CADTH

CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

Nasal Decolonization for the Prevention of Surgical Site Infections: A Review of Clinical Effectiveness and Cost-Effectiveness

Service Line:	Rapid Response Service
Version:	1.0
Publication Date:	May 28, 2020
Report Length:	21 Pages

CADTH

Authors: Kendra Brett, Melissa Severn

Cite As: Nasal decolonization for the prevention of surgical site infections: a review of clinical effectiveness and cost-effectiveness. Ottawa: CADTH; 2020 May. (CADTH rapid response report: summary with critical appraisal).

ISSN: 1922-8147 (online)

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Questions or requests for information about this report can be directed to **Requests@CADTH.ca**

Abbreviations

AMSTAR 2	A MeaSurement Tool to Assess systematic Reviews 2
RCT	randomized controlled trial
SR	systematic review
SSI	surgical site infection

Context and Policy Issues

Surgical site infections (SSIs) are one of the most common health care-associated infections.[1] Patients who develop SSIs have an increased risk of morbidity and mortality and a higher likelihood of requiring a revision surgery, and there is also an increased cost to the health care system due to SSIs.[2] SSIs are typically located at or near the surgical incision, but may also occur in deep tissues,[1] and can result from endogenous infections (i.e., the infecting bacteria was already present on the person), or exogenous (i.e., the infecting bacteria comes from another person or the environment).[3] A common cause of endogenous SSIs is the colonization of the bacteria *Staphylococcus aureus* on a person's skin or mucosal membranes.[1] People who are carriers of *S. aureus* often have high quantities of *S. aureus* in their nose[3] and reducing *S. aureus* nasal carriage prior to surgery could help reduce the risk of SSIs.

There are numerous agents that can be used pre-operatively for reducing or eradicating harmful bacteria on patients. Chlorhexidine gluconate, also known as chlorhexidine, is an antiseptic that can be used for disinfecting the skin, but cannot fully eradicate all bacteria on skin.[1,3] Other agents include povidone-iodine, an antiseptic, and mupirocin, an antibacterial agent, both of which can be applied topically on the skin and on mucous membranes.[3]

Prior to surgery, patients may be provided with a decolonization bundle designed for the prevention of SSIs, which may include washes or wipes, or nasal decolonization treatments. Nasal decolonization treatments include antibiotic or antiseptic ointments (e.g., mupirocin, povidone-iodine), alcohol-based antiseptics (e.g., ethanol), or photodisinfection (i.e., the use of low-intensity light and a photosensitive agent to kill bacteria[4]). However, it is unknown whether nasal decolonization, alone or in combination with other interventions, is effective for preventing SSI in surgical patients.

This report is an upgrade from a recent (published in 2020) CADTH Reference List report,[5] and includes two of the research questions from that report. The purpose of the current report is to summarize and critically appraise the relevant evidence identified in the previous report[5] regarding the clinical effectiveness and cost-effectiveness of pre-operative nasal decolonization for the prevention of SSIs.

Research Questions

1. What is the clinical effectiveness of pre-operative nasal decolonization, with or without chlorhexidine gluconate washes or wipes, for the prevention of surgical site infections?
2. What is the cost-effectiveness of pre-operative nasal decolonization, with or without chlorhexidine gluconate washes or wipes, for the prevention of surgical site infections?

Key Findings

Two systematic reviews with two relevant randomized controlled trials and two randomized controlled trials were identified that addressed the clinical effectiveness of pre-operative nasal decolonization for the prevention of surgical site infections. Evidence regarding nasal decolonization with a pre-operative chlorhexidine shower, with or without a chlorhexidine oral rinse, was neutral for the prevention of surgical site infections and the risk of mortality. However, the body of evidence was small, heterogenous, and had high uncertainty. The evidence for adverse events was inconclusive.

No evidence regarding the cost-effectiveness of pre-operative nasal decolonization for the prevention of surgical site infections was identified.

Methods

Literature Search Methods

This report made use of a literature search that was conducted for a previous CADTH report.[5] A limited literature search was conducted by an information specialist on key resources including PubMed, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were intranasal decolonization in the preoperative setting. No filters were applied to limit the retrieval by study type. The search was also limited to English language documents published between January 1, 2015 and February 27, 2020.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Surgical patients, any age
Intervention	Pre-operative nasal decolonization interventions, including: • topical antibiotics (e.g., nasal mupirocin ointment) • nasal photodisinfection (e.g., MRSAid or Steriwave Nasal Decolonization) • nasal alcohol-based antisepsis • nasal povidone-iodine; alone or in combination with pre-operative use of chlorhexidine gluconate washes, wipes, or bathing
Comparator	Alternative pre-operative interventions for the prevention of surgical site infections (i.e., nasal decolonization interventions, with or without chlorhexidine gluconate, compared with each other or with alternative, non-nasal decolonization interventions)
Outcomes	Q1. Clinical benefits and harms (e.g., surgical site infection rates, adverse events) Q2. Cost-effectiveness outcomes (e.g., incremental cost-effectiveness ratio or incremental cost-utility ratio, cost per health benefit or event avoided)

Study Designs	Health technology assessments, systematic reviews, randomizes controlled trials, non-randomized studies, economic evaluations

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2015.

Critical Appraisal of Individual Studies

The included publications were critically appraised by one reviewer using the following tools as a guide: A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2)[6] for systematic reviews, and the Downs and Black checklist[7] for randomized and non-randomized studies. Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included publication were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 354 citations were identified in the literature search. Following screening of titles and abstracts, 338 citations were excluded and 16 potentially relevant reports from the electronic search were retrieved for full-text review. One potentially relevant publication was retrieved from the grey literature search for full text review. Of these potentially relevant articles, 13 publications were excluded for various reasons, and four publications met the inclusion criteria and were included in this report. These comprised two systematic reviews, and two RCTs. Appendix 1 presents the PRISMA[8] flowchart of the study selection.

Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

Two SRs[9,10] and two RCTs[11,12] were identified and included in this report. Both SRs[9,10] had broader inclusion criteria than the present review. Specifically, both SRs[9,10] included a placebo comparator in addition to an alternative decolonization comparator, and the SR by Ma et al. (2017)[10] also included skin decolonization alone as an eligible intervention (in additional to nasal decolonization). Only the characteristics and results of the subset of relevant studies from these SRs[9,10] will be described in this report.

Additional details regarding the characteristics of included publications are provided in Appendix 2.

Study Design

Two SRs were published in 2017, and searched the literature from inception of the databases to 2016; Ma et al. (2017)[10] searched until June 2016, and Liu et al. (2017)[9] searched until September 2016. One SR[9] included RCTs, of which one RCT was relevant to this report. The other SR[10] included RCTs and non-randomized studies, of which two RCTs were relevant to this report. One of the relevant RCTs[13] overlapped in both SRs,[9,10] however, the data are only presented once in this report based on the more comprehensive findings reported in the SR by Liu et al. (2017).[9]

One RCT[12] was published in 2020, and the other RCT[11] was published in 2018. In both RCTs,[11,12] the patients were screened for *S. aureus* prior to randomization, and patients were not blinded to the intervention.

No cost-effectiveness studies were identified.

Country of Origin

The SRs were led by authors in the UK[9] and in Australia;[10] and included one study conducted by authors in Canada, and one study for which the country was not reported. One RCT[12] was conducted in Switzerland. One RCT[11] was conducted in the US.

Patient Population

In the SR by Liu et al. (2017),[9] the relevant RCT included 257 patients who were *S. aureus* carriers who had cardiac surgery. In the SR by Ma et al. (2017),[10] the relevant RCT included 954 patients who had cardiac surgery; the population in this study was not restricted by *S. aureus* carrier status.

One RCT[12] included adults undergoing elective orthopedic surgery; both carriers and non-carriers of *S. aureus* were eligible for inclusion in the study, but only the patients who were *S. aureus* carriers (N = 465) are relevant to this report due to the different interventions provided to the different groups based on *S. aureus* carrier status (i.e., the intervention provided to the non-carrier group was not relevant to this report). The other RCT[11] included adults who were *S. aureus* carriers (N = 110) and undergoing elective surgery (eligible surgeries included orthopedic, urologic, neurologic, colorectal, cardiovascular, or general).

Interventions and Comparators

In the relevant RCT in the SR by Liu et al. (2017),[9] a pre-operative 2% mupirocin nasal ointment in combination with a pre-operative shower with chlorhexidine soap was compared to a placebo nasal ointment with a pre-operative shower with chlorhexidine soap. In the SR by Ma et al. (2017),[10] the relevant RCT compared a pre-operative bundle of chlorhexidine nasal decolonization, chlorhexidine oral rinse, and a shower with chlorhexidine soap, to a pre-operative shower with chlorhexidine soap with a placebo nasal decolonization but no oral rinse.

In one RCT[12] patients in the intervention group were instructed to apply a 2% mupirocin nasal ointment twice a day for five days prior to surgery in addition to daily showers using 4% chlorhexidine soap; the patients in the control group were instructed to shower prior to the surgery using conventional soap and did not receive a nasal ointment. In the other RCT,[11] the intervention consisted of a five day decolonization bundle composed of mupirocin nasal ointment applied twice daily, a daily shower with chlorhexidine soap, and chlorhexidine mouthwash twice daily; the control group was instructed to have two pre-operative showers with disinfectant soap prior to the surgery. In this RCT,[11] the chlorhexidine mouthwash was added to the intervention bundle after one third of the patients had been randomized, thus some participants in the intervention group only received the mupirocin nasal ointment and chlorhexidine soap but no mouthwash.

Outcomes

All four included studies reported SSIs as an outcome; one SR[9] reported both all-cause and *S. aureus* specific SSIs, one SR[10] reported *S. aureus* specific SSIs, and both RCTs[11,12]

reported all-cause SSIs. Other reported outcomes included mortality,[9,12] adverse events,[9,11] the detection of *S. aureus* colonization,[11] and adverse drug events.[11]

Summary of Critical Appraisal

The critical appraisal of the included studies is summarized below and additional details regarding the strengths and limitations of the included publications are provided in Appendix 3, Table 4 and Table 5.

Systematic Reviews

Both SRs[9,10] had well described eligibility criteria for the review, and both used the Cochrane risk of bias tool to assess the risk of bias from all relevant domains in the included RCTs. One SR included RCTs[9] while the other SR included both RCTs and non-randomized studies,[10] however, neither SR provided an explanation for their selection of study designs for inclusion. One SR[9] had a written protocol, a comprehensive literature search strategy (including searching trial registries and did not have language restrictions), and had two authors perform the study selection and data extraction in duplicate. This SR[9] also provided a list of the excluded studies with the reasons for their exclusion. The other SR[10] did not have a protocol, had a less comprehensive search strategy, and it was unclear whether study selection and data extraction were done in duplicate, which could have resulted in relevant evidence being missed. This SR[10] also did not provide a list of excluded studies or the reasons for exclusion at the full text level, which would have been helpful for determining whether the eligibility criteria were properly applied. The included studies were well described in one SR,[9] including providing the source of funding of the primary studies. In the other SR,[10] the intervention and comparators of the included studies were well described, but the populations, study design, and outcomes lacked detail, reducing our understanding of the findings; and the source of funding of the primary studies was not reported, thus it is unknown if these studies were biased by the funding agency. In one SR[9] there were no conflicts of interest from the authors or from the funding agency, whereas, in the other SR[10] there was no statement regarding potential conflicts of interest from the authors and it was not stated whether the funding agency influenced the report, thus it is unknown if there were any potential conflicts of interest for this report.

Randomized Controlled Trials

Both RCTs[11,12] had detailed descriptions of the objective of the study, the outcomes of interest, the eligibility criteria, and the interventions, and the main findings were clearly described. The reporting was generally well done, with both RCTs reporting confidence intervals with their findings and providing actual probability values, which increases the certainty in the estimates. Both RCTs also reported small losses to follow up that would have been unlikely to affect the outcomes. One RCT[11] reported adverse events as an outcome (by type of event, and by severity of the event), while the other RCT[12] reported that some patients discontinued with the study due to adverse events but did not report what adverse events were experienced, thus the safety of the intervention is unknown in this study. The patients were not blinded to the intervention in either RCT, however, due to the nature of the main outcomes (e.g., SSI, *S. aureus* colonization), it is unlikely that the patients knowing their treatment group would have influenced the outcomes. In both RCTs, the investigators who measured the main outcomes of the intervention were blinded to the intervention, which reduces the likelihood of bias in reporting of the results.

Both RCTs used appropriate methods for randomizing the participants. One RCT[12] used an appropriate method for allocation concealment, but the other RCT[11] did not report how

allocation was concealed, and there is the possibility that allocation might have been exposed possibly biasing the selection of participants into the study. Both RCTs conducted an intention-to-treat analysis, which is important given the varying rates of compliance with these interventions. In one RCT,[12] compliance with the intervention was 87%. In the other RCT,[11] complete compliance with the intervention was 60%, with the lowest compliance observed for the nasal ointment component of the intervention (67% complete compliance). This was also the RCT[11] that added a component to the intervention bundle part way through the trial. Both factors could have affected the success of the intervention.[11]

One RCT[12] had a detailed statistical analysis plan that included an interim safety analysis. This interim analysis resulted in the trial being halted early as it was determined to be futile and not feasible (i.e., based on interim results, the trial would need a sample size five times larger than initially calculated); as such, this RCT was insufficiently powered to detect differences in the outcomes between intervention arms of the trial.[12] The other RCT[11] was sufficiently powered to detect a change in the primary outcome of eradication of *S. aureus* colonization, but the study was not designed to be powered for the secondary outcome (e.g., SSI), and the authors recommended interpreting the findings for the secondary outcomes with caution.

In both RCTs, the source of funding was reported, and there was no influence of the funders on the design or reporting of the studies. In one RCT,[11] the authors declared no conflicts of interest, and it was unclear whether the authors in the other RCT[12] had any conflicts of interest.

Summary of Findings

Relevant findings are summarized below, and a detailed summary of the findings and authors conclusions are presented in Appendix 4, Table 6 and Table 7.

Clinical Effectiveness of Pre-operative Nasal Decolonization

Two SRs[9,10] and two RCTs[11,12] were identified regarding the clinical effectiveness of pre-operative nasal decolonization.

There was one relevant RCT[13] that overlapped in both SRs[9,10] but the data are only presented once in this report, based on the findings reported in Liu et al. (2017).[9]

All of the studies[9-12] included in this report examined the clinical effectiveness of nasal decolonization in combination with one or more decolonization co-interventions. No studies were identified that examined the clinical effectiveness of nasal decolonization alone (i.e., without other co-interventions). Two studies[9,12] examined the clinical effectiveness of a nasal ointment in combination with a pre-operative shower with chlorhexidine soap. Two studies[10,11] examined the clinical effectiveness of a pre-operative bundle composed of a nasal ointment, a chlorhexidine oral rinse, and a pre-operative shower with chlorhexidine soap. The results are reported by separately according to the decolonization components.

SSIs

Nasal Ointment and Chlorhexidine Shower

In the relevant RCT in the SR by Liu et al. (2017),[9] in patients who are carriers *of S. aureus,* the use of a pre-operative mupirocin nasal ointment in combination with a shower with chlorhexidine soap had no difference in the relative risk of SSIs (either all-cause, or *S. aureus* specific SSIs) when compared to a placebo nasal ointment in combination with a

shower with chlorhexidine soap. Although this RCT was assessed by the authors of the SR to have low risk of bias, the authors assessed this finding to have low-certainty resulting from imprecision due to small numbers of events and wide confidence intervals.

In one RCT[12] that was halted early due to futility (i.e., not feasible to reach the necessary re-calculated sample size), in patients who are carriers *of S. aureus* there was no difference in the risk of SSIs among those treated with mupirocin nasal ointment in combination with pre-operative showers with chlorhexidine soap compared to a pre-operative shower with conventional soap.

Nasal Ointment, Chlorhexidine Oral Rinse, and Chlorhexidine Shower

In the SR by Ma et al. (2017),[10] in the relevant RCT, assessed by the authors to have a high risk of reporting bias, in patients with unknown *S. aureus* status there was no difference in the relative risk of *S. aureus* SSIs in the patients treated with a pre-operative decolonization bundle (chlorhexidine nasal decolonization, chlorhexidine oral rinse, and a shower with chlorhexidine soap) compared to those using a placebo nasal ointment in combination with a shower with chlorhexidine soap.

One RCT,[11] that was not powered to detect differences in SSI, reported one case of non-*S. aureus* SSI (1.7%) in the group assigned to decolonization bundle (mupirocin nasal ointment, and chlorhexidine soap and mouthwash) and no SSIs in the control group (pre-operative showers with disinfectant soap). The authors reported that due to the low number of SSIs reported, they were unable to assess the efficacy of the decolonization bundle against SSIs.[11]

Adverse Events

Nasal Ointment and Chlorhexidine Shower

In the SR by Liu et al. (2017),[9] the relevant RCT reported no adverse events in either group (nasal ointment and shower with chlorhexidine soap compared to shower with chlorhexidine soap with placebo nasal ointment).

Nasal Ointment, Chlorhexidine Oral Rinse, and Chlorhexidine Shower

In the RCT[11] comparing a pre-operative decolonization bundle (mupirocin nasal ointment, and chlorhexidine soap and mouthwash) to pre-operative showers with disinfectant soap in patients who are carriers *of S. aureus*, no serious adverse events were reported, but adverse drug events were reported in 45% of the patients in the decolonization group and 21% of the control group. No statistical tests were conducted to compare adverse drug events between groups due to the different ways that adverse events were reported within the groups.[11]

Mortality

Nasal Ointment and Chlorhexidine Shower

In the RCT identified in one SR,[9] in patients who are carriers *of S. aureus,* there was no difference in the relative risk of mortality between those who used pre-operative mupirocin nasal ointment in combination with a shower with chlorhexidine soap compared to those using a placebo nasal ointment in combination with a shower with chlorhexidine soap; however, the authors assessed this finding to have low-certainty due to imprecision resulting from small numbers of events and wide confidence intervals.

In one RCT[12] that was halted early due to futility, no deaths were reported in the patients who are carriers *of S. aureus* in either treatment group (mupirocin nasal ointment in combination with pre-operative showers with chlorhexidine soap versus pre-operative shower with conventional soap).

Eradication of *S. aureus*

Nasal Ointment, Chlorhexidine Oral Rinse, and Chlorhexidine Shower

One RCT[11] found that the use of a pre-operative decolonization bundle (mupirocin nasal ointment, and chlorhexidine soap and mouthwash) in patients who are carriers *of S. aureus* was statistically significantly more effective at eradicating *S. aureus* than pre-operative showers with disinfectant soap. The decolonization bundle was more effective than the pre-operative showers with disinfectant soap for eradicating *S. aureus* (at any site) and methicillin-susceptible *S. aureus*, but no difference was observed for methicillin-resistant *S. aureus*.

Cost-Effectiveness of Pre-operative Nasal Decolonization

No relevant evidence regarding the cost-effectiveness of nasal decolonization, with or without chlorhexidine gluconate washes or wipes, for the prevention of SSIs was identified.

Limitations

There are various limitations with the evidence in this report on the clinical effectiveness and cost-effectiveness of pre-operative nasal decolonization for the prevention of SSIs.

A key limitation of this evidence is the certainty in the findings. Both RCTs[11,12] reported that they were not adequately powered to detect differences in the risk of SSIs between groups. In one SR[9] the authors suggested that the included RCT may not have been adequately powered due to the small sample size (N = 257), and the findings were graded as having low-certainty due to imprecision. The other SR[10] did not report whether the RCT was adequately powered (N = 954) to detect a differences in SSI. The high degree of uncertainty and the underpowered studies limits the ability to draw conclusions from this evidence.

This body of evidence is also limited by the small quantity of heterogenous evidence. This report identified two SRs (containing two unique RCTs, one of which overlapped in both SRs) and two RCTs that were relevant to this report. These four studies varied with regards to the population (e.g., type of surgery, *S. aureus* status of participants), the intervention (e.g., nasal decolonization, oral rinse, and shower), and the comparator (e.g., type of soap for pre-operative showers). It is unclear how the heterogeneity of this body of evidence may affect the certainty of the evidence, and the generalizability of these findings to the clinical context.

The studies included in this report examined the clinical effectiveness of nasal decolonization in combination with one or more decolonization co-interventions (i.e., chlorhexidine soap and oral rinse). No studies were identified that examined the clinical effectiveness of nasal decolonization alone (i.e., without other co-interventions), thus the clinical effectiveness of nasal decolonization alone cannot be determined from this evidence.

In addition, this report did not identify evidence for all types of nasal decolonization interventions. Three of the studies[9,11,12] used a topical nasal antibiotic (i.e., mupirocin

ointment) and one study[10] used a nasal antiseptic (i.e., chlorhexidine), but no studies were identified that used nasal photodisinfection or nasal povidone-iodine, therefore the clinical effectiveness of these types of nasal decolonization techniques is unknown.

No relevant evidence regarding the cost-effectiveness of nasal decolonization for the prevention of SSIs was identified; therefore the cost-effectiveness of nasal decolonization is unknown.

One RCT[13] from the SR by Lui et al. (2017)[9] was conducted in Canada. It is unknown if the studies conducted outside of Canada are generalizable to the Canadian clinical practice as there may be geographical differences between countries in the risk of SSIs.

Conclusions and Implications for Decision or Policy Making

This report was comprised of two SRs[9,10] and two RCTs[11,12] regarding the clinical effectiveness of pre-operative nasal decolonization. No relevant evidence regarding the cost-effectiveness of nasal decolonization for the prevention of SSIs was identified.

Two studies[9,12] examined the clinical effectiveness of mupirocin nasal ointment in combination with a pre-operative shower with chlorhexidine soap in patients who are carriers *of S. aureus*, however, there was a high degree of uncertainty with the findings. When mupirocin nasal ointment plus showering with chlorhexidine soap was compared to a placebo nasal ointment in combination with a shower with chlorhexidine soap there was no difference in the risk of SSIs (all-cause or *S. aureus* related), the risk of mortality, and no adverse events in either group.[9] However, the authors of this SR had low-certainty in these findings due to the low number of events and wide confidence intervals.[9] When compared to a pre-operative shower with conventional soap, there was no difference in the risk of SSIs for those who used the mupirocin nasal ointment and showered with chlorhexidine soap, and no deaths occurred in either treatment group.[12] However, this study was halted early due to futility and was insufficiently powered.[12]

Two studies[10,11] examined the clinical effectiveness of a pre-operative bundle composed of a nasal ointment, a chlorhexidine oral rinse, and a pre-operative shower with chlorhexidine soap; one study[10] used a chlorhexidine nasal ointment and the other study[11] used a mupirocin nasal ointment. In patients with unknown *S. aureus* status, the pre-operative bundle with the chlorhexidine nasal ointment resulted in no difference in the risk of *S. aureus* SSIs when compared to those treated with a placebo nasal ointment with a pre-operative shower with chlorhexidine soap.[10] In patients who are carriers *of S. aureus* the pre-operative bundle with the mupirocin nasal ointment was more effective than pre-operative showers with disinfectant soap at eradicating *S. aureus* colonization prior to surgery at any of the four body sites tested; the effect was observed in methicillin-susceptible *S. aureus* colonization but not methicillin-resistant *S. aureus* colonization.[11] However, this study was not powered to assess the efficacy of the pre-operative decolonization bundle against SSIs,[11] thus it is unknown whether the reduction in *S. aureus* colonization translated into a reduced risk of SSIs. More adverse drug events were reported in the patients assigned to the decolonization bundle, but no statistical comparison was made.[11]

Overall, the limited quantity of heterogenous, low-certainty evidence identified in this report suggests that nasal decolonization (with mupirocin or chlorhexidine) in combination with a pre-operative chlorhexidine shower, with or without a chlorhexidine oral rinse, had no effect on the risk of SSIs or the risk of mortality, when compared to an alternative pre-operative

intervention for the prevention of SSIs.[9,10,12] The evidence for adverse events was inconclusive.[9,11] A pre-operative bundle with mupirocin nasal ointment was shown to be more effective at eradicating *S. aureus* colonization prior to surgery compared with disinfectant soap, but it is unknown if this results in a lower risk of SSIs.[11]

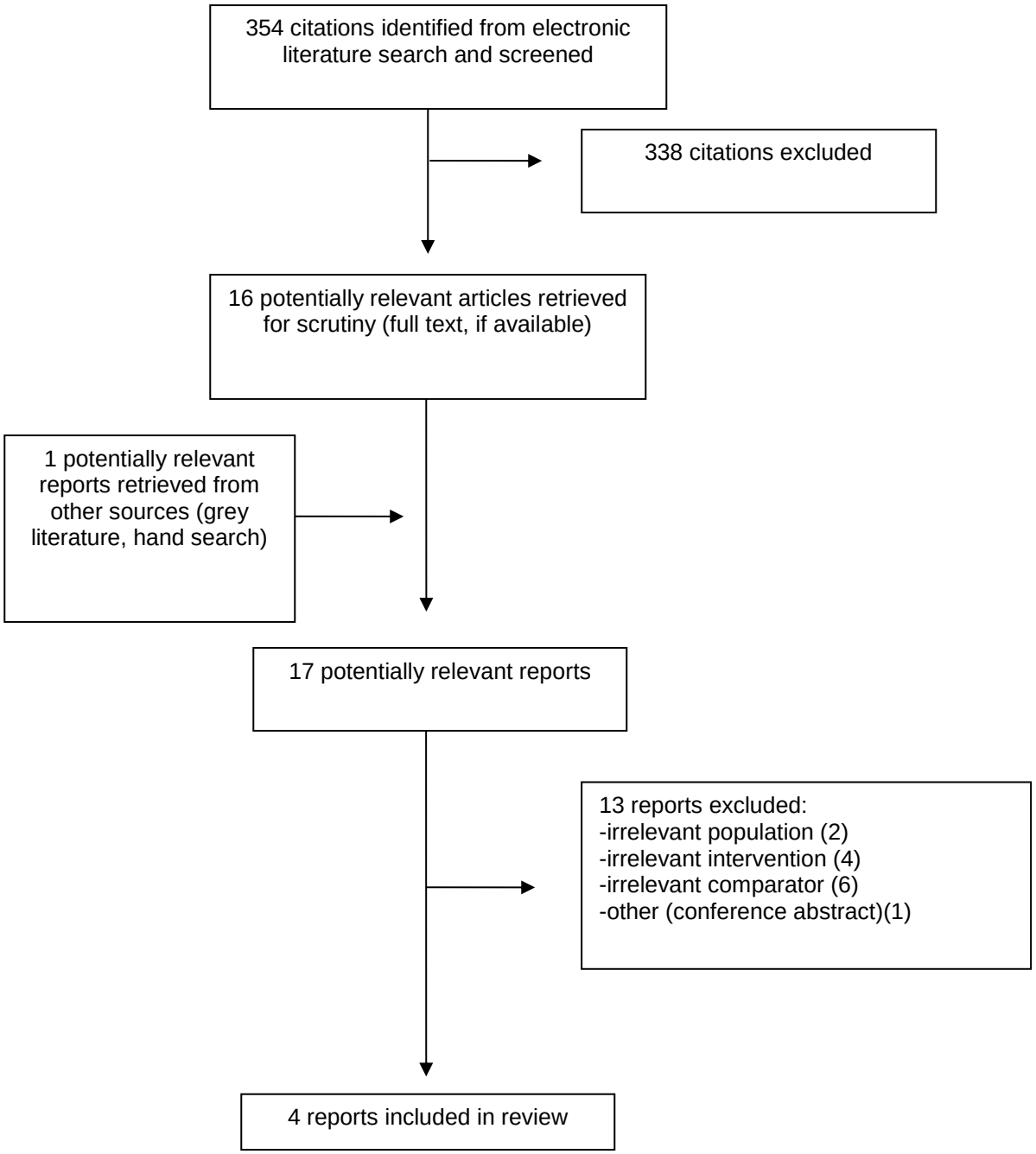
No studies were identified that examined the cost-effectiveness of pre-operative nasal decolonization for the prevention of SSIs, and no studies were identified that used nasal photodisinfection or nasal povidone-iodine as the pre-operative treatment. Studies are needed to investigate the clinical effectiveness of nasal photodisinfection or nasal povidone-iodine treatments, and the cost-effectiveness of nasal decolonization for the prevention of SSIs.

The findings in the report come with a high degree of uncertainty. The limitations of the included studies and of this report should be considered when interpreting the findings. Additional studies that are well designed and adequately powered are needed to determine the clinical effectiveness of pre-operative nasal decolonization for the prevention of SSIs.

References

1. Anderson D. Overview of control measures for prevention of surgical site infection in adults. UpToDate; 2020.
2. Jeans E, Holleyman R, Tate D, Reed M, Malviya A. Methicillin sensitive staphylococcus aureus screening and decolonisation in elective hip and knee arthroplasty. *J Infect.* 2018;77(5):405-409.
3. EJ S. Decolonization in prevention of health care-associated infections. 2016: https://cmr.asm.org/content/29/2/201
4. STERIWAVE ND / MRSAID. https://ondinebio.com/solutions/steriwave/. Accessed MAy 13, 2020.
5. Li Y. Nasal Decolonization for the Prevention of Surgical Site Infections: Clinical Effectiveness, Cost-Effectiveness, and Guidelines. 2020: https://cadth.ca/nasal-decolonization-prevention-surgical-site-infections-clinical-effectiveness-cost-effectiveness.
6. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ.* 2017;358:j4008.
7. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health.* 1998;52(6):377-384.
8. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol.* 2009;62(10):e1-e34.
9. Liu Z, Norman G, Iheozor-Ejiofor Z, Wong JK, Crosbie EJ, Wilson P. Nasal decontamination for the prevention of surgical site infection in Staphylococcus aureus carriers. *Cochrane Database Syst Rev.* 2017;5:CD012462.
10. Ma N, Cameron A, Tivey D, Grae N, Roberts S, Morris A. Systematic review of a patient care bundle in reducing staphylococcal infections in cardiac and orthopaedic surgery. *ANZ J Surg.* 2017;87(4):239-246.
11. Kline SE, Neaton JD, Lynfield R, et al. Randomized controlled trial of a self-administered five-day antiseptic bundle versus usual disinfectant soap showers for preoperative eradication of Staphylococcus aureus colonization. *Infect Control Hosp Epidemiol.* 2018;39(9):1049-1057.
12. Rohrer F, Notzli H, Risch L, et al. Does Preoperative Decolonization Reduce Surgical Site Infections in Elective Orthopaedic Surgery? A Prospective Randomized Controlled Trial. *Clin Orthop Relat Res.* 2020;31:31.
13. Konvalinka A, Errett L, Fong I. Impact of treating Staphylococcus aureus nasal carriers on wound infections in cardiac surgery. *J Hosp Infect.* 2006;64(2):162-168.

Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews

Study citation, country, funding source	Study designs and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Relevant Clinical outcomes, length of follow-up
Liu et al. (2017)[9] UK **Funding source:** University of Manchester; National Institute for Health Research via Cochrane Programme Grant	2 RCTs in total; 1 RCT relevant to the present review	**Includes:** People of any age, who are carriers of *S. aureus* (identified by nasal culture), undergoing surgery **Excludes:** Mixed populations of carriers and non-carriers of *S. aureus.*	**Interventions**: Nasal decontamination procedures, delivered alone or as part of a bundle, but the other co-interventions had to be the same in the control group. **Eligible comparators**: Alternative nasal decontamination procedure, no intervention, treatment as usual, or placebo. **Relevant comparator**: Alternative nasal decontamination procedure, treatment as usual (if it included other pre-operative interventions for reducing SSIs)	**Primary outcomes:** SSIs and adverse events **Secondary outcomes:** - *S. aureus* SSI - mortality **Follow-up:** 30 days to > 12 months
Ma et al. (2017)[10] Australia **Funding source:** New Zealand Health Quality and Safety Commission	25 studies in total; 2 RCTs relevant to this report	**Includes**: Patients of all ages undergoing elective cardiac or orthopedic surgery	**Eligible interventions**: Pre-operative use of nasal and/or skin decolonization **Relevant interventions:** Pre-operative use of nasal decolonization alone or in combination with skin decolonization **Eligible comparators**: Placebo or standard of care (including antibiotic prophylaxis) **Relevant comparator**: standard of care (if it included other pre-operative interventions for reducing SSIs)	**Primary outcome:** SSI **Follow-up:** not reported

RCT = randomized controlled trial; SSI = surgical site infection.

Table 3: Characteristics of Included Randomized Controlled Trials

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Rohrer et al. (2020)[12] Switzerland **Funding source:** The Lindenhof Fund for Teaching and Research, and CHG soap supplied for free by manufacturer	RCT Patients had nasal swabs for *S. aureus* 2 to 4 weeks prior to surgery, and were allocated to the carrier or non-carrier groups. Patients in each group then randomized to control or intervention.	**Inclusion criteria:** Elective orthopedic patients, aged 16 or older, with at least 14 days prior to surgery (i.e., time to perform nasal swab and decolonization). **Excludes:** Patients with allergies to mupirocin or chlorhexidine, or an ongoing intervention for a documented infection. **Number of patients:** Carriers, N = 465 **Age, median (range):** Carriers: 59 (49 to 68)	**Intervention, Carriers:** Decolonization kit one week prior to surgery. Mupirocin 2% nasal Ointment, to be applied to each nostril twice a day for 5 days. Daily shower using 4% CHG soap. Note: intervention for the non-carriers did not include nasal decolonization, and is not relevant to this report **Comparator:** Shower prior to surgery with conventional soap. **Standard procedures for all patients:** Cefuroxime antibiotic prophylaxis prior to incision and post-operatively, and operative field disinfected three times with povidone-iodine alcoholic solution.	**Primary outcome:** overall 90-day post-operative incidence of SSI **Secondary outcomes:** - early (30-day) and late (day 31 to 90) SSI - death due to infection
Kline et al. (2018)[11] US **Funding source:** Agency for Healthcare Research and Quality, National Center for Advancing Translational Sciences of the National Institutes of Health, and the University of Minnesota	RCT Patients screened for *S. aureus* at 4 body sites (nares, throat, axillae, and perianal area).	**Inclusion criteria:** Patients with presumptive *S. aureus* infection, 18 or older, undergoing elective orthopedic, urologic, neurologic, colorectal, cardiovascular, or general surgery. With at least 10 days prior to surgery (i.e., time to perform nasal swab and decolonization). **Excluded:** Patients with an allergy to mupirocin or CHG. **Number of patients:** Decolonization, n = 57 Control, n = 53 **Mean age (SD):** Decolonization: 58.8 (13.3) Control: 52.5 (13.1)	**Intervention:** Decolonization bundle composed of CHG soap (shower once daily), CHG mouthwash (twice daily), and mupirocin nasal ointment (twice daily), self-administered for 5 days. Note: mouthwash added to bundle after October 2013, due to higher than anticipated throat cultures, after 35 patients randomized. **Comparator:** Pre-operative showers with disinfectant soap the night before, and the morning of the surgery. Disinfectant in soap was para-chloro-meta-xylenol (93%) or CHG (7%). **Standard procedures for all patients:** Hospital's standard perioperative antimicrobial therapy	**Primary outcome:** Detection of *S. aureus* colonization at any of the body sites, post treatment **Secondary outcomes:** -SSI, 90 days post-surgery - Serious adverse events - Adverse drug events

CHG = chlorhexidine gluconate; RCT = randomized controlled trial; SSI = surgical site infection.

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR 2[6]

Strengths	Limitations
Liu et al. (2017)[9]	
• Well described eligibility criteria for the review (i.e., population, intervention, comparator, outcomes) • A priori written protocol, with justification of changes to protocol reported in the review • Comprehensive search strategy was used, including searching multiple databases and trial registries, not restricting by language, and provided search strategy • Two authors performed study selection and data extraction in duplicate • Primary studies were described in detail, including reporting of the source of funding of the primary studies • List of excluded studies was provided, including the reason for exclusion • Cochrane risk of bias tool was used to assess risk of bias, and results were reported for each individual study • Level of certainty in each outcome was reported and discussed when interpreting the results • Authors reported potential conflicts of interest • Source of funding was reported and did not influence the review	• Only included RCTs, and excluded other study types (e.g., quasi and non-randomized studies), but did not explain their exclusion. Given dearth of evidence, other study types may have provided some evidence.
Ma et al. (2017)[10]	
• Well described eligibility criteria for the review (i.e., population, intervention, comparator, outcomes) • Includes both RCTs and NRS • Searched multiple databases and provided the complete search strategy • One reviewer extracted the data and another reviewer double checked it, and discrepancies resolved by consensus • The interventions and comparators used in the primary studies were well reported • The Cochrane risk of bias tool was used to assess risk of bias of the RCTs, which covers all relevant areas of potential bias • Discussed reasons for heterogeneity of the findings in the limitations section of the report	• No mention of an a priori protocol • Did not search trial registries or reference lists of included studies • One reviewer screened potential references, which was checked by another reviewer, but unclear if done in duplicate or how consensus was reached • Did not provide list of excluded studies, or provide reasons for excluding the publications excluded after full text review (but did provide reasons for excluding at the abstract level) • Did not describe the populations included within the primary studies, and was lacking detail in the descriptions of the study designs and outcomes • Did not report the source of funding of the primary trials • Did not report whether the authors had any conflicts of interest • Reported the source of funding, but not whether the funding agency influence the review

AMSTAR 2 = A MeaSurement Tool to Assess systematic Reviews 2; RCT = randomized controlled trial; NRS = non-randomized study.

Table 5: Strengths and Limitations of Clinical Studies using the Downs and Black checklist[7]

Strengths	Limitations
Rohrer et al. (2020)[12]	
• Detailed description of the objectives, outcomes, eligibility criteria, and interventions • Confidence intervals reported with results • Minimal loss to follow up • Actual probability values (P values) reported • Participants asked to participate are representative of the entire population from which they were recruited • All patients were recruited from the same hospital and over the same period of time • The surgeon confirming the primary outcome was blinded to the carrier status and the intervention arm • Assessment of the outcome was accurate and reliable • Follow-up time was the same for all participants • Detailed description of an appropriate statistical plan was provided. Hierarchical testing was used to account for double hypothesis testing, and an interim safety analysis was conducted. • Intention-to-treat analysis was used • Appropriate methods for randomization and allocation concealment were used • Source of funding was reported, and also reported that the funder had no influence on the study	• Patient characteristics are described across the carriers and non-carriers, but not between the intervention and control groups (thus unclear if differences between groups) • Some patients discontinued the intervention due to adverse events, but the specifics weren't provided • Participants may be younger and healthier than the representative population, but characteristics of patients not recruited into study not reported • Patients not blinded to the intervention, but unlikely to have impacted the primary outcome • Compliance with the intervention was 87% (carriers) • Trial was halted early following an interim safety analysis. Halted due to futility and non-feasibility. Would have required the recruitment of 5 times the number of patients. • Article did not report whether authors had any conflicts of interest, but disclosure forms are on file with the journal.
Kline et al. (2018)[11]	
• Detailed description of the objectives, outcomes, eligibility criteria, and interventions • Patient characteristics well described for the intervention and control groups • Confidence intervals reported with results • Actual probability values (P values) reported • Similar numbers of patients lost to follow up in both groups and unlikely to impact the results • Detailed description of the adverse drug events provided in the supplementary material • Participants asked to participate are representative of the entire population from which they were recruited • Staff who performed the assessment of the primary outcome were blinded to the intervention arm • Follow-up time was the similar for all participants • Intention-to-treat analysis used • Assessment of the outcomes were accurate and reliable • Appropriate methods for randomization were used • Study was adequately powered for primary outcome (i.e., eradication of *S. aureus* infection) • All authors declared no conflicts of interest • Source of funding was reported, and stated that the funders had no influence on the study	• Modification to the intervention (i.e., addition of mouthwash component) was made half was through the trial after one third of patients randomized, which might affect the findings • Adverse drug reactions collected differently between groups, therefore no statistical comparison • Patients and clinical staff not blinded to the intervention, but unlikely to have impacted the primary outcome • Complete adherence with the intervention arm was only 60% (varied by individual intervention component; with > 85% completing at least 80% of the components) vs. 100% in the control group, which could affect the outcomes of the study • Did not describe methods for allocation concealment, thus unclear if there was inadequate concealment of allocation prior to assignment • Study was not designed or powered to detect differences in outcomes other than the primary outcome

Appendix 4: Main Study Findings and Authors' Conclusions

Table 6: Summary of Findings Included Systematic Reviews

Main Study Findings	Authors' Conclusion
Liu et al. (2017)[9]	
One relevant RCT[13] • N = 257 carriers of *S. aureus* undergoing cardiac surgery in Canada • 2% mupirocin nasal ointment plus pre-operative shower with chlorhexidine soap (n = 130) vs. placebo nasal ointment plus pre-operative shower with chlorhexidine soap (n = 127) • low risk of bias across all domains (assessed by authors) **SSI (n, %)** Mupirocin (18, 13.8%) vs. control (11, 8.6%) RR = 1.60, 95% CI, 0.79 to 3.25 Low-certainty evidence **Adverse events** None reported in either group ***S. aureus* SSI (n, %)** Mupirocin (5, 3.8%) vs. control (4, 3.2%) RR = 1.22, 95% CI, 0.34 to 4.44 Low-certainty evidence **Mortality (n)** Mupirocin (4) vs. control (5; one death directly related to *S. aureus* infection) RR = 0.78, 95% CI, 0.21 to 2.84 Low-certainty evidence	"It is unclear whether mupirocin used as a nasal decontaminant makes any difference in preventing subsequent SSI and mortality amongst *S. aureus* carriers (low-certainty evidence)." (*p16*)
Ma et al. (2017)[10]	
Meta-analysis conducted in this SR includes studies that do not meet the PICO for this report, thus not reported. Two relevant RCTs, one[13] of which was reported more comprehensively in Liu (2017),[9] and not repeated here One unique, relevant RCT • N = 954 cardiac surgery patients (country not reported) • Chlorhexidine nasal decolonization with CHG oral rinse, plus pre-operative shower with chlorhexidine soap vs. placebo nasal decolonization plus pre-operative shower with chlorhexidine soap • Low with of bias across all domains, except reporting bias (assessed by authors) ***S. aureus* SSI (n, %)** Intervention (23, 4.7%) vs. Control (29, 6.8%) RR = 0.77, 95% CI, 0.45 to 1.31	"In contrast, the patient care bundle in RCTs showed a protective trend for S. aureus SSIs without achieving statistical significance." (*p243*) "Since all included studies used surgical antibiotic prophylaxis in both arms, the effect of SSI reduction may be attributable to both the bundle and the use of antibiotics." (*p243*)

CHG = chlorhexidine gluconate; RCT = randomized controlled trial; RR = relative risk; SSI = surgical site infection.

Table 7: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Rohrer et al. (2020)[12]	
Following an interim analysis by the data safety and monitoring board, the trial was halted early due to futility and non-feasibility (i.e., sample size recalculation based on interim results required 14,752 patients vs. original calculation of 2690 patients). Primary analysis was an intention-to-treat analysis. **Risk of SSI among carriers of *S. aureus*** Nasal decolonization intervention (n =1, 0.4%) vs. controls (n = 1, 0.4%) Risk difference: 0.0%, 95% CI, –1.2 to 1.2, P > 0.999 Both SSIs in the carriers were early onset (30 days). No deaths occurred in the carriers.	"*In this prospective, randomized trial, a preoperative decolonization procedure did not decrease SSI risk in patients undergoing elective orthopedic surgery, but these results should be interpreted with caution because event numbers were small. The procedure was not effective in either the S. aureus carrier group or the non-carrier group.*" (*p8*) "*Due to the low event numbers, no definite conclusion about the efficacy of preoperative decolonization can be drawn, but these results could be helpful for future meta-analyses*." (*p10*)
Kline et al. (2018)[11]	
Eradication of *S. aureus* at all four body sites Decolonization (n = 41, 71.9%) vs. control (n = 13, 24.5%) Risk difference: 47.4%, 95% CI, 29.1 to 65.7, P < 0.0001 **Eradication of methicillin-susceptible *S. aureus*** Decolonization (76.5%) vs. control (25.0%) Risk difference: 51.5%, 95% CI, 32.7 to 67.2, P < 0.0001 **Eradication of methicillin-resistant *S. aureus*** Decolonization (33.3%) vs. control (20%) Risk difference: 13.3%, 95% CI, –45.1 to 66.7, P > 0.99 **SSI** Decolonization: 1 non-*S. aureus* SSI (1.7%) Control: 0 **Serious adverse events** No patients experienced a serious adverse event during the study **Adverse drug events** (collected separately for each group, thus no statistical comparison) Decolonization: 45% (e.g., mild burning, dryness, unpleasant taste) Control: 21% (e.g., burning, itching, redness)	"In this randomized trial, a novel 5-day home-administered decolonization bundle was superior to 2 preoperative showers with antiseptic soap for eliminating *S. aureus* prior to surgery." (*p1055*) "This study was not designed to address the outcomes of SSIs and, as expected, too few SSIs occurred for an assessment of the decolonization bundle's preventive efficacy against them. As such, evidence is still lacking that the studied 3-medication, 5-day outpatient decolonization bundle can prevent *S. aureus* SSI" (*p1055*)

SSI = surgical site infection.

Appendix 5: Additional References of Potential Interest

Alternative Comparator – No Pre-operative Intervention for the Prevention of SSIs

Harold RE, Butler BA, Lamplot J, Luu HH, Lawton CD, Manning D. Multifaceted aseptic protocol decreases surgical site infections following hip arthroplasty. *Hip Int*. 2018;28(2):182-188.

Kelley KE, Fajardo AD, Strange NM, et al. Impact of a novel preoperative patient-centered surgical wellness program. *Ann Surg.* 2018;268(4):650-656.

Sadigursky D, Pires HS, Rios SAC, Rodrigues Filho FLB, Queiroz GC, Azi ML. Prophylaxis with nasal decolonization in patients submitted to total knee and hip arthroplasty: systematic review and meta-analysis. *Revista Brasil Ortoped.* 2017;52(6):631-637.