Surgical site infection prevention through bundled interventions in hip replacement surgery: A systematic review

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Abstract:	Background Bundles have shown to improve patient outcomes in several settings. Surgical site infections (SSIs) following joint replacement surgery are associated with severe outcomes. We aimed to determine the effectiveness of non-pathogen specific bundled interventions in reducing SSIs after hip arthroplasty procedures. Materials and Methods A systematic review and meta-analysis were conducted according to the PRISMA statement guidelines (PROSPERO registration number CRD42020203031). PubMed, Embase and Cochrane databases were searched for studies evaluating SSI prevention bundles in hip replacement surgery, excluding studies evaluating pathogen-specific bundles. Records were independently screened by two authors. The primary outcome was the SSI rate in intervention and control groups or before and after bundle implementation. Secondary outcomes of interest were bundle compliance and the number and type of bundle components. A meta-analysis was conducted using raw data, by calculating pooled relative risk (RR) SSI estimates to assess the impact of bundled interventions on SSI reduction. Results Eleven studies were included in the qualitative review and four studies comprising over 20 000 patients were included in the quantitative synthesis. All included studies found bundles were associated with reduced SSI rates. The pooled RR estimated from the fixed-effects model was 0.76 (95% confidence interval 0.61-0.96, p 0.022) with 49.8% heterogeneity. Conclusions Results support the effectiveness of non-pathogen specific bundled interventions in preventing SSIs following hip arthroplasty. A “core” group of evidence-based elements for bundle development were identified.

International Journal of Surgery Author Disclosure Form

The following additional information is required for submission. Please note that failure to respond to these questions/statements will mean your submission will be returned. If you have nothing to declare in any of these categories, then this should be stated.

Please state any conflicts of interest

None to declare.

Please state any sources of funding for your research

None.

Please state whether Ethical Approval was given, by whom and the relevant Judgement's reference number

No (systematic review and meta-analysis).

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Author contribution

Please specify the contribution of each author to the paper, e.g. study design, data collections, data analysis, writing. Others, who have contributed in other ways should be listed as contributors.

Conceptualization CV; Formal analysis VB; Investigation VB, ARC, IC, NM, CV; Supervision CMZ; Writing - original draft CV, NM; Writing - review & editing CMZ.

Guarantor

The Guarantor is the one or more people who accept full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish. Please note that providing a guarantor is compulsory.

Costanza Vicentini (Costanza.vicentini@unito.it)

Turin, 19/07/21

Dear Editors,

We are submitting a manuscript entitled "Surgical site infection prevention through bundled interventions in hip replacement surgery: a systematic review and meta-analysis". Surgical site infections (SSIs) affect a relatively small fraction of patients undergoing hip arthroplasties every year, but they are associated with severe outcomes and significant clinical and economic burdens.

Bundled interventions have shown to improve patient outcomes in several settings, including joint replacement. In this context, existing systematic reviews have focused on pathogen-specific care bundles with the objective of preventing *Staphylococcus aureus* SSIs, as methicillin-sensitive and methicillin-resistant *S aureus* (MSSA and MRSA) are responsible for an important proportion of SSIs following hip arthroplasty. However, other agents are often involved. Therefore, in this study we aimed to determine the effectiveness of bundled interventions not specific for preventing SSIs caused by *S aureus* in reducing SSIs after hip arthroplasty procedures.

This study found bundles were associated with a significant reduction in SSI risk by 24%. Results of this systematic review and meta-analysis suggest non-pathogen specific bundles are important tools for SSI prevention in hip arthroplasty.

Thank you for your time and consideration,

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30/09/2021

Dear Editor,

We are submitting the revised version of our manuscript "Surgical site infection prevention through bundled interventions in hip replacement surgery: a systematic review." We would like to thank the Editor and the expert Reviewers for their time and for their insightful comments and suggestions. We hope to have sufficiently improved on the issues present in our original manuscript.

Reviewer #4: Some question were not addressed properly - please re-revise.

We have improved language and corrected formatting mistakes. As per Reviewer #4's previous comment, we have revised risk of bias assessment. The risk of bias of included studies was assessed using the Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomized studies in meta-analyses as all included studies were observational, which evaluates selection, comparability, and outcome/exposure. As stated in the Methods section, we assigned the following risk of bias categories based on the final score: high (for scores ≤3), intermediate (4-6), and low (7-9). We found that among the included studies, six studies were at low risk of bias, three were at moderate risk, and one was at high risk. Risk of bias of included studies was added as a column to Table 1.

Once again, thank you for your time and consideration.

Highlights

- All studies found bundles were associated with reduced SSI rates.
- Pooled analysis found a significant reduction in SSI risk by 24%.
- Non-pathogen specific bundles are effective for SSI prevention in hip arthroplasty.
- A “core” group of evidence-based elements for bundle development were identified.

Surgical site infection prevention through bundled interventions in hip replacement surgery: a Systematic Review.

Running title: Systematic review of bundles in hip arthroplasty.

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Declaration of interest

None to declare.

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Conceptualization CV; Formal analysis VB; Investigation VB, ARC, IC, NM, CV; Supervision CMZ; Writing - original draft CV, NM; Writing - review & editing CMZ.

Surgical site infection prevention through bundled interventions in hip replacement surgery: a Systematic Review.

Abstract

Background. Bundles have shown to improve patient outcomes in several settings. Surgical site infections (SSIs) following joint replacement surgery are associated with severe outcomes. We aimed to determine the effectiveness of non-pathogen specific bundled interventions in reducing SSIs after hip arthroplasty procedures.

Materials and Methods. A systematic review and meta-analysis were conducted according to the PRISMA statement guidelines (PROSPERO registration number CRD42020203031). PubMed, Embase and Cochrane databases were searched for studies evaluating SSI prevention bundles in hip replacement surgery, excluding studies evaluating pathogen-specific bundles. Records were independently screened by two authors. The primary outcome was the SSI rate in intervention and control groups or before and after bundle implementation. Secondary outcomes of interest were bundle compliance and the number and type of bundle components. A meta-analysis was conducted using raw data, by calculating pooled relative risk (RR) SSI estimates to assess the impact of bundled interventions on SSI reduction.

Results. Eleven studies were included in the qualitative review and four studies comprising over 20 000 patients were included in the quantitative synthesis. All included studies found bundles were associated with reduced SSI rates. The pooled RR estimated from the fixed-effects model was 0.76 (95% confidence interval 0.61-0.96, p 0.022) with 49.8% heterogeneity.

Conclusions. Results support the effectiveness of non-pathogen specific bundled interventions in preventing SSIs following hip arthroplasty. A “core” group of evidence-based elements for bundle development were identified.

Keywords: Healthcare associated infections; surgical site infections; infection control; bundle; hip arthroplasty; joint replacement.

1. Introduction

Surgical site infections (SSIs) affect around 1-2% of hip arthroplasties every year,[1,2] and are associated with severe outcomes. Their treatment may involve extended antibiotic courses, prolonged rehabilitation, and revision procedures.[1] SSIs account for nearly 15% of revisions following hip arthroplasty, which have been estimated to cost as much as 80 000 € per case.[3] The functional ability and quality of life of patients developing SSIs are significantly lower compared to those of patients with uncomplicated arthroplasty, and SSIs in this context are associated with increased mortality rates.[1]

Many SSIs following hip arthroplasty could be prevented through appropriate measures,[4] such as evidence-based bundled interventions.[5–7] The concept of the "bundle" was developed by the Institute for Healthcare Improvement (IHI) and by definition consists of 3–5 evidence-based practices that, when implemented collectively and consistently, significantly improve patient outcomes.[8]

To date, systematic reviews have focused on pathogen-specific care bundles with the objective of preventing *Staphylococcus aureus* SSIs,[9] as methicillin-sensitive and methicillin-resistant *S aureus* (MSSA and MRSA) are responsible for an important proportion of SSIs following hip arthroplasty.[10,11] However, other agents such as coagulase-negative *Staphylococcus* spp, streptococcus and enterococcus organisms are also involved, with varying microbiological epidemiology between countries.[12] Therefore, we aimed to determine the effectiveness of bundled interventions not specific for preventing SSIs caused by *S aureus* in reducing SSIs after hip arthroplasty procedures.

2. Methods

A systematic review and meta-analysis were conducted in line with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and AMSTAR (Assessing the methodological quality of systematic reviews) guidelines.[13,14] The level of compliance with the AMSTAR 2 checklist was high (Supplementary file). The protocol for this study was registered with the PROSPERO international prospective register of systematic reviews (CRD42020203031).

2.1 Search strategy

PubMed, Embase and The Cochrane Library databases were systematically searched for studies evaluating SSI prevention bundles in hip replacement surgery, using medical subject heading (MeSH) terms, keywords and free text terms as follows: terms related to the surgical procedure AND surgical site infection AND care bundle (Supplementary file).

The screening of search results was performed using the web-based, open access platform Colandr[15] and followed a two-step process. After removing duplicates, two out of three authors (VB, NM and CV) independently screened titles and abstracts for potential relevance according to the inclusion/exclusion criteria. The same authors then independently reviewed the full-texts of eligible articles. The reference sections of retrieved review articles were inspected to identify additional studies that might be eligible for inclusion. The first author reviewed all conflicting assessments and any discrepancies at both stages were resolved by reaching agreement through discussion among the three authors involved in the screening process. Reasons for exclusion at the full-text screening phase were recorded.

2.2 Inclusion and exclusion criteria

Randomized controlled trials, observational studies and systematic reviews published from 2001 (the year of inception of bundled interventions)[8] through August 2020, in any language, that assessed bundles for SSI prevention in adult patients undergoing hip arthroplasty were eligible for

inclusion. Studies evaluating pathogen-specific bundles were excluded. Only full-text articles were included in the study.

2.3 Outcomes of interest

The primary outcome was the SSI rate in intervention and control groups or before and after bundle implementation. Secondary outcomes of interest were bundle compliance and the number and type of bundle components.

2.4 Data extraction

The same three authors independently extracted data from included articles, using pre-defined extraction forms which were cross-checked and used to create Tables 1-2. The following data was extracted: study characteristics (authors, year of publication, year of study, country, setting, and study design), characteristics of included patients, SSI definition, duration of follow-up, characteristics of the bundled intervention (number and type of elements, length of the intervention), sample size in each arm, number of SSIs in each arm.

2.5 Quality assessment

The risk of bias of included studies was assessed using the Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomized studies in meta-analyses,[16] which evaluates selection, comparability, and outcome/exposure. We assigned the following risk of bias categories based on the final score: high (for scores $\leq$3), intermediate (4-6), and low (7-9).

2.6 Data synthesis and statistical analysis

All identified studies were included in the qualitative synthesis. Findings were described in relation to the number and type of bundle elements, and to bundle compliance when possible. Studies that reported sufficient raw data on the primary outcome (pre- and post- intervention SSI rates or intervention vs. control groups SSI rates) were included in the quantitative synthesis. If studies had

the potential to be included in this analysis but were missing data, the Authors were contacted to retrieve the necessary information.

A meta-analysis was conducted using raw data, by calculating pooled relative risk (RR) SSI estimates and 95% confidence intervals (CI) to assess the impact of bundled interventions on SSI reduction. Heterogeneity within the studies was assessed by considering clinical (inclusion criteria, SSI definitions, length of follow-up), methodological (design, risk of bias), and statistical characteristics (Cochrane's Q test, I^2 statistic and p value).[17] Heterogeneity was considered statistically significant if $p < 0.05$ or $I^2 > 50$. As heterogeneity among studies was under the consider threshold, SSI RR estimates were pooled using a fixed-effects model. Results of the meta-analysis were illustrated by a forest plot.

A funnel plot was inspected for symmetry to identify publication bias, which was quantified using Egger's linear regression test and Begg and Mazumdar's rank correlation test.[18] Further, to adjust for the observed publication bias, trim and fill technique was used for recalculating the effect size (ES).[19] Analyses were performed using ProMeta software v 3.0 (Internovi, Cesena FC, Italy).

3. Results

3.1 Search results

The initial search yielded 2761 potentially relevant studies. Titles and/or abstracts of 1927 unique records were screened and of these, 39 full-text articles were assessed for eligibility. Eleven studies were included in the qualitative review.[6,7,20–28] The search and selection process and reasons for exclusion are summarized in Figure 1.

3.2 Study characteristics

The characteristics of the included studies, including characteristics of SSI surveillance, are summarized in Table 1. All of the 11 studies that met the criteria for inclusion were observational cohort studies: 9 were retrospective,[7,20–23,25–28] one was prospective[24] and one was

retrospective-prospective.[6] Most interventions were implemented in single-centres,[6,7,21–27] but two articles reported large multicentre studies involving over 60 000 patients from 193 hospitals[20] and over 10 000 patients from 34 hospitals.[28] One study compared three subsequent bundles,[22] and another evaluated the impact of a bundle over time without a comparison group,[25] whereas the rest of the studies compared pre and post-intervention groups[6,7,20,21,23,24,26,27] or intervention vs. usual care groups.[28] In total, six studies were at low risk of bias,[6,20,22-25,28], three were at moderate risk,[7,21,27] and one was at high risk.[26]

3.3 Bundled interventions and outcomes of interest

An overview of the bundled interventions, compliance rates and impact on infection risk of included studies is presented in Table 2. Bundle size ranged from 3[22] to 22[7] elements, with varying components, as summarized in Table 3. The most common components pertained to: antimicrobial prophylaxis appropriateness in general and appropriate timing of administration in particular (9 and 6 out of 11 included studies respectively); skin disinfection, in particular prior to surgery (8 and 7/11 respectively); preoperative showering (6/11); appropriate hair removal (6/11); optimization of patient risk factors prior to surgery, including screening for MRSA/MSSA and decolonization of carriers or nasal mupirocin regardless of MRSA carriage (6/11).

Three studies reported overall compliance rates, which ranged from 77.3% to 94.7%.[7,24,28] Two of these studies evaluated the impact of bundle compliance on SSI risk, finding a significant association between bundle compliance and reduced SSI rates.[24,28]

All studies included in this review reported SSI rates, ranging from 1.3%[24] to 6.9%[6] in the control groups, and from 0%[21] to 3.83%[22] in the intervention groups. All studies comparing intervention vs. control groups found bundles were associated with reduced SSI rates,[6,7,20–28] including five studies reporting a statistically significant effect (Table 2).[6,20,21,26,28] The study comparing three subsequent bundles found a statistically significant reduction in SSIs with the introduction of each bundle,[22] and the study evaluating the impact of a bundle over time found a

steady decrease in SSI incidence over the years.[25] Two studies reported microbiological analysis of SSIs.[6,22] One study, conducted in Switzerland, found *S. aureus* in 66% of cases, coagulase-negative *Staphylococcu*s in 16% of cases, *Streptococcus viridans* in 6% of cases, *Bacteroides fragilis* in 6% of cases, *Proteus mirabilis* in 6% of cases, and *Candida parapsilopsis* with *S aureus* in 6% of cases. No cases of MRSA were found in this study.[6] Another study, performed in the UK, found 57.14% of overall SSIs were associated with MRSA.[22]

Among the 11 studies included in the review, four studies involving 20 868 patients[6,7,21,28] provided sufficient raw data to be included in the quantitative synthesis (Figure 2). Two out of the four studies were at low risk of bias[6,28] and two were at moderate risk risk.[7,21] All included studies showed a protective effect of bundles on SSI risk, with RRs from 0.12[21] to 0.83.[28] The pooled RR estimated from the fixed-effects model was 0.76 (95% CI 0.61-0.96, p 0.022) with 49.8% heterogeneity, as shown in Figure 2. Some asymmetry was visible on the funnel plot (Figure 3), however no significant publication bias was found through trim and fill method (p 0.174). Due to the limited number of studies included in the quantitative synthesis, we could not conduct a meta-regression to evaluate the impact of bundle size on SSI risk.

4. Discussion

Results of this systematic review and meta-analysis support the effectiveness of non-pathogen specific bundled interventions in preventing SSIs following hip arthroplasty. Pooled analysis of results of four included studies comprising over 20 000 patients found a significant reduction in SSI risk by 24%. This result is of important clinical significance as hip replacement surgery is common and expected to increase with the ageing population, and SSIs are associated with increased morbidity and mortality.[1] SSI prevention through bundled interventions could also prove economically advantageous, as SSIs following hip replacement surgery significantly increase length of stay and healthcare costs.[11,21,22,25]

To the best of our knowledge, this is the first systematic review evaluating non-pathogen specific bundled interventions in this context. A previous systematic review and meta-analysis found bundles consisting of nasal decolonization and targeted glycopeptide prophylaxis were associated with a statistically significant reduction in *S aureus* SSIs following orthopaedic surgery (pooled RR 0.33, 95% CI 0.21-0.52 respectively), but no significant effect was found considering Gram negative SSIs or Gram positive SSIs other than *S aureus*.[29]

Although insufficient data were available to conduct a meta-regression, bundles with a higher number of elements appeared to be associated with a greater impact on SSI risk among studies included in this review. This observation is in line with results of analyses conducted by Pop-Vicas *et al* and Tomsic *et al*, which evaluated the role of bundle size on SSI risk in colorectal surgery.[30,31] Both studies found bundles with over 11 components had a higher impact on SSI risk, although it could not be determined whether this success depended on bundle size (as larger bundles included more evidence-based measures) or on the specific components included in the bundles.[31]

According to the IHI, bundles should contain 3 to 5 elements, as the intervention's success is tied to all-or-none compliance and larger bundles may pose implementation issues.[8] Interestingly, our review appears to suggest higher compliance rates were achieved among studies implementing larger bundles.[7,24] In the study by Bullock *et al*, an integrative approach to patient management was applied, which fostered improved relations among surgeons, the anesthesia team, medical specialists, and general practitioners.[7] Manivannan *et al* implemented a surveillance, audit and feedback intervention which led to an improvement in overall compliance with the bundle, accompanied by increased responsibility and accountability among medical and paramedical staff involved in patient care.[24] Other studies included in this review identified communication,[26,27] openness to bidirectional learning,[26] and multi-disciplinary collaboration for both bundle development and implementation as important factors for bundle adoption.[6,25–27] Analyzing the

success of the Ventilator and Central Line Bundles, the IHI also recognized the importance of teamwork, cooperation and communication in ensuring reliable and consistent care.[8] Quality improvement campaigns including a rapid spread network infrastructure and concerted, multifaceted dissemination of resources and educational materials have proven successful on a larger scale.[20]

The five most common components of bundles included in this review were: optimization of patient risk factors prior to surgery (such as smoking and MRSA carriage), appropriate antimicrobial prophylaxis, skin disinfection, preoperative showering, and appropriate hair removal. Considering these elements are guideline-recommended practices supported by high-quality evidence,[32,33] they could be considered "core" measures for SSI prevention through bundled interventions in hip arthroplasty.

Bundles included in this review contained several other interventions, with varying quality of supporting evidence. As evidence quality is important for stakeholder buy-in, which in turn influences bundle adoption,[34] it may be more productive to prioritize elements with high-level evidence. Organizational and staffing aspects were included in three bundles,[7,21,25] although the IHI recommends each bundle element should be patient-based, as including general processes could lead to a mixed measure of compliance which is difficult to assess.[8]

The high variability of bundle components identified in this review reflects the complexity of SSI prevention, with interventions often tailored to the specific clinical setting or developed in response to a particular issue.[6] Gilhooly *et al* conducted a scoping review of barriers to the successful development and implementation of care bundles in acute care,[35] and found designing a new intervention for each clinical setting was a potential challenge, as significant resources and time are required. Establishing a core group of measures, such as those identified by this review, could represent a facilitator for bundle development in this context.

Gilhooly *et al* highlighted the importance of staff and patient engagement in bundle design and implementation.[35] Of note, only two of the bundles included in this review included elements directed at patient education and involvement.[7,21] The most recent National Institute for Health and Care Excellence guidelines for SSI prevention recognize patients' right to be involved in decisions concerning their care and recommend providing information on and engaging patients in SSI prevention and management throughout all stages of care.[32] It would be interesting to further incorporate these elements in future bundles and to evaluate their impact on bundle success.

This study had some limitations that should be addressed. First, as all systematic reviews, our results are only as valid as the studies that were included, which consisted exclusively of observational studies. Further, as our meta-analysis was based on secondary data, it was not possible to assess the effect of potential confounders on SSI risk.[36] Several studies did not report compliance rates in intervention and control groups, therefore we could not evaluate the uptake nor the separate effect of infection control practices. More accurate reporting of compliance is required to allow a comprehensive interpretation of data on the effectiveness of bundled interventions in this setting.

In conclusion, bundles have shown to improve patient outcomes by promoting multidisciplinary communication and collaboration, leading to increased consistency and standardization of care.[8] Despite its limitations, this systematic review suggests non-pathogen specific bundles are important tools for SSI prevention in hip arthroplasty, and identified a group of elements that could be used as a "core" for developing bundled interventions tailored to the clinical context.

Provenance and peer review

Not commissioned, externally peer-reviewed.

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Tables

Table 1. Characteristics of studies evaluating non-pathogen specific bundled interventions for the prevention of surgical site infections (SSIs) following hip arthroplasty.

First Author, year	Country	Study design	Setting	Included procedures	SSI definition	Length of follow-up	Funding	Risk of bias[a]
Acklin, 2011	Switzerland	Retrospective-prospective cohort study	Single trauma unit	Implant surgery for closed fractures of the proximal femur	CDC	1 year	Scientific Foundation of the University Hospital Basel.	Low
Bullock, 2017	USA	Retrospective cohort study	Single hospital	Hip arthroplasty procedures excluding hip resurfacing, hip hemiarthroplasty, simultaneous bilateral arthroplasty, or revision arthroplasty	Musculoskeletal Infection Society criteria and/or confirmed with positive culture results	90 days	None	Moderate
Calderwood, 2018	USA	Retrospective cohort study	193 hospitals in 5 states	Primary hip arthroplasty	ICD-9 codes	90 days	Agency for Healthcare Research and Quality, and Department of Health and Human Services	Low
Fornwalt, 2015	USA	Retrospective cohort study	Single hospital	Total hip procedures	Not reported	Not reported	Not reported	Moderate
Johnson, 2012	UK	Retrospective cohort study	Single level 1 trauma center	Hip hemiarthroplasty following proximal femural fractures	Health Protection Agency	30 days/1 year if with an implant	Not reported	Low

Kritikou, 2019	Greece	Retrospective cohort study	Tertiary care hospital	Knee arthroscopy, knee or hip arthroplasty	CDC	1 year	None	Low
Manivannan, 2017	India	Prospective cohort study	Single tertiary-care hospital	Orthopaedic surgery procedures	CDC	30 days/1 year if with an implant	None	Low
Mok, 2019	Singapore	Retrospective cohort study	Single acute hip unit	Hip surgery procedures	Not reported	Duration of hospital stay	Not reported	Low
Rozario, 2017	Canada	Retrospective cohort study	Single hospital	General and orthopedic surgery (total knee and total hip arthroplasties, hip fractures)	Not reported	Not reported	Not reported	High
Tillman, 2013	USA	Retrospective cohort study	Single tertiary care hospital	Composite, cardiac, colorectal, general, gynecologic, orthopaedic, thoracic, and vascular surgery	ACS NSQIP	Not reported	Not reported	Moderate
Vicentini, 2020	Italy	Retrospective cohort study	34 hospitals	Hip arthroplasty	ECDC HAI-SSI	90 days	None	Low

[a]Assessed using the Newcastle-Ottawa Scale. The following score cut-offs were used: ≤3 high risk of bias, 4-6 intermediate risk, 7-9 low risk.

CDC, Centers for Disease Control and prevention. ICD-9, International Classification of Diseases, 9th revision. ACS NSQIP, American College of Surgeons National Surgical Quality Improvement Program. ECDC HAI-SSI, European Centre for Disease Prevention and Control healthcare-associated infection - surgical site infection.

Table 2. Summary of non-pathogen specific bundled interventions for the prevention of surgical site infections (SSIs) following hip arthroplasty, compliance rates and impact on infection risk.

First Author, year	N of bundle elements	Length of intervention	Overall compliance rate at end of study	Intervention group, N events/total (SSI rate)	Control group, N events/total (SSI rate)	Effect measure statistically significant?
Acklin, 2011	8	10 months	Not reported	3/153 (2%)	15/217 (6.9%)	Yes
Bullock, 2017	22	2 years	92.5%[b]	4/675 (0.59%)	10/641 (1.56%)	No
Calderwood, 2018	5	3 years	Not reported	1.63%	2.19%	Yes
Fornwalt, 2015	13	1 year	Not reported	0/191 (0%)	4/200 (2%)	Yes
Johnson, 2012	3	8 years	Not reported	70/1830 (3.83%)	Not applicable	Not applicable
Kritikou, 2019	8	2 years	Not reported	4/559 (0.7%)[a]	13/740 (1.8%)[a]	No
Manivannan, 2017	8	2 years	94.7%[b]	2/232 (0.9%)	1/77 (1.3%)	No
Mok, 2019	12	3 years	Not reported	14/758 (1.8%)	Not applicable	Not applicable
Rozario, 2017	7[a]	6 months	Not reported	9/844 (1.0%)[b]	28/828 (3.4%)[b]	Yes
Tillman, 2013	3	1 year	Not reported	7/1031 (0.7%)[a]	16/960 (1.7%)[a]	No
Vicentini, 2020	4	8 years	77.3%	138/10661 (1.29%)	127/8130 (1.56%)	Yes

[a]Orthopaedic surgery. [b]All procedure categories.

Table 3. Bundle components of non-pathogen specific bundled interventions for the prevention of surgical site infections (SSIs) following hip arthroplasty.

Component	Acklin, 2011	Bullock, 2017	Calderwood, 2018	Fornwalt, 2015	Johnson, 2012	Kritikou, 2019	Manivannan, 2017	Mok, 2019	Rozario, 2017	Tillman, 2013	Vicentini, 2020
Optimization of patient risk factors prior to surgery											
Smoking		X				X					
Hemoglobin A1c		X				X		X			
BMI		X				X		X			
Screening for MRSA/MSSA and decolonization of carriers/nasal mupirocin regardless of MRSA carriage		X	X	X		X	X	X			
Preoperative blood work/prevention of anemia		X						X			
Preanesthesia appointment		X									
Clinical assessment		X				X					
Minimization of hospital stay prior to surgery						X					
Preoperative educational interventions directed at patients		X		X							
Antimicrobial prophylaxis								X			
Appropriate agent					X				X	X	X
Appropriate dose					X				X		X
Timing within 120 minutes prior to incision	X		X		X		X			X	X
Re-dosing if prolonged surgery									X		
Discontinuation within 24 hours		X									X
Preoperative showering		X	X			X	X		X		X
Appropriate hair removal		X	X			X	X		X		X
Skin disinfection											
Prior to surgery	X		X		X	X	X	X	X		
Intraoperatively	X	X	X								
Prior to closure	X										
Post-operative		X	X								
Gloves											
Double gloving	X								X		
Outer glove change every 60 minutes									X		
Glove change prior to implanting		X									
Glove change prior to closure									X		

Surgical instruments No flash sterilization cycle/only if urgency		X				X					
Closure technique Clips Subcuticular sutures Gentamicin-impregnated collagen implanted under the fascial layer during wound closure					X X X						
Sterile dressing Applied under direct supervision of the surgeon Silver-impregnated Removal after 48 hours (except if blood moisted) Daily changes after 48 h	X X	X		X					X		
Anterior approach to total hip arthroplasties				X							
Hemostasis	X							X			
Maintenance of normothermia Prior to surgery Intra-operatively Post-operatively							 X	 X		 X X X	 X
Glycemic control during surgery							X				
Restricted operating room traffic		X							X		
Post-operative patient management Removal of surgical wound drains after 24-48 hours Aspirin for low-risk patients Early mobilization Coaching Postoperative fever examination Wound care Nutrition optimization Prevention of anemia Discharge planning Follow-up phone call Minimization of hospital stay	 X	 X X		 X X X			 X	 X X X X X X X 			
Organization and staff >50% of nurses passed orthopaedics certification Safety huddles 2 times/day Dedicated unit		 X		 X X							

Isolation of surgical hip patients from patients with MRSA								X			
No food in patient rooms				X							
Procedures scheduled 2-3 times/week and patients grouped by surgery day				X							

Figure captions and legends

Figure 1. PRISMA flow diagram of the search and selection process.

Figure 2. Meta-analysis of studies evaluating the impact of non-pathogen specific bundled interventions on surgical site infections (SSIs) following hip arthroplasty.

Outcome is risk ratio (RR) for SSI. Summary RR calculated with fixed-effects method.

Figure 3. Funnel plot assessing publication bias of studies evaluating non-pathogen specific bundled interventions for the prevention of surgical site infections (SSIs) following hip arthroplasty.

Figure 2

	ES	95% CI	W	Sig.
Acklin 2010	0.28	0.08 / 0.96	3.52%	0.043
Bullock 2017	0.38	0.12 / 1.21	3.95%	0.100
Fornwalt 2015	0.12	0.01 / 2.15	0.62%	0.148
Vicentini 2020	0.83	0.65 / 1.05	91.91%	0.124
Overall (fixed-effect model)	0.76	0.61 / 0.96	100.00%	0.022

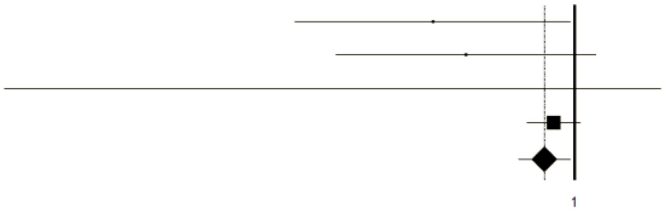
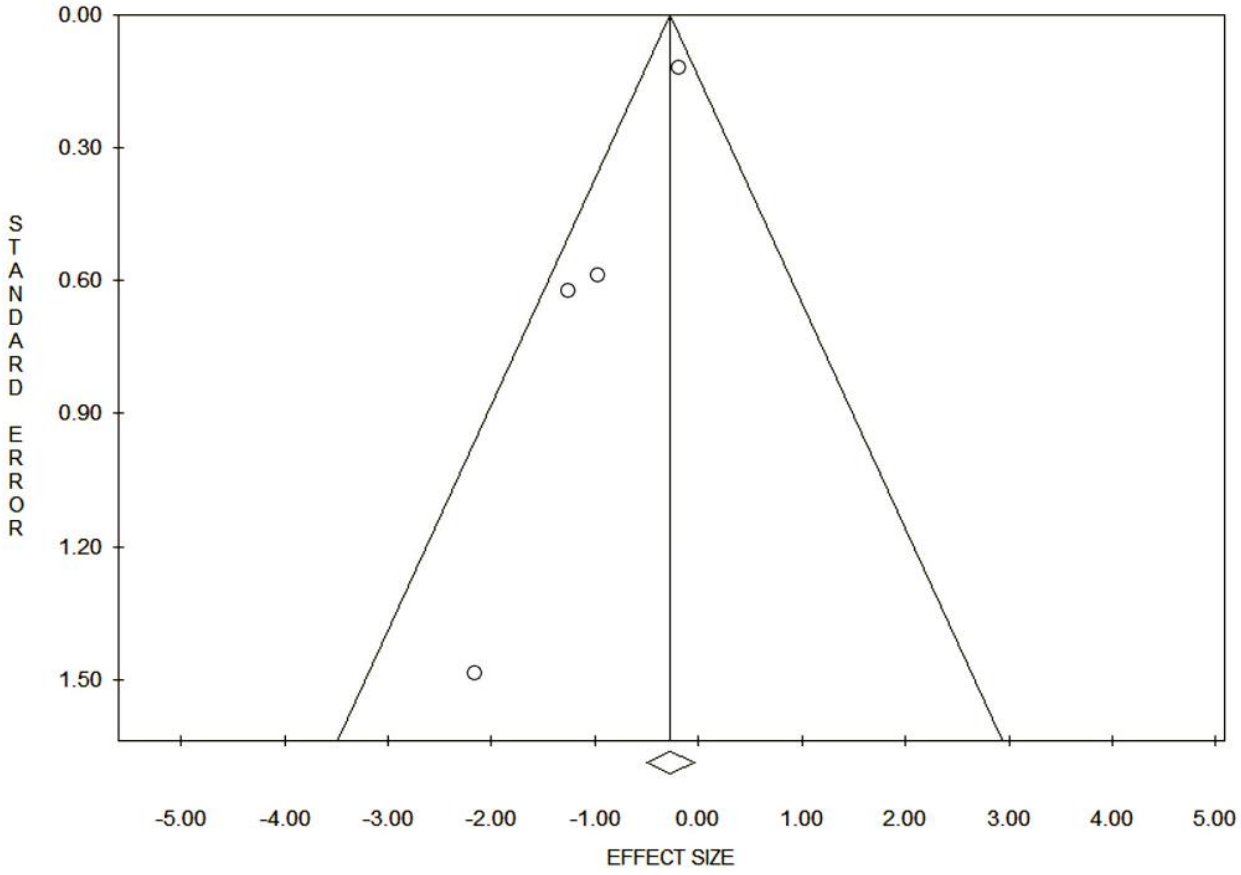
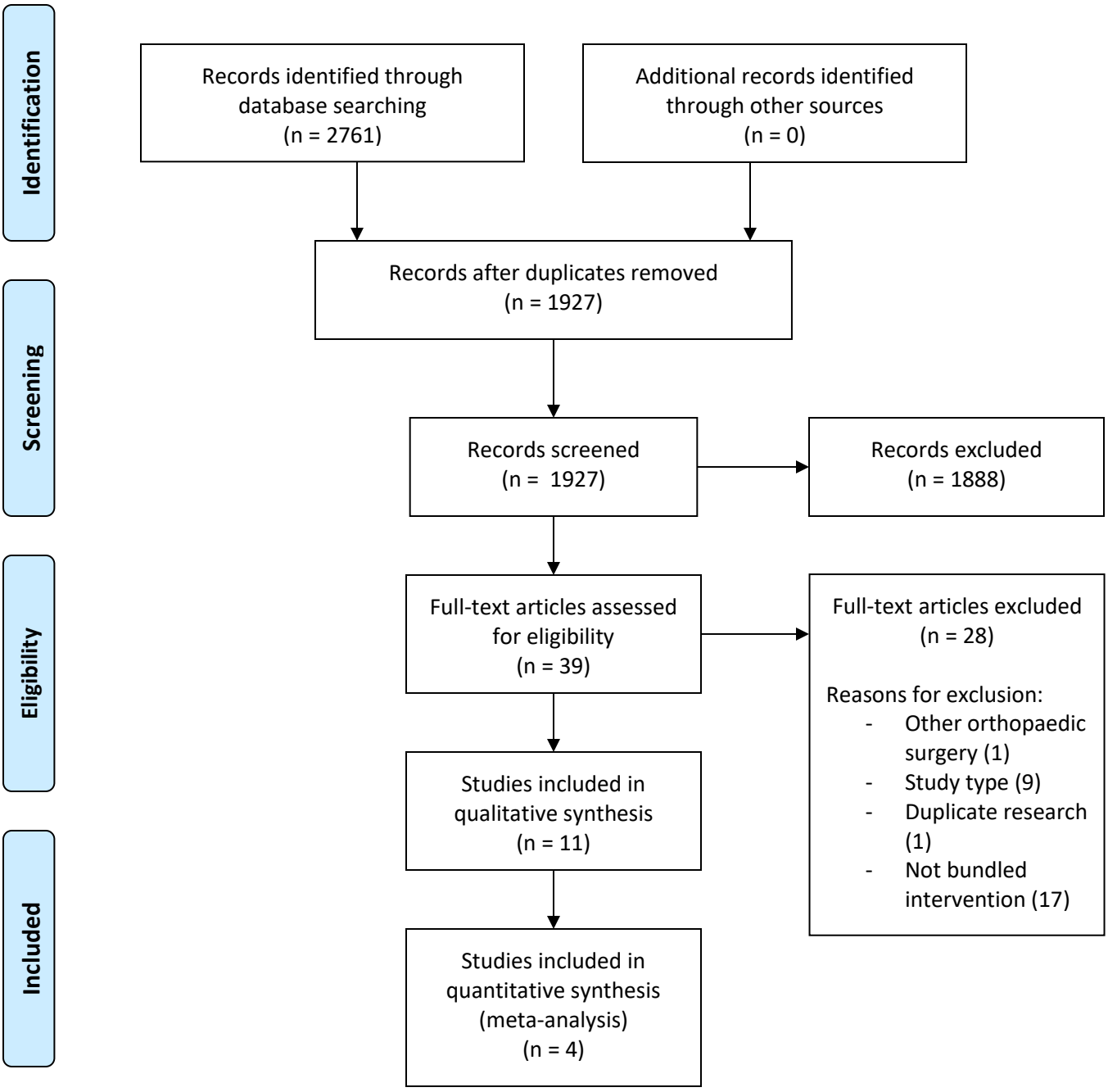


Figure 3



PRISMA 2009 Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3-4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supp. file
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4-5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5-6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6-7, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	6, Table 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7-8, Figure 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7-8, Figure 2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8, Figure 3
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA (8)
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8-11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	NA

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

PRISMA 2009 Checklist

For more information, visit: **www.prisma-statement.org**.

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1. Did the research questions and inclusion criteria for the review include the components of PICO?

For Yes:
- ☑ Population
- ☑ Intervention
- ☑ Comparator group
- ☑ Outcome

Optional (recommended)
- ☑ Timeframe for follow-up

- ☑ Yes
- ☐ No

2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?

For Partial Yes:
The authors state that they had a written protocol or guide that included ALL the following:
- ☑ review question(s)
- ☑ a search strategy
- ☑ inclusion/exclusion criteria
- ☑ a risk of bias assessment

For Yes:
As for partial yes, plus the protocol should be registered and should also have specified:
- ☑ a meta-analysis/synthesis plan, if appropriate, *and*
- ☑ a plan for investigating causes of heterogeneity
- ☑ justification for any deviations from the protocol

- ☑ Yes
- ☐ Partial Yes
- ☐ No

3. Did the review authors explain their selection of the study designs for inclusion in the review?

For Yes, the review should satisfy ONE of the following:
- ☐ *Explanation for* including only RCTs
- ☐ OR *Explanation for* including only NRSI
- ☑ OR *Explanation for* including both RCTs and NRSI

- ☑ Yes
- ☐ No

4. Did the review authors use a comprehensive literature search strategy?

For Partial Yes (all the following):
- ☑ searched at least 2 databases (relevant to research question)
- ☑ provided key word and/or search strategy
- ☑ justified publication restrictions (e.g. language)

For Yes, should also have (all the following):
- ☑ searched the reference lists / bibliographies of included studies
- ☑ searched trial/study registries
- ☐ included/consulted content experts in the field
- ☐ where relevant, searched for grey literature
- ☐ conducted search within 24 months of completion of the review

- ☐ Yes
- ☑ Partial Yes
- ☐ No

5. Did the review authors perform study selection in duplicate?

For Yes, either ONE of the following:
- ☑ at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include
- ☐ OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.

- ☑ Yes
- ☐ No

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6. Did the review authors perform data extraction in duplicate?

For Yes, either ONE of the following:

- [x] at least two reviewers achieved consensus on which data to extract from included studies
- [ ] OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.

- [x] Yes
- [ ] No

7. Did the review authors provide a list of excluded studies and justify the exclusions?

For Partial Yes:

- [x] provided a list of all potentially relevant studies that were read in full-text form but excluded from the review

For Yes, must also have:

- [ ] Justified the exclusion from the review of each potentially relevant study

- [ ] Yes
- [x] Partial Yes
- [ ] No

8. Did the review authors describe the included studies in adequate detail?

For Partial Yes (ALL the following):

- [x] described populations
- [x] described interventions
- [x] described comparators
- [x] described outcomes
- [x] described research designs

For Yes, should also have ALL the following:

- [x] described population in detail
- [x] described intervention in detail (including doses where relevant)
- [x] described comparator in detail (including doses where relevant)
- [x] described study's setting
- [x] timeframe for follow-up

- [x] Yes
- [ ] Partial Yes
- [ ] No

9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?

RCTs

For Partial Yes, must have assessed RoB from

- [ ] unconcealed allocation, *and*
- [ ] lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality)

For Yes, must also have assessed RoB from:

- [ ] allocation sequence that was not truly random, *and*
- [ ] selection of the reported result from among multiple measurements or analyses of a specified outcome

- [ ] Yes
- [ ] Partial Yes
- [ ] No
- [x] Includes only NRSI

NRSI

For Partial Yes, must have assessed RoB:

- [x] from confounding, *and*
- [x] from selection bias

For Yes, must also have assessed RoB:

- [x] methods used to ascertain exposures and outcomes, *and*
- [x] selection of the reported result from among multiple measurements or analyses of a specified outcome

- [x] Yes
- [ ] Partial Yes
- [ ] No
- [ ] Includes only RCTs

10. Did the review authors report on the sources of funding for the studies included in the review?

For Yes

- [x] Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies

- [x] Yes
- [ ] No

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11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?

RCTs

For Yes:

- ☐ The authors justified combining the data in a meta-analysis
  - ☐ AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present.
  - ☐ AND investigated the causes of any heterogeneity

☐ Yes
☐ No
☑ No meta-analysis conducted

For NRSI

For Yes:

- ☑ The authors justified combining the data in a meta-analysis
  - ☑ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present
  - ☑ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available
  - ☑ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review

☑ Yes
☐ No
☐ No meta-analysis conducted

12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?

For Yes:

- ☐ included only low risk of bias RCTs
- ☐ OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.

☐ Yes
☑ No
☐ No meta-analysis conducted

13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?

For Yes:

- ☐ included only low risk of bias RCTs
- ☑ OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results

☑ Yes
☐ No

14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?

For Yes:

- ☑ There was no significant heterogeneity in the results
- ☐ OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review

☑ Yes
☐ No

15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?

For Yes:

- ☑ performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias

☑ Yes
☐ No
☐ No meta-analysis conducted

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16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

For Yes:

- ☑ The authors reported no competing interests OR
- ☐ The authors described their funding sources and how they managed potential conflicts of interest

☑ Yes
☐ No

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