

Pre-surgical Nasal Decolonization of *Staphylococcus aureus*: A Health Technology Assessment

KEY MESSAGES

What Is This Health Technology Assessment About?

Surgery carries a risk of infection as it involves cutting through the skin, which acts as a physical barrier to infectious pathogens. Surgical site infections increase the length of time people spend in hospital and, in severe cases, can increase the risk of death following surgery.

A type of bacteria called *Staphylococcus aureus* (*S. aureus*) is the most common cause of surgical site infections. Most types of *S. aureus* live in the human body, most often in the nose. A treatment called pre-surgical nasal decolonization may reduce the amount of bacteria present in people who are carriers of *S. aureus* and prevent the organisms from being transferred to the surgical site, thus reducing the risk of surgical site infection.

This health technology assessment looked at how safe, effective, and cost-effective nasal decolonization of *Staphylococcus aureus* (*S. aureus*) with or without topical antiseptic body wash in the days prior to a scheduled surgery to prevent surgical site infection is for people undergoing surgery. It also looked at the budget impact of publicly funding nasal decolonization with or without topical antiseptic body wash and at the experiences, preferences, and values of people undergoing surgery.

What Did This Health Technology Assessment Find?

Decolonization using nasal mupirocin with chlorhexidine body wash lowers the incidence of *S. aureus*-related surgical site infection in people who are carriers of *S. aureus*. However, nasal decolonization alone (nasal mupirocin without chlorhexidine body wash) may result in little to no difference, regardless of people's *S. aureus* carrier status. Compared with no nasal decolonization treatment (with or without chlorhexidine body wash), universal nasal decolonization (treating all patients regardless of their *S. aureus* carrier status) with mupirocin combined with chlorhexidine body wash may reduce *S. aureus*-related surgical site infections and lead to cost savings. Targeted nasal decolonization (treating only *S. aureus* carriers) may also reduce *S. aureus*-related surgical site infections but increase the overall cost of treatment for the health care system. Over the next 5 years, publicly funding universal nasal decolonization with mupirocin combined with chlorhexidine body wash would result in a total cost savings of \$45.08 million, whereas publicly funding targeted nasal decolonization with mupirocin combined with chlorhexidine body wash would incur an additional cost of \$1.17 million. People we spoke with who had undergone surgery reported valuing treatments aimed at preventing surgical site infections, including nasal decolonization.

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Abstract

Background

Staphylococcus aureus (*S. aureus*) is the most common cause of surgical site infections, and the nose is the most common site for *S. aureus* colonization. Pre-surgical (in the days prior to surgery) nasal decolonization of *S. aureus* may reduce the bacterial load and prevent the organisms from being transferred to the surgical site, thus reducing the risk of surgical site infection. We conducted a health technology assessment of nasal decolonization of *S. aureus* (including methicillin-susceptible and methicillin-resistant strains) with or without topical antiseptic body wash to prevent surgical site infection in patients undergoing scheduled surgery, which included an evaluation of effectiveness, safety, cost-effectiveness, the budget impact of publicly funding nasal decolonization of *S. aureus*, and patient preferences and values.

Methods

We performed a systematic literature search of the clinical evidence to retrieve systematic reviews and selected and reported results from one review that was recent, of high quality, and relevant to our research question. We complemented the chosen systematic review with a literature search to identify randomized controlled trials published since the systematic review was published in 2019. We used the Risk of Bias in Systematic Reviews (ROBIS) tool to assess the risk of bias of each included systematic review and the Cochrane risk-of-bias tool for randomized controlled trials to assess the risk of bias of each included primary study. We assessed the quality of the body of evidence according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria. We performed a systematic economic literature search and conducted both cost-effectiveness and cost-utility analyses using a decision-tree model with a 1-year time horizon from the perspective of Ontario's Ministry of Health. We also analyzed the budget impact of publicly funding nasal decolonization of *S. aureus* in pre-surgical patients in Ontario. To contextualize the potential value of nasal decolonization, we spoke with people who had recently undergone surgery, some of whom had received nasal decolonization, and one family member of a person who had recently had surgery. We also engaged participants through an online survey.

Results

We included one systematic review and three randomized controlled trials in the clinical evidence review. In universal decolonization, compared with placebo or no intervention, nasal mupirocin alone may result in little to no difference in the incidence of overall and *S. aureus*-related surgical site infections in pre-surgical patients undergoing orthopaedic, cardiothoracic, general, oncologic, gynaecologic, neurologic, or abdominal digestive surgeries, regardless of *S. aureus* carrier status (GRADE: Moderate to Very low). Compared with placebo, nasal mupirocin alone may result in little to no difference in the incidence of overall and *S. aureus*-related surgical site infections in pre-surgical patients who are *S. aureus* carriers undergoing cardiothoracic, vascular, orthopaedic, gastrointestinal, general, oncologic, gynaecologic, or neurologic surgery (GRADE: Moderate to Very low). In targeted decolonization, compared with placebo, nasal mupirocin combined with chlorhexidine body wash lowers the incidence of *S. aureus*-related surgical site infection (risk ratio: 0.32 [95% confidence interval: 0.16–0.62]) in pre-surgical patients who are *S. aureus* carriers undergoing cardiothoracic, vascular, orthopaedic, gastrointestinal, or general surgery (GRADE: High). Compared with no intervention, nasal mupirocin combined with chlorhexidine body wash in pre-surgical patients who are not *S. aureus* carriers undergoing orthopaedic surgery may have little to no effect on overall

surgical site infection, but the evidence is very uncertain (GRADE: Very low). Most included studies did not separate methicillin-susceptible and methicillin-resistant strains of *S. aureus*. No significant antimicrobial resistance was identified in the evidence reviewed; however, the existing literature was not adequately powered and did not have sufficient follow-up time to evaluate antimicrobial resistance.

Our economic evaluation found that universal nasal decolonization using mupirocin combined with chlorhexidine body wash is less costly and more effective than both targeted and no nasal decolonization. Compared with no nasal decolonization treatment, universal and targeted nasal decolonization using mupirocin combined with chlorhexidine body wash would prevent 32 and 22 *S. aureus*-related surgical site infections, respectively, per 10,000 patients. Universal nasal decolonization would lead to cost savings, whereas targeted nasal decolonization would increase the overall cost for the health care system since patients must first be screened for *S. aureus* carrier status before receiving nasal decolonization with mupirocin. The annual budget impact of publicly funding universal nasal decolonization in Ontario over the next 5 years ranges from a savings of \$2.98 million in year 1 to a savings of \$15.09 million in year 5. The annual budget impact of publicly funding targeted nasal decolonization ranges from an additional cost of \$0.08 million in year 1 to an additional cost of \$0.39 million in year 5.

Our interview and survey respondents felt strongly about the value of preventing surgical site infections, and most favoured a universal approach.

Conclusions

Based on the best evidence available, decolonization of *S. aureus* using nasal mupirocin combined with chlorhexidine body wash prior to cardiothoracic, vascular, orthopaedic, gastrointestinal, or general surgery lowers the incidence of surgical site infection caused by *S. aureus* in patients who are *S. aureus* carriers (including methicillin-susceptible and methicillin-resistant strains) (i.e., targeted decolonization). However, nasal mupirocin alone may result in little to no difference in overall surgical site infections and *S. aureus*-related surgical site infections in pre-surgical patients prior to orthopaedic, cardiothoracic, general, oncologic, gynaecologic, neurologic, or abdominal digestive surgeries, regardless of their *S. aureus* carrier status (i.e., universal decolonization). No significant antimicrobial resistance was identified in the evidence reviewed.

Compared with no nasal decolonization treatment, universal nasal decolonization with mupirocin combined with chlorhexidine body wash may reduce *S. aureus*-related surgical site infections and lead to cost savings. Targeted nasal decolonization with mupirocin combined with chlorhexidine body wash may also reduce *S. aureus*-related surgical site infections but increase the overall cost of treatment for the health care system. We estimate that publicly funding universal nasal decolonization using mupirocin combined with chlorhexidine body wash would result in a total cost savings of \$45.08 million over the next 5 years, whereas publicly funding targeted nasal decolonization using mupirocin combined with chlorhexidine body wash would incur an additional cost of \$1.17 million over the next 5 years.

People undergoing surgery value treatments aimed at preventing surgical site infections.

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Objective

This health technology assessment evaluates the effectiveness, safety, and cost-effectiveness of pre-surgical nasal decolonization of *Staphylococcus aureus* (*S. aureus*), including methicillin-susceptible and methicillin-resistant strains, with or without topical antiseptic body wash to prevent surgical site infection in patients undergoing scheduled surgery. It also evaluates the budget impact of publicly funding nasal decolonization of *Staphylococcus aureus* with or without topical antiseptic body wash and the experiences, preferences, and values of patients undergoing scheduled surgery.

Background

Health Condition

Surgery carries a risk of infection as it involves cutting through the skin, which acts as a physical barrier to infectious pathogens. The risk of infection depends on the classification of the surgery: clean, clean-contaminated, contaminated, or dirty.¹ In a clean surgery, no inflammation is encountered, there is no break in the sterile technique, and the respiratory, alimentary, and genitourinary tracts are not entered. In a clean-contaminated surgery, the respiratory, alimentary, or genitourinary tract is entered under controlled conditions, but no gross contamination is encountered. During a contaminated surgery, there is a major break in the sterile technique or gross spillage from the gastrointestinal tract, or an acute, non-purulent inflammation is encountered. During a dirty or infected surgery, the viscera are perforated, or acute inflammation with pus is encountered. In surgeries with a higher risk of infection, nasal decolonization may play a protective role.

According to the US Centers for Disease Control and Prevention, surgical site infections occur at or near the incision site and/or deeper underlying tissue spaces and organs along the tract of surgery within 30 days of a surgical procedure (or up to 90 days for implanted prosthetics).² There are three levels of surgical site infection: (1) a superficial infection affects the skin or subcutaneous tissue of the incision site; (2) a deep incisional infection affects fascia and/or muscular layers; and (3) an organ or deep-space infection involves any part of the anatomy deeper than the incision that is opened or manipulated during the surgical procedure; for example, a joint or peritoneal space. Deep incisional and organ/deep-space infections are considered more severe than superficial infections. Surgical site infections are associated with increased morbidity, mortality, hospital length of stay, and health care use.³ Patients with a surgical site infection have a 2- to 11-fold increase in mortality risk, and 77% of such deaths are directly attributable to surgical site infections.⁴

S. aureus, including both methicillin-susceptible (MSSA) strains and methicillin-resistant (MRSA) strains, is the most common cause of surgical site infections.⁵ The nose is the most common site for *S. aureus* colonization, although colonization can also occur in the oropharynx, skin folds (e.g., groin, armpit), and rectum. *S. aureus* colonization increases the risk of *S. aureus*-related surgical site infections. More than 80% of *S. aureus* strains causing infection are endogenous (present within the body) and are genetically similar to strains isolated from the nostrils of corresponding colonized patients. Although the nose is the site most often swabbed for surveillance, the risk of developing infection is higher when more body sites are colonized.⁶

MRSA is defined as any strain of *S. aureus* that has established resistance to beta-lactam antibiotics, such as methicillin, oxacillin, ceftazidime, and nafcillin.⁷ Based on data obtained from 70 large tertiary

acute care hospitals across Canada, the Canadian Nosocomial Infection Surveillance Program reported that the overall MRSA infection rate increased by 59.1% (0.66 to 1.05 infections per 10,000 patient-days) between 2014 and 2018.⁸ However, this increasing trend was attributed mainly to an increase in community-associated MRSA infections. According to the 2020 Canadian Antimicrobial Resistance Surveillance System Report, the rate of health care-associated MRSA infections increased from 0.40 to 0.51 cases per 10,000 patient-days between 2014 and 2018.⁹ In this time period, all health care-associated MRSA blood isolates were susceptible to vancomycin (the most used antimicrobial agent in this setting).

Clinical Need and Target Population

Surgical site infections occur in 2% to 5% of patients undergoing surgery and are the most common health care-associated infections among surgical patients.¹⁰ Of the 1.3 million surgeries performed in Canada yearly, 26,000 to 65,000 patients acquire a surgical site infection. Surgical site infections are estimated to cost Canadians \$350,000 to \$1 million annually, increase hospital length of stay by an average of 11 days, and result in 60% more time spent in intensive care units. The prevention of surgical site infections is becoming increasingly important to reduce the burden on patients, caregivers, and the health care system. It has been estimated that approximately half of all surgical site infections are preventable by implementing evidence-based strategies.¹¹

Current Treatment Options

The current standard of care in Ontario is for no nasal decolonization (of *S. aureus*) to be performed in pre-surgical populations. However, some hospitals do perform nasal decolonization, but the practice of whether to target *S. aureus* (by first screening patients for the presence of *S. aureus* and then treating only those who are carriers) or to decrease the overall risk of *S. aureus*-related surgical site infection (by performing nasal decolonization on all patients without first screening for the presence of *S. aureus*) varies across the province and depends on each hospital's specific infection prevention and control program.

Health Technology Under Review

The goal of pre-surgical decolonization is to reduce the bacterial load so that less bacteria is able to transfer to the surgical site. Pre-surgical patients who are *S. aureus* carriers with high bacterial loads are at higher risk of infection.¹² The two most common methods of pre-surgical decolonization are the application of an antimicrobial ointment to the nose and the use of an antiseptic body wash on the skin. The decolonization protocol often involves the use of nasal mupirocin twice daily for 3 to 5 days prior to surgery and/or bathing with chlorhexidine gluconate once daily for 2 to 5 days prior to surgery.

Nasal mupirocin is the most widely used topical antibacterial agent for nasal decolonization. It inhibits the synthesis of bacterial proteins by reversibly binding to bacterial isoleucyl-tRNA synthetase and has excellent activity against Gram-negative organisms.¹² Nasal mupirocin is most effective among patients at risk of infection for only a short period of time. In one study, short-term nasal mupirocin was found to be effective for MRSA decolonization with a success rate of 90% at 1 week after treatment.¹³ Twice-daily mupirocin for 5 days is used for nasal decolonization for both MSSA and MRSA.¹⁴ However, the use of mupirocin has led to drug resistance and treatment failures, especially with widespread use over long periods of time.³ Alternative methods of nasal decolonization include antiseptic ointments (e.g., povidone-iodine), alcohol-based antiseptics, and intranasal

photodisinfection.¹² Importantly, recolonization following decolonization is frequent, with between 30% and 60% of patients being recolonized after 7 to 18 months.⁵

Chlorhexidine gluconate is an antiseptic agent that binds to the cell walls of bacteria, altering the osmotic equilibrium of the cells. It has high-level antibacterial activity for several hours and has a strong affinity for skin and mucous membranes by binding electrostatically. It also disrupts the commensal skin microbiota (microorganisms living on the skin). Adverse events associated with chlorhexidine gluconate are mild skin irritation and rare serious allergic reactions.³

Intranasal photodisinfection therapy is a broad-spectrum antimicrobial strategy using light energy to activate a photosensitive methylene blue dye (containing chlorhexidine gluconate) that is applied to the anterior nares (nostrils).¹⁵ The activation of the photosensitizer kills the microorganisms by disrupting microbial cell membranes, resulting in cell death. The treatment takes about 15 minutes to complete. The pathogens are unable to adapt to this mechanism of action, thus eliminating the potential for antimicrobial resistance, which is a concern with the use of antibiotics.

Pre-surgical nasal decolonization may be performed only for patients who are colonized with *S. aureus* or for all patients. Targeted decolonization involves screening patients for the presence of *S. aureus* and then treating only those who are *S. aureus* carriers. Universal decolonization involves performing decolonization on all pre-surgical patients without first screening for the presence of *S. aureus*. Different laboratory tests are available to screen for *S. aureus* colonization for MRSA and MSSA. Real-time polymerase chain reaction (PCR) testing can be used to test nasal swabs within hours.¹² However, it is more expensive than chromogenic agar (test time of 1–2 days), as well as both standard culture and antimicrobial resistance testing (test time of 2–3 days). As a result, targeted decolonization is resource- and time-intensive but confirms the presence of *S. aureus* prior to nasal decolonization treatment. The target population for nasal decolonization of *S. aureus* thus depends on whether a targeted or universal decolonization strategy is adopted.

Regulatory Information

Antibiotic and antiseptic products containing mupirocin or chlorhexidine gluconate that are currently in use for nasal decolonization of *S. aureus* are licensed by Health Canada.

The Steriwave photodisinfection system (Ondine Biomedical Inc., Vancouver, BC) is licensed by Health Canada as a Class II device (licence number 102876). According to Health Canada, it is a laser-based antimicrobial system intended for the decolonization of potentially pathogenic bacteria, including MRSA, from the anterior nasal passages.

Ontario, Canadian, and International Context

In Ontario, the practice of pre-surgical nasal decolonization of *S. aureus* varies widely and depends on the specific infection prevention and control program in place at each hospital. Several hospitals perform targeted nasal decolonization in pre-surgical cardiac and orthopaedic populations only. Some hospitals use antiseptic body wash in pre-surgical populations, either alone or in combination with nasal decolonization. Targeted nasal decolonization may be performed in some high-risk populations or procedures, if a patient has recurrent infections or has had prior infections, or if a patient is identified as a carrier of *S. aureus* through screening upon hospital admission or in a pre-operative clinic. It is unclear if any hospital in Ontario practises universal nasal decolonization. In British Columbia, one hospital uses photodisinfection treatment to prevent surgical site infection

(Robert Bacigalupo, British Columbia Ministry of Health, email communication, February 2021). In Alberta, nasal decolonization of *S. aureus* is performed with mupirocin on an as-needed basis (Tara Klassen, PhD, Alberta Health Services, email communication, February 2021).

We identified six international guidelines providing recommendations on nasal decolonization of *S. aureus* (Table 1).¹⁶⁻²¹ Overall, these guidelines recommend that patients undergoing cardiothoracic or orthopaedic surgery who are known carriers of *S. aureus* should receive perioperative intranasal applications of mupirocin 2% ointment with or without chlorhexidine body wash.

Table 1: Guideline Recommendations on Nasal Decolonization of *Staphylococcus aureus*

Author, year (title)	Recommendation excerpts
American College of Surgeons and Surgical Infection Society, 2016 ¹⁶ (Surgical Site Infection Guidelines, 2016 Update)	<ul style="list-style-type: none"> • Decision about whether or not to implement global <i>S. aureus</i> screening and decolonization protocols should depend on baseline surgical site infection and MRSA rates • Clinical practice guidelines from the American Society of Health-System Pharmacists recommend screening and nasal mupirocin decolonization for <i>S. aureus</i>-colonized patients before total joint replacement and cardiac procedures • No standard decolonization protocol is supported by the literature; consider nasal mupirocin alone vs. nasal mupirocin plus chlorhexidine gluconate bathing • Recommendation strength and evidence level: not reported
American Society of Health-System Pharmacists, Infectious Diseases Society of America, Surgical Infection Society, and Society for Healthcare Epidemiology of America, 2013 ¹⁷ (Clinical Practice Guidelines for Antimicrobial Prophylaxis in Surgery)	<ul style="list-style-type: none"> • Mupirocin should be given intranasally to all patients with documented <i>S. aureus</i> colonization, with a particular focus on patients undergoing cardiac and orthopaedic surgeries • Strength of evidence for prophylaxis: A (from meta-analysis, randomized controlled trials, or well-conducted cohort studies)
Asia Pacific Society of Infection Control, 2019 ¹⁸ (APSIC Guidelines for the Prevention of Surgical Site Infections)	<ul style="list-style-type: none"> • Patients undergoing cardiothoracic and orthopaedic surgery with known nasal carriage of <i>S. aureus</i> should receive a perioperative intranasal application of mupirocin 2% ointment with or without chlorhexidine gluconate body wash • Recommendation strength: A or strong; evidence level: I or moderate
National Institute for Health and Care Excellence, 2019 ²² (Surgical Site Infections: Prevention and Treatment)	<ul style="list-style-type: none"> • Consider nasal mupirocin in combination with chlorhexidine body wash before procedures in which <i>S. aureus</i> is a likely cause of surgical site infection. This should be locally determined and take into account the type of procedure, individual patient risk factors, the increased risk of side effects in pre-term infants, and the potential impact of infection • Recommendation strength: consider; evidence level, GRADE: Very low to High

Author, year (title)	Recommendation excerpts
University of Toronto, 2017 ²⁰ (Surgical Site Infection Prevention)	<ul style="list-style-type: none"> • In cardiac surgery and orthopaedic/spinal surgery with hardware insertion, <i>S. aureus</i> screening with nasal swab and decolonization of carriers with intranasal mupirocin 2% ointment twice daily and chlorhexidine gluconate body wash for 5 days before surgery should be considered <ul style="list-style-type: none"> ○ Evidence level: Low • For MRSA carriers, decolonization in conjunction with hospital infection control practitioners or infectious disease consultants should be considered <ul style="list-style-type: none"> ○ Evidence level: Very low
World Health Organization, 2016 ²¹ (Global Guidelines for the Prevention of Surgical Site Infection)	<p>Patients undergoing cardiothoracic and orthopaedic surgery with known nasal carriage of <i>S. aureus</i> should receive perioperative intranasal applications of mupirocin 2% ointment with or without chlorhexidine gluconate body wash</p> <ul style="list-style-type: none"> ○ Recommendation strength: A or strong; evidence level: I or moderate <ul style="list-style-type: none"> • Consider treating patients with known nasal carriage of <i>S. aureus</i> undergoing other types of surgery with perioperative intranasal applications of mupirocin 2% ointment with or without chlorhexidine gluconate body wash <ul style="list-style-type: none"> ○ Recommendation strength: conditional; evidence level: moderate

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; MRSA, methicillin-resistant *Staphylococcus aureus*; *S. aureus*, *Staphylococcus aureus*.

Expert Consultation

We engaged with experts in the specialty areas of general surgery and infectious disease, as well as infection prevention and control, to help inform our understanding of aspects of nasal decolonization of *S. aureus* and our methodologies and to contextualize the evidence.

PROSPERO Registration

This health technology assessment has been registered in PROSPERO, the international prospective register of systematic reviews (CRD42021257873), available at crd.york.ac.uk/PROSPERO.

Clinical Evidence

Research Question

What are the effectiveness and safety of pre-surgical nasal decolonization of *Staphylococcus aureus* (*S. aureus*), including methicillin-susceptible and methicillin-resistant strains, with or without topical antiseptic body wash to prevent surgical site infection, compared with no intervention or placebo for patients undergoing scheduled surgery?

Methods

Review Approach

To leverage existing evidence, we first systematically searched for a recent systematic review with high methodological quality that addressed our research question. The selection of the systematic review for inclusion was based on the recency of the evidence, a risk-of-bias assessment, the comprehensiveness of outcomes reported, and a quality-of-evidence assessment.

Second, we ran a systematic literature search starting from the end of the search of the selected systematic review to identify any relevant randomized controlled trials (RCTs) published since the previous search was conducted.

Clinical Literature Search

We performed a clinical literature search on May 12, 2021, using a methodological filter to retrieve systematic reviews, meta-analyses, and health technology assessments published from database inception until the search date. We used the Ovid interface in the following databases: MEDLINE, Embase, the Cochrane Database of Systematic Reviews, the Health Technology Assessment database, the National Health Service Economic Evaluation Database (NHS EED), and the EBSCOhost interface to search the Cumulative Index to Nursing & Allied Health Literature (CINAHL).

Once a systematic review with low risk of bias was selected,¹⁹ we updated this study by using our base search strategy and applying a methodological filter to retrieve RCTs published from January 1, 2018, to June 29, 2021. We used the Ovid interface in the following databases: MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, the Health Technology Assessment database, and NHS EED. We used the EBSCOhost interface to search CINAHL.

A medical librarian developed the search strategies using controlled vocabulary (e.g., Medical Subject Headings) and relevant keywords. The final search strategy was peer-reviewed using the PRESS Checklist.²³

For both searches, we created database auto-alerts in MEDLINE, Embase, and CINAHL and monitored them for the duration of the assessment period. We also performed a targeted grey literature search of health technology assessment agency websites as well as clinical trial and systematic review registries. See Appendix 1 for our literature search strategies, including all search terms.

Eligibility Criteria

STUDY DESIGN—SYSTEMATIC REVIEWS

Inclusion Criteria

- English-language full-text publications
- Studies published from database inception until May 12, 2021
- Systematic reviews, meta-analyses, and health technology assessments that included a systematic review of RCTs and that:
 - Specified well-defined research questions and inclusion and exclusion criteria
 - Used a reproducible literature search strategy of two or more electronic databases and provided information on databases searched, search terms, and search dates
 - Assessed and reported the methodological quality of the included studies (e.g., risk-of-bias assessment)
 - Matched our research question and target population, interventions, and comparators
 - Included either all types of surgery or specific surgeries

Exclusion Criteria

- Animal and in vitro studies
- Systematic reviews that included observational studies, non-systematic reviews, narrative reviews, abstracts, editorials, letters, case reports, and commentaries

STUDY DESIGN—PRIMARY STUDIES

Inclusion Criteria

- English-language full-text publications
- Studies published from January 1, 2018, until June 29, 2021
- RCTs
- Studies that matched our research question and target population, interventions, and comparators
- Studies that included either all types of surgery or specific surgeries

Exclusion Criteria

- Animal and in vitro studies
- Observational studies, reviews, abstracts, editorials, letters, case reports, and commentaries

PARTICIPANTS

- Patients of all ages undergoing surgery, including minimally invasive surgery (e.g., arthroscopic, thoracoscopic, laparoscopic), with different wound types (i.e., clean, clean-contaminated, contaminated, dirty)

INTERVENTIONS

- Targeted (*S. aureus* carriers) or universal (all patients) nasal decolonization of *S. aureus* (via antibiotic ointment [e.g., mupirocin], antiseptic ointment [e.g., povidone-iodine], alcohol-based antiseptics, or intranasal photodisinfection) with or without topical antiseptic body wash

COMPARATORS

- No intervention or placebo (i.e., antiseptic body wash with soap in both instances)

OUTCOMES

Primary Outcomes

- Number of surgical site infections
 - Overall
 - By surgical site infection classification (i.e., superficial, deep incisional, organ/deep space)
 - By *S. aureus* type (i.e., methicillin-susceptible, methicillin-resistant, or both)
- Adverse events including antimicrobial resistance

Secondary Outcomes

- Removal of infected prosthetics (for orthopaedic surgeries)
- Hospitalization
- Hospital length of stay
- Other health care visits (i.e., clinic visits, primary care provider visits, emergency department visits)
- Mortality

TIMING

- Pre-surgical

SETTING

- Hospital

Literature Screening

Two reviewers followed the Cochrane rapid review methods²⁴ to screen titles and abstracts using Covidence systematic review management software²⁵ and obtained the full text of studies that appeared eligible for review according to the inclusion criteria. The primary reviewer then examined the full-text articles and selected studies that met the inclusion criteria. The second reviewer screened all excluded full-text articles. Any disagreement between reviewers during screening was resolved by consensus. The reference lists of included studies were also examined by the primary reviewer for any additional relevant studies not identified through the search. Citation flow and

reasons for the exclusion of full-text articles were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.²⁶

Data Extraction

For systematic reviews, the primary reviewer extracted data on populations, interventions, comparators, outcomes, and literature search information to guide the selection of the best-quality systematic review. From the chosen systematic review, data on study characteristics, surgery types, follow-up duration, primary outcome results, and the strength of evidence of the included RCTs were extracted as reported. For primary studies, the primary reviewer extracted data on study characteristics, surgery types, populations, interventions, comparators, and outcomes. The accuracy of the data extraction was validated by the second reviewer.

Statistical Analysis

We used Review Manager²⁷ to compute the risk ratios of the outcomes in the primary studies if relevant data were available. Due to the heterogeneity of the outcomes reported in the included systematic review¹⁹ and in the included primary studies,²⁸⁻³⁰ we did not perform a meta-analysis. Instead, we reported all statistical analyses as they were presented in the selected systematic review and primary studies.

Critical Appraisal of Evidence

The primary reviewer used the Risk of Bias in Systematic Reviews (ROBIS) tool³¹ to assess the risk of bias in the identified systematic reviews and reported the risk of bias of the studies included in the chosen systematic reviews as originally reported. The Cochrane risk-of-bias tool for randomized controlled trials³² was used to assess the risk of bias of each primary study identified following selection of the chosen systematic reviews.

For systematic reviews, the review authors' quality measures were used as a guide or as reported by the authors if Grading of Recommendations Assessment, Development, and Evaluation (GRADE) criteria were used. For primary studies, the primary reviewer evaluated the quality of the body of evidence for each outcome according to the *GRADE Handbook*.³³ The second reviewer verified all judgments (and support statements) made by the primary reviewer.

Results

Clinical Literature Search for Systematic Reviews

The database search for systematic reviews yielded 1,481 citations published from database inception until May 12, 2021. We identified 30 additional systematic reviews from other sources. In total, we identified 11 systematic reviews that met our inclusion criteria. See Appendix 3, Table A11, for a list of selected systematic reviews excluded after full-text review. Figure 1 presents the PRISMA flow diagram for the clinical literature search for systematic reviews.

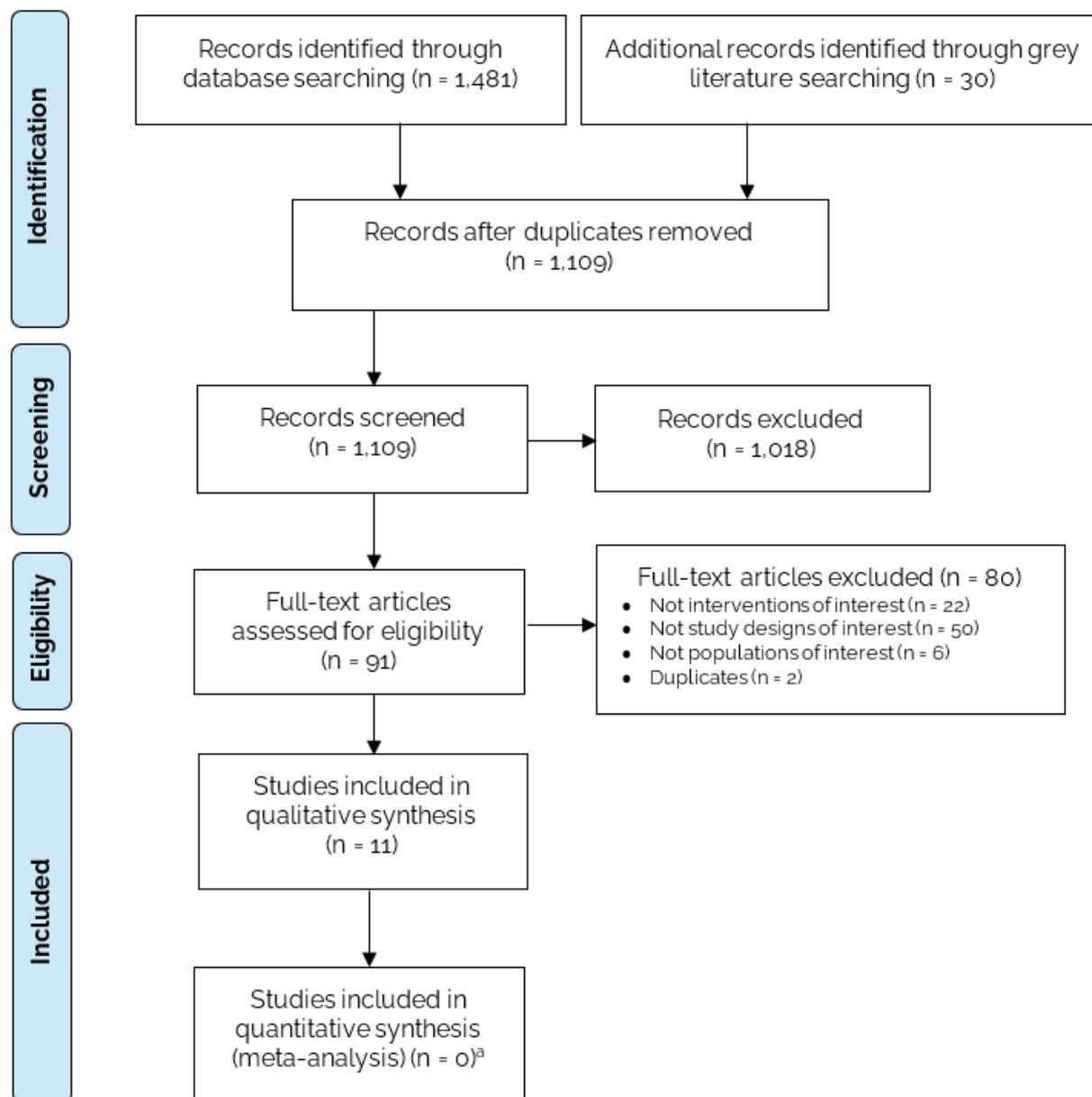


Figure 1: PRISMA Flow Diagram—Clinical Search Strategy for Systematic Reviews

PRISMA flow diagram showing the clinical search strategy for systematic reviews. The database search yielded 1,481 citations published from database inception until May 12, 2021. We identified 30 additional systematic reviews from other sources. After removing duplicates, we screened the abstracts of 1,109 systematic reviews and excluded 1,018. We assessed the full text of 91 systematic reviews and excluded a further 80. In the end, we included 11 systematic reviews in the qualitative synthesis. Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.

^aThe purpose of the systematic review search was to identify a recent high-quality review that addressed the research question to leverage existing evidence; therefore, the included systematic reviews were not meta-analyzed.

Source: Adapted from Moher et al.²⁶

Characteristics of Identified Systematic Review

Eleven systematic reviews initially met our eligibility criteria.^{19,21,34-42} The reviews were published between 2005 and 2020, and all applied selection criteria to capture studies that evaluated nasal decolonization of *S. aureus* in patients undergoing surgery. Appendix 4, Table A13, summarizes the design and characteristics of these reviews. See Appendix 2, Table A1, for the risk-of-bias assessment of these systematic reviews using the ROBIS tool.³¹

For our analysis, we selected a health technology assessment by the National Institute for Health and Care Excellence (NICE)¹⁹ published in 2019 (search end date: December 2018) because it included a comprehensive literature search of studies of both universal and targeted nasal decolonization of *S. aureus*. It also provided detailed information on the included study designs, the characteristics of study populations, outcomes, and risk-of-bias assessment, as well as an assessment of the quality of the body of evidence for each outcome according to the GRADE Working Group criteria. Table 2 provides the inclusion criteria for the selected systematic review.

Among the 10 reviews we excluded, seven were excluded due to high risk of bias, with one or more of the following characteristics: single reviewer, limited description of literature search, limited data extraction, or inappropriate data analyses.^{34-36,38-41} Three reviews were published in or before 2017 and thus had an outdated literature search.^{21,37,42}

Table 2: Inclusion Criteria for the Selected Systematic Review

Author, year, search end date	Population	Interventions	Comparators	Outcomes	Study types
NICE, 2019, ¹⁹ December 2018	People of any age undergoing any surgery, including minimally invasive surgery (arthroscopic, thoracoscopic, or laparoscopic)	The following treatments with or without chlorhexidine body wash or glycopeptide prophylaxis: Intranasal mupirocin Nasal povidone-iodine solution Chlorhexidine nasal gel Chlorhexidine and neomycin cream (Naseptin) Octensan nasal gel	Placebo No nasal decolonization Different nasal decolonization procedures	SSIs (superficial, deep incisional, organ/deep space), including those caused by MSSA and MRSA, defined according to appropriate criteria such as the CDC SSI criteria (including SSIs up to 30 d and 1 y) Other types of nosocomial infections Mortality post-surgery Length of hospital stay Postoperative antibiotic use Hospital readmission Infectious complications such as septicaemia or septic shock Adverse event: antimicrobial resistance	RCTs Systematic reviews of RCTs

Abbreviations: CDC, US Centers for Disease Control and Prevention; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; NICE, National Institute for Health and Care Excellence; RCT, randomized controlled trial; SSI, surgical site infection.

Clinical Literature Search for Primary Studies

The database search for RCTs yielded 611 citations published from January 1, 2018, until June 29, 2021. We identified no additional studies from other sources. In total, we identified three RCTs published after the 2019 NICE guideline¹⁹ that met our inclusion criteria. See Appendix 3, Table A12, for a list of selected studies excluded after full-text review. Figure 2 presents the PRISMA flow diagram for the clinical literature search for RCTs.

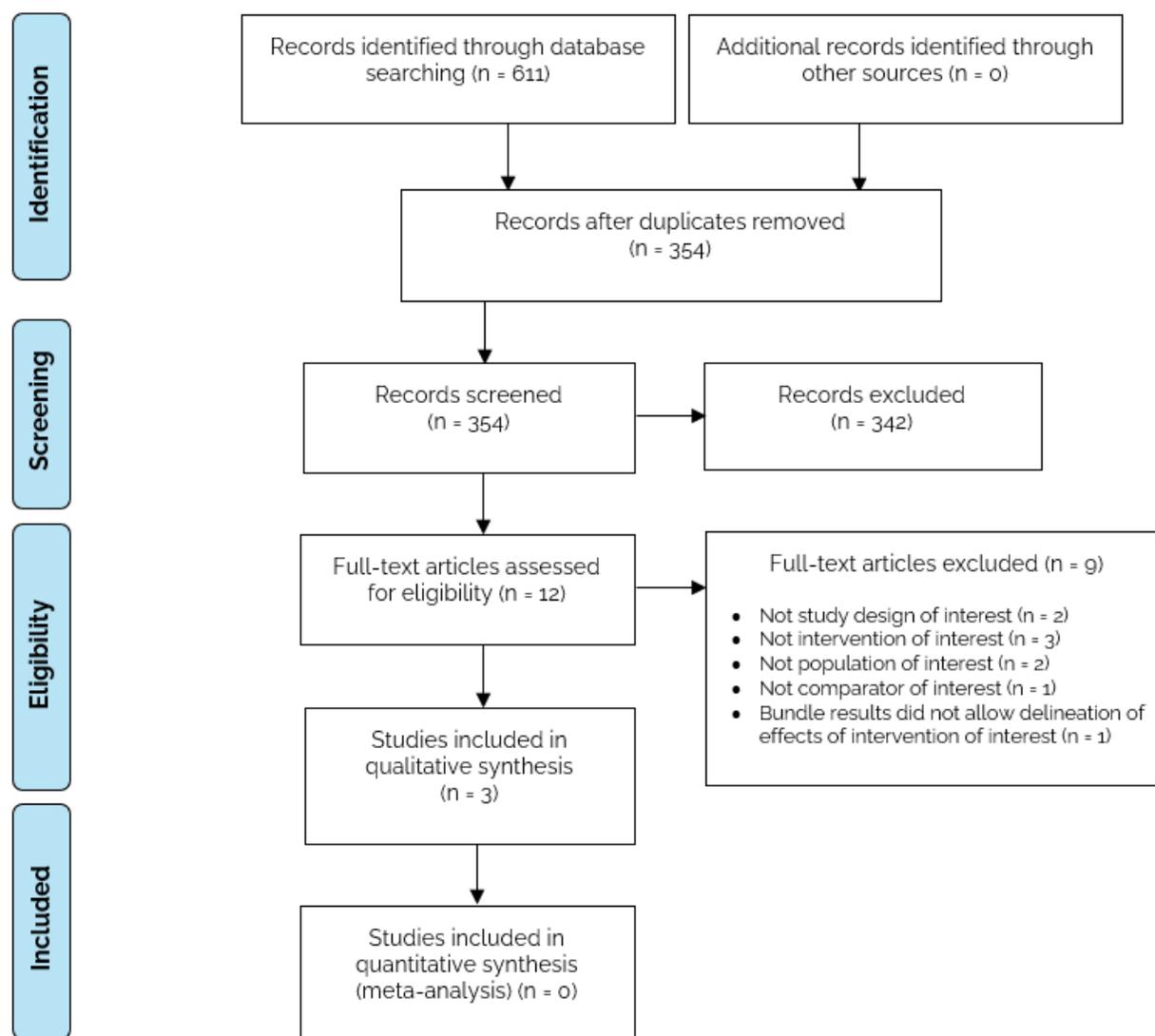


Figure 2: PRISMA Flow Diagram—Clinical Search Strategy for Primary Studies

PRISMA flow diagram showing the clinical search strategy for primary studies. The database search yielded 611 citations published between January 1, 2018, and June 29, 2021. We identified no additional eligible studies from other sources. After removing duplicates, we screened the abstracts of 354 studies and excluded 342. We assessed the full text of 12 articles and excluded a further 9. In the end, we included 3 articles in the qualitative synthesis.

Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.

Source: Adapted from Moher et al, 2009.²⁶

Characteristics of Included Studies

The 2019 NICE guideline¹⁹ included nine RCTs that examined the following six interventions (Table 3):

- Nasal mupirocin vs. placebo nasal ointment
- Nasal mupirocin vs. no nasal decolonization
- Nasal mupirocin vs. nasal 5% povidone-iodine
- Nasal mupirocin combined with chlorhexidine body wash vs. no intervention (i.e., no nasal decolonization or body wash)
- Nasal mupirocin combined with chlorhexidine body wash vs. placebo (i.e., placebo nasal ointment with placebo soap)
- Nasal chlorhexidine vs. placebo

The RCTs included in the 2019 NICE guideline¹⁹ examined different populations, types of surgery, and timings of nasal decolonization, and they explored a number of outcomes. Data on overall surgical site infections (irrespective of pathogen) and *S. aureus*-related surgical site infections were extracted. Where possible, data on superficial, deep incisional, and organ/deep-space surgical site infections, as well as surgical site infections specific to methicillin-susceptible *S. aureus* (MSSA) versus methicillin-resistant *S. aureus* (MRSA), were extracted. The included studies examined a number of surgical procedures, including orthopaedic, cardiac, and Mohs surgeries. The NICE committee identified surgical site infections including superficial, deep incisional, and organ/deep space as outcomes of interests. In addition, outcomes at 30 days and 1 year were identified as important.

The included studies classified infections according to the US Centers for Disease Control and Prevention (CDC) surgical site infection criteria, as well as the National Nosocomial Infections Surveillance System definitions. According to the CDC, a surgical site infection is defined as an infection occurring within 30 days after an operation. A deep surgical site infection is defined as an infection occurring within 30 days after an operation if no implant was left in place or within 1 year if an implant is in place. Therefore, surgical site infections occurring within 30 days and within 1 year were prioritized in the NICE guideline.¹⁹ Follow-up period varied among the included RCTs. Where possible, sub-group analyses by follow-up period were conducted; for example, at 30 days after surgery and within 8 weeks of surgery. Three RCTs included chlorhexidine body wash before surgery as standard practice in both intervention and comparison groups.⁴³⁻⁴⁵ The majority of RCTs used pre-surgical antibiotic prophylactic in both groups.^{28,29,43-48}

We reported results as they were presented in the 2019 NICE guideline¹⁹; however, we did not include interventions that used an alternative treatment as a comparator (i.e., nasal mupirocin vs. 5% povidone-iodine), as the only comparators for our review were no intervention and placebo.

We identified three relevant RCTs that were published after the 2019 NICE guideline.²⁸⁻³⁰ Two studies were conducted in orthopaedic patients, some of whom were *S. aureus* carriers and some of whom were not *S. aureus* carriers.^{28,29} One study was conducted in patients with skin cancer undergoing Mohs surgery who were not *S. aureus* carriers.³⁰ Table 4 summarizes the characteristics of these studies.

Table 3: Characteristics of the Randomized Controlled Trials Included in the Selected Systematic Review

Author, year, country	Number of patients	Population	<i>S. aureus</i> status	Type(s) of surgery	Intervention	Comparator	Follow-up duration
Bode et al, 2010, ⁴⁶ Netherlands	Intervention: 504 Comparator: 413	Adult patients screened for nasal carriage of <i>S. aureus</i>	<i>S. aureus</i> carriers	Cardiothoracic, vascular, orthopaedic, gastrointestinal, general	2% mupirocin nasal ointment twice daily and chlorhexidine body wash daily for 5 days	Placebo nasal ointment and placebo soap	Until 6 weeks after discharge
Kalmeijer et al, 2002, ⁴⁷ Netherlands	Intervention: 315 Comparator: 299	All patients	No screening of <i>S. aureus</i> status	Elective or revision orthopaedic surgeries during which a prosthetic implant material was used (i.e., hip, knee, or back surgery)	2.15% mupirocin nasal ointment twice daily (3 or more doses were administered before surgery)	Placebo nasal ointment	1 month after surgery
Konvalinka et al, 2006, ⁴³ Canada	Intervention: 130 Comparator: 127	Patients screened for nasal carriage of <i>S. aureus</i>	<i>S. aureus</i> carriers	Elective open-heart surgery	2% mupirocin nasal ointment twice daily for 7 days	Placebo nasal ointment	8 weeks
Perl et al, 2002, ⁴⁴ United States	<i>All patients</i> Intervention: 1,933 Comparator: 1,931 <i>S. aureus carriers</i> Intervention: 444 Comparator: 447	All patients	No screening of <i>S. aureus</i> status	Elective and non-emergency cardiothoracic, general, oncologic, gynaecologic, neurologic	2% mupirocin nasal ointment twice daily for up to 5 days	Placebo nasal ointment	30 days
Phillips et al, 2014, ⁴⁹ United States	Intervention: 855 Comparator: 842	Adult patients	No screening of <i>S. aureus</i> status	Primary or revision arthroplasty, spine fusion	2% mupirocin nasal ointment daily for 5 days	Nasal povidone-iodine 5% solution	3 months

Author, year, country	Number of patients	Population	<i>S. aureus</i> status	Type(s) of surgery	Intervention	Comparator	Follow-up duration
Segers et al, 2006, ⁵⁰ Netherlands	Intervention: 485 Comparator: 469	Adult patients	No screening of <i>S. aureus</i> status	Sternotomy for cardiothoracic surgery	0.12% chlorhexidine gluconate solution as an oral rinse and as a nasal gel (4 times per day until the day after surgery)	Placebo oral rinse solution and placebo nasal ointment	30 days
Sousa et al, 2016, ⁴⁸ Portugal	Intervention: 113 Comparator: 115	Patients identified as <i>S. aureus</i> carriers	<i>S. aureus</i> carriers	Elective primary total hip or knee arthroplasty	2% mupirocin nasal ointment twice daily and chlorhexidine body wash once daily for 5 days	No intervention	1 year after surgery
Suzuki et al, 2003, ⁴⁵ Japan	Intervention: 193 Comparator: 202	Consecutive patients during study period	No screening of <i>S. aureus</i> status	Abdominal digestive surgery	2% mupirocin nasal ointment three times daily for 3 days	No intervention	30 days
Tai et al, 2013, ⁵¹ Australia	Intervention: 102 Comparator: 101	Patients with positive nasal cultures of <i>S. aureus</i>	<i>S. aureus</i> carriers	Mohs micrographic surgery	2% mupirocin nasal ointment twice daily and chlorhexidine body wash once daily for 5 days	No intervention	Duration not specified. All patients were followed up in the post-operative period for signs of clinical infection

Abbreviations: NICE, National Institute for Health and Care Excellence; *S. aureus*, *Staphylococcus aureus*.

Source: NICE, 2019.⁴⁹

Table 4: Characteristics of the Included Primary Studies

Author, year, country	Number and characteristics of patients	Population	<i>S. aureus</i> status	Type(s) of surgery	Interventions	Comparator	Outcomes
Rohrer et al, 2020, ²⁸ Switzerland	<p><i>S. aureus</i> carriers</p> <p>Intervention: 232</p> <p>Control: 233</p> <p>Non-<i>S. aureus</i> carriers</p> <p>Intervention: 426</p> <p>Control: 427</p> <p>Median age, y (range): 59 (49–68) (<i>S. aureus</i> carriers) vs. 61 (51–69) (non-<i>S. aureus</i> carriers)</p> <p>Female (%): 45 (<i>S. aureus</i> carriers) vs. 57 (non-<i>S. aureus</i> carriers)</p>	<p>Pre-surgical orthopaedic (spine, pelvic/hip, knee/foot) patients</p> <p>Patients in both arms received IV cefuroxime antibiotic prophylaxis (1.5 g) 30–60 min before incision and at 8 h and 16 h post-operatively</p>	<p><i>S. aureus</i> carriers and non-<i>S. aureus</i> carriers</p>	<p>General elective orthopaedic surgery</p>	<p><i>S. aureus</i> carriers: 5 d of daily chlorhexidine showers and mupirocin nasal ointment twice a day</p> <p>Non-<i>S. aureus</i> carriers: 5 d of daily chlorhexidine showers</p>	<p>Shower before surgery with conventional soap</p>	<p>Primary outcome: SSI occurrence at 90 d post-operative</p> <p>Secondary outcomes: early (30 d post-operative) and late (31–90 d post-operative) SSI, death related to infection, SSI caused by documented bacteria, time from surgery to SSI or death</p>

Author, year, country	Number and characteristics of patients	Population	<i>S. aureus</i> status	Type(s) of surgery	Interventions	Comparator	Outcomes
Rohrer et al, 2021, ²⁹ Switzerland	<i>S. aureus</i> carriers Intervention: 104 Control: 103 Non- <i>S. aureus</i> carriers Intervention: 206 Control: 200 Mean age ± SD, y: 63 ± 11 (intervention) vs. 63 ± 10 (control) Female (%): 49 (intervention) vs. 44 (control)	Pre-surgical patients undergoing orthopaedic pelvic or knee prosthetic surgery	<i>S. aureus</i> carriers and non- <i>S. aureus</i> carriers	Orthopaedic pelvic, knee prosthetic	<i>S. aureus</i> carriers: 5 d of daily chlorhexidine showers and mupirocin nasal ointment twice a day Non- <i>S. aureus</i> carriers: 5 d of daily chlorhexidine showers	Shower before surgery with conventional soap	Delayed-onset periprosthetic joint infections (3–24 mo after surgery)
Smith et al, 2019, ³⁰ Australia	Intervention: 661 Control: 689 Mean age ± SD, y: 64 ± 13 (intervention) vs. 69 ± 12 (control)	Pre-surgical patients with skin cancer undergoing Mohs micrographic surgery	<i>S. aureus</i> carriers and non- <i>S. aureus</i> carriers	Mohs micrographic surgery	Intranasal mupirocin 2% ointment twice daily and application of 50 mL of aqueous 4% chlorhexidine solution from vertex to toes once daily, washed off after 2 min	No intervention	Wound infection within 1 wk of surgery

Abbreviations: *S. aureus*, *Staphylococcus aureus*; SD, standard deviation; SSI, surgical site infection.

Quality of Evidence

The NICE committee considered that the studies included in their 2019 health technology assessment¹⁹ were of low to moderate quality. Most studies provided old evidence (reflected in the 2007 guideline), with new evidence being identified only for the combined use of intranasal mupirocin and chlorhexidine body wash.

The risk of bias in the three RCTs published after the 2019 NICE health technology assessment¹⁹ was moderate. See Appendix 2, Table A2, for the risk-of-bias assessment for these studies using the Cochrane risk-of-bias tool for randomized controlled trials.³²

The quality of evidence for both the NICE health technology assessment¹⁹ and the three included RCTs²⁸⁻³⁰ published afterward is included in the following sections discussing the outcomes of all studies.

All Pre-surgical Patients (Universal Decolonization)

NASAL MUPIROCIN ALONE VERSUS PLACEBO

The 2019 NICE guideline¹⁹ identified two RCTs^{44,47} that compared nasal mupirocin alone versus placebo in pre-surgical patients. One study was on elective or revision orthopaedic surgeries during which a prosthetic implant material was used,⁴⁷ and the other was on elective and non-emergency cardiothoracic, general, oncologic, gynaecologic, or neurologic surgical procedures.⁴⁴ Table 5 summarizes the findings and the quality of the evidence for the effectiveness outcomes of these RCTs. (See Appendix 2, Table A3, for the assessment of the GRADE evidence profile for these outcomes.)

In both RCTs,^{44,47} there was no difference in the rates of overall and *S. aureus*-related surgical site infection between patients who received nasal mupirocin and those who received placebo before surgery.

Kalmeijer et al⁴⁷ could not differentiate the rates of overall superficial and deep incisional surgical site infection between patients who received nasal mupirocin and those who received placebo a day before orthopaedic surgery. In terms of health service use, there was no difference in hospital readmission or mean hospital stay between the intervention and control groups.

Perl et al⁴⁴ could not differentiate the rates of overall and *S. aureus*-related nosocomial infection between patients who received nasal mupirocin and those who received placebo 5 days before surgery.

Based on the RCTs^{44,47} reviewed, the NICE authors assessed the quality of evidence for nasal mupirocin (vs. placebo) in pre-surgical patients as moderate to very low, downgrading because of risk of bias and imprecision.

Table 5: Comparison of Nasal Mupirocin Alone Versus Placebo in All Pre-surgical Patients

Outcome	Number of studies	Number of patients	Results ^a	GRADE
Overall SSI at 30 days	2 ^{44,47}	4,478	RR: 0.92 (95% CI: 0.75, 1.12)	Low
Overall superficial SSI at 30 days	1 ⁴⁷	614	RR: 0.88 (95% CI: 0.41, 1.89)	Low
Overall deep incisional SSI at 30 days	1 ⁴⁷	614	RR: 0.32 (95% CI: 0.01, 7.74)	Very low
<i>S. aureus</i> -related SSI at 30 days	2 ^{44,47}	4,400	RR: 0.88 (95% CI: 0.60, 1.30)	Very low
Overall nosocomial infection ^b at 30 days	1 ⁴⁴	3,864	RR: 0.99 (95% CI: 0.83, 1.18)	Moderate
<i>S. aureus</i> -related nosocomial infection ^b at 30 days	1 ⁴⁴	3,770	RR: 0.82 (95% CI: 0.56, 1.21)	Low
Hospital readmission	1 ⁴⁷	614	RR: 0.63 (95% CI: 0.11, 3.76)	Low
Mean hospital stay (in days)	1 ⁴⁷	614	MD ^c : -0.30 (95% CI: -1.38, 0.78)	Moderate

Abbreviations: CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; MD, mean difference; RR, risk ratio; *S. aureus*, *Staphylococcus aureus*; SSI, surgical site infection.

^aRR < 1 favours mupirocin.

^bIncluded bloodstream, respiratory tract, catheter, and surgical site infections.

^cEffect size below 0 favours mupirocin.

NASAL MUPIROCIN ALONE VERSUS NO INTERVENTION

The 2019 NICE guideline⁴⁹ identified one RCT⁴⁵ that compared nasal mupirocin alone versus no intervention in pre-surgical patients. Table 6 summarizes the findings and the quality of the evidence for the effectiveness outcomes of this RCT. (See Appendix 2, Table A4, for the assessment of the GRADE evidence profile for these outcomes.)

Suzuki et al⁴⁵ found no difference in any surgical site infection outcomes or in the outcome of overall nosocomial infection between patients who received nasal mupirocin and those who received no intervention 3 days before abdominal digestive surgery.

Based on the RCT⁴⁵ reviewed, the NICE authors assessed the quality of evidence for nasal mupirocin (vs. no intervention) in pre-surgical patients as moderate to low, downgrading because of imprecision.

Table 6: Comparison of Nasal Mupirocin Alone Versus No Intervention in All Pre-surgical Patients

Outcome	Number of studies	Number of patients	Results ^a	GRADE
Overall SSI at 30 days	1 ⁴⁵	395	RR: 1.33 (95% CI: 0.79, 2.25)	Low
Overall superficial SSI at 30 days	1 ⁴⁵	395	RR: 0.70 (95% CI: 0.25, 1.92)	Low
Overall deep incisional SSI at 30 days	1 ⁴⁵	395	RR: 1.77 (95% CI: 0.92, 3.42)	Moderate
<i>S. aureus</i> -related SSI at 30 days	1 ⁴⁵	395	RR: 0.47 (95% CI: 0.15, 1.49)	Low
Overall nosocomial infection ^b at 30 days	1 ⁴⁵	395	RR: 0.70 (95% CI: 0.20, 2.43)	Low

Abbreviations: CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RR, risk ratio;

S. aureus, *Staphylococcus aureus*; SSI, surgical site infection.

^aRR < 1 favours mupirocin.

^bDefined as the presence of patchy bronchopneumonic infiltrates or consolidation on chest radiography, with at least one clinical symptom (fever, productive cough, pleuritic chest pain, or dyspnoea), and was confirmed by a positive sputum culture. All pneumonias were diagnosed within 14 days after surgery.

NASAL CHLORHEXIDINE COMBINED WITH CHLORHEXIDINE ORAL RINSE VERSUS PLACEBO

The 2019 NICE guideline⁴⁹ identified one RCT⁵⁰ that compared nasal chlorhexidine combined with chlorhexidine oral rinse versus placebo in pre-surgical patients about to undergo cardiothoracic surgery. Table 7 summarizes the findings and the quality of the evidence for the effectiveness outcomes of these RCTs. (See Appendix 2, Table A5, for the assessment of the GRADE evidence profile for these outcomes.)

Segers et al⁵⁰ demonstrated that administering chlorhexidine in the form of a nasal gel as well as an oral rinse resulted in a significant reduction in the risk of overall deep incisional surgical site infection, overall nosocomial infection, lower respiratory tract infection, and mean hospital stay in pre-surgical patients about to undergo cardiothoracic surgery.

Based on the RCT⁵⁰ reviewed, the NICE authors assessed the quality of the evidence for nasal chlorhexidine combined with chlorhexidine oral rinse (vs. placebo) in pre-surgical patients about to undergo cardiothoracic surgery as moderate to very low, downgrading because of indirectness and imprecision.

Table 7: Comparison of Nasal Chlorhexidine With Chlorhexidine Oral Rinse Versus Placebo in All Pre-surgical Patients

Outcome	Number of studies	Number of patients	Results ^a	GRADE
Overall SSI at 30 days	1 ⁵⁰	954	RR: 0.89 (95% CI: 0.62, 1.29)	Very low
Overall deep incisional SSI at 30 days	1 ⁵⁰	954	RR: 0.36 (95% CI: 0.17, 0.77)	Moderate
<i>S. aureus</i> -related SSI at 30 days	1 ⁵⁰	954	RR: 0.77 (95% CI: 0.45, 1.31)	Very low
Overall nosocomial infection at 30 days	1 ⁵⁰	954	RR: 0.68 (95% CI: 0.56, 0.84)	Low
Nosocomial infection: lower respiratory tract infection at 30 days	1 ⁵⁰	954	RR: 0.59 (95% CI: 0.42, 0.83)	Low
Nosocomial infection: urinary tract infection at 30 days	1 ⁵⁰	954	RR: 0.64 (95% CI: 0.33, 1.25)	Very low
Nosocomial infection: bacteraemia at 30 days	1 ⁵⁰	954	RR: 0.51 (95% CI: 0.23, 1.14)	Low
Mortality at 30 days	1 ⁵⁰	954	RR: 1.29 (95% CI: 0.45, 3.69)	Very low
Mean hospital stay (in days) at 30 days	1 ⁵⁰	954	MD ^b : -7.70 (95% CI: -9.96, -5.44)	Moderate
Hospital readmission at 30 days	1 ⁵⁰	954	RR: 0.80 (95% CI: 0.44, 1.45)	Very low

Abbreviations: CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; MD, mean difference; RR, risk ratio; *S. aureus*, *Staphylococcus aureus*; SSI, surgical site infection.

^aRR < 1 favours mupirocin.

^bEffect size below 0 favours mupirocin.

Pre-surgical Patients Who Are *S. aureus* Carriers (Targeted Decolonization)

NASAL MUPIROCIN ALONE VERSUS PLACEBO

The 2019 NICE guideline¹⁹ identified three RCTs^{43,44,47} that reported surgical site infection outcomes from a comparison of nasal mupirocin alone versus placebo in pre-surgical patients who are *S. aureus* carriers. Kalmeijer et al⁴⁷ assessed patients undergoing elective orthopaedic surgery; Konvalinka et al⁴³ assessed patients undergoing elective open-heart surgery; and Perl et al⁴⁴ assessed patients undergoing elective and non-emergency cardiothoracic, general, oncologic, gynaecologic, or neurologic surgical procedures. Table 8 summarizes the findings and the quality of the evidence for the effectiveness outcomes of these RCTs. (See Appendix 2, Table A6, for the assessment of the GRADE evidence profile for these outcomes.)

In the RCTs by Konvalinka et al⁴³ and Perl et al,⁴⁴ there was no difference in the rate of overall surgical site infection between *S. aureus* carriers who received nasal mupirocin and those who received placebo before surgery, either at 30 days or within 8 weeks of surgery.

In the RCT by Konvalinka et al,⁴³ there was no difference in the rate of superficial, deep incisional, or organ/deep-space surgical site infection between *S. aureus* carriers who received nasal mupirocin and those who received placebo 7 days before cardiac surgery.

Across all three RCTs,^{43,44,47} there was no difference in the rate of *S. aureus*-related surgical site infection between *S. aureus* carriers who received nasal mupirocin and those who received placebo before surgery, either at 30 days or within 8 weeks of surgery.

In the RCT by Perl et al,⁴⁴ *S. aureus* carriers who received nasal mupirocin 5 days before surgery had a lower incidence of *S. aureus* nosocomial infection after surgery compared with those who received placebo. However, there was no difference in the rate of overall nosocomial infection between the intervention and control groups.

Based on the RCTs reviewed,^{43,44,47} the NICE authors assessed the quality of the evidence for nasal mupirocin (vs. placebo) in pre-surgical patients who are *S. aureus* carriers as moderate to very low, downgrading because of risk of bias, imprecision, and inconsistency.

Table 8: Comparison of Nasal Mupirocin Alone Versus Placebo in Pre-surgical Patients Who Are *S. aureus* Carriers

Outcome	Number of studies	Number of patients	Results ^a	GRADE
Overall SSI	2 ^{43,44}	1,148	RR: 1.08 (95% CI: 0.59, 1.97)	Very low
Overall SSI at 30 days	1 ⁴⁴	891	RR: 0.85 (95% CI: 0.58, 1.24)	Low
Overall SSI within 8 weeks of surgery	1 ⁴³	257	RR: 1.60 (95% CI: 0.79, 3.25)	Low
Overall superficial SSI within 8 weeks of surgery	1 ⁴³	257	RR: 1.85 (95% CI: 0.85, 3.99)	Moderate
Overall deep incisional SSI within 8 weeks of surgery	1 ⁴³	257	RR: 0.98 (95% CI: 0.06, 15.45)	Low
Overall organ/deep-space SSI within 8 weeks of surgery	1 ⁴³	257	RR: 0.33 (95% CI: 0.01, 7.92)	Low
<i>S. aureus</i> -related SSI	3 ^{43,44,47}	1,318	RR: 0.66 (95% CI: 0.40, 1.11)	Low
<i>S. aureus</i> -related SSI at 30 days	2 ^{44,47}	1,061	RR: 0.59 (95% CI: 0.33, 1.04)	Low ^c
<i>S. aureus</i> SSI within 8 weeks of surgery	1 ⁴³	257	RR: 1.22 (95% CI: 0.34, 4.44)	Low

Outcome	Number of studies	Number of patients	Results ^a	GRADE
Overall nosocomial infection ^b at 30 days	1 ⁴⁴	891	RR: 0.80 (95% CI: 0.58, 1.10)	Low
<i>S. aureus</i> -related nosocomial infection ^b at 30 days	1 ⁴⁴	869	RR: 0.51 (95% CI: 0.29, 0.90)	Low
Mortality	1 ⁴³	257	RR: 0.78 (95% CI: 0.21, 2.84)	Low

Abbreviations: CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RR, risk ratio;

S. aureus, *Staphylococcus aureus*; SSI, surgical site infection.

^aRR < 1 favours mupirocin.

^bIncluded bloodstream, respiratory tract, catheter, and surgical site infections.

^cIn the NICE guideline, the GRADE rating for this outcome was "Very low." However, it should have been graded "Low" if downgraded one level for risk of bias and one level for imprecision.

NASAL MUPIROICIN COMBINED WITH CHLORHEXIDINE BODY WASH VERSUS PLACEBO

The 2019 NICE guideline⁴⁹ identified one RCT⁴⁶ that compared nasal mupirocin combined with chlorhexidine body wash versus placebo (nasal ointment and body wash with soap) in pre-surgical patients who are *S. aureus* carriers. The population included patients undergoing cardiothoracic, vascular, orthopaedic, gastrointestinal, or general surgery. The primary outcome of this RCT was the cumulative incidence of hospital-associated *S. aureus* infection. Table 9 summarizes the findings and the quality of the evidence for the effectiveness outcomes of this RCT. (See Appendix 2, Table A7, for the assessment of the GRADE evidence profile for these outcomes.)

Bode et al⁴⁶ provided high-quality evidence that demonstrated a significantly lower incidence of *S. aureus*-related surgical site infection, *S. aureus*-related deep incisional surgical site infection, and *S. aureus*-related nosocomial infection in *S. aureus* carriers who received intranasal mupirocin combined with chlorhexidine body wash 4 days before surgery than in those who received placebo. However, this study did not report *S. aureus*-related superficial surgical site infections. There was no difference in mortality between the intervention and control groups.

Based on the RCT⁴⁶ reviewed, the NICE authors assessed the quality of the evidence for nasal mupirocin combined with chlorhexidine body wash (vs. placebo) in pre-surgical patients who are *S. aureus* carriers as high to low, downgrading because of imprecision.

Table 9: Comparison of Nasal Mupirocin Combined With Chlorhexidine Body Wash Versus Placebo in Pre-surgical Patients Who Are *S. aureus* Carriers

Outcome	Number of studies	Number of patients	Results ^a	GRADE
<i>S. aureus</i> -related SSI until 6 weeks after discharge	1 ⁴⁶	808	RR: 0.32 (95% CI: 0.16, 0.62)	High
<i>S. aureus</i> -related superficial SSI until 6 weeks after discharge	1 ⁴⁶	808	RR: 0.45 (95% CI: 0.18, 1.11)	Moderate
<i>S. aureus</i> -related deep incisional SSI until 6 weeks after discharge	1 ⁴⁶	808	RR: 0.21 (95% CI: 0.07, 0.62)	High
<i>S. aureus</i> -related nosocomial infection until 6 weeks after discharge	1 ⁴⁶	808	RR: 0.43 (95% CI: 0.24, 0.77)	High
Mortality	1 ⁴⁶	808	RR: 0.49 (95% CI: 0.19, 1.22)	Moderate
Mortality in <i>S. aureus</i> carriers with <i>S. aureus</i> infection	1 ⁴⁶	808	RR: 0.28 (95% CI: 0.03, 2.66)	Low

Abbreviations: CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RR, risk ratio; *S. aureus*, *Staphylococcus aureus*; SSI, surgical site infection.

^aRR < 1 favours mupirocin.

NASAL MUPIROCIN COMBINED WITH CHLORHEXIDINE BODY WASH VERSUS NO INTERVENTION

The 2019 NICE guideline¹⁹ identified two RCTs^{48,51} that compared nasal mupirocin combined with chlorhexidine body wash versus no intervention (no active placebo) in pre-surgical patients who are *S. aureus* carriers. Two further RCTs^{28,29} on this comparison in patients about to undergo orthopaedic surgery were published after the 2019 NICE guideline. Table 10 summarizes the findings and the quality of the evidence for the effectiveness outcomes of these four RCTs. (See Appendix 2, Table A8, for the assessment of the GRADE evidence profile for these outcomes.)

In the RCT by Tai et al.,⁵¹ *S. aureus* carriers who received mupirocin combined with chlorhexidine body wash 5 days before Mohs surgery had a lower incidence of MSSA surgical site infection post-operatively compared with those who received no intervention. However, there was no difference in the overall rate of *S. aureus*-related or MRSA-related surgical site infection between the intervention and control groups.

In the RCT by Sousa et al,⁴⁸ there was no difference in the rate of overall or *S. aureus*-related deep incisional surgical site infection at 1 year between *S. aureus* carriers who received nasal mupirocin combined with chlorhexidine body wash at least 1 week before elective primary total hip or knee arthroplasty and those who received no intervention.

The RCTs by Rohrer et al^{28,29} could not differentiate the rate of overall surgical site infection at 90 days or the rate of prosthetic joint infection at 2 years between *S. aureus* carriers who received nasal mupirocin twice daily combined with chlorhexidine body wash once daily for 5 days and those who received no intervention before elective orthopaedic surgery. Neither the intervention nor the control group experienced prosthetic joint infection.²⁹

Based on the RCTs identified by NICE^{48,51} and the RCTs published after the NICE review,^{28,29,48,51} the quality of the evidence for nasal mupirocin combined with chlorhexidine body wash (vs. no intervention) in pre-surgical patients who are *S. aureus* carriers was graded low to very low, downgrading because of risk of bias and imprecision.

Table 10: Comparison of Nasal Mupirocin Combined With Chlorhexidine Body Wash Versus No Intervention in Pre-surgical Patients Who Are *S. aureus* Carriers

Outcome	Number of studies	Number of patients	Results ^a	GRADE
Overall SSI at 90 days	1 ²⁸	465	RR: 1.00 (95% CI: 0.06, 15.96)	Very low
Overall deep incisional SSI (prosthetic joint infection) at 1 year	1 ⁴⁸	228	RR: 0.78 (95% CI: 0.20, 3.04)	Very low
Prosthetic joint infection at 2 years	1 ²⁹	207	No estimate because there were no events in either group	Very low
<i>S. aureus</i> -related deep incisional SSI (prosthetic joint infection) at 1 year	1 ⁴⁸	228	RR: 1.04 (95% CI: 0.18, 6.11)	Very low
<i>S. aureus</i> -related SSI during post-operative period	1 ⁵¹	203	RR: 0.36 (95% CI: 0.12, 1.09)	Very low
MRSA-related SSI	1 ⁵¹	203	RR: 4.95 (95% CI: 0.24, 101.87)	Very low
MSSA-related SSI	1 ⁵¹	203	RR: 0.18 (95% CI: 0.04, 0.79)	Low

Abbreviations: CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; RR, risk ratio; *S. aureus*, *Staphylococcus aureus*; SSI, surgical site infection.

^aRR < 1 favours mupirocin.

NASAL MUPIROICIN WITH OR WITHOUT CHLORHEXIDINE BODY WASH VERSUS ALL NON-ACTIVE INTERVENTIONS

The 2019 NICE guideline¹⁹ conducted a meta-analysis of five RCTs^{43,44,46,47,51} comprising nasal mupirocin with or without chlorhexidine body wash compared with all non-active interventions (i.e., placebo or no intervention). The quality of evidence for this comparison was moderate, downgraded because of risk of bias. The NICE report specified that this meta-analysis was conducted to support the economic evaluation. Table 11 summarizes the findings and the quality of evidence for the effectiveness outcome of these five RCTs. (See Appendix 2, Table Ag, for the assessment of the GRADE evidence profile for this outcome.)

Table 11: Comparison of Nasal Mupirocin With or Without Chlorhexidine Body Wash Versus All Non-Active Interventions in Pre-surgical Patients Who Are *S. aureus* Carriers

Outcome	Number of studies	Number of patients	Results	GRADE
<i>S. aureus</i> -related SSI	5 ^{43,44,46,47,51}	2,329	RR: 0.48 (95% CI: 0.33, 0.70)	Moderate

Abbreviations: CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RR, risk ratio;

S. aureus, *Staphylococcus aureus*; SSI, surgical site infection.

^aRR < 1 favours mupirocin.

Pre-surgical Patients Who Are Not S. aureus Carriers

NASAL MUPIROICIN COMBINED WITH CHLORHEXIDINE BODY WASH VERSUS NO INTERVENTION

The 2019 NICE guideline¹⁹ did not identify any RCTs that examined nasal decolonization of *S. aureus* in pre-surgical patients who were not *S. aureus* carriers. However, three RCTs²⁸⁻³⁰ in this population were published after the 2019 NICE guideline.¹⁹ Table 12 summarizes the findings and the quality of the evidence for the effectiveness outcomes of these RCTs. (See Appendix 2, Table A10, for the assessment of the GRADE evidence profile for these outcomes.)

The RCTs by Rohrer et al^{28,29} could not differentiate the rate of overall surgical site infection at 90 days and the rate of prosthetic joint infection at 2 years between non-*S. aureus* carriers who received nasal mupirocin twice daily combined with chlorhexidine body wash once daily for 5 days before elective orthopaedic surgery and those who received no intervention. Neither the intervention nor the control group experienced prosthetic joint infection.²⁹

In the RCT by Smith et al,³⁰ the wound infection rate 1 week after Mohs surgery was lower in non-*S. aureus* carriers who received pre-surgical nasal mupirocin combined with chlorhexidine body wash for 5 days than in those who received no intervention.

Based on the RCTs reviewed,²⁸⁻³⁰ we assessed the quality of the evidence for nasal mupirocin combined with chlorhexidine body wash (vs. no intervention) in pre-surgical patients who are not *S. aureus* carriers as low to very low, downgrading because of risk of bias and imprecision.

Table 12: Comparison of Nasal Mupirocin Combined With Chlorhexidine Body Wash Versus No Intervention in Pre-surgical Patients Who Are Not *S. aureus* Carriers

Outcome	Number of studies	Number of patients	Results ^a	GRADE
Overall SSI at 90 days	1 ²⁸	853	RR: 1.00 (95% CI: 0.06, 15.96)	Very low
Prosthetic joint infection at 2 years	1 ²⁹	406	No estimate because there were no events in either group	Very low
Wound infection within 1 week	1 ³⁰	1,350	RR: 0.50 (95% CI: 0.27, 0.94)	Low

Abbreviations: CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RR, risk ratio; SSI, surgical site infection.

^aRR < 1 favours mupirocin.

Adverse Events

In the 2019 NICE guideline,¹⁹ three RCTs^{43,44,47} examined antimicrobial resistance as an adverse event of nasal decolonization. No comparative data were identified. Perl et al⁴⁴ conducted in vitro susceptibility tests and found that 6 of 1,021 *S. aureus* isolates obtained from six patients were resistant to mupirocin. The authors also reported that four isolates were resistant to mupirocin but that three of these were obtained from patients who had not been treated with nasal mupirocin. Kalmeijer et al⁴⁷ concluded that all isolates were susceptible to mupirocin. Konvalinka et al⁴³ reported that no isolates from either nasal or wound cultures were methicillin resistant. No other adverse events were examined in the included studies.

Ongoing Studies

We are aware of the following ongoing studies that have potential relevance to this review.

On ClinicalTrials.gov, we identified two ongoing clinical studies:

- Decolonization of Patients Carrying *S. aureus* Before Cardiac Surgery: Study of the Risk Factors Associated With Failure (STAdécol) (NCT03685487)
- Infection Prevention Bundle in Brain Tumor Surgery (NCT04285697)

In the German Clinical Trials Register, we identified one ongoing clinical study:

- Ambulatory Screening and Decontamination to Prevent *Staphylococcus aureus* Complications in Patients With Elective Surgery (STAUfrei) (DRKS00016615)

In PROSPERO, we identified two ongoing systematic reviews:

- The Efficacy of Mupirocin and Chlorhexidine Gluconate in Preventing Methicillin-Resistant *Staphylococcus aureus*-Related Surgical Site Infections: a Systematic Review and Meta-analysis (CRD42020168082)
- A Systematic Review and Meta-analysis of the Role of *Staphylococcus aureus* Decolonization Strategies in the Prevention of Surgical Site Infections (CRD42019144781)

Discussion

In this clinical evidence review of nasal decolonization of *Staphylococcus aureus* for pre-surgical patients, we based our evidence synthesis on data reported in a health technology assessment published by the National Institute for Health and Care Excellence in 2019. We included eight RCTs from that review, as well as three RCTs published afterward.

Despite differences in surgery type, follow-up duration, and co-interventions (e.g., prophylactic antibiotics), nasal mupirocin combined with chlorhexidine body wash prior to certain high-risk surgeries may reduce the incidence of surgical site infections caused by *S. aureus* in patients who are *S. aureus* carriers but not in patients who are not *S. aureus* carriers.

Evaluating the effectiveness of nasal decolonization by assessing the outcomes of patients treated via universal decolonization may underestimate the true effect of this treatment, as decolonization may be effective only in *S. aureus* carriers; if so, the treatment will have little effect, if any, on those who are not *S. aureus* carriers.^{12,44} While universal decolonization may be easier to implement than targeted decolonization (i.e., screening patients first, then treating only *S. aureus* carriers),^{12,44} the potential emergence of resistance to the decolonizing agents is a concern, as increased mupirocin use is associated with increased antimicrobial resistance.⁵² However, most studies of short-term use have not found a substantial emergence of mupirocin or chlorhexidine resistance.⁵³ In this clinical evidence review, only three studies included antimicrobial resistance as an adverse event outcome, and only one study reported a small amount of resistance to mupirocin in *S. aureus* isolates (6 of 1,021). Photodisinfection, which does not cause antimicrobial resistance, is an alternative to nasal decolonization. However, no RCT on its effectiveness and safety has yet been published.

A number of the included studies used pre-surgical prophylactic antibiotics in both the intervention and control groups.^{28,29,43-48} The Best Practice in Surgery guidelines for surgical site infection prevention from the University of Toronto²⁰ state that all patients undergoing surgery should receive appropriate prophylactic antibiotics except in the case of some clean surgical procedures (level of evidence: High). The recommended agent for most surgeries is cefazolin. Vancomycin is recommended for people with a beta-lactam allergy. These prophylactic agents also cover MSSA and MRSA infections^{54,55} and may reduce the background risk of post-operative *S. aureus* infection. Recent evidence on pharmacotherapy prophylaxis embedded in Enhanced Recovery After Surgery protocols showed that the intravenous administration of cefazolin 2 g and metronidazole 500 mg within 16 to 30 minutes of incision after chlorhexidine skin preparation was associated with a low rate of surgical site infection in adult patients undergoing elective colorectal and gynecologic/oncology procedures.⁵⁶

The studies reviewed were conducted in different surgical populations, including cardiac, orthopaedic, and Mohs, among others. Considering the concern of antimicrobial resistance, the 2019 NICE guideline¹⁹ recommends against universal decolonization and recommends decolonization only in patients undergoing procedures in which the risk of *S. aureus*-related surgical site infection is high.

Strengths and Limitations

This clinical evidence review leveraged knowledge from existing systematic reviews to avoid duplication of prior work. However, we may have interpreted study results differently if we had examined the included studies independently. No comparative data from RCTs were available to allow comparisons between targeted and universal decolonization. We also did not identify any RCTs investigating targeted MRSA screening and decolonization. The included studies may not have been adequately powered and may not have had sufficient follow-up durations to evaluate microbial resistance; thus, the extent of antimicrobial resistance may not be fully captured in this review.

Conclusions

All Pre-Surgical Patients (Universal Decolonization)

Compared with placebo:

- Nasal mupirocin alone may result in little to no difference in the rate of overall surgical site infection in elective and non-emergent orthopaedic, cardiothoracic, general, oncologic, gynaecologic, and neurologic surgeries (GRADE: Low)
- Nasal mupirocin alone may have little to no effect on the rate of *S. aureus*-related surgical site infection in elective and non-emergent orthopaedic, cardiothoracic, general, oncologic, gynaecologic, and neurologic surgeries, but the evidence is very uncertain (GRADE: Very low)
- Nasal chlorhexidine combined with chlorhexidine oral rinse may have little to no effect on the rate of overall surgical site infection and *S. aureus*-related surgical site infection in cardiothoracic surgery, but the evidence is very uncertain (GRADE: Very low)

Compared with no intervention:

- Nasal mupirocin alone may result in little to no difference in the rate of overall surgical site infection and *S. aureus*-related surgical site infection in abdominal digestive surgery (GRADE: Low)

Pre-Surgical Patients Who Are *S. aureus* Carriers (Targeted Decolonization)

Compared with placebo:

- Nasal mupirocin combined with chlorhexidine body wash lowers the incidence of *S. aureus*-related surgical site infection in patients undergoing cardiothoracic, vascular, orthopaedic, gastrointestinal, or general surgery (GRADE: High)
- Nasal mupirocin combined with chlorhexidine body wash likely has no effect on mortality for patients undergoing cardiothoracic, vascular, orthopaedic, gastrointestinal, or general surgery (GRADE: Moderate)

- Nasal mupirocin alone may have little to no effect on the rate of overall surgical site infection in open-heart surgery, as well as in cardiothoracic, general, oncologic, gynaecologic, and neurologic surgical procedures, but the evidence is very uncertain (GRADE: Very low)
- Nasal mupirocin alone may result in little to no difference in the rate of *S. aureus*-related surgical site infection in orthopaedic and open-heart surgery, as well as cardiothoracic, general, oncologic, gynaecologic, and neurologic surgical procedures (GRADE: Low)
- Nasal mupirocin alone may result in little to no difference in mortality in cardiac surgery (GRADE: Low)

Compared with no intervention:

- Nasal mupirocin alone may have little to no effect on the rate of overall surgical site infection in orthopaedic surgery, but the evidence is very uncertain (GRADE: Very low)

Pre-Surgical Patients Who Are Not *S. aureus* Carriers (Targeted Decolonization)

Compared with no intervention:

- Nasal mupirocin combined with chlorhexidine body wash may have little to no effect on the rate of overall surgical site infection in orthopaedic surgery, but the evidence is very uncertain (GRADE: Very low)

Economic Evidence

Research Question

What is the cost-effectiveness of nasal decolonization of *Staphylococcus aureus* (*S. aureus*), including methicillin-susceptible and methicillin-resistant strains, with or without topical antiseptic body wash to prevent surgical site infection compared with no nasal decolonization (standard care only) for patients undergoing scheduled surgery?

Methods

Economic Literature Search

We performed an economic literature search on May 13, 2021, to retrieve studies published from database inception until the search date. To retrieve relevant studies, we developed a search using the clinical search strategy with an economic and costing filter applied.

We created database auto-alerts in MEDLINE, Embase, and CINAHL and monitored them for the duration of the assessment period. We also performed a targeted grey literature search of health technology assessment agency websites, systematic review registries, and the Tufts Cost-Effectiveness Analysis Registry. See the Clinical Literature Search section, above, for further details on methods used. See Appendix 1 for our literature search strategies, including all search terms.

Eligibility Criteria

STUDIES

Inclusion Criteria

- English-language full-text publications
- Studies published from database inception until May 13, 2021
- Cost-effectiveness analyses or cost-utility analyses
- Studies using clinical data from randomized clinical trials or from a systematic review of randomized clinical trials

Exclusion Criteria

- Reviews, editorials, case reports, commentaries, abstracts, letters, and unpublished studies
- Cost analyses (e.g., no effectiveness outcomes)
- Studies that did not use clinical data (e.g., treatment effectiveness) from randomized clinical trials
- Studies in which patients did not undergo a surgical procedure

POPULATION

- Patients of all ages undergoing surgery, including minimally invasive surgery (e.g., arthroscopic, thoracoscopic, laparoscopic), with different wound types (i.e., clean, clean contaminated, contaminated, dirty)

INTERVENTIONS

- Nasal decolonization of *S. aureus* (antibiotic ointment [e.g., mupirocin], antiseptic ointment [e.g., povidone-iodine], alcohol-based antiseptic, intranasal photodisinfection) with or without antiseptic body wash
 - Targeted decolonization (screen all patients for the presence of *S. aureus* and then treat only *S. aureus* carriers) or universal decolonization (treat all patients without first screening for *S. aureus*)

COMPARATORS

- No nasal decolonization or placebo (standard care only)

OUTCOME MEASURES

- Costs
- Health outcomes
 - Quality-adjusted life-years (QALYs)
 - Number of surgical site infections
 - Overall
 - By surgical site infection classification (i.e., superficial, deep incisional, organ/deep space)
 - By *S. aureus* type (i.e., methicillin-susceptible, methicillin-resistant, or both)
- Incremental costs
- Incremental effectiveness
- Incremental cost-effectiveness ratio (ICER)

Literature Screening

A single reviewer conducted an initial screening of titles and abstracts using Covidence¹ and then obtained the full texts of studies that appeared eligible for review according to the inclusion criteria. The same reviewer then examined the full-text articles and selected studies eligible for inclusion. This reviewer also examined reference lists for any additional relevant studies not identified through the search.

Data Extraction

We extracted relevant data on study characteristics and outcomes to collect information about the following:

- Source (e.g., citation information, study type)
- Methods (e.g., study design, analytic technique, perspective, time horizon, population, intervention[s], comparator[s])
- Outcomes (e.g., health outcomes, costs, incremental cost-effectiveness ratios)

Study Applicability and Limitations

We determined the usefulness of each identified study for decision-making by applying a modified quality appraisal checklist for economic evaluations originally developed by the National Institute for Health and Care Excellence (NICE) in the United Kingdom to inform the development of NICE's clinical guidelines.⁵⁷ We modified the wording of the questions to remove references to guidelines and to make it specific to Ontario. Next, we separated the checklist into two sections. In the first section, we assessed the applicability of each study to the research question (directly, partially, or not applicable). In the second section, we assessed the limitations (minor, potentially serious, or very serious) of the studies that we found to be directly applicable.

Results

Economic Literature Search

The database search of the economic literature yielded 1,397 citations published from database inception until May 13, 2021. We identified 10 additional studies from other sources. In total, we identified four studies (three cost-effectiveness studies and one health technology assessment) that met our inclusion criteria. See Appendix 5 for a list of selected studies excluded after full-text review. Figure 3 presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the economic literature search.

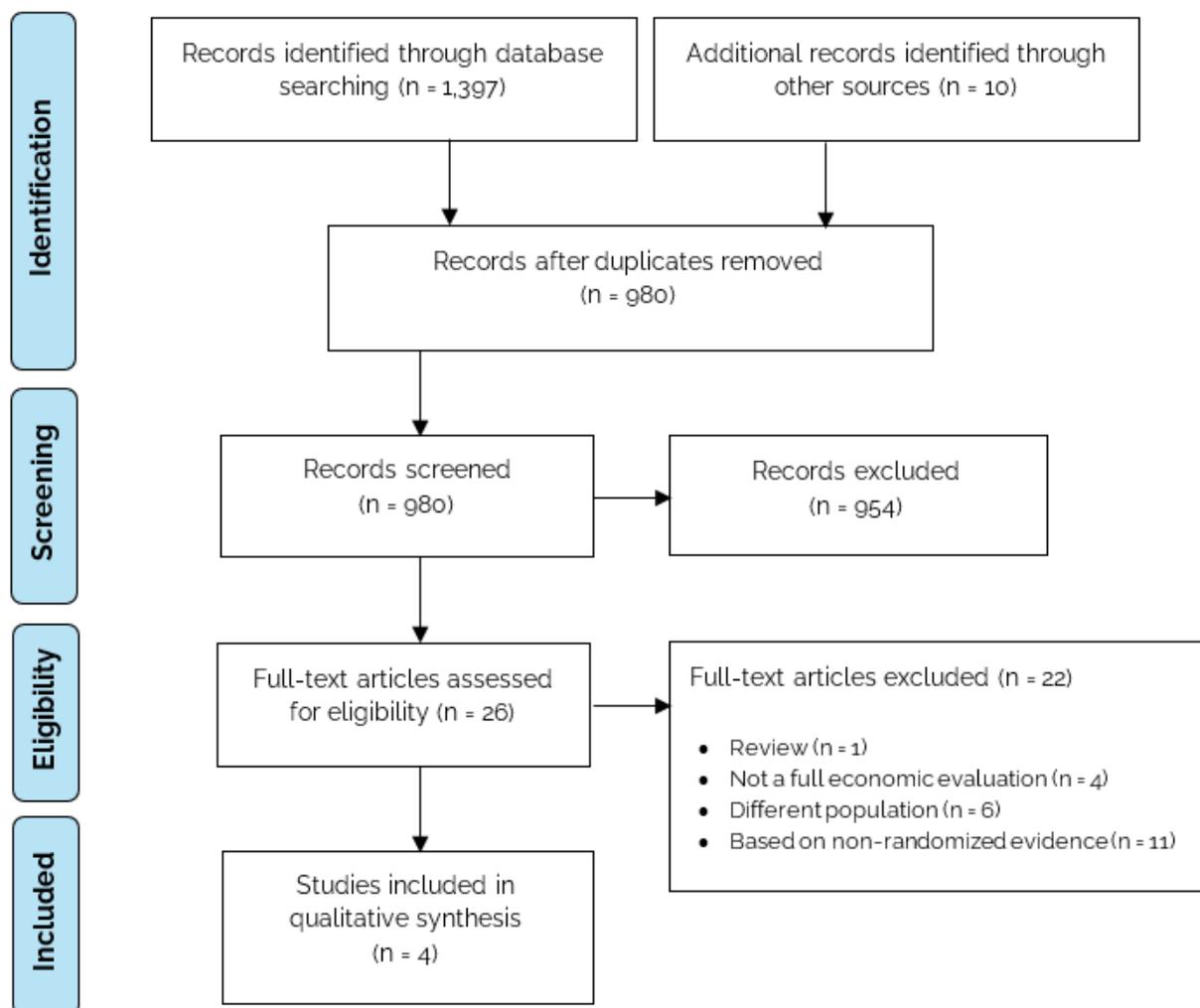


Figure 3: PRISMA Flow Diagram—Economic Search Strategy

PRISMA flow diagram showing the economic search strategy. The database search yielded 1,397 citations published from database inception until May 13, 2021. We identified 10 additional eligible studies from other sources. After removing duplicates, we screened the abstracts of 980 studies and excluded 954. We assessed the full text of 26 articles and excluded a further 22. In the end, we included 4 articles in the qualitative synthesis.

Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.

Source: Adapted from Moher et al, 2009.²⁶

Overview of Included Economic Studies

COST-EFFECTIVENESS STUDIES

Courville et al⁵⁸ used a 1-year decision-tree model to evaluate the cost-effectiveness of pre-operative nasal decolonization with mupirocin given for 5 days to prevent surgical site infection in patients undergoing total hip or knee arthroplasty. This study was conducted in the United States from the societal perspective. The authors compared three strategies: (1) taking pre-operative screening cultures from all patients and treating just those who are *S. aureus* carriers (targeted decolonization); (2) treating all patients without first screening (universal decolonization); and (3) providing no intervention. The main clinical parameter of the model was the relative risk of surgical site infection between treated and untreated *S. aureus* carriers. A relative risk of 0.61 was used; this value was taken from a systematic literature review.³⁶ The authors assumed that if a patient had an *S. aureus*-related surgical site infection, a full hip or knee revision procedure would be required. The sensitivity and specificity of the screening test (nasal swab and culture) were 0.52 and 0.85, respectively. It was assumed that a surgical site infection would reduce a person's quality-of-life utility value by 20%. The costs of primary arthroplasty and revision procedures were calculated in 2005 US dollars. The direct medical costs, including procedure and hospitalization costs, were taken from the orthopaedic literature where available.

Results from the reference case analysis showed that both universal and targeted decolonization were associated with lower costs and greater QALYs compared with no intervention, meaning that both universal and targeted decolonization dominated the no-intervention strategy for patients undergoing total hip or knee arthroplasty.⁵⁸ Sensitivity analyses showed that this result remained unchanged even if the cost of mupirocin exceeded \$100 USD or the cost of treating a surgical site infection exceeded \$250,000 USD per patient. Universal decolonization was found to be the best strategy (i.e., lowest costs and highest QALYs) when either the prevalence of *S. aureus* or the prevalence of surgical site infection was varied across the plausible ranges, even when the risk of mupirocin resistance was high.

Wassenberg et al⁵⁹ evaluated the cost-effectiveness of pre-operative nasal decolonization with mupirocin combined with chlorhexidine body wash to prevent surgical site infection in patients undergoing joint implant or cardiac surgery. This study was conducted in the Netherlands from the societal perspective. The authors compared three strategies: (1) treating all patients without first screening (universal decolonization); (2) performing rapid polymerase chain reaction (PCR) screening in all patients and treating just those who are *S. aureus* carriers (targeted decolonization); and (3) providing no intervention. The main clinical parameter of the model was the relative risk of deep incisional surgical site infection among treated and untreated *S. aureus* carriers. A relative risk of 0.21 was used; this value was taken from a multi-centre, double-blind, placebo-controlled trial.⁴⁶ The sensitivity (0.97) and specificity (0.99) of the PCR screening test were taken from the same trial.⁴⁶ Medical costs were taken from one hospital from the years 2001 through 2010. Costs were reported in 2009 euros.⁵⁹

Compared with no intervention, both targeted and universal decolonization were cost-saving.⁵⁹ Sensitivity analyses showed that when only *S. aureus* carriers were treated, the cost of screening needed to be less than €6.23 per person for targeted decolonization to be the dominant strategy. The sensitivity of the PCR screening test and the efficacy of mupirocin were influential factors on the cost-effectiveness results. The study results showed that compared with no intervention, both universal and targeted decolonization (both combined with chlorhexidine body wash) were

associated with improved health outcomes and cost savings. The number of *S. aureus*-related surgical site infections in the no-intervention, targeted decolonization, and universal decolonization groups was estimated to be 14, 7, and 3, respectively. Universal decolonization was the most beneficial intervention, saving €7,339 per life-year gained. Targeted decolonization saved €3,330 per life-year gained. Sensitivity analyses showed that the model was sensitive to the sensitivity of the PCR screening test and the efficacy of treatment. Reductions in these parameters reduced the cost-effectiveness of targeted decolonization. The authors concluded that both universal and targeted decolonization dominated no intervention. However, universal decolonization generated the most health outcomes and largest savings.

Young and Winston⁶⁰ used a decision-tree model to evaluate the cost-effectiveness of pre-operative nasal decolonization with mupirocin for 5 days before surgery to prevent surgical site infection in patients undergoing elective surgeries (cardiothoracic, neurologic, gynaecologic, and general). This study was conducted in the United States from the societal perspective. The authors compared three strategies: (1) universal decolonization; (2) targeted decolonization based on PCR screening; and (3) no intervention. The model used a 90-day time horizon. Clinical inputs were sourced from a literature review, using RCTs where available. The relative risk of surgical site infection between treated and untreated *S. aureus* carriers was 0.49. The authors assumed that screening was 100% accurate. Direct medical costs were taken from the literature review and Medicare. Loss of productivity incurred by patients was included as an indirect cost. Costs were reported in 2003 US dollars.

For the reference case analysis, the model results showed that both universal and targeted decolonization were cost-saving compared with no intervention.⁶⁰ However, targeted decolonization appeared to be more cost-saving (saving \$102 per patient) than universal decolonization (saving \$88 per patient). Univariate sensitivity analyses showed that the model was robust to all data inputs except for the efficacy of mupirocin. If the efficacy of mupirocin was less than 16.1%, targeted decolonization became a cost-incurring strategy.

HEALTH TECHNOLOGY ASSESSMENT

We included the health economic model report of the 2019 health technology assessment by the National Institute for Health and Care Excellence (NICE) referenced in the clinical evidence review section.⁶¹ The authors developed a decision-tree model to evaluate the cost-effectiveness of pre-operative nasal decolonization with mupirocin to prevent surgical site infection in patients undergoing any type of surgery. The authors compared three strategies: (1) targeted decolonization; (2) universal decolonization; and (3) no intervention. All patients received chlorhexidine body wash. The model was constructed to capture a number of health outcomes (including surgical site infections and QALYs) and costs and used a lifetime horizon. The main outcome of the model was *S. aureus*-related surgical site infections. After the perioperative period, the model applied age-related life expectancy to surviving patients. In this way, the full impact of differences in surgical site infection-related mortality on health gains was captured. The model was conducted from the perspective of the United Kingdom's National Health Service (NHS) for costs and from the patient perspective for health outcomes. A discount rate of 3.5% was applied. The clinical inputs were taken from RCTs. The utility values were measured by the EQ-5D, a health-related quality-of-life instrument. Costing parameters were taken from the NHS Drug Tariff and from a UK hospital database. Costs were reported in 2019 British pounds.

The reference case results of the model showed that both universal and targeted decolonization dominated no intervention. Universal decolonization also dominated targeted decolonization, as it was less costly (£43 vs. £55 per patient) and more effective (8.5745 QALYs vs. 8.5744 QALYs over a lifetime). Probabilistic sensitivity analyses showed that the model results were robust and that the ICER for universal decolonization was £20,000 per QALY or better in 99.6% of simulations. One-way and scenario analyses also showed the reference case results to be robust. The only influential parameter on the cost-effectiveness results was the baseline incidence of surgical site infection. Sensitivity analysis revealed that when the baseline incidence of surgical site infection was very low, mupirocin would not be effective, and thus universal decolonization would not be cost-effective.

Table 13 provides a summary of the four included studies.

Table 13: Results of Economic Literature Review—Summary

Author, year, country of publication	Analytic technique, study design, perspective, time horizon	Population	Interventions and comparator	Results			
				Health outcomes	Costs (currency)	Cost-effectiveness	Uncertainty
Cost-effectiveness studies							
Courville et al, 2012, United States ⁵⁸	Two decision analytic models: one for patients undergoing total hip arthroplasty, one for patients undergoing total knee arthroplasty Societal perspective 1-year time horizon	Adults with end-stage surgical hip or knee osteoarthritis, age 65 y	<p>Interventions</p> <p>Universal ND^a without chlorohexidine body wash</p> <p>Targeted ND^b without chlorohexidine body wash</p> <p>Comparator</p> <p>No treatment^c</p>	<p>Total hip arthroplasty</p> <p>Universal ND: 0.7985 QALYs</p> <p>Targeted ND: 0.7983 QALYs</p> <p>No treatment: 0.7980 QALYs</p> <p>Total knee arthroplasty</p> <p>Universal ND: 0.6787 QALYs</p> <p>Targeted ND: 0.6785 QALYs</p> <p>No treatment: 0.6783 QALYs</p> <p>Discount rate: none</p>	<p>Total hip arthroplasty (2005 USD)</p> <p>Universal ND: 24,258</p> <p>Targeted ND: 24,471</p> <p>No treatment: 24,506</p> <p>Total knee arthroplasty (2005 USD)</p> <p>Universal ND: 24,378</p> <p>Targeted ND: 24,611</p> <p>No treatment: 24,667</p> <p>Discount rate: none</p>	<p>Universal ND vs. no treatment: dominant^d</p> <p>Targeted ND vs. no treatment: dominant</p> <p>Universal ND vs. targeted ND: dominant</p>	<p>The model's parameters were robust across a wide range of data inputs</p> <p>PSA not conducted</p>

Author, year, country of publication	Analytic technique, study design, perspective, time horizon	Population	Interventions and comparator	Results			
				Health outcomes	Costs (currency)	Cost-effectiveness	Uncertainty
Wassenberg et al, 2011, Netherlands ⁵⁹	Cost-effectiveness analysis Piggyback model Societal perspective 1-year time horizon	Patients undergoing prosthetic joint implantation (mean age: 58 y) or cardiopulmonary (mean age: 55 y) surgery	Interventions Universal ND with chlorohexidine body wash Targeted ND with chlorohexidine body wash Comparator No treatment	No. of deep-seated <i>S. aureus</i> infections (per 1,000 patients) Universal ND: 3 Targeted ND: 7 No treatment: 14 Discount rate: 0%	Cost per infection prevented (2009 EUR) Universal ND: 1,457 Targeted ND: 10,395 No treatment: 249,480 Discount rate: 0%	Universal ND vs. no treatment: dominant Targeted ND vs. no treatment: dominant	When screening test sensitivity decreases to 65%, targeted ND is less beneficial Efficacy of mupirocin: at an RR less than 0.53 for targeted ND and 0.62 for universal ND, these interventions are no longer cost saving PSA not conducted
Young and Winston, 2006, United States ⁶⁰	Cost-effectiveness analysis Decision analytic model Societal perspective 90-day time horizon	Adults undergoing nonemergent surgery requiring postoperative hospitalization	Interventions Universal ND without chlorohexidine body wash Targeted ND without chlorohexidine body wash Comparator No treatment	No. of <i>S. aureus</i> infections per 10,000 patients Universal ND: 92 Targeted ND: 92 No treatment: 178 No. of deaths due to <i>S. aureus</i> infection per 10,000 patients Universal ND: 1 Targeted ND: 1 No treatment: 3	Costs NR (2003 USD)	Universal ND vs. no treatment: dominant (\$88 per patient) Targeted ND vs. no treatment: cost saving (\$102 per patient)	If the efficacy of mupirocin is less than 16.1% (base case value: 23%), targeted ND becomes a cost-incurring strategy PSA not conducted

Author, year, country of publication	Analytic technique, study design, perspective, time horizon	Population	Interventions and comparator	Results			
				Health outcomes	Costs (currency)	Cost-effectiveness	Uncertainty
Health technology assessment							
NICE, 2019, United Kingdom ⁶¹	Cost-effectiveness analysis Decision analytic model Patient perspective for health outcomes, NHS perspective for costs Lifetime horizon Discount rate: 3.5%	People of any age undergoing any surgery, including minimally invasive surgery (arthroscopic, thoracoscopic, laparoscopic)	Interventions Universal ND with chlorohexidine body wash Targeted ND with chlorohexidine body wash Comparator No treatment (chlorohexidine body wash only)	QALYs per patient Universal ND: 8.5745 Targeted ND: 8.5744 No treatment: 8.5741	Cost per patient (2019 GBP) Universal ND: 43 Targeted ND: 55 No treatment: 56	Universal ND vs. no treatment: dominant Targeted ND vs. no treatment: dominant Universal ND vs. targeted ND: dominant	The ICER for universal ND was £20,000 or better in 99.6% of PSA model runs One-way sensitivity and scenario analyses showed baseline results to be largely robust. The only parameter of influence was baseline SSI incidence. If baseline SSI risk is very low, treatment with mupirocin is less likely to be cost-effective

Abbreviations: ICER, incremental cost-effectiveness ratio; NHS, National Health Service; ND, preoperative nasal decolonization with mupirocin; NR, not reported; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year; *S. aureus*, *Staphylococcus aureus*; SSI: surgical site infection.

^aUniversal nasal decolonization: empirical treatment of all preoperative patients with mupirocin, with no *S. aureus* screening

^bTargeted nasal decolonization: preoperative nasal screening of all patients for *S. aureus* colonization, followed by mupirocin treatment only for patients with positive cultures

^cNo treatment: standard infection prevention measures without *S. aureus* screening or mupirocin decolonization

^dDominant: less costly and more effective

Applicability and Limitations of the Included Studies

Appendix 6 provides the results of the applicability and quality appraisal checklists for economic evaluations (Tables A14 and A15). Three studies were deemed partially applicable,⁵⁸⁻⁶⁰ and one study was deemed directly applicable.⁶¹

Discussion

We identified three relevant cost-effectiveness studies⁵⁸⁻⁶⁰ and one health technology assessment.⁶¹ All studies investigated the cost-effectiveness of universal and targeted nasal decolonization of *S. aureus* compared with no nasal decolonization (standard care only) among pre-surgical patients. Two studies used decision-tree models with a short time horizon (less than 1 year).^{58,60} The cost-effectiveness studies were conducted from the societal perspective,⁵⁸⁻⁶⁰ and the health technology assessment was conducted from the perspective of the United Kingdom's National Health Service.⁵⁹ Two studies included chlorhexidine body wash in all strategies.^{59,61} Clinical parameters were taken from systematic reviews where possible. Costing parameters were taken from the literature and from the databases of hospitals where studies were conducted. In all studies, the target population was patients undergoing surgery. Two studies were conducted in the United States,^{58,60} one was conducted in the Netherlands, and one was conducted in the United Kingdom.⁶¹ All studies concluded that universal and targeted decolonization were dominant versus no treatment. Two studies found that universal decolonization was dominant over targeted decolonization owing to the high cost of screening for *S. aureus*.^{58,59} Notably, these studies focused only on patients undergoing certain procedures: hip and knee arthroplasty, cardiovascular surgery, and orthopaedic surgery. Only one study (of patients undergoing elective surgery) found that targeted decolonization dominated universal decolonization.⁶⁰ Sensitivity analyses revealed that the sensitivity of the screening test and the efficacy of mupirocin were the most influential factors on the cost-effectiveness results.

All studies captured the number of short-term surgical site infections, that is, those occurring within 30 days after surgery.⁵⁸⁻⁶¹ Two studies captured the long-term impact of nasal decolonization in terms of mortality owing to surgical site infection.^{59,61} Only one study⁵⁹ used PCR screening to test for the presence of *S. aureus*, whereas the remaining studies^{58,60,61} used the nasal swab and culture method. For targeted decolonization, the cost of screening and the baseline incidence of surgical site infection were the parameters that most influenced the cost-effectiveness results. The cost-effectiveness results were sensitive to the efficacy of mupirocin for both universal and targeted decolonization. Probabilistic sensitivity analyses were conducted only in the health technology assessment by NICE.⁶¹

Conclusions

Based on the included economic studies, both universal and targeted decolonization of *S. aureus* dominate no treatment (standard care only). However, it is unclear which strategy is most cost-effective. Three studies^{58,59,61} concluded that universal decolonization dominated targeted nasal decolonization, whereas one study⁶⁰ concluded the opposite. None of the included economic studies was conducted in Canada. Considering these factors, we decided to conduct a primary economic evaluation for the Ontario setting.

Primary Economic Evaluation

Based on the published economic evaluations, nasal decolonization of *Staphylococcus aureus* (*S. aureus*) is cost-saving compared with no nasal decolonization (standard care only). However, it is unclear which strategy is more cost-effective. Among the included economic studies, the decision-tree model developed for the 2019 health technology assessment by the National Institute for Health and Care Excellence (NICE)⁶¹ was considered most applicable to our research question. It included patients undergoing any type of surgery and captured all relevant outcomes of interest such as number of surgical site infections and quality of life. We found no Ontario-based economic studies that compared the cost-effectiveness of nasal decolonization strategies. Therefore, we decided to conduct a primary economic evaluation by adapting the NICE model⁶¹ and applying Canadian costs and epidemiological information.

Research Question

From the perspective of the Ontario Ministry of Health, what is the cost-effectiveness of nasal decolonization of *S. aureus*, including methicillin-susceptible and methicillin-resistant strains, combined with chlorhexidine body wash to prevent surgical site infection compared with no nasal decolonization (standard care only) for patients undergoing scheduled surgery?

Methods

The information presented in this report follows the reporting standards set out by the Consolidated Health Economic Evaluation Reporting Standards Statement.⁶²

Type of Analysis

For the reference case analysis, we conducted a cost-effectiveness analysis using number of surgical site infections as the effectiveness outcome. For the scenario analysis, we conducted a cost-utility analysis using quality-adjusted life-years (QALYs) gained as the effectiveness outcome. QALYs consider both a person's survival and their quality of life (i.e., 1 QALY represents 1 year of perfect health). A generic outcome measure such as the QALY allows decision-makers to make comparisons across conditions and interventions. We chose to conduct a cost-effectiveness analysis for the reference case because for nasal decolonization, the main impact occurs in the short term, making rate of surgical site infection a more appropriate effectiveness outcome than QALYs. Further, there was a lack of data to support quantifying the health outcomes as QALYs, meaning that if we chose to use QALYs, we would have had to make many assumptions for both survival and quality of life. We therefore concluded that the rate of surgical site infection was a more clinically meaningful and credible health outcome to evaluate.

Target Population

Our initial intention was to include both children and adults in the target population. However, since only adults were included in the studies identified in the economic evidence review, we decided to limit our model to adults. Thus, our target population was adults aged 18 years and older undergoing any type of surgery, including minimally invasive surgery (e.g., arthroscopic, thoracoscopic, laparoscopic).

Perspective

We conducted this analysis from the perspective of the Ontario Ministry of Health.

Interventions and Comparators

Based on the findings of our clinical evidence review, we decided to focus on nasal mupirocin ointment as the treatment intervention in the model. Two decolonization strategies were evaluated:

- Universal nasal decolonization of *S. aureus* combined with chlorhexidine body wash for all patients: empirical treatment of all pre-operative patients with nasal mupirocin ointment and antiseptic chlorhexidine body wash, with no *S. aureus* screening (“universal decolonization”)
- Targeted nasal decolonization of *S. aureus* combined with chlorhexidine body wash for all patients: pre-operative antiseptic chlorhexidine body wash for all patients and preoperative screening of all patients for *S. aureus* colonization, followed by treatment with nasal mupirocin ointment only for patients with positive cultures (“targeted decolonization”)

Our comparator was no nasal decolonization of *S. aureus* (standard care only). The practice of pre-surgical nasal decolonization of *S. aureus* varies widely across Ontario. For this analysis, we assumed that the current standard of care in Ontario is no nasal decolonization. According to the literature^{43,63} and a clinical expert (Charles de Mestral, MD, email communication, January 3, 2021), the use of chlorhexidine body wash also varies across the province and depends on the hospital or procedure. Therefore, for simplicity, we assumed that most patients in Ontario currently receive chlorhexidine body wash as part of standard care prior to surgery. In a scenario analysis, however, we assumed that standard care does not include chlorhexidine body wash.

Table 14 summarizes the interventions evaluated in the primary economic model.

Table 14: Interventions, Comparator, and Outcomes Evaluated in the Primary Economic Model

Intervention	Comparator	Population	Outcomes (per 10,000 patients)
Universal nasal decolonization plus chlorhexidine body wash	No nasal decolonization (chlorhexidine body wash only)	Adult pre-surgical patients ≥ 18 y	Total number of SSIs Total number of <i>S. aureus</i> -related SSIs Total QALYs
Targeted nasal decolonization plus chlorhexidine body wash			Total costs Incremental SSIs Incremental <i>S. aureus</i> -related SSIs Incremental QALYs Incremental costs

Abbreviations: *S. aureus*, *Staphylococcus aureus*; SSI, surgical site infection.

Time Horizon and Discounting

For our reference case analysis, we used a 1-year time horizon to capture the immediate effectiveness of nasal decolonization of *S. aureus*, the main goal of which is to reduce the number of surgical site infections. This assumption is in line with the available clinical evidence, which shows that *S. aureus*-related surgical site infections usually occur within the first 30 days following surgery.² Because surgical site infection also affects patients' quality of life, in a scenario analysis we conducted a cost-utility analysis to measure costs and QALYs over a 1-year time horizon. We did not use a longer time horizon because most *S. aureus*-related surgical site infections do not affect patients beyond 1 year after surgery. Additionally, when a patient recovers from a surgery, we assumed that they would have a similar quality of life as in the pre-surgical period. As the time horizon was less than 1 year, no discount rate was applied to either costs or QALYs.

Main Assumptions

As we adapted the decision-tree model used in the 2019 health technology assessment by NICE,⁶¹ we used the assumptions provided in that report. We also added the following assumptions:

- In Ontario, the practice of pre-surgical nasal decolonization of *S. aureus* varies widely.⁶⁴ For the purpose of modelling, we assumed that for the standard-care arm, nasal decolonization would not be implemented prior to surgery. However, we assumed that chlorhexidine body wash would be given to all patients. Therefore, the baseline rate of surgical site infection used in the universal and targeted decolonization arms was assumed to be the same as that in the standard-care arm
- Nasal decolonization of *S. aureus* implicitly targets a reduction in the risk of surgical site infection caused by *S. aureus*; nasal decolonization with mupirocin was therefore assumed to be effective only in people who are *S. aureus* carriers
- Patients with a surgical site infection would have a higher risk of mortality due to the presence of a surgical site infection, and such deaths would occur within the first year following surgery
- Patients who did not experience a surgical site infection would have the risk of general age-related mortality

Model Structure

We adapted the model from the health economic model report of NICE's 2019 health technology assessment⁶¹ to the Canadian setting, as this model met all the criteria of our research question and analyses:

- The model interventions (universal and targeted decolonization) and comparator (no decolonization) are the same as those in our research question
- The model captures important clinical outcomes such as number of surgical site infections (overall and those related to *S. aureus*) and surgical site infection-related mortality
- The model includes patients undergoing any type of surgery

Figure 4 presents a schematic of our model.

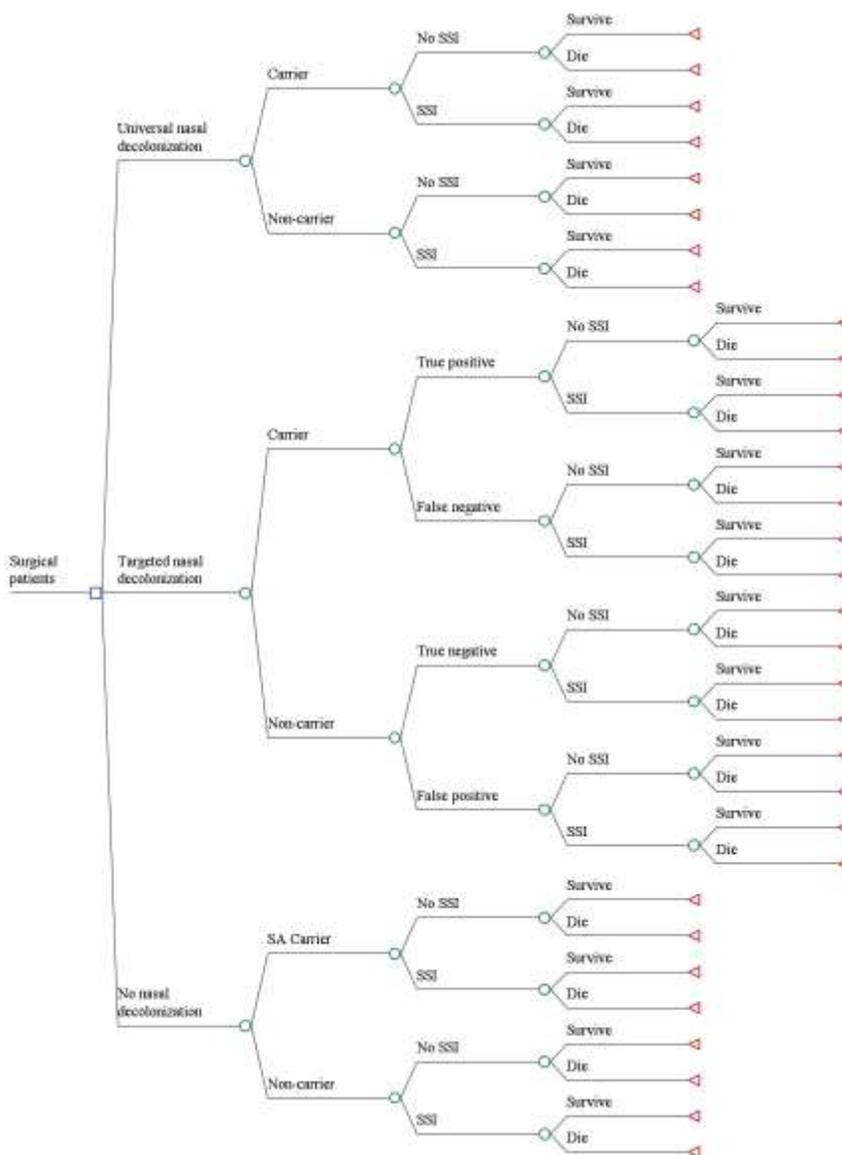


Figure 4: Model Structure

Abbreviations: SA, *Staphylococcus aureus*; SSI, surgical site infection.

In the model, patients could receive one of three treatment strategies prior to surgery: (1) universal decolonization; (2) targeted decolonization; or (3) no decolonization. When undergoing a surgical procedure, patients faced the risk of contracting a surgical site infection during the first 30 days following surgery. The degree of risk depended on whether the patient was a carrier of *S. aureus* and whether they had received nasal decolonization. Patients also faced a risk of natural mortality during the first 30 days following surgery, which may be increased by the presence of a surgical site infection. At the end of those 30 days, patients would go on to experience residual recovery toward their baseline quality of life. Surviving patients would experience the remainder of their life expectancy and general, age-related quality of life.

Clinical Outcomes and Utility Parameters

The model's main clinical parameters were the treatment effect of mupirocin on the occurrence of surgical site infections caused by *S. aureus*, surgical site infection-related mortality, age-specific mortality, and the sensitivity and specificity of the *S. aureus* carrier status screening test (Table 15). We assumed that a swab-based nasal screening test was used to identify *S. aureus* carriers for patients receiving targeted decolonization in the reference case. A polymerase chain reaction (PCR) test was used in a scenario analysis.⁶⁵

Table 15: Model Input Parameters

Parameter	Mean	Range (one-way sensitivity analysis)	Distribution	Source
Prevalence of SA nasal carriage	25.4%	21%–30.3% ^a	Beta	NICE, 2019 ⁶¹
Baseline incidence of SSIs of any type	3.5%	1.3%–5.1%	Fixed	Canadian Patient Safety Institute, 2016 ¹⁰
Proportion of SSIs of any type among SA carriers	0.50	NA	Beta	NICE, 2019 ⁶¹
Proportion of SSIs of any type among non-SA carriers	0.18	NA	Beta	NICE, 2019 ⁶¹
Odds ratio, SA carriers vs. non-SA carriers	1.61	1.20–2.17 ^a	Lognormal	NICE, 2019 ⁶¹
Odd ratio, SA carriers vs. whole population	1.42	NA	Lognormal	NICE, 2019 ⁶¹
Incidence of SA-related SSIs among SA carriers	2.4%	NA	NA	Calculation
Incidence of SA-related SSIs among non-SA carriers	0.6%	NA	NA	Calculation
Relative risk of mupirocin vs. no nasal decolonization: SA-related SSIs in SA carriers	0.48	0.33–0.70 ^a	Lognormal	NICE, 2019 ⁶¹
Mortality odds ratio of patients with an SSI vs. patients with no SSI	1.45	NA	Lognormal	NICE, 2019 ⁶¹
Screening test: nasal swab and culture				
Sensitivity	68.2%	68.2%, 98%	Triangular	NICE, 2019 ⁶¹
Specificity	94.5%	94.5%, 99.8%	Triangular	NICE, 2019 ⁶¹
Screening test: PCR				
Sensitivity	98%	NA	Not varied	NICE, 2019 ⁶¹
Specificity	99.8%	NA	Not varied	NICE, 2019 ⁶¹

Abbreviations: NICE, National Institute for Health and Care Excellence; PCR, polymerase chain reaction; SA, *Staphylococcus aureus*; SSI, surgical site infection.

^a95% confidence interval.

INCIDENCE OF SURGICAL SITE INFECTION

Of the 1.3 million surgeries in Canada yearly, 26,000 to 65,000 patients undergoing surgery may acquire a surgical site infection, which translates into an incidence rate of 2% to 5%.³⁷ For the reference case analysis, we used the mean value of 3.5%. Of these patients, we assumed that 25% would be *S. aureus* carriers.⁶¹

Since our new intervention aims to decolonize *S. aureus* from the nasal passages, we were interested in the rate of surgical site infections caused by *S. aureus*. We therefore required the proportion of surgical site infections caused by *S. aureus* rather than some other cause.

SURGICAL SITE INFECTION CAUSED BY *S. AUREUS*

The effectiveness of nasal decolonization of *S. aureus* likely depends on whether a person is a nasal carrier of *S. aureus*. Therefore, the baseline incidence of surgical site infection between *S. aureus* carriers and non-*S. aureus* carriers is likely to be different. Our model strategies included a "targeted decolonization" component, which aimed to identify *S. aureus* carriers.

We used the following steps to calculate the baseline rates of surgical site infection among *S. aureus* carriers and non-*S. aureus* carriers:

- We first identified the overall incidence of surgical site infection among people undergoing surgery in Ontario. Of these, some would be *S. aureus* carriers, and others would not. In the reference case, we used an overall incidence rate of surgical site infection of 3.5% (see Table 15)³⁷
- We took the odds ratio (OR) of *S. aureus* carriers versus the whole population (i.e., all patients undergoing surgery) from the NICE health technology assessment⁶¹; this was 1.42 (see Table 15)
 - Using this OR and the overall baseline incidence of surgical site infection, we calculated any case of surgical site infection among *S. aureus* carriers
 - Next, we calculated the proportion of all surgical site infections caused by *S. aureus* in *S. aureus* carriers using data provided by Perl et al⁴⁴
- We took the OR of *S. aureus* carriers versus non-*S. aureus* carriers from the NICE health technology assessment⁶¹; this was 1.61
 - Using this OR and the overall baseline incidence of surgical site infection, we calculated any case of surgical site infection among non-*S. aureus* carriers
 - Next, we calculated the proportion of all surgical site infections caused by *S. aureus* in non-*S. aureus* carriers using data provided by Perl et al⁴⁴

TREATMENT EFFECT OF NASAL DECOLONIZATION

We derived the treatment effect of nasal decolonization of *S. aureus* with mupirocin combined with chlorhexidine body wash versus no nasal decolonization from randomized controlled trials identified in the clinical evidence review. In particular, we focused on five trials that reported *S. aureus*-related surgical site infections as an outcome in patients who are *S. aureus* carriers.^{43,44,46,47,51} Since no trial represents the mixed practice in Ontario (i.e., the use of body wash varies by hospital and procedure), we obtained an average treatment effect for nasal decolonization with mupirocin from a meta-analysis included in the NICE health technology assessment.⁶⁶ Based on this meta-analysis, the

relative risk (RR) of *S. aureus*-related surgical site infection between *S. aureus* carriers who received nasal decolonization (with or without chlorhexidine body wash) and carriers who received no nasal decolonization (with or without chlorhexidine body wash) was 0.48 (95% confidence interval [CI]: 0.33–0.70).

For the universal nasal decolonization strategy, treatment with mupirocin was assumed to be effective only in people who are *S. aureus* carriers. Therefore, the relative effectiveness of mupirocin was applied in the economic model as follows:

- In the universal decolonization arm, all patients received mupirocin for 5 days prior to surgery. All *S. aureus* carriers were thus assumed to have a reduced incidence of *S. aureus*-related surgical site infection. The baseline incidence *S. aureus*-related surgical site infection would subsequently be reduced according to the relative effectiveness of mupirocin. As mupirocin was assumed to be effective only in *S. aureus* carriers, non-*S. aureus* carriers would therefore receive no treatment effect from mupirocin and thus were subject to the baseline risk of non-*S. aureus* carriers
- In the targeted decolonization arm, people who screened positive for *S. aureus* received mupirocin for 5 days prior to surgery. Only patients who were correctly identified as *S. aureus* carriers (i.e., true positives) would benefit from treatment with mupirocin. Non-*S. aureus* carriers incorrectly identified as carriers (i.e., false positives) and subsequently treated would experience no reduction in their baseline risk of *S. aureus*-related surgical site infection. On the other hand, patients who screened negative for *S. aureus* (both true and false negatives) would not receive mupirocin and would therefore experience no treatment effect; however, some of these patients would be carriers of *S. aureus* (i.e., false negatives) and would therefore be subject to the baseline risk of *S. aureus*-related surgical site infection
- In the no nasal decolonization arm, no patients received nasal decolonization prior to surgery, but all received chlorhexidine body wash. Therefore, these patients would experience no treatment effect of mupirocin. All *S. aureus* carriers would be subject to the baseline risk of *S. aureus*-related surgical site infection. Non-*S. aureus* carriers would be subject to the baseline risk of non-*S. aureus* carriers

SURGICAL SITE INFECTION-RELATED MORTALITY

We took the mortality OR for surgical site infection versus no surgical site infection from the NICE health technology assessment,⁶¹ which was 1.45 over the first year following surgery. This means that the risk of death is 45% higher among people who experience a surgical site infection. We assumed this relative effect was the same across all types of surgery.

LIFE EXPECTANCY

We used Statistics Canada life tables to estimate the average life expectancy of a person at the mean age (45 years) of the surgical cohort.⁶⁷ In our reference case, we applied a 1-year time horizon.

SCREENING ACCURACY

The screening modality used in the reference case was nasal swab and culture. We used the screening sensitivity (68.2%) and specificity (94.5%) from the NICE health technology assessment.⁶¹ As nasal swab and culture is less accurate and less expensive than PCR testing, we explored the use of the PCR test in a scenario analysis. We also took the screening sensitivity (98%) and specificity (99.8%) of the PCR test from the NICE health technology assessment.⁶¹

HEALTH STATE UTILITIES

In a scenario analysis, we measured health outcomes using quality-adjusted life-years (QALYs). We used EQ-5D health state utility weights from the NICE health technology assessment.⁶¹ Utilities were measured at baseline, 7 days after surgery, and 30 days after surgery in patients who experienced surgical site infection and those who did not (Table 16). Patients who had a surgical site infection would experience utility decrements (disutilities). For patients to recover to their baseline quality of life, we used the same assumption as that of the authors of the NICE health technology assessment: that it would take on average 21.9 days for patients with a surgical site infection to recover to the baseline utility, whereas patients with no surgical site infection would require only 5 days.⁶¹ The utility loss in these periods was calculated at 0.022 and 0.015 for patients with and without a surgical site infection, respectively.⁶¹ Table 16 presents the utility values for the three time points of the model. We assumed these utility data would be applied to surgeries of all types.

Table 16: Utilities Used in the Economic Model

Time point	Utility weight (range)		Distribution	Source
	No SSI	SSI		
Baseline (t = 0)	0.78	0.78	Beta	NICE, 2019 ⁶¹
7 days	0.5226 (0.496–0.556)	0.504 (0.445–0.564)	Beta	
30 days	0.7332 (0.704–0.757)	0.6474 (0.596–0.694)	Beta	
One-time utility loss	0.015	0.022	Not varied	

Abbreviations: NICE, National Institute for Health and Care Excellence; SSI: surgical site infection.

Cost Parameters

We took cost parameters from various Canadian and non-Canadian costing studies that included treatment costs related to *S. aureus*-related surgical site infection.^{61,68,69} Resource use costs, such as those for the nursing time needed to perform screening with the nasal swab method, time needed for consultation with patients on their screening results, and laboratory technician time needed to diagnose samples, were taken from the literature.⁶¹ When data were not available in the literature, we

asked experts to identify model parameters and data sources. We obtained nurse and lab technician salaries from the literature or expert consultation.

UNIVERSAL NASAL DECOLONIZATION

In the reference case, we assumed that for universal nasal decolonisation, mupirocin was self-administered by the patient. According to the published literature,^{60,69} one 3 g tube of mupirocin would be sufficient for a 5-day preoperative treatment course. A 3 g tube costs \$2.56; this cost was obtained from a Canadian study by Rennert-May et al that investigated the cost-effectiveness of mupirocin and chlorhexidine antiseptic body wash for *S. aureus* decolonization prior to hip and knee arthroplasty in Alberta.⁶⁹ In one-way sensitivity analyses, we reduced the mean cost by 50% and increased the mean cost by 10 times to explore the impact of the cost of mupirocin on the cost-effectiveness results.

We took the cost of chlorhexidine body wash from the study by Rennert-May et al.⁶⁹ We inflated this cost to 2021 Canadian dollars, which resulted in a cost of \$5.52 per bottle per patient. For sensitivity analyses, we applied a 50% reduction and a 2-times increase to the mean cost as the lower and upper ranges, respectively, to explore the impact of changes in this cost on the cost-effectiveness results.

TARGETED NASAL DECOLONIZATION

For the targeted decolonization strategy, in which only *S. aureus* carriers are treated with mupirocin, it was appropriate to apply a cost associated with screening for *S. aureus*. For the reference case, in which the nasal swab and culture method was applied, we obtained this cost from the NICE health technology assessment.⁶¹ We converted this cost into 2021 Canadian dollars using the exchange rate from the Bank of Canada.⁷⁰ The screening cost consisted of the cost of a nurse preparing, administering, and sending the swab for testing and amounted to \$18.92 per test. In sensitivity analyses, we tested a 50% reduction of the reference case cost for the lower range and a 2-times increase of the reference case cost for the upper range.

In a scenario analysis, we used PCR testing as the screening modality; this test is more accurate than the nasal swab and culture method but also more expensive. We obtained the unit cost of a PCR test from the NICE health technology assessment.⁶¹

SURGICAL SITE INFECTION TREATMENT COST

We took the cost to treat a surgical site infection from the Ontario Case Costing Initiative (OCCI) database.⁶⁸ We used ICD-10 codes to identify hospitalizations related to surgical site infection. In a study by Calderwood et al,⁷¹ the authors provided a list of ICD-10 codes used to identify surgical site infections after coronary artery bypass graft surgery and hip arthroplasty. According to the literature,^{58,59,69} these types of surgeries are the ones in which patients most commonly experience surgical site infection. We therefore decided to use the ICD-10 codes for these two surgeries to retrieve the treatment cost of a surgical site infection hospitalization through the OCCI database.⁶⁸ The mean treatment costs for surgical site infection hospitalizations related to coronary artery bypass graft surgery and hip arthroplasty were similar. Thus, we decided to use the treatment cost for a hip arthroplasty-related surgical site infection in our reference case analysis. It is important to note that the treatment cost retrieved from the OCCI database captures only the hospitalization cost; physician fees were not included. Therefore, we increased this cost by 25% to account for physician fees. Compared with the treatment costs used in the NICE health technology assessment⁶¹ and the

Canadian study by Rennert-May et al,⁶⁹ our estimate of the total treatment cost per surgical site infection hospitalization, based on data from the OCCI database, was much lower and more conservative.

The NICE authors reported that the average hospitalization to treat a surgical site infection following hip arthroplasty was 26 days.⁶¹ Rennert-May et al reported that the 1-year cost of treating an *S. aureus*-related surgical site infection was \$108,175 per patient, most of which would be incurred during the first month of surgery.⁶⁹ Given that these figures were relevant to the Canadian context, we decided to conduct a one-way sensitivity analysis to explore the impact of the cost of treating a surgical site infection on the cost-effectiveness results. For the lower range, we used the average treatment cost per surgical site infection episode from the OCCI database without adding physician fees. For the upper range, we assumed that most of the treatment cost would be incurred within the first month following surgery and that patients would be in hospital for an average of 26 days (based on the NICE health technology assessment).⁶¹ We estimated the daily hospitalization cost based on data from the OCCI database.⁶⁸

Table 17 describes the cost parameters used in the economic model.

Table 17: Costs Used in the Economic Model

Parameter	Mean (SE), \$	Range (one-way sensitivity analysis)	Distribution	Source
Cost of 5-day nasal decolonization with mupirocin per person	2.56 (0.64)	1.28–20.56	Gamma	Rennert-May et al, 2019 ⁶⁹
Cost of chlorhexidine body wash per person	5.52 (1.38)	2.76–11.14	Gamma	Rennert-May et al, 2019 ⁶⁹
Cost of treating 1 SSI episode	8,582 (627)	6,866–29,530	Gamma	Calderwood et al, 2014 ⁷¹ ; Ministry of Health, 2017 ⁶⁸
Screening test: nasal swab and culture				
Cost per test (including nursing time)	18.92(4.73)	9.46–37.84	Gamma	NICE, 2019 ⁶¹
Screening test: PCR				
Cost per test (including nursing time)	49.36 (12.34)	NA	Gamma	NICE, 2019 ⁶¹

Abbreviations: NA, not applicable; NICE, National Institute for Health and Care Excellence; PCR, polymerase chain reaction; SE, standard error; SSI, surgical site infection.

Internal Validation

Formal internal validation was conducted by the secondary health economist. This included testing the mathematical logic of the model and checking for errors and accuracy of parameter inputs and equations.

Analysis

We conducted a reference case analysis and sensitivity analyses. Our reference case analysis adhered to the Canadian Agency for Drugs and Technologies in Health (CADTH) guidelines⁷² when appropriate. The reference case represents the analysis with the most likely set of input parameters and model assumptions relevant to Ontario. Our scenario and sensitivity analyses explored how the results would be affected by varying input parameters and model assumptions.

For both reference case and scenario analyses, we conducted a probabilistic analysis to capture uncertainty in model parameters. When possible, we specified distributions around input parameters using the mean and standard error. Selected cost parameters were characterized by gamma distributions; probabilities and utilities were characterized by beta distributions; and relative risks were characterized by lognormal distributions. We ran a total of 10,000 simulations and calculated the expected values of costs and outcomes for each strategy. We presented the probability that each strategy was cost-effective over a range of willingness-to-pay values on a cost-effectiveness acceptability curve.

For the reference case analysis, we calculated the number of surgical site infections related to any cause, the number of surgical site infections caused by *S. aureus*, the cost incurred per 10,000 patients undergoing surgery for each intervention, increment surgical site infections, and incremental costs.

SENSITIVITY ANALYSES

We conducted various sensitivity analyses to assess the impact of cost parameters (e.g., the cost of mupirocin, the cost of treating a surgical site infection, and the cost of screening using the nasal swab and culture method) on the cost-effectiveness and cost-utility results of the model.

SCENARIO ANALYSES

We conducted three scenario analyses:

1. Cost-utility analysis: In this analysis, we calculated the mean total costs and mean QALYs associated with each strategy and then calculated the mean incremental costs, mean incremental QALYs, and incremental cost-effectiveness ratios (ICERs) as cost per QALY gained
2. In this analysis, we assumed that PCR testing was used as the screening method for targeted nasal decolonization
3. In this analysis, we assumed that chlorhexidine body wash is not part of standard care. We obtained the treatment effectiveness of nasal decolonization with mupirocin combined with chlorhexidine body wash versus no chlorhexidine body wash from a randomized controlled trial by Bode et al⁴⁶ (identified in the clinical evidence review)

THRESHOLD ANALYSIS

We also conducted a threshold analysis to assess the impact of the cost of treating a surgical site infection on the cost-effectiveness of the model.

Results

Reference Case Analysis

COST-EFFECTIVENESS ANALYSIS

In the reference case analysis, we found that universal decolonization dominated both targeted and no decolonization. This means that universal decolonization is associated with the lowest cost and the lowest number of surgical site infections. Compared with no decolonization, universal and targeted decolonization would prevent 32 and 22 *S. aureus*-related surgical site infections, respectively, for every 10,000 patients. We found that targeted decolonization would lead to fewer surgical site infections prevented because a small number of patients who were *S. aureus* carriers would be missed owing to imperfect screening and therefore would not receive decolonization. Compared with no decolonization, universal decolonization would yield a cost savings of \$249,318 per 10,000 patients due to surgical site infections prevented. Compared with no decolonization, targeted decolonization would lead to a cost increase because the additional cost of screening all patients would exceed the cost savings from surgical site infections prevented (Table 18).

Table 18: Reference Case Analysis Results (per 10,000 Patients)

Strategy ^a	Cost incurred per strategy (95% CrI), \$	Number of SSIs (95% CrI)	Number of <i>S. aureus</i> -related SSIs	Incremental cost (95% CrI), \$	Incremental number of SSIs (95% CrI)	Incremental number of <i>S. aureus</i> -related SSIs (95% CrI)	ICER, \$ per SSI prevented	
							Versus no nasal decolonization	Sequential ICER
Universal nasal decolonization	2,893,428 (2,090,422–3,911,069)	328 (242–433)	71	–	–	–	Dominant ^b	–
No nasal decolonization	3,142,747 (2,302,501–4,210,447)	360 (272–468)	103	249,318 ^c (113,447–420,542)	32 ^d (17–51)	32 (17–51)	N/A	Dominated ^e by universal nasal decolonization
Targeted nasal decolonization	3,149,215 (2,329,664 – 4,180,012)	338 (251 – 433)	81	255,786 ^f (144,612 – 390,590)	10 ^g (2 – 21)	10 (2 – 21)	294	Dominated ^e by universal nasal decolonization

Abbreviations: CrI, credible interval; ICER, incremental cost-effectiveness ratio; *S. aureus*, *Staphylococcus aureus*; SSI, surgical site infection.

^aStrategies are ranked by cost from lowest to highest.

^bA dominant strategy is less costly and more effective than the comparator.

^cIncremental cost compared no nasal decolonization with universal nasal decolonization.

^dIncremental effect compared no nasal decolonization with universal nasal decolonization.

^eA dominated strategy is more costly and less effective than the comparator.

^fIncremental cost compared targeted nasal decolonization with universal nasal decolonization.

^gIncremental effect compared targeted nasal decolonization with universal nasal decolonization.

Scenario Analyses

SCENARIO ANALYSIS 1: COST-UTILITY ANALYSIS

In this analysis, we again found that universal decolonization dominated (i.e., was less costly and more effective than) both targeted decolonization and no decolonization (Table 19). This means that universal decolonization is associated with the lowest cost and highest QALYs.

Figure 5 provides the cost-effectiveness acceptability curve, which represents the uncertainty around the estimated ICER generated in the probabilistic sensitivity analyses for universal, targeted, and no decolonization. The results showed that universal decolonization remained the most cost-effective strategy compared with targeted and no decolonization regardless of the willingness-to-pay values examined.

When we compared targeted decolonization with no decolonization, an additional \$0.64 would need to be spent to gain 0.00002727 QALYs. This translates to an ICER of \$23,893 per QALY gained.

Table 19: Scenario Analysis 1 Results (per Patient)—Cost–Utility Analysis

Strategy ^a	Total cost, mean (95% CrI), \$	Total QALYs, mean (95% CrI)	Incremental cost, mean (95% CrI), \$	Incremental QALYs, mean (95% CrI)	ICER vs. no nasal decolonization, \$/QALY	Sequential ICER, \$/QALY
Universal nasal decolonization	289.34 (209.24 to 391.12)	0.75848 (0.75684 to 0.76004)	-	-	Dominant ^b	NA
No nasal decolonization	314.27 (229.95 to 420.80)	0.75844 (0.71566 to 0.76291)	24.97 ^c (11.39 to 42.11)	-0.00004 ^d (-0.00007 to -0.00002)	NA	Dominated ^e by universal nasal decolonization
Targeted nasal decolonization	314.91 (232.53 to 417.28)	0.75847 (0.75683 to 0.76003)	25.57 ^f (14.49 to 39.09)	-0.00001 ^g (-0.00005 to 0.00001)	23,893	Dominated ^e by universal nasal decolonization

Abbreviations: CrI, credible interval; ICER, incremental cost-effectiveness ratio; NA, not applicable, QALY, quality-adjusted life-year.

^aStrategies are ranked by cost from lowest to highest.

^bA dominant strategy is less costly and more effective than the comparator.

^cIncremental cost compared no nasal decolonization with universal nasal decolonization.

^dIncremental effect compared no nasal decolonization with universal nasal decolonization.

^eA dominated strategy is more costly and less effective than the comparator.

^fIncremental cost compared targeted nasal decolonization with no nasal decolonization.

^gIncremental effect compared targeted nasal decolonization with no nasal decolonization.

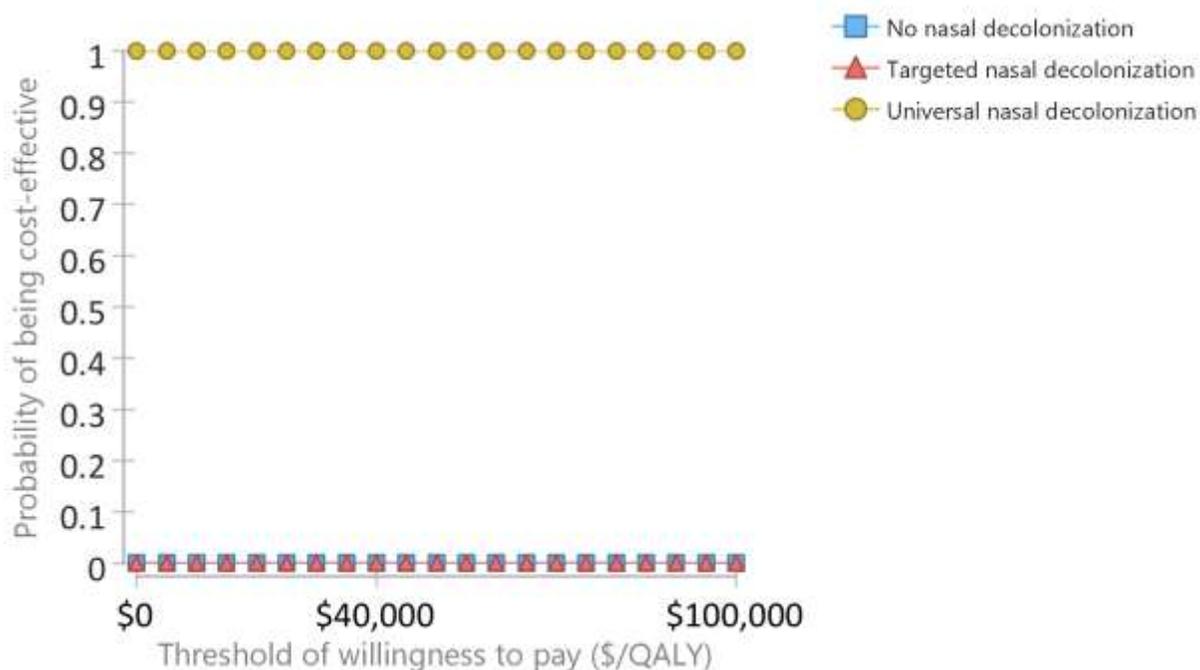


Figure 5: Cost-Effectiveness Acceptability Curve

Abbreviation: QALY, quality-adjusted life-year.

SCENARIO ANALYSIS 2: PCR SCREENING

In this analysis, we found that universal decolonization again dominated both targeted and no decolonization. This means that universal decolonization is associated with the lowest cost and the lowest number of surgical site infections. Compared with no decolonization, both targeted and universal decolonization would prevent 32 *S. aureus*-related surgical site infections for every 10,000 patients, due to the high sensitivity and specificity of PCR testing. Compared with no decolonization, universal decolonization would yield a cost savings of \$249,318 per 10,000 patients (the same as in the reference case analysis). Compared with no decolonization, targeted decolonization would require an additional \$7,236 to prevent one surgical site infection per 10,000 patients (Table 20).

Table 20: Scenario Analysis 2 Results (per 10,000 Patients)—PCR Screening

Strategy ^a	Cost incurred per strategy (95% CrI), \$	Number of SSIs (95% CrI)	Number of <i>S. aureus</i> -related SSIs	Incremental cost (95% CrI), \$	Incremental number of SSIs (95% CrI)	Incremental number of <i>S. aureus</i> -related SSIs (95% CrI)	ICER, \$ per SSI prevented	
							Versus no nasal decolonization	Sequential ICER
Universal nasal decolonization	2,893,428 (2,090,422–3,911,069)	328 (242–433)	71	–	–	–	Dominant ^b	–
No nasal decolonization	3,142,747 (2,302,501–4,210,447)	360 (272–468)	103	249,318 ^c (113,447–420,542)	32 ^d (17–51)	32 (17–51)	NA	Dominated ^e by universal nasal decolonization
Targeted nasal decolonization	3,374,303 (2,537,286–4,430,835)	328 (242–433)	71	480,875 ^f (266,710–754,779)	0 ^g	0	7,236	Dominated ^e by universal nasal decolonization

Abbreviations: CrI, credible interval; ICER, incremental cost-effectiveness ratio; *S. aureus*, *Staphylococcus aureus*; SSI, surgical site infection.

^aStrategies are ranked by cost from lowest to highest.

^bA dominant strategy is less costly and more effective than the comparator.

^cIncremental cost compared no nasal decolonization with universal nasal decolonization.

^dIncremental effect compared no nasal decolonization with universal nasal decolonization.

^eA dominated strategy is more costly and less effective than the comparator.

^fIncremental cost compared targeted nasal decolonization with universal nasal decolonization.

^gIncremental effect compared targeted nasal decolonization with universal nasal decolonization.

SCENARIO ANALYSIS 3: NO CHLORHEXIDINE BODY WASH IN STANDARD CARE

For this analysis, we compared universal nasal decolonization combined with chlorhexidine body wash and targeted nasal decolonization combined with chlorhexidine body wash versus standard care consisting of neither nasal decolonization nor chlorhexidine body wash. We used data from a randomized controlled trial⁴⁶ identified in our clinical evidence review to inform the analysis (RR = 0.32 [95% CI: 0.16, 0.62]).

We found that universal decolonization again dominated both targeted and no decolonization. This means that universal decolonization is associated with the lowest cost and the lowest number of surgical site infections. Compared with no decolonization, universal and targeted decolonization would prevent 42 and 29 *S. aureus*-related surgical site infections, respectively, for every 10,000 patients. Compared with no decolonization, universal decolonization would yield a cost savings of \$274,240 per 10,000 patients. Compared with no decolonization, targeted decolonization would require an additional \$236 to prevent one surgical site infection per 10,000 patients (Table 21).

Table 21: Scenario Analysis 3 Results (per 10,000 Patients)—No Chlorhexidine Body Wash in Standard Care

Strategy ^a	Cost incurred per strategy (95% CrI), \$	Number of SSIs (95% CrI)	Number of <i>S. aureus</i> -related SSIs	Incremental cost (95% CrI), \$	Incremental number of SSIs (95% CrI)	Incremental number of <i>S. aureus</i> -related SSIs (95% CrI)	ICER, \$ per SSI prevented	
							Versus no nasal decolonization	Sequential ICER
Universal nasal decolonization	2,813,145 (2,021,466–2,813,145)	318 (233–424)	61	–	–	–	Dominant ^b	–
No nasal decolonization	3,087,386 (2,248,525–4,155,518)	360 (272–468)	103	274,240 ^c (89,782–491,196)	42 ^d (21–65)	42 (21–65)	NA	Dominated ^e by universal nasal decolonization
Targeted nasal decolonization	3,094,217 (2,276,690–4,116,856)	331 (245–438)	74	281,072 ^f (157,119–434,156)	13 ^g (3–26)	13 (3–26)	236	Dominated ^e by universal nasal decolonization

Abbreviations: CrI, credible interval; ICER, incremental cost-effectiveness ratio; *S. aureus*, *Staphylococcus aureus*; SSI, surgical site infection.

^aStrategies are ranked by cost from lowest to highest.

^bA dominant strategy is less costly and more effective than the comparator.

^cIncremental cost compared no nasal decolonization with universal nasal decolonization.

^dIncremental effect compared no nasal decolonization with universal nasal decolonization.

^eA dominated strategy is more costly and less effective than the comparator.

^fIncremental cost compared targeted nasal decolonization with universal nasal decolonization.

^gIncremental effect compared targeted nasal decolonization with universal nasal decolonization.

Sensitivity Analyses

ONE-WAY SENSITIVITY ANALYSES

We conducted one-way sensitivity analyses by varying several important model parameters, such as the cost of treating a surgical site infection, the cost of mupirocin, the cost of *S. aureus* screening, the prevalence of *S. aureus*, and the effectiveness of mupirocin. In all scenarios, universal decolonization dominated targeted and no decolonization. We therefore decided to focus on the comparison between targeted and no decolonization. Table 22 presents the results of the one-way sensitivity analysis of this comparison.

The model was sensitive to variations in the cost of treating surgical site infection episodes, the cost of the screening test, the prevalence of *S. aureus*, and the efficacy of mupirocin. Targeted decolonization became cost-saving compared with no decolonization when we assumed the cost of treating a surgical site infection to be higher, the cost of screening to be lower, the prevalence of *S. aureus* to be higher, or the effectiveness of mupirocin to be greater.

**Table 22: One-Way Sensitivity Analysis Results (per 10,000 Patients)—
Targeted Decolonization vs. No Decolonization**

Model parameter	Strategy	Numbers of SSIs	Numbers of SSIs prevented	Cost of the strategy, \$	Incremental cost, \$	Incremental cost per SSI prevented, \$
Cost of treating an SSI, \$						
6,866	No decolonization	360		2,525,271		
	Targeted decolonization	338	22	2,568,705	43,434	1,974
29,530	No decolonization	360		10,662,949		
	Targeted decolonization	338	22	10,209,939	-453,009 ^a	Dominant
Cost of mupirocin, \$						
1.28	No decolonization	360		3,142,747		
	Targeted decolonization	338	22	3,146,181	3,430	156
20.56	No decolonization	360		3,142,747		
	Targeted decolonization	338	22	3,187,536	44,790	2,036
Cost of screening, \$						
9.46	No decolonization	360		3,142,747		
	Targeted decolonization	338	22	3,054,535	-88,216 ^a	Dominant

Model parameter		Numbers of SSIs	Numbers of SSI prevented	Cost of the strategy	Incremental costs	Incremental cost per SSI prevented
22.29	No decolonization	360		3,142,747		
	Targeted decolonization	338	22	3,338,000	195,249	8,875
Prevalence of <i>S. aureus</i>						
21%	No decolonization	352		3,075,982		
	Targeted decolonization	334	18	3,113,606	37,624	2,090
30.30%	No decolonization	368		3,217,569		
	Targeted decolonization	342	26	3,187,807	-29,762 ^a	Dominant
Effectiveness of mupirocin						
RR = 0.33	No decolonization	360		3,142,747		
	Targeted decolonization	331	29	3,090,700	-52,051 ^a	Dominant
RR = 0.70	No decolonization	360		3,142,747		
	Targeted decolonization	347	13	3,226,700	83,949	6,458

Abbreviations: *S. aureus*, *Staphylococcus aureus*; SSI: surgical site infection.

^aNegative costs indicate cost savings.

TWO-WAY SENSITIVITY ANALYSES

As universal decolonization remained dominant, we decided to conduct two-way sensitivity analyses comparing targeted decolonization with no decolonization using a selected combination of parameters that were sensitive to the model in the one-way sensitivity analyses. Figures 6 and 7 present the results of the two-way sensitivity analyses comparing the following parameters: (1) the prevalence of *S. aureus* and the efficacy of mupirocin; and (2) the prevalence of *S. aureus* and the cost of treating a surgical site infection.

Figure 6 shows that the model was sensitive to reductions in the relative risk of mupirocin efficacy. When mupirocin efficacy (and thus the relative risk of *S. aureus*-related surgical site infection) was below 0.4125, targeted decolonization would be cost-saving, regardless of the prevalence of *S. aureus*. When the relative risk of *S. aureus*-related surgical site infection between patients receiving mupirocin and those not receiving mupirocin was higher than 0.6375, targeted decolonization would no longer be cost-saving regardless of the prevalence of *S. aureus*.

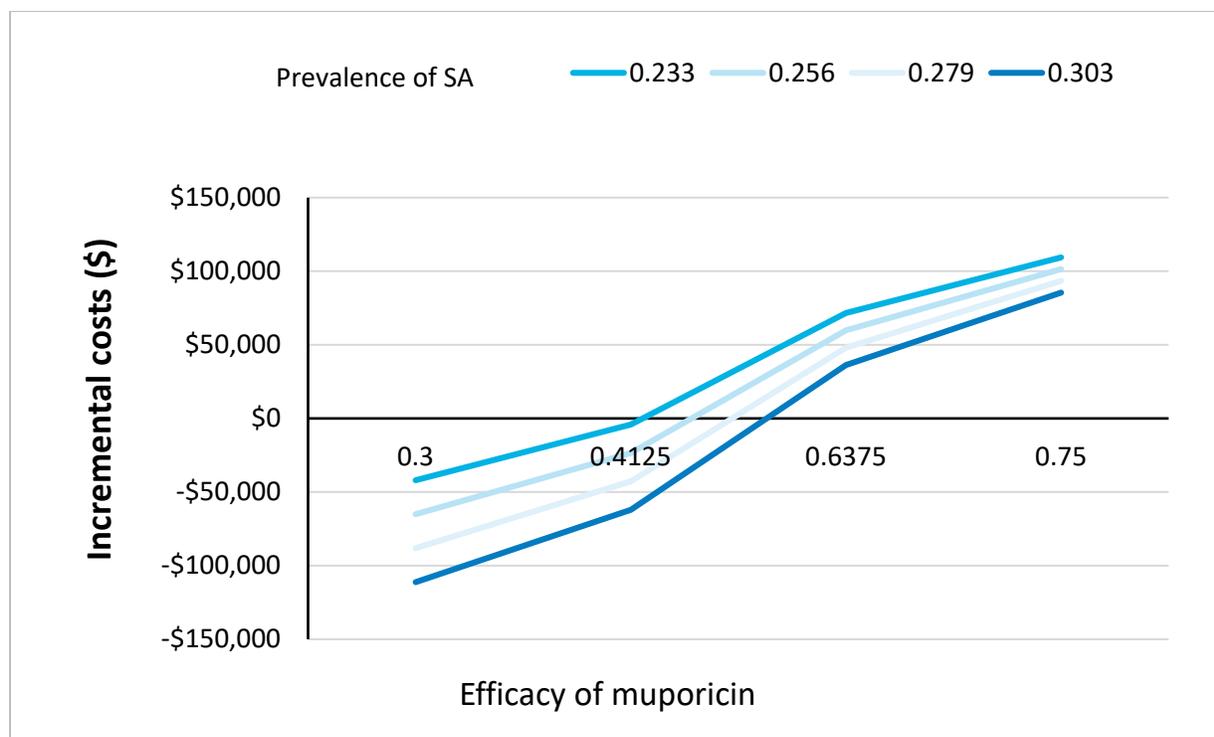


Figure 6: Two-Way Sensitivity Analysis—Prevalence of *S. aureus* and Efficacy of Mupirocin

Abbreviation: SA, *Staphylococcus aureus*.

Figure 7 shows that the model was sensitive to the cost of treating a surgical site infection. When the treatment cost per surgical site infection episode was more than \$12,500, targeted decolonization would be cost-saving compared with no decolonization regardless of the prevalence of *S. aureus*.

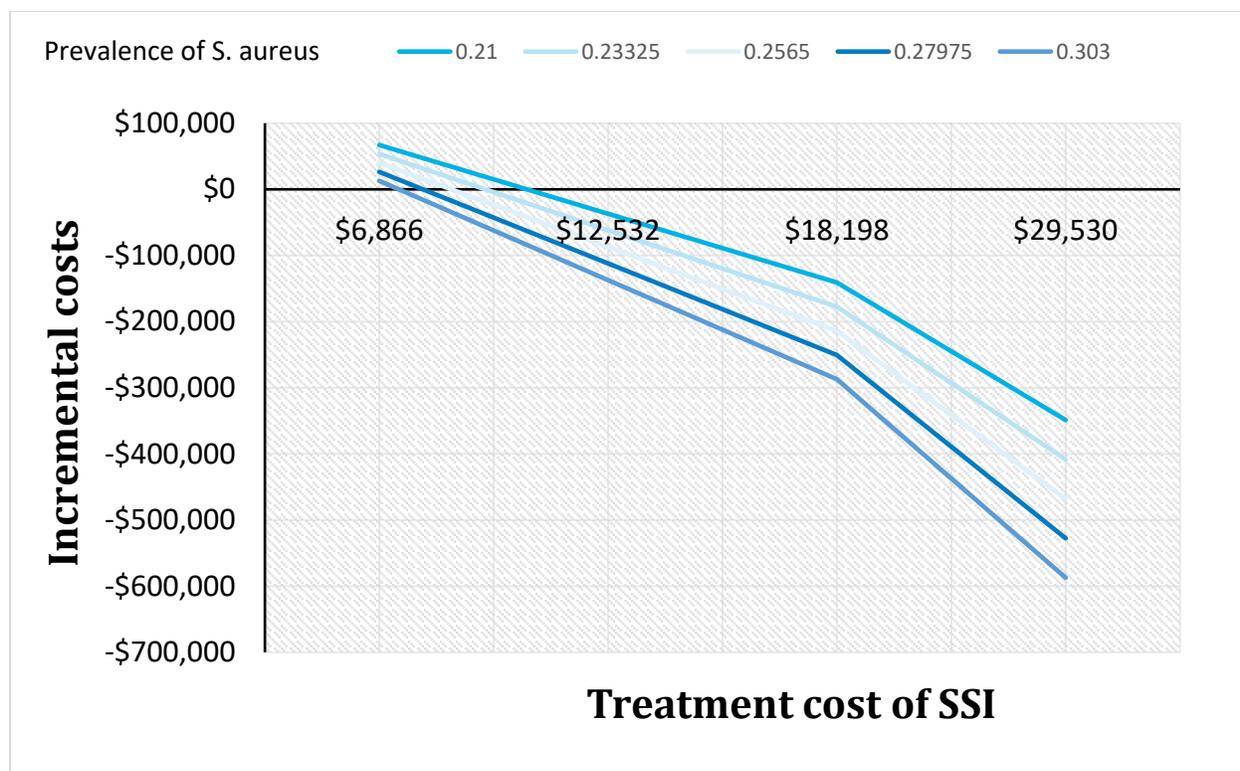


Figure 7: Two-way Sensitivity Analysis—Prevalence of *S. aureus* and Cost of Treating a Surgical Site Infection

Abbreviation: *S. aureus*, *Staphylococcus aureus*; SSI, surgical site infection.

THRESHOLD ANALYSIS

We conducted a threshold analysis of the cost of treating a surgical site infection to identify when universal decolonization would no longer be less costly than no decolonization. Figure 8 shows that when the treatment cost was equal to or less than \$800 per surgical site infection episode, universal decolonization would no longer be less costly than no decolonization. However, universal decolonization would still be more effective than no decolonization.

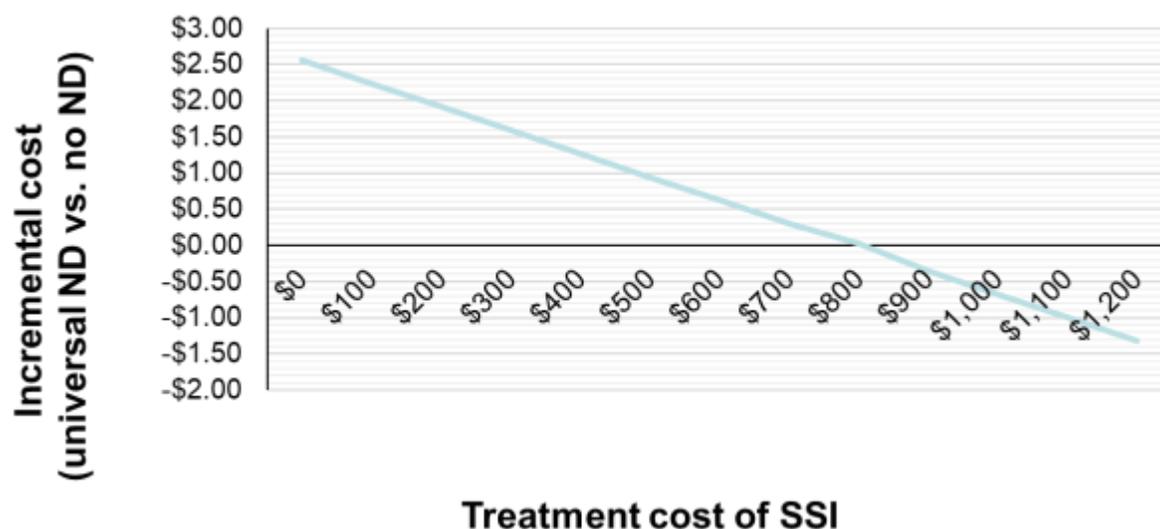


Figure 8: Threshold Analysis—Cost of Treating a Surgical Site Infection

Abbreviations: ND, nasal decolonization; SSI, surgical site infection.

Discussion

Our primary economic analysis investigated the cost-effectiveness of universal nasal decolonization (combined with chlorhexidine body wash) and targeted nasal decolonization (combined with chlorhexidine body wash) compared with no nasal decolonization (chlorhexidine body wash only) from the perspective of the Ontario Ministry of Health.

Our reference case model evaluated the cost-effectiveness of universal and targeted decolonization compared with no decolonization using number of surgical site infections as the main clinical outcome. In terms of the number of surgical site infections prevented, both universal and targeted decolonization would prevent more surgical site infections than no decolonization. In terms of cost, our results showed that universal decolonization would dominate (i.e., be less costly and more effective than) no decolonization. This means that universal decolonization may be cost-saving compared with no decolonization due to the number of surgical site infections prevented.

Targeted decolonization incurs an additional cost compared with no decolonization because the cost savings from surgical site infections prevented are not high enough to offset the cost of screening. Indeed, the results of our one-way sensitivity analyses on the cost of targeted decolonization showed that the model was sensitive to cost of screening and the cost of treating a surgical site

infection. When the cost of screening was lower or the cost of treating a surgical site infection was higher, targeted decolonization would become less costly than no decolonization. We also found that the efficacy of mupirocin and the prevalence of *S. aureus* influenced the cost-effectiveness results of targeted nasal decolonization. Increased mupirocin resistance would decrease the efficacy of the drug and thus would reduce the number of surgical site infections prevented and increase the total cost of targeted decolonization. Similarly, the lower the prevalence of *S. aureus*, the lower the cost savings would be for targeted versus no decolonization.

While it was important to conduct our analyses from the perspective of the Ontario Ministry of Health, it would also be useful to conduct analyses from the societal perspective to explore the impact of indirect costs (e.g., productivity lost owing to surgical site infection and hospitalization, costs incurred by patients to travel to a hospital or clinic for *S. aureus* screening) on the cost-effectiveness of each decolonization strategy.

In the scenario analyses, we found that universal decolonization remained dominant compared with no decolonization and that targeted decolonization was cost-effective compared with no decolonization at a willingness-to-pay value of \$50,000 per QALY. Using PCR screening would identify more cases of *S. aureus*. We found that when PCR was used for screening, both targeted and universal decolonization would prevent the same number of *S. aureus*-related surgical site infections. However, PCR screening is more expensive than the nasal swab and culture method and thus would increase the cost of targeted decolonization.

Our model was sensitive to the efficacy of mupirocin, suggesting that universal decolonization might not be the best decolonization strategy owing to the potential for mupirocin resistance to develop. Given this potential, targeted decolonization may be the preferred strategy. However, this statement must be interpreted cautiously, as we did not model decreased mupirocin effectiveness owing to antimicrobial resistance in the universal decolonization strategy.

Strengths and Limitations

Our analysis had several strengths. First, we adapted it from the model used in the 2019 health technology assessment by NICE.⁶¹ The model captured important clinical outcomes, including number of surgical site infections, surgical site infection-related mortality, and patient quality of life. Where possible, our analysis followed the methodology used by NICE in their economic analysis, which included solid and extensive sensitivity and scenario analyses. We also used the best available data from the literature and applied Canadian data where possible. We used Ontario-specific inputs for the cost of treating a surgical site infection, and we assessed effectiveness using both number of surgical site infections and QALYs.

Our model also had some limitations. As it was a decision-tree model, we did not use a time horizon beyond 1 year to estimate health outcomes. However, surgical site infections typically occur within the first 30 days following surgery, meaning that a 1-year time horizon allowed us to capture the main health outcomes. Owing to a lack of detailed cost data, our model was unable to capture different types of surgical site infections (i.e., superficial, deep incisional, organ/deep space). Further, one of our assumptions was that a patient would experience only one surgical site infection episode. However, it is possible to have two or more surgical site infections during the first year post-surgery. The cost of treating a surgical site infection was based on one type of surgery but was applied to all types. To overcome this limitation, we ran a one-way sensitivity analysis using a wide range of

treatment costs as well as a threshold analysis to assess the impact of treatment cost on the cost-effectiveness model. Finally, in the absence of the local cost of mupirocin and the nasal swab and culture screening test, we opted to use the cost data from the NICE health technology assessment.⁶¹

Conclusions

Our economic analyses showed that universal nasal decolonization with mupirocin combined with chlorhexidine body wash would reduce the incidence of *S. aureus*-related surgical site infections and lead to potential cost savings for the health care system compared with no decolonization treatment. We found that universal nasal decolonization would dominate (i.e., be less costly and more effective than) no nasal decolonization in all scenarios except one in which the cost of treating a surgical site infection was equal to or less than \$800 per episode, which is highly unlikely. Targeted nasal decolonization with mupirocin combined with chlorhexidine body wash would also reduce the incidence of *S. aureus*-related surgical site infections compared with no decolonization but could increase the overall cost of treatment for the health care system since patients must first be screened for *S. aureus* carrier status before receiving nasal decolonization.

Budget Impact Analysis

Research Question

What is the potential 5-year budget impact for the Ontario Ministry of Health of publicly funding nasal decolonization of *Staphylococcus aureus* (*S. aureus*) using mupirocin in pre-surgical patients?

Methods

Analytic Framework

We estimated the budget impact of publicly funding nasal decolonization using mupirocin (with either a universal or targeted approach) in pre-surgical patients using the cost difference between two scenarios: (1) current clinical practice without nasal decolonization (the current scenario); and (2) anticipated clinical practice with nasal decolonization (the new scenario).

In the current scenario, we assumed that pre-surgical patients would not receive nasal decolonization. Therefore, the cost of mupirocin in the current scenario was zero. Although the use of chlorhexidine body wash varies across the province, for simplicity we assumed that most patients do receive chlorhexidine body wash as part of standard care. Therefore, the total cost incurred in this scenario would include the cost of chlorhexidine body wash and the cost of treating surgical site infections.

To account for the variable use of chlorhexidine body wash across the province, we also conducted a scenario analysis in which we assumed that chlorhexidine body wash is not part of standard care.

In the new scenario, there are two options:

- New scenario 1 (universal decolonization using mupirocin combined with chlorhexidine body wash): all patients receive a 5-day course of mupirocin combined with chlorhexidine body wash prior to surgery
- New scenario 2 (targeted decolonization using mupirocin combined with chlorhexidine body wash): all patients are screened for *S. aureus*, and only those who screen positive receive a 5-day course of mupirocin combined with chlorhexidine body wash prior to surgery

In the new scenario, the total cost incurred would include the costs of chlorhexidine body wash, mupirocin, and screening (for the targeted approach) and the cost of treating surgical site infections.

The budget impact is the difference in cost between the current scenario and the new scenario (Figure 9). As it is unclear whether universal or targeted decolonization will be implemented, we calculated the budget impact of both options.

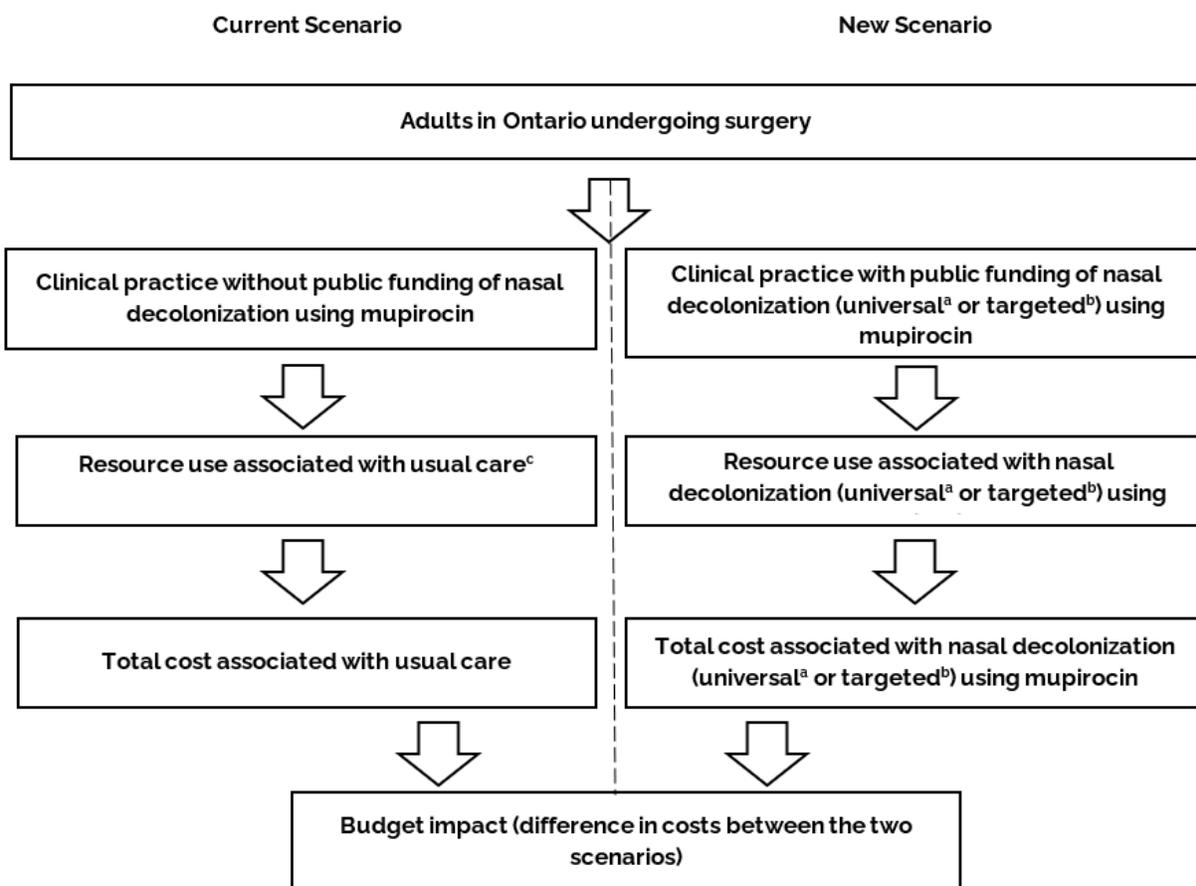


Figure 9: Schematic Model of Budget Impact

^aNew scenario 1 (universal decolonization): all patients receive a 5-day course of mupirocin combined with chlorhexidine body wash prior to surgery.

^bNew scenario 2 (targeted decolonization): all patients are screened for *S. aureus*, and only those who screen positive receive a 5-day course of mupirocin combined with chlorhexidine body wash prior to surgery.

^cUsual care (no decolonization): no patients receive nasal decolonization; all patients receive chlorhexidine body wash.

Key Assumptions

- At present in Ontario, hospital funding practices for nasal decolonization (whether targeted or universal) vary. We therefore assumed that mupirocin is not currently used
- For all urgent and emergent surgical cases requiring immediate surgical intervention, nasal decolonization would not be done as treatment would delay surgery
- All patients receive chlorhexidine body wash regardless of strategy (universal decolonization, targeted decolonization, and no decolonization)

Target Population

The target population is adults undergoing any type of surgery. We obtained the volume of surgical procedures in Ontario between 2017 and 2019 from a study by Wang et al⁷³ (Table 23).

Table 23: Yearly Volumes of Surgical Procedures in Ontario, 2017–2019

	2017	2018	2019
Volume, n	590,918	590,489	593,621

Source: Wang et al, 2020.⁷³

Based on these surgical volumes, we estimated the yearly number of surgical procedures in Ontario for the next five years, from 2022 through 2026. We calculated the average yearly volume of surgical procedures during 2017 and 2019 for all types of surgeries. We found that from 2017 to 2019, there was only a small increase of 0.33% in the volume of procedures conducted. We used this increase to conservatively forecast the volumes of surgical procedures to be conducted between 2022 and 2026 (Table 24).

Table 24: Projected Volumes of Surgical Procedures in Ontario, 2022–2026

	2022	2023	2024	2025	2026
Projected volume, n	597,436	599,394	601,358	603,328	605,305

Current Intervention Mix

As mentioned in the Key Assumptions section, we assumed that mupirocin is not used in the current scenario. However, we assumed that all patients receive chlorhexidine body wash.

Uptake of the New Intervention and New Intervention Mix

We assumed that the uptake of nasal decolonization would be gradual as hospitals may need time to implement such a program. For the reference case analysis, we assumed that the annual uptake rate would increase by 20% each year in the next five years for both the universal and targeted strategies (Table 25).

Table 25: Uptake of the New Intervention by Decolonization Strategy

	Uptake rate				
	2022	2023	2024	2025	2026
New scenario 1: universal decolonization					
Universal decolonization uptake	20%	40%	60%	80%	100%
Standard care	80%	60%	40%	20%	0%
New scenario 2: targeted decolonization					
Targeted decolonization uptake	20%	40%	60%	80%	100%
Standard care	80%	60%	40%	20%	0%

Resources and Costs

For each strategy, we obtained the cost per patient from the primary economic evaluation. We considered the costs of chlorhexidine body wash, mupirocin, screening, and treating a surgical site infection (Table 26).

Table 26: Costs Incurred per Patient by Decolonization Strategy

Resource item	Cost, \$ ^a
Current scenario: no decolonization	
Chlorhexidine body wash	5.52
SSI treatment	308.75
Total	314.27
New scenario 1: universal decolonization	
Chlorhexidine body wash	5.52
Mupirocin	2.56
SSI treatment	281.26
Total	289.34
New scenario 2: targeted decolonization	
Chlorhexidine body wash	5.52
Mupirocin	0.81
Screening	18.92
SSI treatment	289.67
Total	314.92

Abbreviation: SSI, surgical site infection.

^aIn 2021 Canadian dollars.

Internal Validation

The secondary health economist conducted formal internal validation. This process included checking for errors and ensuring the accuracy of parameter inputs and equations in the budget impact analysis.

Analysis

We conducted a reference case analysis and scenario analyses. Our reference case analysis represents the analysis with the most likely set of input parameters and model assumptions.

REFERENCE CASE ANALYSIS

In the reference case analysis, we calculated the required budget to publicly fund both universal and targeted nasal decolonization in adult pre-surgical patients in Ontario. We calculated the budget impact as the cost difference between the new scenario (public funding for nasal decolonization [universal or targeted]) and the current scenario (no public funding for nasal decolonization).

SCENARIO ANALYSES

We explored three scenario analyses: (1) using the lower range (\$9.46) and upper range (\$37.84) of the nasal swab and culture screening test for the targeted decolonization strategy; (2) using polymerase chain reaction (PCR) screening instead of nasal swab and culture for the targeted decolonization strategy (\$337.85 per person); and (3) assuming chlorhexidine body wash is not included in standard care.

Results

Reference Case

The results from the reference analysis showed that universal decolonization would lead to a cost savings of \$45.08 million over the next 5 years, whereas targeted decolonization would incur an additional cost of \$1.17 million over the next 5 years (Table 27).

Table 27: Budget Impact Analysis Results

Resource item	Year 1, \$ million	Year 2, \$ million	Year 3, \$ million	Year 4, \$ million	Year 5, \$ million	Total, \$ million
Current scenario						
Total^a	187.76	188.37	188.99	189.61	190.23	944.97
Chlorhexidine body wash	3.30	3.31	3.32	3.33	3.34	16.60
SSI treatment	184.46	185.07	185.67	186.28	186.89	928.37
New scenario 1: universal decolonization						
Total^b	184.78	182.40	180.00	177.58	175.14	899.89
Chlorhexidine body wash	0.31	0.61	0.92	1.24	1.55	4.63
Mupirocin	3.30	3.31	3.32	3.33	3.34	16.60
SSI treatment	181.18	178.47	175.75	173.01	170.25	878.67
New scenario 2: targeted decolonization						
Total^c	187.84	188.53	189.22	189.92	190.62	946.14
Screening	2.26	4.54	6.83	9.13	11.45	34.21
Chlorhexidine body wash	3.30	3.31	3.32	3.33	3.34	16.60
Mupirocin	0.10	0.19	0.29	0.39	0.49	1.47
SSI treatment	182.18	180.49	178.79	177.07	175.34	893.86
Budget impact: universal decolonization^d	-2.98	-5.98	-9.00	-12.03	-15.09	-45.08
Budget impact: targeted decolonization^d	0.08	0.16	0.23	0.31	0.39	1.17

Abbreviation: SSI, surgical site infection.

^aTotal cost (current scenario) = cost of chlorhexidine body wash + cost of SSI treatment.

^bTotal cost (new scenario 1) = cost of mupirocin + cost of chlorhexidine body wash + cost of SSI treatment.

^cTotal cost (new scenario 2) = cost of screening + cost of mupirocin + cost of chlorhexidine body wash + cost of SSI treatment.

^dBudget impact = cost of new scenario – cost of current scenario.

Scenario Analysis

In a scenario analysis in which the cost of the nasal swab and culture screening test was reduced to \$9.46 per test, the budgets for the universal decolonization strategy were unchanged because no screening is used in this strategy, whereas targeted decolonization became cost-saving, with a total savings of \$15.93 million over the next 5 years (Table 28). When the cost of the nasal swab and culture screening test was increased to \$37.84 per test, implementing targeted decolonization would incur a total additional cost of \$35.38 million over the next 5 years (Table 29).

In a scenario analysis in which PCR screening was used for targeted decolonization, the budgets for universal decolonization were unchanged because no screening is used in this strategy. Implementing targeted decolonization using PCR screening would incur a total additional cost of \$41.87 million over the next 5 years (Table 30).

In a scenario analysis in which chlorhexidine was not used in standard care, universal decolonization would lead to a cost savings of \$28.48 million over the next 5 years, whereas targeted decolonization would incur a total additional cost of \$17.17 million over the next 5 years (Table 31).

Table 28: Budget Impact Analysis Results—Scenario Analysis, Targeted Decolonization, Reduced Cost of Nasal Swab and Culture Test

Resource item	Year 1, \$ million	Year 2, \$ million	Year 3, \$ million	Year 4, \$ million	Year 5, \$ million	Total, \$ million
Current scenario						
Total^a	187.76	188.37	188.99	189.61	190.23	944.97
Chlorhexidine body wash	3.30	3.31	3.32	3.33	3.34	16.60
SSI treatment	184.46	185.07	185.67	186.28	186.89	928.37
New scenario 2: targeted decolonization						
Total^b	186.71	186.26	185.81	185.36	184.90	929.03
Screening	1.13	2.27	3.41	4.57	5.73	17.10
Chlorhexidine body wash	3.30	3.31	3.32	3.33	3.34	16.60
Mupirocin	0.10	0.19	0.29	0.39	0.49	1.47
SSI treatment	182.18	180.49	178.79	177.07	175.34	893.86
Budget impact: targeted decolonization^c	-1.05	-2.11	-3.18	-4.25	-5.33	-15.93

Abbreviation: SSI, surgical site infection.

^aTotal cost (current scenario) = cost of chlorhexidine body wash + cost of SSI treatment.

^bTotal cost (new scenario 2) = cost of screening + cost of mupirocin + cost of chlorhexidine body wash + cost of SSI treatment.

^cBudget impact = cost of new scenario – cost of current scenario.

Table 29: Budget Impact Analysis Results—Scenario Analysis, Targeted Decolonization, Increased Cost of Nasal Swab and Culture Test

Resource item	Year 1, \$ million	Year 2, \$ million	Year 3, \$ million	Year 4, \$ million	Year 5, \$ million	Total, \$ million
Current scenario						
Total^a	187.76	188.37	188.99	189.61	190.23	944.97
Chlorhexidine body wash	3.30	3.31	3.32	3.33	3.34	16.60
SSI treatment	184.46	185.07	185.67	186.28	186.89	928.37
New scenario 2: targeted decolonization						
Total^b	190.10	193.07	196.05	199.05	202.08	980.34
Screening	4.52	9.07	13.65	18.26	22.90	68.42
Chlorhexidine body wash	3.30	3.31	3.32	3.33	3.34	16.60
Mupirocin	0.10	0.19	0.29	0.39	0.49	1.47
SSI treatment	182.18	180.49	178.79	177.07	175.34	893.86
Budget impact: targeted decolonization^c	2.34	4.69	7.06	9.44	11.84	35.38

Abbreviation: SSI, surgical site infection.

^aTotal cost (current scenario) = cost of chlorhexidine body wash + cost of SSI treatment.

^bTotal cost (new scenario 2) = cost of screening + cost of mupirocin + cost of chlorhexidine body wash + cost of SSI treatment.

^cBudget impact = cost of new scenario – cost of current scenario.

Table 30: Budget Impact Analysis Results—Scenario Analysis, Targeted Decolonization, PCR Screening

Resource item	Year 1, \$ million	Year 2, \$ million	Year 3, \$ million	Year 4, \$ million	Year 5, \$ million	Total, \$ million
Current scenario						
Total^a	187.76	188.37	188.99	189.61	190.23	944.97
Chlorhexidine body wash	3.30	3.31	3.32	3.33	3.34	16.60
SSI treatment	184.46	185.07	185.67	186.28	186.89	928.37
New scenario 2: targeted decolonization						
Total^b	190.53	193.93	197.35	200.79	204.25	986.83
Screening	5.90	11.83	17.81	23.82	29.88	89.24
Chlorhexidine body wash	3.30	3.31	3.32	3.33	3.34	16.60
Mupirocin	0.08	0.15	0.23	0.31	0.39	1.16
SSI treatment	181.25	178.63	175.99	173.32	170.64	879.83
Budget impact: targeted decolonization^c	2.77	5.55	8.35	11.18	14.02	41.87

Abbreviation: SSI, surgical site infection.

^aTotal cost (current scenario) = cost of chlorhexidine body wash + cost of SSI treatment.

^bTotal cost (new scenario 2) = cost of screening + cost of mupirocin + cost of chlorhexidine body wash + cost of SSI treatment.

^cBudget impact = cost of new scenario – cost of current scenario.

Table 31: Budget Impact Analysis—Scenario Analysis, Universal and Targeted Decolonization, Chlorhexidine Body Wash Not Used in Standard Care

Resource item	Year 1, \$ million	Year 2, \$ million	Year 3, \$ million	Year 4, \$ million	Year 5, \$ million	Total, \$ million
Current scenario						
Total^a	184.46	185.07	185.67	186.28	186.89	928.37
SSI treatment	184.46	185.07	185.67	186.28	186.89	928.37
New scenario 1: universal decolonization						
Total^b	184.78	182.40	180.00	177.58	175.14	899.89
Chlorhexidine body wash	0.31	0.61	0.92	1.24	1.55	4.63
Mupirocin	3.30	3.31	3.32	3.33	3.34	16.60
SSI treatment	181.18	178.47	175.75	173.01	170.25	878.67
New scenario 2: targeted decolonization						
Total^c	187.84	188.53	189.22	189.92	190.62	946.14
Screening	2.26	4.54	6.83	9.13	11.45	34.21
Chlorhexidine body wash	3.30	3.31	3.32	3.33	3.34	16.60
Mupirocin	0.10	0.19	0.29	0.39	0.49	1.47
SSI treatment	182.18	180.49	178.79	177.07	175.34	893.86
Budget impact: universal decolonization^d	0.32	-2.67	-5.67	-8.70	-11.75	-28.48
Budget impact: targeted decolonization^d	3.38	3.46	3.55	3.64	3.73	17.77

Abbreviation: SSI, surgical site infection.

^aTotal cost (current scenario) = cost of SSI treatment.

^bTotal cost (new scenario 1) = cost of mupirocin + cost of chlorhexidine body wash + cost of SSI treatment.

^cTotal cost (new scenario 2) = cost of screening + cost of mupirocin + cost of chlorhexidine body wash + cost of SSI treatment.

^dBudget impact = cost of new scenario – cost of current scenario.

Discussion

In the reference case analysis, we found that publicly funding universal decolonization would lead to cost savings owing to the number of surgical site infections that would be prevented. Publicly funding targeted decolonization using the nasal swab and culture method over the next 5 years would incur an additional cost of \$1.17 million because the additional cost of screening would exceed the cost offset from surgical site infections prevented. This estimate was based on a realistic volume of surgical procedures conducted in Ontario hospitals. The results of a scenario analysis showed that when the cost of the nasal swab and culture test was reduced to \$9.46 per test, targeted decolonization would become a cost-saving strategy. We also explored the budget impact of using PCR screening instead of nasal swab and culture; these tests are more accurate but also more expensive. In this scenario, publicly funding targeted decolonization would incur an additional cost of \$41.87 million over the next 5 years.

We also considered a very small increase in the annual volume of surgical procedures conducted in Ontario based on historical data. We considered that owing to the impact of the COVID-19 pandemic, the number of surgical procedures currently being performed may be smaller compared to the pre-pandemic level. However, we decided to use the pre-pandemic surgical volume to estimate the potential budget impact so that it would produce a conservative estimate.

A potential limitation is that our budget impact analysis included only adult patients. However, this is because we were able to estimate the cost of treating a surgical site infection only for adult patients, as our included studies included only adults. Another limitation of our analysis is related to the uptake of both universal and targeted decolonization. We assumed that the annual uptake for both strategies would increase by 20% per year. Under this assumption, by year 5, all hospitals in Ontario would be implementing either a universal or targeted decolonization program. If actual implementation is slower, our 5-year budget impact estimates might be slightly overestimated.

Although universal decolonization was the most cost-saving strategy, it may not be easily implemented owing to concerns about the development of antimicrobial resistance to mupirocin. Although targeted decolonization would incur an additional cost, the total 5-year budget impact is considered small. Therefore, targeted nasal decolonization may be a more feasible approach to implement.

Conclusions

We found that publicly funding universal nasal decolonization with mupirocin combined with chlorhexidine body wash would result in a total cost savings of \$45.08 million over the next 5 years, whereas publicly funding targeted decolonization with mupirocin combined with chlorhexidine body wash would incur an additional cost of \$1.17 million. The cost of screening for the presence of *S. aureus* was the main factor influencing the budget impact.

Preferences and Values Evidence

Objective

The objective of this analysis was to explore the underlying values, needs, and priorities of those who have lived experience of recent scheduled surgery and pre-surgical treatment to prevent surgical site infection. We also sought to understand people's perceptions of the value of pre-surgical infection prevention treatments such as nasal decolonization of *Staphylococcus aureus* (*S. aureus*) and the impact of surgical site infection on patients and family members.

Background

Exploring patient preferences and values provides a unique source of information about people's experiences of a health condition and the health technologies or interventions used to manage or treat that health condition. It includes the impact of the condition and its treatment on the person with the health condition, their family and other caregivers, and the person's personal environment. Engagement also provides insights into how a health condition is managed by the province's health system.

Information shared from lived experience can also identify gaps or limitations in published research (e.g., outcomes important to those with lived experience that are not reflected in the literature).⁷⁴⁻⁷⁶ Additionally, lived experience can provide information and perspectives on the ethical and social values implications of health technologies or interventions.

Because the needs, preferences, priorities, and values of those with lived experience in Ontario are important to consider to understand the impact of the technology in people's lives, we may speak directly with people who live with a given health condition, including those with experience of the technology or intervention we are exploring.

For this analysis, we examined the preferences and values of people who had recently undergone scheduled surgery, some of whom had received pre-surgical treatment to prevent surgical site infection, including nasal decolonization. We did this through direct engagement by Ontario Health, engaging with participants through phone interviews and an online survey.

Direct Patient Engagement

Methods

PARTNERSHIP PLAN

The partnership plan for this health technology assessment focused on consultation to examine the experiences of people who had recently undergone scheduled surgery, some of whom had received pre-surgical treatment to prevent surgical site infection, including nasal decolonization. We engaged participants through phone interviews and an online survey.

We used a qualitative interview, as this method of engagement allowed us to explore the meaning of central themes in the experiences of people who had recently undergone scheduled surgery.⁷⁷ The sensitive nature of exploring people's experiences of a health condition and their quality of life are other factors that support our choice of an interview methodology. Using an online survey allowed us

to complement the information gained through interviews by allowing for a greater number and range of participants and experiences.

Participant Outreach

We used an approach called purposive sampling,⁷⁸⁻⁸¹ which involves actively reaching out to people with direct experience of the health condition and health technology or intervention being reviewed. We approached a variety of partner organizations and clinical experts to spread the word about this engagement activity and to contact people with experience of recent scheduled surgery and pre-surgical infection prevention treatments such as nasal decolonization of *S. aureus*.

Inclusion Criteria

We sought to speak with adults with lived experience of recent scheduled surgery and pre-surgical infection prevention treatments such as nasal decolonization. Participants did not need to have direct experience with nasal decolonization to participate.

Exclusion Criteria

We did not set exclusion criteria.

Participants

For this project, we spoke with 11 people who had recently undergone scheduled surgery and one family member of a person who had recently had surgery. Six participants had direct experience with nasal decolonization. Interviewees lived in the Greater Toronto Area, London, and Ottawa. Additionally, we received 14 responses to our online survey, 11 from people who had recently undergone scheduled surgery and three from family members of people who had recently had surgery.

APPROACH

At the beginning of the interview, we explained the role of our organization, the purpose of this health technology assessment, the risks of participation, and how participants' personal health information would be protected. We gave this information to participants both verbally and in a letter of information (Appendix 7) if requested. We then obtained participants' verbal consent before starting the interview. With participants' consent, we audio-recorded and then transcribed the interviews.

Interviews lasted approximately 15 to 40 minutes. The interview was loosely structured and consisted of a series of open-ended questions. Questions were based on a list developed by the Health Technology Assessment International Interest Group on Patient and Citizen Involvement in Health Technology Assessment.⁸² Questions focused on the experiences of the person leading up to surgery, experiences of pre-surgical infection prevention treatments, and experiences with nasal decolonization for those with experience of that procedure. Participants also spoke of the impact of surgical site infection and their perceptions of different treatments to prevent surgical site infection. See Appendix 8 for our interview guide and Appendix 9 for the online survey questions.

DATA EXTRACTION AND ANALYSIS

We used a modified version of a grounded-theory methodology to analyze interview transcripts and survey responses. The grounded-theory approach allowed us to organize and compare information on experiences across participants. This method consists of a repetitive process of obtaining, documenting, and analyzing responses while simultaneously collecting, analyzing, and comparing

information.^{83,84} We used the qualitative data analysis software program NVivo³⁹ to identify and interpret patterns in the data. The patterns we identified allowed us to highlight the impact of surgical site infection on patients and their perceptions of treatments to prevent surgical site infection, including nasal decolonization.

Results

EXPERIENCE LEADING UP TO SURGERY

Interview participants reported a variety of experiences leading up to their surgeries and a diverse range of surgical procedures received. While some participants reported undergoing a single surgical experience, several underwent many surgical procedures. Each person's experience was unique. Interview participants' surgeries included planned surgeries, such as Caesarean section (C-section), and unplanned emergency surgeries. Survey respondents reported a range of surgical procedures, including oral and cardiac surgeries, hip replacement, and knee replacement.

I've had in total seven ... shoulder replacement surgeries, which sounds funny, but some of them were a gong show and I got an infection, and some of them went well, and [for] some of them, I had to ... go back in [for the surgeon to] put in some cadaver bone, and then they put some of my own bone in. So, there [have] been a lot of surgeries.

I had two surgeries. I had one surgery in 2020. That was an emergency surgery. It was a laparoscopy for an ovarian torsion. And then the second one I had ... was a planned C-section.

Many participants reported feeling some anxiety and stress prior to their surgical procedures. Some expressed concerns about the risk of negative clinical outcomes and whether surgery would result in a better quality of life. Others expressed more optimism, reporting looking forward to the successful resolution of a health condition and the journey toward full recovery.

Of course [I experienced anxiety] because it's cancer. It's a very frightening time, so there were multiple concerns. It was my first big surgery probably ever, and my second biopsy got infected. Just in that area, it was ... really quite large. And so I was kind of concerned about it. I was very concerned actually.

I was a nervous wreck. I am high risk, so there was more risk to me going into the surgery. There was a lot of high risk if I ... needed to be intubated, if they put me under.... It was very nerve-racking. The surgery took longer than expected.

[I was] not really [anxious]; I had [had] several other previous surgeries, and I never had a bad experience. My knees were in bad enough shape that I figured that getting some new [ones] was the only solution to the problem, so I was looking forward to it. Not necessarily the surgeries per se but the end result. So, I was feeling pretty positive going in.

Along with these emotions and concerns, most participants also reported that developing a surgical site infection was a particular concern. Some participants reported having friends or family members who had experienced a surgical site infection and wanted to avoid experiencing that themselves.

Survey respondents indicated that the possibility of developing a surgical site infection was a substantial concern, as were post-surgical pain and recovery time.

Besides not having complications during the surgery, my biggest concern was recuperation afterwards, and infection was a huge part of it. They were very worried about me getting [an] infection post-operation.

You've always got concerns when a loved one is going into surgery. I am very aware of some hospital-acquired infections because I knew people, some included my family, who had surgeries and had caught the hospital infections. Namely, an older sister of mine had contracted MRSA [methicillin-resistant S. aureus]. And for years after we're [still] trying to fight it, so I was very aware of the fact that, yes, he could get [a] hospital-acquired infection, but we didn't have a choice. He had to have a surgery.

You hear ... about the super bugs that are floating around hospitals and C. difficile. And that they can be quite, quite difficult. I guess my idea ... when I was going into the hospital for surgeries was to get out as fast as I could. That that's the reality ... the less time I spent in the hospital, the less likely I [would] be to catch something that would be antibiotic resistant.

Some participants commented that a surgical site infection could be a serious complication when they (or their family member) were in a fragile state. If overall health was poor, an infection could have serious consequences for recovery and could even be fatal, which caused additional worry and anxiety.

Infection control is important mostly because my health is very fragile. A small infection—even if it's a simple fix for a healthy person, it's not for me. It means if I were to get MRSA or another staph [Staphylococcus] infection, my body would react very poorly. I might be someone who would have to be intubated, and [the] likeliness of coming back from intubation is very low. So, it's always a risk and worry for me. Even from a small outpatient procedure, I am constantly worried about getting an infection because my body doesn't have the capability to fight it.

Every time I get an infection, it's kind of like you're taking my health points away, so my meter of what I could tolerate goes down further, which really affects my mental health and how I'm dealing with just surviving... So, besides physically, you being sick really does take an emotional and mental toll on you.

AWARENESS OF TREATMENTS TO PREVENT SURGICAL SITE INFECTION

While most interview participants expressed concern about the possibility of developing a surgical site infection, fewer reported having been informed of the risk of surgical site infection or about pre-surgical infection prevention treatments. Most participants who did receive some information reported not learning about these issues until their pre-operative appointments or until just before surgery. Nurses or physicians provided this information, either verbally or through written documents provided to patients and family members. Overall, however, participants reported a great deal of

inconsistency in the amount of information provided and in the sources of that information. About half the survey respondents reported feeling informed about the risk of surgical site infection.

It had been about my fifth surgery, so they very clearly [talked] about the surgical risks, and I was very knowledgeable that [infection] was one of them and that I was at a higher risk given the meds I was on and ... my arthritis in general. So yeah, I was very aware that [infection] could be a possibility.

I had a surgery on my arm on [date] and carpal tunnel releases on [date] and prostate surgery on [date], and I remember each of those times being warned fairly emphatically about the risks involved in infection and also in pre- and post-op.

I was told [via] multiple channels, so verbally and in written form.

A few participants expressed disappointment, frustration, and concern that they were not provided information about the risk of surgical site infection prior to surgery. They reported feeling that this was important information and should be provided in a standardized way to all patients. Some participants felt that having this information would provide reassurance in a stressful situation. Some who had been given information on infection prevention reported that it had not been explained clearly enough to be understood.

But truthfully, at the end of the day, this is my life, and it would have been nice to know all the risk factors involved beforehand. Everybody knows that there's obviously going to be some risks, but once again, to actually be sat down and explained these things would have been different.

Honestly, I don't remember a lot about infection control beforehand. I did a pre-op [appointment], and you know, it was ... blood test, check your temperature, all those sorts of things. But there was really not a lot [of information] around infection control.

I think that giving somebody the information ahead of time is extremely valuable because it eases... [I had] a lot on my mind. Having someone there to kind of reassure [me], "This is what you can look for. Everything will be OK." Just being told what to look for, I would know what to look for, so I would feel better, personally.

EXPERIENCE OF TREATMENTS TO PREVENT SURGICAL SITE INFECTION

Interview participants reported receiving various treatments to prevent surgical site infection, including nasal decolonization, washing the surgical site themselves prior to surgery, and the application of a chemical wash or cleansing agent (chlorhexidine gluconate).

Before the operation, they do ... clean the area in question. The operating room was exactly what you expected it to be: very well organized and very professional. I had no problems because they knew what they were doing.

There was no hair removal of the chest at all whatsoever. He didn't have a lot of hair on his chest, but no, there was no talk of hair removal. They left a special soap in his room for [him] to bathe with the night before the surgery.

The night before and the morning of surgery, I was to take [chlorhexidine], the wash. So ... the night before I had some very specific instructions about washing the surgical site for 10 minutes with this ... antibacterial soap or whatever it was. And so I was in the shower scrubbing my shoulder, and then [I] put on clean clothes. You do it in the morning again. You put on more clean clothes, and you go to the hospital.

Some participants commented on having trust that the health care facility would do its best to prevent surgical site infection. These participants expressed confidence that they were going to be as protected as possible during and after their surgical procedure.

Essentially, I just want the surgery over with ... hopefully to take care of the pain... I'm not smarter than they are ... so I'm not going to say no to anything [to prevent surgical site infection] that is suggested there.

It was certainly in my mind. It was not something that was going to deter me from having the surgeries. I had considerable confidence in the hospitals that I was going to. Not that any of them would have been immune to having C. difficile or other things of that kind. But I know how important it is for hospitals not to have that stuff floating around and to take measures to protect patients. I was aware, it was a minor concern, but it did not deter me from having the surgery.

Participants reported receiving various amounts of information following surgery regarding the risk of post-operative infection, how to prevent infection, and what signs of infection to look for. Some participants reported receiving a great deal of information about how to care for their surgical wounds to prevent post-operative infections. This information was provided verbally by health care staff, within the patient's discharge papers, or as a separate information package. Others felt that they had not received enough information or that what information they had received was unclear. This caused anxiety as patients recuperated at home following surgery.

I was told to watch for infections and not to not bathe for a period of time, at least not to bathe the knee for a period of time. The second time, COVID was intruding on everybody, so I was asked to take pictures of my knee and send them to my doctor, and I removed the dressing myself.

I feel like I didn't get a lot of information in regard to the wound, even though they give you paperwork. And I don't know if this is because it was my first surgery. I kind of felt a little overwhelmed with the whole experience because I didn't really know how to properly take care of the wound.

In regard to the infection itself, I really didn't know what it was going to look like and how much care was needed. Like, they gave you the paperwork, and I don't know if it's just me because I'm not anybody else, but I really didn't know how to

properly take care of it, even after I read the paper. It said you could remove the Band-Aid or the dressing. And then you've got this wound there, [and] I'm thinking, "What do I do? How do I properly take care of it? I don't want it to be infected."

EXPERIENCE AND IMPACT OF SURGICAL SITE INFECTION

During the recruitment for this engagement, experience with surgical site infection was emphasized, so it is not surprising that most participants had experience with one or more surgical site infections. Some interview participants who had undergone several surgeries experienced multiple infections. Participants reported that infections could be discovered weeks or even months after the surgical procedure.

This would have been about three to four months after the replacement had been put in, and they had discovered an infection... It wasn't [there] at the time of surgery, but I guess after post-op, when they went back in ... to remove the screws, that's when they discovered it.

It ended up he had to go back into ICU [intensive care unit] because he was very, very sick. Eventually, when he was in ICU, they took biopsies of the wounds because by this time the wounds were even opening up on his legs. Those black spots were opening up, and they took biopsies of them, and it took a matter of a week or so for the results to come back, and that's when I was told that he had contracted [a bacterial infection].

Participants reported that having a surgical site infection had a negative impact on their healing and recovery. Often, a substantial amount of time was required to clear the infection, resulting in a longer hospital stay or a return to hospital if the patient had already been discharged. If further medical interventions were planned, these could be delayed or cancelled because of the infection, which could have serious consequences for patients' health.

I went on a PICC [peripherally inserted central catheter] for six to eight weeks to get IV [intravenous] antibiotics [to treat a surgical site infection]. They took out my shoulder, so I had to have another shoulder surgery. They put in a cement spacer infused with antibiotics. I was in that for six months. No, wait, it gets better. And then after a bunch of testing to make sure that I didn't have any more infection, they put a new shoulder in.

The incision was leaking fluid ... it was just a clear-type fluid. So, I waited for probably a week and then went back to emergency, and boy, it was "Don't pass go... You're here to stay."

Surgical site infections had a serious impact on patients' physical and emotional well-being. Participants who had had surgery and the family member we interviewed spoke of the extra burden an infection could cause: more time in hospital could lead to slower recovery and reduce the patient's quality of life. The emotional strain of dealing with an infection was also substantial.

It was devastating. It was devastating. I had two daughters who actually live in Alberta, and they would take turns flying down during those three months while he was in hospital because I myself got very sick.

I was at work, and I had to go home. I had to get someone to give me a ride home. I don't have a car. I usually walk everywhere, so I couldn't walk places because it [swelling around the infection site] was so big, right? And so swollen and so painful. And I tried ice and all those things to chill it out, right? And yes, quality of life for sure was impacted.

One of the infections was right after I'd gotten married. So, I had to go into the hospital because I was sick. So, I had to stay in the hospital for a month afterwards when I was supposed to be living in marital bliss. I was away from my husband, and I couldn't see my family, and it really put a strain on us and not just a strain on our relationship, but I [was] strained financially, as well, because I had to be at the hospital.

AWARENESS OF AND EXPERIENCE WITH NASAL DECOLONIZATION

The majority of interview participants and survey respondents reported being unaware prior to surgery of the procedure of nasal decolonization to prevent surgical site infection. This finding is not unexpected given that the treatment is not consistently or widely used across the province. Those with direct experience of nasal decolonization reported the procedure as relatively benign with no substantial side effects. Some participants reported performing the procedure themselves at home for several days prior to surgery, whereas others received treatment in hospital.

They swabbed my nose to see if I had any nasty bugs there. I did get a washing kit. It was two days before, I think, I was asked to shower with this particular soap. I was [also] given a prescription for the nasal ointments, which I was asked to apply to each nostril for, I think, about a week each day before the surgery.

No [side effects]. The first time I did it, I was like, "Am I doing it right?" ... But no, it was nothing. I didn't have a problem with that at all.

I didn't mind putting that small task into my morning routine; it certainly wasn't a big deal.

Nothing [in terms of side effects] that I can remember vividly. I think there was a bit of an odour, but it wasn't a problem. And there were no negative reactions.

For those without direct experience of nasal decolonization, we provided information about the treatment verbally during interviews and in written form in the online survey. Interview participants and survey respondents were then asked about two different methods of nasal decolonization: (1) one in which the patient applies an ointment to their nostrils twice daily for five days before surgery, and (2) one in which a solution is placed in both nostrils by health care staff two hours prior to surgery. Participants were asked which would be their preferred method and why.

Most interview participants and survey respondents reported that they would prefer the in-hospital method. Several participants reported having more confidence in the treatment when performed by

health care professionals, rather than leaving it up to patients who might forget to do it, choose not to do it, perform the procedure incorrectly, or not complete the full regimen of the treatment.

I guess maybe, from a point of view of the principle of the thing, there may be some benefit in having it done by staff in the hospital a couple hours before. I kind of wonder if some people might decide it wasn't worth their bother or would forget. Just to ensure that it was done. In principle, it might be better to have staff to do [it].

If I was older, if I was not as cognizant, I would never go for the one at home. But I'm a young older person, so I was very cognizant of everything that I needed to do. But if I were to, you know, not have the support systems or anything, I would definitely make sure that the doctors and the nurses and whoever is in charge do that [provide decolonization treatment].

I'd be more comfortable to have the nurses do it just because they're the experts and what if I'm doing it ... even with explicit instructions, what if I'm doing it wrong? At that point, as soon as I check into the hospital, I'm basically at the hands of the medical professionals, so, you know, I let them do their thing, basically. So, I'd get the nurse to do it.

We also provided interview participants and survey respondents with information regarding targeted versus universal nasal decolonization. Both procedures are performed in hospital, but targeted decolonization involves first screening pre-surgical patients to determine if they are *S. aureus* carriers. Only those who are confirmed to be carriers are then treated. Universal decolonization involves providing nasal decolonization to all pre-surgical patients regardless of carrier status, as no screening is done.

We then asked participants and respondents which method they would prefer and why. The majority of both participants and respondents reported preferring universal nasal decolonization, citing safety, consistency of treatment, and logistics as reasons for their choice.

I don't have a particular reason; I just think that people deserve to have [nasal decolonization]. Everybody deserves to have it. Because I don't always believe in what happens with the screening process. I don't always know if they're going to do it right, or if it's going to come out a certain way. But I think that everybody should be entitled to have that protection.

The "all" one [universal decolonization] has to be a must. Because one of the problems that people undergoing surgery are faced with is what is known as hospital-acquired infections. So, I would rather see this is a standard procedure that everybody gets.

I think having everyone do it is the safest option. Personally, I know they do a very similar thing with birth. They have you swab for bacteria and whether you're positive or negative for the baby coming out, and they do it for everyone. Personally, I wouldn't mind it being done to me, whether I'm positive or negative, just to take out that risk factor.

While most participants and respondents reported preferring universal decolonization, others were unsure which method was best. Some also raised concerns about the overuse of antibiotics leading to the development of antibiotic-resistant bacteria. A similar concern was raised about giving patients medication they don't need. The participants who raised such concerns reported a preference for targeted decolonization.

Well, I know the higher the frequency of use of any antibiotics, the higher or the greater the likelihood that resistant organisms will evolve. And so, yeah, that is a concern. And at the at the same time, it makes sense to protect patients from the possibility of a post-op infection. It's a trade-off. And I'm not sure which way the scale should tip.

I think it would make more sense to actually be tested for something before you're given medication for it. Do you know what I mean? So, if they test me and I have it, then it makes more sense for them to give me that ointment going into surgery. Otherwise, they're giving me something that I may or may not need.

I think for a typically healthy person, it gives them more options. For them, it would make sense to look at their health, their risk factors, [and] say, "We should test you beforehand." [This] versus someone who is immunocompromised or has a higher risk of infection regardless—the risk of them developing, let's say, a higher tolerance towards antibiotic working for them in the future is so much more minimal compared to the rest of them contracting an infection during that specific procedure. I think that's where I see the line being. You have to weigh the risks, and whichever one is less likely to hurt the patient is the one that should be done.

Although participants differed in their preference for targeted versus universal nasal decolonization, many emphasized the importance of preventing surgical site infections. As reported, most participants had experience with surgical site infections and knew of the detrimental impact these can have on quality of life for both patients and family members. Therefore, most participants viewed surgical site infection prevention treatments as valuable, though many were unable to speak to the clinical efficacy of such treatments directly. Participants also viewed preventing infections as a more effective use of hospital resources than treating infections.

I work with feet, so I know [how] surgical wound infection could lead to loss of [a] limb or loss of a digit, or an internal infection that leads to something more complicated, where it impacts your entire standard of life. I had a cousin who had an appendix removed, and then he developed an infection and had to have part of his intestines removed because they became infected, and now he's on medication for the rest of his life. So, it's definitely something that's very important.

Because it is a lot less expensive to the health care system to do [provide infection prevention treatment] than it [is] to pay for me going through two more surgeries plus all of the doctors' time.

I guess the one comment that I would make is that I would strongly support this kind of activity being publicly funded. I think leaving it up to the hospitals leads potentially to variations in the way patients are treated ... across the province. I think it's a worthwhile endeavour. I think infection prevention is strongly preferred over infection fighting, so it seems to me like an intelligent thing to do and therefore ought to be publicly funded.

It's very, very important. I want to know that in every instance the hospitals had to make sure they took all the precautions to prevent [an infection] from happening.

BARRIERS TO ACCESSING NASAL DECOLONIZATION

Participants did not report any barriers to accessing nasal decolonization beyond simply not being aware that the treatment existed or was offered in some hospitals. A number of participants were not offered nasal decolonization and therefore could not access it. However, upon learning of the treatment, some reflected that they would ask if it could be used for future surgeries.

I think I will be looking at all kinds of ideas, suggestions, and ways to mitigate any sort of surgical site infection because I think having had two, I would be very concerned about being prone to them.

Some participants commented on the issue of cost for the chemical wash treatment (chlorhexidine gluconate). When patients were required to obtain this chemical wash and administer it themselves for several days prior to surgery, the cost was borne by the patient, either out of pocket or through private insurance. For some patients, this cost could be a barrier to accessing effective surgical site infection prevention treatment.

When I got the antibacterial wash, I had to purchase that myself, and it's only available at Shoppers Home Health [Care]. It's not even available at your regular Shoppers [Drug Mart], so that can be disadvantageous ... for individuals who don't have access to a vehicle, don't have ... I mean, it was \$10, so it's not a lot of money, but getting there and doing that errand is out of reach for a lot of people. Now I never said anything to the hospital about not being able to do that because I knew I could. I would hope that if I wasn't able to get there and get that or afford it that the hospital would give it to me. But in all of my surgeries, I had to go purchase that myself.

I'm really fortunate, even though I only get to work three days a week. I do have a really good benefit plan so that the benefits covered that.

Discussion

Engaging participants through direct interviews and an online survey allowed for a robust examination of the experiences, preferences, and values of patients regarding surgical site infection and infection prevention treatments such as nasal decolonization. All participants had recently undergone surgery, most had direct experience with surgical site infections, and a few had direct experience with nasal decolonization. Participants were also able to speak to the impact of surgical site infection, both for themselves and their family members.

Our participants came from diverse backgrounds and had experienced a wide range of surgical procedures. Some had experience multiple surgeries. Most procedures had occurred recently, so participants were able to provide detailed descriptions of their experiences and outcomes. In this way, both direct interviews and survey responses allowed for a thematic analysis of a wide variety of perspectives and for a thorough examination of the perceived value of surgical site infection prevention treatments and the impact of surgical site infection.

Nasal decolonization is not widely or consistently used across Ontario. The relatively limited number of people living in Ontario who are aware of or have had direct experience with this treatment was a limitation of this engagement. Additional interviews with people who had received pre-surgical nasal decolonization may have added valuable context.

Conclusions

Surgical site infection can have a substantial impact on the health and quality of life of patients following surgery. Participants felt strongly about the value of preventing surgical site infections. Most participants were not aware of and had not received nasal decolonization, but those who had reported it as a benign experience with no substantial side effects. The people we interviewed and surveyed favoured universal decolonization over targeted decolonization, and having the treatment administered by health care professionals in hospital was favoured over having patients administer it themselves at home.

Conclusions of the Health Technology Assessment

Based on the best evidence available, decolonization of *S. aureus* using nasal mupirocin combined with chlorhexidine body wash prior to scheduled cardiothoracic, vascular, orthopaedic, gastrointestinal, or general surgery reduces the incidence of surgical site infection caused by *S. aureus* in patients who are carriers of *S. aureus* (including methicillin-susceptible and methicillin-resistant strains). However, nasal mupirocin alone may result in little to no difference in the rates of overall surgical site infection and *S. aureus*-related surgical site infection in pre-surgical patients prior to scheduled orthopaedic, cardiothoracic, general, oncologic, gynaecologic, neurologic, or abdominal digestive surgeries, regardless of their *S. aureus* carrier status. No significant antimicrobial resistance was identified in the evidence reviewed.

Compared with no decolonization, universal decolonization may be cost-saving, and targeted decolonization may be cost-effective. Publicly funding universal decolonization with mupirocin combined with chlorhexidine body wash would result in a total cost savings of \$45.08 million over the next 5 years, whereas publicly funding targeted decolonization with mupirocin combined with chlorhexidine body wash would incur an additional cost of \$1.17 million over the next 5 years.

People we spoke with who had recently undergone scheduled surgery reported valuing treatments aimed at preventing surgical site infections, including nasal decolonization.

Abbreviations

CDC: US Centers for Disease Control and Prevention

CI: Confidence interval

GRADE: Grading of Recommendations Assessment, Development, and Evaluation

ICER: Incremental cost-effectiveness ratio

MRSA: Methicillin-resistant *Staphylococcus aureus*

MSSA: Methicillin-susceptible *Staphylococcus aureus*

NICE: National Institute for Health and Care Excellence

OR: Odds ratio

PCR: Polymerase chain reaction

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses

QALY: Quality-adjusted life-year

RCT: Randomized controlled trial

ROBIS: Risk of Bias in Systematic Reviews

RR: Relative risk or risk ratio

S. aureus: *Staphylococcus aureus*

SD: Standard deviation

SSI: Surgical site infection

Glossary

Adverse event: An adverse event is an unexpected medical problem that happens during treatment for a health condition. Adverse events may be caused by something other than the treatment.

Budget impact analysis: A budget impact analysis estimates the financial impact of adopting a new health care intervention on the current budget (i.e., the affordability of the new intervention). It is based on predictions of how changes in the intervention mix will impact the level of health care spending for a specific population. Budget impact analyses are typically conducted for a short-term period (e.g., 5 years). The budget impact, sometimes referred to as the net budget impact, is the estimated cost difference between the current scenario (i.e., the anticipated amount of spending for a specific population without using the new intervention) and the new scenario (i.e., the anticipated amount of spending for a specific population following the introduction of the new intervention).

Cost-effective: A health care intervention is considered cost-effective when it provides additional benefits, compared with relevant alternatives, at an additional cost that is acceptable to a decision-maker based on the maximum willingness-to-pay value.

Cost-effectiveness acceptability curve: In economic evaluations, a cost-effectiveness acceptability curve is a graphical representation of the results of a probabilistic analysis. It illustrates the probability of health care interventions being cost-effective over a range of willingness-to-pay values. Willingness-to-pay values are plotted on the horizontal axis of the graph, and the probability of the intervention of interest and its comparator(s) being cost-effective at corresponding willingness-to-pay values is plotted on the vertical axis.

Cost-effectiveness analysis: Used broadly, "cost-effectiveness analysis" may refer to an economic evaluation used to compare the benefits of two or more health care interventions with their costs. It may encompass several types of analysis (e.g., cost-effectiveness analysis, cost-utility analysis). Used more specifically, "cost-effectiveness analysis" may refer to a type of economic evaluation in which the main outcome measure is the incremental cost per natural unit of health (e.g., life-year, symptom-free day) gained.

Cost-utility analysis: A cost-utility analysis is a type of economic evaluation used to compare the benefits of two or more health care interventions with their costs. The benefits are measured using quality-adjusted life-years, which capture both the quality and quantity of life. In a cost-utility analysis, the main outcome measure is the incremental cost per quality-adjusted life-year gained.

Decision tree: A decision tree is a type of economic model used to assess the costs and benefits of two or more alternative health care interventions. Each intervention may be associated with different outcomes, which are represented by distinct branches in the tree. Each outcome may have a different probability of occurring and may lead to different costs and benefits.

Discounting: Discounting is a method used in economic evaluations to adjust for the differential timing of the costs incurred and the benefits generated by a health care intervention over time. Discounting reflects the concept of positive time preference, whereby future costs and benefits are reduced to reflect their present value. The health technology assessments conducted by Ontario Health use an annual discount rate of 1.5% for both future costs and future benefits.

Dominant: A health care intervention is considered dominant when it is more effective and less costly than its comparator(s).

EQ-5D: The EQ-5D is a generic health-related quality-of-life classification system widely used in clinical studies. In economic evaluations, it is used as an indirect method of obtaining health state preferences (i.e., utility values). The EQ-5D questionnaire consists of five questions relating to different domains of quality of life: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. For each domain, there are three response options: no problems, some problems, or severe problems. A newer instrument, the EQ-5D-5L, includes five response options for each domain. A scoring table is used to convert EQ-5D scores to utility values.

Generic preference-based measures: Generic preference-based measures are generic (i.e., not disease specific) instruments used to obtain the quality-adjusted weight (i.e., the utility value) of being in a given health state. Generic preference-based measures typically consist of a self-completed questionnaire, a health-state classification system, and a scoring formula that calculates the utility value. Examples include the Health Utilities Index Mark 3 (HUI3), the EQ-5D, and the Short Form–Six Dimensions (SF-6D). The quality-adjusted weights are obtained from the public or from patients, who are provided with a descriptive profile of each predefined health state and asked to fill out a questionnaire. The benefit of using a generic instrument is the ability to obtain utility values that are comparable across different health care interventions and diseases.

Health-related quality of life: Health-related quality of life is a measure of the impact of a health care intervention on a person's health. It includes the dimensions of physiology, function, social life, cognition, emotions, sleep and rest, energy and vitality, health perception, and general life satisfaction.

Health state: A health state is a particular status of health (e.g., sick, well, dead). A health state is associated with some amount of benefit and may be associated with specific costs. Benefit is captured through individual or societal preferences for the time spent in each health state and is expressed in quality-adjusted weights called utility values. In a Markov model, a finite number of mutually exclusive health states are used to represent discrete states of health.

Incremental cost: The incremental cost is the additional cost, typically per person, of a health care intervention versus a comparator.

Incremental cost-effectiveness ratio (ICER): The incremental cost-effectiveness ratio (ICER) is a summary measure that indicates, for a given health care intervention, how much more a health care consumer must pay to get an additional unit of benefit relative to an alternative intervention. It is obtained by dividing the incremental cost by the incremental effectiveness. Incremental cost-effectiveness ratios are typically presented as the cost per life-year gained or the cost per quality-adjusted life-year gained.

Ministry of Health perspective: The perspective adopted in economic evaluations determines the types of costs and health benefits to include. Ontario Health develops health technology assessment reports from the perspective of the Ontario Ministry of Health. This perspective includes all costs and health benefits attributable to the Ministry of Health, such as treatment costs (e.g., drugs, administration, monitoring, hospital stays) and costs associated with managing adverse events

caused by treatments. This perspective does not include out-of-pocket costs incurred by patients related to obtaining care (e.g., transportation) or loss of productivity (e.g., absenteeism).

One-way sensitivity analysis: A one-way sensitivity analysis is used to explore uncertainty in the results of an economic evaluation. It is done by varying one model input (i.e., a parameter) at a time between its minimum and maximum values to observe the potential impact on the cost-effectiveness of the health care intervention of interest.

Probabilistic analysis: A probabilistic analysis (also known as a probabilistic sensitivity analysis) is used in economic models to explore uncertainty in several parameters simultaneously and is done using Monte Carlo simulation. Model inputs are defined as a distribution of possible values. In each iteration, model inputs are obtained by randomly sampling from each distribution, and a single estimate of cost and effectiveness is generated. This process is repeated many times (e.g., 10,000 times) to estimate the number of times (i.e., the probability) that the health care intervention of interest is cost-effective.

Quality-adjusted life-year (QALY): The quality-adjusted life-year (QALY) is a generic health outcome measure commonly used in cost-utility analyses to reflect the quantity and quality of life-years lived. The life-years lived are adjusted for quality of life using individual or societal preferences (i.e., utility values) for being in a particular health state. One year of perfect health is represented by one quality-adjusted life-year.

Reference case: The reference case is a preferred set of methods and principles that provide the guidelines for economic evaluations. Its purpose is to standardize the approach of conducting and reporting economic evaluations, so that results can be compared across studies.

Scenario analysis: A scenario analysis is used to explore uncertainty in the results of an economic evaluation. It is done by observing the potential impact of different scenarios on the cost-effectiveness of a health care intervention. Scenario analyses include varying structural assumptions from the reference case.

Sensitivity analysis: Every economic evaluation contains some degree of uncertainty, and results can vary depending on the values taken by key parameters and the assumptions made. Sensitivity analysis allows these factors to be varied and shows the impact of these variations on the results of the evaluation. There are various types of sensitivity analysis, including deterministic, probabilistic, and scenario.

Societal perspective: The perspective adopted in an economic evaluation determines the types of costs and health benefits to include. The societal perspective reflects the broader economy and is the aggregation of all perspectives (e.g., health care payer and patient perspectives). It considers the full effect of a health condition on society, including all costs (regardless of who pays) and all benefits (regardless of who benefits).

Time horizon: In economic evaluations, the time horizon is the time frame over which costs and benefits are examined and calculated. The relevant time horizon is chosen based on the nature of the disease and health care intervention being assessed, as well as the purpose of the analysis. For instance, a lifetime horizon would be chosen to capture the long-term health and cost consequences over a patient's lifetime.

Uptake rate: In instances where two technologies are being compared, the uptake rate is the rate at which a new technology is adopted. When a new technology is adopted, it may be used in addition to an existing technology, or it may replace an existing technology.

Utility: A utility is a value that represents a person's preference for various health states. Typically, utility values are anchored at 0 (death) and 1 (perfect health). In some scoring systems, a negative utility value indicates a state of health valued as being worse than death. Utility values can be aggregated over time to derive quality-adjusted life-years, a common outcome measure in economic evaluations.

Willingness-to-pay value: A willingness-to-pay value is the monetary value a health care consumer is willing to pay for added health benefits. When conducting a cost-utility analysis, the willingness-to-pay value represents the cost a consumer is willing to pay for an additional quality-adjusted life-year. If the incremental cost-effectiveness ratio is less than the willingness-to-pay value, the health care intervention of interest is considered cost-effective. If the incremental cost-effectiveness ratio is more than the willingness-to-pay value, the intervention is considered not to be cost-effective.

Appendices

Appendix 1: Literature Search Strategies

Clinical Evidence Search

CLINICAL SYSTEMATIC REVIEW LITERATURE SEARCH

Search date: May 12, 2021

Databases searched: Ovid MEDLINE, Embase, Cochrane Database of Systematic Reviews, CRD Health Technology Assessment Database, NHS Economic Evaluation Database, and CINAHL

Database segments: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to May 5, 2021>, EBM Reviews - Health Technology Assessment <4th Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2021 Week 18>, Ovid MEDLINE(R) ALL <1946 to May 11, 2021>

Search strategy:

-
- 1 exp Staphylococcus aureus/ (253122)
 - 2 exp Staphylococcal Infections/ (112641)
 - 3 ((staph* adj3 (aureus* or infect*)) or s aureus* or "staph a" or (methicillin adj3 (resist* or suscept*)) or MRSA or MSSA).ti,ab,kf. (286801)
 - 4 Administration, Intranasal/ (28433)
 - 5 exp Nasal Mucosa/ (41649)
 - 6 Nasal Cavity/ (24366)
 - 7 Nose/ (46484)
 - 8 (nasal or intranasal or nose or noses or nares).ti,ab,kf. (372028)
 - 9 or/1-8 (783892)
 - 10 Mupirocin/ (8644)
 - 11 (mupirocin* or pseudomonic acid* or bactroban* or centany* or eismycin* or plasimine*).ti,ab,kf. (4796)
 - 12 Chlorhexidine/ (26645)
 - 13 (chlorhex* or CHG or novalsan* or naseptin* or sebidin* or tubulicid* or octenid* or octenisan*).ti,ab,kf. (26559)
 - 14 Povidone-Iodine/ (13558)
 - 15 (povidone iodine* or povidine iodine* or PVP iodine* or PVPiodine* or PVPI or PVP I or polyvinylpyrrolidone iodine* or polyvinyl pyrrolidone iodine* or providine* or alphadine* or betadine* or betaisodona* or disadine* or isodine* or pharmadine* or betasept* or soluprep*).ti,ab,kf. (9375)
 - 16 Phototherapy/ (34307)
 - 17 (photodisinfect* or photo disinfect* or steriwave* or mrsaid* or periowave* or (photodynamic adj3 (therap* or treatment*))).ti,ab,kf. (50441)
 - 18 Antibiotic Prophylaxis/ (48246)
 - 19 (antibiotic* adj3 (premedicat* or pre medicat* or prophylaxis or pre surg* or presurg* or preop* or pre op*).ti,ab,kf. (29223)
 - 20 exp Anti-Infective Agents, Local/ (829206)
 - 21 exp Anti-Bacterial Agents/ (4337891)

- 22 Preoperative Care/ (102772)
- 23 (20 or 21) and 22 (6870)
- 24 ((pre op* or preop* or pre surg* or presurg*) adj3 (antisept* or antibacteri* or antimicrobi* or anti microbi* or antiinfect* or anti infect* or microbicid* or disinfect* or nasal)).ti,ab,kf. (2160)
- 25 ((antisept* or antibacteri* or antimicrobi* or anti microbi* or antiinfect* or anti infect* or microbicid* or antibiotic* or disinfect* or pre op* or preop* or pre surg* or presurg*) adj2 (bundle* or soap* or shower* or bath* or wipe* or wash* or ointment*)).ti,ab,kf. (4976)
- 26 (body wash* or bodywash* or body wipe* or bodywipe* or (wash adj2 lotion*) or skin preparation*).ti,ab,kf. (3469)
- 27 Decontamination/ (8520)
- 28 (decoloni* or de-coloni* or decontam*).ti,ab,kf. (33081)
- 29 or/10-19,23-28 (245121)
- 30 9 and 29 (22753)
- 31 ((nasal or intranasal or universal or target* or pre op* or preop* or post op* or postop* or peri op* or periop* or surgical or surger* or operation or operations or operativ*) adj3 (decoloni* or de-coloni* or decontam*)).ti,ab,kf. (1381)
- 32 or/30-31 (23287)
- 33 exp Animals/ not Humans/ (15713804)
- 34 32 not 33 (17688)
- 35 Case Reports/ or Comment.pt. or Editorial.pt. or (Letter not (Letter and Randomized Controlled Trial)).pt. or Congress.pt. (5834489)
- 36 34 not 35 (16445)
- 37 limit 36 to english language [Limit not valid in CDSR; records were retained] (14863)
- 38 37 use coch.clhta,cleed (36)
- 39 (Systematic Reviews or Meta Analysis).pt. (131459)
- 40 Systematic Review/ or Systematic Reviews as Topic/ or Meta-Analysis/ or exp Meta-Analysis as Topic/ or exp Technology Assessment, Biomedical/ (718095)
- 41 ((systematic* or methodologic*) adj3 (review* or overview*)).ti,ab,kf. (507333)
- 42 (meta analy* or metaanaly* or met analy* or metanaly* or meta review* or metareview* or health technolog* assess* or HTA or HTAs or (technolog* adj (assessment* or overview* or appraisal*))).ti,ab,kf. (493119)
- 43 (evidence adj (review* or overview* or synthes#s)).ti,ab,kf. (18227)
- 44 (review of reviews or overview of reviews).ti,ab,kf. (1776)
- 45 umbrella review*.ti,ab,kf. (1268)
- 46 GRADE Approach/ (985)
- 47 ((pool* adj3 analy*) or published studies or published literature or hand search* or handsearch* or manual search* or ((database* or systematic*) adj2 search*) or reference list* or bibliograph* or relevant journals or data synthes* or data extraction* or data abstraction*).ti,ab,kf. (503989)
- 48 (medline or pubmed or medlars or embase or cinahl or web of science or ovid or ebsco* or scopus).ab. (554275)
- 49 cochrane.ti,ab,kf. (235322)
- 50 (meta regress* or metaregress*).ti,ab,kf. (23574)
- 51 (((integrative or collaborative or quantitative) adj3 (review* or overview* or synthes*)) or (research adj3 overview*)).ti,ab,kf. (30210)
- 52 (cochrane or (health adj2 technology assessment) or evidence report or systematic review*).jw. (69847)
- 53 ((comparative adj3 (efficacy or effectiveness)) or relative effectiveness or ((indirect or indirect treatment or mixed-treatment) adj comparison*)).ti,ab,kf. (48335)

- 54 or/39-53 (1399976)
- 55 37 and 54 (731)
- 56 55 use medall (298)
- 57 38 or 56 (334)
- 58 exp Staphylococcus aureus/ (253122)
- 59 exp Staphylococcus aureus infection/ (80446)
- 60 ((staph* adj3 (aureus* or infect*)) or s aureus* or "staph a" or (methicillin adj3 (resist* or suscept*))) or MRSA or MSSA).tw,kw. (286055)
- 61 intranasal drug administration/ (29041)
- 62 mucosal drug administration/ (350)
- 63 exp nose mucosa/ (15091)
- 64 nose cavity/ (13151)
- 65 nose/ (46484)
- 66 (nasal or intranasal or nose or noses or nares).tw,kw. (372658)
- 67 or/58-66 (762511)
- 68 pseudomonic acid/ (8644)
- 69 (mupirocin* or pseudomonic acid* or bactroban* or centany* or eismycin* or plasimine*).tw,kw,dv. (5283)
- 70 chlorhexidine/ (26645)
- 71 octenidine/ (641)
- 72 (chlorhex* or CHG or novalsan* or naseptin* or sebidin* or tubulicid* or octenid* or octenisan*).tw,kw,dv. (26991)
- 73 povidone iodine/ (13558)
- 74 (povidone iodine* or povidine iodine* or PVP iodine* or PVPiodine* or PVPI or PVP I or polyvinylpyrrolidone iodine* or polyvinyl pyrrolidone iodine* or providine* or alphadine* or betadine* or betaisodona* or disadine* or isodine* or pharmadine* or betasept* or soluprep*).tw,kw,dv. (10586)
- 75 phototherapy/ (34307)
- 76 photodynamic therapy device/ (253)
- 77 (photodisinfest* or photo disinfect* or steriwave* or mrsaid* or periowave* or (photodynamic adj3 (therap* or treatment*))).tw,kw,dv. (51192)
- 78 antibiotic prophylaxis/ (48246)
- 79 (antibiotic* adj3 (premedicat* or pre medicat* or prophylaxis or pre surg* or presurg* or preop* or pre op*)).tw,kw,dv. (30075)
- 80 exp antiinfective agent/ (3589534)
- 81 exp disinfectant agent/ (471194)
- 82 preoperative care/ (102772)
- 83 (80 or 81) and 82 (4397)
- 84 ((pre op* or preop* or pre surg* or presurg*) adj3 (antisept* or antibacteri* or antimicrobi* or anti microbi* or antiinfect* or anti infect* or microbicid* or disinfect* or nasal)).tw,kw,dv. (2211)
- 85 ((antisept* or antibacteri* or antimicrobi* or anti microbi* or antiinfect* or anti infect* or microbicid* or antibiotic* or disinfect* or pre op* or preop* or pre surg* or presurg*) adj2 (bundle* or soap* or shower* or bath* or wipe* or wash* or ointment*)).tw,kw,dv. (5230)
- 86 (body wash* or bodywash* or body wipe* or bodywipe* or (wash adj2 lotion*) or skin preparation*).tw,kw,dv. (3538)
- 87 decontamination/ (8520)
- 88 (decoloni* or de-coloni* or decontam*).tw,kw,dv. (33829)
- 89 or/68-79,83-88 (246055)
- 90 67 and 89 (22462)

- 91 ((nasal or intranasal or universal or target* or pre op* or preop* or post op* or postop* or peri op* or periop* or surgical or surger* or operation or operations or operativ*) adj3 (decoloni* or de-coloni* or decontam*)),tw,kw,dv. (1398)
- 92 or/90-91 (22997)
- 93 (exp animal/ or nonhuman/) not exp human/ (11095688)
- 94 92 not 93 (19829)
- 95 Case Report/ or Comment/ or Editorial/ or (letter.pt. not (letter.pt. and randomized controlled trial/)) or conference abstract.pt. or conference review.pt. (11915189)
- 96 94 not 95 (15951)
- 97 limit 96 to english language [Limit not valid in CDSR; records were retained] (14445)
- 98 Systematic review/ or "systematic review (topic)"/ or exp Meta Analysis/ or "Meta Analysis (Topic)"/ or Biomedical Technology Assessment/ (696679)
- 99 (meta analy* or metaanaly* or health technolog* assess* or systematic review*).hw. (693614)
- 100 ((systematic* or methodologic*) adj3 (review* or overview*)),tw,kw. (519270)
- 101 (meta analy* or metaanaly* or met analy* or metanaly* or meta review* or metareview* or health technolog* assess* or HTA or HTAs or (technolog* adj (assessment* or overview* or appraisal*))),tw,kw. (520567)
- 102 (evidence adj (review* or overview* or synthes#s)),tw,kw. (18755)
- 103 (review of reviews or overview of reviews),tw,kw. (2000)
- 104 umbrella review*.tw,kw. (1327)
- 105 ((pool* adj3 analy*) or published studies or published literature or hand search* or handsearch* or manual search* or ((database* or systematic*) adj3 search*) or reference list* or bibliograph* or relevant journals or data synthes* or data extraction* or data abstraction*),tw,kw. (529324)
- 106 (medline or pubmed or medlars or embase or cinahl or web of science or ovid or ebsco* or scopus).ab. (554275)
- 107 cochrane.tw,kw. (238860)
- 108 (meta regress* or metaregress*),tw,kw. (24561)
- 109 (((integrative or collaborative or quantitative) adj3 (review* or overview* or synthes*)) or (research adj3 overview*)),tw,kw. (31170)
- 110 (cochrane or (health adj2 technology assessment) or evidence report or systematic review*).jw. (69847)
- 111 ((comparative adj3 (efficacy or effectiveness)) or relative effectiveness or ((indirect or indirect treatment or mixed-treatment) adj comparison*)),tw,kw. (50059)
- 112 or/98-111 (1420552)
- 113 97 and 112 (1069)
- 114 113 use emez (585)
- 115 57 or 114 (919)
- 116 115 use medall (298)
- 117 115 use coch (14)
- 118 115 use clhta (1)
- 119 115 use cleed (21)
- 120 115 use emez (585)
- 121 remove duplicates from 115 (668)

CINAHL

#	Query	Results
S1	(MH "Staphylococcus Aureus+")	12,101
S2	(MH "Staphylococcal Infections+")	12,036
S3	((staph* N3 (aureus* or infect*)) or s aureus* or "staph a" or (methicillin N3 (resist* or suscept*)) or MRSA or MSSA)	24,314
S4	(MH "Administration, Intranasal")	2,812
S5	(MH "Nasal Mucosa")	1,648
S6	(MH "Nasal Cavity")	1,548
S7	(MH "Nose")	3,661
S8	(nasal or intranasal or nose or noses or nares)	30,570
S9	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8	53,612
S10	(MH "Mupirocin")	467
S11	(mupirocin* or pseudomonic acid* or bactroban* or centany* or eismycin* or plasimine*)	668
S12	(MH "Chlorhexidine")	3,609
S13	(chlorhex* or CHG or novalsan* or naseptin* or sebidin* or tubulicid* or octenid* or octenisan*)	4,794
S14	(MH "Povidone-Iodine")	911
S15	(povidone iodine* or povidine iodine* or PVP iodine* or PVPiodine* or PVPI or PVP I or polyvinylpyrrolidone iodine* or polyvinyl pyrrolidone iodine* or providine* or alphadine* or betadine* or betaisodona* or disadine* or iodine* or pharmane* or betasept* or soluprep*)	1,363
S16	(MH "Phototherapy")	3,526
S17	(photodisinfec* or photo disinfect* or steriwave* or mrsaid* or periowave* or (photodynamic N3 (therap* or treatment*)))	2,466
S18	(MH "Antibiotic Prophylaxis")	6,089
S19	(antibiotic* N3 (premedicat* or pre medicat* or prophylaxis or pre surg* or presurg* or preop* or pre op*))	7,428
S20	(MH "Antiinfective Agents, Local+")	12,625
S21	(MH "Preoperative Care+")	23,254
S22	S20 AND S21	446
S23	((pre op* or preop* or pre surg* or presurg*) N3 (antisept* or antibacteri* or antimicrobi* or anti microbi* or antiinfect* or anti infect* or microbicid* or disinfect* or nasal))	1,599
S24	(MH "Skin Preparation, Surgical")	613
S25	((antisept* or antibacteri* or antimicrobi* or anti microbi* or antiinfect* or anti infect* or microbicid* or antibiotic* or disinfect* or pre op* or preop* or pre surg* or presurg*) N2 (bundle* or soap* or shower* or bath* or wipe* or wash* or ointment*))	5,057
S26	(body wash* or bodywash* or body wipe* or bodywipe* or (wash N2 lotion*) or skin preparation*)	1,164
S27	(MH "Decontamination, Hazardous Materials")	1,371
S28	(decoloni* or de-coloni* or decontam*)	4,315
S29	S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28	28,776
S30	S9 AND S29	3,336

	((nasal or intranasal or universal or target* or pre op* or preop* or post op* or postop* or peri op* or periop* or surgical or surger* or operation or operations or operativ*) N3 (decoloni* or de-coloni* or decontam*))	1,081
S32	S30 OR S31	3,989
S33	PT (Case Study or Commentary or Editorial or Letter or Proceedings)	1,263,110
S34	S32 NOT S33	3,526
S35	(PT "Meta Analysis") or (PT "Systematic Review")	124,703
S36	(MH "Systematic Review") OR (MH "Meta Analysis")	119,888
S37	((systematic* or methodologic*) N3 (review* or overview*)) (meta analy* or metaanaly* or met analy* or metanaly* or meta review* or metareview* or health technolog* assess* or HTA or HTAs or (technolog*	154,008
S38	N1 (assessment* or overview* or appraisal*))	97,647
S39	(evidence N2 (review* or overview* or synthesis or syntheses)))	23,299
S40	((review or overview) N2 reviews)	644,140
S41	umbrella review* ((pool* N3 analy*) or published studies or published literature or hand search* or handsearch* or manual search* or ((database* or systematic*) N2 search*) or reference list* or bibliograph* or relevant journals or	321
S42	data synthes* or data extraction* or data abstraction*) AB(medline or pubmed or medlars or embase or cinahl or web of science	143,302
S43	or ovid or ebSCO* or scopus)	94,451
S44	cochrane	56,220
S45	(meta regress* or metaregress*) (((integrative or collaborative or quantitative) N3 (review* or overview*	3,760
S46	or synthes*)) or (research N3 overview*)) SO(cochrane or (health N2 technology assessment) or evidence report or	10,538
S47	systematic review*) (comparative N3 (efficacy or effectiveness)) or relative effectiveness or	11,344
S48	((indirect or indirect treatment or mixed-treatment) N1 comparison*)) S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44	8,367
S49	OR S45 OR S46 OR S47 OR S48	731,978
S50	S34 AND S49 S34 AND S49	574
S51	Limiters - English Language	562

CLINICAL PRIMARY STUDY LITERATURE SEARCH

Search date: June 29, 2021

Databases searched: Ovid MEDLINE, Embase, Cochrane Central Register of Controlled Trials, CRD Health Technology Assessment Database, NHS Economic Evaluation Database, and CINAHL

Database segments: EBM Reviews - Cochrane Central Register of Controlled Trials <May 2021>, EBM Reviews - Health Technology Assessment <4th Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2021 Week 25>, Ovid MEDLINE(R) ALL <1946 to June 28, 2021>

Search strategy:

-
- 1 exp Staphylococcus aureus/ (255215)
 - 2 exp Staphylococcal Infections/ (114435)
 - 3 ((staph* adj3 (aureus* or infect*)) or s aureus* or "staph a" or (methicillin adj3 (resist* or suscept*)) or MRSA or MSSA).ti,ab,kf. (291433)
 - 4 Administration, Intranasal/ (31130)
 - 5 exp Nasal Mucosa/ (42726)
 - 6 Nasal Cavity/ (24826)
 - 7 Nose/ (47304)
 - 8 (nasal or intranasal or nose or noses or nares).ti,ab,kf. (398346)
 - 9 or/1-8 (815474)
 - 10 Mupirocin/ (8834)
 - 11 (mupirocin* or pseudomonic acid* or bactroban* or centany* or eismycin* or plasimine*).ti,ab,kf. (5304)
 - 12 Chlorhexidine/ (28975)
 - 13 (chlorhex* or CHG or novalsan* or naseptin* or sebidin* or tubulicid* or octenid* or octenisan*).ti,ab,kf. (31434)
 - 14 Povidone-Iodine/ (14258)
 - 15 (povidone iodine* or povidine iodine* or PVP iodine* or PVPIodine* or PVPI or PVP I or polyvinylpyrrolidone iodine* or polyvinyl pyrrolidone iodine* or providine* or alphadine* or betadine* or betaisodona* or disadine* or isodine* or pharmadine* or betasept* or soluprep*).ti,ab,kf. (11022)
 - 16 Phototherapy/ (35554)
 - 17 (photodisinfect* or photo disinfect* or steriwave* or mrsaid* or periowave* or (photodynamic adj3 (therap* or treatment*)))ti,ab,kf. (53038)
 - 18 Antibiotic Prophylaxis/ (49378)
 - 19 (antibiotic* adj3 (premedicat* or pre medicat* or prophylaxis or pre surg* or presurg* or preop* or pre op*).ti,ab,kf. (32445)
 - 20 exp Anti-Infective Agents, Local/ (839816)
 - 21 exp Anti-Bacterial Agents/ (4362333)
 - 22 Preoperative Care/ (107360)
 - 23 (20 or 21) and 22 (7226)
 - 24 ((pre op* or preop* or pre surg* or presurg*) adj3 (antisept* or antibacteri* or antimicrobi* or anti microbi* or antiinfect* or anti infect* or microbicid* or disinfect* or nasal)).ti,ab,kf. (2483)
 - 25 ((antisept* or antibacteri* or antimicrobi* or anti microbi* or antiinfect* or anti infect* or microbicid* or antibiotic* or disinfect* or pre op* or preop* or pre surg* or presurg*) adj2 (bundle* or soap* or shower* or bath* or wipe* or wash* or ointment)).ti,ab,kf. (5498)

- 26 (body wash* or bodywash* or body wipe* or bodywipe* or (wash adj2 lotion*) or skin preparation*).ti,ab,kf. (4011)
- 27 Decontamination/ (8786)
- 28 (decoloni* or de-coloni* or decontam*).ti,ab,kf. (34424)
- 29 or/10-19,23-28 (261042)
- 30 9 and 29 (23965)
- 31 ((nasal or intranasal or universal or target* or pre op* or preop* or post op* or postop* or peri op* or periop* or surgical or surger* or operation or operations or operativ*) adj3 (decoloni* or de-coloni* or decontam*)).ti,ab,kf. (1559)
- 32 or/30-31 (24562)
- 33 32 use cctr (1227)
- 34 Clinical Trials as Topic/ (313236)
- 35 controlled clinical trials as topic/ (16075)
- 36 exp Randomized Controlled Trials as Topic/ (363086)
- 37 controlled clinical trial.pt. (186394)
- 38 randomized controlled trial.pt. (1057057)
- 39 Pragmatic Clinical Trial.pt. (3509)
- 40 Random Allocation/ (213228)
- 41 Single-Blind Method/ (93283)
- 42 Double-Blind Method/ (465334)
- 43 Placebos/ (357806)
- 44 trial.ti. (922710)
- 45 (random* or sham or placebo* or RCT*1).ti,ab,kf. (4410007)
- 46 ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,kf. (713988)
- 47 ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,kf. (4730)
- 48 or/34-47 (5499430)
- 49 32 and 48 (3802)
- 50 33 or 49 (3977)
- 51 exp Animals/ not Humans/ (15655854)
- 52 50 not 51 (3262)
- 53 Case Reports/ or Comment.pt. or Editorial.pt. or (Letter not (Letter and Randomized Controlled Trial)).pt. or Congress.pt. (5836647)
- 54 52 not 53 (3213)
- 55 limit 54 to english language (2687)
- 56 limit 55 to yr="2018 -Current" (521)
- 57 56 use medall,cctr,clhta,cleed (261)
- 58 exp Staphylococcus aureus/ (255215)
- 59 exp Staphylococcus aureus infection/ (81165)
- 60 ((staph* adj3 (aureus* or infect*)) or s aureus* or "staph a" or (methicillin adj3 (resist* or suscept*)) or MRSA or MSSA).tw,kw. (290889)
- 61 intranasal drug administration/ (31738)
- 62 mucosal drug administration/ (353)
- 63 exp nose mucosa/ (15035)
- 64 nose cavity/ (13124)
- 65 nose/ (47304)
- 66 (nasal or intranasal or nose or noses or nares).tw,kw. (398927)
- 67 or/58-66 (793697)
- 68 pseudomonic acid/ (8834)

- 69 (mupirocin* or pseudomonic acid* or bactroban* or centany* or eismycin* or plasimine*).tw,kw,dv. (5760)
- 70 chlorhexidine/ (28975)
- 71 octenidine/ (652)
- 72 (chlorhex* or CHG or novalsan* or naseptin* or sebidin* or tubulicid* or octenid* or octenisan*).tw,kw,dv. (31782)
- 73 povidone iodine/ (14258)
- 74 (povidone iodine* or povidine iodine* or PVP iodine* or PVPiodine* or PVPI or PVP I or polyvinylpyrrolidone iodine* or polyvinyl pyrrolidone iodine* or providine* or alphadine* or betadine* or betaisodona* or disadine* or isodine* or pharmadine* or betasept* or soluprep*).tw,kw,dv. (12152)
- 75 phototherapy/ (35554)
- 76 photodynamic therapy device/ (257)
- 77 (photodisinfest* or photo disinfect* or steriwave* or mrsaid* or periowave* or (photodynamic adj3 (therap* or treatment*)))tw,kw,dv. (53797)
- 78 antibiotic prophylaxis/ (49378)
- 79 (antibiotic* adj3 (premedicat* or pre medicat* or prophylaxis or pre surg* or presurg* or preop* or pre op*).tw,kw,dv. (33812)
- 80 exp antiinfective agent/ (3576993)
- 81 exp disinfectant agent/ (470263)
- 82 preoperative care/ (107360)
- 83 (80 or 81) and 82 (4394)
- 84 ((pre op* or preop* or pre surg* or presurg*) adj3 (antisept* or antibacteri* or antimicrobi* or anti microbi* or antiinfect* or anti infect* or microbicid* or disinfect* or nasal)).tw,kw,dv. (2521)
- 85 ((antisept* or antibacteri* or antimicrobi* or anti microbi* or antiinfect* or anti infect* or microbicid* or antibiotic* or disinfect* or pre op* or preop* or pre surg* or presurg*) adj2 (bundle* or soap* or shower* or bath* or wipe* or wash* or ointment)).tw,kw,dv. (5716)
- 86 (body wash* or bodywash* or body wipe* or bodywipe* or (wash adj2 lotion*) or skin preparation*).tw,kw,dv. (4053)
- 87 decontamination/ (8786)
- 88 (decoloni* or de-coloni* or decontam*).tw,kw,dv. (35176)
- 89 or/68-79,83-88 (262219)
- 90 67 and 89 (23589)
- 91 ((nasal or intranasal or universal or target* or pre op* or preop* or post op* or postop* or peri op* or periop* or surgical or surger* or operation or operations or operativ*) adj3 (decoloni* or de-coloni* or decontam*).tw,kw,dv. (1584)
- 92 or/90-91 (24198)
- 93 "clinical trial (topic)"/ (112888)
- 94 "controlled clinical trial (topic)"/ (11699)
- 95 "randomized controlled trial (topic)"/ (205643)
- 96 randomization/ (196405)
- 97 Single Blind Procedure/ (42938)
- 98 Double Blind Procedure/ (182181)
- 99 placebo/ (354177)
- 100 trial.ti. (922710)
- 101 (random* or sham or placebo* or RCT*1).tw,kw. (4480871)
- 102 ((singl* or doubl*) adj (blind* or dumm* or mask*).tw,kw. (744111)
- 103 ((tripl* or trebl*) adj (blind* or dumm* or mask*).tw,kw. (4768)
- 104 or/93-103 (5104599)

- 105 92 and 104 (3614)
 106 (exp animal/ or nonhuman/) not exp human/ (11072986)
 107 105 not 106 (3444)
 108 Case Report/ or Comment/ or Editorial/ or (letter.pt. not (letter.pt. and randomized controlled trial/)) or conference abstract.pt. or conference review.pt. (11954283)
 109 107 not 108 (3193)
 110 limit 109 to english language (2791)
 111 limit 110 to yr="2018 -Current" (492)
 112 111 use emez (224)
 113 57 or 112 (485)
 114 113 use medall (138)
 115 113 use cctr (123)
 116 113 use clhta (0)
 117 113 use cleed (0)
 118 113 use emez (224)
 119 remove duplicates from 113 (325)

CINAHL

#	Query	Results
S1	(MH "Staphylococcus Aureus+")	12,203
S2	(MH "Staphylococcal Infections+") (staph* N3 (aureus* or infect*)) or s aureus* or "staph a" or (methicillin N3	12,100
S3	(resist* or suscept*) or MRSA or MSSA)	24,474
S4	(MH "Administration, Intranasal")	2,844
S5	(MH "Nasal Mucosa")	1,652
S6	(MH "Nasal Cavity")	1,560
S7	(MH "Nose")	3,685
S8	(nasal or intranasal or nose or noses or nares)	30,975
S9	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8	54,174
S10	(MH "Mupirocin") (mupirocin* or pseudomonic acid* or bactroban* or centany* or eismycin*	467
S11	or plasimine*)	671
S12	(MH "Chlorhexidine") (chlorhex* or CHG or novalsan* or naseptin* or sebidin* or tubulicid*	3,636
S13	or octenid* or octenisan*)	4,835
S14	(MH "Povidone-Iodine") (povidone iodine* or povidine iodine* or PVP iodine* or PVPiodine* or PVPI	925
S15	or iodine* or pharladine* or betadine* or betaisodona* or disadine* or PVP I or polyvinylpyrrolidone iodine* or polyvinyl pyrrolidone iodine* or providine* or alphadine* or betadine* or betaisodona* or disadine*	1,388
S16	(MH "Phototherapy") (photodisinfest* or photo disinfect* or steriwave* or mrsaid* or periowave*	3,560
S17	or (photodynamic N3 (therap* or treatment*)))	2,491
S18	(MH "Antibiotic Prophylaxis") (antibiotic* N3 (premedicat* or pre medicat* or prophylaxis or pre surg*	6,136
S19	or presurg* or preop* or pre op*)	7,488
S20	(MH "Antiinfective Agents, Local+")	12,726

S21	(MH "Preoperative Care+")	23,453
S22	S20 AND S21 ((pre op* or preop* or pre surg* or presurg*) N3 (antise* or antibacteri* or antimicrobi* or anti microbi* or antiinfect* or anti infect* or microbicid* or S23 disinfect* or nasal))	454
S24	(MH "Skin Preparation, Surgical") ((antise* or antibacteri* or antimicrobi* or anti microbi* or antiinfect* or anti S25 infect* or microbicid* or antibiotic* or disinfect* or pre op* or preop* or pre S26 surg* or presurg*) N2 (bundle* or soap* or shower* or bath* or wipe* or S27 wash* or ointment*))	1,626
S28	(MH "Skin Preparation, Surgical") ((antise* or antibacteri* or antimicrobi* or anti microbi* or antiinfect* or anti S29 infect* or microbicid* or antibiotic* or disinfect* or pre op* or preop* or pre S30 surg* or presurg*) N2 (bundle* or soap* or shower* or bath* or wipe* or S31 wash* or ointment*))	619
S25	(body wash* or bodywash* or body wipe* or bodywipe* or (wash N2 lotion*) S26 or skin preparation*)	5,124
S26	(MH "Decontamination, Hazardous Materials")	1,180
S27	(decoloni* or de-coloni* or decontam*)	1,383
S28	S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19	4,388
S29	OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28	29,092
S30	S9 AND S29 ((nasal or intranasal or universal or target* or pre op* or preop* or post op* or postop* or peri op* or periop* or surgical or surger* or operation or S31 operations or operativ*) N3 (decoloni* or de-coloni* or decontam*))	3,370
S32	S30 OR S31	1,095
S33	(MH "Randomized Controlled Trials+")	4,033
S34	(PT "randomized controlled trial")	116,824
S35	(MH "Random Assignment")	130,411
S36	(MH "Single-Blind Studies")	68,331
S37	(MH "Double-Blind Studies")	14,909
S38	(MH "Placebos")	50,867
S39	TI trial	13,270
S40	(random* or sham or placebo* or RCT or RCTs)	151,197
S41	((singl* or doubl*) N1 (blind* or dumm* or mask*))	474,210
S42	((tripl* or trebl*) N1 (blind* or dumm* or mask*))	80,665
S43	S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42	589
S44	S32 AND S43	529,319
S45	(MH "Animals+") not (MH "Animals+" and MH "Human")	537
S46	S44 NOT S45	88,509
S47	PT (Case Study or Commentary or Editorial or Letter or Proceedings)	534
S48	S46 NOT S47 S46 NOT S47	1,273,812
S49	Limiters - English Language S46 NOT S47	507
S50	Limiters - Published Date: 20180101-20211231; English Language	504
		126

Economic Evidence Search

Search date: May 13, 2021

Databases searched: Ovid MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Centre for Reviews and Dissemination (CRD) Health Technology Assessment Database, National Health Service (NHS) Economic Evaluation Database, and CINAHL

Database segments: EBM Reviews - Cochrane Central Register of Controlled Trials <April 2021>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to May 12, 2021>, EBM Reviews - Health Technology Assessment <4th Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2021 Week 18>, Ovid MEDLINE(R) ALL <1946 to May 12, 2021>

Search strategy:

-
- 1 exp Staphylococcus aureus/ (253928)
 - 2 exp Staphylococcal Infections/ (113866)
 - 3 ((staph* adj3 (aureus* or infect*)) or s aureus* or "staph a" or (methicillin adj3 (resist* or suscept*)) or MRSA or MSSA).ti,ab,kf. (290719)
 - 4 Administration, Intranasal/ (31128)
 - 5 exp Nasal Mucosa/ (42630)
 - 6 Nasal Cavity/ (24760)
 - 7 Nose/ (47121)
 - 8 (nasal or intranasal or nose or noses or nares).ti,ab,kf. (397082)
 - 9 or/1-8 (813388)
 - 10 Mupirocin/ (8862)
 - 11 (mupirocin* or pseudomonic acid* or bactroban* or centany* or eismycin* or plasimine*).ti,ab,kf. (5304)
 - 12 Chlorhexidine/ (28902)
 - 13 (chlorhex* or CHG or novalsan* or naseptin* or sebidin* or tubulicid* or octenid* or octenisan*).ti,ab,kf. (31313)
 - 14 Povidone-Iodine/ (14212)
 - 15 (povidone iodine* or povidine iodine* or PVP iodine* or PVPiodine* or PVPI or PVP I or polyvinylpyrrolidone iodine* or polyvinyl pyrrolidone iodine* or providine* or alphadine* or betadine* or betaisodona* or disadine* or isodine* or pharmadine* or betasept* or soluprep*).ti,ab,kf. (10973)
 - 16 Phototherapy/ (35124)
 - 17 (photodisinfest* or photo disinfect* or steriwave* or mrsaid* or periowave* or (photodynamic adj3 (therap* or treatment*)))ti,ab,kf. (52667)
 - 18 Antibiotic Prophylaxis/ (49466)
 - 19 (antibiotic* adj3 (premedicat* or pre medicat* or prophylaxis or pre surg* or presurg* or preop* or pre op*).ti,ab,kf. (32475)
 - 20 exp Anti-Infective Agents, Local/ (838595)
 - 21 exp Anti-Bacterial Agents/ (4367292)
 - 22 Preoperative Care/ (107059)
 - 23 (20 or 21) and 22 (7217)

- 24 ((pre op* or preop* or pre surg* or presurg*) adj3 (antisept* or antibacteri* or antimicrobi* or anti microbi* or antiinfect* or anti infect* or microbicid* or disinfect* or nasal)).ti,ab,kf. (2466)
- 25 ((antisept* or antibacteri* or antimicrobi* or anti microbi* or antiinfect* or anti infect* or microbicid* or antibiotic* or disinfect* or pre op* or preop* or pre surg* or presurg*) adj2 (bundle* or soap* or shower* or bath* or wipe* or wash* or ointment*)).ti,ab,kf. (5473)
- 26 (body wash* or bodywash* or body wipe* or bodywipe* or (wash adj2 lotion*) or skin preparation*).ti,ab,kf. (3998)
- 27 Decontamination/ (8603)
- 28 (decoloni* or de-coloni* or decontam*).ti,ab,kf. (34180)
- 29 or/10-19,23-28 (260022)
- 30 9 and 29 (23910)
- 31 ((nasal or intranasal or universal or target* or pre op* or preop* or post op* or postop* or peri op* or periop* or surgical or surger* or operation or operations or operativ*) adj3 (decoloni* or de-coloni* or decontam*)).ti,ab,kf. (1562)
- 32 or/30-31 (24506)
- 33 exp Animals/ not Humans/ (15713653)
- 34 32 not 33 (18906)
- 35 Case Reports/ or Comment.pt. or Editorial.pt. or (Letter not (Letter and Randomized Controlled Trial)).pt. or Congress.pt. (5838468)
- 36 34 not 35 (17661)
- 37 limit 36 to english language [Limit not valid in CDSR; records were retained] (15667)
- 38 37 use coch.clhta,cleed (36)
- 39 economics/ (261736)
- 40 economics, medical/ or economics, pharmaceutical/ or exp economics, hospital/ or economics, nursing/ or economics, dental/ (921829)
- 41 economics.fs. (447154)
- 42 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmaco-economic* or pharmaco-economic*).ti,ab,kf. (1048614)
- 43 exp "costs and cost analysis"/ (632297)
- 44 (cost or costs or costing or costly).ti. (296849)
- 45 cost effective*.ti,ab,kf. (382128)
- 46 (cost* adj2 (util* or efficacy* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*)).ab,kf. (249414)
- 47 models, economic/ (14524)
- 48 markov chains/ or monte carlo method/ (93172)
- 49 (decision adj1 (tree* or analy* or model*)).ti,ab,kf. (51394)
- 50 (markov or markow or monte carlo).ti,ab,kf. (150290)
- 51 quality-adjusted life years/ (46828)
- 52 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).ti,ab,kf. (90363)
- 53 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).ti,ab,kf. (149773)
- 54 or/39-53 (2901870)
- 55 37 and 54 (1111)
- 56 55 use medall,cctr (383)
- 57 38 or 56 (419)
- 58 exp Staphylococcus aureus/ (253928)
- 59 exp Staphylococcus aureus infection/ (80444)
- 60 ((staph* adj3 (aureus* or infect*)) or s aureus* or "staph a" or (methicillin adj3 (resist* or suscept*)) or MRSA or MSSA).tw,kw. (290405)

- 61 intranasal drug administration/ (31736)
- 62 mucosal drug administration/ (350)
- 63 exp nose mucosa/ (15091)
- 64 nose cavity/ (13151)
- 65 nose/ (47121)
- 66 (nasal or intranasal or nose or noses or nares).tw,kw. (398552)
- 67 or/58-66 (792716)
- 68 pseudomonic acid/ (8862)
- 69 (mupirocin* or pseudomonic acid* or bactroban* or centany* or eismycin* or plasimine*).tw,kw,dv. (5792)
- 70 chlorhexidine/ (28902)
- 71 octenidine/ (650)
- 72 (chlorhex* or CHG or novalsan* or naseptin* or sebidin* or tubulicid* or octenid* or octenisan*).tw,kw,dv. (31792)
- 73 povidone iodine/ (14212)
- 74 (povidone iodine* or povidine iodine* or PVP iodine* or PVPiodine* or PVPI or PVP I or polyvinylpyrrolidone iodine* or polyvinyl pyrrolidone iodine* or providine* or alphadine* or betadine* or betaisodona* or disadine* or isodine* or pharmadine* or betasept* or soluprep*).tw,kw,dv. (12207)
- 75 phototherapy/ (35124)
- 76 photodynamic therapy device/ (253)
- 77 (photodisinfec* or photo disinfect* or steriwave* or mrsaid* or periowave* or (photodynamic adj3 (therap* or treatment*))).tw,kw,dv. (53486)
- 78 antibiotic prophylaxis/ (49466)
- 79 (antibiotic* adj3 (premedicat* or pre medicat* or prophylaxis or pre surg* or presurg* or preop* or pre op*).tw,kw,dv. (34003)
- 80 exp antiinfective agent/ (3589534)
- 81 exp disinfectant agent/ (471194)
- 82 preoperative care/ (107059)
- 83 (80 or 81) and 82 (4397)
- 84 ((pre op* or preop* or pre surg* or presurg*) adj3 (antisept* or antibacteri* or antimicrobi* or anti microbi* or antiinfect* or anti infect* or microbicid* or disinfect* or nasal)).tw,kw,dv. (2517)
- 85 ((antisept* or antibacteri* or antimicrobi* or anti microbi* or antiinfect* or anti infect* or microbicid* or antibiotic* or disinfect* or pre op* or preop* or pre surg* or presurg*) adj2 (bundle* or soap* or shower* or bath* or wipe* or wash* or ointment)).tw,kw,dv. (5749)
- 86 (body wash* or bodywash* or body wipe* or bodywipe* or (wash adj2 lotion*) or skin preparation*).tw,kw,dv. (4067)
- 87 decontamination/ (8603)
- 88 (decoloni* or de-coloni* or decontam*).tw,kw,dv. (34995)
- 89 or/68-79,83-88 (261587)
- 90 67 and 89 (23682)
- 91 ((nasal or intranasal or universal or target* or pre op* or preop* or post op* or postop* or peri op* or periop* or surgical or surger* or operation or operations or operativ*) adj3 (decoloni* or de-coloni* or decontam*).tw,kw,dv. (1591)
- 92 or/90-91 (24290)
- 93 (exp animal/ or nonhuman/) not exp human/ (11095543)
- 94 92 not 93 (21121)
- 95 Case Report/ or Comment/ or Editorial/ or (letter.pt. not (letter.pt. and randomized controlled trial/)) or conference abstract.pt. or conference review.pt. (11939728)

- 96 94 not 95 (17232)
 97 limit 96 to english language [Limit not valid in CDSR; records were retained] (15303)
 98 Economics/ (261736)
 99 Health Economics/ or Pharmacoeconomics/ or Drug Cost/ or Drug Formulary/ (139979)
 100 Economic Aspect/ or exp Economic Evaluation/ (498902)
 101 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).tw,kw. (1075940)
 102 exp "Cost"/ (632297)
 103 (cost or costs or costing or costly).ti. (296849)
 104 cost effective*.tw,kw. (395103)
 105 (cost* adj2 (util* or efficac* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*)).ab,kw. (262169)
 106 Monte Carlo Method/ (73015)
 107 (decision adj1 (tree* or analy* or model*)).tw,kw. (55308)
 108 (markov or markow or monte carlo).tw,kw. (155395)
 109 Quality-Adjusted Life Years/ (46828)
 110 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).tw,kw. (94314)
 111 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).tw,kw. (171210)
 112 or/98-111 (2502268)
 113 97 and 112 (1313)
 114 113 use emez (748)
 115 57 or 114 (1167)
 116 115 use medall (336)
 117 115 use emez (748)
 118 115 use cctr (47)
 119 115 use coch (14)
 120 115 use cleed (21)
 121 115 use clhta (1)
 122 remove duplicates from 115 (881)

CINAHL

#	Query	Results
S1	(MH "Staphylococcus Aureus+")	12,103
S2	(MH "Staphylococcal Infections+") (staph* N3 (aureus* or infect*) or s aureus* or "staph a" or (methicillin N3	12,036
S3	(resist* or suscept*) or MRSA or MSSA)	24,314
S4	(MH "Administration, Intranasal")	2,813
S5	(MH "Nasal Mucosa")	1,648
S6	(MH "Nasal Cavity")	1,548
S7	(MH "Nose")	3,662
S8	(nasal or intranasal or nose or noses or nares)	30,572
S9	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8	53,614
S10	(MH "Mupirocin") (mupirocin* or pseudomonic acid* or bactroban* or centany* or eismycin* or	467
S11	plasimine*)	668
S12	(MH "Chlorhexidine")	3,609

	(chlorhex* or CHG or novalsan* or naseptin* or sebidin* or tubulicid* or	
S13	octenid* or octenisan*)	4,795
S14	(MH "Povidone-Iodine")	911
	(povidone iodine* or povidine iodine* or PVP iodine* or PVPiodine* or PVPI	
	or PVP I or polyvinylpyrrolidone iodine* or polyvinyl pyrrolidone iodine* or	
	providine* or alphadine* or betadine* or betaisodona* or disadine* or	
S15	isodine* or pharmadine* or betasept* or soluprep*)	1,363
S16	(MH "Phototherapy")	3,527
	(photodisinfest* or photo disinfect* or steriwave* or mrsaid* or periowave*	
S17	or (photodynamic N3 (therap* or treatment*)))	2,466
S18	(MH "Antibiotic Prophylaxis")	6,090
	(antibiotic* N3 (premedicat* or pre medicat* or prophylaxis or pre surg* or	
S19	presurg* or preop* or pre op*))	7,430
S20	(MH "Antiinfective Agents, Local+")	12,626
S21	(MH "Preoperative Care+")	23,257
S22	S20 AND S21	446
	((pre op* or preop* or pre surg* or presurg*) N3 (antisept* or antibacteri* or	
	antimicrobi* or anti microbi* or antiinfect* or anti infect* or microbicid* or	
S23	disinfest* or nasal))	1,599
S24	(MH "Skin Preparation, Surgical")	613
	((antisept* or antibacteri* or antimicrobi* or anti microbi* or antiinfect* or anti	
	infect* or microbicid* or antibiotic* or disinfect* or pre op* or preop* or pre	
	surg* or presurg*) N2 (bundle* or soap* or shower* or bath* or wipe* or	
S25	wash* or ointment*))	5,060
	(body wash* or bodywash* or body wipe* or bodywipe* or (wash N2 lotion*)	
S26	or skin preparation*)	1,165
S27	(MH "Decontamination, Hazardous Materials")	1,371
S28	(decoloni* or de-coloni* or decontam*)	4,317
	S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19	
S29	OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28	28,785
S30	S9 AND S29	3,336
	((nasal or intranasal or universal or target* or pre op* or preop* or post op*	
	or postop* or peri op* or periop* or surgical or surger* or operation or	
S31	operations or operativ*) N3 (decoloni* or de-coloni* or decontam*))	1,081
S32	S30 OR S31	3,989
S33	PT (Case Study or Commentary or Editorial or Letter or Proceedings)	1,263,221
S34	S32 NOT S33	3,526
S35	(MH "Economics")	14,585
S36	(MH "Economic Aspects of Illness")	10,145
S37	(MH "Economic Value of Life")	654
S38	MH "Economics, Dental"	147
S39	MH "Economics, Pharmaceutical"	2,313
S40	MW "ec"	190,415
	(econom* or price or prices or pricing or priced or discount* or expenditure*	
S41	or budget* or pharmacoeconomic* or pharmaco-economic*)	321,972
S42	(MH "Costs and Cost Analysis+")	124,933
S43	TI cost*	56,801

S44	(cost effective*)	44,552
S45	AB (cost* N2 (util* or efficacy* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*))	34,870
S46	(decision N1 (tree* or analy* or model*))	9,327
S47	(markov or markow or monte carlo)	6,458
S48	(MH "Quality-Adjusted Life Years")	5,078
S49	(QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs)	12,856
S50	((adjusted N1 (quality or life)) or (willing* N2 pay) or sensitivity analysis or sensitivity analyses)	20,338
S51	S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44	435,783
S52	OR S45 OR S46 OR S47 OR S48 OR S49 OR S50	232
S53	S34 AND S51	230
	S34 AND S51	
	Limiters - English Language	

Grey Literature Search

Performed: May 14–18, 2021; June 30, 2021

Websites searched:

Alberta Health Evidence Reviews, Alberta Health Services, BC Health Technology Assessments, Canadian Agency for Drugs and Technologies in Health (CADTH), Institut national d'excellence en santé et en services sociaux (INESSS), Institute of Health Economics (IHE), McGill University Health Centre Health Technology Assessment Unit, Centre Hospitalier de l'Université de Québec-Université Laval, Health Technology Assessment Database, World Health Organization, Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Centers, Centers for Medicare & Medicaid Services Technology Assessments, Veterans Affairs Health Services Research and Development, Institute for Clinical and Economic Review, Oregon Health Authority Health Evidence Review Commission, Washington State Health Care Authority Health Technology Reviews, National Institute for Health and Care Excellence (NICE), Healthcare Improvement Scotland, Health Technology Wales, Ireland Health Information and Quality Authority Health Technology Assessments, Australian Government Medical Services Advisory Committee, Council of Australian Governments Health Technologies, Australian Safety and Efficacy Register of New Interventional Procedures -Surgical (ASERNIP-S), Italian National Agency for Regional Health Services (AGENAS), Belgian Health Care Knowledge Centre, Ludwig Boltzmann Institute for Health Technology Assessment, Swedish Agency for Health Technology Assessment and Assessment of Social Services, Ministry of Health Malaysia Health Technology Assessment Section, Tuft's Cost-Effectiveness Analysis Registry, Sick Kids PEDE Database, PROSPERO, EUnetHTA, clinicaltrials.gov

Keywords used:

nasal, intranasal, decolonization, decolonisation, decontamination, colonization, colonisation, staphylococcus, staphylococcal, aureus, MRSA, MSSA, mupirocin, chlorhexidine, povidone iodine, povidine iodine, PVP iodine, photodisinfection, photodynamic, steriwave, periowave, surgical site infection, décolonisation nasale, décontamination nasale, staphylocoque doré, mupirocine, chlorhexidine, povidone iodée, photodésinfection

Clinical results (included in PRISMA): 30

Economic results (included in PRISMA): 10

Ongoing HTAs (PROSPERO/EUnetHTA/): 12

Ongoing RCTs (clinicaltrials.gov): 28

Appendix 2: Critical Appraisal of Clinical Evidence

Table A1: Risk of Bias^a Among Systematic Reviews (ROBIS Tool)

Author, year	Phase 2			Phase 3	
	Study eligibility criteria	Identification and selection of studies	Data collection and study appraisal	Synthesis and findings	Risk of bias in the review
Banerjee et al, 2017 ³⁴	Low ^b	High ^{c,d}	High ^e	Low	High
CADTH, 2020 ³⁵	Low ^b	High ^{c,d}	High ^e	Low	High
Kallen et al, 2005 ³⁶	Low ^b	Low	High ^f	Low	High
Liu et al, 2017 ³⁷	Low	Low	Low	Low	Low
Ma et al, 2017 ³⁸	Low ^b	High ^g	High ^f	Low	High
NICE, 2019 ¹⁹	Low ^h	Low	Low	Low	Low
Schweizer et al, 2013 ³⁹	Low	Low	High ^f	Low	High
Tang et al, 2020 ⁴⁰	Low	Low	Low	High ⁱ	High
van Rijen et al, 2008 ⁴¹	Low ^b	High ^j	High ^f	High ^k	High
van Rijen et al, 2008 ⁴²	Low	Low	Low	Low	Low
WHO, 2016 ²¹	Low ^b	Low	Low	Low	Low

Abbreviations: CADTH, Canadian Agency for Drugs and Technologies in Health; NICE, National Institute for Health and Care Excellence; ROBIS, Risk of Bias in Systematic Reviews; WHO, World Health Organization.

^aPossible risk of bias levels: low, high, unclear.

^bNo information on whether study protocol was registered a priori or pre-defined.

^cLimited literature search.

^dSingle reviewer on study selection.

^eSingle reviewer on data extraction.

^fLimited information on patient characteristics of included studies.

^gReasons for excluding full texts not provided.

^hProtocol was not registered as evidence review was presented to the NICE committee prior to the protocol being signed off.

ⁱStudies with nasal decolonization and other interventions (i.e., antiseptic body wash and antibiotic prophylactic) were combined in the meta-analysis.

^jLimited search terms.

^kNo information provided on exploring heterogeneity between studies.

Table A2: Risk of Bias^a Among Randomized Controlled Trials (Cochrane Risk-of-Bias Tool)

Author, year	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Incomplete outcome data	Selective reporting	Other bias
Rohrer et al, 2020 ²⁸	Low	Low	Low	Low	Low	High ^{b,c,d}
Rohrer et al, 2021 ²⁹	Low	Low	Low	Low	Low	High ^b
Smith et al, 2019 ³⁰	Low	Unclear ^e	High ^f	Low	Low	High ^g

^aPossible risk-of-bias levels: low, high, unclear.

^bOutcomes were assessed by telephone screening.

^cParticipant characteristics reported by carrier status; unclear if there were differences in risk factors of surgical site infections by intervention group.

^dSome patients were prescribed antibiotics due to poor wound healing despite a formal diagnosis of surgical site infection not being made.

^eNo information on allocation concealment.

^fNo blinding of participants and outcome assessors. Some clinical outcomes (e.g., pain, inflammation on inspection) were subjective.

^gMultiple interventions changed for various reasons after the trial commenced.

Table A3: GRADE Evidence Profile for Comparison of Nasal Mupirocin Versus Placebo in All Pre-surgical Patients

Number of studies (design)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Upgrade considerations	Quality
Overall surgical site infection at 30 days							
2 (RCTs)	Serious limitations (-1) ^a	No serious limitations	No serious limitations	Serious limitations (-1) ^b	Undetected	None	⊕⊕ Low
Overall superficial surgical site infection at 30 days							
1 (RCT)	No serious limitations	Not applicable ^c	No serious limitations	Very serious limitations (-2) ^d	Undetected	None	⊕⊕ Low
Overall deep incisional surgical site infection at 30 days							
1 (RCT)	Serious limitations (-1) ^e	Not applicable ^c	No serious limitations	Very serious limitations (-2) ^d	Undetected	None	⊕ Very low
<i>S. aureus</i>-related surgical site infection at 30 days							
2 (RCTs)	Serious limitations (-1) ^a	No serious limitations	No serious limitations	Very serious limitations (-2) ^d	Undetected	None	⊕ Very Low
Overall nosocomial infection at 30 days							
1 (RCT)	Serious limitations (-1) ^e	Not applicable ^c	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕ Moderate
<i>S. aureus</i>-related nosocomial infection at 30 days							
1 (RCT)	Serious limitations (-1) ^e	Not applicable ^c	No serious limitations	Serious limitations (-1) ^b	Undetected	None	⊕⊕ Low
Hospital readmission							
1 (RCT)	No serious limitations	Not applicable ^c	No serious limitations	Very serious limitations (-2) ^d	Undetected	None	⊕⊕ Low

Number of studies (design)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Upgrade considerations	Quality
Mean hospital stay							
1 (RCT)	No serious limitations	Not applicable ^c	No serious limitations	Serious limitations (-1) ^f	Undetected	None	⊕⊕⊕ Moderate

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCT, randomized controlled trial; *S. aureus*, *Staphylococcus aureus*.

^aMore than 33.3% of the weight in the meta-analysis came from a study at moderate risk of bias.

^b95% confidence interval crosses one end of a defined minimal clinically important difference interval (0.8, 1.25).

^cInconsistency not applicable.

^d95% confidence interval crosses both ends of a defined MID interval (0.8, 1.25).

^eStudy demonstrated unclear random sequence generation, allocation concealment, and blinding of outcome assessment.

^fNon-significant result.

Table A4: GRADE Evidence Profile for Comparison of Nasal Mupirocin Versus No Intervention in All Pre-surgical Patients

Number of studies (design)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Upgrade considerations	Quality
Overall surgical site infection at 30 days							
1 (RCT)	No serious limitations	Not applicable ^a	No serious limitations	Very serious limitations (-2) ^b	Undetected	None	⊕⊕ Low
Overall superficial surgical site infection at 30 days							
1 (RCT)	No serious limitations	Not applicable ^a	No serious limitations	Very serious limitations (-2) ^b	Undetected	None	⊕⊕ Low
Overall deep incisional surgical site infection at 30 days							
1 (RCT)	No serious limitations	Not applicable ^a	No serious limitations	Serious limitations (-1) ^c	Undetected	None	⊕⊕⊕ Moderate
<i>S. aureus</i>-related surgical site infection at 30 days							
1 (RCT)	No serious limitations	Not applicable ^a	No serious limitations	Very serious limitations (-2) ^b	Undetected	None	⊕⊕ Low
Overall nosocomial infection at 30 days							
1 (RCT)	No serious limitations	Not applicable ^a	No serious limitations	Very serious limitations (-2) ^b	Undetected	None	⊕⊕ Low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCT, randomized controlled trial; *S. aureus*, *Staphylococcus aureus*.

^aInconsistency not applicable.

^b95% confidence interval crosses both ends of a defined minimal clinically important difference interval (0.8, 1.25).

^c95% confidence interval crosses one end of a defined minimal clinically important difference interval (0.8, 1.25).

Table A5: GRADE Evidence Profile for Comparison of Nasal Chlorhexidine Combined With Chlorhexidine Oral Rinse Versus Placebo in All Pre-surgical Patients

Number of studies (design)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Upgrade considerations	Quality
Overall surgical site infection at 30 days							
1 (RCT)	No serious limitations	Not applicable ^a	Serious limitations (-1) ^b	Very serious limitations (-2) ^c	Undetected	None	⊕ Very low
Overall deep incisional surgical site infection at 30 days							
1 (RCT)	No serious limitations	Not applicable ^a	Serious limitations (-1) ^b	No serious limitations	Undetected	None	⊕⊕⊕ Moderate
<i>S. aureus</i>-related surgical site infection at 30 days							
1 (RCT)	No serious limitations	Not applicable ^a	Serious limitations (-1) ^b	Very serious limitations (-2) ^c	Undetected	None	⊕ Very low
Overall nosocomial infection at 30 days							
1 (RCT)	No serious limitations	Not applicable ^a	Serious limitations (-1) ^b	Serious limitations (-1) ^d	Undetected	None	⊕⊕ Low
Nosocomial infection: lower respiratory tract infection at 30 days							
1 (RCT)	No serious limitations	Not applicable ^a	Serious limitations (-1) ^b	Serious limitations (-1) ^d	Undetected	None	⊕⊕ Low
Nosocomial infection: urinary tract infection at 30 days							
1 (RCT)	No serious limitations	Not applicable ^a	Serious limitations (-1) ^b	Very serious limitations (-2) ^c	Undetected	None	⊕ Very low
Nosocomial infection: bacteraemia at 30 days							
1 (RCT)	No serious limitations	Not applicable ^a	Serious limitations (-1) ^b	Serious limitations (-1) ^d	Undetected	None	⊕⊕ Low

Number of studies (design)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Upgrade considerations	Quality
Mortality at 30 days							
1 (RCT)	No serious limitations	Not applicable ^a	Serious limitations (-1) ^b	Very serious limitations (-2) ^c	Undetected	None	⊕ Very low
Mean hospital stay at 30 days							
1 (RCT)	No serious limitations	Not applicable ^a	Serious limitations (-1) ^b	No serious limitations	Undetected	None	⊕⊕⊕ Moderate
Hospital readmission at 30 days							
1 (RCT)	No serious limitations	Not applicable ^a	Serious limitations (-1) ^b	Very serious limitations (-2) ^c	Undetected	None	⊕ Very low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCT, randomized controlled trial; *S. aureus*, *Staphylococcus aureus*.

^aChlorhexidine was given in the form of a nasal gel and mouthwash.

^bInconsistency not applicable.

^c95% confidence interval crosses both ends of a defined minimal clinically important difference interval (0.8, 1.25).

^d95% confidence interval crosses one end of a defined minimal clinically important difference interval (0.8, 1.25).

Table A6: GRADE Evidence Profile for Comparison of Nasal Mupirocin Alone Versus Placebo in Pre-surgical Patients Who Are *S. aureus* Carriers

Number of studies (design)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Upgrade considerations	Quality
Overall surgical site infection							
2 (RCTs)	Serious limitations (-1) ^a	Serious limitations (-1) ^b	No serious limitations	Very serious limitations (-2) ^c	Undetected	None	⊕ Very low
Overall surgical site infection at 30 days							
1 (RCT)	Serious limitations (-1) ^d	Not applicable ^e	No serious limitations	Serious limitations (-1) ^f	Undetected	None	⊕⊕ Low
Overall surgical site infection within 8 weeks of surgery							
1 (RCT)	No serious limitations	Not applicable ^e	No serious limitations	Very serious limitations (-2) ^c	Undetected	None	⊕⊕ Low
Overall superficial surgical site infection within 8 weeks of surgery							
1 (RCT)	No serious limitations	Not applicable ^e	No serious limitations	Serious limitations (-1) ^f	Undetected	None	⊕⊕⊕ Moderate
Overall deep incisional surgical site infection within 8 weeks of surgery							
1 (RCT)	No serious limitations	Not applicable ^e	No serious limitations	Very serious limitations (-2) ^c	Undetected	None	⊕⊕ Low
Overall organ/deep-space surgical site infection within 8 weeks of surgery							
1 (RCT)	No serious limitations	Not applicable ^e	No serious limitations	Very serious limitations (-2) ^c	Undetected	None	⊕⊕ Low
<i>S. aureus</i>-related surgical site infection							
3 (RCTs)	Serious limitations (-1) ^a	No serious limitations	No serious limitations	Serious limitations (-1) ^f	Undetected	None	⊕⊕ Low

Number of studies (design)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Upgrade considerations	Quality
<i>S. aureus</i>–related surgical site infection at 30 days							
2 (RCTs)	Serious limitations (-1) ^a	No serious limitations	No serious limitations	Serious limitations (-1) ^f	Undetected	None	⊕ Low ^g
<i>S. aureus</i>–related surgical site infection within 8 weeks of surgery							
1 (RCT)	No serious limitations	Not applicable ^e	No serious limitations	Very serious limitations (-2) ^c	Undetected	None	⊕⊕ Low
Overall nosocomial infection at 30 days							
1 (RCT)	Serious limitations (-1) ^d	Not applicable ^e	No serious limitations	Serious limitations (-1) ^f	Undetected	None	⊕⊕ Low
<i>S. aureus</i>–related nosocomial infection at 30 days							
1 (RCT)	Serious limitations (-1) ^d	Not applicable ^e	No serious limitations	Serious limitations (-1) ^f	Undetected	None	⊕⊕ Low
Mortality							
1 (RCT)	No serious limitation	Not applicable ^e	No serious limitations	Very serious limitations (-2) ^c	Undetected	None	⊕⊕ Low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCT, randomized controlled trial; *S. aureus*, *Staphylococcus aureus*.

^aMore than 33.3% of the weight in the meta-analysis came from a study at moderate risk of bias.

^bThe I² statistic was between 33.3% and 66.7%.

^c95% confidence interval crosses both ends of a defined minimal clinically important difference interval (0.8, 1.25).

^dStudy demonstrated unclear random sequence generation, allocation concealment, and blinding of outcome assessment.

^eInconsistency not applicable.

^f95% confidence interval crosses one end of a defined minimal clinically important difference interval (0.8, 1.25).

^gIn the NICE health technology assessment,¹⁹ the GRADE rating for this outcome was "Very Low." However, it should have been graded as "Low" if downgraded one level for risk of bias and one level for imprecision.

Table A7: GRADE Evidence Profile for Comparison of Nasal Mupirocin Combined With Chlorhexidine Body Wash Versus Placebo in Pre-surgical Patients Who Are *S. aureus* Carriers

Number of studies (design)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Upgrade considerations	Quality
<i>S. aureus</i>–related surgical site infection until 6 weeks after discharge							
1 (RCT)	No serious limitation	Not applicable ^a	No serious limitation	No serious limitation	Undetected	None	⊕⊕⊕⊕ High
<i>S. aureus</i>–related superficial surgical site infection until 6 weeks after discharge							
1 (RCT)	No serious limitation	Not applicable ^a	No serious limitation	Serious limitation (–1) ^b	Undetected	None	⊕⊕⊕ Moderate
<i>S. aureus</i>–related deep incisional surgical site infection until 6 weeks after discharge							
1 (RCT)	No serious limitation	Not applicable ^a	No serious limitation	No serious limitation	Undetected	None	⊕⊕⊕⊕ High
<i>S. aureus</i>–related nosocomial infection until 6 weeks after discharge							
1 (RCT)	No serious limitation	Not applicable ^a	No serious limitation	No serious limitation	Undetected	None	⊕⊕⊕⊕ High
Mortality							
1 (RCT)	No serious limitation	Not applicable ^a	No serious limitation	Serious limitation (–1) ^b	Undetected	None	⊕⊕⊕ Moderate
Mortality in <i>S. aureus</i> carriers with <i>S. aureus</i> infection							
1 (RCT)	No serious limitation	Not applicable ^a	No serious limitation	Very serious limitations (–2) ^c	Undetected	None	⊕⊕ Low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCT, randomized controlled trial; *S. aureus*, *Staphylococcus aureus*.

^aInconsistency not applicable.

^b95% confidence interval crosses one end of a defined minimal clinically important difference interval (0.8, 1.25); downgraded one level.

^c95% confidence interval crosses both ends of a defined minimal clinically important difference interval (0.8, 1.25); downgraded two levels.

Table A8: GRADE Evidence Profile for Comparison of Nasal Mupirocin Combined With Chlorhexidine Body Wash Versus No Intervention in Pre-surgical Patients Who Are *S. aureus* Carriers

Number of studies (design)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Upgrade considerations	Quality
Overall surgical site infection at 90 days							
1 (RCT)	Serious limitations (-1) ^{a,b}	Not applicable ^c	No serious limitation	Very serious limitations (-2) ^d	Undetected	None	⊕ Very low
Overall deep incisional surgical site infection (prosthetic joint infection) at 1 year							
1 (RCT)	Very serious limitations (-2) ^e	Not applicable ^c	No serious limitation	Very serious limitations (-2) ^f	Undetected	None	⊕ Very low
Prosthetic joint infection at 2 years							
1 (RCT)	Serious limitations (-1) ^a	Not applicable ^c	No serious limitation	Very serious limitations (-2) ^g	Undetected	None	⊕ Very low
<i>S. aureus</i>-related deep incisional surgical site infection (prosthetic joint infection) at 1 year							
1 (RCT)	Very serious limitations (-2) ^h	Not applicable ^c	No serious limitation	Very serious limitations (-2) ^f	Undetected	None	⊕ Very low
<i>S. aureus</i>-related surgical site infection during post-operative period in <i>S. aureus</i> carriers							
1 (RCT)	Serious limitations (-1) ^d	Not applicable ^c	Serious limitations (-1) ⁱ	Serious limitations (-1) ^j	Undetected	None	⊕ Very low
MRSA-related surgical site infection							
1 (RCT)	Serious limitations (-1) ^d	Not applicable ^c	Serious limitations (-1) ⁱ	Very serious limitations (-2) ^f	Undetected	None	⊕ Very Low
MSSA-related surgical site infection							
1 (RCT)	Serious limitations (-1) ^d	Not applicable ^c	Serious limitations (-1) ⁱ	No serious limitations	Undetected	None	⊕⊕ Low

Notes for Table A8:

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCT, randomized controlled trial; *S. aureus*, *Staphylococcus aureus*.

^aOutcomes were assessed by telephone screening.

^bCharacteristics of participants reported by carrier status; unclear if there were differences in surgical site infection by intervention group.

^cInconsistency not applicable.

^dTrial was terminated early for futility and infeasibility reasons.

^eUnclear allocation concealment and blinding of outcome assessment; intention-to-treat analysis not conducted.

^f95% confidence interval crosses both ends of a defined minimal clinically important difference interval (0.8, 1.25).

^gUncertain if sample size was adequate, as it was calculated for overall surgical site infections in general orthopaedic surgery instead of prosthetic surgery (the population of this follow-up study).

^hUnclear random sequence generation, allocation concealment, and blinding of outcome assessment.

ⁱFollow-up of surgical site infection and criteria used to define surgical site infection were not specified.

^j95% confidence interval crosses one end of a defined minimal clinically important difference interval (0.8, 1.25).

Table Ag: GRADE Evidence Profile for Comparison of Nasal Mupirocin With or Without Chlorhexidine Body Wash Versus All Non-active Interventions in Pre-surgical Patients Who Are *S. aureus* Carriers

Number of studies (design)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Upgrade considerations	Quality
<i>S. aureus</i>–related surgical site infection							
5 (RCTs)	Serious limitations (-1) ^b	No serious limitation	No serious limitation	No serious limitation	Undetected	None	⊕⊕⊕ Moderate

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCT, randomized controlled trial; *S. aureus*, *Staphylococcus aureus*.

^aMore than 33.3% of the weight in the meta-analysis came from a study at moderate risk of bias.

Note: According to the 2019 NICE health technology assessment,¹⁹ this meta-analysis was conducted to support the economic evaluation.

Table A10: GRADE Evidence Profile for Comparison of Nasal Mupirocin Combined With Chlorhexidine Body Wash Versus No Intervention in Pre-surgical Patients Who Are Not *S. aureus* Carriers

Number of studies (design)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Upgrade considerations	Quality
Overall surgical site infection at 90 days							
1 (RCT)	Serious limitations (-1) ^{a,b}	Not applicable ^c	No serious limitation	Very serious limitations (-2) ^d	Undetected	None	⊕ Very low
Prosthetic joint infection at 2 years							
1 (RCT)	Serious limitations (-1) ^a	Not applicable ^c	No serious limitation	Very serious limitations (-2) ^e	Undetected	None	⊕ Very low
Wound infection within 1 week							
1 (RCT)	Very serious limitations (-2) ^{f,g}	Not applicable ^c	No serious limitation	No serious limitation	Undetected	None	⊕⊕ Low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCT, randomized controlled trial.

^aOutcomes were assessed by telephone screening.

^bCharacteristics of participants reported by carrier status; unclear if there were differences in surgical site infection by intervention group.

^cInconsistency not applicable.

^dTrial was terminated early for futility and infeasibility reasons.

^eUncertain if sample size was adequate as it was calculated for overall surgical site infections in general orthopaedic surgery instead of prosthetic surgery (the population of this follow-up study).

^fNo information on allocation concealment. No blinding of participants and outcome assessors.

^gMultiple interventions changed for various reasons after the trial has commenced.

Appendix 3: Selected Excluded Studies—Clinical Evidence

For transparency, we provide a list of studies that readers might have expected to see but that did not meet our inclusion criteria, along with the primary reason for exclusion.

Table A11: Selected Excluded Systematic Reviews—Clinical Evidence

Citation	Primary reason for exclusion
Chen AF, Wessel C, Rao N. Staphylococcus aureus screening and decolonization in orthopaedic surgery and reduction of surgical site infections. <i>Clinical Orthopaedics and Related Research</i> . 2013;471(7):2383-99.	SR included both RCTs and observational studies. No separate analysis of results from RCTs and from observational studies
George S, Leasure AR, Horstmanshof D. Effectiveness of decolonization with chlorhexidine and mupirocin in reducing surgical site infections: a systematic review. <i>Dimensions of Critical Care Nursing</i> . 2016;35(4):204-22.	SR included both RCTs and observational studies. No separate analysis of results from RCTs and from observational studies
Humphreys H, Becker K, Dohmen PM, Petrosillo N, Spencer M, van Rijen M, et al. Staphylococcus aureus and surgical site infections: benefits of screening and decolonization before surgery. <i>Journal of Hospital Infection</i> . 2016;94(3):295-304.	Not an SR
Levy PY, Ollivier M, Drancourt M, Raoult D, Argenson JN. Relation between nasal carriage of Staphylococcus aureus and surgical site infection in orthopedic surgery: the role of nasal contamination. A systematic literature review and meta-analysis. <i>Orthopaedics & Traumatology, Surgery & Research</i> . 2013;99(6):645-5.	SR included both RCTs and observational studies. No separate analysis of results from RCTs and from observational studies
Li Y, Severn M. Preoperative interventions for the prevention of surgical site infections: a review of guidelines. <i>CADTH Rapid Response Reports</i> . 2020;6:18.	Not an SR
Lin L, Ke ZY, Wang Y, Chen XL, Zhong D, Cheng S. Efficacy of preoperative screening and decolonization for staphylococcus aureus in total joint arthroplasty: a meta-analysis. <i>Asian Journal of Surgery</i> . 2021;16:16.	SR of observational studies
Nair R, Perencevich EN, Blevins AE, Goto M, Nelson RE, Schweizer ML. Clinical effectiveness of mupirocin for preventing Staphylococcus aureus infections in nonsurgical settings: a meta-analysis. <i>Clinical Infectious Diseases</i> . 2016;62(5):618-30.	Not population of interest
Ning J, Wang J, Zhang S, Sha X. Nasal colonization of Staphylococcus aureus and the risk of surgical site infection after spine surgery: a meta-analysis. <i>Spine Journal</i> . 2020;20(3):448-56.	SR of observational studies

Citation	Primary reason for exclusion
Ribau AI, Collins JE, Chen AF, Sousa RJ. Is preoperative Staphylococcus aureus screening and decolonization effective at reducing surgical site infection in patients undergoing orthopedic surgery? A systematic review and meta-analysis with a special focus on elective total joint arthroplasty. <i>Journal of Arthroplasty</i> . 2021;36(2):752-66.e6.	SR included both RCTs and observational studies. No separate analysis of results from RCTs and from observational studies
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. <i>Revista Brasileira de Ortopedia</i> . 2017;52(6):631-7.	SR of observational studies
Wang L, Ji Q, Hu X. Role of targeted and universal mupirocin-based decolonization for preventing surgical-site infections in patients undergoing cardiothoracic surgery: a systematic review and meta-analysis. <i>Experimental and Therapeutic Medicine</i> . 2021;21(5):416.	SR included both RCTs and observational studies. No separate analysis of results from RCTs and from observational studies
Zhu X, Sun X, Zeng Y, Feng W, Li J, Zeng J, et al. Can nasal Staphylococcus aureus screening and decolonization prior to elective total joint arthroplasty reduce surgical site and prosthesis-related infections? A systematic review and meta-analysis. <i>Journal of Orthopaedic Surgery</i> . 2020;15(1):60.	SR of observational studies

Abbreviations: RCT, randomized controlled trial; SR, systematic review.

Table A12: Selected Excluded Primary Studies—Clinical Evidence

Citation	Primary reason for exclusion
Bauer A, Grunewald M, Eberhardt H, Schulz R, Martus P, Bruggenjurgen B, et al. Ambulatory screening and decontamination to prevent <i>Staphylococcus aureus</i> complications in patients undergoing elective surgery (STAUfrei): study protocol for a controlled intervention study. <i>BMC Infectious Diseases</i> 2020;20(1):95.	Study protocol
D'Journo XB, Falcoz PE, Alifano M, Le Rochais JP, D'Annoville T, Massard G, et al. Oropharyngeal and nasopharyngeal decontamination with chlorhexidine gluconate in lung cancer surgery: a randomized clinical trial. <i>Intensive Care Medicine</i> . 2018 May;44(5):578-87.	Not intervention of interest
Ghaddara HA, Kumar JA, Cadnum JL, Ng-Wong YK, Donskey CJ. Efficacy of a povidone iodine preparation in reducing nasal methicillin-resistant <i>Staphylococcus aureus</i> in colonized patients. <i>American Journal of Infection Control</i> . 2020;48(4):456-9.	Not population of interest
Huang SS, Septimus E, Kleinman K, Moody J, Hickok J, Heim L, et al. Chlorhexidine versus routine bathing to prevent multidrug-resistant organisms and all-cause bloodstream infections in general medical and surgical units (ABATE Infection trial): a cluster-randomized trial. <i>Lancet</i> . 2019;393(10177):1205-15.	Not intervention of interest
Kanwar A, Kumar JA, Ng-Wong YK, Thakur M, Cadnum JL, Alhmidi H, et al. Evaluation of an alcohol-based antiseptic for nasal decolonization of methicillin-resistant <i>Staphylococcus aureus</i> in colonized patients. <i>Infection Control and Hospital Epidemiology</i> . 2019;40(12):1436-7.	Not population of interest
Kline SE, Neaton JD, Lynfield R, Ferrieri P, Kulasingam S, Dittes K, et al. Randomized controlled trial of a self-administered five-day antiseptic bundle versus usual disinfectant soap showers for preoperative eradication of <i>Staphylococcus aureus</i> colonization. <i>Infection Control and Hospital Epidemiology</i> . 2018;39(9):1049-57.	Not comparator of interest
Loftus RW, Dexter F, Goodheart MJ, McDonald M, Keech J, Noiseux N, et al. The effect of improving basic preventive measures in the perioperative arena on <i>Staphylococcus aureus</i> transmission and surgical site infections: a randomized clinical trial. <i>JAMA Network Open</i> 2020;3(3):e201934.	Bundled interventions and usual care; results did not allow delineation of effects of nasal decolonization
Ng BHK, Tang IP, Narayana P, Raman R, Carrau RL. Effects of nasal lavage with and without mupirocin after endoscopic endonasal skull base surgery: a randomized controlled study. <i>Journal of Laryngology and Otology</i> . 2019;133(12):1059-63.	Not intervention of interest

Citation	Primary reason for exclusion
Schlatterer D. CORR Insights: Does preoperative decolonization reduce surgical site infections in elective orthopaedic surgery? A prospective randomized controlled trial. Clinical Orthopaedics and Related Research. 2020;478(8):1801-4.	Commentary

Appendix 4: Summary of Identified Systematic Reviews and Health Technology Assessments Meeting Study Selection Criteria

Table A13: Characteristics of Systematic Reviews and Health Technology Assessments Considered for Inclusion

Author, year, search end date	Population	Intervention(s)	Comparator(s)	Outcome(s)
Banerjee et al, 2017, ³⁴ March 2017	Pre-surgical patients of any age receiving topical antibiotics to prevent skin and wound infections	Topic antibiotics, including mupirocin (Bactroban cream/ ointment)	Placebo, topical antimicrobials compared with each other, oral antibiotics	Clinical effectiveness (infection prevention), safety and harms, antimicrobial resistance
CADTH, 2020, ³⁵ February 2020	Surgical patients, any age	Pre-operative nasal decolonization interventions alone or in combination with pre-operative use of chlorhexidine gluconate washes, wipes, or bathing	Alternative pre-operative interventions for the prevention of SSIs (i.e., nasal decolonization interventions, with or without chlorhexidine gluconate, compared with each other or with alternative, non-nasal decolonization interventions)	Clinical benefits and harms (e.g., SSI rates, adverse events), cost-effectiveness outcomes (e.g., incremental cost-effectiveness ratio, incremental cost-utility ratio, cost per health benefit or event avoided)
Kallen et al, 2005, ³⁶ November 2004	Patients undergoing general or non-general surgery (e.g., cardiothoracic surgery, orthopaedic surgery, neurosurgery)	Perioperative intranasal mupirocin	Usual care	SSIs

Author, year, search end date	Population	Intervention(s)	Comparator(s)	Outcome(s)
Liu et al, 2017, ³⁷ September 2016	People of any age undergoing surgery who were nasal carriers of <i>S. aureus</i>	Nasal decontamination as a single intervention and as part of a bundle of interventions aimed at SSI reduction	No intervention or with placebo; different nasal decontamination interventions; different schedules, timings, or doses of the same nasal decontamination intervention compared with the same topical antibiotics applied with an alternative schedule, timing, or dose	Primary outcomes: SSIs, adverse events Secondary outcomes: <i>S. aureus</i> -related SSIs, other nosocomial MSSA- and MRSA-related infections, 30-day mortality/in-hospital mortality, resource use (including measurements of resource use such as length of hospital stay and re-operation/intervention and length of absence from work/time to return to work), cost (both direct and indirect costs), health-related quality of life
Ma et al, 2017, ³⁸ June 2016	Patients undergoing cardiac or total joint replacement procedures	Patient care bundle, including nasal decolonization, skin decolonization, and additional antiseptic measures	Placebo, no intervention	SSI whether reported as all-cause, infections caused by <i>S. aureus</i> , MSSA, or MRSA

Author, year, search end date	Population	Intervention(s)	Comparator(s)	Outcome(s)
NICE, 2019, ¹⁹ March 2018	People of any age undergoing any surgery, including minimally invasive surgery (i.e., arthroscopic, thoracoscopic, laparoscopic)	The usage and timing of the following treatments with or without a chlorhexidine body wash or glycopeptide prophylaxis: intranasal mupirocin, nasal povidone-iodine solution, chlorhexidine nasal gel, chlorhexidine and neomycin cream (Naseptin), Octensan nasal gel	Placebo, no decolonization, different nasal decolonization procedures	SSIs (superficial, deep incisional, and organ/deep space), including those caused by MSSA and MRSA, defined according to appropriate criteria (e.g., CDC SSI criteria), up to 30 days and 1 year
Schweizer et al, 2013, ³⁹ January 2012	Patients undergoing cardiac surgery or total joint arthroplasty	Nasal decolonization, glycopeptide prophylaxis, or both	Standard care	MSSA- and MRSA-related SSIs
Tang et al, 2020, ⁴⁰ December 2019	People who are <i>S. aureus</i> carriers undergoing different types of surgeries	Diverse measures of decolonization including nasal decolonization	Placebo, no intervention	SSIs
van Rijen et al, 2008, ⁴¹ July 2007	Surgical patients who are nasal <i>S. aureus</i> carriers	Intranasal mupirocin ointment applied before surgery	Placebo, no treatment	Primary outcomes: post-operative <i>S. aureus</i> infection rate (both MSSA and MRSA) Secondary outcomes: rate of infections caused by micro-organisms other than <i>S. aureus</i> , development of mupirocin resistance

Author, year, search end date	Population	Intervention(s)	Comparator(s)	Outcome(s)
van Rijen et al, 2008, ⁴² September 2010 (update)	Surgical patients who are nasal <i>S. aureus</i> carriers	Intranasal mupirocin ointment applied before surgery	Placebo, no treatment, alternative topical treatment	Primary outcomes: post-operative <i>S. aureus</i> infection rate (both MSSA and MRSA) Secondary outcomes: time to infection, mortality, adverse events, rate of infections caused by micro-organisms other than <i>S. aureus</i>
WHO, 2016, ²¹ January 2016	Surgical patients of any age with nasal carriage of <i>S. aureus</i> (either MSSA or MRSA) identified by microbiological culture techniques	Intranasal mupirocin ointment applied before surgery with or without CHG body wash	Placebo, no treatment	<i>S. aureus</i> -related infection rate (overall health care-associated infections and SSIs), SSI-attributable mortality

Abbreviations: CADTH, Canadian Agency for Drugs and Technologies in Health; CDC, US Centers for Disease Control and Prevention; CHG, chlorhexidine gluconate; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; *S. aureus*, *Staphylococcus aureus*; SSI, surgical site infection.

Appendix 5: Selected Excluded Studies—Economic Evidence

For transparency, we provide a list of studies that readers might have expected to see but that did not meet the inclusion criteria, along with the primary reason for exclusion.

Citation	Primary reason for exclusion
Bloom BS, Fendrick AM, Chernew ME, Patel P. Clinical and economic effects of mupirocin calcium on preventing <i>Staphylococcus aureus</i> infection in hemodialysis patients: a decision analysis. <i>Am J Kidney Dis.</i> 1996;27(5):687-94.	Based on non-randomized data
Boelaert JR, De Baere YA, Geernaert MA, Godard CA, Van Landuyt HW. The use of nasal mupirocin ointment to prevent <i>Staphylococcus aureus</i> bacteraemias in haemodialysis patients: an analysis of cost-effectiveness. <i>J Hosp Infect.</i> 1991;19 Suppl B:41-6.	Wrong population
Clancy CJ, Bartsch SM, Nguyen MH, Stuckey DR, Shields RK, Lee BY. A computer simulation model of the cost-effectiveness of routine <i>Staphylococcus aureus</i> screening and decolonization among lung and heart-lung transplant recipients. <i>Eur J Clin Microbiol Infect Dis.</i> 2014;33(6):1053-61.	Based on non-randomized data
Cunha BA, Thekkel V, Schoch P, Cosgrove L. Clinical and cost ineffectiveness of preoperative screening for methicillin-resistant <i>Staphylococcus aureus</i> and intranasal mupirocin in preventing methicillin-resistant <i>S aureus</i> infections in cardiothoracic surgery. <i>Am J Infect Control.</i> 2011;39(3):243-6.	Based on non-randomized data
Davey P. Eradication of nasal carriage of <i>Staphylococcus aureus</i> --is it cost-effective? <i>J Hosp Infect.</i> 1998;40 Suppl B:S31-7.	Review article
Gidengil CA, Gay C, Huang SS, Platt R, Yokoe D, Lee GM. Cost-effectiveness of strategies to prevent methicillin-resistant <i>Staphylococcus aureus</i> transmission and infection in an intensive care unit. <i>Infect Control Hosp Epidemiol.</i> 2015;36(1):17-27.	Based on non-randomized data
Hadi H, Jabalameli M, Bagherifard A, Ghaznavi-Rad E, Behrouzi A, Joorabchi A, et al. <i>Staphylococcus aureus</i> colonization in patients undergoing total hip or knee arthroplasty and cost-effectiveness of decolonization programme. <i>Arch Bone Jt Surg.</i> 2018;6(6):554-9.	Based on non-randomized data
Hong JC, Saraswat MK, Ellison TA, Magruder JT, Crawford T, Gardner JM, et al. <i>Staphylococcus aureus</i> prevention strategies in cardiac surgery: a cost-effectiveness analysis. <i>Ann Thorac Surg.</i> 2018;105(1):47-53.	Based on non-randomized data
Kerbel YE, Sunkerneni AR, Kirchner GJ, Prodromo JP, Moretti VM. The cost-effectiveness of preoperative <i>Staphylococcus aureus</i> screening and decolonization in total joint arthroplasty. <i>J Arthroplasty.</i> 2018;33(7S):S191-S5.	Not a full economic evaluation (break-even analysis only)

Citation	Primary reason for exclusion
Kirchner GJ, Ghazaryan H, Lieber AM, Sunkerneni AR, McKinnon BJ. Cost-effectiveness of preoperative <i>Staphylococcus aureus</i> screening and decolonization in cochlear implantation. <i>OTO Open</i> . 2019;3(3):2473974X19866391.	Not a full economic evaluation (break-even analysis only)
Lee BY, Song Y, McGlone SM, Bailey RR, Feura JM, Tai JH, et al. The economic value of screening haemodialysis patients for methicillin-resistant <i>Staphylococcus aureus</i> in the USA. <i>Clin Microbiol Infect</i> . 2011;17(11):1717-26.	Wrong population
Lee BY, Wiringa AE, Bailey RR, Goyal V, Lewis GJ, Tsui BY, et al. Screening cardiac surgery patients for MRSA: an economic computer model. <i>Am J Manag Care</i> . 2010;16(7):e163-73.	Wrong population
Noskin GA, Rubin RJ, Schentag JJ, Kluytmans J, Hedblom EC, Jacobson C, et al. Budget impact analysis of rapid screening for <i>Staphylococcus aureus</i> colonization among patients undergoing elective surgery in US hospitals. <i>Infect Control Hosp Epidemiol</i> . 2008;29(1):16-24.	Not a full economic evaluation
Robotham JV, Graves N, Cookson BD, Barnett AG, Wilson JA, Edgeworth JD, et al. Screening, isolation, and decolonisation strategies in the control of methicillin resistant <i>Staphylococcus aureus</i> in intensive care units: cost effectiveness evaluation. <i>BMJ</i> . 2011;343:d5694.	Wrong population
Slover J, Haas JP, Quirno M, Phillips MS, Bosco JA, 3rd. Cost-effectiveness of a <i>Staphylococcus aureus</i> screening and decolonization program for high-risk orthopedic patients. <i>J Arthroplasty</i> . 2011;26(3):360-5.	Based on non-randomized data
Stambough JB, Nam D, Warren DK, Keeney JA, Clohisy JC, Barrack RL, et al. Decreased hospital costs and surgical site infection incidence with a universal decolonization protocol in primary total joint arthroplasty. <i>J Arthroplasty</i> . 2017;32(3):728-34.e1.	Based on non-randomized data
Tonotsuka H, Sugiyama H, Amagami A, Yonemoto K, Sato R, Saito M. What is the most cost-effective strategy for nasal screening and <i>Staphylococcus aureus</i> decolonization in patients undergoing total hip arthroplasty? <i>BMC Musculoskelet Disord</i> . 2021;22(1):129.	Based on non-randomized data
Torres EG, Lindmair-Snell JM, Langan JW, Burnikel BG. Is preoperative nasal povidone-iodine as efficient and cost-effective as standard methicillin-resistant <i>Staphylococcus aureus</i> screening protocol in total joint arthroplasty? <i>J Arthroplasty</i> . 2016;31(1):215-8.	Based on non-randomized data

Appendix 6: Results of Applicability and Limitation Checklists for Studies Included in the Economic Literature Review

Table A14: Assessment of the Applicability of Studies Evaluating the Cost-Effectiveness of Nasal Decolonization of *Staphylococcus aureus* for People Undergoing Surgery

Author, year, country	Is the study population similar to the question?	Are the interventions similar to the question?	Is the health care system studied sufficiently similar to Ontario?	Were the perspectives clearly stated? If yes, what were they?	Are all direct effects included? Are all other effects included where they are material?	Are all future costs and outcomes discounted? If yes, at what rate?	Is the value of health effects expressed in terms of quality-adjusted life-years?	Are costs and outcomes from other sectors fully and appropriately measured and valued?	Overall judgment ^a
Courville et al, 2012, United States ⁵⁸	Yes	Yes	Yes	Yes, societal	Yes	No, 1-year time horizon	No	Yes	Partially applicable
Wassenberg et al, 2011, Netherlands ⁵⁹	Yes	Yes	Yes	Yes, societal	Yes	Yes, 3%	No	Yes	Partially applicable
Young and Winston, 2006, United States ⁶⁰	Yes	Yes	Yes	Yes, societal	Yes	No, 3-month time horizon	No	Yes	Partially applicable
NICE, 2019, United Kingdom ⁶¹	Yes	Yes	Yes	Yes, NHS	Yes	Yes, 3.5%	Yes	NA	Directly applicable

Abbreviations: NHS, National Health Service; NICE, National Institute for Health and Care Excellence.

Note: Response options for all items were "yes," "partially," "no," "unclear," and "NA" (not applicable).

^aOverall judgment may be "directly applicable," "partially applicable," or "not applicable."

Table A15: Assessment of the Limitations of Studies Assessing the Cost-Effectiveness of Nasal Decolonization of *Staphylococcus aureus* for People Undergoing Surgery

Author, year, country	Does the model structure adequately reflect the nature of the health condition under evaluation?	Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Are all important and relevant health outcomes included?	Are the clinical inputs ^a obtained from the best available sources?	Do the clinical inputs ^a match the estimates contained in the clinical sources?	Are all important and relevant costs included in the analysis?	Are the estimates of resource use obtained from the best available sources?	Are the unit costs of resources obtained from the best available sources?	Is an appropriate incremental analysis presented, or can it be calculated from the reported data?	Are all important and uncertain parameters subjected to appropriate sensitivity analysis?	Is there a potential conflict of interest?	Overall judgment ^b
Courville et al, 2012, United States ⁵⁸	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Minor limitations
Wassenberg et al, 2011, Netherlands ⁵⁹	No (no model constructed)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Minor limitations
Young and Winston, 2006, United States ⁶⁰	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Minor limitations
NICE, 2019, United Kingdom ⁶¹	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Minor limitations

Abbreviation: NICE, National Institute for Health and Care Excellence.

Note: Response options for all items were "yes," "partially," "no," "unclear," and "NA" (not applicable).

^aClinical inputs include relative treatment effects, natural history, and utilities.

^bOverall judgment may be "minor limitations," "potentially serious limitations," or "very serious limitations."

Appendix 7: Letter of Information

LETTER OF INFORMATION



Ontario Health is conducting a review of **Nasal Decolonization**. The purpose is to understand whether this should be publicly funded in Ontario.

An important part of this review involves gathering perspectives of patients and caregivers with experience with surgery and infection control procedures that may or may not have used nasal decolonization.

WHAT DO YOU NEED FROM ME

- ✓ Willingness to share your story
- ✓ 30 minutes of your time for a phone
- ✓ Permission to audio- (not video-) record the interview

WHAT YOUR PARTICIPATION INVOLVES

If you agree to share your experiences, you will be asked to have an interview with Ontario Health staff. The interview will last about 30 minutes. It will be held over the telephone. With your permission, the interview will be audio-taped. The interviewer will ask you questions about your or your loved one's condition and your perspectives about treatment options in Ontario.

Participation is voluntary. You may refuse to participate, refuse to answer any questions or withdraw before or at any point during your interview. Withdrawal will in no way affect the care you receive.

CONFIDENTIALITY

All information you share will be kept confidential and your privacy will be protected except as required by law. The results of this review will be published, however no identifying information will be released or published. Any records containing information from your interview will be stored securely until project completion. After the project completion, the records will be destroyed.

RISKS TO PARTICIPATION

There are no known physical risks to participating. Some participants may experience discomfort or anxiety after speaking about their experience.

IF YOU ARE INTERESTED, PLEASE CONTACT US BEFORE NOVEMBER 1, 2021:

Appendix 8: Interview Guide

Interview Guide: Nasal decolonization

Explain Ontario Health purpose, HTA process, and purpose of interview

I would like your permission to have an audio recording of this conversation so I can use your direct quotes and other information from this conversation to make a case for the decision makers. Your name or any other identifiers will not be placed in the report or the presentation and your privacy and your confidentiality will be protected. So do I have your permission to audio record this conversation?

Intro

Explain HTA process, and purpose of interview

Lived Experience

Type of surgery and when

Feelings about surgery , concerns going into surgery

Impact on quality of life? (Loss of independence?)

Impact on loved ones/caregivers, work, etc.?

Therapies

Were you informed of the risks of infection going into surgery

Pre-operative care - how did you prep: in hospital vs at home, what infection control measures were used - bathing, hair removal from surgical area, etc.

Was nasal decolonization used?

Discharge information-signs of infection

Nasal decolonization general

One of the ways to reduce surgical wound infections is by a process called Nasal Decontamination. The **first** method of nasal decontamination involves you placing an ointment in the nose twice daily for 5 days before your surgery. The **second** method involves a solution being placed in both nostrils by staff 2 hours prior to your surgery. Of the 2 options above, which option would you prefer.

There are 2 main processes on how nasal decontamination is done in hospitals. The **first** involves screening a patient to see if they are carriers of the Staphylococcus aureus bacteria which can cause surgical wound infections. If they are carriers, an antibiotic or antiseptic ointment is place in the nose to kill the bacteria. The **second** involves universally providing all patients undergoing surgery an antibiotic or antiseptic ointment in the nose. Which option would you prefer?

Nasal decolonization experience

What method was used?

Any side effects or reactions?

Do you have a preference on the type of method or ointment used: cream, lotion, solution, gel, tincture, foam, paste, powder, and gauze

Surgical Wound Infection

Is prevention of surgical wound infections important to you

Are you familiar with infections that are resistant to anti-biotics= where did you hear about it, was it a fear you had?

For patients who developed an SSI (if applicable)

How did the infection impact you?

Treatment and care journey? - hospital readmission or increased stay, impact on original surgery

Quality of life

Impact on loved ones

How did you feel when diagnosed?

What treatment options were you offered?

How was the treatment process? Were there any issues with accessibility?

Lived- Experience for those who developed SSI (if applicable)

Day-to-day routine- work, home life

What is the impact on your quality of life? (Loss of independence?)

Impact on loved-ones/caregivers, work, etc?

Mental health

Anything else you want to add

Appendix 9: Online Survey

Which of the following applies to you (select all that apply):

- I had surgery
- I am a caregiver/ family member to someone that had surgery
- Other

What type of surgery did you (or your family member) have:

When did you (or your family member) have your last surgery

- 6 months ago
- A year ago
- 2 years
- 3+ years ago

Were you (or your family member) informed of the risk surgical infections prior to surgery?

- Yes
- No
- I don't remember

What were your (or your family member) concerns going into surgery (select all that apply)

- Getting a surgical infection
- Pain after the operation
- Excess bleeding
- Fear of surgery not working
- Recovery time
- I had no concerns
- I don't remember
- Other

What methods were used to prevent infection before your (or your family member's) surgery (select all that apply)?

- Cleaning of the surgical site
- Given Antibiotics
- Swab with an ointment placed in the nose
- Hair removal
- Information on smoking cessation
- Information on controlling your blood glucose levels (if diabetic)
- Information on how to take care of your surgical wound
- Other
- I don't remember

How important are measure that prevent surgical infections to you?

- Extremely important, Very important, Important, Somewhat Important, Not Important At All

Have you heard about infections that are resistant to antibiotics?

- Yes
- No

Where did you hear about bacterial resistant infection? Select all that apply

Media (TV, Radio)

Social Media (facebook, twitter)

From friends, relatives, acquaintances

Physician

Other

Was getting a bacterial resistant infection a fear you (or your family member) had going into surgery.

Yes

No

I cant remember

In your lifetime, have you experienced a surgical infection

Yes

No

If yes:

If you are interested in sharing your experience with a surgical infection, please email ___ to book an interview.

Please feel free to share any additional thoughts you have with us about the surgical infections.

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