2012 USA	Respective cohort	Patients receiving cardiac surgery with median sternotomy	NR	618	618	224 /200	111 /83	Median = 10, Range = [0, 235] (in months)	Median = 9, Range = [0, 254] (in months)	NR	NR	Non-cardiac nos = 53 (13%)	Non-cardiac nos = 13 (7%)	Patients were followed for 30 days for superficial infections and 1 year for deeper infections per NHSN guidelines
Baratz et al. 2015 USA	Retrospective cohort	Patients receiving elective primary and revision hip and knee arthroplasty over a 2-year period (2012-2013)	History of infection at the operative site	6514	6514	NR	NR	NR	NR	NR	NR	NR	NR	NR
Bebko et al. 2015 USA	Prospective cohort	English speakers, 18 years of age or older, and able to visit the clinic 5 days prior to surgery	Patients without available follow-up information within 30 days after surgery and those who developed a chronic joint or bone infection at the surgical site were excluded.	723	723	328 /37	318 /26	56.6, SD = 13.37	56.9. SD = 14.8	29.5, SD = 5.7	29.8, SD = 5.6	Diabetes mellitus = 66, (18.1%); Hypertension = 227 (62.2%); Coronary artery disease = 54 (14.8%); Chronic kidney disease = 16 (4.4%); COPD = 37 (10.1%)	Diabetes mellitus = 77, (22.4%); Hypertension = 218 (63.4%); Coronary artery disease = 52 (15.1%); Chronic kidney disease = 17 (4.9%); COPD = 27 (7.8%)	Follow-up for a 30-day postoperative period

Author Year Country	Design	Inclusion criteria	Exclusion criteria	Patients enrolled	Patients included	[I] Gender [M/F]	[C] Gender [M/F]	[I] Mean age	[C] Mean age	[I] Mean BMI	[C] Mean BMI	[I] Co-morbidities	[C] Co-morbidities	Length of follow-up
Katayanagi 2015 Japan	Retrospective cohort	Patients aged ≤15 years who underwent paediatric open-heart surgery between October 2002 and October 2010	Patients were exclude when one or more component of SSI prevention program is missing, and on patient death	174	174	NR	NR	2.2, SD = 3.7	3.4, SD = 3.9	NR	NR	NR	NR	NR
Kohler et al. 2015 Switzerland	Prospective cohort	all cardiac surgery patients undergoing sternotomy procedures, including coronary artery bypass grafts and valve repairs in our tertiary care institution	Heart transplantation and pacemaker surgery were excluded	1787	1787	469 /177	804/ 337	64.4, SD = 13.5	65.2, SD = 13.0	26.7, SD = 4.4	26.9, SD = 4.9	ASA score < 3 = 468 (72.4%) Contamination class I = 635 (98.3%)	ASA score < 3 = 565 (59.8%) Contamination class I = 928 (98.2%)	A telephone interview with at least 5 attempts to reach the patient within 30 days post-operatively or after 1 year if implants, including sternal plates and wire cerclages, were involved
Rao et al. 2011 USA	Prospective cohort	Patients who underwent elective TJA between October 2005 and October 2007 were in the intervention group whereas all 741 between October 2004 and October 2005 served as a pre-intervention control group	NR	3724	892	NR	NR	NR	NR	NR	NR	NR	NR	Up to 2 years of follow up

Author Year Country	Design	Inclusion criteria	Exclusion criteria	Patients enrolled	Patients included	[I] Gender [M/F]	[C] Gender [M/F]	[I] Mean age	[C] Mean age	[I] Mean BMI	[C] Mean BMI	[I] Co-morbidities	[C] Co-morbidities	Length of follow-up
Schweizer et al. 2015 USA	Prospective cohort	18 years or older and had scheduled, urgent, or emergent primary hip or knee arthroplasty or primary cardiac operation through a median sternotomy incision	Arthroplasty revisions, cardiac transplants, transapical valve implantation, and operations performed using percutaneous or thoracotomy approaches, and patients with pre-existing surgical site infections	42534	42534	13140 /15069	6582 /7734	Median = 67.5, Range = [18, 101]	Median = 67.5, Range = [18, 107]	NR	NR	Diabetes mellitus = 3525 (24.6%); Renal disease = 15 (0.2%); Cancer = 200 (1.3%)	Diabetes mellitus = 7178 (25.4%); Renal disease = 42 (0.14%); Cancer = 377 (1.3%)	Up to 90 days after their operations by infection preventionists at participating hospitals
Walsh et al. 2011 USA	Prospective cohort	Underwent cardiac surgery and required a median sternotomy incision	NR	5262	NR	NR	NR	NR	NR	NR	NR	NR	NR	30 days or 1 year if the sternum or deep-organ space was involved

Notes: [I] = intervention; [C] = comparator; NR = not reported; nos = not otherwise specified; BMI = body mass index; SD = standard deviation; CI = confidence interval; SSI = surgical site infection; ASA = American Society of Anaesthesiologists; RCT = randomised controlled trial; s.aureus = staphylococcus aureus; RR = relative risk; CI = confidence interval; SSI = surgical site infection; SSI = surgical site infection; s.aureus = staphylococcus aureus; MRSA = methicillin-resistance staphylococcus aureus; MSSA = methicillin-sensitive staphylococcus aureus.

Table.a 7   Quality assessment of observational studies (new)

Author	Year	Country	Design	Reporting (10)	External validity (3)	Internal Validity – Bias (7)	Internal validity - confounding (6)	Total score	Power
Baratz et al.	2015	USA	Retrospective cohort	6	3	2	1	12	Yes
Schweizer et al.	2015	USA	Prospective cohort	9	3	3	1	16	Yes
Kohler et al.	2015	Switzerland	Prospective cohort	10	3	3	3	19	No
Bebko et al.	2015	USA	Prospective cohort	9	3	2	3	17	Yes
Rao et al.	2011	USA	Prospective cohort	7	3	3	2	15	Yes
Adler et al.	2012	USA	Respective cohort	8	3	2	1	14	No
Walsh et al.	2011	USA	Prospective cohort	4	3	2	2	11	No
Katayanagi	2015	Japan	Retrospective cohort	7	3	2	2	14	No

Appendix II   Search Strategies

PubMed search strategies

(Vancomycin/therapeutic use[MeSH]) OR ((((((((((Staphylococcus aureus[MeSH]) OR Methicillin-Resistant Staphylococcus aureus[MeSH]) OR Methicillin-sensitive staphylococcus aureus[MeSH])) OR (((Staphylococcus aureus[Title/Abstract]) OR Methicillin-Resistant Staphylococcus aureus[Title/Abstract]) OR Methicillin-sensitive Staphylococcus aureus[Title/Abstract])) OR ((Gram-Positive Bacterial Infections[MeSH]) OR Gram-Positive Bacterial Infections[Title/Abstract])) OR ((MRSA[Title/Abstract]) OR MSSA[Title/Abstract])) AND ((((((Methicillin[Title/Abstract]) OR Staphylococcal[Title/Abstract]) OR Staphylococcus[Title/Abstract]) OR S aureus[Title/Abstract])) AND(((resist* [Title/Abstract]) OR sensitiv* [Title/Abstract]) OR suscept* [Title/Abstract])))) OR ((((surgical wound infection[MeSH]) OR surgical wound infect* [Title/Abstract]) OR surgical site infect* [Title/Abstract]) OR SSI* [Title/Abstract]))

AND

(((((((((orthopedic procedure[MeSH]) OR orthopaedic* [Title/Abstract]) OR orthopedic* [Title/Abstract])) OR ((arthroplasty[MeSH]) OR arthroplast* [Title/Abstract])) OR ((TJA[Title/Abstract]) OR TKA[Title/Abstract])) OR joint surgery[MeSH]) OR (((replac* [Title/Abstract] OR surg* [Title/Abstract]) AND (((joint[Title/Abstract]) OR knee[Title/Abstract]) OR hip[Title/Abstract])))) OR (((((Arthrodesis[MeSH]) OR musculoskeletal disease/surgery[MeSH Terms]) OR bone fracture/surgery[MeSH]) OR joint/surgery[MeSH]) OR bone surgery[MeSH]) OR (((((cardiac surgical procedures[MeSH]) AND thoracic surgery[MeSH]))) OR ((((procedure* [Title/Abstract]) OR surg* [Title/Abstract])) AND (((cardiac* [Title/Abstract]) OR cardiothoracic* [Title/Abstract]) OR heart* [Title/Abstract])))

AND

((((((((Antibiotic Prophylaxis[MeSH]) OR Cross Infection/prevention and control[MeSH]) OR antibiotic prophyla* [Title/Abstract]))) OR (((((decoloni* [Title/Abstract]) OR de-coloni* [Title/Abstract]) OR uncoloni* [Title/Abstract]) OR un-coloni*)) OR(((((Carrier State[MeSH]) OR carr* [Title/Abstract]) AND noncarr* [Title/Abstract]) AND non-carr* [Title/Abstract])) OR (((Vancomycin[MeSH]) OR Mupirocin[MeSH]) OR Glycopeptides/therapeutic use[MeSH])

Embase Search strategies

'methicillin resistant staphylococcus aureus'/exp OR 'staphylococcus aureus'/exp OR 'methicillin-sensitive staphylococcus aureus'/exp OR 'staphylococcus aureus':ab,ti OR 'methicillin-resistant staphylococcus aureus':ab,ti OR 'methicillin-sensitive staphylococcus aureus':ab,ti OR 'mrsa':ab,ti OR 'mssa':ab,ti OR 'gram positive infection'/exp OR 'gram positive infection*':ab,ti OR 'surgical infection'/exp OR 'surgical wound infection*':ab,ti OR 'surgical site infection*':ab,ti OR 'ssi*':ab,ti OR ('resist*':ab,ti OR 'sensitiv*':ab,ti OR 'suscept*':ab,ti AND ('methicillin':ab,ti OR 'staphylococcal':ab,ti OR 'staphylococcus':ab,ti OR 's aureus':ab,ti)) OR 'vancomycin':ab,ti AND ('orthopedic surgery'/exp OR 'orthopaedic*':ab,ti OR 'orthopedic*':ab,ti OR 'tja':ab,ti OR 'tka':ab,ti OR ('replac*':ab,ti OR 'surg*':ab,ti AND ('joint*':ab,ti OR 'knee*':ab,ti OR 'hip*':ab,ti)) OR 'arthroplasty'/exp OR 'joint surgery'/exp OR 'arthroplast*':ab,ti OR 'cardiac surgery'/exp OR 'thorax surgery'/exp OR ('procedure*':ab,ti OR 'surg*':ab,ti AND ('cardiac*':ab,ti OR 'cardiothoracic*':ab,ti OR 'heart*':ab,ti))) AND ('antibiotic prophylaxis'/exp OR 'infection prevention and control' OR 'antibiotic prophyla*':ab,ti OR 'decolonization' OR 'decoloni*':ab,ti OR 'de-coloni*':ab,ti OR 'uncoloni*':ab,ti OR 'un-coloni*':ab,ti OR 'bacterium carrier'/exp OR 'carr*':ab,ti OR 'noncarr*':ab,ti OR 'non-carr*':ab,ti OR 'vancomycin'/exp OR 'mupirocin'/exp OR 'glycopeptides'/exp)