National Institute for Health and Care Excellence

Guideline version (FINAL)

Surgical site infection: prevention and treatment

[B] Evidence review for the effectiveness of skin antiseptics in the prevention of surgical site infection

NICE guideline NG125

Evidence reviews

April 2019

FINAL

These evidence reviews were developed by NICE Guideline Updates Team

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Effectiveness of preoperative skin antiseptics in the prevention of surgical site infection

Review question

Is the use of preoperative skin antiseptics clinically effective in the prevention of surgical site infection?

Introduction

Skin antiseptics are antimicrobial agents that can slow or stop the growth of microorganisms. These are routinely used to cleanse the skin before a surgical incision is made to reduce endogenous bacteria present on the skin. The aim of this procedure is to reduce the risk of surgical site infection. There are a number of different skin antiseptics which can be used. Skin antiseptics can also be available in both alcohol and aqueous preparations.

The 2008 NICE guideline on the prevention and treatment of surgical site infection recommended for the skin at the surgical site to be prepared immediately before skin incision using an antiseptic (aqueous or alcohol-based) preparation, with povidone iodine and chlorhexidine being identified as most suitable. The recommendations also stated that if diathermy is to be used, it should be ensured that antiseptic skin preparations are dried by evaporation and pooling of alcohol-based preparations is avoided. Since the publication of this guideline, new evidence has become available that might impact on these recommendations. Therefore, this research question is being updated. This review question does not focus on intestinal or urinary tract decolonisation.

This review identified studies that fulfilled the conditions specified in PICO table. For full details of the review protocol, see appendix A.

Table 1 PICO table: Is the use of preoperative skin antiseptics clinically effective in the prevention of surgical site infection?

Population	People of any age undergoing any surgery, including minimally invasive surgery (arthroscopic, thoracoscopic and laparoscopic surgery)

Interventions	Following interventions used for wound antisepsis:
	• Iodine at various concentrations in alcohol and aqueous preparations
	• Iodophors including:
	  ○ iodophor films
	  ○ povidone iodine in alcohol and aqueous preparations
	  ○ aqueous iodophor scrub and paint
	  ○ aqueous iodophor one-step preparation with polymer
	  ○ alcoholic iodophor with water insoluble polymer
	• Alcohol at various concentrations

	• Chlorhexidine in alcohol and aqueous preparations, including chlorhexidine gluconate
Comparator	• Interventions compared to each other including alcohol based antiseptic solutions compared with aqueous solutions. • Single preparation of an intervention compared to double preparation of the same intervention

Outcomes	• Surgical site infection (superficial, deep and organ/space SSI), including SSIs up to 30 days and 1 year, defined using appropriate criteria such as CDC SSI criteria.
	• Mortality post-surgery
	• Length of hospital stay
	• Postoperative antibiotic use
	• Hospital readmission
	• Infectious complications such as septicaemia or septic shock
	• Adverse events:
	  ○ Antimicrobial resistance
	  ○ Anaphylaxis
	  ○ Skin and other allergic reactions.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual (2014). Methods specific to this review question are described in the review protocol in appendix B.

Declarations of interest were recorded according to NICE's 2018 conflicts of interest policy.

A search strategy was used to identify all studies which examined the effectiveness of skin antiseptics (outlined in Table 1) applied to the skin prior incision to reduce the risk of SSIs. Additionally, an available Cochrane review (Dumville 2015) which examined the effectiveness of skin antiseptics prior to clean surgery was used as an additional source of studies and information. The search strategies used in this review are detailed in appendix C.

Randomised controlled trials (RCTs) and systematic reviews of RCTs were considered for inclusion. The review protocol specified that in the event of less than 5 RCTs being identified, quasi randomised trials would also be considered for inclusion.

Studies were also excluded if they:

- Included patients undergoing a surgical procedure that does not involve a visible incision and therefore does not result in the presence of a conventional surgical wound
- were not in English

- were not full reports of the study (for example, published only as an abstract)

Data on the incidence of SSI was extracted. Where possible, data on superficial, deep and organ space SSI was also examined. According to the Centres for Disease Control and Prevention (CDC) an SSI is defined as an infection occurring within 30 days after operation. A deep SSI is defined as an infection which occurs within 30 days after the operation if no implant is left in place, or within 1 year if an implant is inserted. Therefore SSIs reported within 30 days and 1 year were prioritised in this review.

Studies included in the review explored a number of different follow up periods including within 30 days after surgery. In terms of pairwise analyses, meta- analyses was conducted combining data from different follow up periods. Additional subgroup analyses were conducted which examined data based on the follow up period.

Furthermore, surgery and surgical wounds can be classified as the following:

- Clean –incision in which no inflammation is encountered in a surgical procedure, without a break in sterile technique, and during which the respiratory, alimentary and genitourinary tracts are not entered.
- Clean-contaminated – an incision through which the respiratory, alimentary or genitourinary tract is entered under controlled conditions but with no contamination encountered.
- Contaminated – an incision undertaken during an operation in which there is a major break in sterile technique or gross spillage from the gastrointestinal tract, or an incision in which acute, non-purulent inflammation is encountered. Open traumatic wounds that are more than 12–24 hours old also fall into this category
- Dirty or infected – an incision undertaken during an operation in which the viscera are perforated or when acute inflammation with pus is encountered during the operation (for example, emergency surgery for faecal peritonitis), and for traumatic wounds where treatment is delayed, and there is faecal contamination or devitalised tissue present.

Where available data on surgical wound classification was extracted. Studies which provided adequate information, data on different surgical wound classifications was calculated. Additionally, Dumville (2015) was used to extract data on clean surgeries. Where possible, subgroup analysis based on surgical wound classification was conducted.

With the review examining a number of interventions, pairwise meta-analysis of direct evidence alone was of limited use. Therefore a network-meta analysis was conducted to combine all direct and indirect evidence to produce estimate of relative effectiveness for all comparators in the reduction in SSI and the ranking of different interventions.

Three different approaches were utilised to model the SSI dataset. Firstly, a ‘split’ approach was taken where data was modelled based on application and concentration. A ‘lumped’ approach was also further utilised to construct a simpler model which disregarded any heterogeneity of concentration and application. Lastly, a simpler model of the 4 node ‘lumped’ network was constructed using a meta-regression approach.

General methods relating to network meta-analysis are descried in appendix B. Information on methods specific to this particular analysis and on model selection can be found in appendix H.

Clinical evidence

Included studies

From a database of 3,808 studies, 110 studies were identified, which included a Cochrane review (Dumville 2015) as being potentially relevant. Dumville 2015 was also used as an additional source of studies. 2 further studies [Berry 1982 and Howard 1991] were identified through Dumville 2015. Additionally, 1 study [Roberts 1995] was also identified through CG74 2008 guideline and also appeared in Dumville 2015.

Following the full text review of 112 studies, 28 RCTs were included. Full text versions of 2 studies [Howard 1991 and Roberts 1995] identified through Dumville 2015 and CG74 2008 guideline could not be obtained. Information on these 2 studies were adapted from Dumville (2015). The NICE CG74 2008 guideline was also used to extract information from Roberts 1995. The process of study identification is summarised in the diagram in appendix D.

Overall, the 28 studies identified explored a number of different interventions. As a number of different preparations and concentrations were identified. Additionally, studies exploring iodophors such as povidone iodine were identified. The interventions were grouped in the following manner:

- Alcohol alone
- Iodine in various alcohol preparations
- Aqueous chlorhexidine:
    - Aqueous chlorhexidine scrub (4%) and paint (2%)
    - 0.5% chlorhexidine in aqueous solution
- Aqueous povidone iodine:
    - 5% Aqueous povidone iodine
    - 10% aqueous povidone iodine
    - Aqueous Povidone Iodine scrub (7.5%) and paint (10%)
- Chlorhexidine in alcohol preparation:
    - 0.5% chlorhexidine with 70% alcohol
    - 2% or 2.5% chlorhexidine with 70% alcohol
    - 4% chlorhexidine with 70% alcohol
- Povidone iodine (including other iodophors) in alcohol preparation:
    - 8.3% povidone iodine in 72.5% alcohol
    - 10% povidone iodine in alcohol
    - Iodophor (0.7%) in alcohol (74%)

Excluded studies

List of papers excluded at full text, with reasons for exclusion, is given in Appendix L.

Summary of clinical studies included in the evidence review

The included studies are summarised in Table 2 below. See appendix E for full evidence tables.

Table 2. Summary table of included studies

Short Title	Title	Study details	Interventions	Comparator	Outcome measure(s)
Abreu (2014)	Surgical site infection in surgery for benign prostatic hyperplasia: comparison of two skin antiseptics and risk factors	• Study location Uruguay • Study setting Department of urology • Study dates February 2009-August 2009 • Duration of follow-up All patients had a minimum postoperative follow up of 3 years • Sources of funding Not reported.	•Chlorhexidine in alcohol preparation 0.5% chlorhexidine in an alcohol base (Chemisol) Assumed to be in 70% isopropyl alcohol.	• Aqueous Povidone Iodine Aqueous 5% povidone iodine	• SSI
Alexander (1985)	Development of a safe and effective one-minute preoperative skin preparation	• Study location USA • Study setting Hospital setting • Study dates Overall: 1981-July 1984 Preliminary 2 study: 1982-1983 Definitive study: 1983-1984 • Duration of follow-up within 30 days of surgery • Sources of funding Not specified.	• Alcohol Preliminary study 2: 70% alcohol Definitive study: 70% alcohol • Iodine in alcohol Preliminary study 2: 2% iodine in 50% alcohol 2% iodine in 70% alcohol 2% iodine in 90% alcohol		• SSI
Berry (1982)	A comparison of the use of povidone-iodine and chlorhexidine in the prophylaxis of postoperative wound infection.	• Study location UK • Study setting Hospital setting • Study dates May 1978 and February 1980 • Duration of follow-up At time of discharge • Sources of funding Not reported.	• Chlorhexidine in alcohol preparation 0.5% chlorhexidine in spirit	• Povidone iodine in alcohol preparation 10% Povidone iodine in alcohol	• SSI
Bibbo (2005)	Chlorhexidine provides superior skin decontaminati on in foot and ankle surgery:	• Study location USA • Study setting Department of orthopaedics • Study dates	• Aqueous povidone iodine scrub and paint	• Aqueous Chlorhexidine scrub and paint Aqueous chlorhexidine	• SSI

Short Title	Title	Study details	Interventions	Comparator	Outcome measure(s)
	a prospective randomized study	Not specified. • Duration of follow-up Not reported. • Sources of funding Not reported.	Aqueous 7.5% povidone iodine and 10% paint	gluconate (4%) and isopropyl alcohol (70%)	
Bibi (2015)	Is chlorhexidine-gluconate superior than Povidone-Iodine in preventing surgical site infections? A multicenter study	• Study location Pakistan • Study setting Two public-sector hospitals • Study dates May 2012 and April 2013 • Duration of follow-up Until 30 days. • Sources of funding Grant received from Pakistan Research Council	• Chlorhexidine in alcohol preparation 2% chlorhexidine gluconate in 70% isopropyl alcohol	• Aqueous Povidone Iodine 10% Povidone Iodine	• SSI • Skin and other allergic reactions
Broach (2017)	Randomized Controlled Trial of Two Alcohol-based Preparations for Surgical Site Antisepsis in Colorectal Surgery	• Study location USA • Study setting Hospital setting • Study dates January 2011 and January 2015 • Duration of follow-up Within 30 days post discharge • Sources of funding Not reported.	• Iodophor in alcohol 0.7% available iodine with 74% isopropyl alcohol (Duraprep).	• Chlorhexidine in alcohol preparation 2% chlorhexidine and 70% isopropyl	• SSI • Superficial SSI • Deep SSI • Organ/space SSI • Length of hospital stay • Cellulitis
Brown (1984)	A clinical evaluation of chlorhexidine gluconate spray as compared with iodophor scrub for preoperative skin preparation	• Study location USA • Study setting University Hospital • Study dates December 1979 and November 1980 • Duration of follow-up In-hospital follow up • Sources of funding Not reported	• Chlorhexidine in alcohol preparation 0.5% chlorhexidine with 70% isopropyl alcohol	• Aqueous Povidone iodine scrub and paint Aqueous povidone iodine scrub (7.5%) and paint (assumed to be 10%).	• SSI
Casey (2015)	A comparison of the efficacy of 70% v/v	• Study location UK • Study setting	• Chlorhexidine in alcohol preparation	• Chlorhexidine in alcohol	• Superficial SSI

Short Title	Title	Study details	Interventions	Comparator	Outcome measure(s)
	isopropyl alcohol with either 0.5% w/v or 2% w/v chlorhexidine gluconate for skin preparation before harvest of the long saphenous vein used in coronary artery bypass grafting	Hospital setting • Study dates Not reported • Duration of follow-up Within 30 days after surgery • Sources of funding Not reported	0.5% chlorhexidine with 70% isopropyl alcohol	preparation 2% chlorhexidine with 70% isopropyl alcohol (ChloraPrep)	
Charles (2017)	Alcoholic versus aqueous chlorhexidine for skin antisepsis: the AVALANCHE trial	• Study location Australia • Study setting 4 private general practices • Study dates October 2015 to August 2016 • Duration of follow-up within 30 days after surgery • Sources of funding Study received funding from Royal Australian College of General Practitioners, a Royal Australian College of General Practitioners Family Medical Care Education and Research Grant, the Mackay Private Practitioners Fund and James Cook University Honours Program grant.	• Chlorhexidine in alcohol preparation 0.5% chlorhexidine with 70% ethanol	• Aqueous chlorhexidine 0.5% chlorhexidine in aqueous solution	• SSI • Adverse events
Cheng (2009)	Quantitative analysis of bacteria in forefoot surgery: a comparison of skin	• Study location UK • Study setting Hospital setting • Study dates August 2007 and January 2008 • Duration of	• Povidone iodine in alcohol preparation 10% povidone iodine in isopropyl alcohol	• Chlorhexidine in alcohol preparation 0.5% chlorhexidine with 70%	• SSI

Short Title	Title	Study details	Interventions	Comparator	Outcome measure(s)
	preparation techniques	follow-up not specified. • Sources of funding Not specified.		isopropyl alcohol	
Darouiche (2010)	Chlorhexidine-Alcohol versus Povidone-Iodine for Surgical-Site Antisepsis	• Study location USA • Study setting 6 university affiliated hospitals • Study dates April 2004 and May 2008 • Duration of follow-up Within 30 days after surgery • Sources of funding Research and educational grants from Cardinal Health.	• Chlorhexidine in alcohol preparation 2% Chlorhexidine gluconate and 70% isopropyl alcohol (Chloraprep, Cardinal Health).	• Aqueous Povidone iodine scrub and paint Aqueous 7.5% povidone iodine scrub and 10% paint (Care skin prep tray, Cardinal Health).	• SSI • Superficial SSI • Deep SSI • Organ/space SSI • Sepsis from SSI
Ellenhorn (2005)	Paint-only is equivalent to scrub-and-paint in preoperative preparation of abdominal surgery sites	• Study location USA • Study setting Cancer Centre • Study dates Not specified. • Duration of follow-up within 30 days after surgery • Sources of funding Not specified.	• Aqueous povidone iodine scrub and paint Aqueous povidone iodine scrub (7.5%) and paint (10%)	• Aqueous Povidone Iodine Aqueous 10% povidone iodine	• SSI
Gilliam (1990)	Comparison of a one-step iodophor skin preparation versus traditional preparation in total joint surgery	• Study location USA • Study setting Department of othopaedic Surgery • Study dates Not specified. • Duration of follow-up Not specified. • Sources of funding Not specified.	• Aqueous povidone iodine scrub and paint Aqueous povidone iodine scrub (7.5%) and paint (10%) (assumed)	• Iodophor in alcohol 0.7% available iodine and 74% isopropyl alcohol (assumed) - DuraPrep	• SSI
Howard (1991)	Comparison of a 10 minute aqueous iodophor and 2 minute water-insoluble	• Study location USA • Duration of follow-up at least 30 days postoperatively	• Aqueous povidone iodine scrub and paint	• Iodophor in alcohol Iodophor in alcohol (DuraPrep)	• SSI

Short Title	Title	Study details	Interventions	Comparator	Outcome measure(s)
	iodophor in alcohol preoperative skin preparation.		Aqueous povidone iodine (7.5%) scrub and paint (10%)		
Kunkle (2015)	Chlorhexidine gluconate versus povidone iodine at cesarean delivery: a randomized controlled trial	• Study location USA • Study setting Department of obstetrics and gynecology • Study dates Not specified. • Duration of follow-up 2 weeks • Sources of funding Not reported.	• Chlorhexidine in alcohol preparation 2% chlorhexidine with 70% isopropyl alcohol (Chloraprep)	• Aqueous Povidone Iodine Aqueous povidone iodine scrub (7.5%) and paint (10%) assumed.	• SSI
Ngai (2015)	Skin Preparation for Prevention of Surgical Site Infection After Cesarean Delivery: A Randomized Controlled Trial	• Study location USA • Study setting Medical Centre labour and delivery units • Study dates January 2013 through July 2014 • Duration of follow-up within 30 days of discharge • Sources of funding Not reported.	• Chlorhexidine in alcohol preparation 2% chlorhexidine gluconate with 70% isopropyl alcohol	• Povidone iodine in alcohol preparation 8.3% povidone iodine with 72.5% isopropyl alcohol	• SSI. • Superficial SSI • Deep SSI • Organ/space SSI
Paocharoe n (2009)	Comparison of surgical wound infection after preoperative skin preparation with 4% chlorhexidine [correction of chlohexidine] and povidone iodine: a prospective randomized trial	• Study location Bangkok, Thailand • Study setting Department of surgery • Study dates June 2006 and November 2008 • Duration of follow-up 1 month after surgery • Sources of funding Not reported	• Aqueous povidone iodine scrub and paint Aqueous 7.5% povidone iodine scrub followed by aqueous 10% povidone iodine paint	• Aqueous Chlorhexidine scrub and paint 4% chlorhexidine in 70% isopropyl alcohol (Hibitane) scrub followed by hibitane paint	• SSI
Park (2017)	Randomized clinical trial of preoperative skin antisepsis with	• Study location South Korea • Study setting Centre for Liver Cancer	• Aqueous chlorhexidine scrub and paint	• Aqueous Povidone iodine scrub and paint	• SSI • Superficial SSI • Deep SSI •

Short Title	Title	Study details	Interventions	Comparator	Outcome measure(s)
	chlorhexidine gluconate or povidone-iodine	• Study dates October 2011 to October 2014 • Duration of follow-up SSI at 30 days after surgery • Sources of funding Not reported	4% chlorhexidine soap and then painted with aqueous solution of 2% chlorhexidine.	7.5% povidone iodine and then painted with an aqueous solution of 10% PI.	Organ/space SSI
Roberts (1995)	Skin preparation in CA BG surgery: A prospective randomized trial	• Study location USA • Duration of follow-up 30 days • Sources of funding Not reported	• Aqueous povidone iodine scrub and paint Aqueous povidone iodine (7.5%) and paint (10%) (assumed)	• Iodophor in alcohol Iodophor in alcohol (DuraPrep)	• SSI
Saltzman (2009)	Efficacy of surgical preparation solutions in shoulder surgery	• Study location USA • Study setting Hospital setting • Study dates September 2007 and February 2008 • Duration of follow-up 10 months after surgery • Sources of funding Funding/ grant from Enturia.	• Chlorhexidine in alcohol preparation 2% chlorhexidine gluconate and 70% isopropyl alcohol (ChloraPrep) • Aqueous povidone iodine scrub and paint Aqueous povidone iodine (7.5%) scrub and paint (10%) • Iodophor in alcohol 0.7% iodophor and 74% isopropyl alcohol (DuraPrep)		• SSI
Savage (2012)	Efficacy of surgical preparation solutions in lumbar spine surgery	• Study location USA • Study setting University of Orthopaedic surgery and neurological surgery • Study dates February to August 2010 • Duration of follow-up 6 months after surgery. • Sources of funding External funding obtained from 3M, the company that manufactures DuraPrep.	• Iodophor in alcohol 0.7% available iodine and 74% isopropyl alcohol (DuraPrep)	• Chlorhexidine in alcohol preparation 2% chlorhexidine gluconate with 70% isopropyl alcohol (ChloraPrep)	• SSI

Short Title	Title	Study details	Interventions	Comparator	Outcome measure(s)
Segal (2002)	Preoperative skin preparation of cardiac patients	• Study location USA • Study setting Hospital setting • Study dates Not specified. • Duration of follow-up Patients were followed for up to 6 weeks postoperatively • Sources of funding Not specified	• Aqueous povidone iodine Aqueous (10%) povidone iodine • Aqueous povidone iodine scrub and paint Aqueous povidone iodine (7.5%) 5 minute scrub with paint (10%) • Iodophor in alcohol 0.7% available iodine and 74% isopropyl alcohol		• SSI
Sistla (2010)	Minimizing wound contamination in a 'clean' surgery: comparison of chlorhexidine-ethanol and povidone-iodine	• Study location India • Study setting Medical centre • Study dates Not reported. • Duration of follow-up within 30 days after surgery • Sources of funding Not reported.	• Aqueous povidone iodine Aqueous 10% povidone iodine	• Chlorhexidine in alcohol preparation 2.5% chlorhexidine with 70% ethanol	• SSI
Springel (2017)	A randomized open-label controlled trial of chlorhexidine-alcohol vs povidone-iodine for cesarean antisepsis: the CAPICA trial	• Study location USA • Study setting Urban tertiary care institution • Study dates March 2014 to June 2016 • Duration of follow-up Within 30 days after delivery • Sources of funding Not reported	• Chlorhexidine in alcohol preparation 2% chlorhexidine gluconate in 70% isopropyl alcohol paint (Chloraprep).	• Aqueous Povidone iodine scrub and paint Povidone-iodine aqueous scrub (0.75% available iodine solution) followed by povidone iodine aqueous paint (1.0% available iodine solution, wet skin scrub preparation tray).	• SSI. • Superficial SSI • Deep SSI •Organ/space SSI • Skin and other allergic reactions
Srinivas (2015)	Comparison of the efficacy of chlorhexidine gluconate versus povidone iodine as preoperative skin preparation for the prevention of surgical site	• Study location India • Study setting Department of General Surgery • Study dates January 2011 to June 2012 • Duration of follow-up Within 30 days after surgery	• Chlorhexidine in alcohol preparation 0.5% chlorhexidine gluconate with 70% isopropyl alcohol	• Aqueous Povidone Iodine 5% povidone iodine	• SSI • Superficial SSI • Deep SSI •Organ/space SSI

Short Title	Title	Study details	Interventions	Comparator	Outcome measure(s)
	infections in clean-contaminated upper abdominal surgeries	• Sources of funding Not reported			
Tuuli (2016)	A Randomized Trial Comparing Skin Antiseptic Agents at Caesarean Delivery	• Study location USA • Study setting Department of Obstetrics and Gynaecology • Study dates September 2011 through June 2015 • Duration of follow-up Within 30 days after caesarean delivery. • Sources of funding Supported by a Woman's Reproductive Health Research Career development grant from Eunice Kennedy Shriver National institute of child health and human development of National institutes of Health.	• Chlorhexidine in alcohol preparation 2% chlorhexidine gluconate with 70% isopropyl alcohol	• Povidone iodine in alcohol preparation 8.3% povidone iodine with 72.5% isopropyl alcohol	• SSI • Superficial SSI • Deep SSI • Skin and other allergic reactions
Xu (2017)	Prospective Randomized Trial Comparing the Efficacy of Surgical Preparation Solutions in Hand Surgery	• Study location USA • Study setting Department of orthopaedics • Study dates May 2013 to August 2014 • Duration of follow-up 6 weeks of surgery • Sources of funding Funding for study via the University of Pittsburgh Department of Orthopaedics and a grants from the	• Chlorhexidine in alcohol preparation 2% chlorhexidine gluconate and 70% isopropyl alcohol (Chloraprep, Enturia) • Aqueous povidone iodine Aqueous 10% povidone iodine (Betadine) • Iodophor in alcohol 0.7% available iodine and 74% isopropyl alcohol		• SSI

Short Title	Title	Study details	Interventions	Comparator	Outcome measure(s)
		Pittsburgh Foundation, and a National Institutes of Health grant.			
Zdeblick (1986)	Preoperative use of povidone-iodine. A prospective, randomized study	• Study location USA • Study setting Hospital setting • Study dates Not specified. • Duration of follow-up Not specified. • Sources of funding Not specified.	• Aqueous povidone iodine scrub and paint Aqueous povidone iodine scrub (7.5%) and paint (10%) (assumed)	• Aqueous Povidone Iodine Aqueous 10% povidone iodine (assumed)	• SSI

See appendix E for full evidence tables.

Quality assessment of clinical studies included in the evidence review

All studies included in the review were RCTs. A number of studies demonstrated unclear blinding of participants and personnel however, as the outcomes measures were objective, these studies were not downgraded in this domain. Studies were mainly downgraded for unclear random sequence generation, allocation concealment and blinding of outcome assessment.

Full texts of Howard 1991 and Roberts 1995 could not be obtained. Therefore, information on the quality of evidence was identified through Dumville 2015.

A number of studies included in the review classified infections using different criteria including the Centres for Disease Control and Prevention (CDC) SSI criteria. Studies which did not explicitly describe criteria used for the classification of infection were downgraded for serious indirectness.

Outcomes at a number of different follow-up periods were reported in the studies included. Studies which did not specify a follow-up period were downgraded for serious indirectness. In such studies the follow-up period was assumed be the postoperative phase.

See appendix G for full GRADE tables.

Economic evidence

Included studies

A literature search was conducted to identify cost–utility analyses comparing different types of preoperative skin antiseptics. Standard health economic filters were applied to a clinical search, returning a total of 2,248 citations. Following review of all titles and abstracts, 9 studies were identified as being potentially relevant to this decision problem, and were ordered for full review. After reviewing the full texts, 1 study was included as economic evidence for this decision problem. The selection process is illustrated in Appendix I.

Excluded studies

Studies that were excluded upon full review are listed in Appendix L, including the primary reason for exclusion.

Summary of studies included in the economic evidence review

A summary of the economic evidence is provided below. An economic evidence profile is provided in Appendix J.

Lee et al. (2010) conducted a systematic review and cost analysis comparing chlorhexidine 2% in 70% isopropyl alcohol solution with single-preparation aqueous povidone iodine 7.5% for preoperative skin antisepsis to prevent surgical site infection (SSI). Nine RCTs, comprising a total of 3,614 patients across various surgical specialties, were included in the meta-analysis. This analysis found that chlorhexidine antisepsis was associated with significantly fewer SSIs (adjusted risk ratio, 0.64 [95% confidence interval 0.51 to 0.80]) and positive skin culture results (adjusted risk ratio, 0.44 [0.35 to 0.56]) than povidone iodine antisepsis.

A resource use review of all surgical cases at the Hospital of the University of Pennsylvania during fiscal year 2007 determined the mean costs associated with patients who did and patients who did not develop SSI. In the base case, where only povidone iodine was used, the authors found that the average cost of a patient who developed an SSI was $13,537 (approximately £10,231 – see Appendix J for conversion), whilst the expected cost of a patient who did not develop an SSI was $5,356 (£4,048).

We identified inconsistencies in subsequent calculations carried out in the paper, so recalculated the results.

In the base case, our calculations estimated savings of $38 (£29) per surgical case with chlorhexidine compared with povidone iodine. Our calculations also considered 2 scenarios using a reduced efficacy of chlorhexidine: a 25% risk reduction led to savings of $26 (£20) per surgical case and a 15% risk reduction led to savings of $16 (£12) per surgical case compared with povidone iodine.

Given the assumption that there is always a risk reduction of SSIs with chlorhexidine, relative to povidone iodine, our calculations found that there was always an associated cost saving. The authors concluded that chlorhexidine is a dominant strategy over povidone iodine for preoperative skin antisepsis to prevent surgical site infection.

Although this paper was not a cost-utility analysis, we felt that this study enabled us to conduct a simple calculation to estimate the cost-savings generated as a result of avoiding an SSI. The overall savings per patient for avoided SSIs for the cohort enable the calculation of the amount that we would be willing to pay for a technology at is as least as effective.

Economic model

People who contract an SSI have a higher risk of mortality, lower quality of life, and increased cost of management than those who do not contract an SSI. We developed an economic model to examine the effects of 4 types of perioperative skin antiseptics (aqueous povidone iodine, povidone iodine + alcohol, aqueous chlorhexidine and chlorhexidine + alcohol) on costs and outcomes for people undergoing surgical procedures.

This model was based on the economic model developed for the review question on 'nasal decontamination in prevention of surgical site infection' as part of this guideline update. The methods and input parameters for both models are identical, except where stated in this report. A full description of methods and results is provided in the health economic report.

Methods

Effectiveness estimates (odds ratios for any SSI) were taken from the network meta-analysis undertaken for this review (see Methods and process, above). Class-level effects were assumed for the 4 options, as there was no evidence in the review that different preparations, concentrations or approaches had significantly different results within each class. Base-case model results use the meta-regression NMA; we used the 'lumped' NMA in a scenario analysis.

Absolute probabilities of SSI were generated by combining odds ratios from the network meta-analysis with a 'baseline' risk of SSI derived from Jenks et al. (2014), using additional details provided by the investigators regarding how often each of the 4 types of skin antiseptics was used during the period covered by the paper (see Appendix L for details).

The guideline committee agreed that the results of the model should be presented at a class level for each of the 4 options, using the costs of a single product that is considered representative of that class in an English NHS setting. These costs were sourced from the NHS Supply Chain catalogue (August 2018) and can be seen in Table 3**Error! Reference source not found.**. We found only a single cost for the aqueous povidone iodine, povidone iodine + alcohol and aqueous chlorhexidine class of products. However, there were 4 relevant costs for the chlorhexidine + alcohol class of product. As the model assumes a class-level effect for all of these products, it would not be sensible to assess them in a single, incremental analysis, as the cheapest would always be dominant. However, the committee was interested in knowing whether the costs associated with each product would lead to different conclusions when chlorhexidine + alcohol is compared with other classes of antiseptic. Therefore, separate analyses were undertaken using the price of each of these products.

For the base-case analysis for all solutions, the guideline committee advised that 150 ml of solution should be assumed. In sensitivity analyses, we examined the effects of using 50 ml (lower value) or a full bottle (upper value: 500 ml for all solutions except 600 ml for 0.5% chlorhexidine + alcohol). The guideline committee also advised that, in all analyses involving a solution, a red-staining dye (£1.55 for 12 ml) would be added to the full bottle to help surgeons see which parts of the skin had been coated. The guideline committee also advised that, where solutions were used, 2 Rampley sponge holders would be required, each of which would need sterilisation after each patient (£1.57 per instrument).

In analyses where applicators were used, the guideline committee advised that one applicator would be used in the base case. In sensitivity analysis, we examined the impact of number of applicators on cost–utility results. We also conducted a threshold analysis to examine the effect of a disposal costs for applicators, which are uncertain (see Appendix L).

For parameters related to the cost of dealing with an SSI, utility values and the risk of mortality if a patient contracts an SSI, the model used values identical to those found in the 'nasal decontamination in prevention of surgical site infection' model.

Table 3. Treatments and their costs in the model

Treatment Class	Active ingredient	Brand Name	Volume	Price	Price for 150mls
Chlorhexidine (aqueous)	Chlorhexidine 4%	HiBiScrub	500 ml	£3.80	£1.14
Chlorhexidine (alcohol)	Chlorhexidine gluconate 2% + isopropyl alcohol 70%	ChloraPrep	Box of 25 applicators	£211.69	£8.46 per 26 ml applicator
	Chlorhexidine gluconate 2% + isopropyl alcohol 70%	ChloraPrep Tint	Box of 25 applicators	£222.36	£8.89 per 26 ml applicator
	0.5% Chlorhexidine denatured ethanol 70% solution pink	Hydrex	600 ml	£2.95	£0.74
	Chlorhexidine 2% in 70% IPA Bottle	Ecolab	500 ml	£5.76	£1.73
Povidone Iodine (aqueous)	7.5% Povidone iodine surgical scrub solution	Videne	500 ml	£5.49	£1.65
Povidone Iodine (alcohol)	10% Povidone Iodine antiseptic solution	Videne Antiseptic	500 ml	£5.49	£1.65

Results

In all deterministic and probabilistic analyses, chlorhexidine + alcohol is associated with the lowest number of SSIs and, as a result, dominates all other comparators (that is, it is associated with lower costs and greater benefits). This is true when the price of any of the 4 chlorhexidine + alcohol products is used – see Table 4.

Table 4: Original cost–utility analysis: base-case deterministic results where chlorhexidine + alcohol costs = 0.5% chlorhexidine in 70% alcohol (Hydrex)

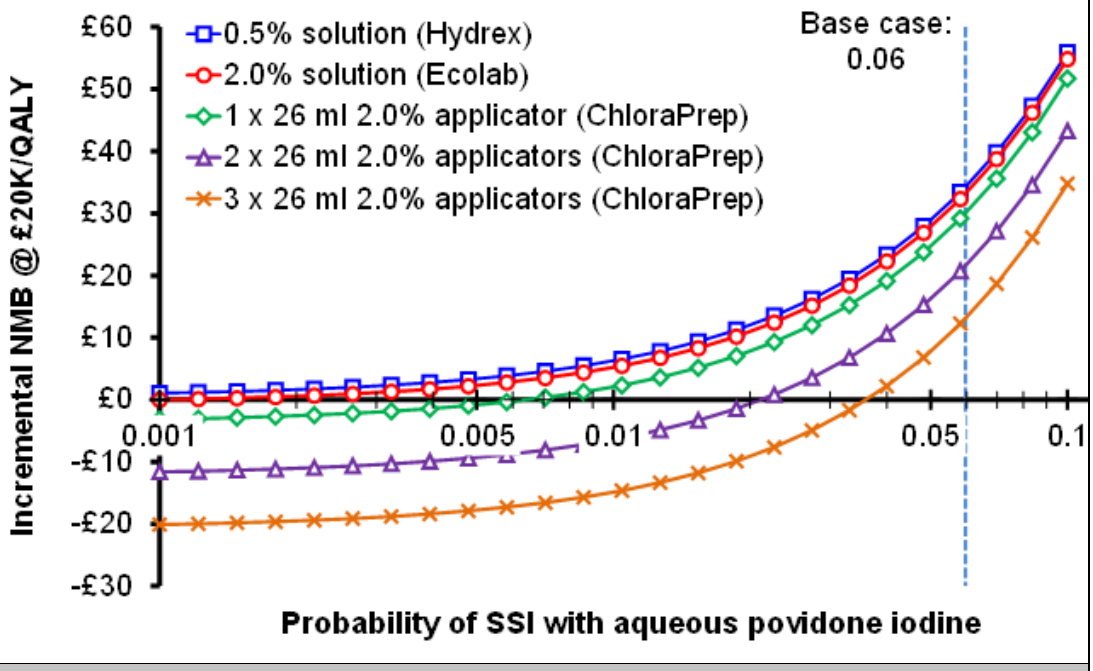
Strategy	Absolute		Incremental			No. of SSIs per 1,000 operations
	Costs	QALYs	Costs (£)	Effects (QALYs)	ICER (£/QALY)	
Chlorhexidine + alcohol costs = 0.5% chlorhexidine in 70% alcohol (Hydrex)						
Chlorhexidine (alcohol)	£129.70	8.9216				40.17
Chlorhexidine (aqueous)	£154.63	8.9211	£24.94	−0.00046	Dominated	48.00
Povidone Iodine (alcohol)	£161.26	8.9210	£31.56	−0.00058	Dominated	49.96
Povidone Iodine (aqueous)	£191.30	8.92045	£61.61	−0.00115	Dominated	59.58
Chlorhexidine + alcohol costs = 2% chlorhexidine in 70% alcohol (Ecolab)						
Chlorhexidine (alcohol)	£130.77	8.9216				40.17
Chlorhexidine (aqueous)	£154.63	8.9211	£23.87	−0.00046	Dominated	48.00
Povidone Iodine (alcohol)	£161.26	8.9210	£30.49	−0.00058	Dominated	49.96
Povidone Iodine (aqueous)	£191.30	8.92045	£60.54	−0.00115	Dominated	59.58
Chlorhexidine + alcohol costs = 2% chlorhexidine in 70% alcohol 26 ml applicator (ChloraPrep)						
Chlorhexidine (alcohol)	£133.91	8.9216				40.17
Chlorhexidine (aqueous)	£154.63	8.9211	£20.72	-0.00046	Dominated	48.00
Povidone Iodine (alcohol)	£161.26	8.9210	£27.35	-0.00058	Dominated	49.96
Povidone Iodine (aqueous)	£191.30	8.92045	£57.39	-0.00115	Dominated	59.58
Chlorhexidine + alcohol costs = 2% chlorhexidine in 70% alcohol 26 ml applicator with dye (ChloraPrep+Tint)						
Chlorhexidine (alcohol)	£134.34	8.9216				40.17
Chlorhexidine (aqueous)	£154.63	8.9211	£20.30	-0.00046	Dominated	48.00
Povidone Iodine (alcohol)	£161.26	8.9210	£26.92	-0.00058	Dominated	49.96
Povidone Iodine (aqueous)	£191.30	8.92045	£56.97	-0.00115	Dominated	59.58

In probabilistic analysis, chlorhexidine + alcohol was always associated with a probability of at least 83% of being cost-saving.

The baseline rate of SSIs used in model was 5.1% – implying that an SSI rate of approximately 6% would have been observed if all operations in Jenks et al.'s (2014) series had used aqueous iodine. This dataset comprises SSIs from 17 different categories of surgery, which are associated with different SSI rates (ranging from 1.0% to 13.0%), different patient demographics (mean age ranging from 51 to 84) and different mortality risks (ranging from 0.0% to 6.2%). Across all 17 populations, chlorhexidine + alcohol dominates all other comparators.

When the baseline risk of SSI alone is altered, chlorhexidine + alcohol provides good value for money at all baseline rates compared with its closest competitor (aqueous chlorhexidine), if the model uses the costs of 0.5% solution (Hydrex) or 2.0% solution (Ecolab). If the costs of 1, 2 or 3 x 2% 26 ml applicators (ChloraPrep) are used,

expected baseline SSI risks of 0.5%, 2.0% and 3.5%, respectively, would be required to justify the costs of chlorhexidine + alcohol. See Figure 1.

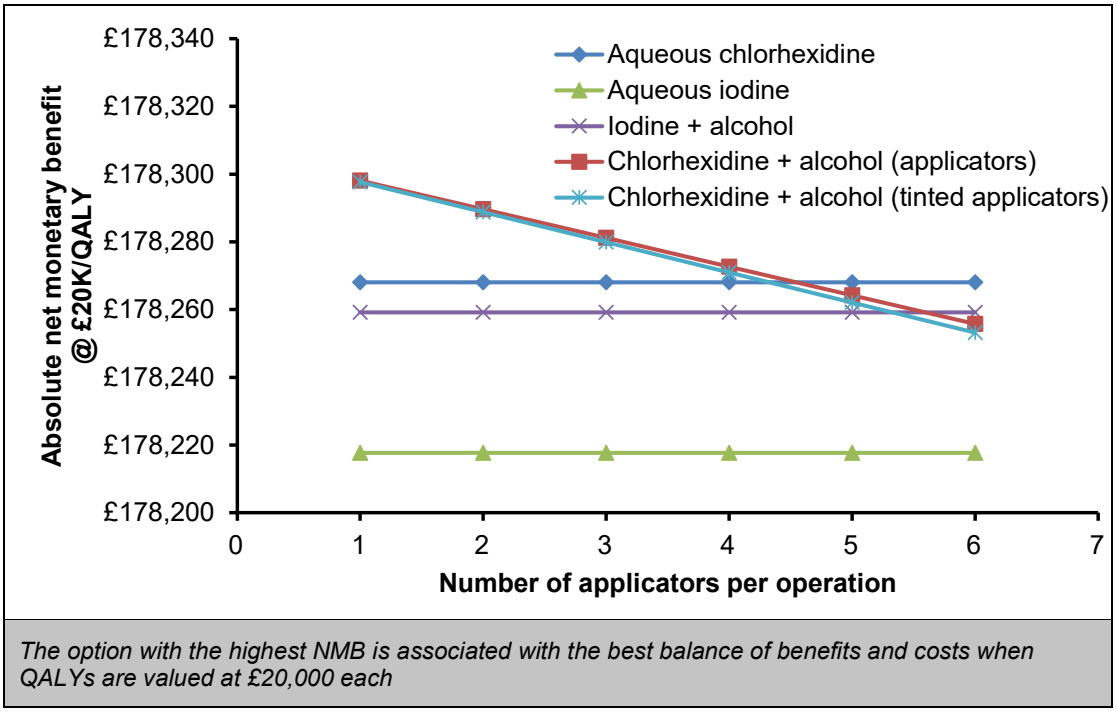


Incremental NMB values greater than 0 indicate that a given chlorhexidine + alcohol product would be associated with an ICER better than £20,000 per QALY compared with the next cheapest non-dominated option (aqueous chlorhexidine)

Figure 1: One-way sensitivity analysis: cost effectiveness of chlorhexidine + alcohol as a function of baseline probability of SSI

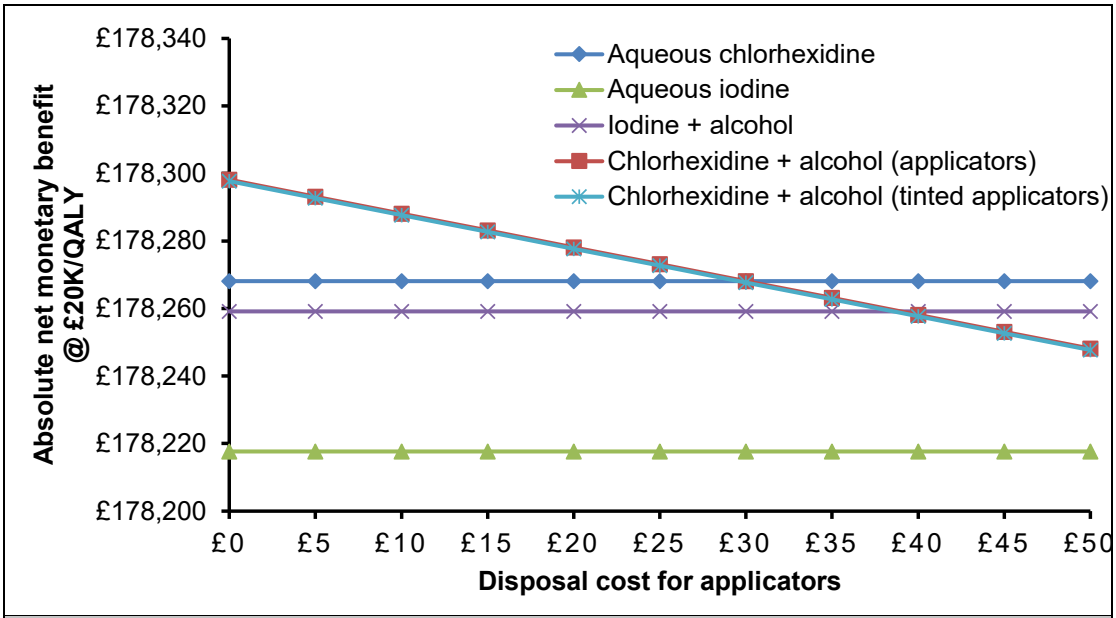
The committee requested 2 additional sensitivity analyses that explored uncertainty around the use of chlorhexidine + alcohol applicators. The first examined the number of applicators per operation – see Figure 2. This analysis shows that, if the number of applicators used per operation is 4 or less, chlorhexidine + alcohol will be associated with an ICER of better than £20,000 / QALY compared with all alternatives. If the number of applicators rises to 5, aqueous chlorhexidine would be preferred and, if as many as 6 applicators per operation were used, chlorhexidine + alcohol would also provide worse value for money than povidone iodine + alcohol. The guideline committee advised that these numbers are extremely unlikely; therefore, the cost effectiveness of chlorhexidine + alcohol does not appear to be materially affected by this uncertainty.

The second sensitivity analysis requested by the committee concerns the disposal costs of chlorhexidine + alcohol applicators, which is a source of uncertainty (see Appendix L). This analysis (Figure 3) shows that chlorhexidine + alcohol would be the preferred option unless disposal costs per operation exceed £30, at which point aqueous chlorhexidine would be preferred; if they exceeded £40 per operation, it would also be overtaken by povidone iodine + alcohol. Again, the committee advised that these values are beyond the range of plausible disposal costs; therefore, the results appear robust to this uncertainty.



The option with the highest NMB is associated with the best balance of benefits and costs when QALYs are valued at £20,000 each

Figure 2: One-way sensitivity analysis: number of 26 ml 2.0% chlorhexidine (ChloraPrep) applicators per operation



The option with the highest NMB is associated with the best balance of benefits and costs when QALYs are valued at £20,000 each

Figure 3: One-way sensitivity analysis: disposal cost for chlorhexidine applicators (ChloraPrep) per operation

Evidence statements

Clinical evidence

Network meta-analysis (meta-regression model)

Moderate-quality evidence from a network meta-analysis containing 20 studies and 9,647 participants found that:

- People who received chlorhexidine had a lower incidence of SSIs than people who received povidone iodine.
- There is around 95% probability that chlorhexidine in alcohol is associated with lowest incidence of SSIs and a similar probability that aqueous povidone iodine is associated with most SSIs.

Pairwise analysis

Alcohol

SSI

Very low quality evidence from 1 RCT, including 62 people could not differentiate SSI between people who received 70% alcohol for skin preparation before incision and those who received 2% iodine in 50% alcohol.

Very low quality evidence from 1 RCT, including 57 people could not differentiate SSI between people who received 70% alcohol for skin preparation before incision and those who received 2% iodine in 70% alcohol.

Very low quality evidence from the preliminary and definitive study from 1 RCT, including 369 people could not differentiate SSI between people who received 70% alcohol for skin preparation before incision and those who received 2% iodine in 90% alcohol.

Superficial SSI

Very low quality evidence from 1 RCT, including 311 people could not differentiate superficial SSI between people who received 70% alcohol for skin preparation before incision and those who received 2% iodine in 90% alcohol.

Very low quality evidence from 1 RCT, including 157 people could not differentiate superficial SSI between people who received 70% alcohol for skin preparation before incision during **clean surgery** and those who received 2% iodine in 90% alcohol.

Very low quality evidence from 1 RCT, including 132 people could not differentiate superficial SSI between people who received 70% alcohol for skin preparation before incision during **clean-contaminated surgery** and those who received 2% iodine in 90% alcohol.

Very low quality evidence from 1 RCT, including 132 people could not differentiate superficial SSI between people who received 70% alcohol for skin preparation before incision during **contaminated surgery** and those who received 2% iodine in 90% alcohol.

Iodine in alcohol preparation

SSI

Very low quality evidence from 1 RCT, including 30 people could not differentiate SSI between people who received 2% iodine in 50% alcohol for skin preparation before incision and those who received 2% iodine in 90% alcohol.

Very low quality evidence from 1 RCT, including 25 people could not differentiate SSI between people who received 2% iodine in 70% alcohol for skin preparation before incision and those who received 2% iodine in 90% alcohol.

Aqueous Chlorhexidine

Low quality evidence from 1 RCT, including 534 people could not differentiate the following outcomes between people who received aqueous chlorhexidine scrub (4%) and paint (2%) for skin preparation before incision and those who received aqueous povidone iodine scrub (7.5%) and paint (10%)

- SSI
- Superficial SSI
- Deep SSI
- Organ Space SSI

Aqueous povidone iodine

SSI

Moderate quality evidence from 2 RCTs, including 407 people could not differentiate between people who received 5% aqueous povidone iodine for skin preparation before incision and those who received 0.5% chlorhexidine with 70% alcohol.

- No significant difference was identified within 30 days (moderate quality)
- No significant difference was identified during 3 year follow up (very low quality)

Very low quality evidence from 3 RCTs, including 443 people could not differentiate between people who received 10% aqueous povidone iodine for skin preparation before incision and those who received aqueous povidone iodine scrub (7.5%) and paint (10%).

- No significant difference was identified within 30 days surgery (very low quality)
- No significant difference was identified 6 weeks postoperatively (low quality)
- No significant difference was identified during postoperative phase (very low quality)

- Very low quality evidence from 2 RCTs, including 178 people could not differentiate between people who received 10% aqueous povidone iodine for skin preparation before incision during **clean surgery** and those who received aqueous povidone iodine scrub (7.5%) and paint (10%).
- Very low quality evidence from 1 RCT, including 164 people could not differentiate between people who received 10% aqueous povidone iodine for skin preparation before incision during **clean-contaminated surgery** and those who received aqueous povidone iodine scrub (7.5%) and paint (10%).

Superficial SSI

Moderate quality evidence from 1 RCT, including 351 people could not differentiate superficial SSI between people who received 5% aqueous povidone iodine for skin preparation before incision and those who received 0.5% chlorhexidine with 70% alcohol.

Deep SSI

Low quality evidence from 1 RCT, including 351 people could not differentiate deep SSI between people who received 5% aqueous povidone iodine for skin preparation before incision and those who received 0.5% chlorhexidine with 70% alcohol.

Chlorhexidine in alcohol preparation

SSI

Low quality evidence from 1 RCT, including 909 people could not differentiate SSI between people who received 0.5% chlorhexidine with 70% alcohol for skin preparation before incision and those who received 0.5% chlorhexidine in aqueous solution.

Low quality evidence from 1 RCT, including 737 people could not differentiate SSI between people who received aqueous povidone iodine scrub (7.5%) and paint for skin preparation before incision during clean surgery and those who received aqueous povidone iodine scrub (7.5%) and paint (10%).

Low quality evidence from 1 RCT, including 85 people could not differentiate superficial SSI between people who received 2% chlorhexidine with 70% alcohol for skin preparation before incision and those who received 0.5% chlorhexidine with 70% alcohol.

Moderate quality evidence from 3 RCTs, including 947 people could not differentiate SSI between people who received either 2% or 2.5% chlorhexidine with 70% alcohol for skin preparation before incision and those who received aqueous 10% povidone iodine.

- No significant difference was identified within 30 days (moderate quality)
- No significant difference was identified 6 weeks post-surgery (low quality)
- Moderate evidence from 3 RCTs, including 815 people could not differentiate SSI between people who received either 2% or 2.5% chlorhexidine with 70% alcohol for skin preparation before incision during **clean surgery** and those who received aqueous 10% povidone iodine.
- Low quality evidence from 1 RCT, including 132 people could not differentiate SSI between people who received either 2% or 2.5% chlorhexidine with 70% alcohol for skin preparation before incision during **clean-contaminated surgery** and those who received aqueous 10% povidone iodine.

Moderate quality evidence from 4 RCTs, including 1,924 people indicated that people who received 2% chlorhexidine with 70% alcohol for skin preparation before incision had a lower incidence of SSI compared to those who received aqueous povidone iodine scrub (7.5%) and paint (10%).

- Significant difference was identified within 30 days of surgery (moderate)

- Moderate quality evidence from 3 RCTs, including 1,824 people indicated that people who received 2% chlorhexidine with 70% alcohol for skin preparation before incision during **clean- contaminated surgery** had a lower incidence of

SSI compared to those who received aqueous povidone iodine scrub (7.5%) and paint (10%).

Very low quality evidence from 2 RCT, including 627 people could not differentiate SSI between people who received 4% chlorhexidine with 70% alcohol for skin preparation before incision and those who received aqueous povidone iodine scrub (7.5%) and paint (10%).

- No significant difference within 30 days of surgery (very low)
- Very low quality evidence from 2 RCTs, including 310 people could not differentiate SSI between people who received 4% chlorhexidine with 70% alcohol for skin preparation before incision during **clean surgery** and those who received aqueous povidone iodine scrub (7.5%) and paint (10%).

Low quality evidence from 1 RCT, including 85 people indicated that people who received 2% chlorhexidine with 70% alcohol for skin preparation (including surgeon scrub) before incision had a lower incidence of SSI compared to those who received 10% povidone iodine in alcohol (including surgeon scrub).

- A significant difference was also identified among people undergoing **clean surgery** (Low quality)

Superficial SSI

Low quality evidence from 1 RCT, including 159 people could not differentiate superficial SSI between people who received either 2% or 2.5% chlorhexidine with 70% alcohol for skin preparation before incision and those who received aqueous 10% povidone iodine.

Low quality evidence from 2 RCTs, including 1,781 people indicated that people who received 2% chlorhexidine with 70% alcohol for skin preparation before incision had a lower incidence of superficial SSI compared to those who received aqueous povidone iodine scrub (7.5%) and paint (10%).

Deep SSI

Low quality evidence from 2 RCTs, including 1,781 people indicated that people who received 2% chlorhexidine with 70% alcohol for skin preparation before incision had a lower incidence of deep SSI compared to those who received aqueous povidone iodine scrub (7.5%) and paint (10%).

Organ space SSI

Low quality evidence from 2 RCTs, including 1,781 people could not differentiate organ space SSI between people who received either 2% or 2.5% chlorhexidine with 70% alcohol for skin preparation before incision and those who received aqueous povidone iodine scrub (7.5%) and paint (10%).

Adverse reactions

Low quality evidence from 1 RCT, including 909 people could not differentiate adverse reactions between people who received 0.5% chlorhexidine with 70% alcohol for skin preparation before incision and those who received 0.5% chlorhexidine in aqueous solution.

Skin irritation

Low quality evidence from 1 RCT, including 388 people could not differentiate skin irritation between people who received either 2% or 2.5% chlorhexidine with 70% alcohol for skin preparation before incision and those who received aqueous 10% povidone iodine.

Sepsis

Low quality evidence from 1 RCT, including 849 people could not differentiate sepsis between people who received either 2% or 2.5% chlorhexidine with 70% alcohol for skin preparation before incision and those who received aqueous povidone iodine scrub (7.5%) and paint (10%).

Skin reaction

Low quality evidence from 1 RCT, including 932 people could not differentiate skin reaction between people who received either 2% or 2.5% chlorhexidine with 70% alcohol for skin preparation before incision and those who received aqueous povidone iodine scrub (7.5%) and paint (10%).

Povidone iodine in alcohol preparation

SSI

Very low quality evidence from 2 RCTs, including 2,084 women could not differentiate SSI between women who received with 8.3% povidone iodine in 72.5% alcohol and those who received 2% chlorhexidine with 70% alcohol.

- A significant difference was identified within 30 days of delivery, indicating that incidence of SSI was lower in women who received 2% chlorhexidine with 70% alcohol (moderate quality)
- No significant difference was identified within 30 days of discharge (low quality)
- Moderate quality evidence from 1 RCT, including 669 women undergoing **scheduled caesarean** indicated that women who received 2% chlorhexidine with 70% alcohol had lower incidence of SSI compared to those who received 8.3% povidone iodine in 72.5% alcohol.
- Low quality evidence from 1 RCT, including 478 women people undergoing **unscheduled caesarean** could not differentiate SSI between women who received with 8.3% povidone iodine in 72.5% alcohol and those who received 2% chlorhexidine with 70% alcohol.

Low quality evidence from 2 RCTs, including 267 people could not differentiate SSI between people who received iodophor (0.7%) in alcohol (74%) and those who received aqueous 10% povidone iodine.

Moderate quality evidence from 4 RCTs, including 1,148 people could not differentiate SSI between people who received iodophor (0.7%) in alcohol (74%) and those who received 2% chlorhexidine with 70% alcohol

- No significant difference was identified within 30 days surgery (moderate quality)
- No significant difference was identified 6 weeks after surgery (low quality)

Superficial SSI

Low quality evidence from 2 RCTs, including 2,084 women could not differentiate superficial SSI between women who received with 8.3% povidone iodine in 72.5% alcohol and those who received 2% chlorhexidine with 70% alcohol.

Low quality evidence from 1 RCT, including 161 people could not differentiate superficial SSI between people who received iodophor (0.7%) in alcohol (74%) and those who received aqueous 10% povidone iodine.

Low quality evidence from 2 RCTs, including 948 people could not differentiate superficial SSI between people who received iodophor (0.7%) in alcohol (74%) and those who received 2% chlorhexidine with 70% alcohol.

Deep SSI

Low quality evidence from 2 RCTs, including 2,084 women could not differentiate deep SSI between women who received with 8.3% povidone iodine in 72.5% alcohol and those who received 2% chlorhexidine with 70% alcohol

Low quality evidence from 1 RCT, including 788 people could not differentiate deep SSI between people who received iodophor (0.7%) in alcohol (74%) and those who received 2% chlorhexidine with 70% alcohol

Organ space SSI

Low quality evidence from 1 RCT, including 937 women could not differentiate organ space SSI between women who received with 8.3% povidone iodine in 72.5% alcohol and those who received 2% chlorhexidine with 70% alcohol

Low quality evidence from 1 RCT, including 788 people could not differentiate organ space SSI between people who received iodophor (0.7%) in alcohol (74%) and those who received 2% chlorhexidine with 70% alcohol

Hospital readmission

Low quality evidence from 1 RCT, including 1,147 women could not differentiate hospital readmission between women who received with 8.3% povidone iodine in 72.5% alcohol and those who received 2% chlorhexidine with 70% alcohol.

Moderate quality evidence from 1 RCT, including 1,147 women could not differentiate hospital length of stay between women who received with 8.3% povidone iodine in 72.5% alcohol and those who received 2% chlorhexidine with 70% alcohol.

Adverse skin reactions

Low quality evidence from 1 RCT, including 1,147 women could not differentiate adverse skin reactions between women who received with 8.3% povidone iodine in 72.5% alcohol and those who received 2% chlorhexidine with 70% alcohol.

Erythema at operative site

Low quality evidence from 1 RCT, including 1,147 women could not differentiate erythema at operative site between women who received with 8.3% povidone iodine in 72.5% alcohol and those who received 2% chlorhexidine with 70% alcohol.

Skin irritation

Low quality evidence from 1 RCT, including 1,147 women could not differentiate skin irritation between women who received with 8.3% povidone iodine in 72.5% alcohol and those who received 2% chlorhexidine with 70% alcohol.

Allergic reactions

Low quality evidence from 1 RCT, including 1,147 women could not differentiate allergic reactions between women who received with 8.3% povidone iodine in 72.5% alcohol and those who received 2% chlorhexidine with 70% alcohol.

Cellulitis

Low quality evidence from 1 RCT, including 788 people could not cellulitis between people who received iodophor (0.7%) in alcohol (74%) and those who received 2% chlorhexidine with 70% alcohol

Hospital length of stay

Low quality evidence from 1 RCT, including 788 people could not hospital length of stay between people who received iodophor (0.7%) in alcohol (74%) and those who received 2% chlorhexidine with 70% alcohol

Alcohol preparation vs aqueous preparation

Moderate quality evidence from 18 RCTs, including 6,119 people, indicated that people who received alcohol skin preparations had a lower incidence of SSI compared to those who received aqueous skin preparations.

Single preparation vs double preparation

Very low quality evidence from 3 RCTs, including 443 people, could not differentiate SSI between people who received single skin preparation compared to those who received double skin preparation.

Economic evidence

One partially applicable cost-benefit analysis with potentially serious limitations compared the use of chlorhexidine 2% in an alcohol solution with use of single preparation povidone-iodine 7.5% for preoperative skin antisepsis. The authors found that chlorhexidine was a dominant strategy as it reduced SSIs, which were associated with a significant cost, leading to an average cost saving of £29 per patient.

One directly applicable original cost–utility analysis with minor limitations showed that chlorhexidine in alcohol has a high probability of being associated with higher QALYs and lower costs than all other alternatives. This remains the case when the costs of all preparations that are currently available are used.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee identified SSI, including superficial SSI, deep SSI and organ space SSI as outcomes of interest. Studies included in the review captured SSI at different

follow up times. Based on the CDC's definition of SSIs, the committee identified SSI up to 30 days and 1 year after surgery to be an important outcome. Therefore subgroup analysis was conducted based on follow up period.

The quality of the evidence

Overall, 3 studies [Berry 1982, Cheng 2009 and Casey 2015] were identified which were conducted in the UK. With regards to the risk of bias, studies were mainly downgraded for unclear random sequence generation, allocation concealment and blinding of outcome assessment. A number of studies did demonstrate unclear or no blinding of participants and personnel, however due to the nature of the outcomes, these studies were not downgraded in this domain

A number of studies were downgraded for indirectness. One such study was Berry 1982, in which the effectiveness of 0.5% chlorhexidine in alcohol was compared to 10% povidone iodine in alcohol. However, in this study patients as well as surgeons were randomly allocated to receive different skin preparation and surgeon scrub. While this study demonstrated a significant reduction in SSI in people undergoing mixed and clean surgery, this evidence was downgraded for being indirect as surgeon scrub in both arms were different and this was not an intervention of interest.

In this review, SSI up to 30 days and 1 year after surgery was prioritised. SSIs at different follow up periods such as during in hospital follow up and 6 weeks after surgery were reported in studies. However, 4 studies [Cheng 2009, Bibbo 2005, Zdeblick 1986 and Gillam 1990] were identified which did not state the follow up period. For the purpose of the review, it was assumed that outcomes were captured at some point during the postoperative phase; however, these studies were further downgraded for indirectness as the applicability of these studies to the evidence base of unclear.

SSIs can involve different layers of skin and tissue and therefore can be broken down into superficial (involving the skin and subcutaneous tissue of the incision), deep (involving soft tissue such as fascia and muscle) or organ space (involving any part of the body deeper than the fascia and muscle layers). Each type of surgical site infection has specific characteristics therefore it is important the infections are defined correctly. In the review, it was identified that SSIs should be defined using an appropriate criteria such as the CDC SSI criteria. The majority of the studies used the CDC criteria to define infection. However, 6 studies [Cheng 2009, Bibbo 2005, Gilliam 1990, Zdeblick 1986, Saltzman 2009 and Savage 2012] were identified which did not specify the criteria used to define infection. These studies were downgraded for indirectness as the applicability of these studies to the evidence base was unclear.

It was identified that a number of studies were not adequately powered to capture SSIs. Among these studies, 7 were identified [Xu 2017, Cheng 2009, Saltzman 2009, Gilliam 1990, Zdeblick 1986, Bibbo 2005 and Savage 2012] in which the secondary aim of study was to assess incidence of SSI. Six studies [Xu 2017, Savage 2012, Saltzman 2009, Cheng 2009, Zdeblick 1986 and Bibbo 2005] were identified which examined the antimicrobial activity of different antiseptics by obtaining cultures before and after skin preparation. One study was identified [Gilliam 1990] which compared the efficacy in reduction of skin flora between two skin preparations by taking cultures before and after surgery.

One study [Xu 2017] demonstrated low number of events, while 5 studies [Cheng 2009, Bibbo 2005, Gillaim 1990, Saltzman 2009 and Savage 2012] identified zero events in terms of occurrence of an SSI. While a low number of events could be attributed to the type of surgical procedure being assessed, it is clear that these

studies were underpowered. Studies which reported zero events were not included in the network meta-analysis as these did not contribute to the estimation of relative treatment effects.

Two separate network meta-analyses and a meta-regression were conducted to produce an estimate of effectiveness of all comparators in the reduction in SSI and the ranking of different interventions. Moderate quality evidence from the meta-regression was used in the decision making.

While the committee noted the quality of the meta-regression, they identified that a number of studies included in the model received grants from research councils and manufacturers. One study [Darouiche 2010] was identified which examined the incidence of SSI in people receiving 2 % chlorhexidine with 70% alcohol and those receiving aqueous povidone iodine paint (7.5%) and scrub (10%). It was noted that research and educational grants were received from Cardinal Health, the manufacturers of the interventions examined in the study.

This study was an adequately powered study, which demonstrated a significant reduction in SSI, including superficial SSI, in people who received 2% chlorhexidine with 70% alcohol. In the same analysis a more up-to-date study was included which demonstrated similar power and also examined people undergoing clean-contaminated surgery. This study was not funded by the manufactures of the interventions. This study could not demonstrate a significant difference in SSI, including superficial SSI or deep SSI.

It was noted that due to the significance of the Darouiche 2010 study, the analysis demonstrated a significant reduction in SSI when 2% chlorhexidine in 70% alcohol was utilised as skin preparation prior to skin incision compared with aqueous povidone iodine scrub (7.5%) and paint (10%). The committee identified the source of funding and the unreproducible significant results as a potential limitation.

In this review, the studies included examined a number of different surgical procedures and different clinical settings. Studies included people undergoing clean surgical procedures such foot and ankle surgery. The committee noted that the one study [Casey 2015] included people undergoing coronary artery bypass grafting. This was identified as a very narrow study. Furthermore, one study [Charles 2017] was identified which included people undergoing minor skin excisions in general practice. While this is an important setting to take into consideration, the committee noted that general practice settings does not provide a sterile environment. Additionally, minor skin excision was identified as a minor operation, which meant the incidence of SSI may be low. This raised the question about the applicability of these studies to the overall effect.

Taking into consideration the limitations presented with regards to quality of evidence, the committee were unable to make strong recommendations. However, the committee did find the evidence provided by the meta-regression compelling enough to make recommendations for healthcare professionals to consider these interventions for skin preparation prior incision.

Benefits and harms

SSIs are associated with increased costs and poor patient outcomes. The risk of SSIs can also vary between surgical procedures and wound classification. With regards to surgical wound categories, clean surgical procedures are considered as clean wounds which present the least risk of an infection. However, clean-contaminated surgical procedures are at a higher risk of surgical site infection due to the site of surgery and the added risk of contamination.

In the review, studies examining different surgical procedures were identified which were used in a network meta-analysis. The evidence demonstrated that 2% chlorhexidine with 70% alcohol reduced the incidence of SSIs (including superficial and deep SSI) in clean-contaminated surgeries. The surgical procedures included in this category include caesarean surgery, colorectal, small intestinal, gastroesophageal, biliary, thoracic, gynaecologic or urologic operations.

People undergoing such procedures are already at risk of an infection, therefore preparation of the skin before incision is crucial to ensure that this risk is reduced and patient outcomes are improved. Therefore the committee recommended the use of antiseptic preparations before incision and recommended that alcohol preparations of chlorhexidine to be considered as the first line choice of antiseptic.

However, the committee noted that while alcoholic preparations of chlorhexidine do demonstrate some benefits, contraindications need to be taken into account when considering their use. With regards to the use of chlorhexidine, which is a broad spectrum antimicrobial, hypersensitivity can occur, including generalised allergic reactions and anaphylactic shock.

In this review, outcomes such as anaphylaxis and skin and other allergic reactions were examined. Springel 2017 compared the incidence of skin reactions in people who were given a 2% chlorhexidine with 70% alcohol skin preparation and those who received aqueous povidone iodine scrub (7.5%) and paint (10%). However, the result was not statistically significant. Tuuli 2016 compared the incidence of adverse skin reactions such as erythema, skin irritation and allergic reactions in people who were administered 2% chlorhexidine with 70% alcohol and those who received 8.3% povidone iodine in 72.5% alcohol. These results were not statistically significant.

While non-significant results were obtained from the analysis, the committee noted that hypersensitivity is a major concern with the use of chlorhexidine. The prevalence of chlorhexidine hypersensitivity is rare but products containing chlorhexidine should not be given to anyone with a possible history of an allergic reaction to chlorhexidine.

The committee also further noted that alcohol cannot be used in surgical procedures such as colorectal surgery as the site is adjacent to a mucous membrane. Taking these issues into consideration, the committee recommended that alcohol preparations of chlorhexidine should be considered unless contraindicated, in which case alcohol povidone iodine should be used. However, if the surgical site is adjacent to a mucous membrane, in which case aqueous chlorhexidine should be considered instead. In cases in which both chlorhexidine and alcohol were not suitable, aqueous povidone iodine should be considered to ensure people are receiving skin preparation before incision.

The new recommendations allow healthcare professionals to consider the use of different antiseptics for skin preparation. This may result in the increased use of antiseptics, which raises the question on antimicrobial resistance. While antimicrobial resistance was an outcome of interest in this review, no data was identified. The committee noted that while resistance to chlorhexidine is not widely reported, multidrug resistance may occur. Taking the lack of data into consideration, antimicrobial resistance was included as an important outcome in the 3 research recommendations drafted by the committee (see the section on other factors the committee took into account for details of these recommendations).

Most of the studies included in this review included an adult population. Therefore, data cannot be extrapolated to infants and in neonates in whom skin preparation prior to incision may be required. While no evidence is available on the effectiveness

of the antiseptics in this population group, risks need to be considered. It was noted that regular use of povidone iodine should be avoided in neonates and children.

Furthermore, the committee discussed that manufacturers tend to only recommend products such as 2% chlorhexidine with 70% alcohol to be used in neonates, if no alternative antiseptics are available. 0.5% chlorhexidine with 70% alcohol should also be used with care in premature infants. Additionally, the Medicines and Healthcare products Regulatory Agency (MHRA) has published advice on the use of chlorhexidine for skin disinfection which states that the risk of severe chemical injuries should be assessed when considering the use of alcohol-based or aqueous-based chlorhexidine solution on premature infants. Taking this advice into consideration, the committee made a recommendation to highlight the risk associated with the use of skin antiseptics in this population group.

The committee also discussed that some surgical procedures may require diathermy. This means that care is required when using alcohol antiseptic solutions as these are flammable substances and can result in burns. The product summary of 2% chlorhexidine in alcohol (Chloraprep) highlighted that along with avoiding pooling of alcohol- based preparations, any soaked materials, drapes or gowns should also be removed before electrocautery procedures. Additionally, excessive quantities of solution should not be used and ensure no excess product is present prior to application of an occlusive dressing after the use of antiseptics skin preparation. While these cautions are listed specifically for the use of chlorhexidine in alcohol the committee wished to highlight that these are applicable to all alcohol based antiseptics. Therefore, the committee recommended antiseptic skin preparations should be dried by evaporation, with avoidance of pooling of alcohol to be avoid burns.

Cost effectiveness and resource use

The original economic model was driven by the results of the network meta-analysis, and showed that the most effective class of skin preparation agent at reducing SSIs was chlorhexidine + alcohol. All 4 types of chlorhexidine + alcohol products, including solutions and applicators, were dominant when compared with all other classes of antiseptic. Extensive sensitivity analysis showed that this finding was robust to all major uncertainties. The committee agreed that the levels of additional resource use that would be necessary before chlorhexidine + alcohol applicators would be considered an ineffective use of NHS resources were implausible – for example, the need to use an average of more than 4 applicators per operation, or disposal costs exceeding £30 per operation.

The guideline committee agreed that, in any situations where the recommendation to use chlorhexidine + alcohol represents a departure from current practice, any additional up-front resource impact will be more than outweighed by savings associated with reduced incidence of SSIs.

Other factors the committee took into account

In this review, effectiveness of single application of the same intervention was compared to double application of the same intervention. Three RCTs were identified, which compared single application of povidone iodine (10% aqueous povidone iodine solution) to double application of the same agent (Aqueous povidone iodine scrub (7.5%) and paint (10%). This very low quality evidence could not differentiate SSI between single application and double application of the same intervention. The committee identified this as an important area which required

further research. Therefore, the committee made a research recommendation to drive research in this area.

Evidence on different concentrations of the same intervention was identified. For example, evidence on 0.5%, 2%, 2.5% and 4% chlorhexidine with 70% alcohol was identified. The different concentrations of the same intervention were taken into account, and 'split' and 'lumped' models were developed when conducting the network meta-analysis (as described in the methods and process section).

In terms of the pair-wise analysis, only 1 study [Casey 2015] was identified which compared 2% chlorhexidine with 70% alcohol with 0.5% chlorhexidine with 70% alcohol. The committee noted that as a recommendation has been made which allows chlorhexidine in alcohol to be considered as a skin antiseptic, more evidence is required to identify the clinical effectiveness of chlorhexidine in alcohol at different concentrations. Therefore, the committee made a research recommendation for this to be further explored.

The committee also noted that the mode of application should be taken into account when considering the effect of the different antiseptics. Products can be applied to the skin prior to skin incision through different mechanical methods such as sponges and swabs or non-mechanical methods such as sprays. However, there are limitations associated with different modes of application.

Applicators can be used which contain the antiseptic in an ampoule, which is gently broken to release the antiseptic solution onto a sponge which is then used to apply the antiseptic to the skin. In this review, the mode of application was not examined, however it was identified that some interventions were applied using specially designed applicators while others were applied using swabs and forceps.

It was also further noted that some studies did not clearly specify how product was applied to the skin prior to closure, and this mechanical action could have been a confounding factor. Therefore the committee made a research recommendation to examine the clinical effectiveness and cost effectiveness of different modes of application, including mechanical and non-mechanical methods.

With regards to different modes of application, the committee further noted that disposal and reusability of different applicators. Sponge applicators, such as those which can be used to apply 2% chlorhexidine in 70% alcohol are single use products which need to be disposed of as clinical waste. Products applied using swabs require the use of forceps. While the swabs are disposed of as part of clinical waste, the forceps can be cleaned and reused, making this mode of application more environmentally friendly.

Appendices

Appendix A – Review protocol

Review protocol for effectiveness of skin antiseptics in the prevention of surgical site infection

ID	Field	Content
0.	PROSPERO registration number	CRD42018097223
1.	Review title	Choice of preoperative skin antiseptics
2.	Review question	RQ2: Is the use of preoperative skin antiseptics clinically effective in the prevention of surgical site infection?
3.	Objective	• To determine the clinical effectiveness of preoperative skin antiseptics for the prevention of SSI • To determine whether alcohol solvents should be preferred over aqueous solvents
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Cumulated Index to Nursing and Allied Health Literature (CINAHL) • Database of Abstracts of Reviews of Effectiveness (DARE) • Embase • MEDLINE/MEDLINE in Process

		• ClinicalTrials.gov • Current Controlled Trials • United Kingdom Clinical Research Network's (UKCRN) Portfolio Database • NHS EED Searches will be restricted by: • No date limit applied • English language • Human studies Other searches: • Reference searching • Inclusion lists of systematic reviews Full search strategies for all databases will be published in the final review.
5.	Condition or domain being studied	Surgical site infection is a type of health-care associated infection in which a wound infection occurs after an invasive procedure. Surgical site infections have been shown to compose up to 20% of all of healthcare-associated infections. At least 5% of patients undergoing a surgical procedure develop a surgical site infection.
6.	Population	Inclusion: People of any age undergoing any surgery, including minimally invasive surgery (arthroscopic, thoracoscopic and laparoscopic surgery)

		Exclusion: Patients undergoing a surgical procedure that does not involve a visible incision, and therefore does not result in the presence of a conventional surgical wound.

7.	Intervention/Exposure/Test	• Following interventions used for wound antisepsis:
		• Iodine at various concentrations in alcohol and aqueous preparations
		• Iodophors including:
		  ○ iodophor films
		  ○ povidone iodine in alcohol and aqueous preparations
		  ○ aqueous iodophor scrub and paint
		  ○ aqueous iodophor one-step preparation with polymer
		  ○ alcoholic iodophor with water insoluble polymer
		• Alcohol at various concentrations
		• Chlorhexidine in alcohol and aqueous preparations, including chlorhexidine gluconate

8.	Comparator/Reference standard/Confounding factors	• Interventions compared to each other including alcohol based antiseptic solutions compared with aqueous solutions. • Single preparation compared to double preparation

9.	Types of study to be included	• RCTs • Systematic reviews of RCTs If less than five RCTs identified, quasi randomised trials will be used
10.	Other exclusion criteria	• Conference abstracts and non-published studies will be excluded from the review. • Non-English language publications
11.	Context	Surgical site infection: prevention and treatment was published in October 2008. This guideline includes recommendations on information for patients and carers, the preoperative phase, the intraoperative phase and the post-operative phase. The guideline underwent regular surveillance at 3, 6 and 8 years following publication. During the 8 year surveillance process new evidence on the choice of preoperative skin antiseptics was identified. This warranted an update of this review question.
12.	Primary outcomes (critical outcomes)	• Surgical site infection (including SSIs at up to 30 days and 1 year) defined using an appropriate criteria such as the CDC SSI criteria.

13.	Secondary outcomes (important outcomes)	• Mortality post-surgery • Length of hospital stay • Postoperative antibiotic use • Hospital readmission • Infectious complications such as septicaemia or septic shock • Adverse events: • Antimicrobial resistance • Anaphylaxis • Skin and other allergic reactions.
14.	Data extraction (selection and coding)	See Appendix B
15.	Risk of bias (quality) assessment	See Appendix B
16.	Strategy for data synthesis	See Appendix B
17.	Analysis of sub-groups	• Type of surgery (including cardiac and orthopaedic surgery) • Wound classification (clean, clean-contaminated, contaminated, dirty) • Elective surgery • Emergency surgery
18.	Type and method of review	☒ Intervention ☐ Diagnostic

		☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)		
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	June 2018		
22.	Anticipated completion date	April 2019		
23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
		Preliminary searches	☑ ☑	☐ ☐

		Piloting of the study selection process	☐ ☐	☐ ☐
		Formal screening of search results against eligibility criteria	☐ ☐	☐ ☐
		Data extraction	☐ ☐	☐ ☐
		Risk of bias (quality) assessment	☐ ☐	☐ ☐
		Data analysis	☐ ☐	☐ ☐
24.	Named contact	**5a. Named contact** Guideline Updates Team		

		5b Named contact e-mail SSI@nice.org.uk **5c Named contact address** NICE Guideline Updates Team Centre for Guidelines NICE 10 Spring Gardens London, SW1A 2BU **5d Named contact phone number** +44 (0) 300 323 0410 **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE) and NICE Guideline Updates Team
25.	Review team members	From the Centre for Guidelines: • Caroline Mulvihill, Guideline Lead • Shreya Shukla, Technical Analyst • Jamie Elvidge, Health Economist • Sarah Glover, Information Specialist
26.	Funding sources/sponsor	This systematic review is being completed by the Centre for Guidelines which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with

		NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are: Chair: Damien Longson Members: • Melanie Burden, Infection Control Nurse • Pamela Carroll, Theatre Practitioner • Annie Hitchman, Patient/ carer • Peter Jenks, Microbiologist • David Leaper, Surgeon • Thomas Pinkney, Surgeon • Melissa Rochon, Infection Control Nurse • Giovanni Satta, Microbiologist • David Saunders, Anaesthetist • Nigel Westwood, Patient/ carer
29.	Other registration details	
30.	Reference/URL for published protocol	

31.	Dissemination plans	The reviewers and guideline committee work with NICE's communications team to disseminate and promote awareness of the guideline at the time of publication and afterwards. Members from the NICE communications team discuss with the reviewers and the committee opportunities for promoting the guideline. Committee members may be asked to take part in such activities. With help from the guideline committee and the developer, they identify how to reach relevant audiences for the guideline, including people using services, carers, the public, practitioners and providers. NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE. NICE may also use other means of raising awareness of the guideline – for example, newsletters, websites, training programmes, conferences, implementation workshops, NICE field team support and other speaking engagements. Some of these may be suggested by guideline committee members (particularly members affiliated to organisations for people using services and carer organisations). Each guideline is different and activities for raising awareness will vary depending on the type and content of the guideline.
32.	Keywords	Intervention, surgical site infections, invasive surgery, superficial SSI, deep SSI, deep organ space SSI, chlorhexidine, povidone iodine, alcohol preparation, aqueous preparation.

33.	Details of existing review of same topic by same authors	N/ A – this is a new review
34.	Current review status	☒ Ongoing ☐ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35..	Additional information	
36.	Details of final publication	www.nice.org.uk

Appendix B – Methods

Priority screening

The reviews undertaken for this guideline all made use of the priority screening functionality with the EPPI-reviewer systematic reviewing software. This uses a machine learning algorithm (specifically, an SGD classifier) to take information on features (1, 2 and 3 word blocks) in the titles and abstract of papers marked as being 'includes' or 'excludes' during the title and abstract screening process, and re-orders the remaining records from most likely to least likely to be an include, based on that algorithm. This re-ordering of the remaining records occurs every time 25 additional records have been screened.

As an additional check to ensure this approach did not miss relevant studies, the included studies lists of included systematic reviews were searched to identify any papers not identified through the primary search.

Quality assessment

Individual systematic reviews were quality assessed using the ROBIS tool, with each classified into one of the following three groups:

- High quality – It is unlikely that additional relevant and important data would be identified from primary studies compared to that reported in the review, and unlikely that any relevant and important studies have been missed by the review.
- Moderate quality – It is possible that additional relevant and important data would be identified from primary studies compared to that reported in the review, but unlikely that any relevant and important studies have been missed by the review.
- Low quality – It is possible that relevant and important studies have been missed by the review.

Each individual systematic review was also classified into one of three groups for its applicability as a source of data, based on how closely the review matches the specified review protocol in the guideline. Studies were rated as follows:

- Fully applicable – The identified review fully covers the review protocol in the guideline.
- Partially applicable – The identified review fully covers a discrete subsection of the review protocol in the guideline.
- Not applicable – The identified review, despite including studies relevant to the review question, does not fully cover any discrete subsection of the review protocol in the guideline.

Using systematic reviews as a source of data

If systematic reviews were identified as being sufficiently applicable and high quality, and were identified sufficiently early in the review process (for example, from the surveillance review or early in the database search), they were used as the primary source of data, rather than extracting information from primary studies. The extent to which this was done depended on the quality and applicability of the review, as defined in Table 5. When systematic reviews were used as a source of primary data, any unpublished or additional data included in the review which is not in the primary studies was also included. Data from these systematic reviews was then quality assessed and presented in GRADE tables as described below, in the same way as if data had been extracted from primary studies. In questions where data was extracted from both systematic reviews and primary studies, these were cross-referenced to ensure none of the data had been double counted through this process.

Table 5: Criteria for using systematic reviews as a source of data

Quality	Applicability	Use of systematic review
High	Fully applicable	Data from the published systematic review were used instead of undertaking a new literature search or data analysis. Searches were only done to cover the period of time since the search date of the review.
High	Partially applicable	Data from the published systematic review were used instead of undertaking a new literature search and data analysis for the relevant subsection of the protocol. For this section, searches were only done to cover the period of time since the search date of the review. For other sections not covered by the systematic review, searches were undertaken as normal.
Moderate	Fully applicable	Details of included studies were used instead of undertaking a new literature search. Full-text papers of included studies were still retrieved for the purposes of data analysis. Searches were only done to cover the period of time since the search date of the review.
Moderate	Partially applicable	Details of included studies were used instead of undertaking a new literature search for the relevant subsection of the protocol. For this section, searches were only done to cover the period of time since the search date of the review. For other sections not covered by the systematic review, searches were undertaken as normal.

Evidence of effectiveness of interventions

Quality assessment

Individual RCTs were quality assessed using the Cochrane Risk of Bias Tool. Other study were quality assessed using the ROBINS-I tool. Each individual study was classified into one of the following three groups:

- Low risk of bias – The true effect size for the study is likely to be close to the estimated effect size.
- Moderate risk of bias – There is a possibility the true effect size for the study is substantially different to the estimated effect size.
- High risk of bias – It is likely the true effect size for the study is substantially different to the estimated effect size.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, intervention, comparator and/or outcomes in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, intervention, comparator and/or outcomes.
- Partially indirect – Important deviations from the protocol in one of the population, intervention, comparator and/or outcomes.
- Indirect – Important deviations from the protocol in at least two of the following areas: population, intervention, comparator and/or outcomes.

Methods for combining intervention evidence

Meta-analyses of interventional data were conducted with reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011).

For continuous outcomes analysed as mean differences, where change from baseline data was reported in the trials and was accompanied by a measure of spread (for example standard deviation), these were extracted and used in the meta-analysis. Where different studies presented continuous data measuring the same outcome but using different numerical scales (e.g. a 0-10 and a 0-100 visual analogue scale), these outcomes were all converted to the same scale before meta-analysis was conducted on the mean differences. Where outcomes measured the same underlying construct but used different instruments/metrics, data were analysed using standardised mean differences (Hedges' g).

A pooled relative risk was calculated for dichotomous outcomes (using the Mantel–Haenszel method). Both relative and absolute risks were presented, with absolute risks calculated by applying the relative risk to the pooled risk in the comparator arm of the meta-analysis.

Fixed- and random-effects models (der Simonian and Laird) where appropriate, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models were the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model were clearly not met, even after appropriate pre-specified subgroup analyses were conducted, random-effects results are presented. Fixed-effects models were deemed to be inappropriate if one or both of the following conditions was met:

- Significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. This decision was made and recorded before any data analysis was undertaken.
- The presence of significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$.

In any meta-analyses where some (but not all) of the data came from studies at high risk of bias, a sensitivity analysis was conducted, excluding those studies from the analysis. Results from both the full and restricted meta-analyses are reported. Similarly, in any meta-analyses where some (but not all) of the data came from indirect studies, a sensitivity analysis was conducted, excluding those studies from the analysis.

Meta-analyses were performed in Cochrane Review Manager v5.3.

Minimal clinically important differences (MIDs)

The Core Outcome Measures in Effectiveness Trials (COMET) database was searched to identify published minimal clinically important difference thresholds relevant to this guideline. Identified MIDs were assessed to ensure they had been developed and validated in a methodologically rigorous way, and were applicable to the populations, interventions and outcomes specified in this guideline. In addition, the Guideline Committee were asked to prospectively specify any outcomes where they felt a consensus MID could be defined from their experience. In particular, any questions looking to evaluate non-inferiority (that one treatment is not meaningfully worse than another) required an MID to be defined to act as a non-inferiority margin.

No MIDs were identified. Therefore, a default MID interval for dichotomous outcomes of 0.8 to 1.25 was used.

When decisions were made in situations where MIDs were not available, the 'Evidence to Recommendations' section of that review should make explicit the committee's view of the expected clinical importance and relevance of the findings. In particular, this includes consideration of whether the whole effect of a treatment (which may be felt across multiple independent outcome domains) would be likely to be clinically meaningful, rather than simply whether each individual sub outcome might be meaningful in isolation.

GRADE for pairwise meta-analyses of interventional evidence

GRADE was used to assess the quality of evidence for the selected outcomes as specified in 'Developing NICE guidelines: the manual (2014)'. Data from all study designs was initially rated as high quality and the quality of the evidence for each outcome was downgraded or not from this initial point, based on the criteria given in **Error! Reference source not found.**6.

Table 6: Rationale for downgrading quality of evidence for intervention studies

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies at high and low risk of bias.
Indirectness	Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between direct and indirect studies.
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the I^2 statistic. N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study. Not serious: If the I^2 was less than 33.3%, the outcome was not downgraded. Serious: If the I^2 was between 33.3% and 66.7%, the outcome was downgraded one level. Very serious: If the I^2 was greater than 66.7%, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies with the smallest and largest effect sizes.
Imprecision	If an MID other than the line of no effect was defined for the outcome, the outcome was downgraded once if the 95% confidence interval for the effect size crossed one line of the MID, and twice if it crosses both lines of the MID. If the line of no effect was defined as an MID for the outcome, it was downgraded once if the 95% confidence interval for the effect size crossed the line of no effect (i.e. the outcome was not statistically significant), and twice if the sample size of the study was sufficiently small that it is not plausible any realistic effect size could have been detected. Outcomes were downgraded 1 level if presented as difference in medians without measure of spread. Evidence was further downgraded 1 level if the outcome was not statistically significant.

GRADE criteria	Reasons for downgrading quality
	Outcomes were downgraded 2 levels if effect size could not be calculated. Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios.

The quality of evidence for each outcome was upgraded if any of the following three conditions were met:

- Data from non-randomised studies showing an effect size sufficiently large that it cannot be explained by confounding alone.
- Data showing a dose-response gradient.
- Data where all plausible residual confounding is likely to increase our confidence in the effect estimate.

Publication bias

Publication bias was assessed in two ways. First, if evidence of conducted but unpublished studies was identified during the review (e.g. conference abstracts, trial protocols or trial records without accompanying published data), available information on these unpublished studies was reported as part of the review. Secondly, where 10 or more studies were included as part of a single meta-analysis, a funnel plot was produced to graphically assess the potential for publication bias.

Evidence statements

Evidence statements for pairwise intervention data are classified in to one of four categories:

- Situations where the data are only consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is 'statistically significant'), and the magnitude of that effect is most likely to meet or exceed the MID (i.e. the point estimate is not in the zone of equivalence). In such cases, we state that the evidence showed that there is an effect.
- Situations where the data are only consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is 'statistically significant'), but the magnitude of that effect is most likely to be less than the MID (i.e. the point estimate is in the zone of equivalence). In such cases, we state that the evidence could not demonstrate a meaningful difference.
- Situations where the data are consistent, at a 95% confidence level, with an effect in either direction (i.e. one that is not 'statistically significant') but the confidence limits are smaller than the MIDs in both directions. In such cases, we state that the evidence demonstrates that there is no difference.
- In all other cases, we state that the evidence could not differentiate between the comparators.

For outcomes without a defined MID or where the MID is set as the line of no effect, evidence statements are divided into 2 groups as follows:

- We state that the evidence showed that there is an effect if the 95% CI does not cross the line of no effect.
- The evidence could not differentiate between comparators if the 95% CI crosses the line of no effect.

Methods for combining direct and indirect evidence (network meta-analysis) for interventions

Conventional 'pairwise' meta-analysis involves the statistical combination of direct evidence about pairs of interventions that originate from two or more separate studies (for example, where there are two or more studies comparing A vs B).

In situations where there are more than two interventions, pairwise meta-analysis of the direct evidence alone is of limited use. This is because multiple pairwise comparisons need to be performed to analyse each pair of interventions in the evidence, and these results can be difficult to interpret. Furthermore, direct evidence about interventions of interest may not be available. For example studies may compare A vs B and B vs C, but there may be no direct evidence comparing A vs C. Network meta-analysis overcomes these problems by combining all evidence into a single, internally consistent model, synthesising data from direct and indirect comparisons, and providing estimates of relative effectiveness of all interventions compared to each other and the ranking of different interventions. Network meta-analyses were undertaken in all situations where the following three criteria were met:

- At least three treatment alternatives.
- A connected network to enable valid estimates to be made.
- The aim of the review was to produce recommendations on the most effective option,

Synthesis

Hierarchical Bayesian Network Meta-Analysis (NMA) was performed using OpenBUGS version 3.2.2. The models used reflected the recommendations of the NICE Decision Support Unit's Technical Support Documents (TSDs) on evidence synthesis, particularly TSD 2 ('A generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials'; see http://www.nicedsu.org.uk). The WinBUGS code provided in the appendices of TSD 2 was used without substantive alteration to specify synthesis models. Additionally, the models used for the detection of inconsistency in the evidence networks reflected the recommendations presented in TSD 4 ('Inconsistency in networks of evidence based on randomised controlled trials'; see http://www.nicedsu.org.uk)

Results were reported summarising 100,000 samples from the posterior distribution of each model, thinned by 10 to reduce autocorrelation, having first run and discarded 10,000 'burn-in' iterations. Three separate chains with different initial values were used. The MC error in all three models was less than 1% of the SD of each parameter.

Non-informative prior distributions were used in all models. Unless otherwise specified, trial-specific baselines and treatment effects were assigned Normal (0,100,000) priors, and the between-trial standard deviations used in random-effects models were given Uniform(0,5) priors. These are consistent with the recommendations in TSD 2 for dichotomous outcomes.

- Fixed- and random-effects models were explored for each outcome, with the final choice of model based on residual deviance and deviance information criterion (DIC): if DIC was at least 3 points lower for the random-effects model, it was preferred; otherwise, the fixed effects model was considered to provide an equivalent fit to the data in a more simpler analysis, and was preferred. Where sufficient studies were available, meta-regression was undertaken to explore the effect of study level covariates.

Modified GRADE for network meta-analyses

A modified version of the standard GRADE approach for pairwise interventions was used to assess the quality of evidence across the network meta-analyses undertaken. While most criteria for pairwise meta-analyses still apply, it is important to adapt some of the criteria to

take into consideration additional factors, such as how each 'link' or pairwise comparison within the network applies to the others. As a result, the following was used when modifying the GRADE framework to a network meta-analysis. It is designed to provide a single overall quality rating for an NMA, which can then be combined with pairwise quality ratings for individual comparisons (if appropriate), to judge the overall strength of evidence for each comparison.

Table 7: Rationale for downgrading quality of evidence for intervention studies

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If fewer than 33.3% of the studies in the network meta-analysis were at moderate or high risk of bias, the overall network was not downgraded. Serious: If greater than 33.3% of the studies in the network meta-analysis were at moderate or high risk of bias, the network was downgraded one level. Very serious: If greater than 33.3% of the studies in the network meta-analysis were at high risk of bias, the network was downgraded two levels.
Indirectness	Not serious: If fewer than 33.3% of the studies in the network meta-analysis were partially indirect or indirect, the overall network was not downgraded. Serious: If greater than 33.3% of the studies in the network meta-analysis were partially indirect or indirect, the network was downgraded one level. Very serious: If greater than 33.3% of the studies in the network meta-analysis were indirect, the network was downgraded two levels.
Inconsistency	N/A: Inconsistency was marked as not applicable if there were no links in the network where data from multiple studies (either direct or indirect) were synthesised. For network meta-analyses conducted under a Bayesian framework, the network was downgraded one level if the DIC for a random-effects model was lower than the DIC for a fixed-effects model. In addition, the direct and indirect treatment estimates were compared as a check on the consistency of the network.
Imprecision	Whether two options were meaningfully distinct was judged using the MIDs defined above for pairwise meta-analysis of the outcomes. Not serious: If at least one of the pairwise credible intervals from the NMA did not cross both ends of the defined MID Serious: If all pairwise credible intervals from the NMA crossed at least one end of the defined MID Very serious: If all pairwise credible intervals from the NMA crossed both ends of the defined MID.

Additional sensitivity analyses was conducted excluding studies which demonstrated high risk of bias.

Health economics

Literature reviews seeking to identify published cost–utility analyses of relevance to the issues under consideration were conducted for all questions. In each case, the search undertaken for the clinical review was modified, retaining population and intervention descriptors, but removing any study-design filter and adding a filter designed to identify relevant health economic analyses. In assessing studies for inclusion, population, intervention and comparator, criteria were always identical to those used in the parallel clinical search; only cost–utility analyses were included. Economic evidence profiles, including critical appraisal according to the Guidelines manual, were completed for included studies.

Economic studies identified through a systematic search of the literature are appraised using a methodology checklist designed for economic evaluations (NICE guidelines manual; 2014). This checklist is not intended to judge the quality of a study per se, but to determine whether

an existing economic evaluation is useful to inform the decision-making of the committee for a specific topic within the guideline.

There are 2 parts of the appraisal process. The first step is to assess applicability (that is, the relevance of the study to the specific guideline topic and the NICE reference case); evaluations are categorised according to the criteria in Table 4.

Table 4 Applicability criteria

Level	Explanation
Directly applicable	The study meets all applicability criteria, or fails to meet one or more applicability criteria but this is unlikely to change the conclusions about cost effectiveness
Partially applicable	The study fails to meet one or more applicability criteria, and this could change the conclusions about cost effectiveness
Not applicable	The study fails to meet one or more applicability criteria, and this is likely to change the conclusions about cost effectiveness. These studies are excluded from further consideration

In the second step, only those studies deemed directly or partially applicable are further assessed for limitations (that is, methodological quality); see categorisation criteria in Table 5.

Table 5 Methodological criteria

Level	Explanation
Minor limitations	Meets all quality criteria, or fails to meet one or more quality criteria but this is unlikely to change the conclusions about cost effectiveness
Potentially serious limitations	Fails to meet one or more quality criteria and this could change the conclusions about cost effectiveness
Very serious limitations	Fails to meet one or more quality criteria and this is highly likely to change the conclusions about cost effectiveness. Such studies should usually be excluded from further consideration

Studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly applicable UK analysis was available, then other less relevant studies may not have been included. Where selective exclusions were made on this basis, this is noted in the relevant section.

Where relevant, a summary of the main findings from the systematic search, review and appraisal of economic evidence is presented in an economic evidence profile alongside the clinical evidence.

Appendix C – Literature search strategies

Databases	Date searched	Version/files
Cochrane Central Register of Controlled Trials (CENTRAL)	25/05/2018	Issue 4 of 12, April 2018
Cochrane Database of Systematic Reviews (CDSR)	25/05/2018	Issue 5 of 12, May 2018
Database of Abstracts of Reviews of Effect (DARE)	25/05/2018	Issue 2 of 4, April 2015
HTA	25/05/2018	Issue 4 of 4, October 2016
Embase (Ovid)	25/05/2018	1974 to 2018 May 24
MEDLINE (Ovid)	25/05/2018	1946 to Present with Daily Update
MEDLINE In-Process (Ovid)	25/05/2018	May 24, 2018
MEDLINE Epub Ahead of Print[a]	25/05/2018	May 24, 2018
CINAHL Plus with full text (EBSCO)	25/05/2018	-
MHRA – Drug Safety Alerts	25/05/2018	-

The MEDLINE search strategy is presented below. This was translated for use in all of the other databases listed. The aim of the search was to identify evidence for the clinical question being asked. Randomised Controlled Trial and Systematic Review filters were used to identify the study designs specified in the Review Protocol.

1 Surgical Wound Infection/
2 Wound Infection/
3 SURGICAL WOUND DEHISCENCE/
4 Infection Control/
5 (infection adj4 control).tw.
6 Postoperative Complications/
7 ((wound? or incision* or suture*) adj4 (infect* or sepsis or septic* or dehiscen* or site* or contaminat* or disrupt* or ruptur* or separat*)).tw.
8 (SSI or SSIs or SSTI or SSTIs).tw.
9 Bacterial Infections/pc [Prevention & Control]
10 exp Specialties, surgical/
11 exp Surgical Procedures, Operative/
12 surgery.fs.

13 (surger* or surgical* or operat* or procedure*).tw.
14 exp Minimally Invasive Surgical Procedures/
15 (arthroscop* or laparoscop* or thoracoscop* or endoscop*).tw.
16 or/1-15
17 Water/ or Ethanol/ or Disinfection/ or exp Detergents/
18 (disinfect* or predisinfect* or pre-disinfect* or pre disinfect* or anti infect* or anti-infect* or antiinfect* or antisep* or alcohol* or ethanol or aqueous or aqua or water).tw.
19 (anti microbial* or anti-microbial* or antimicrobial*).tw.
20 Iodine/ or Iodine Compounds/
21 iodine*.tw.
22 ((iod or iodide) adj4 derivative*).tw.
23 (iodinated adj4 compound*).tw.
24 (bioiodine or steribath or thysat or estroven or nasciodine or tcp).tw.
25 Chlorhexidine/
26 (chlorhexidine or CHG).tw.
27 (novalsan or tubulicid or "sebidan a" or mk 412a or mk-412a or mk412a).tw.
28 (acriflex or bacticlens or bactigras or "cx powder" or cepton or chlorasept or chlorohex or clorhexitulle or corsodyl or curasept or dispray or eczmol or elgydium or hibidil or hibiscrub or hibitane or hydrex or periochip or perioguard or rotersept or savlon or serotulle or spotoway or sterexidine or steripod or gluconate or uniscrub or unisept or "uriflex c" or phiso-med or CB12 or cetriclens or chloraprep or Clearasil or covonia or cyteal or dermol or eludril or germolene or germoloid* or hibi or hibicet or hibisol or instillagel or medi-swab or medi-wipe or mycil or nystaform* or quinoderm or savloclens or savlodil or sterets or steriwipe or tisept or torbetol or travasept or tri-ac or xylocaine).tw.
29 iodophor*.tw.
30 Povidone-Iodine/
31 ((povidone adj4 iodine) or povidone-iodine).tw.
32 ((povidine adj4 iodine) or povidine-iodine).tw.
33 (PVP-I or PVPI or PVP I or PVP-iodine or PVPiodine or pvp iodine or polyvinylpyrrolidoneiodine* or polyvinylpyrrolidone-iodine* or polyvinylpyrrolidone iodine*).tw.
34 (alphadine* or betadine* or betaisodona or betasept or "brush off" or "cold sore lotion" or disadine* or inadine or pharmadine* or povidine* or "savlon dry" or videne or codella).tw.
35 or/17-34
36 administration, topical/ or administration, cutaneous/ or Skin/
37 (skin or topical* or cutan* or dermal* or dermis* or local* or cutis or derma or epicutaneous or transcutan* or percutan*).tw.
38 36 or 37
39 35 and 38
40 exp Anti-Infective Agents, Local/
41 39 or 40
42 Preoperative Care/ or Preoperative Period/
43 (presurg* or pre-surg* or pre surg* or preop* or pre-op* or pre op or periop* or peri-op* or peri op* or intraop* or perop*).tw.
44 Perioperative Care/ or Perioperative Period/ or Perioperative Nursing/ or Intraoperative care/ or Intraoperative Period/
45 ((before or plan* or ahead* or prepar* or prior or during or duration) adj4 (surg* or operat* or procedure* or repair* or care* or implant*)).tw.
46 or/42-45
47 16 and 41 and 46
48 animals/ not humans/
49 47 not 48
50 limit 49 to english language
51 Randomized Controlled Trial.pt.
52 Controlled Clinical Trial.pt.
53 Clinical Trial.pt.
54 exp Clinical Trials as Topic/

55 Placebos/
56 Random Allocation/
57 Double-Blind Method/
58 Single-Blind Method/
59 Cross-Over Studies/
60 ((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw.
61 (random$ adj3 allocat$).tw.
62 placebo$.tw.
63 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw.
64 (crossover$ or (cross adj over$)).tw.
65 or/51-64
66 Meta-Analysis.pt.
67 Network Meta-Analysis/
68 Meta-Analysis as Topic/
69 Review.pt.
70 exp Review Literature as Topic/
71 (metaanaly$ or metanaly$ or (meta adj3 analy$)).tw.
72 (review$ or overview$).ti.
73 (systematic$ adj5 (review$ or overview$)).tw.
74 ((quantitative$ or qualitative$) adj5 (review$ or overview$)).tw.
75 ((studies or trial$) adj2 (review$ or overview$)).tw.
76 (integrat$ adj3 (research or review$ or literature)).tw.
77 (pool$ adj2 (analy$ or data)).tw.
78 (handsearch$ or (hand adj3 search$)).tw.
79 (manual$ adj3 search$).tw.
80 or/66-79
81 65 or 80
82 50 and 81

Economic evaluations and quality of life data

Search filters to retrieve economic evaluations and quality of life papers were appended to the strategy listed above to identify relevant evidence. The MEDLINE economic evaluations and quality of life search filters are presented below. They were translated for use in MEDLINE in Process, Embase, The Cochrane Library, CINAHL and Econlit databases.

Sources searched to identify economic evaluations:

Databases	Date searched
Embase (Ovid)	25/05/2018
MEDLINE (Ovid)	25/05/2018
MEDLINE In-Process (Ovid)	25/05/2018
EconLit (Ovid)	25/05/2018

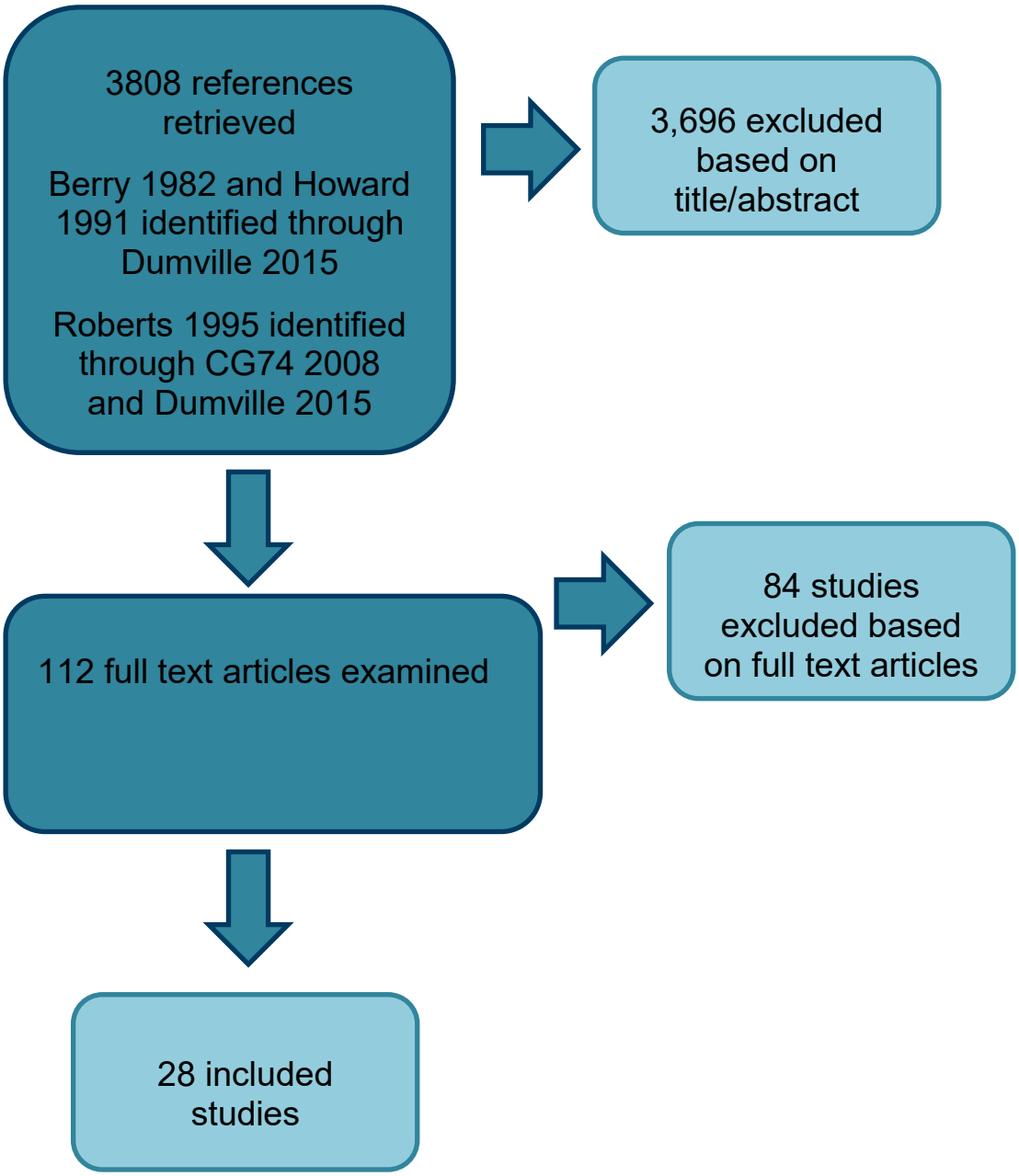
NHS Economic Evaluation Database (NHS EED) (legacy database)	25/05/2018
Health Technology Assessment (HTA Database)	25/05/2018
CINAHL Plus with Fulltext (EBSCO)	29/05/2018

Economic evaluations
1. Economics/
2. exp "Costs and Cost Analysis"/
3. Economics, Dental/
4. exp Economics, Hospital/
5. exp Economics, Medical/
6. Economics, Nursing/
7. Economics, Pharmaceutical/
8. Budgets/
9. exp Models, Economic/
10. Markov Chains/
11. Monte Carlo Method/
12. Decision Trees/
13. econom$.tw.
14. cba.tw.
15. cea.tw.
16. cua.tw.
17. markov$.tw.
18. (monte adj carlo).tw.
19. (decision adj3 (tree$ or analys$)).tw.
20. (cost or costs or costing$ or costly or costed).tw.
21. (price$ or pricing$).tw.
22. budget$.tw.
23. expenditure$.tw.
24. (value adj3 (money or monetary)).tw.
25. (pharmacoeconomic$ or (pharmaco adj economic$)).tw.
26. or/1-25

Quality of Life
1. "Quality of Life"/
2. quality of life.tw.
3. "Value of Life"/
4. Quality-Adjusted Life Years/
5. quality adjusted life.tw.
6. (qaly$ or qald$ or qale$ or qtime$).tw.
7. disability adjusted life.tw.
8. daly$.tw.
9. Health Status Indicators/
10. (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
11. (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
12. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.

13. (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
14. (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
15. (euroqol or euro qol or eq5d or eq 5d).tw.
16. (qol or hql or hqol or hrqol).tw.
17. (hye or hyes).tw.
18. health$ year$ equivalent$.tw.
19. utilit$.tw.
20. (hui or hui1 or hui2 or hui3).tw.
21. disutili$.tw.
22. rosser.tw.
23. quality of wellbeing.tw.
24. quality of well-being.tw.
25. qwb.tw.
26. willingness to pay.tw.
27. standard gamble$.tw.
28. time trade off.tw.
29. time tradeoff.tw.
30. tto.tw.
31. or/1-30

Appendix D – Clinical evidence study selection



Appendix E – Clinical evidence tables

E.1 Systematic Review

E.1.1 Dumville 2015

Full citation	Dumville (2015)
Study details	Study type: systematic review Location: UK Aim(s): to determine whether preoperative skin antisepsis immediately prior to surgical incision for clean surgery prevents SSI and to determine the comparative effectiveness of alternative antiseptics. Study dates: literature searched for publications up to January 2015 Follow-up: up to 10 months Sources of funding: this study was supported by funding from the UK National Institute of Health Research (NIHR)
Participants	Population: people of any age undergoing clean surgery as defined by the Centres for Disease Control Sample size: 13 RCTs including 2,623 participants Inclusion criteria: RCTs comparing different types of preoperative skin antiseptics with each other or no antiseptic treatment in people undergoing clean surgery were included. Antiseptics comprised powders or solutions that were applied to the patient's skin at the site of surgery, under sterile conditions before a surgical incision was made. The following comparisons were eligible for inclusion: • One or more antiseptics (solution, powder) compared with a control. • One type of antiseptic compared with another type of antiseptic. • One antiseptic applied more than once compared with the same antiseptic applied in a single application. • One antiseptic applied more than once compared with another antiseptic applied more than once. Authors stated that the settings were not limited to a specific clinical area as clean surgery can take place in a variety of environments. Exclusion criteria: studies which assessed cleansing techniques (such as antiseptic showers or body washes), and studies that compared the use of incise drapes were excluded.
Methods	This systematic review is the third update of a systematic review initially published in 2004. Literature searches were performed on the Cochrane Wounds Group Specialised Register and the Cochrane Central Register of Controlled Trials (CENTRAL) (constructed

Full citation	Dumville (2015)
	from weekly electronic searches of MEDLINE, Embase, and CINAHL databases). Additional searches were also performed on the Guideline Finder Specialist Library, Research Findings Register, and Centre for Reviews and Dissemination web site, National Electronic Library for Health. Bibliographies of included studies were reviewed to identify any additional studies that were relevant to the review question. Reviewers contacted manufacturers and distributors of antiseptic agents as well as professional organisations to obtain details about unpublished and ongoing studies. No restrictions were made relating to publication date, language or publication status. Two independent reviewers were involved in study selection, data extraction, and risk of bias assessments. Any disagreements were resolved through discussion.
Intervention	Paints, soaps, scrubs, and solutions comprising iodine-containing products, chlorhexidine-containing products or alcohol alone
Comparison	Each other, placebo or different doses/applications of the same antiseptic
Outcomes measures	Postoperative SSI as defined by CDC criteria, SSI as defined by authors, quality of life (as assessed by EQ-5D, SF-36, SF-12 or SF-6 or wound-specific questionnaires), adverse events, and resource use such as length of stay
Study Appraisal using ROBIS (Risk of bias in systematic reviews)	Domain 1- Study eligibility : Low risk of bias Domain 2- Identification and selection of studies: Low of bias Domain 3- Data collection and study appraisal: Low risk of bias Domain 4- Synthesis and findings: Low of risk Overall risk of bias: Low risk of bias Directness: Partially Directly applicable- study only examined clean surgery and data on superficial and deep SSI was not extracted from studies.

E.2 Primary Studies

E.2.1 Abreu 2014

	Abreu (2014)
Title	Surgical site infection in surgery for benign prostatic hyperplasia: comparison of two skin antiseptics and risk factors
Study details	**Study type** • Randomised controlled trial • Study location *Uruguay* • Study setting *Department of urology* • Study dates *February 2009- August 2009* • Duration of follow-up *All patients had a minimum postoperative follow up of 3 years* • Sources of funding *Not reported.* **Inclusion criteria** • *Patients undergoing surgery for benign prostatic hyperplasia* **Exclusion criteria** • None reported • Sample size *56* **Sample characteristics** • Split between study groups *Intervention group: 32* *Comparator group: 24* • Loss to follow-up *Not reported* • Mean Age (range) *Overall: 72 years (57-87 years)*
Interventions	• Chlorhexidine in alcohol preparation 0.5% chlorhexidine in an alcohol base (Chemisol) Assumed to be in 70% isopropyl alcohol. Antibiotic prophylaxis (ciprofloxacin) administered during the induction of anaesthesia and repeated every 12 hours until withdrawal of the catheter postoperatively.

	Abreu (2014)
Comparator	• Aqueous Povidone Iodine Aqueous 5% povidone iodine Antibiotic prophylaxis (ciprofloxacin) administered during the induction of anaesthesia and repeated every 12 hours until withdrawal of the catheter postoperatively.
Outcome measure(s)	• SSI Defined using CDC criteria.
Risk of bias Directness	**Random sequence generation** • Unclear risk of bias *Insufficient information provided* **Allocation concealment** • Unclear risk of bias *Insufficient information provided* **Blinding of participants and personnel** • Unclear risk of bias *Insufficient information provided. However, as outcomes were objective measures, study was not downgraded in this domain.* **Blinding of outcome assessment** • Unclear risk of bias *Insufficient information provided.* **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Moderate *Unclear random sequence generation, allocation concealment and blinding of outcome assessment.* **Directness** • Directly applicable

E.2.2 Alexander 1985

	Alexander (1985)
Title	Development of a safe and effective one-minute preoperative skin preparation

	Alexander (1985)
Study details	**Study type** • Randomised controlled trial *Paper reports data from preliminary studies and definitive study. Data from Preliminary study 2 (5-arm trial) and Definitive study (3-arm trial) extracted.* • Study location *USA* • Study setting *Hospital setting* • Study dates *Overall: 1981-July 1984 Preliminary 2 study: 1982-1983 Definitive study: 1983-1984* • Duration of follow-up *within 30 days of surgery* • Sources of funding *Not specified.* **Inclusion criteria** *• Patients on the surgical services of University Hospital, Cincinnati, and the Cincinnati Veterans Administration Hospital who underwent scheduled, elective operations* *• Operations had to involve the use of incise drapes* **Exclusion criteria** *•Operations involving the perineal area, genitalia, feet, upper extremities, head and neck* *•Patients allergic to iodine* *• Dirty wounds* • Sample size *Preliminary study: 115* *Definitive study: 480* **Sample characteristics** • Split between study groups *Preliminary study 2:* *Group 1 (70% alcohol + incise drape): 45* *Group 2 (Tincture of CH(Hibitane) + incise drape): 28* *Group 3 (2% iodine in 50% alcohol+ incise drape): 17* *Group 4 (2% iodine in 70% alcohol + incise drape):12* *Group 5 (2% iodine in 90% alcohol + incise drape): 13*

	Alexander (1985)
	Data on Group 1, 3,4 and 5 were extracted. Authors reported that skin preparation with Hibitane did not appear to have an advantage over 70% alcohol so this agent was dropped from evaluation after 28 patient entries. *Definitive study:* *Group 1 (70% alcohol + incise drapes): 147* *Group 2 (2% iodine in 90% in 70% alcohol + incise drapes):164* *Group 3 (Betadine): 169* *Data on Group 3 was not extracted as it did not include use of drape.* • Loss to follow-up *Not reported.*
Interventions	• Alcohol Preliminary study 2: 70% alcohol One minute scrub with 70% alcohol. The skin was allowed to dry thoroughly before application of the polyester antimicrobial incise drape. All patients had the operative area washed the night before with an antibacterial soap and hair was removed by clipper the morning of the operation. Definitive study: 70% alcohol One minute scrub with 70% alcohol. All patients had the operative area washed the night before with an antibacterial soap. Incise drapes were also applied. • Iodine in alcohol Preliminary study 2: 2% iodine in 50% alcohol one minute scrub with 2% iodine in 50% iodine. The skin was allowed to dry thoroughly before application of the polyester antimicrobial incise drape. All patients had the operative area washed the night before with an antibacterial soap and hair was removed by clipper the morning of the operation. 2% iodine in 70% alcohol

	Alexander (1985)
	One minute scrub with 2% iodine in 70% iodine. The skin was allowed to dry thoroughly before application of the polyester antimicrobial incise drape. All patients had the operative area washed the night before with an antibacterial soap and hair was removed by clipper the morning of the operation. 2% iodine in 90% iodine One minute scrub with 2% iodine in 90% iodine. The skin was allowed to dry thoroughly before application of the polyester antimicrobial incise drape. All patients had the operative area washed the night before with an antibacterial soap and hair was removed by clipper the morning of the operation. Definitive study: 2% iodine in 90% iodine. One minute scrub with 2% iodine in 90% iodine. All patients had the operative area washed the night before with an antibacterial soap. Incise drapes were also applied.
Outcome measure(s)	• SSI Infection was defined as the discharge of pus whether or not cultures were positive, but culture was taken where possible.
Risk of bias Directness	**Random sequence generation** • Unclear risk of bias *Insufficient information provided* **Allocation concealment** • Unclear risk of bias *insufficient information provided* **Blinding of participants and personnel** • Unclear risk of bias *Insufficient information provided. However, as outcomes were objective measures, study was not downgraded in this domain.* **Blinding of outcome assessment** • Unclear risk of bias *Insufficient information provided.* **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Moderate

	Alexander (1985)
	Unclear random sequence generation, allocation concealment and blinding of outcome assessment. **Directness** • Directly applicable

E.2.3 Berry 1982

	Berry (1982)
Title	A comparison of the use of povidone-iodine and chlorhexidine in the prophylaxis of postoperative wound infection.
Study details	**Study type** • Randomised controlled trial • Study location *UK* • Study setting *Hospital setting* • Study dates *May 1978 and February 1980* • Duration of follow-up *At time of discharge* • Sources of funding *Not reported.* **Inclusion criteria** • *All elective surgical cases* **Exclusion criteria** • *Patients sensitive to preparations* • Sample size *866* **Sample characteristics** • Split between study groups *Intervention group: 453* *Comparator group: 413* *Clean surgery only (Data from Dumville 2015)* *intervention group: 286*

	Berry (1982)
	Comparator group: 256 • Loss to follow-up *Not reported.*
Interventions	• Chlorhexidine in alcohol preparation 0.5% chlorhexidine in spirit Patients undergoing colonic and rectal surgery received 200 mg of metronidazole three times daily and neomycin 1 g four hourly for three days. No other group of patients received prophylaxis routinely. 0.5% chlorhexidine in spirit also used for surgical scrub. A sterile brush was used to scrub the hands, paying particular attention to areas under the nails and in the nail folds.
Comparator	• Povidone iodine in alcohol preparation 10% Povidone iodine in alcohol Patients undergoing colonic and rectal surgery received 200 mg of metronidazole three times daily and neomycin 1 g four hourly for three days. No other group of patients received prophylaxis routinely. 7.55 povidone iodine also used for surgical scrub. A sterile brush was used to scrub the hands, paying particular attention to areas under the nails and in the nail folds.
Outcome measure(s)	• SSI Wounds were judged at each inspection as fitting one or more of the following categories: normal, erythematous, oedematous, discharging or purulent. Swabs for bacterial examination were taken for all moist wounds. Data on clean surgery only extracted from Duumville 2015.
Risk of bias Directness	**Random sequence generation** • Low risk of bias **Allocation concealment** • Low risk of bias **Blinding of participants and personnel** • Unclear risk of bias *Study reported that assessment was blinded when possible, however on occasion wounds had to be assessed by staff who were present during the operating session.* **Blinding of outcome assessment** • Low risk of bias **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias

	Berry (1982)
	Other sources of bias • Low risk of bias **Overall risk of bias** • Low **Directness** • Partially directly applicable *Patients and surgeons were allocated to different skin preparations and surgical scrub.*

E.2.4 Bibbo 2005

	Bibbo (2005)
Title	Chlorhexidine provides superior skin decontamination in foot and ankle surgery: a prospective randomized study
Study details	**Study type** • Randomised controlled trial • Study location *USA* • Study setting *Department of orthopaedics* • Study dates *Not specified.* • Duration of follow-up *Not reported.* • Sources of funding *Not reported.* **Inclusion criteria** • *Patients with intact, uninfected skin having clean, elective foot and ankle surgery* **Exclusion criteria** • *Patients with open wounds* • *Patients with skin ulcers and/or sores* • *Patients with an active acute or chronic infection* • *Patients who were on active antimicrobial therapy which could alter skin flora* • Sample size *127*

	Bibbo (2005)
	Sample characteristics • Split between study groups *Intervention group: 67* *Comparator group: 60* • Loss to follow-up *Not reported* • %female *Intervention group: 48%* *Comparator group: 57%* • Mean Age (range) *Intervention group: 45 years (16-85)* *Comparator group: 48 years (16-79 years)*
Interventions	• Aqueous povidone iodine scrub and paint *Aqueous 7.5% povidone iodine and 10% paint* *7 minute scrub with aqueous 7.5% povidone iodine and 10% paint of the foot and ankle. No special instructions for bathing or showering were implemented before surgery, patients followed their usual personal hygiene routine on the day of surgery. Foot scrubs were administered and timed by orthopaedic registered nurse. Each extremity was allowed to dry after skin preparation before draping. Sterile surgical barriers were not used.*
Comparator	• Aqueous Chlorhexidine scrub and paint *Aqueous chlorhexidine gluconate (4%) and isopropyl alcohol (70%) paint* *7 minute scrub with aqueous chlorhexidine gluconate (4%) and isopropyl alcohol (70%) paint of the foot and ankle. No special instructions for bathing or showering were implemented before surgery, patients followed their usual personal hygiene routine on the day of surgery. Foot scrubs were administered and timed by orthopaedic registered nurse. Each extremity was allowed to dry after skin preparation before draping. Sterile surgical barriers were not used.*
Outcome measure(s)	• SSI *Criteria used for classifying infections not specified.*
Risk of bias Directness	**Random sequence generation** • Unclear risk of bias *Insufficient information provided.* **Allocation concealment** • Unclear risk of bias *Insufficient information provided.*

	Bibbo (2005)
	Blinding of participants and personnel • Unclear risk of bias *Insufficient information provided. However, as outcomes were objective measures, study was not downgraded in this domain.* **Blinding of outcome assessment** • Unclear risk of bias Insufficient information provided. **Incomplete outcome data** • Unclear risk of bias Insufficient information provided. **Selective reporting** • Low risk of bias **Other sources of bias** • Unclear risk of bias **Overall risk of bias** • High Unclear random sequence generation, allocation concealment, blinding of outcome assessment and incomplete outcome data. **Directness** • Partially directly applicable *Criteria used to classify SSIs not specified. Follow-up period not specified.*

E.2.5 Bibi 2015

	Bibi (2015)
Title	Is chlorhexidine-gluconate superior than Povidone-Iodine in preventing surgical site infections? A multicenter study
Study details	**Study type** • Randomised controlled trial • **Study location** *Pakistan* • **Study setting** *Two public-sector hospitals* • **Study dates** *May 2012 and April 2013* • **Duration of follow-up**

	Bibi (2015)
	Until 30 days. • **Sources of funding** *Grant received from Pakistan Research Council* **Inclusion criteria** • *All patients aged 18-60 years undergoing elective clean or clean contaminated surgery in selected wards* **Exclusion criteria** • *Patients who had diabetes, infection adjacent to the site of surgery or those undergoing emergency surgery and unwilling to participate.* • **Sample size** *388* **Sample characteristics** • **Split between study groups** *Intervention group: 168* *Comparator group:220* • **Loss to follow-up** *Loss to follow up not reported but authors noted that loss to follow up was mainly attributable to the wrong contact numbers provided by the patients since the follow up was being done simultaneously on telephone.* • **%female** *Intervention group: 62.5%* *Comparator group: 59.6%* • **Mean age (SD)** *Intervention group: 40.4 (13.91)* *Comparator group: 41.32 (15.5)*
Interventions	**Chlorhexidine in alcohol preparation** 2% chlorhexidine gluconate in 70% isopropyl alcohol Patients were scrubbed with 2% chlorhexidine gluconate in 70% isopropyl alcohol. Antibiotic prophylaxis was provided.
Comparator	**Aqueous Povidone Iodine** 10% Povidone Iodine Patients were scrubbed with 10% povidone iodine. Antibiotic prophylaxis was provided.
Outcome measure(s)	• **SSI**

	Bibi (2015)
	Classified using CDC definition. • **Skin and other allergic reactions**
Risk of bias Directness	**Random sequence generation** • Low risk of bias **Allocation concealment** • Unclear risk of bias *Insufficient information* **Blinding of participants and personnel** • High risk of bias *Patients unaware however operating surgeon and operating theatre technician were informed about preparation used. However, as outcomes were objective measures, study was not downgraded in this domain.* **Blinding of outcome assessment** • Unclear risk of bias *Insufficient information provided.* **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Low **Directness** • Directly applicable

E.2.6 Broach 2017

	Broach (2017)
Title	Randomized Controlled Trial of Two Alcohol-based Preparations for Surgical Site Antisepsis in Colorectal Surgery
Study details	**Study type** • Randomised controlled trial • Study location *USA* • Study setting *Hospital setting*

	Broach (2017)
	• Study dates *January 2011 and January 2015* • Duration of follow-up *Within 30 days post discharge* • Sources of funding *Not reported.* **Inclusion criteria** *• 18 years or age or above undergoing an elective clean-contaminated colorectal procedure* **Exclusion criteria** *• Antibiotic use within 5 days before surgery* *• Infected or dirty wound classification* *• Preoperative plan to leave the incision open* *• Ongoing radiation or chemotherapy* *• History of laparotomy within 60 days* *• Current abdominal wall infection* *• Known allergy to chlorhexidine or iodine* *• Participating in any concomitant preoperative antibiotic or skin antisepsis trial* *• Women who were pregnant or breastfeeding* • Sample size *802* **Sample characteristics** • Split between study groups *Intervention group: 402* *Comparator group: 400* • Loss to follow-up *Intervention group: 4 excluded due to reoperation within 30 days, 2 bowel resection aborted, 18 insufficient follow up* *Comparator group: 6 excluded due to reoperation within 30 days, 2 bowl resection aborted, 12 insufficient follow up* • %female *Intervention group: 51.3%* *Comparator group: 51.5%* • Mean age (SD) *Intervention group: 56.8 (15.8)*

	Broach (2017)
	Comparator group: 57.0 (16.7) • Body Mass Index (SD) *Intervention group: 28.1(5.8)* *Comparator group: 27.9 (5.5)* • Diabetes (%) *Intervention group: 12.2%* *Comparator group: 14.8%*
Interventions	• Iodophor in alcohol *0.7% available iodine with 74% isopropyl alcohol (Duraprep)* *A single applicator was used for most patients. Those who were morbidly obese required a second applicator. The group required a single pass application. Allowed to dry for 3 minutes before draping. All preparation sticks were used according to manufacturer's instructions by attending surgeons, residents or fellow who underwent live and video training.*
Comparator	• Chlorhexidine in alcohol preparation *2% chlorhexidine and 70% isopropyl alcohol* *A single applicator was used for most patients. Those who were morbidly obese required a second applicator. The group required a several passes of the applicator in a circular motion. Allowed to dry for 3 minutes before draping. All preparation sticks were used according to manufacturer's instructions by attending surgeons, residents or fellow who underwent live and video training.*
Outcome measure(s)	• SSI *CDC criteria used to define infection.* • Superficial SSI *CDC criteria used to define infection.* • Deep SSI *CDC criteria used to define infection.* • Organ/space SSI *CDC criteria used to define infection.* • Length of hospital stay • Cellulitis
Risk of bias Directness	**Random sequence generation** • Low risk of bias **Allocation concealment** • Low risk of bias **Blinding of participants and personnel** • Unclear risk of bias *Insufficient information provided. However, as outcomes were objective measures, study was not downgraded in this domain.* **Blinding of outcome assessment**

	Broach (2017)
	• Low risk of bias **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Low **Directness** • Directly applicable

E.2.7 Brown 1984

	Brown (1984)
Title	A clinical evaluation of chlorhexidine gluconate spray as compared with iodophor scrub for preoperative skin preparation
Study details	**Study type** • Randomised controlled trial • Study location *USA* • Study setting *University Hospital* • Study dates *December 1979 and November 1980* • Duration of follow-up *In-hospital follow up* • Sources of funding *Not reported* **Inclusion criteria** • *Patients undergoing laparotomy of all types, mastectomy and caesarean section* • *Patients from both private and clinic services* **Exclusion criteria** • *Patients undergoing surgery not included in the study protocol* • Sample size *737*

	Brown (1984)
	Sample characteristics • Split between study groups *Intervention group: 378* *Comparator group: 359*
Interventions	• Chlorhexidine in alcohol preparation *0.5% chlorhexidine with 70% isopropyl alcohol* *The study technique consisted of removal of obvious foreign material present in the umbilicus or skin fold with a clean sponge followed by a soap application of 0.5% isopropyl alcohol.*
Comparator	• Aqueous Povidone iodine scrub and paint *Aqueous povidone iodine scrub (7.5%) and paint (assumed to be 10%).* *6 minute scrub with soap. The soap was absorbed with a sterile towel and then the skin was painted with aqueous povidone iodine solution.*
Outcome measure(s)	• SSI *Minor wound: an infected wound with superficial separation (less than 1 centimetre) involving less than one-third of the incision or induration of the wound edge believed by surgeon to be secondary to infection.* *Major wound: infected wound with separation of the wound edges greater than one-third of the length of the incision or frank wound infection with evidence of purulent exudate or abscess.*
Risk of bias Directness	**Random sequence generation** • Unclear risk of bias *Insufficient information provided.* **Allocation concealment** • Low risk of bias **Blinding of participants and personnel** • Unclear risk of bias *Insufficient information provided. Study was not downgraded in this domain.* **Blinding of outcome assessment** • Unclear risk of bias *Insufficient information provided.* **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias

	Brown (1984)
	Overall risk of bias • Low **Directness** • Directly applicable

E.2.8 Casey 2015

	Casey (2015)
Title	A comparison of the efficacy of 70% v/v isopropyl alcohol with either 0.5% w/v or 2% w/v chlorhexidine gluconate for skin preparation before harvest of the long saphenous vein used in coronary artery bypass grafting
Study details	**Study type** • Randomised controlled trial • Study location *UK* • Study setting *Hospital setting* • Study dates *Not reported* • Duration of follow-up *Within 30 days after surgery* • Sources of funding *Not reported* **Inclusion criteria** *• Patients who were aged 18 years or older, able to give fully informed written consent, and due to undergo elective isolated or combined CABG with planned harvest of the long saphenous vein for conduit with postoperative admission to the cardiac critical care unit* **Exclusion criteria** *•Known history of chlorhexidine allergy or dermatoses* *• Inflammation* *•Injuries to the potential harvest site* • Sample size *100*

	Casey (2015)
	Sample characteristics • Split between study groups *Intervention group: 50* *Comparator group: 50* • Loss to follow-up *Intervention group: 8 not contactable, 1 had change of surgical plan in regard to conduit harvest site.* *Comparator group: 2 died, 4 not contactable* • %female *Intervention group: 12%* *Comparator group: 8%* • Median age (range) *Intervention group: 68 (35-83)* *Comparator group: 69.5 (41-85)* • Diabetes (%) *Intervention group: 38%* *Comparator group: 50%*
Interventions	• Chlorhexidine in alcohol preparation *0.5% chlorhexidine with 70% isopropyl alcohol* *On the morning of the surgery, patients underwent shower with 4% chlorhexidine and if hair was present it was clipped. All patients' received prophylactic antibiotics within 1 hour before incision. Applied using back and forth stokes using sterile forceps and gauze.*
Comparator	• Chlorhexidine in alcohol preparation *2% chlorhexidine with 70% isopropyl alcohol (ChloraPrep)* *On the morning of the surgery, patients underwent shower with 4% chlorhexidine and if hair was present it was clipped. All patients' received prophylactic antibiotics within 1 hour before incision. The patients had skin on their legs painted using 26 mL singl use applicators containing 2% CHG/60% IPA using back and forth strokes of the applicator over the entire area of both legs for 30 seconds.*
Outcome measure(s)	• Superficial SSI *SSI defined in line with modified CDC definitions.*
Risk of bias Directness	**Random sequence generation** • Low risk of bias **Blinding of participants and personnel** • High risk of bias *Surgical team could not be blinded as the applicator and colour of tint were different in each group. However, patients were unaware of the group assignments. However, as outcomes were objective measures, study was not downgraded in this domain.*

	Casey (2015)
	Blinding of outcome assessment • Low risk of bias **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Low **Directness** • Directly applicable

E.2.9 Charles 2017

	Charles (2017)
Title	Alcoholic versus aqueous chlorhexidine for skin antisepsis: the AVALANCHE trial
Study details	**Study type** • Randomised controlled trial • Study location *Australia* • Study setting *4 private general practices* • Study dates *October 2015 to August 2016* • Duration of follow-up *within 30 days after surgery* • Sources of funding *Study received funding from Royal Australian College of General Practitioners, a Royal Australian College of General Practitioners Family Medical Care Education and Research Grant, the Mackay Private Practitioners Fund and James Cook University Honours Program grant.* **Inclusion criteria** •*Consecutive patients presenting for minor skin excision (ie. excision of benign or malignant skin lesions under local anaesthetic, performed in general practice)* **Exclusion criteria** • *Patients already taking antibiotics*

	Charles (2017)
	• *Sebaceous cyst* • *Allergy to alcohol or chlorhexidine* • *Did not plan to exclude periocular excision however during the first week of data collection, 1 patient experienced ocular irritation from an alcoholic solution, and patients with this type of lesion were excluded thereafter.* • Sample size *916* **Sample characteristics** • Split between study groups *Intervention group: 454* *Comparator group: 462* • Loss to follow-up *7 patients lost to follow up* • %female *Intervention group: 41.4%* *Comparator group: 45.7%* • Mean age (SD) *Intervention group: 65.1 (14.2)* *Comparator group: 64.8 (13.9)* • Diabetes (%) *Intervention group: 9.7%* *Comparator group: 11.5%*
Interventions	• Chlorhexidine in alcohol preparation *0.5% chlorhexidine with 70% ethanol The antiseptic solution was applied using sterile forceps and gauze over an area 1 cm beyond surgical field. The clinicians used a diathermy protocol to minimize the risk of fires.*
Comparator	• Aqueous chlorhexidine *0.55 chlorhexidine in aqueous solution The antiseptic solution was applied using sterile forceps and gauze over an area 1 cm beyond surgical field.*
Outcome measure(s)	• SSI *Determined according to modified version of CDC definition. The infection was required to occur within 30 days of the excision and to involve only skin or subcutaneous tissue. Additionally, at least 1 of following had ot have occurred: - purulent discharge with or without laboratory confirmation from the superficial excision -at least 1 of pain or tenderness - localised swelling -redness or heat -or diagnosis of superficial infection by physician*

	Charles (2017)
	• Adverse events *Manifesting as anyone of anaphylaxis, skin irritation contact dermatitis or rash*
Risk of bias Directness	**Random sequence generation** • Low risk of bias **Allocation concealment** • Low risk of bias **Blinding of participants and personnel** • High risk of bias *Blinding of personnel and patients was not feasible due to smell of the alcoholic preparations. However, as outcomes were objective measures, study was not downgraded in this domain.* **Blinding of outcome assessment** • Low risk of bias *Treating doctor was blinded to treatment assessment.* **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Low **Directness** • Directly applicable

E.2.10 Cheng 2009

	Cheng (2009)
Title	Quantitative analysis of bacteria in forefoot surgery: a comparison of skin preparation techniques
Study details	**Study type** • Randomised controlled trial **Study details** • Study location *UK* • Study setting *Hospital setting*

	Cheng (2009)
	• Study dates *August 2007 and January 2008* • Duration of follow-up *not specified.* • Sources of funding *Not specified.* **Inclusion criteria** • *Patients undergoing foot surgery* **Exclusion criteria** • *Patients that had current open wounds, skin ulcer and/or sores* • *Patients with history of onychomycosis, paronychia or nail deformity* • *Patients with poorly controlled diabetes or recent antibiotic use (within 1 week of surgery).* • Sample size *50* **Sample characteristics** • Split between study groups *Intervention group: 25* *Comparator group: 25* • Loss to follow-up *Not reported* • Mean age (SD) *Overall: 51.1 (17.4)*
Interventions	• Povidone iodine in alcohol preparation *10% povidone iodine in isopropyl alcohol* *A sterile surgical brush was used to generously apply the solution using the foam part of the brush. The bristled side was then used to scrub the foot for a standardised 3 minute. Each extremity was allowed to dry prior to draping.*
Comparator	• Chlorhexidine in alcohol preparation *0.5% chlorhexidine with 70% isopropyl alcohol* *A sterile surgical brush was used to generously apply the solution using the foam part of the brush. The bristled side was then used to scrub the foot for a standardised 3 minute. Each extremity was allowed to dry prior to draping.*
Outcome measure(s)	• SSI *Criteria used to defined SSI not specified.*
Risk of bias Directness	**Random sequence generation** • Unclear risk of bias

	Cheng (2009)
	Insufficient information provided. **Allocation concealment** • Unclear risk of bias *Insufficient information provided.* **Blinding of participants and personnel** • Unclear risk of bias *Insufficient information provided. However, as outcomes were objective measures, study was not downgraded in this domain.* **Blinding of outcome assessment** • Unclear risk of bias *Insufficient information provided.* **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Unclear risk of bias **Overall risk of bias** • High *Unclear random sequence generation, allocation concealment, blinding of outcome assessment and other sources of bias.* **Directness** • Partially directly applicable *Criteria used to define SSI not specified. Follow up period not specified.*

E.2.11 Darouiche 2010

	Darouiche (2010)
Title	Chlorhexidine-Alcohol versus Povidone-Iodine for Surgical-Site Antisepsis
Study details	**Study type** • Randomised controlled trial • **Study location** *USA* • **Study setting** *6 university affiliated hospitals* • **Study dates** *April 2004 and May 2008* • **Duration of follow-up**

	Darouiche (2010)
	Within 30 days after surgery • **Sources of funding** *Research and educational grants from Cardinal Health.* **Inclusion criteria** • *Patients 18 years of age or older who were undergoing clean-contaminated surgery (i.e. colorectal, small intestinal, gastroesophageal, biliary, thoracic, gynaecologic, or urologic operations performed under controlled conditions without substantial spillage or unusual contamination)* **Exclusion criteria** • *History of allergy to chlorhexidine, alcohol, or iodophors* • *Evidence of infection at or adjacent to the operative site* • *perceived inability to follow the patient's course for 30 days after surgery.* • **Sample size** *897* **Sample characteristics** • **Split between study groups** *Intervention group: 431* *Comparator group: 466* • **Loss to follow-up** *Intervention group: 12 patients had clean instead of clean-contaminated surgery, 2 dropped out of study and 4 died during 30 day follow up* *Comparator group: 13 patients had clean instead of clean-contaminated surgery, 2 dropped out of study and 3 died during 30 day follow up* • **%female** *Intervention group: 41.1%* *Comparator group: 44.1 %* • **Mean age (SD)** *Intervention group: 53.3 (14.6)* *Comparator group: 52.9 (14.2)*

	Darouiche (2010)
Interventions	• **Chlorhexidine in alcohol preparation** 2% Chlorhexidine gluconate and 70% isopropyl alcohol (Chloraprep, Cardinal Health). Skin at surgical site either preoperatively scrubbed with an applicator that contained 2% chlorhexidine gluconate and 70% isopropyl alcohol. More than one chlorhexidine-alcohol applicator was used if the coverage area exceeded 33 by 33 cm.
Comparator	• **Aqueous Povidone iodine scrub and paint** Aqueous 7.5% povidone iodine scrub and 10% paint (Care skin prep tray, Cardinal Health).
Outcome measure(s)	• **SSI** Defined using CDC criteria. • **Superficial SSI** Defined using CDC criteria. Involves only skin and subcutaneous tissue and excluded stitch-related abscesses. • **Deep SSI** Defined using CDC criteria. Infection involving fascia and muscle. • **Organ/space SSI** Defined CDC criteria. Involved any organ or space other than the incised layer of body wall that was opened or manipulated during the operation. • **Sepsis from SSI**
Risk of bias Directness	**Random sequence generation** • Low risk of bias **Allocation concealment** • Unclear risk of bias *Insufficient information provided.* **Blinding of participants and personnel** • High risk of bias *Patients blinded to allocation however operating surgeon became aware of which of assignment. However, as outcomes were objective measures, study was not downgraded in this domain.* **Blinding of outcome assessment** • Low risk of bias **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias

	Darouiche (2010)
	Overall risk of bias • Low **Directness** • Directly applicable

E.2.12 Ellenhorn 2005

	Ellenhorn (2005)
Title	Paint-only is equivalent to scrub-and-paint in preoperative preparation of abdominal surgery sites
Study details	**Study type** • Randomised controlled trial • Study location *USA* • Study setting *Cancer Centre* • Study dates *Not specified.* • Duration of follow-up *within 30 days after surgery* • Sources of funding *Not specified.* **Inclusion criteria** • *Patients undergoing elective abdominal operation* **Exclusion criteria** • *Patients with active infection at the time of operation, neutropenia defined as a white blood cell count of <2000 or an absolute neutrophil count of <500* • *Patients with history of skin reaction to iodine* • *Anticipated use of prosthetic material as part of the surgical procedure.* • Sample size *234* **Sample characteristics** • Split between study groups *Intervention group: 115* *Comparator group: 119* • Loss to follow-up *Not reported.*
Interventions	• Aqueous povidone iodine scrub and paint *Aqueous povidone iodine scrub (7.5%) and paint (10%)* *Patients underwent a vigorous 5 minute scrub using urethane sponges saturated with povidone iodine detergent. Detergent was then absorbed with a blotting towel, before painting the operative site with aqueous povidone iodine solution, which was allowed to air dry.*

	Ellenhorn (2005)
	Before preoperative skin preparation, patients had all gross foreign material removed from the skin using a dry sponge and tape remover, if necessary. Use of perioperative IV antibiotics was left to the discretion of the operating surgeon. Study participants were not instructed to shower with any antibacterial agent before the operation.
Comparator	• Aqueous Povidone Iodine *Aqueous 10% povidone iodine* *Single application of aqueous povidone iodine solution was allowed to air dry. Before preoperative skin preparation, patients had all gross foreign material removed from the skin using a dry sponge and tape remover, if necessary. Use of perioperative IV antibiotics was left to the discretion of the operating surgeon. Study participants were not instructed to shower with any antibacterial agent before the operation.*
Outcome measure(s)	• SSI *Infection was defined by clinical criteria as presence of wound erythema or purulence requiring therapeutic intervention within the first 30 days after surgical procedure.* Data on clean surgery only extracted from Duumville 2015. Data on clean-contaminated surgery was calculated using information provided in paper.
Risk of bias Directness	**Random sequence generation** • Unclear risk of bias *Insufficient information provided.* **Allocation concealment** • Unclear risk of bias *Insufficient information provided.* **Blinding of participants and personnel** • Unclear risk of bias *Insufficient information provided. However, as outcomes were objective measures, study was not downgraded in this domain.* **Blinding of outcome assessment** • Unclear risk of bias *Insufficient information provided.* **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Unclear risk of bias **Overall risk of bias** • High

	Ellenhorn (2005)
	Unclear random sequence generation, allocation concealment, blinding of outcome assessment and other sources of bias. **Directness** • Directly applicable

E.2.13 Gilliam 1990

	Gilliam (1990)
Title	Comparison of a one-step iodophor skin preparation versus traditional preparation in total joint surgery
Study details	**Study type** • Randomised controlled trial • Study location *USA* • Study setting *Department of orthopaedic Surgery* • Study dates *Not specified.* • Duration of follow-up *Not specified.* • Sources of funding *Not specified.* **Inclusion criteria** • *Patients having clean total joint surgery* **Exclusion criteria** • None reported • Sample size *60* **Sample characteristics** • Split between study groups *Intervention group: 30* *Comparator group: 30* • Loss to follow-up *Not reported.* • %female *Intervention group: 73%* *Comparator group: 63%* • Mean Age (range) *Intervention group: 61 (18-86)* *Comparator group: 65 (35-79)*

	Gilliam (1990)
Interventions	• Aqueous povidone iodine scrub and paint *Aqueous povidone iodine scrub (7.5%) and paint (10%) (assumed)* *All hair was removed by dry shave just prior to preparing the skin. The skin was allowed to dry before covering the surgical area with a sterile non-antimicrobial plastic incise drape. All patients showered the night before surgery with a chlorhexidine gluconate soap, no additional scrub of the operative site was done on the ward prior to surgery.*
Comparator	• Iodophor in alcohol *0.7% available iodine and 74% isopropyl alcohol (assumed) - DuraPrep* *All hair was removed by dry shave just prior to preparing the skin. The skin was allowed to dry before covering the surgical area with a sterile non-antimicrobial plastic incise drape. All patients showered the night before surgery with a chlorhexidine gluconate soap, no additional scrub of the operative site was done on the ward prior to surgery.*
Outcome measure(s)	• SSI *Criteria used to define SSI not specified.*
Risk of bias Directness	**Random sequence generation** • Unclear risk of bias *Insufficient information provided.* **Allocation concealment** • Unclear risk of bias *Insufficient information provided.* **Blinding of participants and personnel** • Unclear risk of bias *Insufficient information provided. However, as outcomes were objective measures, study was not downgraded in this domain.* **Blinding of outcome assessment** • Unclear risk of bias *Insufficient information provided.* **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Unclear risk of bias **Overall risk of bias** • Moderate *Unclear random sequence generation, allocation concealment and blinding of outcome assessment.* **Directness**

	Gilliam (1990)
	• Partially directly applicable *Criteria used to define SSI not specified. Follow up period not specified.*

E.2.14 Howard 1991

	Howard (1991)
Title	Comparison of a 10 minute aqueous iodophor and 2 minute water-insoluble iodophor in alcohol reoperative skin preparation.
Study details	**Study type** • Randomised controlled trial ***Data extracted from Dumville 2015*** • Study location *USA* • Duration of follow-up *at least 30 days postoperatively* **Inclusion criteria** • *General surgery patients. (**Dumville 2015 extracted data on patients undergoing clean surgery specifically**)* • Sample size *240 general surgery patients* *159 patients identified as undergoing clean surgery* **Sample characteristics** • Split between study groups *Intervention group: 75* *Comparator group: 84*
Interventions	• Aqueous povidone iodine scrub and paint *Aqueous povidone iodine (7.5 %(scrub) and paint (10%) 10 minute scrub.*
Comparator	• Iodophor in alcohol *Iodophor in alcohol (DuraPrep)*
Outcome measure(s)	• SSI *SSI defined as drainage of pus, significant erythema at wound margins, wound drained serous fluid was opened by surgeon, wound was felt by the operating surgeon.*

	Howard (1991)
Risk of bias Directness	**Random sequence generation** • Unclear risk of bias *Insufficient information provided. (As reported by Dumville 2015)* **Allocation concealment** • Unclear risk of bias *Insufficient information provided. (As reported by Dumville 2015)* **Blinding of participants and personnel** • Unclear risk of bias *Paper unavailable to make judgement.* **Blinding of outcome assessment** • Unclear risk of bias *Insufficient information provided. (As reported by Dumville 2015)* **Incomplete outcome data** • High risk of bias *55 participants excluded from analysis. (As reported by Dumville 2015)* **Selective reporting** • Unclear risk of bias *Paper unavailable to make judgement.* **Other sources of bias** • Unclear risk of bias *Paper unavailable to make judgement.* **Overall risk of bias** • High *Unclear random sequence generation, allocation concealment, blinding of outcome assessment and incomplete outcome data.* **Directness** • Directly applicable

E.2.15 Kunkle 2015

	Kunkle (2015)
Title	Chlorhexidine gluconate versus povidone iodine at caesarean delivery: a randomized controlled trial
Study details	**Study type** • Randomised controlled trial **Study details**

	Kunkle (2015)
	• Study location *USA* • Study setting *Department of obstetrics and gynaecology* • Study dates *Not specified.* • Duration of follow-up *2 weeks* • Sources of funding *Not reported.* **Inclusion criteria** • Women aged 18-45 years undergoing scheduled caesarean at 36 gestational weeks or greater **Exclusion criteria** • *Inability to give informed consent* • *Presence of labour* • *current use of antimicrobials* • *known allergy to one or both of the disinfectants* • *Current use of immunosuppressant drugs* •*current history of cancer* • *presence of an open wound* • *presence of skin ulcer, sore, severe acne* • *history of MRSA colonisation or oxacillin- resistance S. aureus colonisation* • Sample size *60* **Sample characteristics** • Split between study groups *Intervention group: 27* *Comparator group: 33* • Loss to follow-up *Intervention group: 6* *Comparator group: 11* • Mean age (SD) *Intervention group: 31.0 (4.4)*

	Kunkle (2015)
	Comparator group: 29.1 (6.5) • Body Mass Index (SD) *Intervention group: 31.3 (6.1)* *Comparator group: 33.2 (5.9)*
Interventions	• Chlorhexidine in alcohol preparation *2% chlorhexidine with 70% isopropyl alcohol (Chloraprep)* *After the placement of anaesthesia, a member of the nursing staff cleaned the patient's skin and applied the chosen agent using standard nursing protocol. The caesarean technique was left to the discretion of the attending obstetrician. All patients received antibiotic prophylaxis.*
Comparator	• Aqueous Povidone Iodine *Aqueous povidone iodine scrub (7.5%) and paint (10%) assumed.* *After the placement of anaesthesia, a member of the nursing staff cleaned the patient's skin and applied the chosen agent using standard nursing protocol. The caesarean technique was left to the discretion of the attending obstetrician. All patients received antibiotic prophylaxis.*
Outcome measure(s)	• SSI *Wound infection defined as the presence of purulent drainage, or treatment with antibiotics for a clinical diagnosis of infection.*
Risk of bias Directness	**Random sequence generation** • Unclear risk of bias *Insufficient information provided.* **Allocation concealment** • Unclear risk of bias *Insufficient information provided.* **Blinding of participants and personnel** • High risk of bias *The operating surgeons would not be blinded due to appearance of antiseptics once applied to the skin. However, as outcomes were objective measures, study was not downgraded in this domain.* **Blinding of outcome assessment** • Unclear risk of bias *Insufficient information provided.* **Incomplete outcome data** • High risk of bias *Intention to treat analysis not conducted.* **Selective reporting** • Low risk of bias **Other sources of bias**

	Kunkle (2015)
	• Unclear risk of bias **Overall risk of bias** • High *Unclear random sequence generation, allocation concealment and blinding of outcome assessment. Intention to treat analysis not conducted.* **Directness** • Directly applicable

E.2.16 Ngai 2015

	Ngai (2015)
Title	Skin Preparation for Prevention of Surgical Site Infection After Cesarean Delivery: A Randomized Controlled Trial
Study details	**Study type** • Randomised controlled trial *3 arm trial (however review focused on 2 out of 3 interventions)* • **Study location** *USA* • **Study setting** *Medical Centre labour and delivery units* • **Study dates** *January 2013 through July 2014* • **Duration of follow-up** *within 30 days of discharge* • **Sources of funding** *Not reported.* **Inclusion criteria** • *Women who reached 37 weeks of gestation based on best obstetric estimate* • *Undergoing scheduled or non-emergent (e.g. for labour abnormalities) caesarean delivery.* **Exclusion criteria** • *Patients who had a urogenital tract infection within2 weeks of delivery* • *a 2 week or more history of steroid delivery during their pregnancy*

	Ngai (2015)
	• *If they were younger than 18 years old.* • *Emergency caesarean deliveries* • Sample size *1404* **Sample characteristics** • **Split between study groups** *Group A (povidone iodine and alcohol): 463* *Group B (chlorhexidine and alcohol): 474* *Group C: (combination of PI and CH): 467 -Data on Group C was not extracted as this intervention did not match review protocol.* • **Loss to follow-up** *Group A (povidone iodine and alcohol): 5* *Group B (chlorhexidine and alcohol): 13* • **Mean age (SD)** *Group A (povidone iodine and alcohol): 29.9 (6.0)* *Group B (chlorhexidine and alcohol): 30.3 (5.7)* • **Body Mass Index (SD)** *Group A (povidone iodine and alcohol): 34.3 (6.5)* *Group B (chlorhexidine and alcohol): 34.8 (6.6)* • **Diabetes (%)** ***Pre-gestational diabetes*** *Group A (povidone iodine and alcohol): 4.1%* *Group B (chlorhexidine and alcohol): 2.3%* ***Gestational diabetes*** *Group A (povidone iodine and alcohol): 11.9%* *Group B (chlorhexidine and alcohol): 2.3%*
Interventions	• **Chlorhexidine in alcohol preparation** 2% chlorhexidine gluconate with 70% isopropyl alcohol

	Ngai (2015)
	Authors contacted for information on preparation. All participants' received preoperative prophylactic antibiotics within 1 hours of skin incision. The selected skin preparation was applied according to the manufacturer with a minimum of 4 complete minutes drying time before surgical drapes were placed.
Comparator	• **Povidone iodine in alcohol preparation** 8.3% povidone iodine with 72.5% isopropyl alcohol Authors contacted for information on preparation. All participants' received preoperative prophylactic antibiotics within 1 hours of skin incision. The selected skin preparation was applied according to the manufacturer with a minimum of 4 complete minutes drying time before surgical drapes were placed.
Outcome measure(s)	• **SSI** Surgical site infection was defined according to Horan et al. and the CDC definition. A surgical site infection outcome was defined as the patient reporting the requirement of antibiotic use for a wound infection or documented wound infection in the medical record at the outpatient visit within 30 days of discharge. • **Superficial SSI** Surgical site infection was defined according to Horan et al. and the CDC definition. A surgical site infection outcome was defined as the patient reporting the requirement of antibiotic use for a wound infection or documented wound infection in the medical record at the outpatient visit within 30 days of discharge. • **Deep SSI** Surgical site infection was defined according to Horan et al. and the CDC definition. A surgical site infection outcome was defined as the patient reporting the requirement of antibiotic use for a wound infection or documented wound infection in the medical record at the outpatient visit within 30 days of discharge. • **Organ/space SSI** Surgical site infection was defined according to Horan et al. and the CDC definition. A surgical site infection outcome was defined as the patient reporting the requirement of antibiotic use for a wound infection or documented wound infection in the medical record at the outpatient visit within 30 days of discharge.
Risk of bias Directness	**Random sequence generation** • Low risk of bias **Allocation concealment** • Low risk of bias **Blinding of participants and personnel** • Unclear risk of bias *Insufficient information provided. Study was not downgraded in this domain.* **Blinding of outcome assessment** • Unclear risk of bias

	Ngai (2015)
	Insufficient information provided. However, as outcomes were objective measures, study was not downgraded in this domain. **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Low **Directness** • Directly applicable

E.2.17 Paochareon 2009

	Paocharoen (2009)
Title	Comparison of surgical wound infection after preoperative skin preparation with 4% chlorhexidine [correction of chlorhexidine] and povidone iodine: a prospective randomized trial
Study details	**Study type** • Randomised controlled trial • **Study location** *Bangkok, Thailand* • **Study setting** *Department of surgery* • **Study dates** *June 2006 and November 2008* • **Duration of follow-up** *1 month after surgery* • **Sources of funding** *Not reported* **Inclusion criteria** • *Age 18-60 years* • *Clean, clean-contaminated and contaminated wounds* • *ASA class 1 and 2*

	Paocharoen (2009)
	Exclusion criteria • *Patient refusal* • *dirty wounds* • *uncontrolled diabetes* • *on immunosuppressive drugs* • *Serum albumin less than 3.0 mg/dL* • *history of allergy to study agent* • **Sample size** *500* **Sample characteristics** • **Split between study groups** *Intervention group: 250* *Comparator group: 250* • **Loss to follow-up** *Not reported* • **%female** *Intervention group: 49%* *Comparator group: 36%* • **Mean Age (range)** *Intervention group: 56.2 (20-79)* *Comparator group: 50.5 (18-78)*
Interventions	• **Aqueous povidone iodine scrub and paint** 5 minute aqueous 7.5% povidone iodine scrub followed by aqueous 10% povidone iodine paint (information obtained from Dumville 2015)
Comparator	• **Aqueous Chlorhexidine scrub and paint** 4% chlorhexidine in 70% isopropyl alcohol (Hibitane) scrub followed by hibitane paint
Outcome measure(s)	• **SSI** *An incisional surgical site infection was defined as drainage of purulent material or if the surgeon judged wound to be infected when opened.*

	Paocharoen (2009)
	Study reports combined data for clean, clean-contaminated and contaminated surgeries. Data on clean surgery alone extracted from Dumville 2015.
Risk of bias Directness	**Random sequence generation** • Unclear risk of bias Insufficient information provided **Allocation concealment** • Unclear risk of bias Insufficient information provided **Blinding of participants and personnel** • Unclear risk of bias Insufficient information provided. *However, as outcomes were objective measures, study was not downgraded in this domain.* **Blinding of outcome assessment** • Unclear risk of bias Insufficient information provided. **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Moderate Unclear random sequence generation, allocation concealment and blinding of outcome assessment. **Directness** • Directly applicable

E.2.18 Park 2017

	Park (2017)
Title	Randomized clinical trial of preoperative skin antisepsis with chlorhexidine gluconate or povidone-iodine
Study details	**Study type** • Randomised controlled trial • **Study location** *South Korea* • **Study setting** *Centre for Liver Cancer* • **Study dates** *October 2011 to October 2014* • **Duration of follow-up** *SSI at 30 days after surgery* • **Sources of funding** *Not reported* **Inclusion criteria** • *Consecutive patients undergoing hepatobiliary- pancreatic surgery* **Exclusion criteria** • *Patients allergic to chlorhexidine or povidone iodine* • *Those taking immunosuppressant* • *Patients with uncontrolled diabetes* • *BMI of 30 kg/m^2 or more* • Sample size *581* **Sample characteristics** • Split between study groups *Intervention group: 292* *Comparator group: 289* • Loss to follow-up *0 loss to follow up in both arms*

	Park (2017)
	• %female *Intervention group: 26%* *Comparator group: 33%* • Age *Intervention group* *Comparator group* *<50 25.5% 29.2%* *50-59 28.1% 31.8%* *60-69 25.1% 21.0%* *70-79 20.2% 17.6%* *>80 1.1% 0.4%* • Body Mass Index (SD) *Intervention group* *Comparator group* *<25 70.4% 69.3%* *>25 29.6% 30.7%* • Diabetes (%) *Intervention group: 20.2%* *Comparator group: 20.6%*
Interventions	• Aqueous chlorhexidine scrub and paint *Before surgery, patients in the CG group were soaped with 4% chlorhexidine and then painted with aqueous solution of 2% chlorhexidine. After waiting for 3 minutes to allow drying of antiseptics, nurses then dried the skin with a sterile fabric towel. All patients in this study received perioperative antibiotics at induction of general anaesthesia, within 1 h of skin incision.*
Comparator	• Aqueous Povidone iodine scrub and paint *Those in the PI group were soaped with 7.5% povidone iodine and then painted with an aqueous solution of 10% PI. After waiting for 3 minutes to allow drying of antiseptics, nurses then dried the skin with a sterile fabric towel. All patients in this study received perioperative antibiotics at induction of general anaesthesia, within 1 h of skin incision.*
Outcome measure(s)	• SSI *If SSI was suspected, microbiological samples were sent for culture using cotton swab. Primary end point was the SSI rate at 30 days after surgery. SSI was defined as an infection arising from a surgical procedure and occurrence within 30 days of surgery. SSI classified according to the CDC criteria.* • Superficial SSI

	Park (2017)
	If SSI was suspected, microbiological samples were sent for culture using cotton swab. Primary end point was the SSI rate at 30 days after surgery. SSI was defined as an infection arising from a surgical procedure and occurrence within 30 days of surgery. SSI classified according to the CDC criteria. • Deep SSI *If SSI was suspected, microbiological samples were sent for culture using cotton swab. Primary end point was the SSI rate at 30 days after surgery. SSI was defined as an infection arising from a surgical procedure and occurrence within 30 days of surgery. SSI classified according to the CDC criteria.* • Organ/space SSI *If organ-space SSI was suspected, drained body fluid was sent for Gram staining in a culture bottle. Primary end point was the SSI rate at 30 days after surgery. SSI was defined as an infection arising from a surgical procedure and occurrence within 30 days of surgery. SSI classified according to the CDC criteria.*
Risk of bias Directness	**Random sequence generation** • Unclear risk of bias *Insufficient information provided.* **Allocation concealment** • Low risk of bias **Blinding of participants and personnel** • Unclear risk of bias *Insufficient information provided. Study was not downgraded in this domain.* **Blinding of outcome assessment** • Low risk of bias **Incomplete outcome data** • Low risk of bias *47 patients (CG 25, PI, 22) were excluded from analysis, 31 had cancer dissemination (CG 15, PI 16), 12 had colorectal surrey (CG 6, PI 6), 3 died within 30 days of surgery (CG 3, P1, 0), and one underwent further surgery within 30 days of the first operation (CG 1, P1, 0).* **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Low **Directness** • Directly applicable

E.2.19 Roberts 1995

	Roberts (1995)
Title	Skin preparation in CA BG surgery: A prospective randomized trial
Study details	**Study type** • Randomised controlled trial ***Information identified from CG74 2008 guideline and Dumville 2015.*** **Study details** • Study location *USA* • Duration of follow-up *30 days* • Sources of funding *Not reported (**information from CG74 2008**)* **Inclusion criteria** • *Consecutive consenting patients undergoing CABG* **Exclusion criteria** • *Allergy to iodine* • Sample size *200* **Sample characteristics** • Split between study groups *Intervention group: 96* *Comparator group: 104*
Interventions	• Aqueous povidone iodine scrub and paint *Aqueous povidone iodine (7.5%) and paint (10%) (assumed)* *5- 10 minute scrub. Paint blotted dry with sterile towel (Information from NG74 2008). All patients had antimicrobial (iodophor) preoperative showers on the night prior to surgery. Prophylactic antibiotics with cefuroxime was started in the operating theatre approximately 30 minutes prior to surgical incision and continued 6 hours for 36 hours pot-op in all participants. Hair removal was performed on all participants.*
Comparator	• Iodophor in alcohol *Iodophor in alcohol (DuraPrep)* *Painted on chest and each leg and allowed to air dry for 2–3 minutes (information from CG74 2008) All patients had antimicrobial (iodophor) preoperative showers on the night prior to surgery. Prophylactic antibiotics with cefuroxime was started in the operating*

	Roberts (1995)
	theatre approximately 30 minutes prior to surgical incision and continued 6 hours for 36 hours pot-op in all participants. Hair removal was performed on all participants. Iodophor- impregnated incise drape used on all chest wounds, but not leg wounds.
Outcome measure(s)	• SSI *CDC guidelines – wound appearance, drainage and cultured organisms. Purulent material drained, not necessarily positive culture. Superficial infection being skin, subcutaneous tissue and muscle above fascial layer. Deep infection being below fascial layer. (**information from CG74 2008**)*
Risk of bias Directness	**Random sequence generation** • Unclear risk of bias *Insufficient information provided. (As reported by Dumville 2015)* **Allocation concealment** • Unclear risk of bias *Insufficient information provided. (As reported by Dumville 2015)* **Blinding of participants and personnel** • Unclear risk of bias *Paper unavailable to make judgement.* **Blinding of outcome assessment** • Unclear risk of bias *Insufficient information provided. (As reported by Dumville 2015)* **Incomplete outcome data** • Low risk of bias *All data reported (As reported by Dumville 2015)* **Selective reporting** • Unclear risk of bias *Paper unavailable to make judgement.* **Other sources of bias** • Unclear risk of bias *Paper unavailable to make judgement.* **Overall risk of bias** • High *Unclear random sequence generation, allocation concealment and blinding of outcome assessment.* **Directness** • Directly applicable

E.2.20 Saltzman 2009

	Saltzman (2009)
Title	Efficacy of surgical preparation solutions in shoulder surgery
Study details	**Study type** • Randomised controlled trial *3 arm trial* **Study details** • **Study location** *USA* • **Study setting** *Hospital setting* • **Study dates** *September 2007 and February 2008* • **Duration of follow-up** *10 months after surgery* • **Sources of funding** *Funding/ grant from Enturia.* **Inclusion criteria** • *Patients undergoing shoulder surgery.* **Exclusion criteria** • None reported • **Sample size** *150* **Sample characteristics** • Split between study groups *Group A (CH in alcohol): 50* *Group B (iodophor in alcohol): 50* *Group C (PI in alcohol): 50* • **Loss to follow-up** *Not reported* • **%female** *Overall: 44%*

	Saltzman (2009)
	• **Age range** *Overall: 17-89 years*
Interventions	• **Chlorhexidine in alcohol preparation** 2% chlorhexidine gluconate and 70% isopropyl alcohol(Chloraprep, Enturia) Each shoulder was prepared according to the manufacturer's instructions by the attending surgeon. • **Aqueous povidone iodine scrub and paint** Aqueous povidone iodine (7.5%) scrub and paint (10%) Each shoulder was prepared according to the manufacturer's instructions by the attending surgeon. • **Iodophor in alcohol** 0.7% iodophor and 74%isopropyl alcohol (Duraprep, 3M healthcare) Each shoulder was prepared according to the manufacturer's instructions by the attending surgeon.
Outcome measure(s)	• **SSI** Classification used to define SSI was not reported.
Risk of bias Directness	**Random sequence generation** • Unclear risk of bias *Insufficient information provided.* **Allocation concealment** • Low risk of bias **Blinding of participants and personnel** • Unclear risk of bias *Insufficient information provided. However, as outcomes were objective measures, study was not downgraded in this domain.* **Blinding of outcome assessment** • Unclear risk of bias *Insufficient information provided.* **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Unclear risk of bias **Overall risk of bias** • Moderate *Unclear random sequence generation, blinding of outcome assessment and other sources of bias.* **Directness**

	Saltzman (2009)
	• Partially directly applicable *Classification used to define SSI not specified.*

E.2.21 Savage 2012

	Savage (2012)
Title	Efficacy of surgical preparation solutions in lumbar spine surgery
Study details	**Study type** • Randomised controlled trial • Study location *USA* • Study setting *University of Orthopaedic surgery and neurological surgery* • Study dates *February to August 2010* • Duration of follow-up *6 months after surgery.* • Sources of funding *External funding obtained from 3M, the company that manufactures DuraPrep.* **Inclusion criteria** • *Patients undergoing elective lumbar spine surgery* **Exclusion criteria** •*Patients who had an open wound at the incision site, abrasion in the vicinity of the planned incision, an active infection at or near the surgical site, or an active infection elsewhere in the body.* • Sample size *100* **Sample characteristics** • Split between study groups *Intervention group: 50* *Comparator group: 50* • Loss to follow-up *Not reported* • Age *Intervention group: 54*

	Savage (2012)
	Comparator group: 51 • Body Mass Index (SD) *Intervention group: 29.2* *Comparator group: 29.9*
Interventions	• Iodophor in alcohol *0.7% available iodine and 74% isopropyl alcohol (DuraPrep)* *The lumbar spine was prepared according to the manufacturer's instructions by the attending surgeon. Each preparation solution was allowed to adequately dry for approximately 3 to 5 minutes in order to minimize the recognised risk of fire associated with alcohol-based solutions. There was no specific cleansing or shaving protocol prior to surgery, and patients were instructed to adhere to their routine bathing practices. If necessary, the skin hair in the surgical area was removed with clippers in the operating room before surgery.*
Comparator	• Chlorhexidine in alcohol preparation *2% chlorhexidine gluconate with 70% isopropyl alcohol (ChloraPrep)* *The lumbar spine was prepared according to the manufacturer's instructions by the attending surgeon. Each preparation solution was allowed to adequately dry for approximately 3 to 5 minutes in order to minimize the recognised risk of fire associated with alcohol-based solutions. There was no specific cleansing or shaving protocol prior to surgery, and patients were instructed to adhere to their routine bathing practices. If necessary, the skin hair in the surgical area was removed with clippers in the operating room before surgery.*
Outcome measure(s)	• SSI *Criteria used to define SSI not specified.*
Risk of bias Directness	**Random sequence generation** • Unclear risk of bias *Insufficient information provided.* **Allocation concealment** • Unclear risk of bias *Insufficient information provided.* **Blinding of participants and personnel** • Unclear risk of bias *Insufficient information provided. However, as outcomes were objective measures, study was not downgraded in this domain.* **Blinding of outcome assessment** • Unclear risk of bias *Insufficient information provided.* **Incomplete outcome data** • Low risk of bias

	Savage (2012)
	Selective reporting • Low risk of bias **Other sources of bias** • Unclear risk of bias **Overall risk of bias** • High *Unclear random sequence generation, allocation concealment, blinding of outcome assessment and other sources of bias.* **Directness** • Partially directly applicable *Criteria used to define SSI not specified.*

E.2.22 Segal 2002

	Segal (2002)
Title	Preoperative skin preparation of cardiac patients
Study details	**Study type** • Randomised controlled trial *4 arm trial (however review only focuses on 3 out of the 4 interventions)* **• Study location** *USA* **• Study setting** *Hospital setting* **• Study dates** *Not specified.* **• Duration of follow-up** *Patients were followed for up to 6 weeks postoperatively* **• Sources of funding** *Not specified* **Inclusion criteria** *• Patients undergoing CABG who had one or more of the high risk predictive factors* **Exclusion criteria** *• Patients with an allergy to topical iodine* *• Patients with a pre-existing infection, indicated by white blood cell counts higher than 10,000 or by a temperature higher than 100.5F (38.06C)*

	Segal (2002)
	• **Sample size** *209* **Sample characteristics** • **Split between study groups** *Intervention group A (Povidone iodine paint): 56* *Intervention group B (Povidone iodine 5 min scrub with paint): 52* *Intervention group C (One-step iodophor/ alcohol water insoluble film):50* *Intervention group D (One=step iodophor/alcohol water insoluble film with iodine impregnated incise drape): 51- Information on Group D was not extracted as this intervention did not match review protocol.* • **Loss to follow-up** *Not reported* • **Mean Age** *In whole cohort: 60.9 years*
Interventions	• **Aqueous povidone iodine** Aqueous (10%) povidone iodine All patients were prepped according to the hospital policy by experienced RNs with only one type of prep varying. The nurse instructed patients to take an antimicrobial shower the evening before and morning of surgery, or, if they were inpatients, they were given a preoperative antimicrobial shower in the hospital. If hair removal was necessary, a qualified patient care assistant clipped patients' hair the morning of surgery. All patients received a prophylactic preoperative antibiotic (i.e. cefuroxime), or if they had a documented allergy to penicillin, they received vancomycin in the appropriate dosing window to provide adequate coverage at the time of incision. • **Aqueous povidone iodine scrub and paint** Aqueous povidone iodine (7.5%) 5 minute scrub with paint (10%) All patients were prepped according to the hospital policy by experienced RNs with only one type of prep varying. The nurse instructed patients to take an antimicrobial shower the evening before and morning of surgery, or, if they were inpatients, they were given a preoperative antimicrobial shower in the hospital. If hair removal was necessary, a qualified patient care assistant clipped patients' hair the morning of surgery. All patients received a prophylactic preoperative antibiotic (i.e. cefuroxime), or if they had a documented allergy to penicillin, they received vancomycin in the appropriate dosing window to provide adequate coverage at the time of incision. • **Iodophor in alcohol** 0.7% available iodine and 74% isopropyl alcohol All patients were prepped according to the hospital policy by experienced RNs with only one type of prep varying. The nurse instructed patients to take an antimicrobial shower the evening before and morning of surgery, or, if they were inpatients, they were given a

	Segal (2002)
	preoperative antimicrobial shower in the hospital. If hair removal was necessary, a qualified patient care assistant clipped patients' hair the morning of surgery. All patients received a prophylactic preoperative antibiotic (i.e. cefuroxime), or if they had a documented allergy to penicillin, they received vancomycin in the appropriate dosing window to provide adequate coverage at the time of incision.
Outcome measure(s)	• **SSI** Defined using CDC criteria
Risk of bias Directness	**Random sequence generation** • Low risk of bias **Allocation concealment** • Unclear risk of bias Insufficient information provided. **Blinding of participants and personnel** • Unclear risk of bias Insufficient information provided. *However, as outcomes were objective measures, study was not downgraded in this domain.* **Blinding of outcome assessment** • Unclear risk of bias Insufficient information provided. **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Low **Directness** • Directly applicable

E.2.23 Sistla 2010

	Sistla (2010)
Title	Minimizing wound contamination in a 'clean' surgery: comparison of chlorhexidine-ethanol and povidone-iodine

	Sistla (2010)
Study details	**Study type** • Randomised controlled trial • Study location *India* • Study setting *Medical centre* • Study dates *Not reported.* • Duration of follow-up *within 30 days after surgery* • Sources of funding *Not reported.* **Inclusion criteria** *•Patents undergoing elective inguinal hernia repair* **Exclusion criteria** *• Patients with recurrent or complication inguinal hernia* *•Patients with a history of allergy to the antiseptics* • Sample size *556* **Sample characteristics** • Split between study groups *Intervention group: 285* *Comparator group: 271* • Loss to follow-up *Intervention group: 85 lost to follow up/ questionnaire not completed.* *Comparator group: 71 lost to follow up/ questionnaire not completed* • %female *Intervention group: 1%* *Comparator group: 3.5%*
Interventions	• Aqueous povidone iodine *Aqueous 10% povidone iodine*

	Sistla (2010)
	Patients undergoing prosthetic repair received a single dose of cefazolin intravenously an hour before surgery. Sterile dressing was applied after surgery and the wounds were left exposed after 48h. The antiseptic was applied in concentric circles beginning from the site of incision to the periphery and allowed to dry before the surgical site was draped.
Comparator	• Chlorhexidine in alcohol preparation *2.5% chlorhexidine with 70% ethanol* *Patients undergoing prosthetic repair received a single dose of cefazolin intravenously an hour before surgery. Sterile dressing was applied after surgery and the wounds were left exposed after 48h. The antiseptic was applied in concentric circles beginning from the site of incision to the periphery and allowed to dry before the surgical site was draped.*
Outcome measure(s)	• SSI *- redness and pain around the wound which settled without treatment* *- redness and pain around the wound which required antibiotics* *- discharge of pus from the wound* *- wound broke down* *- needed hospitalisation.*
Risk of bias Directness	**Random sequence generation** • Unclear risk of bias *Insufficient information provided.* **Allocation concealment** • Unclear risk of bias *Insufficient information provided.* **Blinding of participants and personnel** • High risk of bias *Blinding of surgeons was not possible due to the difference in physical characteristics of the antiseptics used. Information regarding the antiseptic used was not available to the investigators or patients during the assessment of wounds. However, as outcomes were objective measures, study was not downgraded in this domain.* **Blinding of outcome assessment** • Low risk of bias *Patient reported outcomes. Patients were blinded to allocation.* **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias**

	Sistla (2010)
	• Low **Directness** • Directly applicable

E.2.24 Springel 2017

	Springel (2017)
Title	A randomized open-label controlled trial of chlorhexidine-alcohol vs povidone-iodine for caesarean antisepsis: the CAPICA trial
Study details	**Study type** • Randomised controlled trial • Study location *USA* • Study setting *Urban tertiary care institution* • Study dates *March 2014 to June 2016* • Duration of follow-up *Within 30 days after delivery* • Sources of funding *Not reported* **Inclusion criteria** • *Patients aged 18 year and older.* **Exclusion criteria** • *Excluded if no key study personnel were available to complete study- related procedures* • *If they were allergic to iodine or chlorhexidine* • *Diagnosed with clinical Chorioamnionitis* • *If incarcerated* • *If study personnel perceived that he patient was unlikely to return to complete postoperative assessments* • *patients unwilling to consent for study participation in English or Spanish.* • Sample size *932*

	Springel (2017)
	Sample characteristics • Split between study groups *Intervention group: 461* *Comparator group: 471* • **Loss to follow-up** *Intervention group: 6 lost to follow up* *Comparator group: 16 lost to follow up* • **Mean Age (range)** *Intervention group: 28 (24-33)* *Comparator group: 28 (24-32)*
Interventions	• **Chlorhexidine in alcohol preparation** *2% chlorhexidine gluconate in 70% isopropyl alcohol paint 26-mL single step applicator (Chloraprep). Manufacturer recommendations regarding application were reviewed with key study personnel within they agreed to participate and periodically thereafter. All other procedures related to caesarean delivery and postoperative care were performed per the surgical team's judgement.*
Comparator	• **Aqueous Povidone iodine scrub and paint** *Povidone-iodine aqueous scrub (0.75% available iodine solution) followed by povidone iodine aqueous paint (1.0% available iodine solution, wet skin scrub preparation tray). Manufacturer recommendations regarding application were reviewed with key study personnel within they agreed to participate and periodically thereafter. All other procedures related to caesarean delivery and postoperative care were performed per the surgical team's judgement.*
Outcome measure(s)	• **SSI** *Surgical site infections were defined by the US National Healthcare Safety Network (NHSN) of the CDC. Subjects who attended a postoperative visit within 30 days after delivery. had a documented well-healed incision on exam with no mention of any surgical site infection at this or any other postoperative assessment, and for whom there was no notification to our infection control team by an outside institution regarding postoperative infection, were considered to have completed follow-up. If criteria was not met, of if there was any suspicion or uncertainty about the possible occurrence of surgical site infection, the patient was contacted directly and interviewed regarding possible surgical site infection diagnosis.* • **Superficial SSI** *Surgical site infections were defined by the US National Healthcare Safety Network (NHSN) of the CDC.* • **Deep SSI** *Surgical site infections were defined by the US National Healthcare Safety Network (NHSN) of the CDC.* • **Organ/space SSI**

	Springel (2017)
	Defined as endometritis. Surgical site infections were defined by the US National Healthcare Safety Network (NHSN) of the CDC. • **Skin and other allergic reactions**
Risk of bias Directness	**Random sequence generation** • Low risk of bias **Allocation concealment** • Low risk of bias **Blinding of participants and personnel** • Low risk of bias *Authors noted that masking of key personnel was not feasible. However, as outcomes were objective measures, study was not downgraded in this domain.* **Blinding of outcome assessment** • Low risk of bias **Incomplete outcome data** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Low **Directness** • Directly applicable

E.2.25 Srivinas 2015

	Srinivas (2015)
Title	Comparison of the efficacy of chlorhexidine gluconate versus povidone iodine as preoperative skin preparation for the prevention of surgical site infections in clean-contaminated upper abdominal surgeries
Study details	**Study type** • Randomised controlled trial • Study location *India* • Study setting *Department of General Surgery* • Study dates *January 2011 to June 2012* • Duration of follow-up *Within 30 days after surgery* • Sources of funding *Not reported* **Inclusion criteria** • *All patients undergoing upper abdominal clean-contaminated surgeries in the elective setting, who had given consent and who uniformly received the preoperative antibiotic during the induction of anaesthesia* **Exclusion criteria** • *No consent given for participation in the trial* • *a history of allergy to chlorhexidine, alcohol, or idophors* • *clinical/ microbiological evidence of infection at/ adjacent to the surgical site* • *Ongoing systemic sepsis* • *Patients who died intra-operatively or before the completion of the 30 day follow up period* • *patients who left the hospital against medical advice or who were lost to follow up* • *those who required a second operation within two weeks of the first operation.* • Sample size *351* **Sample characteristics** • Split between study groups *Intervention group: 163*

	Srinivas (2015)
	Comparator group: 188 • Loss to follow-up *Intervention group: 3 lost to follow up, 2 had contaminated surgery* *Comparator group: 2 lost to follow up, 1 underwent contaminated surgery, 1 underwent redo surgery* • %female *Intervention group: 62%* *Comparator group: 62%* • Mean age (SD) *Intervention group: 44.7 (13.737)* *Comparator group: 47.4 (13.1)* • Body Mass Index (SD) *Intervention group: 23.09 (2.265)* *Comparator group: 23.12 (2.227)* • Diabetes (%) *Intervention group: 10.1%* *Comparator group: 10.9%*
Interventions	• Chlorhexidine in alcohol preparation *0.5% chlorhexidine gluconate with 70% isopropyl alcohol* *Applied using applicator. Painted 3 times. All patients underwent a preoperative soap and water shower on the day of surgery and had their hair shaved prior to surgery. All patients' received preoperative antibiotic treatment.*
Comparator	• Aqueous Povidone Iodine *5% povidone iodine solution* *Antiseptic painted preoperatively. Applied 3 times. All patients underwent a preoperative soap and water shower on the day of surgery and had their hair shaved prior to surgery. All patients' received preoperative antibiotic treatment.*
Outcome measure(s)	• SSI *CDC definition used to define SSI.* • Superficial SSI *CDC definition used to define SSI.* • Deep SSI *CDC definition used to define SSI.* •Organ/space SSI *CDC definition used to define SSI.*
Risk of bias	**Random sequence generation** • Unclear risk of bias

	Srinivas (2015)
Directness	*Insufficient information provided.* **Allocation concealment** • Low risk of bias **Blinding of participants and personnel** • Low risk of bias **Blinding of outcome assessment** • Low risk of bias **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Low **Directness** • Directly applicable

E.2.26 Tuuli 2016

	Tuuli (2016)
Title	A Randomized Trial Comparing Skin Antiseptic Agents at Caesarean Delivery
Study details	**Study type** • Randomised controlled trial • **Study location** *USA* • **Study setting** *Department of Obstetrics and Gynaecology* • **Study dates** *September 2011 through June 2015* • **Duration of follow-up** *Within 30 days after caesarean delivery.* • **Sources of funding** *Supported by a Woman's Reproductive Health Research Career development grant from Eunice Kennedy Shriver National institute of child health and human development of National institutes of Health. Authors noted that funders had no role in the design or conduct of the study, the collection, management, analysis, or interpretation, review, or approval of the manuscript.* **Inclusion criteria** • *Pregnant women undergoing caesarean delivery.* **Exclusion criteria** • *Women who had known allergy to chlorhexidine, alcohol, iodine or shellfish* • *Women who had a skin infection adjacent to the operative site.* • **Sample size** *1147* **Sample characteristics** • **Split between study groups** *Intervention group:572* *Comparator group:575* • **Loss to follow-up** *Intervention group: 43 lost to follow up (29 did not have postoperative follow-up, 5 discontinued study) Comparator group: 31 lost to follow up (28 did not have postoperative follow-up, 3 discontinued study)* • **Mean age (SD)** *Intervention group: 28.3 (5.8)*

	Tuuli (2016)
	Comparator group: 28.4 (5.8) • **Body Mass Index (SD)** *Intervention group: 35.1 (8.9)* *Comparator group: 34.1 (8.1)* • **Diabetes (%)** *Intervention group: 9.6%* *Comparator group: 11.3%*
Interventions	• **Chlorhexidine in alcohol preparation** 2% chlorhexidine gluconate with 70% isopropyl alcohol Skin preparation was performed by circulating nurse following the manufacturer's instructions. In brief, the pre-packaged antiseptic applicator was opened and used to scrub the operative site. A wait time of 3 minutes was allowed between application of the antiseptic agent and skin incision except in emergency cases in which this step was skipped. Patients also received standard infection-prevention measures, including body weight based preoperative antibiotic prophylaxis
Comparator	• **Povidone iodine in alcohol preparation** *8.3% povidone iodine with 72.5% isopropyl alcohol* *Skin preparation was performed by circulating nurse following the manufacturer's instructions. In brief, the pre-packaged antiseptic applicator was opened and used to scrub the operative site. A wait time of 3 minutes was allowed between application of the antiseptic agent and skin incision except in emergency cases in which this step was skipped. Patients also received standard infection-prevention measures, including body weight based preoperative antibiotic prophylaxis.*
Outcome measure(s)	• **SSI** Classified using National Healthcare Safety Network definitions of the Centres for Disease Control and Prevention (CDC). The diagnosis was made by the treating physician and verified by means of chart review by the principal investigator, who was unaware of the study-group assignments. • **Superficial SSI** Classified using National Healthcare Safety Network definitions of the Centres for Disease Control and Prevention (CDC). The diagnosis was made by the treating physician and verified by means of chart review by the principal investigator, who was unaware of the study-group assignments. • **Deep SSI** Classified using National Healthcare Safety Network definitions of the Centres for Disease Control and Prevention (CDC). The diagnosis was made by the treating physician and verified by means of chart review by the principal investigator, who was unaware of the study-group assignments. • **Skin and other allergic reactions**
Risk of bias	**Random sequence generation**

	Tuuli (2016)
Directness	• Low risk of bias **Allocation concealment** • Low risk of bias **Blinding of participants and personnel** • Unclear risk of bias Insufficient information provided. *However, as outcomes were objective measures, study was not downgraded in this domain.* **Blinding of outcome assessment** • Low risk of bias **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Low **Directness** • Directly applicable

E.2.27 Xu 2017

	Xu (2017)
Title	Prospective Randomized Trial Comparing the Efficacy of Surgical Preparation Solutions in Hand Surgery
Study details	**Study type** • Randomised controlled trial *3 arm trial* • Study location *USA* • Study setting *Department of orthopaedics* • Study dates *May 2013 to August 2014* • Duration of follow-up *6 weeks of surgery* • Sources of funding *Funding for study via the University of Pittsburgh Department of Orthopaedics and a grants from the Pittsburgh Foundation, and a National Institutes of Health grant.* **Inclusion criteria** *• Patient undergoing elective clean soft tissue hand surgery (carpal tunnel release, trigger finger, de Quervain release, mass excision or excision ganglion cyst, or other elective clean hand surgeries)* *• being able to read and understand English* **Exclusion criteria** *•Open wound* *• Previous infection in the operative hand or ongoing infection elsewhere in the body* *•Fracture* *• Allergy to any component of the skin preparation solutions* *• Hardware implantation* • Sample size *240* **Sample characteristics** • Split between study groups *Group A (PI in alcohol): 81* *Group B (CH in alcohol): 79*

	Xu (2017)
	Group C (Aqueous PI): 80 • Loss to follow-up *No losses to follow up* • %female *Group A (PI in alcohol): 69%* *Group B (CH in alcohol): 73%* *Group C (Aqueous PI): 63%* • Mean age (SD) *Group A (PI in alcohol): 56 (7)* *Group B (CH in alcohol): 53 (14)* *Group C (Aqueous PI): 53 (14)* • Body Mass Index (SD) *Group A (PI in alcohol): 30.6 (8.6)* *Group B (CH in alcohol): 30.5 (7.8)* *Group C (Aqueous PI): 31.1 (8.0)*
Interventions	• Chlorhexidine in alcohol preparation *2% chlorhexidine gluconate and 70% isopropyl alcohol (Chloraprep, Enturia)* *The surgical extremity was prepared according to the manufacturer's instructions by the attending surgeon or resident. Each preparation was allowed to dry.* • Aqueous povidone iodine *Aqueous 10% povidone iodine (Betadine)* *The surgical extremity was prepared according to the manufacturer's instructions by the attending surgeon or resident. Each preparation was allowed to dry.* • Iodophor in alcohol *0.7% available iodine and 74% isopropyl alcohol (DuraPrep)* *The surgical extremity was prepared according to the manufacturer's instructions by the attending surgeon or resident. Each preparation was allowed to dry.*
Outcome measure(s)	• SSI *Defined as the need for antibiotics or surgical intervention.*
Risk of bias Directness	**Random sequence generation** • Unclear risk of bias *Insufficient information.*

	Xu (2017)
	Allocation concealment • Low risk of bias. **Blinding of participants and personnel** • Unclear risk of bias *Insufficient information. However, as outcomes were objective measures, study was not downgraded in this domain.* .**Blinding of outcome assessment** • Unclear risk of bias *Insufficient information.* **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Low **Directness** • Directly applicable

E.2.28 Zdeblick 1986

	Zdeblick (1986)
Title	Preoperative use of povidone-iodine. A prospective, randomized study
Study details	**Study type** • Randomised controlled trial • Study location *USA* • Study setting *Hospital setting* • Study dates *Not specified.* • Duration of follow-up

	Zdeblick (1986)
	Not specified. • Sources of funding *Not specified.* **Inclusion criteria** • *Elective adult orthopaedic surgical cases.* **Exclusion criteria** • *Patients undergoing total joint arthroplasties* • *Infected cases* • Sample size *105* **Sample characteristics** • Split between study groups *Intervention group: 45* *Comparator group: 56* • Loss to follow-up *Not specified.*
Interventions	• Aqueous povidone iodine scrub and paint *Aqueous povidone iodine scrub (7.5%) and paint (10%) (assumed)* *All inpatients received a hexachlorophene shower the evening before surgery and were treated with an intravenous cephalosporin preoperatively. Outpatient surgical cases did not receive preoperative antiseptic showers. Scrubbing carried out using sterile gloves and handheld gauze sponges soaked with povidone iodine detergent. The scrub was timed and lasted 5 to 7 minutes. The detergent was blotted dry, then the operative site was painted twice with povidone iodine solution. The antiseptic was allowed to dry.*
Comparator	• Aqueous Povidone Iodine *Aqueous 10% povidone iodine (assumed)* *All inpatients received a hexachlorophene shower the evening before surgery and were treated with an intravenous cephalosporin preoperatively. Outpatient surgical cases did not receive preoperative antiseptic showers.*
Outcome measure(s)	• SSI *Criteria used to define SSI not specified.*
Risk of bias Directness	**Random sequence generation** • Unclear risk of bias *Insufficient information provided.* **Allocation concealment** • Unclear risk of bias *Insufficient information provided.*

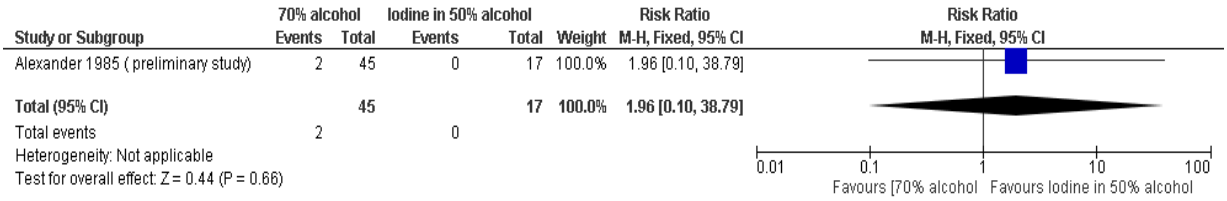
	Zdeblick (1986)
	Blinding of participants and personnel • Unclear risk of bias *Insufficient information provided. Study not downgraded in this domain* **Blinding of outcome assessment** • Unclear risk of bias *Insufficient information provided. However, as outcomes were objective measures, study was not downgraded in this domain.* **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Unclear risk of bias **Overall risk of bias** • High *Unclear random sequence generation, allocation concealment, blinding of outcome assessment and other sources of bias.* **Directness** • Partially directly applicable *Criteria used to define SSI not specified. Follow up period not specified.*

Appendix F – Forest plots

F.1 Alcohol

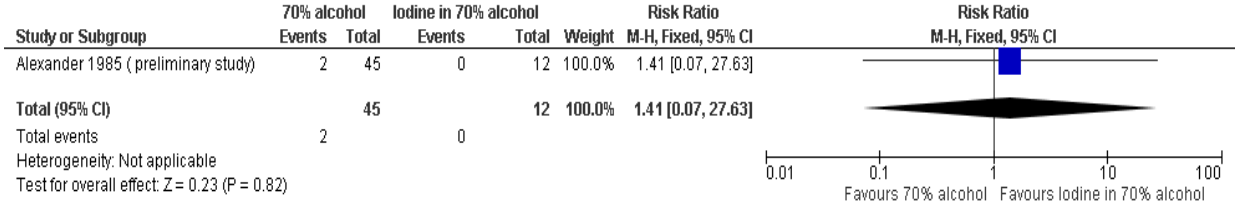
F.1.1 70% alcohol vs 2% iodine in 50% alcohol

SSI



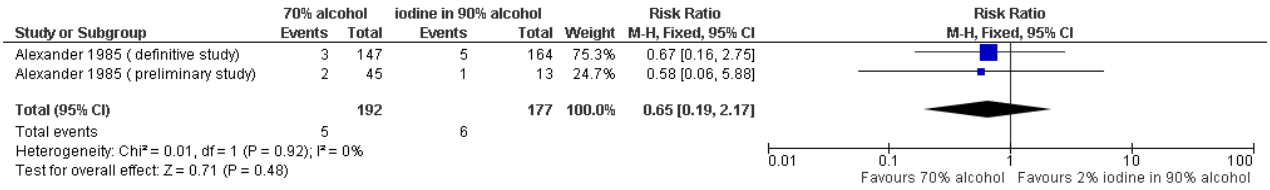
F.1.2 70% alcohol vs 2% iodine in 70% alcohol

SSI

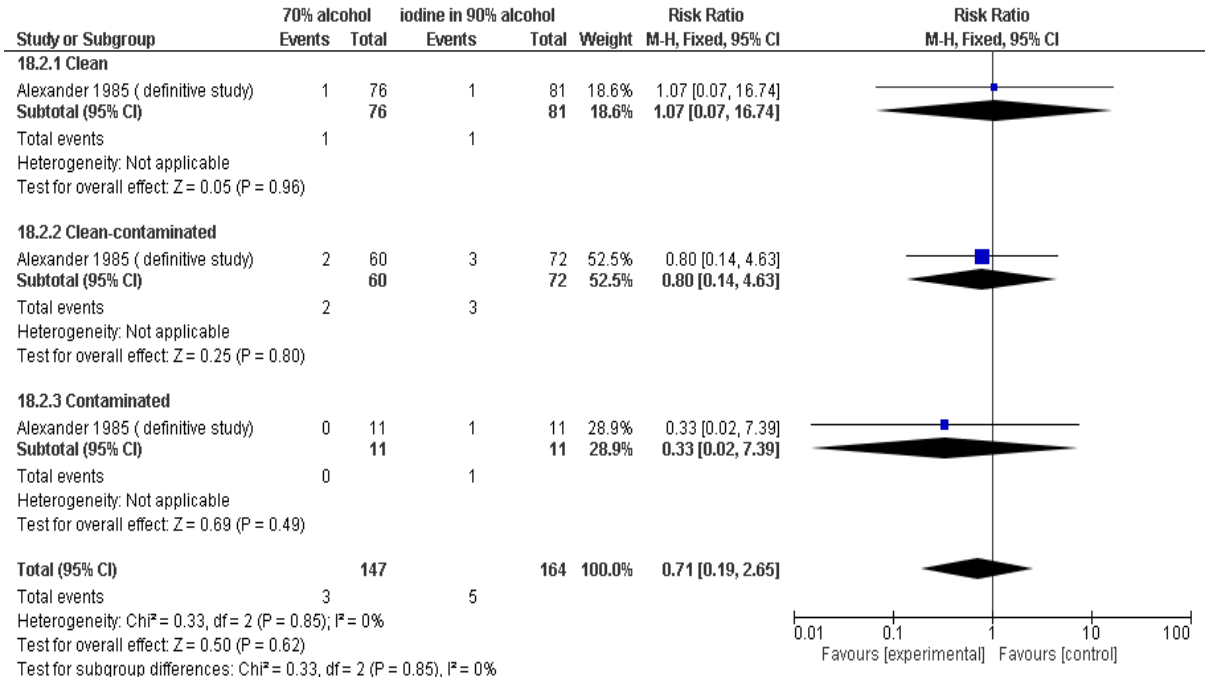


F.1.3 70% alcohol vs 2% iodine in 90% alcohol

SSI



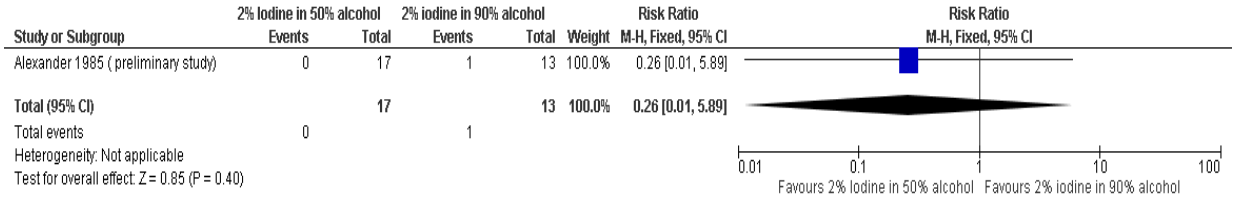
Superficial SSI



F.2 Iodine in alcohol preparation

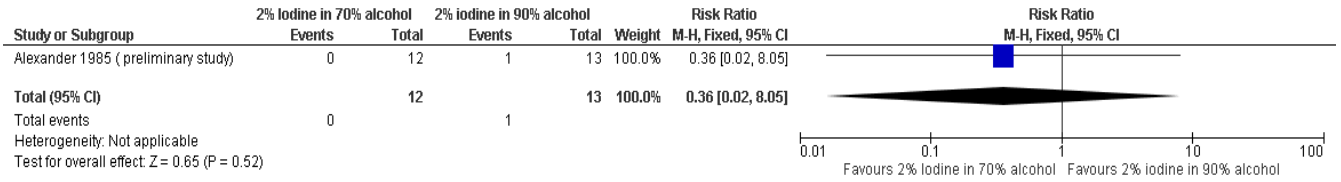
F.2.1 2% Iodine in 50% alcohol vs 2% iodine in 90% alcohol

SSI



F.2.2 2% Iodine in 70% alcohol vs 2% iodine in 90% alcohol

SSI



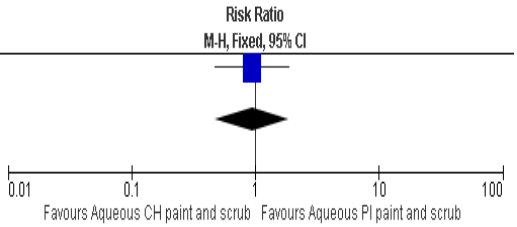
F.3 Aqueous Chlorhexidine

F.3.1 Aqueous chlorhexidine scrub (4%) and paint (2%) vs. aqueous povidone iodine scrub (7.5%) and paint (10%)

SSI

Study or Subgroup	Aqueous CH scrub (4%) and paint (2%) Events	Total	Aqueous PI scrub (7.5%) and paint (10%) Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Park 2016	15	267	16	267	100.0%	0.94 [0.47, 1.86]
Total (95% CI)		**267**		**267**	**100.0%**	**0.94 [0.47, 1.86]**
Total events	15		16			

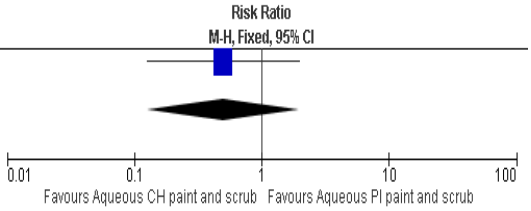
Heterogeneity: Not applicable
Test for overall effect: Z = 0.19 (P = 0.85)



Superficial SSI

Study or Subgroup	Aqueous CH scrub (4%) and paint (2%) Events	Total	Aqueous PI scrub (7.5%) and paint (10%) Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Park 2016	3	267	6	267	100.0%	0.50 [0.13, 1.98]
Total (95% CI)		**267**		**267**	**100.0%**	**0.50 [0.13, 1.98]**
Total events	3		6			

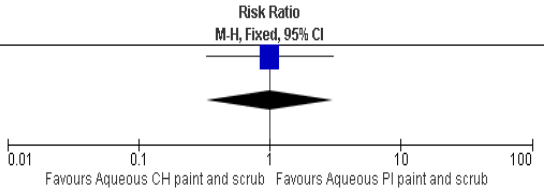
Heterogeneity: Not applicable
Test for overall effect: Z = 0.99 (P = 0.32)



Deep SSI

Study or Subgroup	Aqueous CH scrub (4%) and paint (2%) Events	Total	Aqueous PI scrub (7.5%) and paint (10%) Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Park 2016	6	267	6	267	100.0%	1.00 [0.33, 3.06]
Total (95% CI)		**267**		**267**	**100.0%**	**1.00 [0.33, 3.06]**
Total events	6		6			

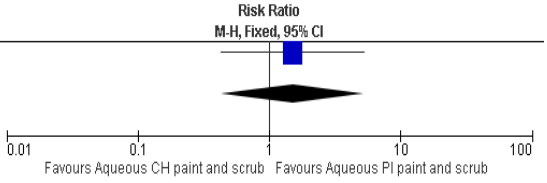
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)



Organ space SSI

Study or Subgroup	Aqueous CH scrub (4%) and paint (2%) Events	Total	Aqueous PI scrub (7.5%) and paint (10%) Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Park 2016	6	267	4	267	100.0%	1.50 [0.43, 5.26]
Total (95% CI)		**267**		**267**	**100.0%**	**1.50 [0.43, 5.26]**
Total events	6		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.63 (P = 0.53)

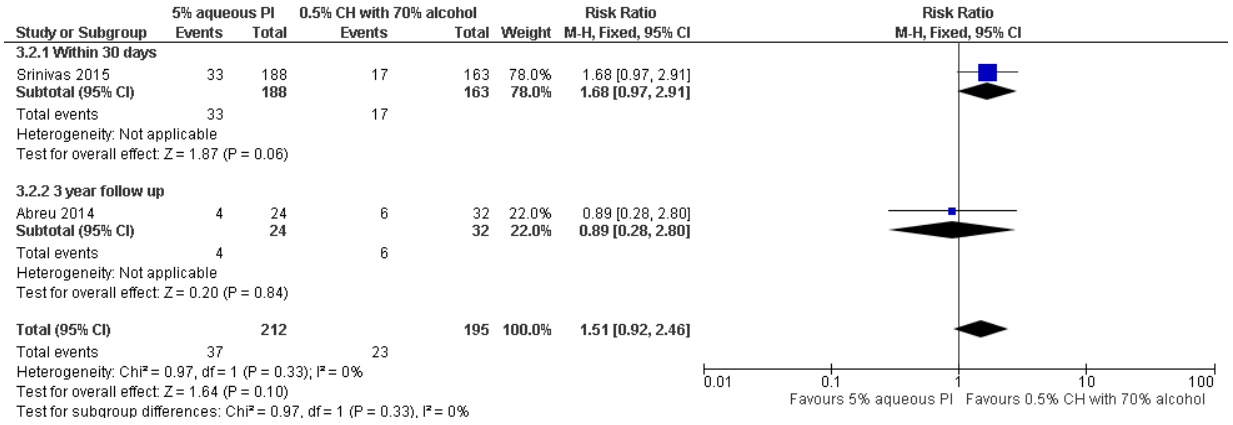


F.4 Aqueous Povidone Iodine

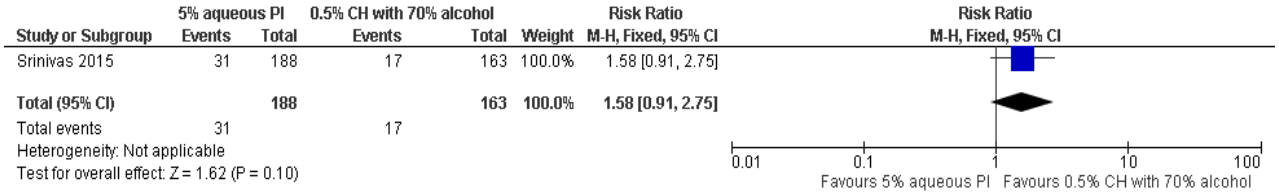
F.4.1 5% Aqueous Povidone Iodine vs 0.5% CH with 70% alcohol

SSI

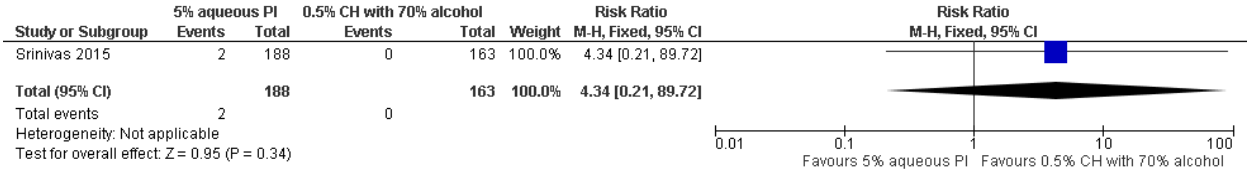
SSI by follow up



Superficial SSI

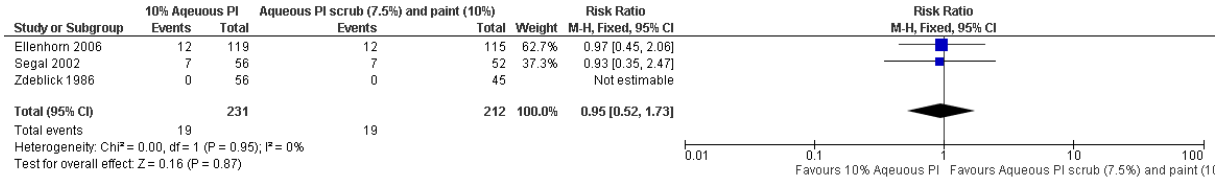


Deep SSI

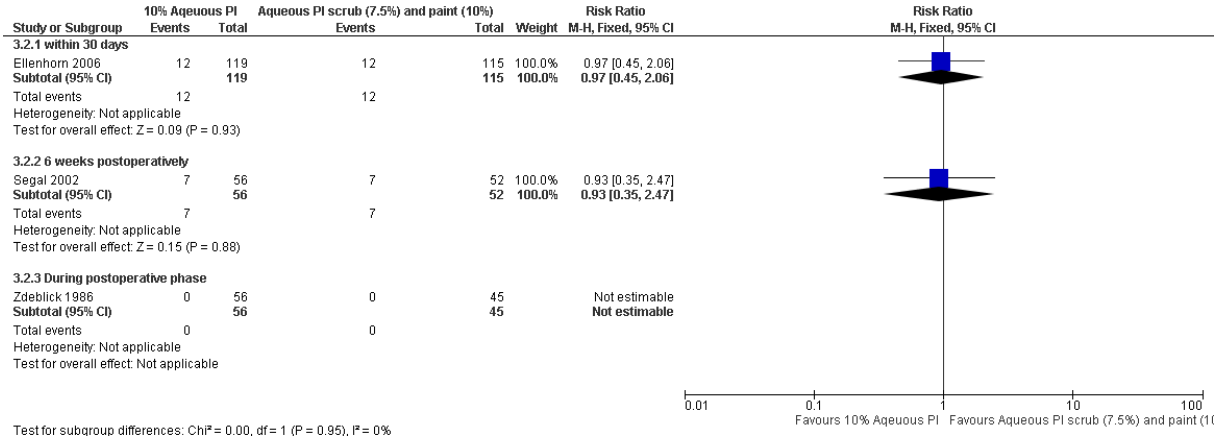


F.4.2 10% Aqueous Povidone Iodine vs Aqueous Povidone Iodine scrub (7.5%) and paint (10%)

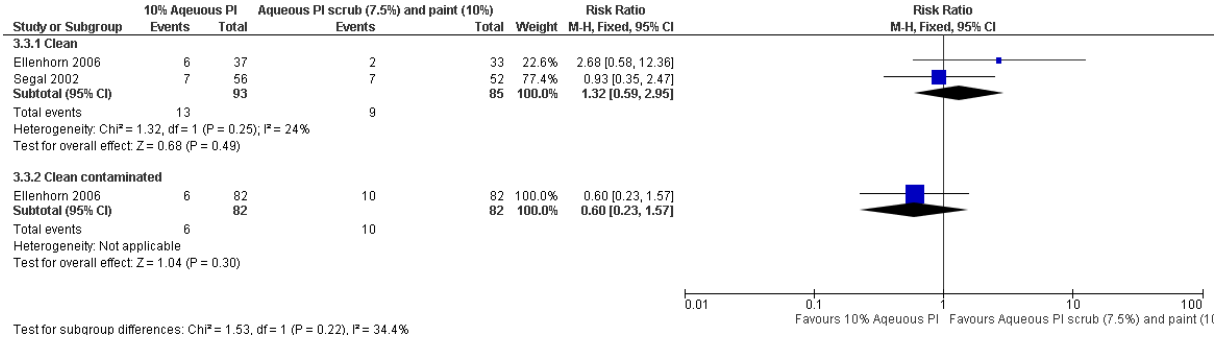
SSI



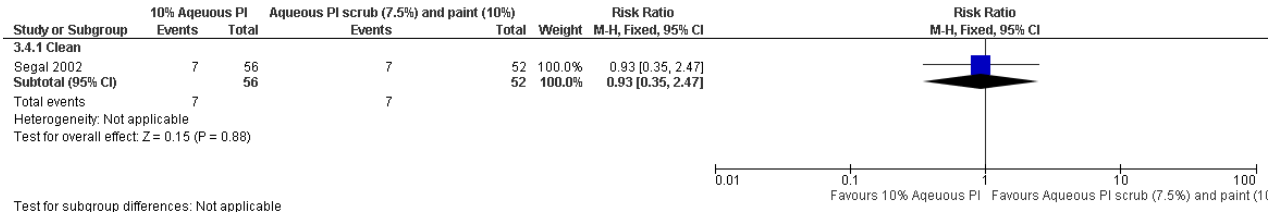
SSI by follow up



SSI by wound category



Sensitivity analysis (excluding studies at high risk of bias): SSI by wound category



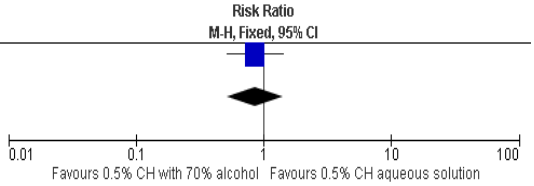
F.5 Chlorhexidine in alcohol preparation

F.5.1 0.5% Chlorhexidine with 70% alcohol vs. 0.5% chlorhexidine in aqueous solution

SSI

Study or Subgroup	0.5% CH with 70% alcohol Events	Total	0.5% CH in aqueous solution Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Charles 2017	26	451	31	458	100.0%	0.85 [0.51, 1.41]
Total (95% CI)		**451**		**458**	**100.0%**	**0.85 [0.51, 1.41]**
Total events	26		31			

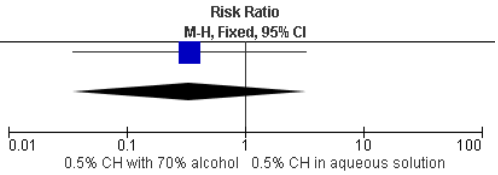
Heterogeneity: Not applicable
Test for overall effect: Z = 0.62 (P = 0.53)



Adverse reactions

Study or Subgroup	0.5% CH with 70% alcohol Events	Total	0.5% CH in aqueous solution Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Charles 2017	1	451	3	458	100.0%	0.34 [0.04, 3.24]
Total (95% CI)		**451**		**458**	**100.0%**	**0.34 [0.04, 3.24]**
Total events	1		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.94 (P = 0.35)

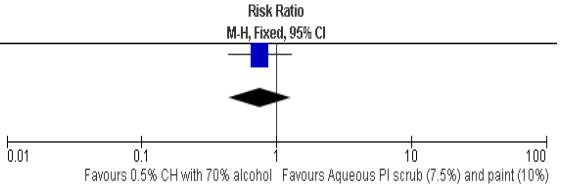


F.5.2 0.5% Chlorhexidine with 70% alcohol vs. Aqueous Povidone Iodine scrub (7.5%) and paint (10%)

SSI

Study or Subgroup	0.5% CH with 70% alcohol Events	Total	Aqueous PI scrub (7.5%) and paint (10%) Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Brown 1984	23	378	29	359	100.0%	0.75 [0.44, 1.28]
Total (95% CI)		**378**		**359**	**100.0%**	**0.75 [0.44, 1.28]**
Total events	23		29			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.05 (P = 0.29)

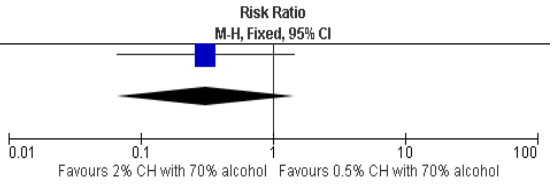


F.5.3 2% Chlorhexidine with 70% alcohol vs. 0.5% CH with 70% alcohol

Superficial SSI

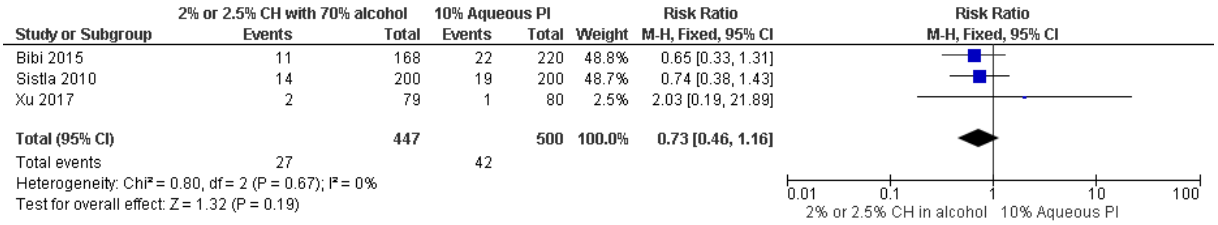
Study or Subgroup	2% CH with 70% alcohol Events	Total	0.5% CH with 70% alcohol Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Casey 2015	2	44	6	41	100.0%	0.31 [0.07, 1.45]
Total (95% CI)		**44**		**41**	**100.0%**	**0.31 [0.07, 1.45]**
Total events	2		6			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.49 (P = 0.14)

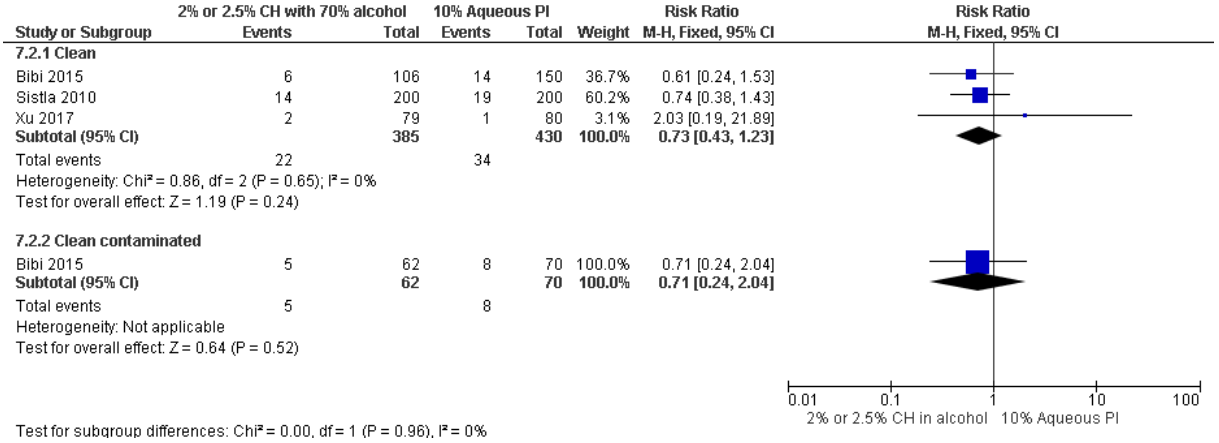


F.5.4 2% or 2.5% Chlorhexidine with 70% alcohol vs. 10% Aqueous Povidone Iodine

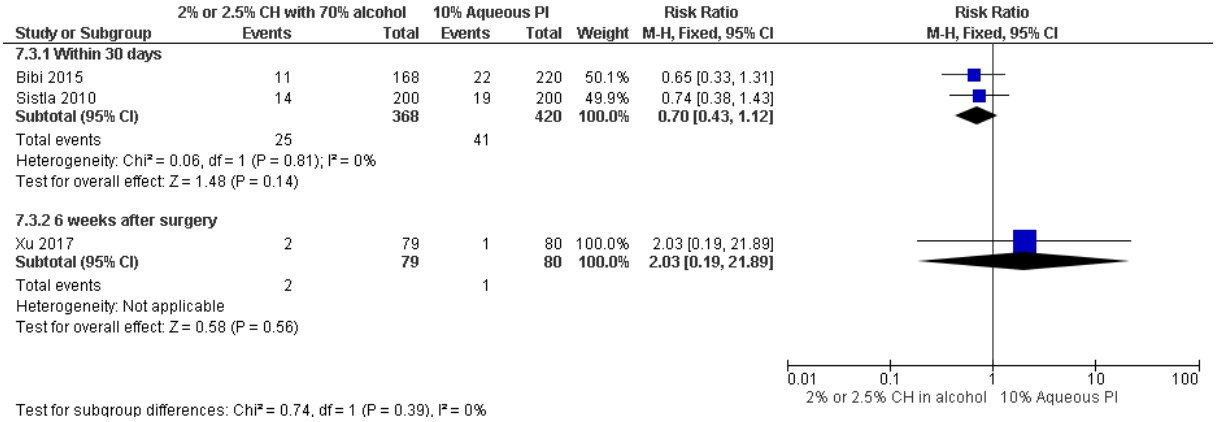
SSI



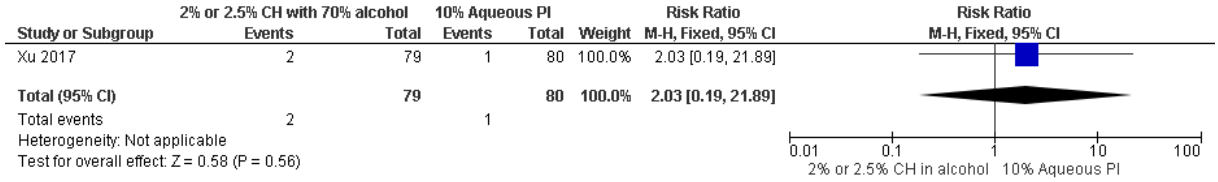
SSI by wound category



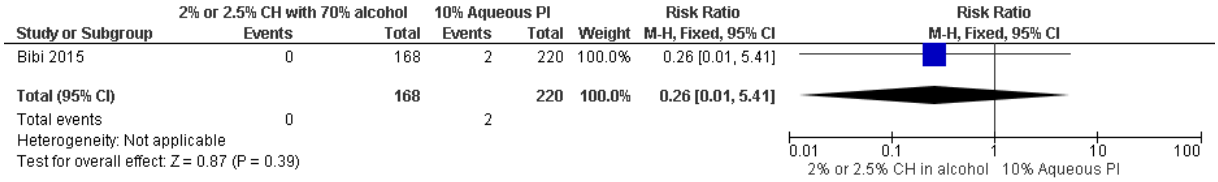
SSI by follow up



Superficial SSI

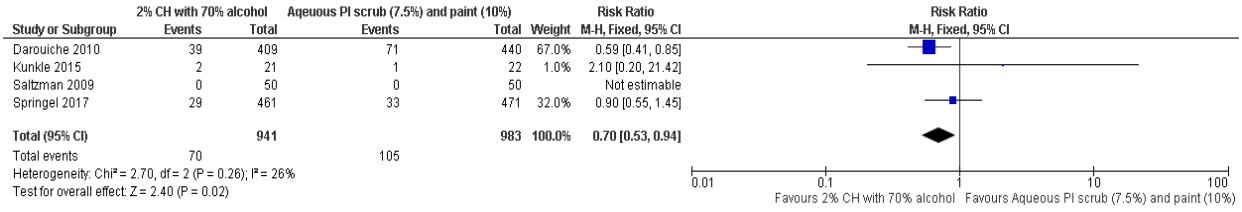


Skin irritation

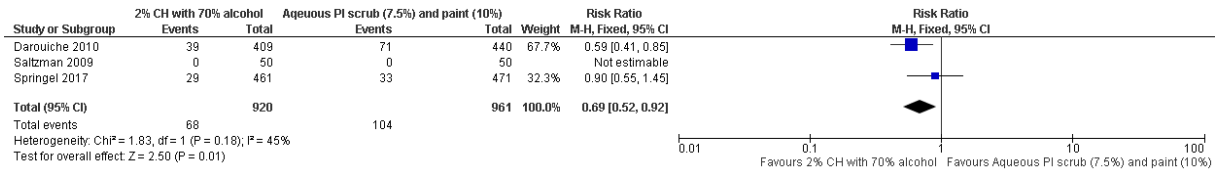


F.5.5 2% Chlorhexidine with 70% alcohol vs. Aqueous Povidone Iodine scrub (7.5%) and paint (10%)

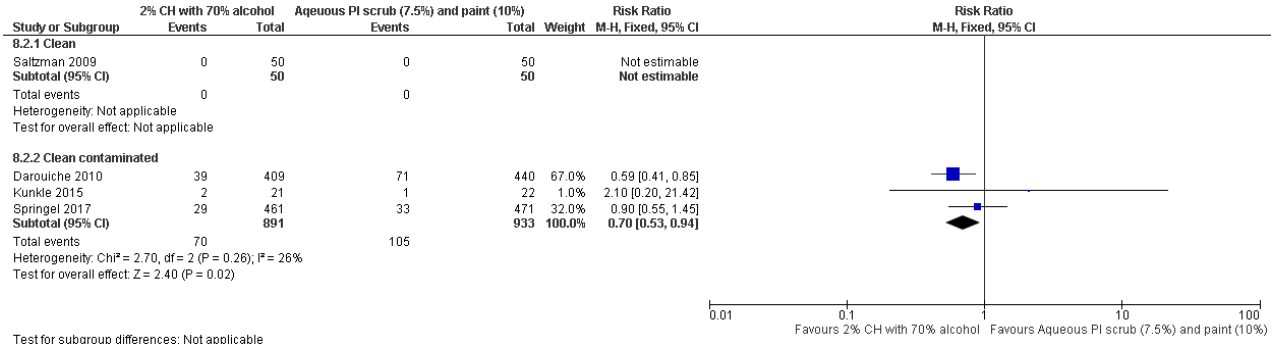
SSI



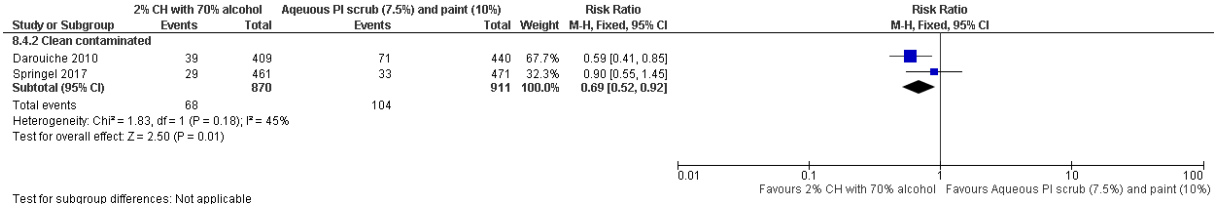
Sensitivity analysis (excluding studies at high risk of bias): SSI



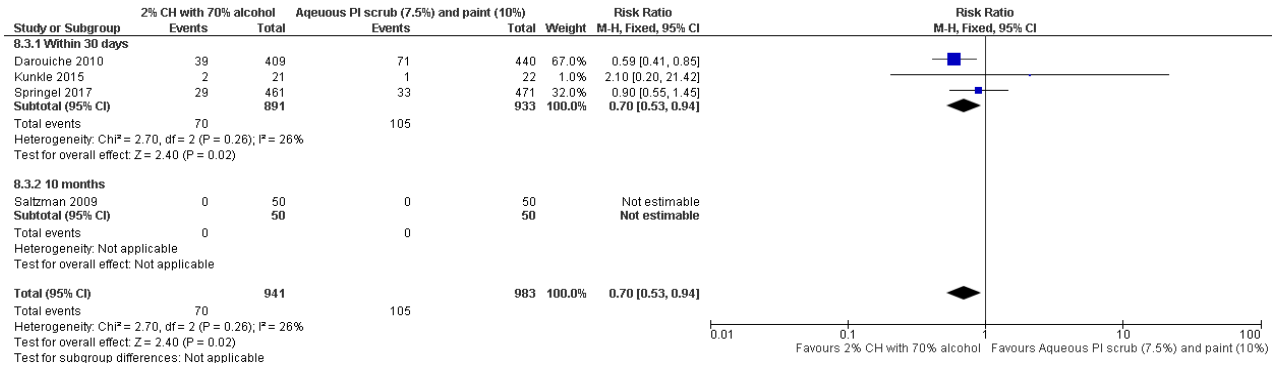
SSI by wound classification



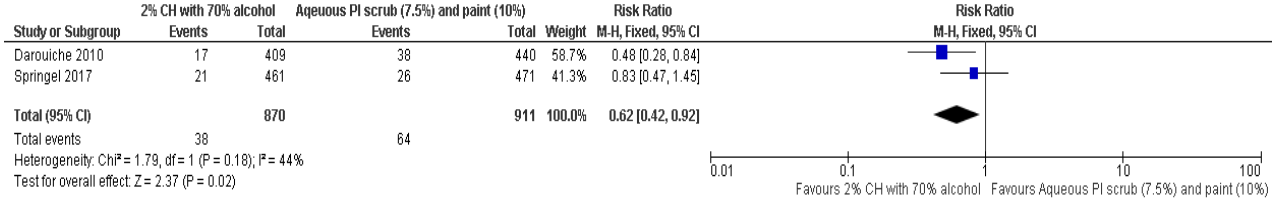
Sensitivity analysis (excluding studies at high risk of bias): SSI by wound classification



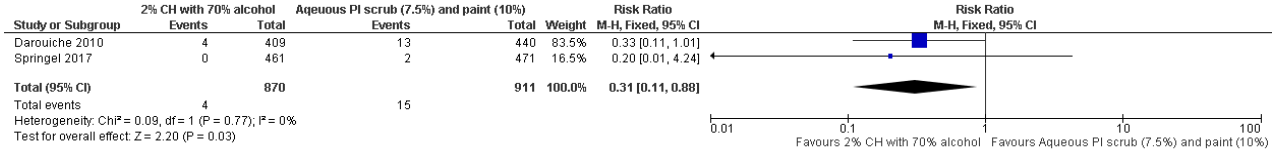
SSI by follow up



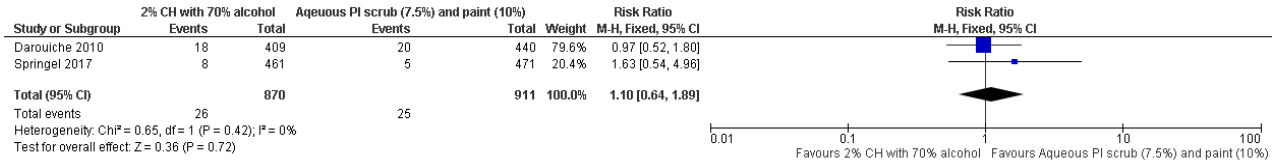
Superficial SSI



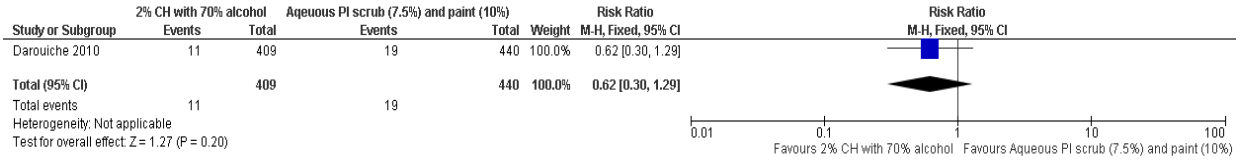
Deep SSI



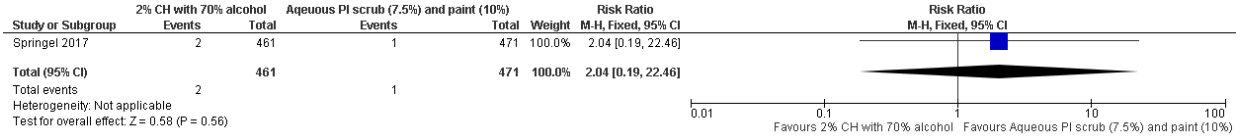
Organ Space SSI



Sepsis

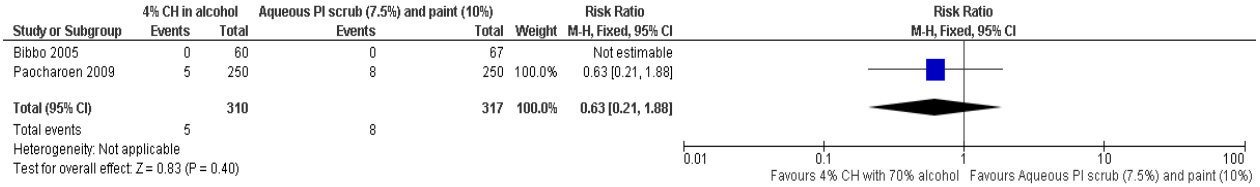


Skin reaction

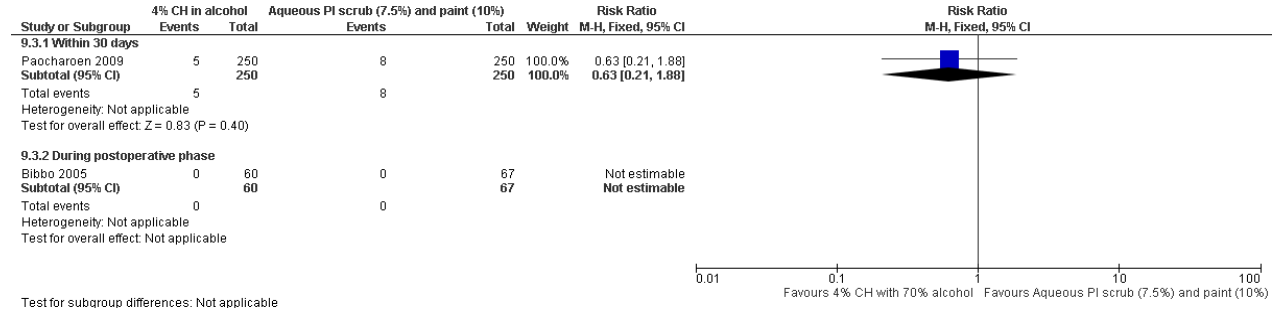


F.5.5 4% Chlorhexidine with 70% alcohol vs. Aqueous Povidone Iodine scrub (7.5%) and paint (10%)

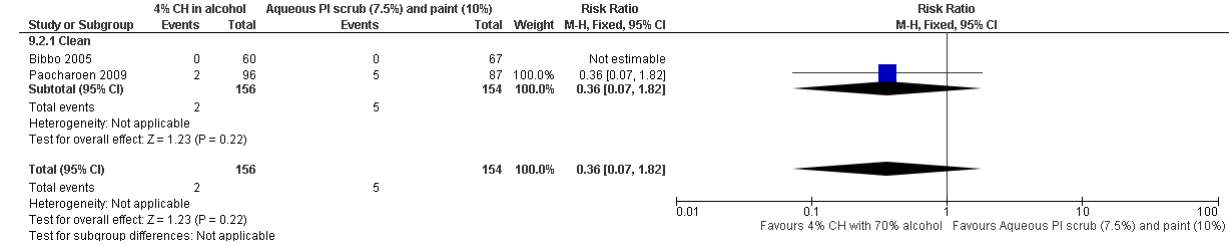
SSI



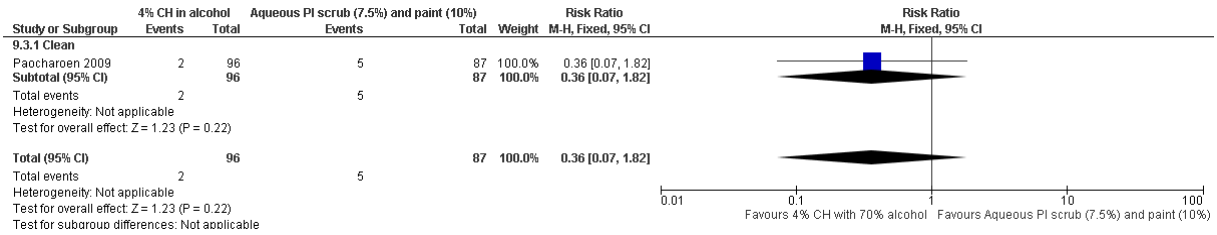
SSI by follow up



SSI by wound classification

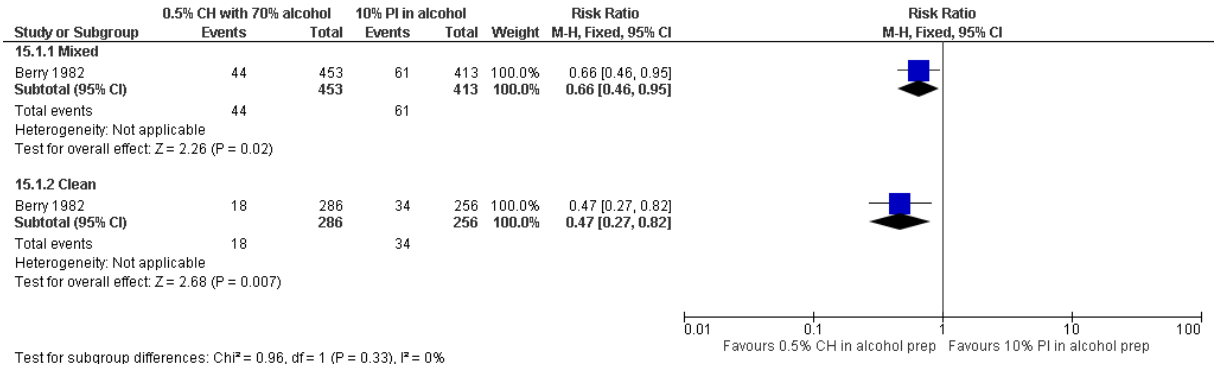


Sensitivity analysis (excluding high risk of bias studies): SSI by wound classification



F.5.6 0.5% CH with 70% alcohol (+surgeon scrub) vs 10% PI in alcohol (+surgeon scrub)

SSI by wound classification



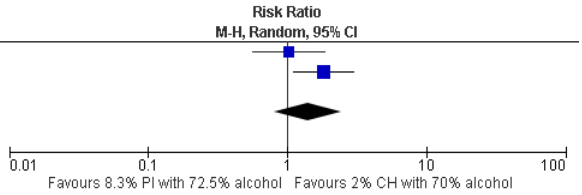
F.6 Povidone Iodine in alcohol preparation

F.6.1 8.3% Povidone Iodine in 72.5% alcohol vs 2% CH with 70% alcohol

SSI

Study or Subgroup	8.3% PI in 72.5% alochol Events	Total	2% CH with 70% alcohol Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Ngai 2015	21	463	21	474	45.9%	1.02 [0.57, 1.85]
Tuuli 2016	42	575	23	572	54.1%	1.82 [1.11, 2.98]
Total (95% CI)		**1038**		**1046**	**100.0%**	**1.40 [0.80, 2.44]**
Total events	63		44			

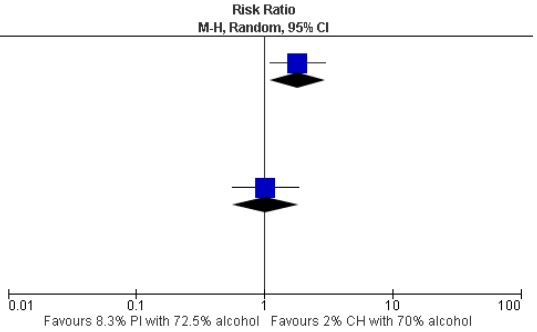
Heterogeneity: Tau² = 0.09; Chi² = 2.13, df = 1 (P = 0.14); I² = 53%
Test for overall effect: Z = 1.17 (P = 0.24)



SSI by follow up

Study or Subgroup	8.3% PI in 72.5% alochol Events	Total	2% CH with 70% alcohol Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
10.2.1 Within 30 days of delivery						
Tuuli 2016	42	575	23	572	100.0%	1.82 [1.11, 2.98]
Subtotal (95% CI)		**575**		**572**	**100.0%**	**1.82 [1.11, 2.98]**
Total events	42		23			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.36 (P = 0.02)						
10.2.2 Within 30 days of discharge						
Ngai 2015	21	463	21	474	100.0%	1.02 [0.57, 1.85]
Subtotal (95% CI)		**463**		**474**	**100.0%**	**1.02 [0.57, 1.85]**
Total events	21		21			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.08 (P = 0.94)						

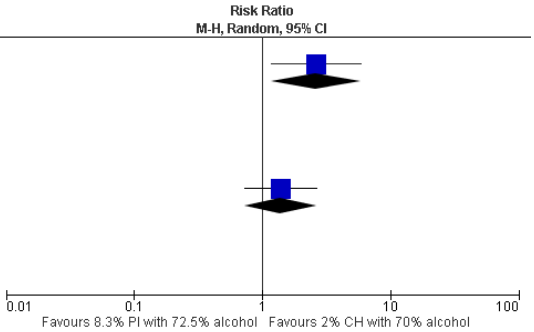
Test for subgroup differences: Chi² = 2.12, df = 1 (P = 0.14), I² = 52.9%



SSI by type of delivery

Study or Subgroup	8.3% PI in 72.5% alochol Events	Total	2% CH with 70% alcohol Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
10.3.1 Scheduled cases						
Tuuli 2016	21	335	8	334	100.0%	2.62 [1.18, 5.83]
Subtotal (95% CI)		**335**		**334**	**100.0%**	**2.62 [1.18, 5.83]**
Total events	21		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.36 (P = 0.02)						
10.3.2 Unscheduled cases						
Tuuli 2016	21	240	15	238	100.0%	1.39 [0.73, 2.63]
Subtotal (95% CI)		**240**		**238**	**100.0%**	**1.39 [0.73, 2.63]**
Total events	21		15			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.01 (P = 0.31)						

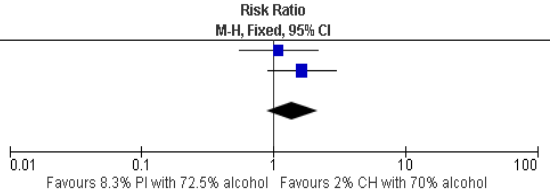
Test for subgroup differences: Chi² = 1.47, df = 1 (P = 0.22), I² = 32.2%



Superficial SSI

Study or Subgroup	8.3% PI in 72.5% alochol Events	Total	2% CH with 70% alcohol Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ngai 2015	16	463	15	474	46.5%	1.09 [0.55, 2.18]
Tuuli 2016	28	575	17	572	53.5%	1.64 [0.91, 2.96]
Total (95% CI)		**1038**		**1046**	**100.0%**	**1.38 [0.88, 2.17]**
Total events	44		32			

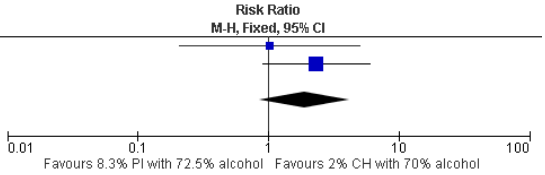
Heterogeneity: Chi² = 0.76, df = 1 (P = 0.38); I² = 0%
Test for overall effect: Z = 1.42 (P = 0.15)



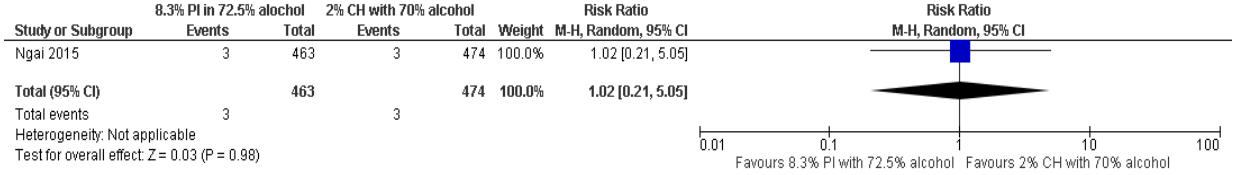
Deep SSI

Study or Subgroup	8.3% PI in 72.5% alochol Events	Total	2% CH with 70% alcohol Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ngai 2015	3	463	3	474	33.0%	1.02 [0.21, 5.05]
Tuuli 2016	14	575	6	572	67.0%	2.32 [0.90, 6.00]
Total (95% CI)		**1038**		**1046**	**100.0%**	**1.89 [0.85, 4.23]**
Total events	17		9			

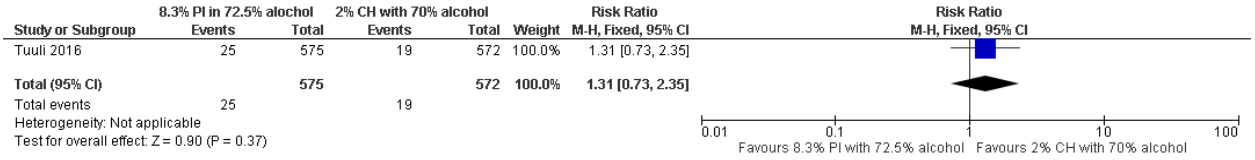
Heterogeneity: Chi² = 0.75, df = 1 (P = 0.39); I² = 0%
Test for overall effect: Z = 1.56 (P = 0.12)



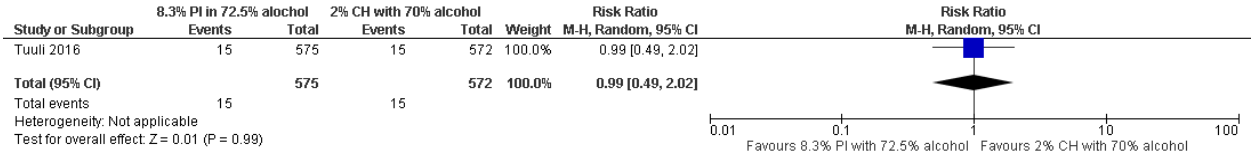
Organ space SSI



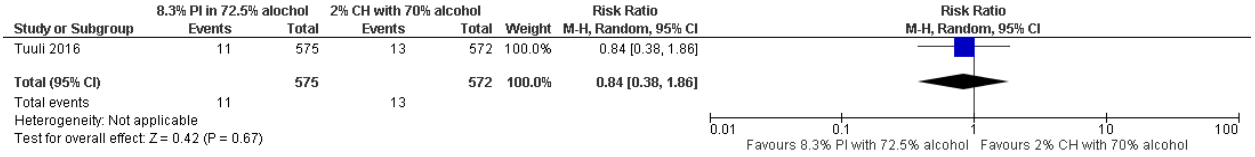
Hospital readmission



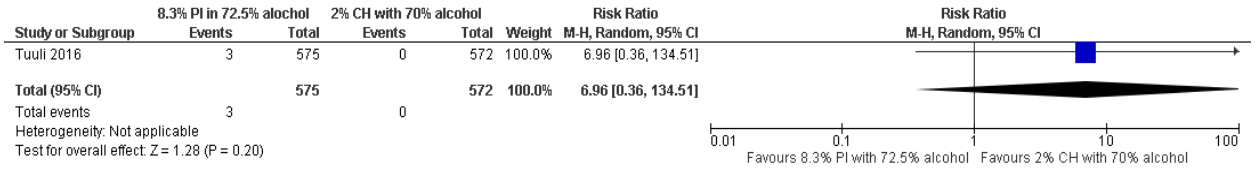
Adverse skin reactions



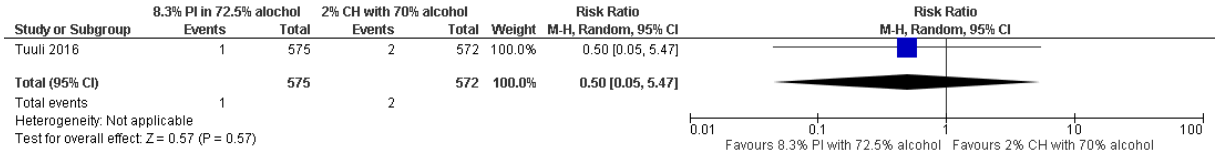
Erythema at operative site



Skin irritation

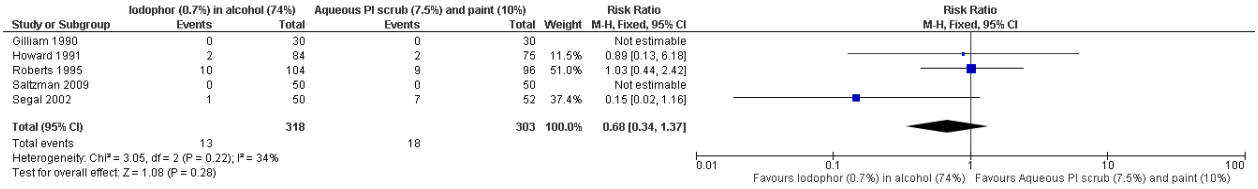


Allergic reactions

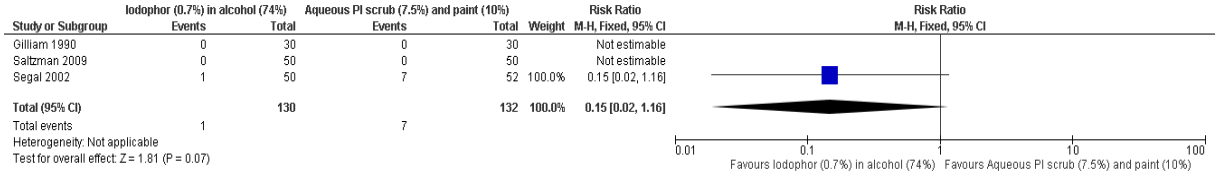


F.6.2 Iodophor (0.7%) in alcohol (74%) vs Aqueous PI scrub (7.5%) and paint (10%)

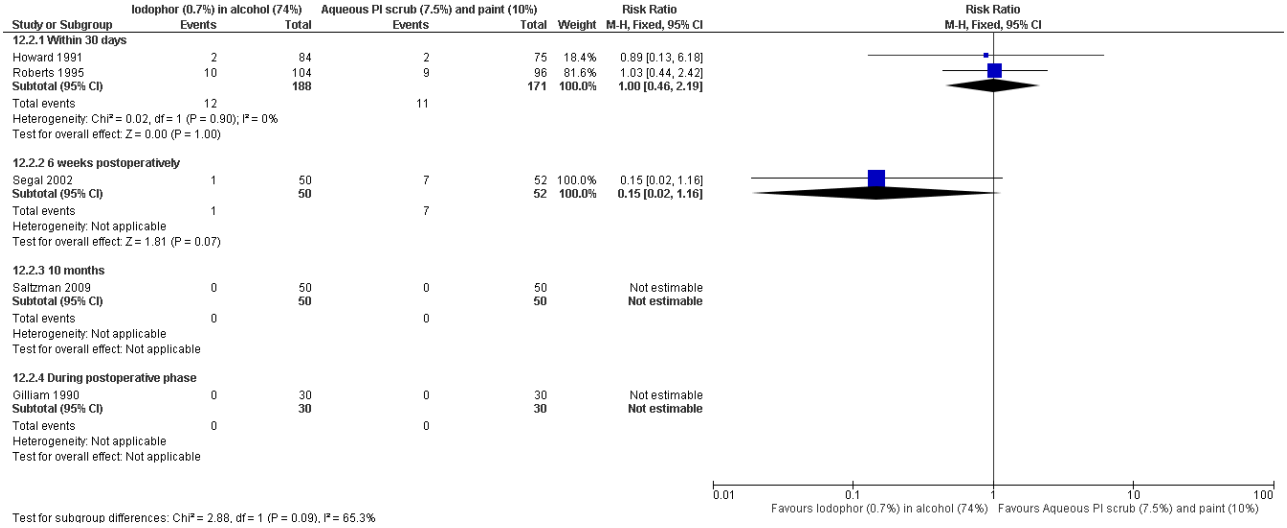
SSI



Sensitivity analysis (excluding studies at high risk of bias): SSI

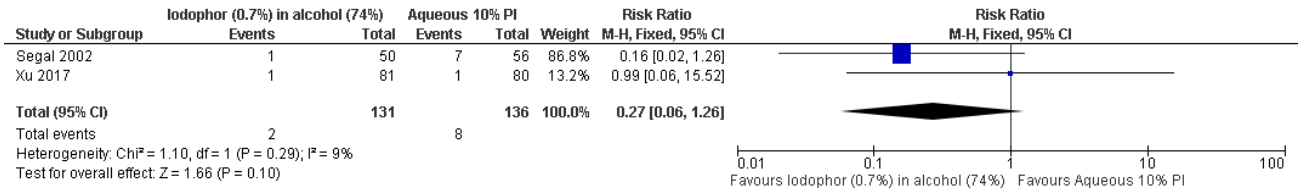


SSI by follow up



F.6.3 Iodophor (0.7%) in alcohol (74%) vs Aqueous 10% PI

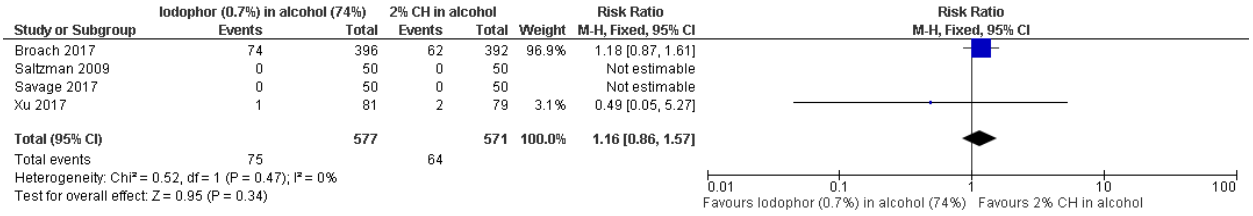
SSI



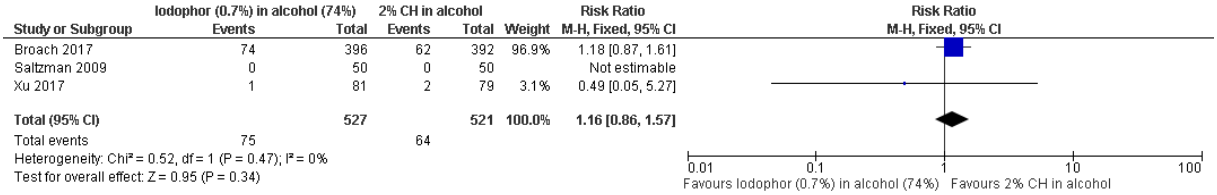
Superficial SSI

F.6.4 Iodophor (0.7%) in alcohol (74%) vs 2% CH in alcohol

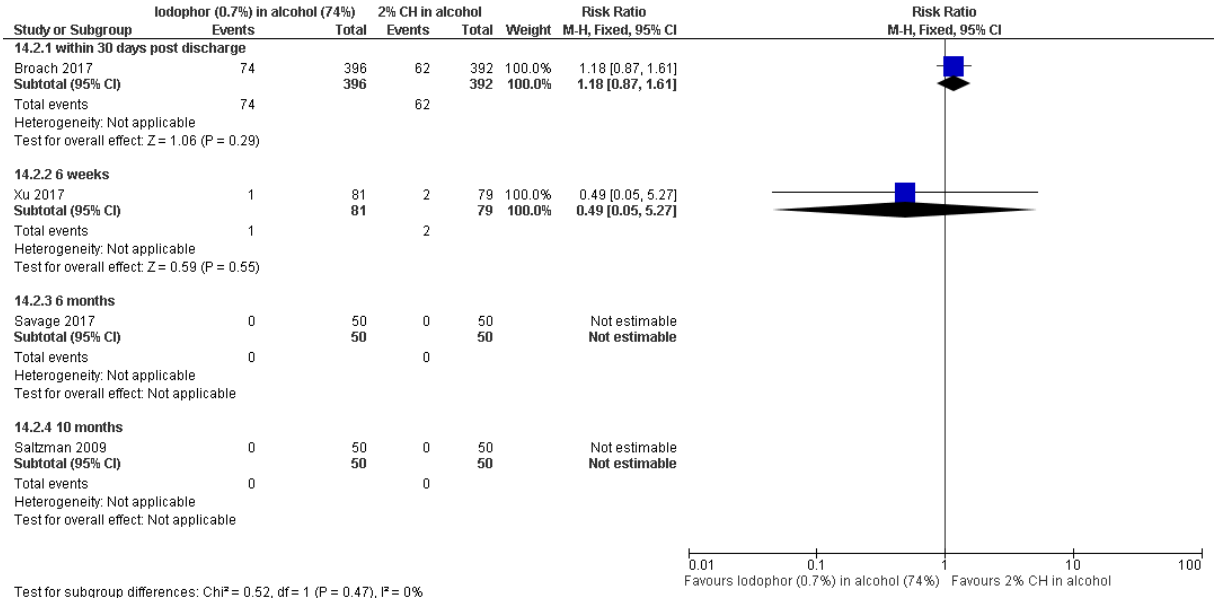
SSI



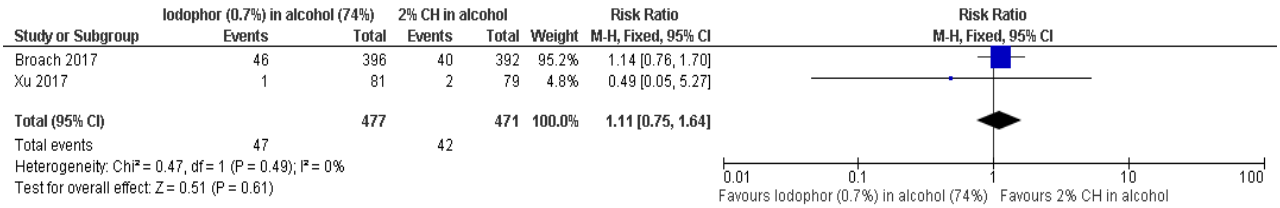
Sensitivity analysis (excluding studies at high risk of bias): SSI



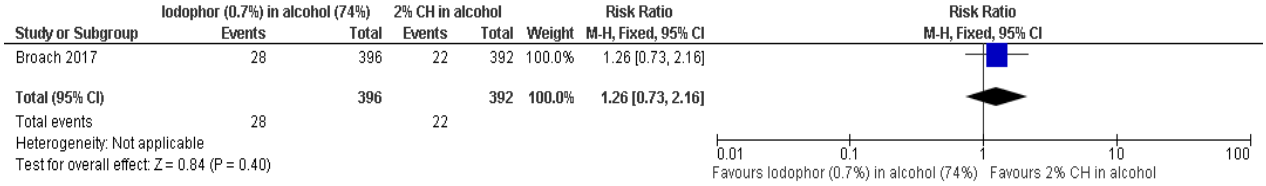
SSI by follow up



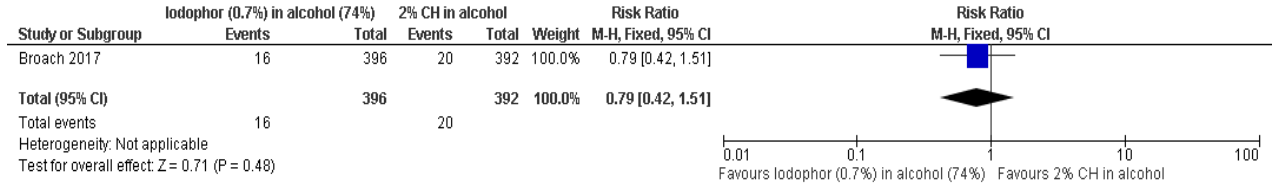
Superficial SSI



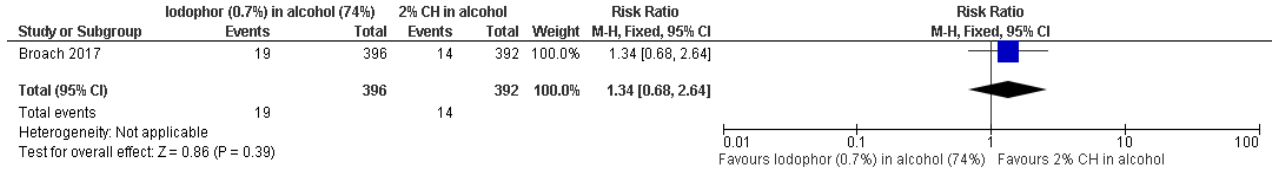
Deep SSI



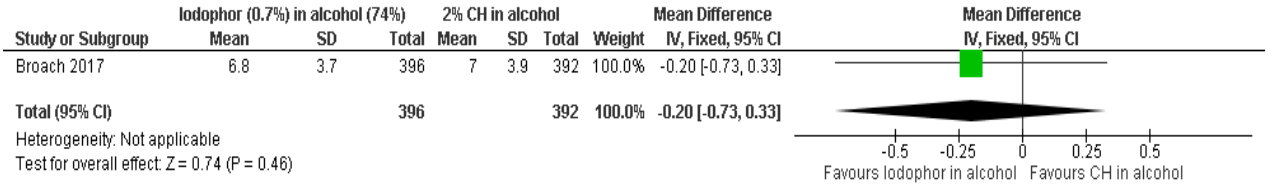
Organ space SSI



Cellulitis

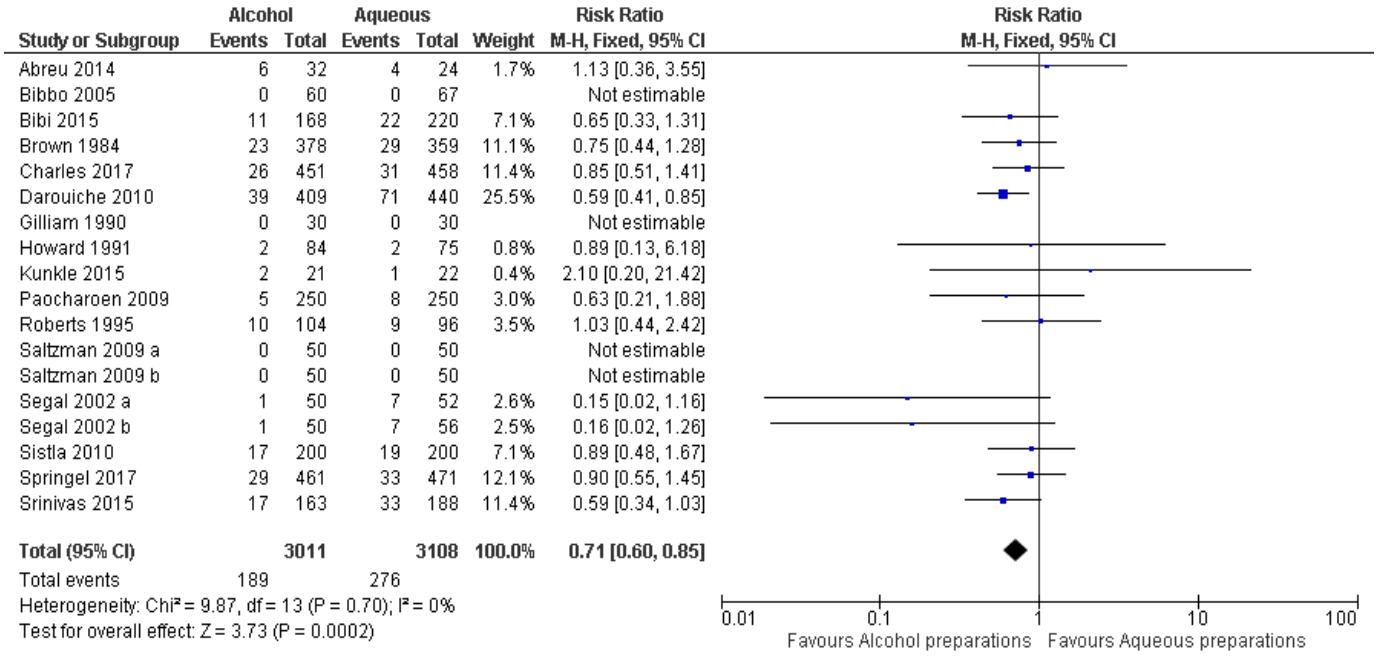


Length of stay



F.7 Alcohol preparation vs aqueous preparation

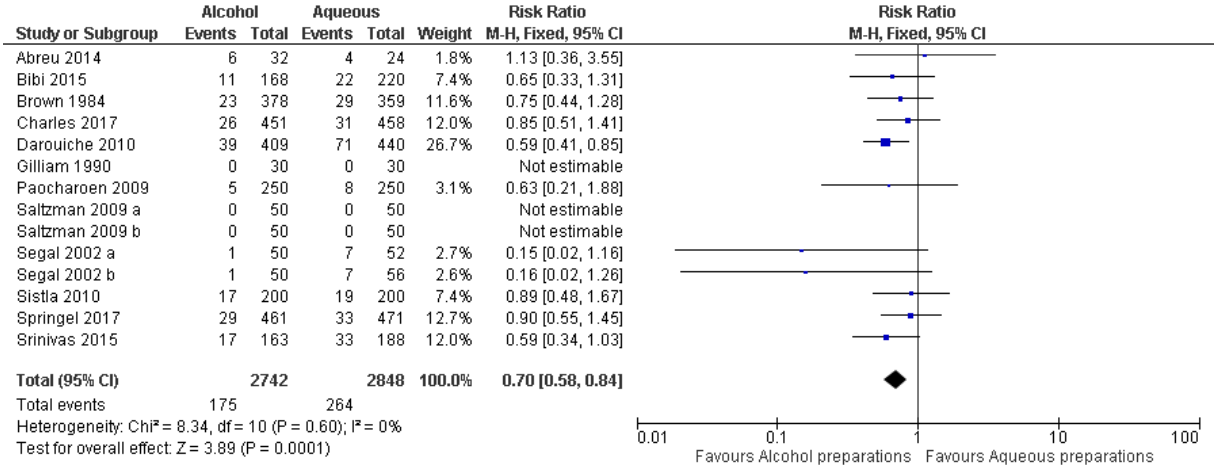
SSI



Study or Subgroup	Alcohol Events	Alcohol Total	Aqueous Events	Aqueous Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Abreu 2014	6	32	4	24	1.7%	1.13 [0.36, 3.55]
Bibbo 2005	0	60	0	67		Not estimable
Bibi 2015	11	168	22	220	7.1%	0.65 [0.33, 1.31]
Brown 1984	23	378	29	359	11.1%	0.75 [0.44, 1.28]
Charles 2017	26	451	31	458	11.4%	0.85 [0.51, 1.41]
Darouiche 2010	39	409	71	440	25.5%	0.59 [0.41, 0.85]
Gilliam 1990	0	30	0	30		Not estimable
Howard 1991	2	84	2	75	0.8%	0.89 [0.13, 6.18]
Kunkle 2015	2	21	1	22	0.4%	2.10 [0.20, 21.42]
Paocharoen 2009	5	250	8	250	3.0%	0.63 [0.21, 1.88]
Roberts 1995	10	104	9	96	3.5%	1.03 [0.44, 2.42]
Saltzman 2009 a	0	50	0	50		Not estimable
Saltzman 2009 b	0	50	0	50		Not estimable
Segal 2002 a	1	50	7	52	2.6%	0.15 [0.02, 1.16]
Segal 2002 b	1	50	7	56	2.5%	0.16 [0.02, 1.26]
Sistla 2010	17	200	19	200	7.1%	0.89 [0.48, 1.67]
Springel 2017	29	461	33	471	12.1%	0.90 [0.55, 1.45]
Srinivas 2015	17	163	33	188	11.4%	0.59 [0.34, 1.03]
Total (95% CI)		**3011**		**3108**	**100.0%**	**0.71 [0.60, 0.85]**
Total events	189		276			

Heterogeneity: Chi² = 9.87, df = 13 (P = 0.70); I² = 0%
Test for overall effect: Z = 3.73 (P = 0.0002)

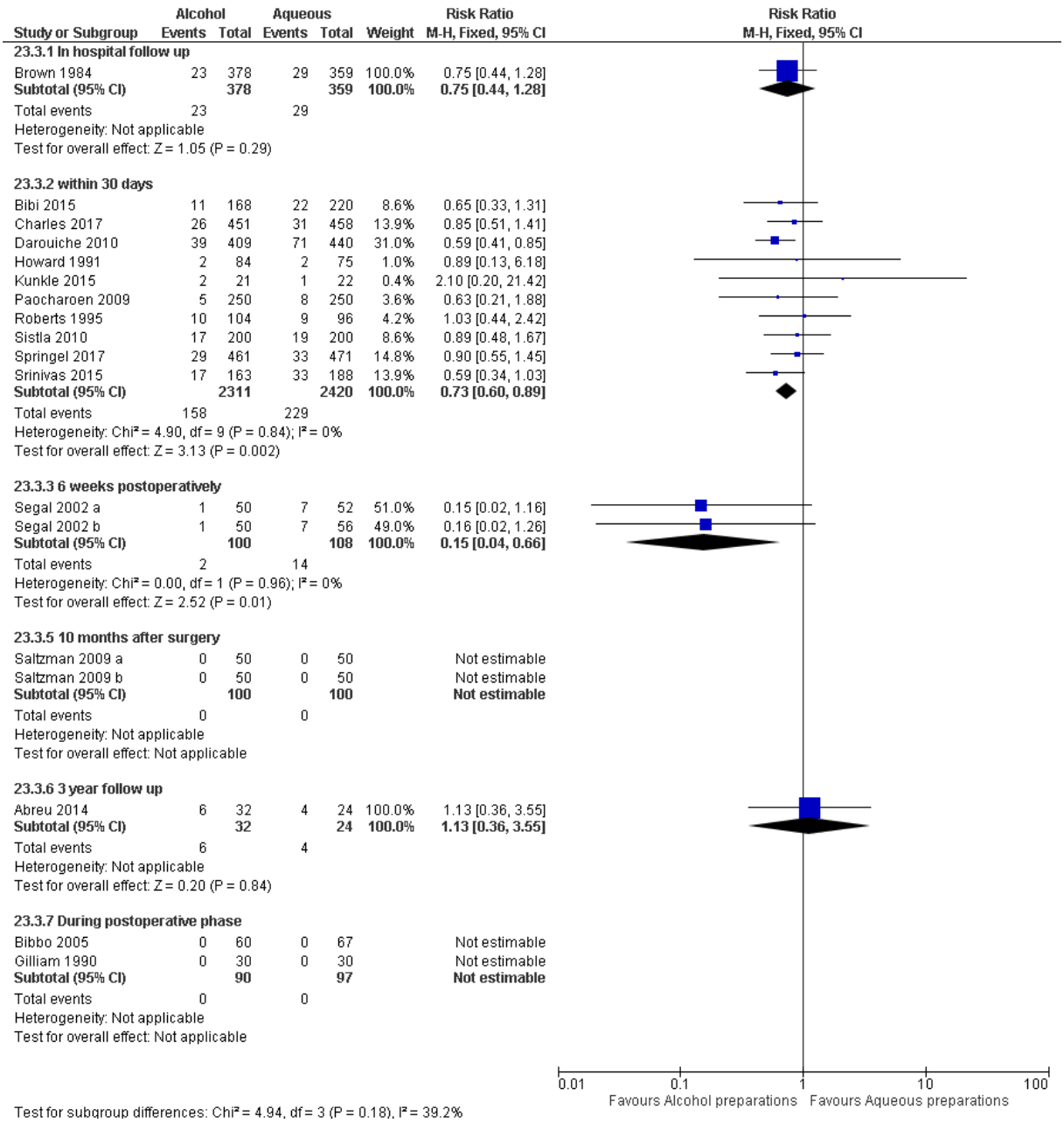
Sensitivity analysis (excluding studies at high risk of bias): SSI

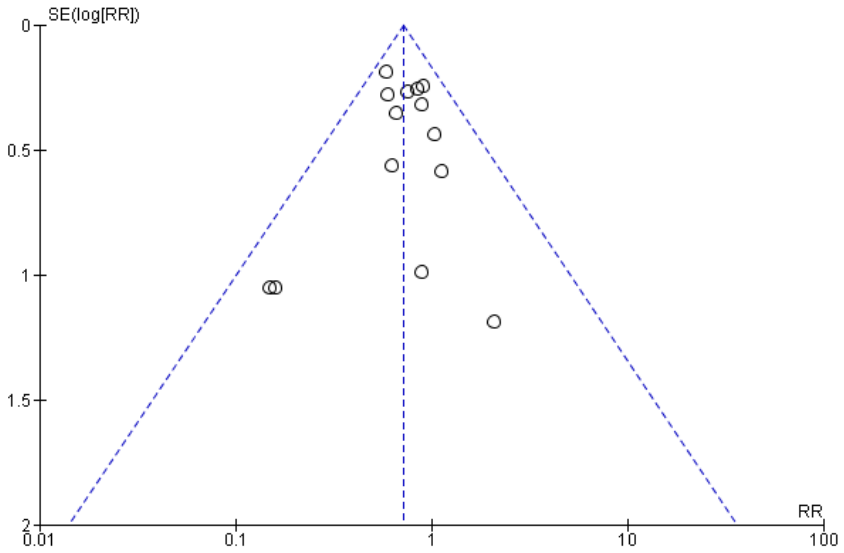


Study or Subgroup	Alcohol Events	Alcohol Total	Aqueous Events	Aqueous Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Abreu 2014	6	32	4	24	1.8%	1.13 [0.36, 3.55]
Bibi 2015	11	168	22	220	7.4%	0.65 [0.33, 1.31]
Brown 1984	23	378	29	359	11.6%	0.75 [0.44, 1.28]
Charles 2017	26	451	31	458	12.0%	0.85 [0.51, 1.41]
Darouiche 2010	39	409	71	440	26.7%	0.59 [0.41, 0.85]
Gilliam 1990	0	30	0	30		Not estimable
Paocharoen 2009	5	250	8	250	3.1%	0.63 [0.21, 1.88]
Saltzman 2009 a	0	50	0	50		Not estimable
Saltzman 2009 b	0	50	0	50		Not estimable
Segal 2002 a	1	50	7	52	2.7%	0.15 [0.02, 1.16]
Segal 2002 b	1	50	7	56	2.6%	0.16 [0.02, 1.26]
Sistla 2010	17	200	19	200	7.4%	0.89 [0.48, 1.67]
Springel 2017	29	461	33	471	12.7%	0.90 [0.55, 1.45]
Srinivas 2015	17	163	33	188	12.0%	0.59 [0.34, 1.03]
Total (95% CI)		**2742**		**2848**	**100.0%**	**0.70 [0.58, 0.84]**
Total events	175		264			

Heterogeneity: Chi² = 8.34, df = 10 (P = 0.60); I² = 0%
Test for overall effect: Z = 3.89 (P = 0.0001)

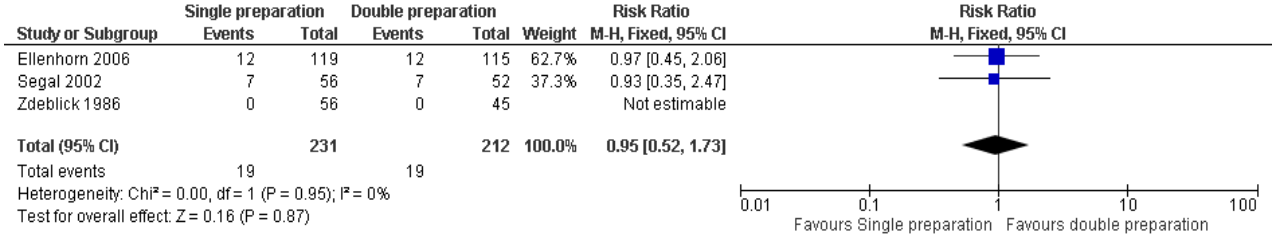
SSI by follow up





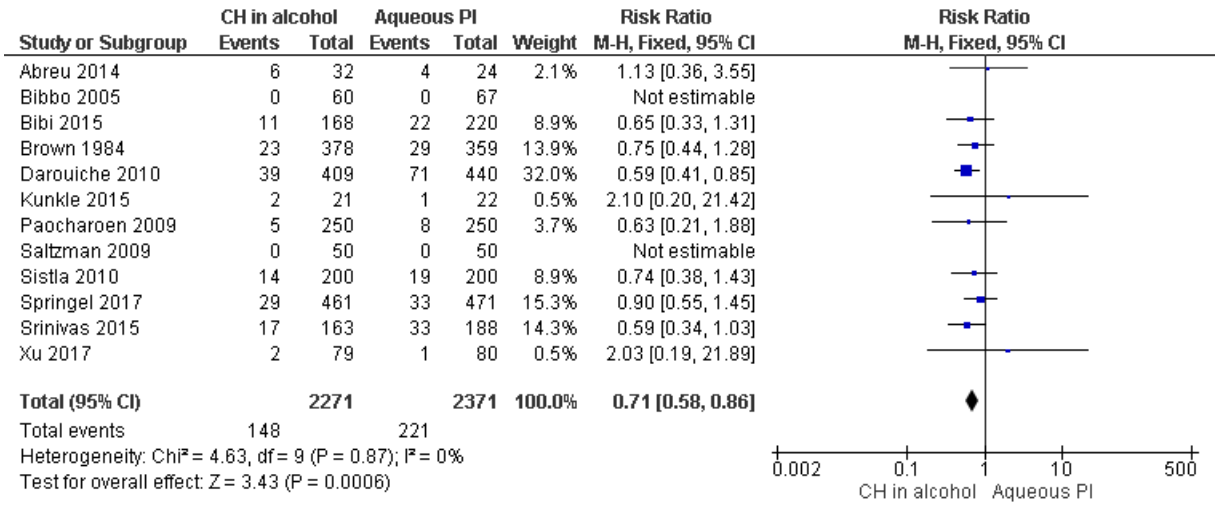
F.8 Single preparation vs double preparation

SSI

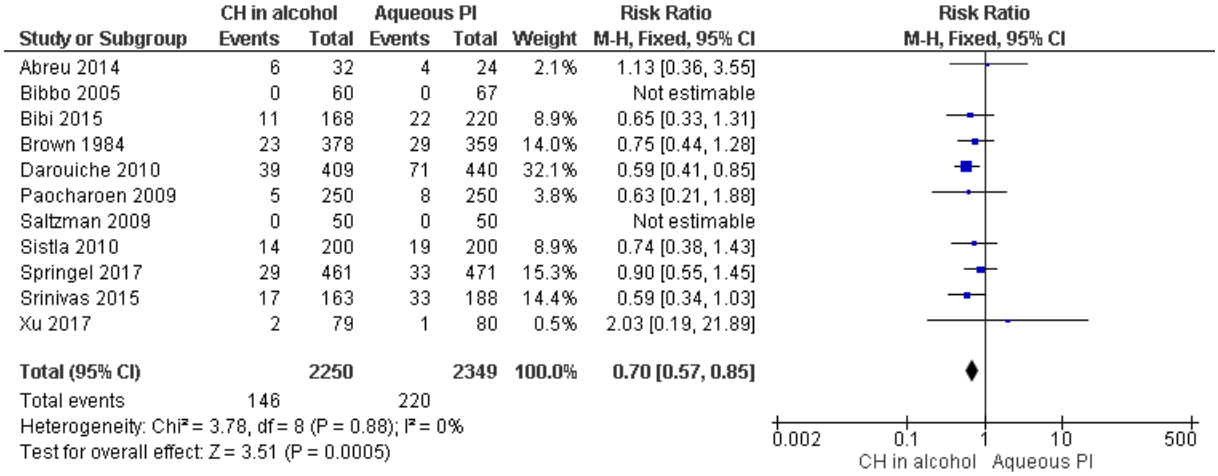


F.9 Chlorhexidine in alcohol vs Aqueous Povidone Iodine (Lumped NMA model)

SSI

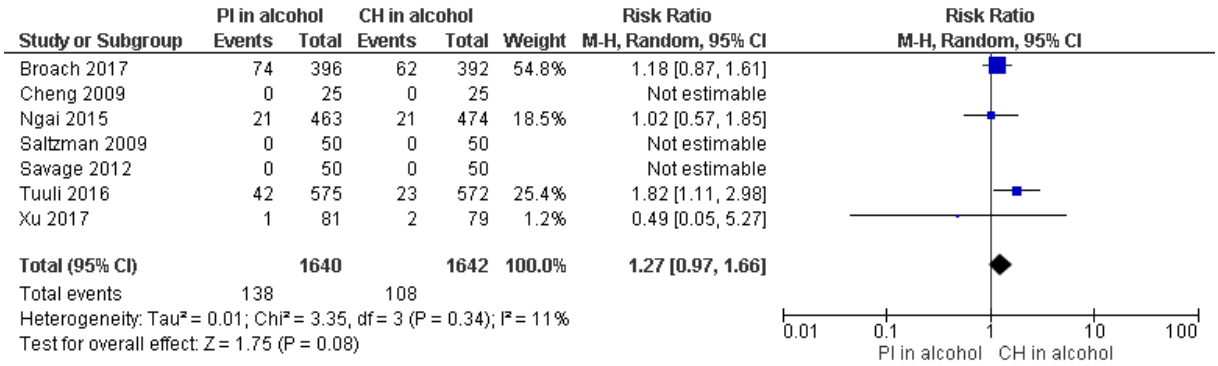


Sensitivity analysis: SSI



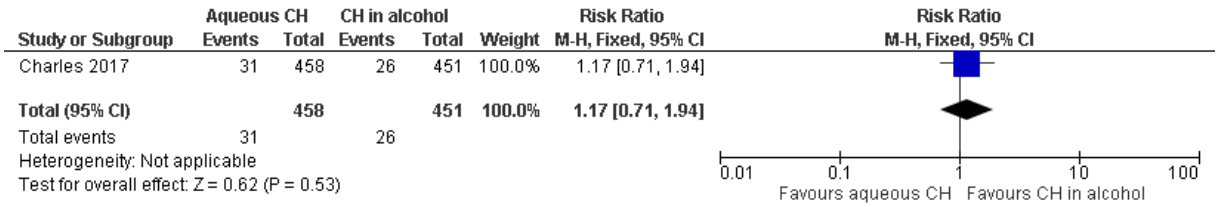
F.10 Povidone Iodine in alcohol vs chlorhexidine in alcohol (Lumped NMA model)

SSI



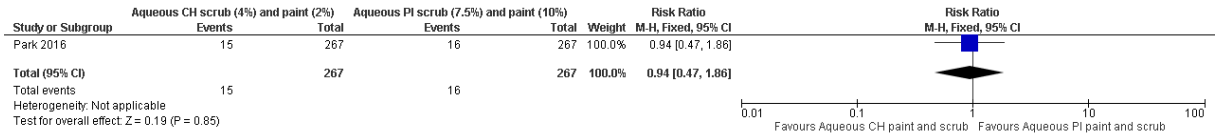
F.10 Aqueous chlorhexidine vs chlorhexidine in alcohol (Lumped NMA model)

SSI



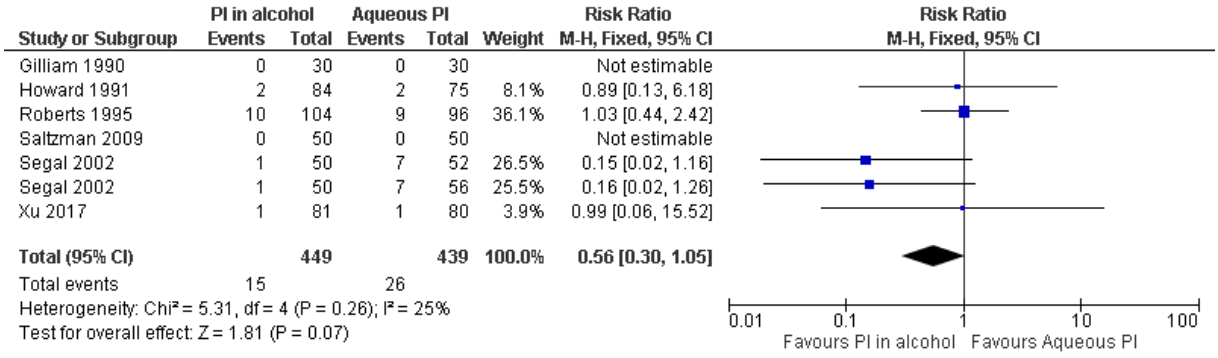
F.11 Aqueous chlorhexidine vs aqueous povidone iodine (Lumped NMA model)

SSI

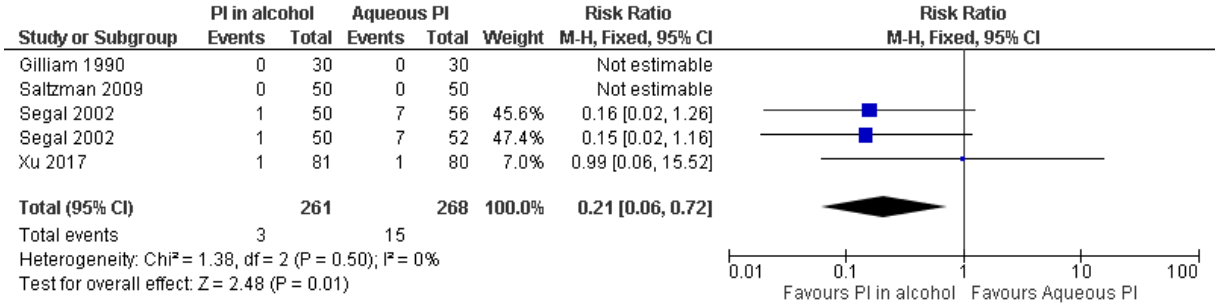


F.11 Povidone iodine in alcohol vs aqueous povidone iodine (Lumped NMA model)

SSI



Sensitivity analysis (excluding studies at high risk of bias): SSI



Appendix G – GRADE tables

G.1 GRADE tables for pairwise evidence

Alcohol

70% alcohol vs 2% iodine in 50% alcohol

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
SSI - RR <1 favours 70% alcohol										
Alexander 1985 (preliminary study)	RCT	62	RR 1.96 (95% CI: 0.10, 38.79)	Not calculable[4]	Not calculable[4]	Serious[1]	Not serious	NA[2]	Very serious[3]	Very low

1. Downgrade 1 level for serious risk of bias. Study demonstrated unclear random sequence generation, allocation concealment and blinding of outcome assessment.
2. Inconsistency not applicable
3. 95% confidence interval crosses both ends of a defined MID interval (0.8, 1.25). Downgrade 2 levels.
4. The absolute risk was not calculable as there were no events in the control arm.

* Derived by taking the overall number of event/ total number of participants and multiplying by 100

70% alcohol vs 2% iodine in 70% alcohol

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
SSI - RR <1 favours 70% alcohol										
Alexander 1985 (preliminary study)	RCT	57	RR 1.41 (95% CI: 0.07, 27.63)	Not calculable[4]	Not calculable[4]	Serious[1]	Not serious	NA[2]	Very Serious[3]	Very low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality

1. Downgrade 1 level for serious risk of bias. Study demonstrated unclear random sequence generation, allocation concealment and blinding of outcome assessment.
2. Inconsistency not applicable
3. 95% confidence interval crosses both ends of a defined MID interval (0.8, 1.25). Downgrade 2 levels.
4. The absolute risk was not calculable as there were no events in the control arm.

* Derived by taking the overall number of event/ total number of participants and multiplying by 100

70% alcohol vs 2% iodine in 90% alcohol

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
SSI - RR <1 favours 70% alcohol										
Alexander 1985 (preliminary study and definitive study)	RCT	369	RR 0.65 (95% CI: 0.19, 2.17)	3 per 100 people	2 per 100 people (1,7)	Serious[1]	Not serious	NA[2]	Very Serious[3]	Very low
Superficial SSI (all wound categories) - RR <1 favours 70% alcohol										
Alexander 1985 (definitive study)	RCT	311	RR 0.71 (95% CI: 0.19, 2.65)	3 per 100 people	2 per 100 people (0, 18)	Serious[1]	Not serious	NA[2]	Very Serious[3]	Very low
Superficial SSI (clean)										
Alexander 1985 (definitive study)	RCT	157	RR 1.07 (95% CI: 0.07, 16.74)	1 per 100 people	1 per 100 people (0,12)	Serious[1]	Not serious	NA[2]	Very Serious[3]	Very low
Superficial SSI (Clean- contaminated) - RR <1 favours 70% alcohol										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Alexander 1985 (definitive study)	RCT	132	RR 0.80 (95% CI: 0.14, 4.63)	4 per 100 people	3 per 100 people (1,19)	Serious[1]	Not serious	NA[2]	Very Serious[3]	Very low
Superficial SSI (contaminated) - RR <1 favours 70% alcohol										
Alexander 1985 (definitive study)	RCT	22	RR 0.33 (95% CI: 0.02, 7.39)	9 per 100 people	3 per 100 people (0,42)	Serious[1]	Not serious	NA[2]	Very Serious[3]	Very low

1. Downgrade 1 level for serious risk of bias. Study demonstrated unclear random sequence generation, allocation concealment and blinding of outcome assessment.
2. Inconsistency not applicable
3. 95% confidence interval crosses both ends of a defined MID interval (0.8, 1.25). Downgrade 2 levels.

* Derived by taking the overall number of event/ total number of participants and multiplying by 100

Iodine in alcohol preparation

2% iodine in 50% alcohol vs 2% iodine in 70% alcohol

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
SSI - RR <1 favours 2% iodine in 50% alcohol										
Alexander 1985 (preliminary study)	RCT	29	RR not estimable due to no occurrence of event in either study arm.			Serious[1]	Not serious	NA[2]	Very serious[3]	Very low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality

1. Downgrade 1 level for serious risk of bias. Study demonstrated unclear random sequence generation, allocation concealment and blinding of outcome assessment.
2. Inconsistency not applicable
3. Unable to calculate effect size. Downgrade 2 levels

* Derived by taking the overall number of event/ total number of participants and multiplying by 100

2% iodine in 50% alcohol vs 2% iodine in 90% alcohol

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
SSI - RR <1 favours 2% iodine in 50% alcohol										
Alexander 1985 (preliminary study)	RCT	30	RR 0.26 (95% CI: 0.01, 5.89)	8 per 100 people	2 per 100 people (0, 45)	Serious[1]	Not serious	NA[2]	Very Serious[3]	Very low

1. Downgrade 1 level for serious risk of bias. Study demonstrated unclear random sequence generation, allocation concealment and blinding of outcome assessment.
2. Inconsistency not applicable
3. 95% confidence interval crosses both ends of a defined MID interval (0.8, 1.25). Downgrade 2 levels.

* Derived by taking the overall number of event/ total number of participants and multiplying by 100

2% iodine in 70% alcohol vs 2% iodine in 90% alcohol

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
SSI - RR <1 favours 2% iodine in 70% alcohol										
Alexander 1985	RCT	25	RR 0.36 (95% CI: 0.02, 8.05)	8 per 100 people	3 per 100 people (0,62)	Serious[1]	Not serious	NA[2]	Very Serious[3]	Very low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
(preliminary study)										

1. Downgrade 1 level for serious risk of bias. Study demonstrated unclear random sequence generation, allocation concealment and blinding of outcome assessment.
2. Inconsistency not applicable
3. 95% confidence interval crosses both ends of a defined MID interval (0.8, 1.25). Downgrade 2 levels.

* Derived by taking the overall number of event/ total number of participants and multiplying by 100

Aqueous Chlorhexidine

Aqueous chlorhexidine scrub (4%) and paint (2%) vs aqueous povidone iodine scrub (7.5%) and paint (10%)

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
SSI - RR <1 favours aqueous chlorhexidine scrub (4%) and paint (2%)										
Park 2016	RCT	534	RR 0.94 (95% CI: 0.47, 1.86)	6 per 100 people	6 per 100 people (3,11)	Not serious	Not serious	NA[1]	Very serious[2]	Low
Superficial SSI - RR <1 favours aqueous chlorhexidine scrub (4%) and paint (2%)										
Park 2016	RCT	534	RR 0.50 (95% CI:0.13, 1.98)	2 per 100 people	1 per 100 people (0,4)	Not serious	Not serious	NA[1]	Very serious[2]	Low
Deep SSI - RR <1 favours aqueous chlorhexidine scrub (4%) and paint (2%)										
Park 2016	RCT	534	RR 1.00 (95% CI:0.33, 3.06)	2 per 100 people	2 per 100 people (1,7)	Not serious	Not serious	NA[1]	Very serious[2]	Low
Organ Space SSI - RR <1 favours aqueous chlorhexidine scrub (4%) and paint (2%)										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Park 2016	RCT	534	RR 1.50 (95% CI:0.43, 5.26)	1 per 100 people	2 per 100 people (1,8)	Not serious	Not serious	NA[1]	Very serious[2]	Low

1. Inconsistency not applicable
2. 95% confidence interval crosses both ends of a defined MID interval (0.8, 1.25). Downgrade 2 levels.

* Derived by taking the overall number of event/ total number of participants and multiplying by 100

Aqueous Povidone Iodine

5% Aqueous Povidone Iodine vs 0.5% CH with 70% alcohol

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
SSI - RR <1 favours 5% aqueous povidone iodine										
Abreu 2014 Srinivas 2015	RCT	407	RR 1.51 (95% CI:0.92, 2.46)	12 per 100 people	18 per 100 people (11,29)	Not serious	Not serious	Not serious	Serious [1]	Moderate
SSI (within 30 days) - RR <1 favours 5% aqueous povidone iodine										
Srinivas 2015	RCT	351	RR 1.68 (95% CI: 0.97, 2.80)	10 per 100 people	18 per 100 people (10, 30)	Not serious	Not serious	NA[2]	Serious[1]	Moderate
SSI (3 year follow up) - RR <1 favours 5% aqueous povidone iodine										
Abreu 2014	RCT	56	RR 0.89 (95% CI: 0.28, 2.46)	19 per 100 people	17 per 100 people (5, 53)	Serious[3]	Not serious	NA[2]	Very serious[4]	Very low
Superficial SSI - RR <1 favours 5% aqueous povidone iodine										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Srinivas 2015	RCT	351	RR 1.58 (95% CI:0.91, 2.75)	10 per 100 people	16 per 100 people (9, 29)	Not serious	Not serious	NA[2]	Serious[1]	Moderate
Deep SSI - RR <1 favours 5% aqueous povidone iodine										
Srinivas 2015	RCT	351	RR 4.34 (95% CI: 0.21, 89.72)	Not calculable[6]	Not calculable[6]	Not serious	Not serious	NA[2]	Very serious[4]	Low
Organ Space SSI - RR <1 favours 5% aqueous povidone iodine										
Srinivas 2015	RCT	351	RR not estimable due to no occurrence of event in either study arm.			Not serious	Not serious	NA[2]	Very serious[5]	Low

1. 95% confidence interval crosses end of a defined MID interval (0.8, 1.25). Downgrade 1 level.
2. Inconsistency not applicable
3. Downgrade 1 level for serious risk of bias. Study demonstrated *unclear random sequence generation, allocation concealment and blinding of outcome assessment.*
4. 95% confidence interval crosses both ends of a defined MID interval (0.8, 1.25). Downgrade 2 levels.
5. Unable to calculate effect size. Downgrade 2 levels
6. The absolute risk was not calculable as there were no events in the control arm.

* Derived by taking the overall number of event/ total number of participants and multiplying by 100

10% Aqueous Povidone Iodine vs Aqueous Povidone Iodine scrub (7.5%) and paint (10%)

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
SSI - RR <1 favours 10% aqueous povidone iodine										
Ellenhorn 2006	RCT	443	RR 0.95 (95% CI: 0.52, 1.73)	12 per 100 people	11 per 100 people (6,20)	Very serious [1]	Not serious	Not serious	Very serious[2]	Very low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Segal 2002 Zdeblick 1986										
SSI (within 30 days) - RR <1 favours 10% aqueous povidone iodine										
Ellenhorn 2006	RCT	234	RR 0.97 (95% CI:0.45, 2.06)	10 per 100 people	10 per 100 people (5, 21)	Very Serious[3]	Not serious	NA[4]	Very serious[2]	Very low
SSI (6 weeks postoperatively) - RR <1 favours 10% aqueous povidone iodine										
Segal 2002	RCT	108	RR 0.93 (95% CI:0.35, 2.47)	13 per 100 people	13 per 100 people (5, 33)	Not serious	Not serious	NA[4]	Very serious[2]	Low
SSI (during postoperative phase) - RR <1 favours 10% aqueous povidone iodine										
Zdeblick 1986	RCT	101	RR not estimable due to no occurrence of event in either study arm.			Very serious[3]	Serious[5]	NA[4]	Very serious[6]	Very low
SSI (clean) - RR <1 favours 10% aqueous povidone iodine										
Ellenhorn 2006 Segal 2002	RCT	178	RR 1.33 (95% CI: 0.50, 3.57)	11 per 100 people	14 per 100 people (5, 38)	Very serious [1]	Not serious	Not serious	Very serious[2]	Very low
Sensitivity analysis (excluding studies at high risk of bias): SSI (clean) - RR <1 favours 10% aqueous povidone iodine										
Segal 2002	RCT	108	RR 0.93 (95% CI:0.35, 2.47)	13 per 100 people	13 per 100 people (5, 33)	Not serious	Not serious	NA[4]	Very serious[2]	Low
SSI (Clean- contaminated) - RR <1 favours 10% aqueous povidone iodine										
Ellenhorn 2006	RCT	164	RR 0.60 (95% CI: 0.23, 1.57)	12 per 100 people	7 per 100 people (3, 19)	Very Serious[3]	Not serious	NA[4]	Very serious[2]	Very low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality

1. Greater than 33.3% of the weight in the meta-analysis came from a study at high risk of bias. Downgrade 2 levels for very serious risk of bias.
2. 95% confidence interval crosses both ends of a defined MID interval (0.8, 1.25). Downgrade 2 levels.
3. Downgrade 2 levels for very serious risk of bias. Study demonstrated unclear random sequence generation, allocation concealment and blinding of outcome assessment.
4. Inconsistency not applicable
5. Downgrade 1 level for serious indirectness. Study did not specify criteria used to define SSI. Furthermore, study did not specify follow up period.
6. Unable to calculate effect size. Downgrade 2 levels

* Derived by taking the overall number of event/ total number of participants and multiplying by 100

Chlorhexidine in alcohol preparation

0.5% Chlorhexidine with 70% alcohol vs 0.5% chlorhexidine in aqueous solution

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
SSI - RR <1 favours 0.5% chlorhexidine with 70% alcohol										
Charles 2017	RCT	909	RR 0.85 (95% CI:0.51, 1.41)	7 per 100 people	6 per 100 people (3,10)	Not serious	Not serious	NA[1]	Very serious[2]	Low
Adverse reactions - RR <1 favours 0.5% chlorhexidine with 70% alcohol										
Charles 2017	RCT	909	RR 0.34 (95% CI:0.03, 3.25)	1 per 100 people	0 per 100 people (0,2)	Not serious	Not serious	NA[1]	Very serious[2]	Low

1. Inconsistency not applicable
2. 95% confidence interval crosses both ends of a defined MID interval (0.8, 1.25). Downgrade 2 levels.

* Derived by taking the overall number of event/ total number of participants and multiplying by 100

0.5% Chlorhexidine with 70% alcohol (spray) vs aqueous povidone iodine scrub (7.5%) and paint (10%)

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
SSI - RR <1 favours 0.5% chlorhexidine with 70% alcohol (spray)										
Brown 1984	RCT	737	RR 0.75 (95% CI: 0.44, 1.28)	8 per 100 people	6 per 100 people (4,10)	Not serious	Not serious	NA[1]	Very serious[2]	Low

1. Inconsistency not applicable
2. 95% confidence interval crosses both ends of a defined MID interval (0.8, 1.25). Downgrade 2 levels.

* Derived by taking the overall number of event/ total number of participants and multiplying by 100

2% chlorhexidine with 70% alcohol vs 0.5% Chlorhexidine with 70% alcohol

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Superficial SSI - RR <1 favours 2% chlorhexidine with 70% alcohol										
Casey 2015	RCT	85	RR 0.31 (95% CI: 0.07, 1.45)	15 per 100 people	5 per 100 people (1,21)	Not serious	Not serious	NA[1]	Very serious[2]	Low

1. Inconsistency not applicable
2. 95% confidence interval crosses both ends of a defined MID interval (0.8, 1.25). Downgrade 2 levels.

* Derived by taking the overall number of event/ total number of participants and multiplying by 100

2% or 2.5% Chlorhexidine with 70% alcohol vs Aqueous 10% Povidone Iodine

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
SSI - RR <1 favours 2% or 2.5% chlorhexidine with 70% alcohol										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Bibi 2015 Sistla 2010 Xu 2017	RCT	947	RR 0.73 (95% CI: 0.46, 1.16)	8 per 100 people	6 per 100 people (4, 10)	Not serious	Not serious	Not serious	Serious[1]	Moderate
SSI (Clean) - RR <1 favours 2% or 2.5% chlorhexidine with 70% alcohol										
Bibi 2015 Sistla 2010 Xu 2017	RCT	815	RR 0.73 (95% CI: 0.43, 1.23)	8 per 100 people	6 per 100 people (3, 10)	Not serious	Not serious	Not serious	Serious[1]	Moderate
SSI (clean - contaminated) - RR <1 favours 2% or 2.5% chlorhexidine with 70% alcohol										
Bibi 2015	RCT	132	RR 0.71 (95% CI: 0.24, 2.04)	11 per 100 people	8 per 100 people (3, 14)	Not serious	Not serious	NA[2]	Very Serious[3]	Low
SSI (within 30 days) - RR <1 favours 2% or 2.5% chlorhexidine with 70% alcohol										
Bibi 2015 Sistla 2010	RCT	788	RR 0.70 (95% CI: 0.43, 1.12)	10 per 100 people	7 per 100 people (4, 11)	Not serious	Not serious	Not serious	Serious[1]	Moderate
SSI (6 weeks after surgery) - RR <1 favours 2% or 2.5% chlorhexidine with 70% alcohol										
Xu 2017	RCT	159	RR 2.03 (95% CI: 0.19, 21.89)	1 per 100 people	3 per 100 people (0, 27)	Not serious	Not serious	NA[2]	Very Serious[3]	Low
Superficial SSI - RR <1 favours 2% or 2.5% chlorhexidine with 70% alcohol										
Xu 2017	RCT	159	RR 2.03 (95% CI: 0.19, 21.89)	1 per 100 people	per 100 people (0, 27)	Not serious	Not serious	NA[2]	Very Serious[3]	Low
Skin irritation - RR <1 favours 2% or 2.5% chlorhexidine with 70% alcohol										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Bibi 2015	RCT	388	RR 0.26 (95% CI: 0.01, 5.41)	1 per 100 people	0 per 100 people (0, 5)	Not serious	Not serious	NA[2]	Very Serious[3]	Low

1. 95% confidence interval crosses one end of a defined MID interval (0.8, 1.25). Downgrade 2 levels.
2. Inconsistency not applicable
3. 95% confidence interval crosses both ends of a defined MID interval (0.8, 1.25). Downgrade 2 levels.

* Derived by taking the overall number of event/ total number of participants and multiplying by 100

2% Chlorhexidine with 70% alcohol vs Aqueous Povidone Iodine Scrub (7.5%) and paint (10%)

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
SSI - RR <1 favours 2% chlorhexidine with 70% alcohol										
Darouiche 2010, Kunkle 2015, Saltzman 2009, Springel 2017	RCT	1,924	RR 0.70 (95% CI: 0.53, 0.94)	11 per 100 people	7 per 100 people (6, 10)	Not serious	Not serious	Not serious	Serious[1]	Moderate
Sensitivity analysis (excluding studies at high risk of bias): SSI - RR <1 favours 2% chlorhexidine with 70% alcohol										
Darouiche 2010, Saltzman 2009, Springel 2017	RCT	1,881	RR 0.69 (95% CI: 0.52, 0.92)	11 per 100 people	7 per 100 people (6, 10)	Not serious	Not serious	Serious[6]	Serious[1]	Low
SSI (Clean) - RR <1 favours 2% chlorhexidine with 70% alcohol										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Saltzman 2009	RCT	100	RR not estimable due to no occurrence of event in either study arm.			Serious[2]	Serious[3]	NA[4]	Very serious[5]	Very low
SSI (Clean-contaminated) - RR <1 favours 2% chlorhexidine with 70% alcohol										
Darouiche 2010, Kunkle 2015, Springel 2017	RCT	1,824	RR 0.70 (95% CI: 0.53, 0.94)	11 per 100 people	8 per 100 people (6, 11)	Not serious	Not serious	Not serious	Serious[1]	Moderate
Sensitivity analysis (excluding studies at high risk of bias): SSI (Clean-contaminated) - RR <1 favours 2% chlorhexidine with 70% alcohol										
Darouiche 2010, Springel 2017	RCT	1,781	RR 0.69 (95% CI: 0.52, 0.92)	11 per 100 people	8 per 100 people (6,11)	Not serious	Not serious	Serious[6]	Serious[1]	Low
SSI (within 30 days) - RR <1 favours 2% chlorhexidine with 70% alcohol										
Darouiche 2010, Kunkle 2015, Springel 2017	RCT	1,824	RR 0.70 (95% CI: 0.53, 0.94)	11 per 100 people	8 per 100 people (6, 11)	Not serious	Not serious	Not serious	Serious[1]	Moderate
SSI (10 months) - RR <1 favours 2% chlorhexidine with 70% alcohol										
Saltzman 2009	RCT	100	RR not estimable due to no occurrence of event in either study arm.			Serious[2]	Serious[3]	NA[4]	Very serious[5]	Very low
Superficial SSI - RR <1 favours 2% chlorhexidine with 70% alcohol										
Darouiche 2010,	RCT	1,781	RR 0.62 (95% CI: 0.42,0.92)	7 per 100 people	4 per 100 people (3, 6)	Not serious	Not serious	Serious[6]	Serious[1]	Low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Springel 2017										
Deep SSI- RR <1 favours 2% chlorhexidine with 70% alcohol										
Darouiche 2010, Springel 2017	RCT	1,781	RR 0.31 (95% CI: 0.11, 0.88)	2 per 100 people	1 per 100 people (0,1)	Not serious	Not serious	Not serious	Serious[1]	Moderate
Organ Space SSI - RR <1 favours 2% chlorhexidine with 70% alcohol										
Darouiche 2010, Springel 2017	RCT	1,781	RR 1.10 (95% CI: 0.64, 1.89)	3 per 100 people	3 per 100 people (2,5)	Not serious	Not serious	Not serious	Very serious[7]	Low
Sepsis - RR <1 favours 2% chlorhexidine with 70% alcohol										
Darouiche 2010	RCT	849	RR 0.62 (95% CI: 0.30, 1.29)	4 per 100 people	3 per 100 people (1,6)	Not serious	Not serious	NA[4]	Very serious[7]	Low
Skin reaction - RR <1 favours 2% chlorhexidine with 70% alcohol										
Springel 2017	RCT	932	RR 2.04 (95% CI: 0.19, 22.46)	2 per 100 people	4 per 100 people (0, 48)**	Not serious	Not serious	NA[4]	Very serious[7]	Low

1. 95% confidence interval crosses one end of a defined MID interval (0.8, 1.25). Downgrade 1 level.
2. Downgrade 1 level for serious risk of bias. Study demonstrated *unclear random sequence generation, blinding of outcome assessment and other sources of bias.*
3. *Downgrade 1 level for serious indirectness. Study did not specify classification used to define SSI.*
4. Inconsistency not applicable
5. Unable to calculate effect size. Downgrade 2 levels
6. Downgrade 1 level for serious inconsistency. I^2 between 33.3% and 66.7%
7. 95% confidence interval crosses both ends of a defined MID interval (0.8, 1.25). Downgrade 2 levels.

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
* Derived by taking the overall number of event/ total number of participants and multiplying by 100 ** Derived by taking the overall number of event/ total number of participants and multiplying by 1000										

4% CH with 70% alcohol vs Aqueous Povidone Iodine Scrub (7.5%) and paint

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
SSI (mixed) - RR <1 favours 4% chlorhexidine with 70% alcohol										
Bibbo 2005 Paocharoen 2009	RCT	627	RR 0.63 (95% CI: 0.21, 1.88)	3 per 100 people	2 per 100 people (1,5)	Serious[1]	Not serious	Not serious	Very serious[4]	Very low
SSI (within 30 days) - RR <1 favours 4% chlorhexidine with 70% alcohol										
Paocharoen 2009	RCT	500	RR 0.63 (95% CI: 0.21, 1.88)	3 per 100 people	2 per 100 people (1,6)	Serious[2]	Not serious	NA[3]	Very serious[4]	Very low
SSI (during postoperative phase) - RR <1 favours 4% chlorhexidine with 70% alcohol										
Bibbo 2005	RCT	127	RR not estimable due to no occurrence of event in either study arm.			Very serious[5]	Serious[6]	NA[3]	Very serious [7]	Very low
SSI (clean) - RR <1 favours 4% chlorhexidine with 70% alcohol										
Bibbo 2005 Paocharoen 2009	RCT	310	RR 0.36 (95% CI: 0.07, 1.82)	3 per 100 people	1 per 100 people (0,6)	Serious[1]	Not serious	Not serious	Very serious[4]	Very low
Sensitivity analysis (excluding high risk of bias studies) : SSI (clean) - RR <1 favours 4% chlorhexidine with 70% alcohol										
Paocharoen 2009	RCT	183	RR 0.36 (95% CI: 0.07, 1.82)	6 per 100 people	2 per 100 people (0,10)	Serious[2]	Not serious	NA[3]	Very serious[4]	Very low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality

1. Greater than 33.3% of the weight of meta-analysis came from studies at moderate or high risk of bias. Downgrade 1 level.
2. Downgrade 1 level for serious risk of bias. Study demonstrated unclear random sequence generation and allocation concealment.
3. Inconsistency not applicable
4. 95% confidence interval crosses both ends of a defined MID interval (0.8, 1.25). Downgrade 2 levels.
5. Downgrade 2 levels for very serious risk of bias. *Unclear random sequence generation, allocation concealment, blinding of outcome assessment and incomplete outcome data.*
6. Downgrade 1 level for serious indirectness. Study did not specify criteria used to classify SSI and did not specify follow up period.
7. Unable to calculate effect size. Downgrade 2 levels

* Derived by taking the overall number of event/ total number of participants and multiplying by 100

0.5% Chlorhexidine with 70% alcohol (+ surgeon scrub) vs. 10% Povidone Iodine in alcohol (+ surgeon scrub)

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
SSI (all wound categories) - RR <1 favours 0.5% chlorhexidine with 70% alcohol (+surgeon scrub)										
Berry 1982	RCT	85	RR 0.66 (95% CI: 0.46, 0.95)	15 per 100 people	10 per 100 people (7,14)	Not serious	Serious[1]	NA[2]	Serious[3]	Low
SSI (Clean) - RR <1 favours 0.5% chlorhexidine with 70% alcohol (+surgeon scrub)										
Berry 1982	RCT	52	RR 0.47 (95% CI: 0.27, 0.82)	13 per 100 people	6 per 100 people (4,11)	Not serious	Serious[1]	NA[2]	Serious[3]	Low

1. Downgrade 1 level for serious indirectness. In the study patients and surgeons were allocated to different skin preparations and surgical scrub.
2. Inconsistency not applicable
3. 95% confidence interval crosses one end of a defined MID interval (0.8, 1.25). Downgrade 1 level.

* Derived by taking the overall number of event/ total number of participants and multiplying by 100

Povidone Iodine in alcohol preparation

8.3% povidone iodine in 72.5% alcohol vs 2% Chlorhexidine with 70% alcohol

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
SSI - RR <1 favours 8.3% povidone iodine in 72.5% alcohol										
Ngai 2015 Tuuli 2016	RCT	2,084	RR 01.40 (95% CI: 0.80, 2.44)	4 per 100 people	6 per 100 people (3, 10)	Not serious	Not serious	Serious[1]	Very Serious[2]	Very low
SSI (within 30 days of delivery) - RR <1 favours 8.3% povidone iodine in 72.5% alcohol										
Tuuli 2016	RCT	1,147	RR 1.82 (95% CI: 1.11, 2.98)	4 per 100 people	7 per 100 people (4, 12)	Not serious	Not serious	NA[3]	Serious[4]	Moderate
SSI (Within 30 days of discharge) - RR <1 favours 8.3% povidone iodine in 72.5% alcohol										
Ngai 2015	RCT	937	RR 1.02 (95% CI: 0.57, 1.85)	4 per 100 people	5 per 100 people (3,8)	Not serious	Not serious	NA[3]	Very Serious[2]	Low
SSI (Scheduled cases) - RR <1 favours 8.3% povidone iodine in 72.5% alcohol										
Tuuli 2016	RCT	669	RR 2.62 (95% CI: 1.18, 5.83)	2 per 100 people	6 per 100 people (3, 14)	Not serious	Not serious	NA[3]	Serious[4]	Moderate
SSI (Unscheduled cases) - RR <1 favours 8.3% povidone iodine in 72.5% alcohol										
Tuuli 2016	RCT	478	RR 1.39 (95% CI: 0.73, 2.63)	6 per 100 people	9 per 100 people (5, 17)	Not serious	Not serious	NA[3]	Very Serious[2]	Low
Superficial SSI - RR <1 favours 8.3% povidone iodine in 72.5% alcohol										
Ngai 2015 Tuuli 2016	RCT	2,084	RR 1.38 (95% CI: 0.88, 2.17)	3 per 100 people	4 per 100 people (3, 7)	Not serious	Not serious	Not serious	Serious[4]	Low
Deep SSI - RR <1 favours 8.3% povidone iodine in 72.5% alcohol										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Ngai 2015 Tuuli 2016	RCT	2,084	RR 1.89 (95% CI: 0.85, 4.23)	1 per 100 people	2 per 100 people (1,4)	Not serious	Not serious	Not serious	Serious[4]	Low
Organ space SSI- RR <1 favours 8.3% povidone iodine in 72.5% alcohol										
Ngai 2015	RCT	937	RR 1.02 (95% CI: 0.21, 5.05)	1 per 100 people	1 per 100 people (0,3)	Not serious	Not serious	NA[3]	Very serious[2]	Low
Hospital Readmission - RR <1 favours 8.3% povidone iodine in 72.5% alcohol										
Tuuli 2016	RCT	1,147	RR 1.31 (95% CI: 0.73, 2.35)	3 per 100 people	3 per 100 people (2,7)	Not serious	Not serious	NA[3]	Very Serious[2]	Low
Hospital Length of stay- effect size below zero favours 8.3% povidone iodine in 72.5% alcohol										
Tuuli 2016	RCT	1,147	Difference in medians: 0 days (Non-significant according to the Mann-Whitney test)			Not serious	Not serious	NA[3]	Very Serious[5]	Low
Adverse skin reactions (combined) - RR <1 favours 8.3% povidone iodine in 72.5% alcohol										
Tuuli 2016	RCT	1,147	RR 0.99 (95% CI: 0.49, 2.02)	3 per 100 people	3 per 100 people (1,5)	Not serious	Not serious	NA[3]	Very Serious[2]	Low
Erythema at operative site - RR <1 favours 8.3% povidone iodine in 72.5% alcohol										
Tuuli 2016	RCT	1,147	RR 0.84 (95% CI: 0.38, 1.86)	2 per 100 people	2 per 100 people (1,4)	Not serious	Not serious	NA[3]	Very Serious[2]	Low
Skin irritation - RR <1 favours 8.3% povidone iodine in 72.5% alcohol										
Tuuli 2016	RCT	1,147	RR 6.96 (95% CI: 0.36, 134.51)	0 per 100 people	0 per 100 people	Not serious	Not serious	NA[3]	Very Serious[2]	Low
Allergic reactions - RR <1 favours 8.3% povidone iodine in 72.5% alcohol										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Tuuli 2016	RCT	1,147	RR 0.50(95% CI: 0.05, 5.47)	3 per 100 people	2 per 100 people (0, 19)**	Not serious	Not serious	NA[3]	Very Serious[2]	Low

1. I^2 between 33.3% and 66.7%. Downgrade 1 level for serious inconsistency.
2. 95% confidence interval crosses both ends of a defined MID interval (0.8, 1.25). Downgrade 2 levels.
3. Inconsistency not applicable
4. 95% confidence interval crosses one end of a defined MID interval (0.8, 1.25). Downgrade 1 level.
5. Downgrade 2 levels for no measure of spread and non-significant results.

* Derived by taking the overall number of event/ total number of participants and multiplying by 100

** Derived by taking the overall number of event/ total number of participants and multiplying by 1000

10% povidone iodine in alcohol vs 0.5% chlorhexidine with 70% alcohol

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
SSI - RR <1 favours 10% povidone iodine in alcohol										
Cheng 2009	RCT	50	RR not estimable due to no occurrence of event in either study arm.			Very serious [1]	Serious[2]	NA[3]	Very serious[4]	Very low

1. Downgrade 2 levels for very serious risk of bias. Study demonstrated *unclear random sequence generation, allocation concealment, blinding of outcome assessment and other sources of bias.*
2. Downgrade 1 level for serious indirectness. Study did not specify criteria used to define SSI. Furthermore, study did not specify follow up period.
3. Inconsistency not applicable
4. Unable to calculate effect size. Downgrade 2 levels

* Derived by taking the overall number of event/ total number of participants and multiplying by 100

Iodophor (0.7%) in alcohol (74%) vs Aqueous Povidone Iodine Scrub (7.5%) and paint

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
SSI - RR <1 favours iodophor (0.75) in alcohol (74%)										
Gilliam 1990, Howard 1991, Roberts 1995, Saltzman 2009, Segal 2002	RCT	621	RR 0.68 (95% CI: 0.34, 1.37)	6 per 100 people	4 per 100 people (2,8)	Very serious[1]	Not serious	Serious[2]	Very serious[3]	Very low
Sensitivity analysis (excluding studies at high risk of bias): SSI- RR <1 favours iodophor (0.75) in alcohol (74%)										
Gilliam 1990, Saltzman 2009, Segal 2002	RCT	262	RR 0.15 (95% CI: 0.02, 1.16)	5 per 100 people	1 per 100 people (0,6)	Not serious	Not serious	Not serious	Serious[5]	Moderate
SSI (within 30 days) - RR <1 favours iodophor (0.75) in alcohol (74%)										
Howard 1991, Roberts 1995	RCT	359	RR 1.00 (95% CI: 0.46, 2.19)	6 per 100 people	6 per 100 people (3, 14)	Very serious[1]	Not serious	Not serious	Very serious[3]	Very low
SSI (6 weeks after surgery) - RR <1 favours iodophor (0.75) in alcohol (74%)										
Segal 2002	RCT	102	RR 0.15 (95% CI: 0.02, 1.16)	13 per 100 people	13 per 100 people (0, 16)	Not serious	Not serious	NA[4]	Serious[5]	Moderate
SSI (10 months) - RR <1 favours iodophor (0.75) in alcohol (74%)										
Saltzman 2009	RCT	100	RR not estimable due to no occurrence of event in either study arm.			Serious[6]	Serious [7]	NA[4]	Very serious[8]	Very low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
SSI (during postoperative phase) - RR <1 favours iodophor (0.75) in alcohol (74%)										
Gilliam 1990	RCT	60	RR not estimable due to no occurrence of event in either study arm.			Serious[9]	Serious[10]	NA[4]	Very serious[8]	Very low

1. Greater than 33.3% of the weight in the meta-analysis came from studies at high risk of bias. Downgrade 2 levels for very serious risk of bias.
2. I^2 between 33.3% and 66.7%. Downgrade 1 level for serious inconsistency.
3. 95% confidence interval crosses both ends of a defined MID interval (0.8, 1.25). Downgrade 2 levels.
4. Inconsistency not applicable
5. 95% confidence interval crosses one end of a defined MID interval (0.8, 1.25). Downgrade 1 level.
6. Downgrade 1 level for serious risk of bias. Study (Saltzman 2009) demonstrated *unclear random sequence generation, blinding of outcome assessment and other sources of bias.*
7. Downgrade 1 level for serious indirectness. Study (Saltzman 2009) did not specify criteria used to classify SSI.
8. Unable to calculate effect size. Downgrade 2 levels
9. Downgrade 1 level for serious risk of bias. Study (Gilliam 1990) demonstrated Unclear random sequence generation, allocation concealment and blinding of outcome assessment.
10. Downgrade 1 level for serious indirectness. Study (Gilliam 1990) did not specify criteria used to classify SSI. Furthermore, Follow up period not specified.

* Derived by taking the overall number of event/ total number of participants and multiplying by 100

Iodophor (0.7%) in alcohol (74%) vs aqueous 10% povidone iodine

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
SSI - RR <1 favours iodophor (0.75) in alcohol (74%)										
Segal 2002 Xu 2017	RCT	267	RR 0.27 (95% CI: 0.06, 1.26)	6 per 100 people	2 per 100 people (0,7)	Not Serious	Not Serious	Not serious	Very serious[1]	Low
Superficial SSI- RR <1 favours iodophor (0.75) in alcohol (74%)										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Xu 2017	RCT	161	RR 0.99 (95% CI: 0.06, 15.52)	1 per 100 people	1 per 100 people (0, 19)	Not serious	Not serious	NA[2]	Very serious[1]	Low

1. 95% confidence interval crosses both ends of a defined MID interval (0.8, 1.25). Downgrade 2 levels.
2. Inconsistency not applicable

* Derived by taking the overall number of event/ total number of participants and multiplying by 100

Iodophor (0.7%) in alcohol (74%) vs 2% chlorhexidine with 70% alcohol

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
SSI - RR <1 favours iodophor (0.75) in alcohol (74%)										
Broach 2017, Saltzman 2009, Savage 2017, Xu 2017	RCT	1,148	RR 1.16 (95% CI: 0.86, 1.57)	11 per 100 people	13 per 100 people (10, 18)	Not serious	Not serious	Not serious	Serious[1]	Moderate
Sensitivity analysis (excluding studies at high risk of bias): SSI - RR <1 favours iodophor (0.75) in alcohol (74%)										
Broach 2017, Saltzman 2009, Xu 2017	RCT	1,048	RR: 1.16 (95% CI: 0.86, 1.57)	12 per 100 people	14 per 100 people (11,19)	Not serious	Not serious	Not serious	Serious[1]	Moderate
SSI (within 30 days post discharge) - RR <1 favours iodophor (0.75) in alcohol (74%)										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Broach 2017	RCT	788	RR 1.18 (95% CI: 0.87, 1.61)	16 per 100 people	19 per 100 people (14, 25)	Not serious	Not serious	NA[2]	Serious[1]	Moderate
SSI (6 weeks after surgery) - RR <1 favours iodophor (0.75) in alcohol (74%)										
Xu 2017	RCT	160	RR 0.49 (95% CI: 0.05, 5.27)	1 per 100 people	1 per 100 people (0, 13)	Not serious	Not serious	NA[2]	Very Serious[3]	Low
SSI (6 months) - RR <1 favours iodophor (0.75) in alcohol (74%)										
Savage 2017	RCT	100	RR not estimable due to no occurrence of event in either study arm.			Very serious [4]	Serious[5]	NA[2]	Very serious[6]	Very low
SSI (10 months) - RR <1 favours iodophor (0.75) in alcohol (74%)										
Saltzman 2009	RCT	100	RR not estimable due to no occurrence of event in either study arm.			Serious [7]	Serious[8]	NA[2]	Very serious[6]	Very low
Superficial SSI- RR <1 favours iodophor (0.75) in alcohol (74%)										
Broach 2017 Xu 2017	RCT	948	RR 1.11 (95% CI: 0.75, 1.64)	9 per 100 people	10 per 100 people (7,15)	Not serious	Not serious	Not serious	Very Serious[3]	Low
Deep SSI- RR <1 favours iodophor (0.75) in alcohol (74%)										
Broach 2017	RCT	788	RR 1.26 (95% CI: 0.73, 2.16)	6 per 100 people	7 per 100 people (4,12)	Not serious	Not serious	NA[2]	Very Serious[3]	Low
Organ Space SSI - RR <1 favours iodophor (0.75) in alcohol (74%)										
Broach 2017	RCT	788	RR 0.79 (95% CI: 0.42, 1.51)	5 per 100 people	4 per 100 people (2,8)	Not serious	Not serious	NA[2]	Very Serious[3]	Low
Cellulitis - RR <1 favours iodophor (0.75) in alcohol (74%)										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Broach 2017	RCT	788	RR 1.34 (95% CI: 0.68, 2.64)	4 per 100 people	5 per 100 people (2,9)	Not serious	Not serious	NA[2]	Very Serious[3]	Low
Hospital Length of stay- Effect size below 0 favours iodophor (0.75) in alcohol (74%)										
Broach 2017	RCT	788	MD: -0.20 (-0.73, 0.33)	-	-	Not serious	Not serious	NA[2]	Serious[9]	Moderate

1. 95% confidence interval crosses one end of a defined MID interval (0.8, 1.25). Downgrade 1 level.
2. Inconsistency not applicable
3. 95% confidence interval crosses both ends of a defined MID interval (0.8, 1.25). Downgrade 2 levels.
4. Downgrade 2 levels for very serious risk of bias. Study (Savage 2017) demonstrated *unclear random sequence generation, allocation concealment, blinding of outcome assessment and other sources of bias.*
5. Downgrade 1 level for serious indirectness. Study (Savage 2017) did not specify criteria used to classify SSI.
6. Unable to calculate effect size. Downgrade 2 levels
7. Downgrade 1 level for very serious risk of bias. Study (Saltzman 2009) demonstrated *unclear random sequence generation, blinding of outcome assessment and other sources of bias.*
8. Downgrade 1 level for serious indirectness. Study (Saltzman) did not specify criteria used to classify SSI.
9. Non-significant result

* Derived by taking the overall number of event/ total number of participants and multiplying by 100

Alcohol preparation vs aqueous preparation

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
SSI - RR <1 favours alcohol preparation										
18 studies[1]	RCT	6,119	RR 0.71 (95% CI: 0.60, 0.85)	9 per 100 people	6 per 100 people (5,8)	Not serious	Not serious	Not serious	Serious[2]	Moderate

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Sensitivity analysis (excluding studies at high risk of bias): SSI - RR <1 favours alcohol preparation										
14 studies[3]	RCT	5,590	RR 0.70 (95% CI: 0.58, 0.84)	9 per 100 people	6 per 100 people (5,8)	Not serious	Not serious	Not serious	Serious[2]	Moderate
SSI (in hospital follow up) RR <1 favours alcohol preparation										
Brown 1984	RCT	737	RR 0.75 (95% CI: 0.44, 1.28)	8 per 100 people	6 per 100 people (4,10)	Not serious	Not serious	NA[4]	Very serious[5]	Low
SSI (within 30 days) RR <1 favours alcohol preparation										
Bibi 2015, Charles 2017, Darouiche 2010, Howard 1991, Kunkle 2015, Paocharoen 2009, Roberts 1995, Sistla 2010, Springel 2017, Srinivas 2015	RCT		RR 0.73 (95% CI: 0.60, 0.89)			Not serious	Not serious	Not serious	Serious[2]	Moderate
SSI (6 weeks postoperatively) RR <1 favours alcohol preparation										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Segal 2002 a, Segal 2002b	RCT		RR 0.15 (95% CI: 0.04, 0.66)			Not serious	Not serious	Not serious	Not serious	High
SSI (10 months after surgery) RR <1 favours alcohol preparation										
Saltzman 2009a, Saltzman 2009b	RCT		RR not estimable due to no occurrence of event in either study arm.			Serious[6]	Serious[7]	NA[4]	Very serious[8]	Very low
SSI (3 year follow up) RR <1 favours alcohol preparation										
Abreu 2014	RCT		RR 1.13 (95% CI: 0.36, 3.55)			Serious[9]	Not serious	NA[4]	Very serious[8]	Very low
SSI (during postoperative phase) RR <1 favours alcohol preparation										
Bibbo 2005, Gilliam 1990	RCT		RR not estimable due to no occurrence of event in either study arm.			Very serious	Serious[11]	Not serious	Very serious[8]	

1. Abreu 2014, Bibbo 2005, Bibi 2015, Brown 1984, Charles 2017, Darouiche 2010, Gilliam 1990, Howard 1991, Kunkle 2015, Paocharoen 2009, Roberts 1995, Saltzman 2009 a, Saltzman 2009 b, Segal 2002 a, Segal 2002 b, Sistla 2010, Springel 2017 and Srinivas 2015.
2. 95% confidence interval crosses one end of a defined MID interval (0.8, 1.25). Downgrade 1 level.
3. Abreu 2014, Bibi 2015, Brown 1984, Charles 2017, Darouiche 2010, Gilliam 1990, Paocharoen 2009, Saltzman 2009 a, Saltzman 2009 b, Segal 2002 a, Segal 2002 b, Sistla 2010, Springel 2017 and Srinivas 2015.
4. Inconsistency not applicable
5. 95% confidence interval crosses both ends of a defined MID interval (0.8, 1.25). Downgrade 2 levels.
6. Downgrade 1 level for serious risk of bias. Study demonstrated *unclear random sequence generation, blinding of outcome assessment and other sources of bias.*
7. *Downgrade 1 level for serious indirectness. Study did not specify classification used to define SSI.*
8. Unable to calculate effect size. Downgrade 2 levels
9. Downgrade 1 level for serious risk of bias. Study demonstrated *unclear random sequence generation, allocation concealment and blinding of outcome assessment.*

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
10. Greater than 33.3% of the weight in the meta-analysis came from studies at high risk of bias. Downgrade 2 levels for very serious risk of bias. 11. Greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies. Downgrade 1 level for serious risk of bias. * Derived by taking the overall number of event/ total number of participants and multiplying by 100										

Single Preparation vs double preparation

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
SSI - RR <1 favours single preparation										
Ellenhorn 2006, Segal 2002, Zdeblick 1986	RCT	443	RR 0.95 (95% CI: 0.52, 1.73)	9 per 100 people	9 per 100 people (5, 16)	Very serious[1]	Not serious	Not serious	Very serious[2]	Very low
1. Greater than 33.3% of the weight in the meta-analysis came from studies at high risk of bias. Downgrade 2 levels for very serious risk of bias. 2. 95% confidence interval crosses both ends of a defined MID interval (0.8, 1.25). Downgrade 2 levels. * Derived by taking the overall number of event/ total number of participants and multiplying by 100										

G.2 GRADE tables for pairwise evidence used in lumped NMA model

Chlorhexidine in alcohol vs Aqueous Povidone Iodine

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
SSI - RR <1 favours CH in alcohol										
12 studies[1]	RCT	4642	RR 0.71 (95% CI:0.58, 0.86)	9 per 100 people	7 per 100 people (7,21)	Not serious	Not serious	Not serious	Serious[2]	Moderate
Sensitivity analysis (excluding studies at high risk of bias): SSI - RR <1 favours CH in alcohol										
11 studies[3]	RCT	4599	RR 0.70 (95% CI: 0.57, 0.85)	9 per 100 people	7 per 100 people (5,8)	Not serious	Not serious	Not serious	Serious[2]	Moderate

1. Abreu 2014, Bibbo 2005, Bibi 2015, Brown 1984, Darouiche 2010, Kunkle 2015, Paocharoen 2009, Saltzman 2009, Sistla 2010, Springel 2017, Srinivas 2015 and Xu 2017.
2. 95% confidence interval crosses one end of a defined MID interval (0.8, 1.25). Downgrade 1 level.
3. Abreu 2014, Bibbo 2005, Bibi 2015, Brown 1984, Darouiche 2010, Paocharoen 2009, Saltzman 2009, Sistla 2010, Springel 2017, Srinivas 2015 and Xu 2017.

* Derived by taking the overall number of event/ total number of participants and multiplying by 100

Povidone Iodine in alcohol vs Chlorhexidine in alcohol

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
SSI - RR <1 favours povidone Iodine in alcohol										
7 studies[1]	RCT	3282	RR 1.27 (95% CI:0.97, 1.66)	7 per 100 people	8 per 100 people (6,11)	Not serious	Not serious	Not serious	Serious[2]	Moderate

1. Broach 2017, Cheng 2009, Ngai 2015, Saltzman 2009, Savage 2012, Tuuli 2016, Xu 2017
2. 95% confidence interval crosses one end of a defined MID interval (0.8, 1.25). Downgrade 1 level.

* Derived by taking the overall number of event/ total number of participants and multiplying by 100

Aqueous chlorhexidine vs Chlorhexidine in alcohol

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
SSI - RR <1 favours aqueous chlorhexidine										
Charles 2017	RCT	909	RR 1.17 (95% CI: 0.71, 1.94)	6 per 100 people	7 per 100 people (4,11)	Not serious	Not serious	NA[1]	Very serious[2]	Low

1. Inconsistency not applicable
2. 95% confidence interval crosses both ends of a defined MID interval (0.8, 1.25). Downgrade 2 levels.

* Derived by taking the overall number of event/ total number of participants and multiplying by 100

Aqueous chlorhexidine vs aqueous povidone iodine

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
SSI - RR <1 favours aqueous chlorhexidine										
Park 2016	RCT	534	RR 0.94 (95% CI: 0.47, 1.86)	6 per 100 people	6 per 100 people (3,11)	Not serious	Not serious	NA[1]	Very serious[2]	Low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality

1. Inconsistency not applicable
2. 95% confidence interval crosses both ends of a defined MID interval (0.8, 1.25). Downgrade 2 levels.

* Derived by taking the overall number of event/ total number of participants and multiplying by 100

Povidone Iodine in alcohol vs aqueous povidone iodine

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
SSI - RR <1 favours povidone Iodine in alcohol										
7 studies[1]	RCT	888	RR 0.56 (95% CI:0.30, 1.05)	6 per 100 people	3 per 100 people (2,6)	Very serious[2]	Not serious	Not serious	Serious[3]	Very low
Sensitivity analysis (excluding studies at high risk of bias): SSI - RR <1 favours povidone Iodine in alcohol										
Gilliam 1990, Saltzman 2009, Segal 2002a, Segal 2002b, Xu 2016	RCT	529	RR 0.21 (95% CI: 0.06, 0.72)	6 per 100 people	1 per 100 people (0,4)	Not serious	Not serious	Not serious	Not serious	High

1. Gilliam 1990, Howard 1991, Roberts 1995, Saltzman 2009, Segal 2002a, Segal 2002b and Xu 2017
2. Greater than 33.3% of the weight in the meta-analysis came from studies at high risk of bias. Downgrade 2 levels for very serious risk of bias.
3. 95% confidence interval crosses one end of a defined MID interval (0.8, 1.25). Downgrade 1 level.
4. Gilliam 1990, Saltzman 2009, Segal 2002a, Segal 2002b and Xu 2017

* Derived by taking the overall number of event/ total number of participants and multiplying by 100

G.3 GRADE tables for network meta-analysis (Meta-regression)

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	No of participants	Effect size (95% CI)	Quality
SSI								
20	RCT	Not serious	Not serious	Not serious	Serious[1;]	9,647	See Appendix H	Moderate

1. All pairwise credible intervals from the NMA cross at least one end of the defined MID (0.8,1.25)

Appendix H- Network meta-analysis

H.1 General Methods

For details of the generic methods adopted for these analyses, please see Appendix B.

H.1.1 Analyses undertaken

During protocol development, surgical site infections (SSIs) within 30 days and up to 1 year were prioritised. While some studies reported SSI within 30 days, studies examining SSI at different follow up periods were also identified. Preliminary examinations were conducted in which 30 day dataset was compared to the dataset containing data from different follow up periods. Through this comparison, it was identified that both datasets produced similar estimates. Pairwise analyses were also conducted in which subgroup analyses were conducted based on follow up period, and no serious heterogeneity was identified (See Appendix G for GRADE tables).

Based on the data, it can be assumed while the absolute probability of SSI is bound to be different at different follow up periods, the relative difference between treatments is constant over time. This was further discussed with the committee who identified this to be an adequate assumption. Therefore, in the current analyses, data from all follow up periods were combined to assess the overall incidence of surgical site infection.

Based on the Centres for the Disease Control and Prevention (CDC) SSI definitions, SSIs can be further classified as being either superficial SSI, deep SSI or organ space SSI. This classification is based on if the infection involved the skin and subcutaneous tissue or deeper soft tissue. A number of studies were identified which reported overall SSI incidence but also applied a classification criteria to further subdivide the evidence in superficial, deep or organ space SSI. In the current analyses, data on overall SSI incidence was utilised to assemble the models. Two studies were identified [Xu 2017 and Casey 2015] in which only superficial SSI were identified. These studies were included in the present analyses.

Trials examining a number of different interventions were identified which were grouped according to 6 groups:

- Alcohol alone
- Iodine in various alcohol preparations
- Aqueous chlorhexidine
- Aqueous povidone iodine
- Chlorhexidine in alcohol preparation
- Povidone iodine (including other iodophors) in alcohol preparation

Trials examining alcohol alone and iodine at various alcohol preparations could not be fitted into the network, as no connections could be made between these interventions and the other interventions included in the analysis. Furthermore, trials which had 0 events in both arms could not be included in the analyses as these studies did not contribute to the estimation of relative treatment effects.

H.2 Model Selection

H.2.1 Potential models

The data set included evidence on a number of different interventions. Due to this, it was important that an appropriate method of defining interventions was identified. It was identified that interventions of the same active ingredient and preparation (e.g. aqueous chlorhexidine) varied in terms of application and concentration as evidence on 0.5% chlorhexidine in aqueous solution and aqueous chlorhexidine scrub (4%) and paint (2%) was identified. Due to these differences, a 'split' approach was considered in which the data was separated out based on application (e.g. scrub and paint vs solution) and concentration. Based on the data available, the following interventions were considered for the 'split' model:

- Aqueous povidone iodine (7.5%) and paint (10%)
- Aqueous chlorhexidine scrub (4%) and paint (2%)
- 0.5% chlorhexidine in aqueous solution
- 0.5% chlorhexidine with 70% alcohol
- 5% Aqueous povidone iodine
- 10% aqueous povidone iodine
- 2% or 2.5% chlorhexidine with 70% alcohol
- Iodophor (0.7%) in alcohol (74%)
- 4% chlorhexidine with 70% alcohol
- 8.3% povidone iodine in 72.5% alcohol

In the 'split' model, aqueous povidone iodine (7.5%) and paint (10%) was used as the reference treatment. In order to convert odds ratio into relative risk, baseline was estimated using the posterior mean and standard deviation for the reference treatment from the meta-regression model. In the meta-regression model, the baseline was estimated using a surveillance study in an English hospital (Jenks et al. 2014).

While some studies included in the review mentioned applying the antiseptic as a scrub before a second application of antiseptic, some studies did not explicitly detail the mode of antiseptic application. Furthermore, during preliminary discussions, the committee agreed that it would be interesting to explore how well the data are modelled in a simpler network which disregards any heterogeneity of concentration and application method and concentrates only on active ingredient in different preparations. Due to this a 'lumped' approach was considered which involved the four distinct groups to be explored which incorporated interventions of different concentrations:

- Chlorhexidine in alcohol:
    - 0.5% CH with 70% alcohol
    - 2% or 2.5% CH with 70% alcohol
    - 4% CH with 70% alcohol
- Chlorhexidine in aqueous solution
    - Aqueous CH scrub (4%) and paint (2%)
    - 0.5% CH in aqueous solution
- Povidone Iodine in alcohol
    - 8.3% PI with 72.5% alcohol
    - Iodophor (0.7%) in alcohol (74%)
- Povidone iodine in aqueous solution
    - 5% aqueous PI
    - 10% aqueous PI
    - Aqueous PI scrub (7.5%) and paint (10%)

The povidone iodine in alcohol group also included other iodophors in alcohol.

See Appendix G for GRADE tables for pairwise analyses.

In this model, 3 main parameters were explored with povidone iodine in aqueous solution used as a reference treatment. In order to convert odds ratio into relative risk, baseline was estimated using a surveillance study in an English hospital (Jenks et al. 2014).

The 'lumped' model allowed us to examine the effect of active ingredient in different preparations. To further explore these interventions, questions were raised about the additive effect of the agent (chlorhexidine) and excipient (alcohol). Consideration was also given to whether a simpler model of the 4-node network could be constructed using a meta-regression approach to quantify the shared effect of the two covariates, assuming that these effects were independent and additive on a logit scale. In this model, it was assumed that the difference between the 4 treatment groups can be broken down to alcohol versus aqueous preparation and povidone iodine versus chlorhexidine, and these agents and excipients are independent.

Based on this, the following assumptions were made:

- Chlorhexidine in alcohol contains both covariates of interest and the effect of both chlorhexidine and alcohol are independent and additive
- Povidone iodine in contains excipient of interest
- Aqueous chlorhexidine contains agent of interest

The reference group in the meta-regression was also the aqueous povidone iodine treatment group. Comparison of this reference group to chlorhexidine in alcohol would be the sum of the difference between povidone iodine and chlorhexidine and the difference between alcohol and aqueous preparations. Similarly to the 'lumped' model, baseline was estimated using a surveillance study in an English hospital (Jenks et al. 2014).

Data incorporated into the split and lumped networks are summarised in Table 9.

H.2.2 Choosing the best model

Both fixed effects and random effects models were explored, with final model selection for each network based on the methods described in Appendix B.

Goodness-of-fit measures for the candidate models are presented in Table 8. The following observations can be made:

- As random effects terms appeared to add no meaningful improvement to the model fit, fixed effects models were preferred

- All three models fit the data well and this could be demonstrated through the comparison of total residual deviance, which should be approximately equal to the number of data points (See Appendix B)

- In comparison to the split model, the lumped model formed of a 4 node network, also demonstrated good model fit and the reduction in parameters lead to a meaningfully lower DIC

- In comparison to the lumped model, the meta-regression approach, which had only 2 unconstrained parameters, demonstrated a similar goodness of fit, with a lower DIC. This suggested that the data was wall represented by a model that comprised of 2 unconstrained parameters.

Because the data was well modelled by the simplest approach, the meta-regression model was preferred for the base case reported analyses. The meta-regression was used for decision making therefore the quality of this evidence was assessed using GRADE and evidence statements were formulated based on the findings from this model.

An inconsistency model (Figure 4) was run using the ‘split’ dataset. This model demonstrated that there was no major inconsistency. However, two studies, Xu 2017 and Segal 2002 demonstrated high deviance. Upon inspection, it was identified that these 3 arm contributed to the comparison between 10% aqueous povidone iodine and iodophor (0.7%) in alcohol (74%). Compared to other trials included in the review, both studies examined SSI during a 6 week follow up. Furthermore, Xu 2017 only identified superficial SSI.

An inconsistency model (Figure 10) was also run using the ‘lumped’ dataset. This model demonstrated that there was no major inconsistency. However, similar to the ‘split’ model, Segal 2002 demonstrated high deviance. Segal 2002 compared iodophor (0.7%) in alcohol (74%) with 10% aqueous povidone iodine as well as aqueous povidione iodine scrub (7.5%) and paint (10%). In the lumped model, interventions were grouped based on active ingredient and preparation. This meant that 10% aqueous povidone iodine and aqueous povidone iodine scrub (7.5%) and paint (10%) were incorporated into the same group. This meant that Segal 2002 contributed two data points under the same comparison.

Additionally, 3 studies [Ellenhorn 2006, Howard 1991 and Roberts 1995] were identified, which demonstrated high risk of bias. Sensitivity analysis was undertaken to remove these studies. The sensitivity analysis found no difference in the overall results. Therefore, these studies remained in the final NMA.

Table 8: Model selection for network meta-analysis

Outcomes	Number of studies	Participants	Datapoints	Model	Number of unique options	FE/RE	Total residual deviance	DIC	Standard deviation of random effects distribution (95%CI)
SSI	20	9,647	42	1. Split	10	FE	42.47	244.8	n/a
						RE	40.76	246.1	0.21 (0.01, 0.70)
				2. Lumped	4	FE	38.46	234.8	n/a
						RE	26.32	236.6	0.006 (0.001,0.109)
				3. Meta-regression	4[a]	FE	37.53	232.8	n/a
						RE	37.18	234.7	0.1 (0.04,0.35)

[a] *All combinations of 2 binary covariates*

n/a *Not applicable*

Table 9: Data incorporated to form split model (10 nodes) and lumped model (4 node)

	Chlorhexidine in alcohol						Aqueous chlorhexidine				Povidone Iodine in alcohol				Aqueous Povidone Iodine					
	0.5% CH with 70% alcohol		2% or 2.5% CH with 70% alcohol		4% CH in 70% alcohol		Aqueous CH scrub (4%) and paint (2%)		0.5% CH in aqueous solution		8.3% PI in 72.5% alcohol		Iodophor (0.7%) in alcohol (74%)		5% Aqueous PI		10% Aqueous PI		Aqueous PI scrub (7.5%) and paint (10%)	
	Within 30 days [b]	Over 30 days [c]	Within 30 days [b]	Over 30 days [c]	Within 30 days [b]	Over 30 days [c]	Within 30 days [b]	Over 30 days [c]	Within 30 days [b]	Over 30 days [c]	Within 30 days [b]	Over 30 days [c]	Within 30 days [b]	Over 30 days [c]	Within 30 days [b]	Over 30 days [c]	Within 30 days [b]	Over 30 days [c]	Within 30 days [b]	Over 30 days [c]
Abreu 2014		6/32														4/24				
Bibi 2015			11/168														22/220			
Broach 2017				62/392										74/396						
Brown 1984	23/378																		29/359	
Casey 2015[a]	6/41		2/44																	
Charles 2017	26/451								31/458											
Darouiche 2010			39/409																71/440	
Ellenhorn 2006																	12/119		12/115	
Howard 1991													2/84						2/75	
Kunkle 2015			2/21																	
Ngai 2015				21/474								21/463								
Paocharoen 2009					5/250														8/250	
Park 2016							15/267												16/267	
Roberts 1995													10/104						9/96	
Segal 2002														1/50				7/56		7/52
Sistla 2010			14/200														19/200			
Springel 2017			29/461																33/471	
Srinivas 2015	17/163														33/188					
Tuuli 2016			23/572								42/575									
Xu 2017[a]						2/79								1/81				1/80		

[a] Studies only reported superficial SSI

[b] Within 30 days, includes all follow up periods up to 30 days after surgery (e.g. in-hospital follow up and 2 weeks after surgery)

[c] Over 30 days, includes all follow up periods over 30 days after surgery (e.g. 30 days after discharge, 6 weeks after surgery and up to 3 years)

H.3 Results – SSI

Figure 4: Network diagram of the network of studies underlying the split NMA with the number of trials for each comparison. Thickness of line indicates number of studies included.

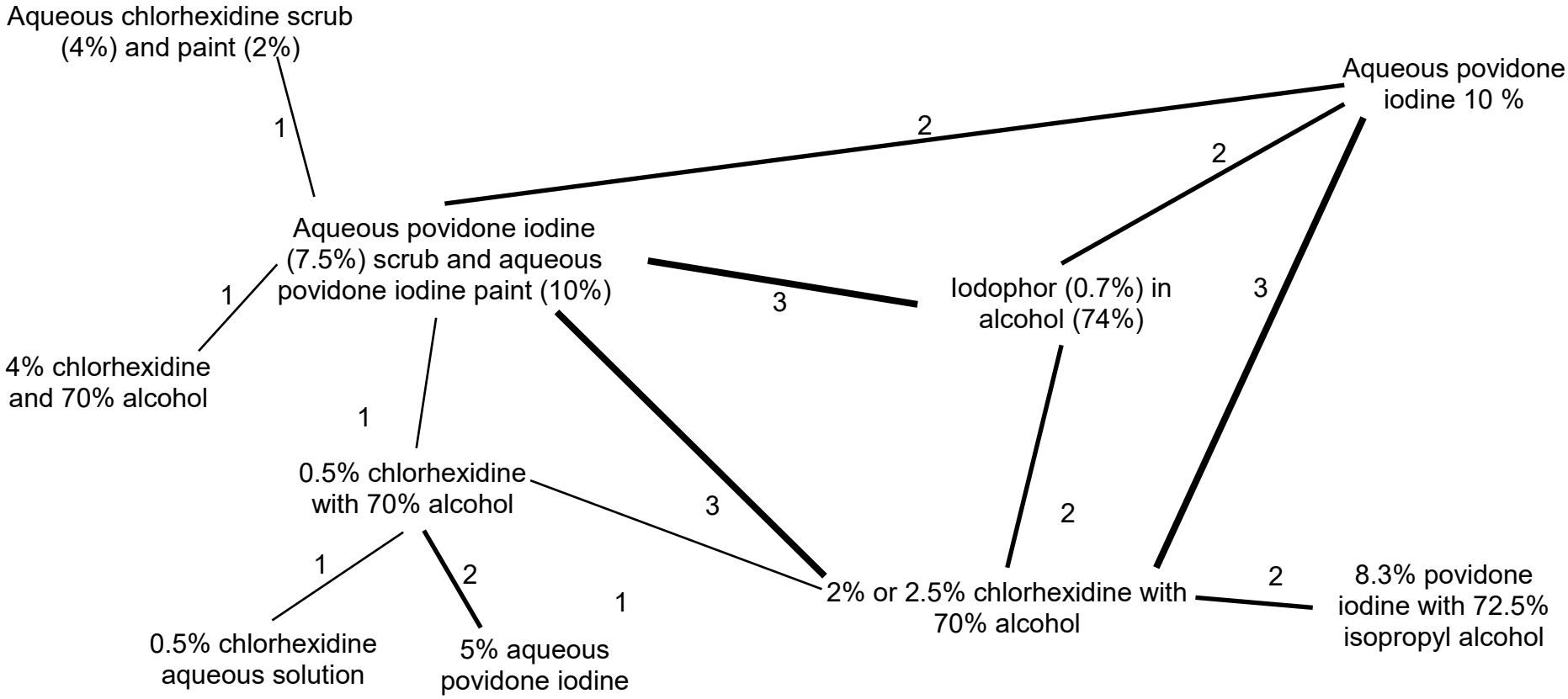


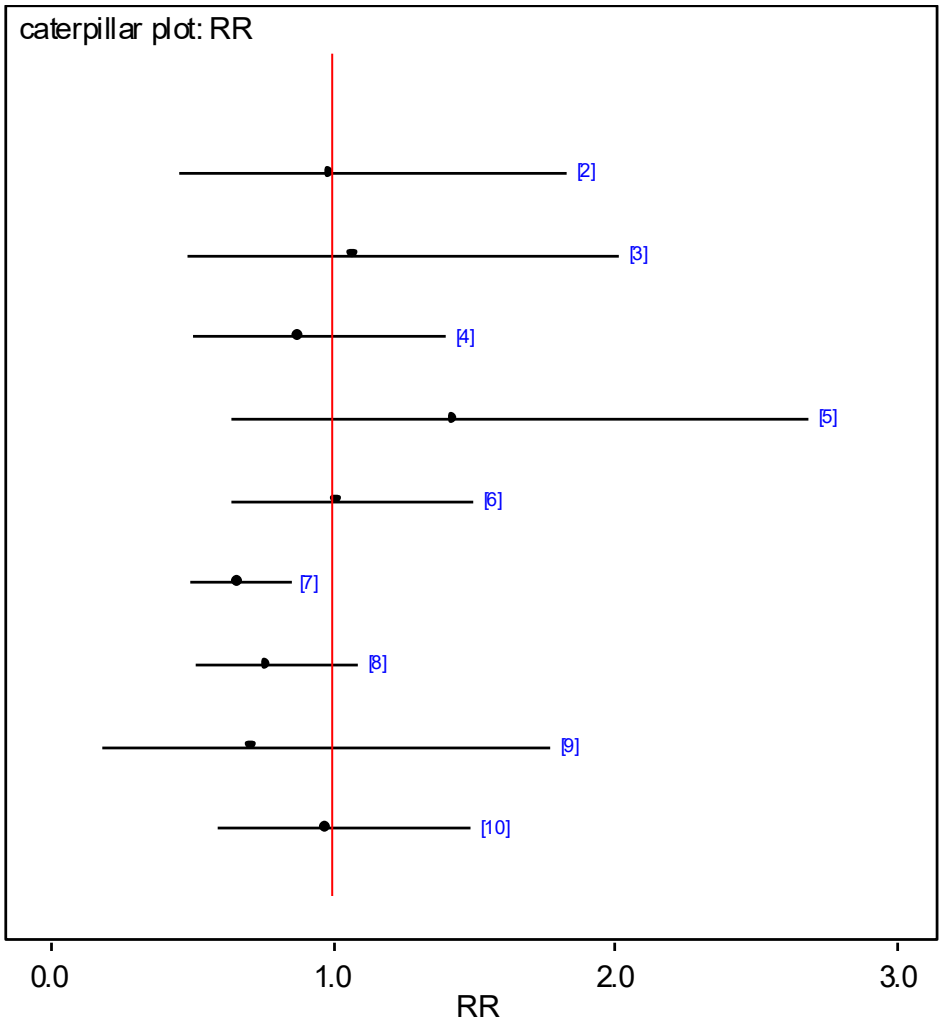
Table 10: split model (FE)

		PAIR WISE									
		Aqueous PI scrub (7.5%) and paint (10%)	Aqueous CH scrub (4%) and paint (2%)	0.5% CH in aqueous solution	0.5% CH with 70% alcohol	5% Aqueous PI	10% Aqueous PI	2% or 2.5% CH with 70% alcohol	Iodopohor (0.7%) in alcohol (74%)	4% CH in 70% alcohol	8.3% PI in 72.5% alcohol
NMA	Aqueous PI scrub (7.5%) and paint (10%)		0.94 (0.47, 1.86)	-	0.75 (0.44, 1.28)	-	0.95 (0.52, 1.73)	**0.70 (0.53, 0.94)**	0.68 (0.34, 1.37)	0.63 (0.21, 1.88)	-
	Aqueous CH scrub (4%) and paint (2%)	0.94 (0.46, 1.82)		-	-	-	-	-	-	-	-
	0.5% CH in aqueous solution	1.01 (0.48, 2.03)	1.08 (0.40, 2.93)		0.85 (0.51, 1.14)	-	-	-	-	-	-
	0.5% CH with 70% alcohol	0.85 (0.51, 1.41)	0.91 (0.39, 2.19)	0.85 (0.51, 1.42)		1.51 (0.92, 2.46)	-	0.31 (0.07, 1.45)	-	-	-
	5% Aqueous PI	1.35 (0.64, 2.71)	1.44 (0.54, 3.92)	1.34 (0.64, 2.78)	1.58 (0.93, 2.65)		-	-	-	-	-
	10% Aqueous PI	0.99 (0.65, 1.50)	1.06(0.48, 2.43)	0.99 (0.44, 2.27)	1.16 (0.61, 2.22)	0.73 (0.32, 1.71)		0.73 (0.46, 1.16)	0.27 (0.06, 1.26)	-	-
	2% or 2.5% CH with 70% alcohol	**0.65 (0.50, 0.86)**	0.70 (0.34, 1.52)	0.65 (0.31, 1.41)	0.77 (0.44, 1.35)	0.48 (0.23, 1.06)	**0.66 (0.45, 0.98)**		1.16 (0.86, 1.57)	-	1.40 (0.80, 2.44)
	Iodophor (0.7%) in alcohol (74%)	0.75 (0.51, 1.09)	0.81 (0.37, 1.81)	0.75 (0.34, 1.68)	0.88 (0.48, 1.64)	0.56 (0.26, 1.26)	0.76 (0.47, 1.22)	1.15 (0.84, 1.57)		-	-
	4% CH in 70% alcohol	0.61 (0.19, 1.75)	0.66 (0.17, 2.33)	0.61 (0.15, 2.21)	0.72 (0.20, 2.33)	0.46 (0.11, 1.66)	0.62 (0.17, 1.93)	0.94 (0.27, 2.77)	0.82 (0.23, 2.52)		-
	8.3% PI in 72.5% alcohol	0.95 (0.59, 1.50)	1.02 (0.45, 2.36)	0.94 (0.41, 2.22)	1.12 (0.57, 2.17)	0.70 (0.31, 1.67)	0.96 (0.56, 1.64)	**1.45 (1.00, 2.12)**	1.26 (0.77, 2.06)	1.55 (0.49, 5.53)	

Values given are relative risk.
The lower diagonal segment of the chart is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects. The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. RR< 1 favours row defining treatment

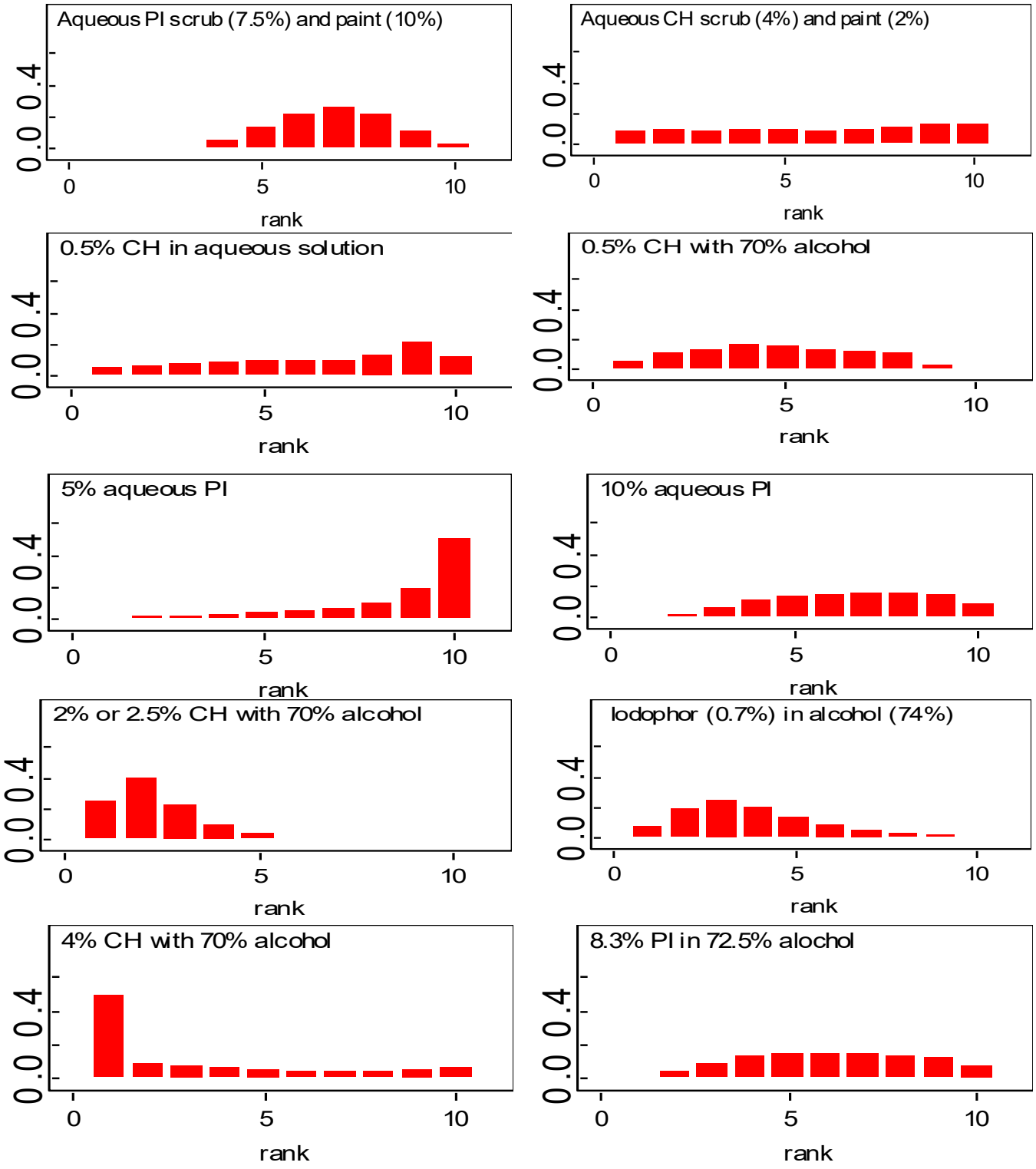
The upper diagonal segment of the chart gives pooled direct evidence (fixed-effect pairwise meta-analysis), where available. Numbers in parentheses are 95% confidence intervals. RR> 1 favours row defining treatment

Figure 5: Split model; fixed effects- relative effect of all options versus aqueous povidone iodine scrub (7.5%) and paint (10%)



Intervention codes	
1	Aqueous PI scrub (7.5%) and paint (10%)
2	Aqueous CH scrub (4%) and paint (2%)
3	0.5% CH in aqueous solution
4	0.5% CH with 70% alcohol
5	5% Aqueous PI
6	10% Aqueous PI
7	2% or 2.5% CH with 70% alcohol
8	Iodophor (0.7%) in alcohol (74%)
9	4% CH in 70% alcohol
10	8.3% PI in 72.5% alcohol

Figure 6: Split model, fixed effects- rankograms



Histograms show probability that each treatment is ranked in each position relative to the other treatments in the network. Rank 1 always reflects whatever is desirable (a high probability of good outcomes or a low probability of bad outcomes).

Figure 7 Split- Fixed Effects- Inconsistency Model

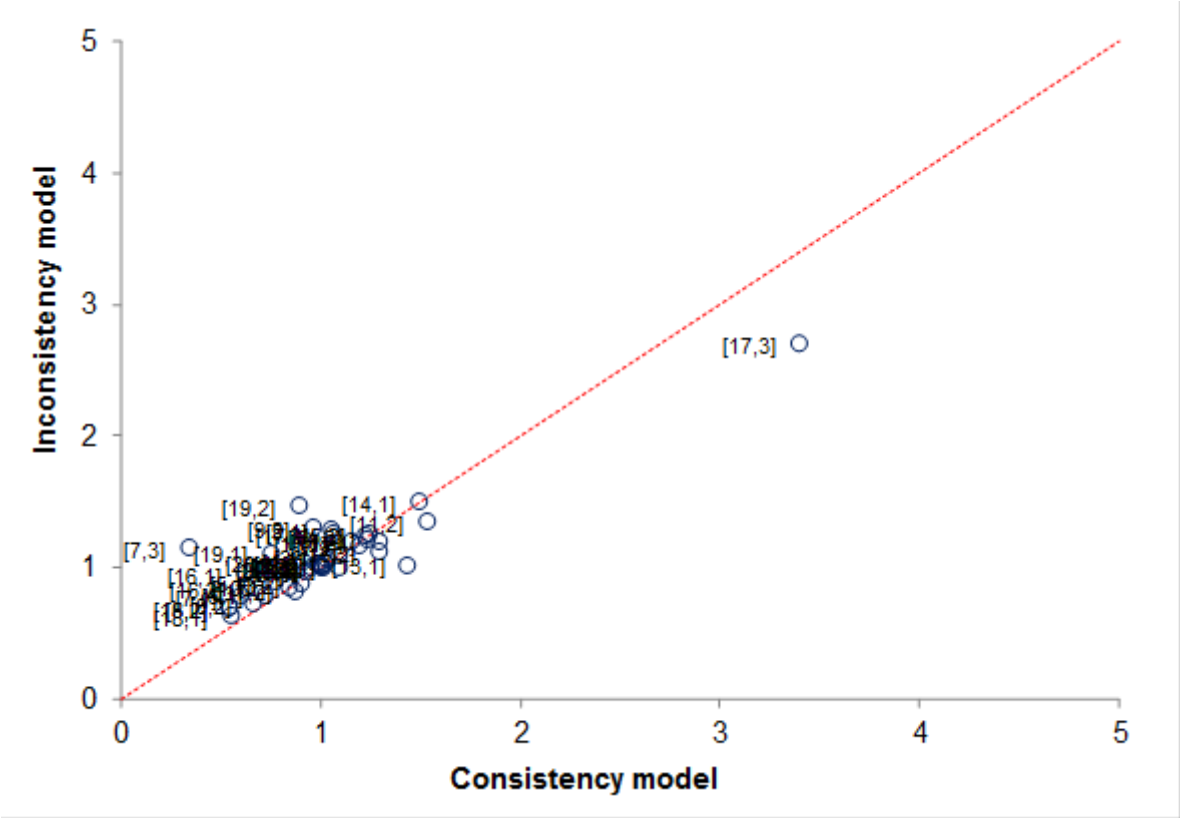


Figure 8: Network diagram of the network of studies underlying the combined NMA with the number of trials for each comparison

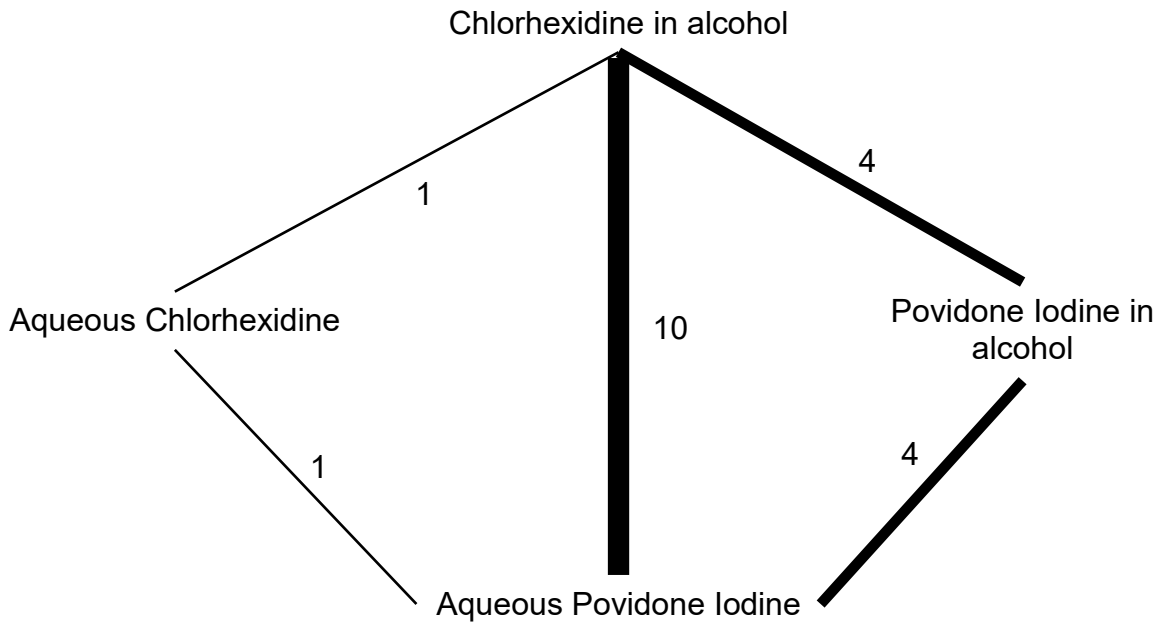


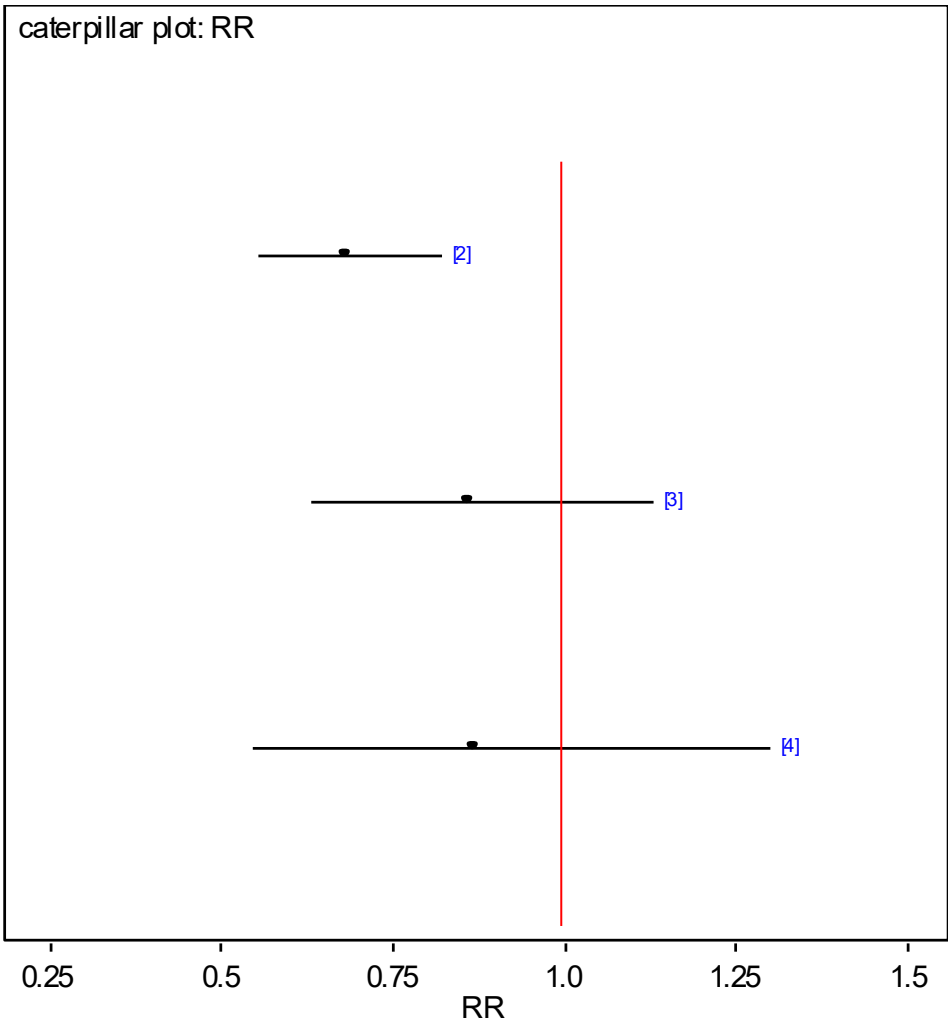
Table 11: Lumped model (FE)

		PAIR WISE			
NMA		Aqueous Povidone Iodine	Chlorhexidine in alcohol	Povidone Iodine in alcohol	Aqueous Chlorhexidine
	Aqueous Povidone Iodine		**0.71 (0.58, 0.86)**	0.56 (0.30, 1.05)	0.94 (0.47,1.86)
	Chlorhexidine in alcohol	**0.68 (0.56, 0.82)**		1.27 (0.97, 1.66)	1.17 (0.71,1.94)
	Povidone Iodine in alcohol	0.85 (0.63, 1.13)	1.25 (0.98, 1.60)		-
	Aqueous Chlorhexidine	0.85 (0.55, 1.31)	1.25 (0.82, 1.89)	1.00 (0.61, 1.61)	

Values given are relative risk.
The lower diagonal segment of the chart is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects. The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. RR< 1 favours row defining treatment

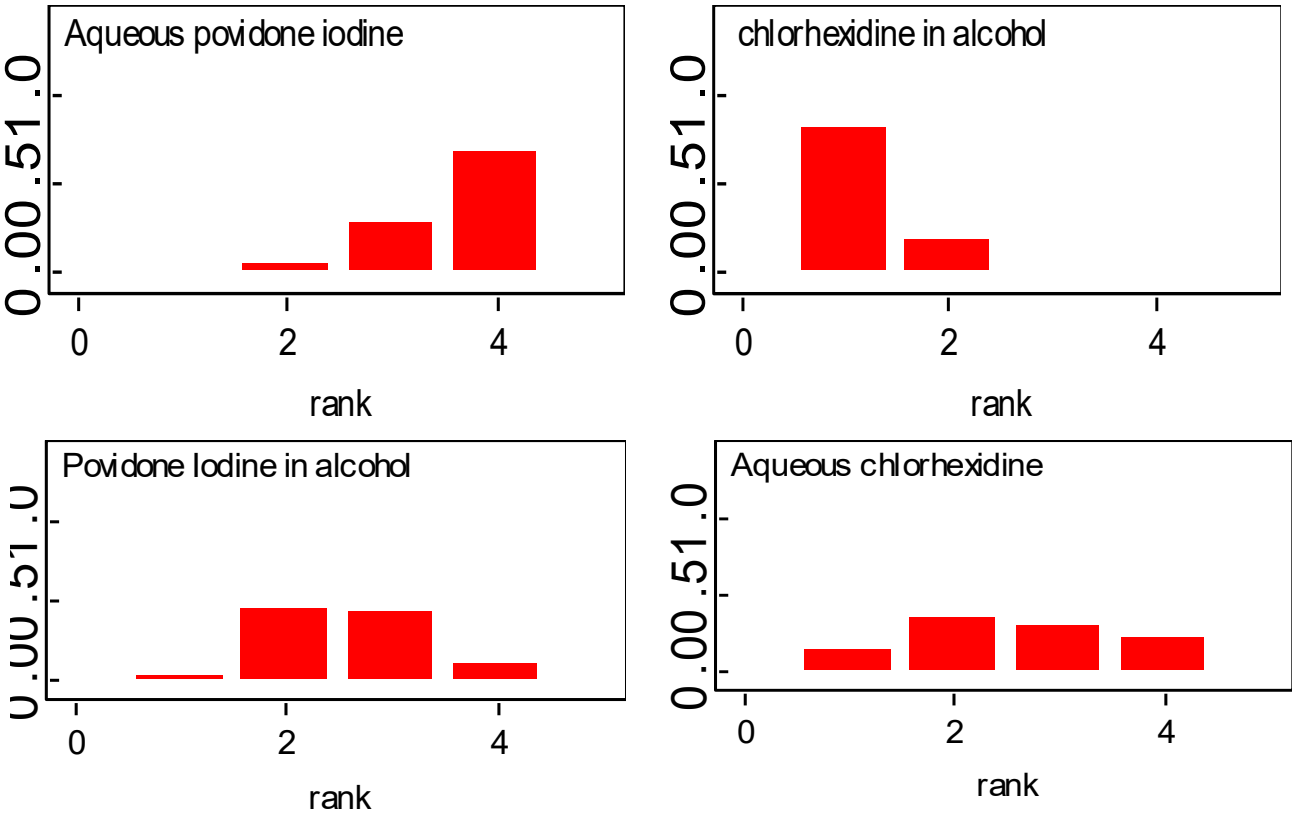
The upper diagonal segment of the chart gives pooled direct evidence (fixed-effect pairwise meta-analysis), where available. Numbers in parentheses are 95% confidence intervals. RR> 1 favours row defining treatment

Figure 9: Lumped model; fixed effects- relative effect of all options versus aqueous povidone iodine



Intervention codes	
1	Aqueous povidone iodine
2	Chlorhexidine in alcohol
3	Povidone Iodine in alcohol
4	Aqueous chlorhexidine

Figure 10: Lumped model, fixed effects- rankograms



Histograms show probability that each treatment is ranked in each position relative to the other treatments in the network. Rank 1 always reflects whatever is desirable (a high probability of good outcomes or a low probability of bad outcomes).

Figure 11 Lumped- Fixed Effects- Inconsistency Model

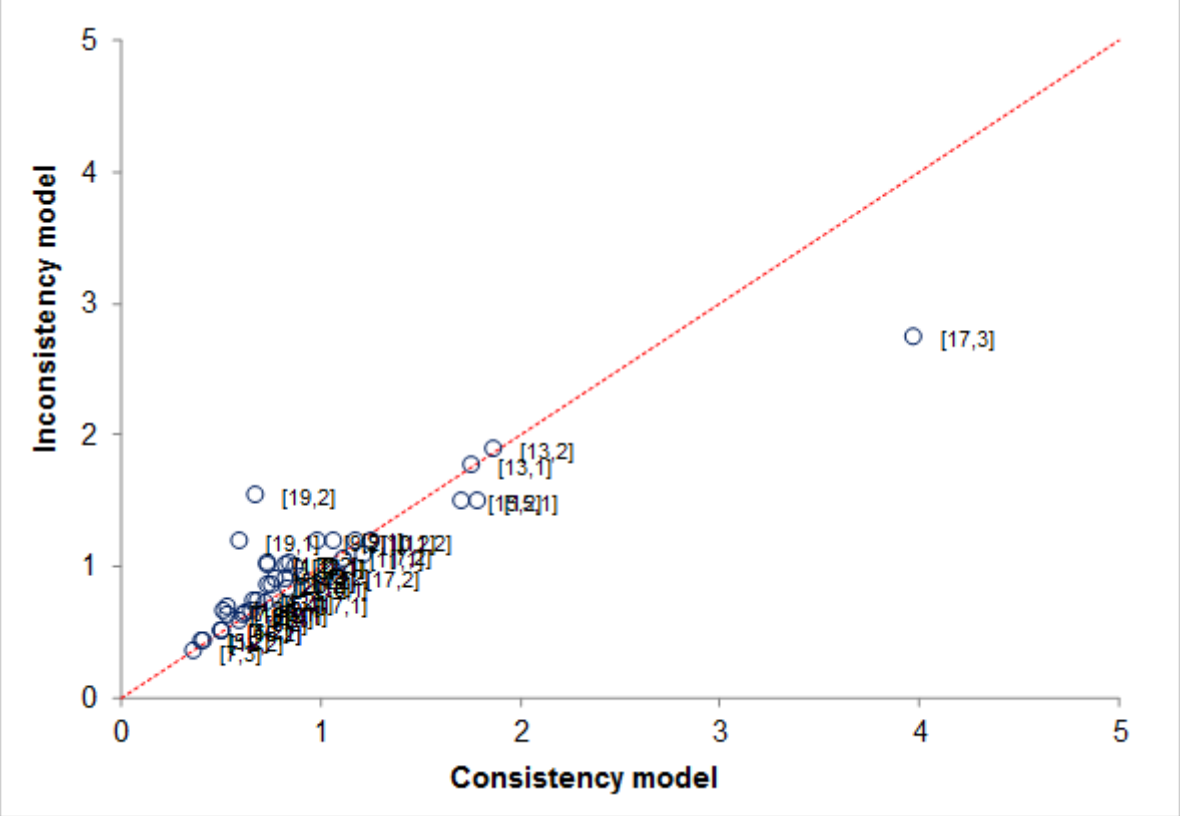


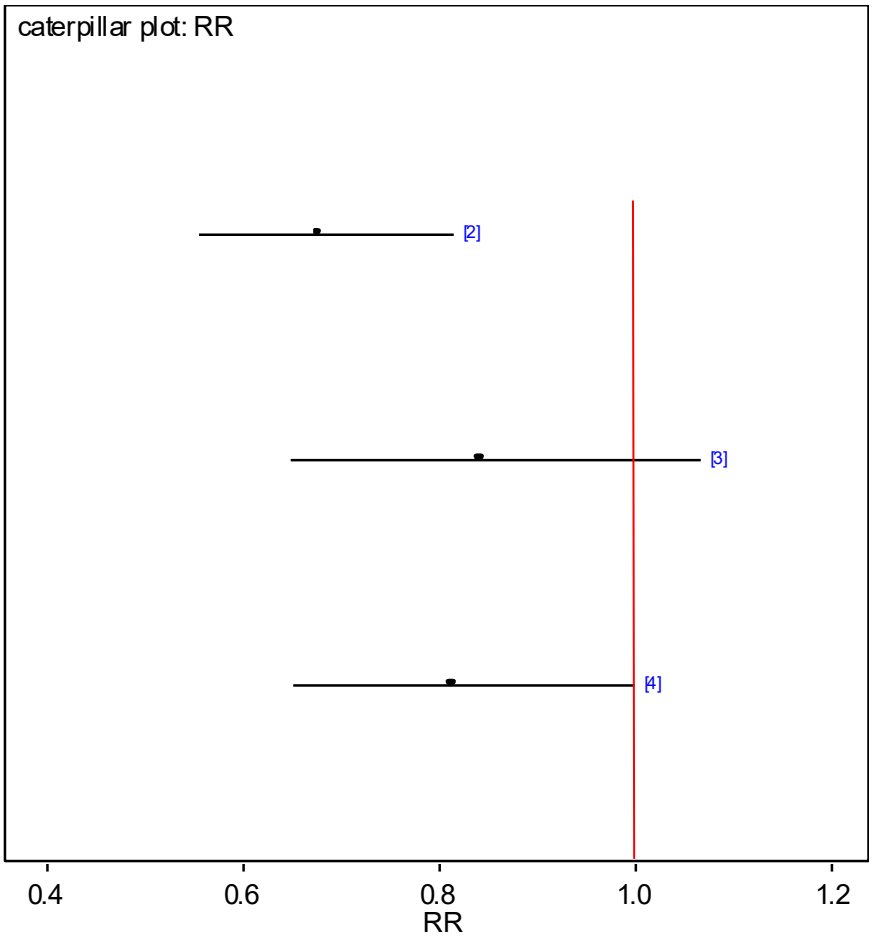
Table 12: Meta regression (FE)

		PAIR WISE			
NMA		Aqueous Povidone Iodine	Chlorhexidine in alcohol	Povidone Iodine in alcohol	Aqueous Chlorhexidine
	Aqueous Povidone Iodine		**0.71 (0.58, 0.86)**	0.56 (0.30, 1.05)	0.94 (0.47,1.86)
	Chlorhexidine in alcohol	**0.67 (0.55, 0.82)**		1.27 (0.97, 1.66)	1.17 (0.71,1.94)
	Povidone Iodine in alcohol	0.84 (0.65, 1.07)	**1.24 (1.00, 1.53)**		-
	Aqueous Chlorhexidine	**0.81 (0.65, 1.00)**	1.20 (0.94, 1.54)	0.97 (0.64, 1.48)	

Values given are relative risk.
The lower diagonal segment of the chart is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects. The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. RR< 1 favours row defining treatment

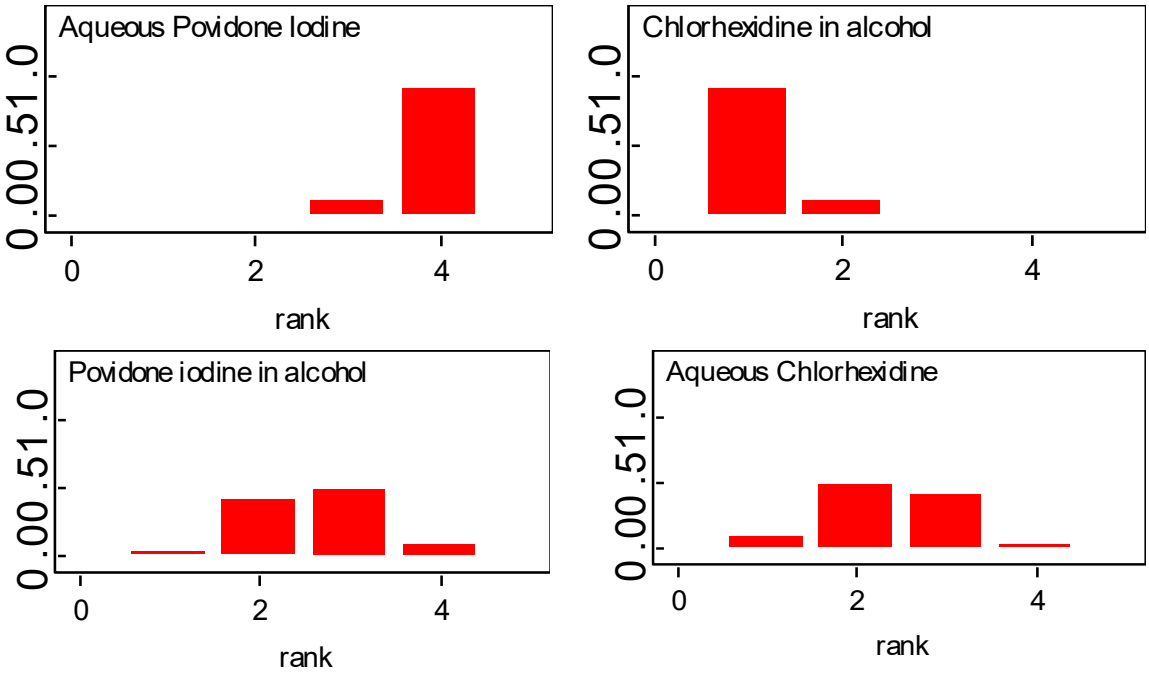
The upper diagonal segment of the chart gives pooled direct evidence (fixed-effect pairwise meta-analysis), where available. Numbers in parentheses are 95% confidence intervals. RR> 1 favours row defining treatment

Figure 12: Meta-regression; fixed effects- relative effect of all options versus aqueous povidone iodine



Intervention codes	
1	Aqueous povidone iodine
2	Chlorhexidine in alcohol
3	Povidone Iodine in alcohol
4	Aqueous chlorhexidine

Figure 13: Meta-regression, fixed effects- rankograms



Histograms show probability that each treatment is ranked in each position relative to the other treatments in the network. Rank 1 always reflects whatever is desirable (a high probability of good outcomes or a low probability of bad outcomes).

H.4 WinBUGS code

Split (Fixed effect)

```
model{
for(i in 1:ns){                    # LOOP THROUGH STUDIES
        mu[i] ~ dnorm(0,.0001)             # vague priors for all trial baselines
        for (k in 1:na[i]) {               # LOOP THROUGH ARMS
                r[i,k] ~ dbin(p[i,k],n[i,k])       # binomial likelihood
 logit(p[i,k]) <- mu[i] + d[t[i,k]] - d[t[i,1]] # model (split)
        rhat[i,k] <- p[i,k] * n[i,k]         # expected value of the numerators
        dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k])) # Deviance contribution
      + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
        }
        resdev[i] <- sum(dev[i,1:na[i]])     # summed residual deviance contribution for trial
}
totresdev <- sum(resdev[])             # Total Residual Deviance

d[1] <-0                           # treatment effect is zero for reference treatment
for (k in 2:nt){d[k] ~ dnorm(0,.0001)}  # vague priors for treatment effects


# pairwise ORs and LORs for all possible pair-wise comparisons, if nt>2
for (c in 1:(nt-1)) {
        for (k in (c+1):nt) {
                or[c,k] <- exp(d[k] - d[c])
                lor[c,k] <- (d[k]-d[c])
        }
}

#A ~  dnorm(0, 0.00001)        # vague prior for ln(Odds) with treatment 1
pMean <- -2.759
pSD <- 0.05704
pPrec <- pow(pSD, -2)
A ~  dnorm(pMean, pPrec)       # vague prior for ln(Odds) with treatment 1

for (k in 1:nt) { logit(T[k]) <- A + d[k] }

# Provide estimates of number needed to treat NNT[k], Risk Difference RD[k],
# and Relative Risk RR[k], for each treatment, relative to treatment 1
RR[1] <- 1
for (k in 2:nt) {
        RR[k] <- T[k]/T[1]
}

for (c in 1:(nt-1)) {
        for (k in (c+1):nt) {
                RRR[c,k] <- T[k]/T[c]
        }
}
} # *** PROGRAM ENDS
```

Split (Random effects)

```
model{
for(i in 1:ns){                    # LOOP THROUGH STUDIES
        w[i,1] <- 0                        # adjustment for multi-arm trials is 0 for control
        delta[i,1] <- 0                    # treatment effect is zero for control arm
        mu[i] ~ dnorm(0,.0001)             # vague priors for all trial baselines
        for (k in 1:na[i]) {               # LOOP THROUGH ARMS
                r[i,k] ~ dbin(p[i,k],n[i,k])       # binomial likelihood
                logit(p[i,k]) <- mu[i] + delta[i,k] # model
                rhat[i,k] <- p[i,k] * n[i,k]       # expected value of the numerators
                dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k])) #Deviance contribution
                                                                + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
        }
        resdev[i] <- sum(dev[i,1:na[i]])     # summed residual deviance contribution for trial
        for (k in 2:na[i]) {               # LOOP THROUGH ARMS
        delta[i,k] ~ dnorm(md[i,k],taud[i,k]) # trial-specific LOR distributions
md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k] # model (split)
        taud[i,k] <- tau *2*(k-1)/k                                     # precision of LOR distributions
```

```
                                                                                    # (with multi-arm trial correction)
 w[i,k] <- delta[i,k] - d[t[i,k]] + d[t[i,1]]
            sw[i,k] <- sum(w[i,1:k-1])/(k-1) # cumulative adjustment for multi-arm trials
            }
}
totresdev <- sum(resdev[])          # Total Residual Deviance
sd      ~  dunif(0,5)             # vague prior for between-trial SD
tau     <- pow(sd,-2)                                                          # between-trial precision

d[1] <-0                          # treatment effect is zero for reference treatment
for (k in 2:nt){d[k] ~ dnorm(0,.0001)}  # vague priors for treatment effects

# pairwise ORs and LORs for all possible pair-wise comparisons, if nt>2
for (c in 1:(nt-1)) {
            for (k in (c+1):nt) {
                        or[c,k] <- exp(d[k] - d[c])
                        lor[c,k] <- (d[k]-d[c])
            }
}

meanA <- -2.762
precA <- pow(0.05904, -2)
A ~  dnorm(meanA, precA)       # defined from posterior of A from meta-reg model

for (k in 1:nt) {
  d.cut[k] <- cut(d[k])
  logit(T[k]) <- A + d.cut[k]
 }

# Provide estimates of number needed to treat NNT[k], Risk Difference RD[k],
# and Relative Risk RR[k], for each treatment, relative to treatment 1
RR[1] <- 1
for (k in 2:nt) {
            RR[k] <- T[k]/T[1]
}

for (c in 1:(nt-1)) {
            for (k in (c+1):nt) {
                        RRR[c,k] <- T[k]/T[c]
            }
}
} # *** PROGRAM ENDS
```

Lumped (Fixed effect)

```
model{
for(i in 1:ns){                   # LOOP THROUGH STUDIES
            mu[i] ~ dnorm(0,.0001)            # vague priors for all trial baselines
            for (k in 1:na[i]) {                                                # LOOP THROUGH ARMS
                        r[i,k] ~ dbin(p[i,k],n[i,k])       # binomial likelihood
logit(p[i,k]) <- mu[i] + dd[alc[t[i,k]], chl[t[i,k]]] -  dd[alc[t[i,1]], chl[t[i,1]]] # model (lumped)
            rhat[i,k] <- p[i,k] * n[i,k]          # expected value of the numerators
            dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k])) # Deviance contribution
          + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
            }
            resdev[i] <- sum(dev[i,1:na[i]])     # summed residual deviance contribution for trial
}
totresdev <- sum(resdev[])          # Total Residual Deviance

dd[1,1]<-0                        # treatment effect is zero for reference treatment
dd[1,2] ~  dnorm(0,.0001)               # vague priors for treatment effect
dd[2,1] ~  dnorm(0,.0001)               # vague priors for treatment effect
dd[2,2] ~  dnorm(0,.0001)               # vague priors for treatment effect
d[1]    <- dd[1,1]                 # map to 1d array
d[2]    <- dd[2,2]                 # map to 1d array
```

```
d[3]    <- dd[2,1]                  # map to 1d array
d[4]    <- dd[1,2]                  # map to 1d array


# pairwise ORs and LORs for all possible pair-wise comparisons, if nt>2
for (c in 1:(nt-1)) {
            for (k in (c+1):nt) {
                        or[c,k] <- exp(d[k] - d[c])
                        lor[c,k] <- (d[k]-d[c])
            }
}

rA <- 733                   # data - number of SSIs
nA <- 14300                 # data - number of operations
rA ~  dbin(pA, nA)          # binomial for observed prob
pA <- inprod(T[], prop[])    # observed prob is weighted average of treatment-specific
                    # probs and observed relative frequencies

prop[1:4] ~ ddirch(alpha[])   # Dirichlet for observed relative frequencies
alpha[1] <- 45              # data - number of people receiving treatment 1
alpha[2] <- 31              # data - number of people receiving treatment 2
alpha[3] <- 7               # data - number of people receiving treatment 3
alpha[4] <- 11              # data - number of people receiving treatment 4

A ~  dnorm(0, 0.00001)       # vague prior for ln(Odds) with treatment 1

for (k in 1:nt) {
  d.cut[k] <- cut(d[k])
  logit(T[k]) <- A + d.cut[k]
 }

# Provide estimates of number needed to treat NNT[k], Risk Difference RD[k],
# and Relative Risk RR[k], for each treatment, relative to treatment 1
RR[1] <- 1
for (k in 2:nt) {
            RR[k] <- T[k]/T[1]
}

for (c in 1:(nt-1)) {
            for (k in (c+1):nt) {
                        RRR[c,k] <- T[k]/T[c]
            }
}
} # *** PROGRAM ENDS
```

Lumped (Random effects)

```
model{
for(i in 1:ns){                     # LOOP THROUGH STUDIES
            w[i,1] <- 0                     # adjustment for multi-arm trials is 0 for control
            delta[i,1] <- 0                 # treatment effect is zero for control arm
            mu[i] ~ dnorm(0,.0001)              # vague priors for all trial baselines
            for (k in 1:na[i]) {                # LOOP THROUGH ARMS
                        r[i,k] ~ dbin(p[i,k],n[i,k])        # binomial likelihood
                        logit(p[i,k]) <- mu[i] + delta[i,k] # model
                        rhat[i,k] <- p[i,k] * n[i,k]        # expected value of the numerators
                        dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k])) #Deviance contribution
                                                                    + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
            }
            resdev[i] <- sum(dev[i,1:na[i]])      # summed residual deviance contribution for trial
            for (k in 2:na[i]) {                # LOOP THROUGH ARMS
            delta[i,k] ~ dnorm(md[i,k],taud[i,k]) # trial-specific LOR distributions
md[i,k] <- dd[alc[t[i,k]], chl[t[i,k]]] - dd[alc[t[i,1]], chl[t[i,1]]] + sw[i,k]  # model (lumped)

            taud[i,k] <- tau *2*(k-1)/k                                     # precision of LOR distributions

                                                                            # (with multi-arm trial correction)
w[i,k] <- delta[i,k] - dd[alc[t[i,k]], chl[t[i,k]]] + dd[alc[t[i,1]], chl[t[i,1]]]
```

```
                        # adjustment for multi-arm RCTs (lumped)

            sw[i,k] <- sum(w[i,1:k-1])/(k-1) # cumulative adjustment for multi-arm trials
            }
}
totresdev <- sum(resdev[])          # Total Residual Deviance
sd      ~  dunif(0,5)             # vague prior for between-trial SD
tau     <- pow(sd,-2)                                                    # between-trial precision

dd[1,1]<-0                      # treatment effect is zero for reference treatment
dd[1,2] ~  dnorm(0,.0001)           # vague priors for treatment effect
dd[2,1] ~  dnorm(0,.0001)           # vague priors for treatment effect
dd[2,2] ~  dnorm(0,.0001)           # vague priors for treatment effect
d[1]    <- dd[1,1]                  # map to 1d array
d[2]    <- dd[2,2]                  # map to 1d array
d[3]    <- dd[2,1]                  # map to 1d array
d[4]    <- dd[1,2]                  # map to 1d array
# pairwise ORs and LORs for all possible pair-wise comparisons, if nt>2
for (c in 1:(nt-1)) {
            for (k in (c+1):nt) {
                        or[c,k] <- exp(d[k] - d[c])
                        lor[c,k] <- (d[k]-d[c])
            }
}

rA <- 733                   # data - number of SSIs
nA <- 14300                 # data - number of operations
rA ~  dbin(pA, nA)          # binomial for observed prob
pA <- inprod(T[], prop[])    # observed prob is weighted average of treatment-specific probs and observed relative frequencies
prop[1:4] ~ ddirch(alpha[])  # Dirichlet for observed relative frequencies
alpha[1] <- 45              # data - number of people receiving treatment 1
alpha[2] <- 31              # data - number of people receiving treatment 2
alpha[3] <- 7               # data - number of people receiving treatment 3
alpha[4] <- 11              # data - number of people receiving treatment 4
A ~  dnorm(0, 0.00001)      # vague prior for ln(Odds) with treatment 1

for (k in 1:nt) {
  d.cut[k] <- cut(d[k])
  logit(T[k]) <- A + d.cut[k]
 }
# Provide estimates of number needed to treat NNT[k], Risk Difference RD[k],
# and Relative Risk RR[k], for each treatment, relative to treatment 1
RR[1] <- 1
for (k in 2:nt) {
            RR[k] <- T[k]/T[1]
}

for (c in 1:(nt-1)) {
            for (k in (c+1):nt) {
                        RRR[c,k] <- T[k]/T[c]
            }
}
} # *** PROGRAM ENDS
```

Meta-regression (Fixed effect)

```
model{
for(i in 1:ns){                     # LOOP THROUGH STUDIES
            mu[i] ~ dnorm(0,.0001)              # vague priors for all trial baselines
            for (k in 1:na[i]) {                                                    # LOOP THROUGH ARMS
                        r[i,k] ~ dbin(p[i,k],n[i,k])       # binomial likelihood

logit(p[i,k]) <- mu[i] + dAlc * (alc[t[i,k]] - alc[t[i,1]]) + dChl * (chl[t[i,k]] - chl[t[i,1]]) # model (meta-regression)
            rhat[i,k] <- p[i,k] * n[i,k]          # expected value of the numerators
            dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k])) # Deviance contribution
          + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
            }
            resdev[i] <- sum(dev[i,1:na[i]])     # summed residual deviance contribution for trial
}
totresdev <- sum(resdev[])          # Total Residual Deviance
```

```
dAlc ~  dnorm(0,.0001)              # vague prior of excipient coefficient
dChl ~  dnorm(0,.0001)              # vague prior of agent coefficient
d[1] <- 0                       # treatment effect is 0 for aqueous iodine
d[2] <- dAlc + dChl                 # chlorhexidine in alcohol
d[3] <- dAlc                    # iodine in alcohol
d[4] <- dChl                    # aqueous chlorhexidine

# pairwise ORs and LORs for all possible pair-wise comparisons, if nt>2
for (c in 1:(nt-1)) {
        for (k in (c+1):nt) {
                or[c,k] <- exp(d[k] - d[c])
                lor[c,k] <- (d[k]-d[c])
        }
}

rA <- 733               # data - number of SSIs
nA <- 14300             # data - number of operations
rA ~  dbin(pA, nA)          # binomial for observed prob
pA <- inprod(T[], prop[])   # observed prob is weighted average of treatment-specific
                    # probs and observed relative frequencies

prop[1:4] ~ ddirch(alpha[])  # Dirichlet for observed relative frequencies
alpha[1] <- 45          # data - number of people receiving treatment 1
alpha[2] <- 31          # data - number of people receiving treatment 2
alpha[3] <- 7           # data - number of people receiving treatment 3
alpha[4] <- 11          # data - number of people receiving treatment 4

A ~  dnorm(0, 0.00001)      # vague prior for ln(Odds) with treatment 1

for (k in 1:nt) {
  d.cut[k] <- cut(d[k])
  logit(T[k]) <- A + d.cut[k]
 }

# Provide estimates of number needed to treat NNT[k], Risk Difference RD[k],
# and Relative Risk RR[k], for each treatment, relative to treatment 1
RR[1] <- 1
for (k in 2:nt) {
        RR[k] <- T[k]/T[1]
}

for (c in 1:(nt-1)) {
        for (k in (c+1):nt) {
                RRR[c,k] <- T[k]/T[c]
        }
}
} # *** PROGRAM ENDS
```

Meta-regression (Random effects)

```
model{
for(i in 1:ns){                 # LOOP THROUGH STUDIES
        w[i,1] <- 0                     # adjustment for multi-arm trials is 0 for control
        delta[i,1] <- 0                 # treatment effect is zero for control arm
        mu[i] ~ dnorm(0,.0001)              # vague priors for all trial baselines
        for (k in 1:na[i]) {            # LOOP THROUGH ARMS
                r[i,k] ~ dbin(p[i,k],n[i,k])        # binomial likelihood
                logit(p[i,k]) <- mu[i] + delta[i,k] # model
                rhat[i,k] <- p[i,k] * n[i,k]        # expected value of the numerators
                dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k])) #Deviance contribution
                                                                + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
        }
        resdev[i] <- sum(dev[i,1:na[i]])      # summed residual deviance contribution for trial
        for (k in 2:na[i]) {            # LOOP THROUGH ARMS
        delta[i,k] ~ dnorm(md[i,k],taud[i,k]) # trial-specific LOR distributions
        md[i,k] <- dAlc * (alc[t[i,k]] - alc[t[i,1]]) + dChl * (chl[t[i,k]] - chl[t[i,1]]) + sw[i,k]        # model (meta-regression)
        taud[i,k] <- tau *2*(k-1)/k                                                 # precision of LOR distributions

                                                                                # (with multi-arm trial correction)
        w[i,k] <- delta[i,k] - dAlc * (alc[t[i,k]] - alc[t[i,1]]) - dChl * (chl[t[i,k]] - chl[t[i,1]])                  # adjustment for multi-
arm RCTs (meta-reg)
        sw[i,k] <- sum(w[i,1:k-1])/(k-1) # cumulative adjustment for multi-arm trials
```

```
            }
}
totresdev <- sum(resdev[])            # Total Residual Deviance
sd        ~  dunif(0,5)               # vague prior for between-trial SD
tau       <- pow(sd,-2)                                                    # between-trial precision


dAlc ~  dnorm(0,.0001)                # vague prior of excipient coefficient
dChl ~  dnorm(0,.0001)                # vague prior of agent coefficient
d[1] <- 0                             # treatment effect is 0 for aqueous iodine
d[2] <- dAlc + dChl                   # chlorhexidine in alcohol
d[3] <- dAlc                          # iodine in alcohol
d[4] <- dChl                          # aqueous chlorhexidine

# pairwise ORs and LORs for all possible pair-wise comparisons, if nt>2
for (c in 1:(nt-1)) {
            for (k in (c+1):nt) {
                        or[c,k] <- exp(d[k] - d[c])
                        lor[c,k] <- (d[k]-d[c])
            }
}

rA <- 733                   # data - number of SSIs
nA <- 14300                 # data - number of operations
rA ~  dbin(pA, nA)          # binomial for observed prob
pA <- inprod(T[], prop[])   # observed prob is weighted average of treatment-specific probs and observed relative frequencies
prop[1:4] ~ ddirch(alpha[])  # Dirichlet for observed relative frequencies
alpha[1] <- 45              # data - number of people receiving treatment 1
alpha[2] <- 31              # data - number of people receiving treatment 2
alpha[3] <- 7               # data - number of people receiving treatment 3
alpha[4] <- 11              # data - number of people receiving treatment 4
A ~  dnorm(0, 0.00001)      # vague prior for ln(Odds) with treatment 1

for (k in 1:nt) {
  d.cut[k] <- cut(d[k])
  logit(T[k]) <- A + d.cut[k]
 }

# Provide estimates of number needed to treat NNT[k], Risk Difference RD[k],
# and Relative Risk RR[k], for each treatment, relative to treatment 1
RR[1] <- 1
for (k in 2:nt) {
            RR[k] <- T[k]/T[1]
}

for (c in 1:(nt-1)) {
            for (k in (c+1):nt) {
                        RRR[c,k] <- T[k]/T[c]
            }
}
} # *** PROGRAM END
```

Inconsistency model

```
model {
for(i in 1:ns) {
  mu[i] ~ dnorm(0, .0001)                    # vague priors for trial baselines
  for (j in 1:na[i]) {                       # indexes arms
    r[i,j]       ~  dbin(p[i,j], n[i,j])     # binomial likelihood
    logit(p[i,j]) <- mu[i] + d[t[i,1],t[i,j]]   # model for linear predictor
    rhat[i,j]    <- p[i,j] * n[i,j]          # expected value of numerators
    dev[i,j]     <- 2 * (r[i,j] * (log(r[i,j])-log(rhat[i,j]))
                  + (n[i,j]-r[i,j]) * (log(n[i,j]-r[i,j]) - log(n[i,j]-rhat[i,j])))
                                             # deviance contribution
    }                                        # close arm loop
  resdev[i]    <- sum(dev[i,1:na[i]])        # summed deviance contribution
  }
totresdev <- sum(resdev[])                   # total residual deviance
for (j in 1:nt) {
  d[j,j] <- 0                                # effect=0 for j vs j
  }
for (c in 1:(nt-1)) {
```

```
  for (j in (c+1):nt) {
    d[c,j]  ~  dnorm(0, .0001)
                          OR[c,j] <- exp(d[c,j])
    }
  }
}
```

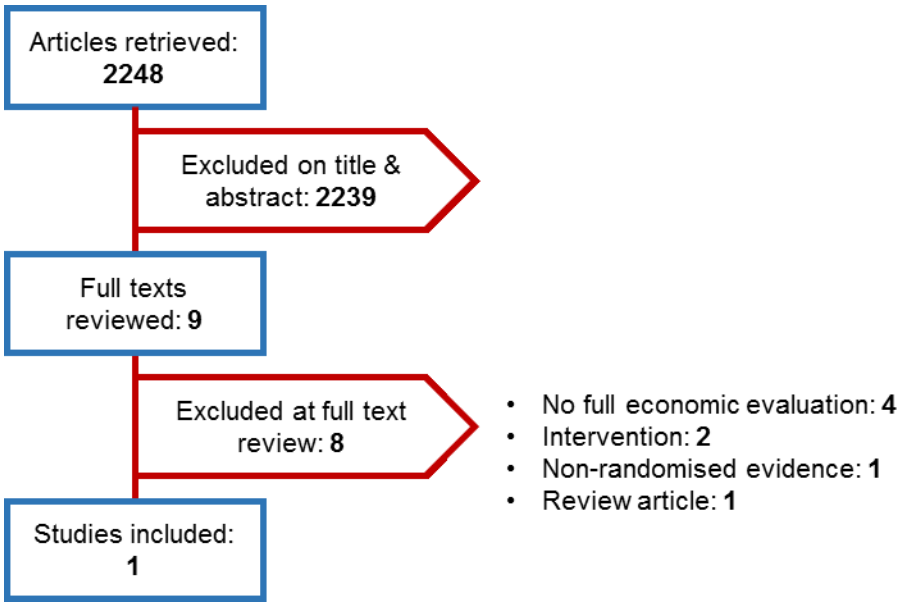
Consistency model

```
model {
for(i in 1:ns) {                          # indexes studies
  mu[i] ~ dnorm(0, .0001)                       # vague priors for all trial baselines
  for (j in 1:na[i]) {                    # indexes arms
    r[i,j]        ~  dbin(p[i,j],n[i,j])        # binomial likelihood
    logit(p[i,j]) <- mu[i] + d[t[i,j]] - d[t[i,1]]   # model for linear predictor
    rhat[i,j]     <- p[i,j] * n[i,j]            # expected value of the numerators
    dev[i,j]      <- 2 * (r[i,j] * (log(r[i,j])-log(rhat[i,j]))
                  + (n[i,j]-r[i,j]) * (log(n[i,j]-r[i,j]) - log(n[i,j]-rhat[i,j])))
                                          # deviance contribution
    }                                     # close arm loop
  resdev[i]     <- sum(dev[i,1:na[i]])          # summed deviance contribution
  }                                       # close study loop
totresdev     <- sum(resdev[])                  # total residual deviance

d[1]<-0                                   # effect is 0 for reference treatment
for (j in 2:nt) {                         # indexes treatments
  d[j] ~ dnorm(0, .0001)                        # vague priors for treatment effects
  }                                       # close treatment loop

# pairwise ORs and LORs for all possible pair-wise comparisons
for (c in 1:(nt-1)) {
  for (j in (c+1):nt) {
    lOR[c,j] <- (d[j]-d[c])
    OR[c,j]  <- exp(lOR[c,j])
    }
  }
}
```

Appendix I – Economic evidence study selection



Appendix J – Economic evidence tables

Study, population, country and quality	Data sources	Other comments	Results	Conclusions	Uncertainty
Lee et al. (2010) Patients undergoing surgery who are at risk of developing a surgical site infection. United States **Partially applicable** [a,b] **Potentially serious limitations** [c,d,e,f]	**Effects** Effects in study consists of whether patient had a surgical site infection (SSI) or not from meta-analysis (9 RCT's) conducted in the same paper. Chlorhexidine was found to have a relative risk of 0.64 [95% confidence interval, [0.51–0.80]) incidence of SSI relative to povidone iodine. **Costs and resource use** A resource-use review of all surgical cases at the Hospital of the University of Pennsylvania (HUP) during fiscal year 2007 (FY2007) determined the mean costs associated with patients who did and patients who did not develop SSI. These cost calculations accounted for all direct variable supply costs associated with each surgical encounter, including use of rooms (eg, patient, operating, and procedure rooms), personnel (eg, physician, physical therapy, nursing, and	The model compared the intervention group (chlorhexidine scrub and/or paint in varying concentrations) and the comparator group (povidone-iodine or iodophor scrub and/or paint in varying concentrations). The base line number of patients who had a SSI (n=285) and those who did not (n=21,869) were taken from Hospital of the University of Pennsylvania (HUP). The average cost of patients with SSI was £10,231	**Base case:** **36% greater reduction in SSI's** Incremental cost saving of £29 ($38) per surgical case.	The authors concluded that preoperative skin antisepsis with chlorhexidine is more effective than preoperative skin antisepsis with povidone iodine for preventing SSI and results in cost savings.	The authors considered two scenarios with very conservative estimates of the relative risk reduction effect of Chlorhexidine on SSIs. **15% greater reduction in SSI's** Incremental cost saving of £12 ($16) per surgical case. **25% greater reduction in SSI's** Incremental cost saving of £20 ($27) per surgical case. The authors conducted another analysis where they considered differing levels of increased cost of an patient with an SSI over a patient without an SSI, and found that Chlorhexidine was always a dominant strategy.

	technician personnel), and medical supplies (eg, reagents for laboratory tests, tubes and stoppers, slides, and imaging materials). Costs were converted to 2009 and expressed in US dollars **Utility** This study did not consider utility.	($13,537) and the average cost of patients who did not get an SSI was £4,048 ($5,356). The analysis time horizon is unclear.			No probabilistic sensitivity analysis was reported.
a) Not a cost-utility analysis *b) US study* *c) Limited description regarding specific unit cost components of health state costs (e.g. presence or absence of an SSI).* *d) No confidence intervals are provided around average costs of health states (presence of absence of an SSI).* *e) Time horizon is unclear, but is assumed to be short-term in order for post-surgery infections to be categorised as SSI.* *f) We were unable to replicate the model results, using the figures given in the report.*					
Note: (1) US dollars converted to UK pounds using a conversion rate of: $1.3231 per £1.00 (HM Treasury exchange rate as at 6th July 2018).					

Appendix K – Excluded studies

Clinical studies

Short Title	Title	New column
Afonso (2013)	The value of chlorhexidine gluconate wipes and prepacked washcloths to prevent the spread of pathogens--a systematic review	• Systematic review did not contain new relevant papers
Ahmed (2016)	Chlorhexidine vaginal wipes prior to elective cesarean section: does it reduce infectious morbidity? A randomized trial	• Comparator in study does not match that specified in protocol
Ahmed (2017)	Chlorhexidine vaginal wipes prior to elective cesarean section: does it reduce infectious morbidity? A randomized trial	• Duplicate reference
Anggrahita (2017)	Chlorhexidine-alcohol versus povidone-Iodine as preoperative skin preparation to prevent surgical site infection: A meta-analysis	• Systematic review did not contain new relevant papers
Art (2005)	Combination povidone-iodine and alcohol formulations more effective, more convenient versus formulations containing either iodine or alcohol alone: a review of the literature	• Review article but not a systematic review
Ayoub (2015)	Chlorhexidine-alcohol versus povidone-iodine for pre-operative skin preparation: A systematic review and meta-analysis	• Systematic review did not contain new relevant papers
Bajaj (2014)	Diluting chlorhexidine gluconate: one scrub or two?	• Study does not contain any of the outcomes of interest
Banerjee (2014)	Preoperative skin disinfection methodologies for reducing prosthetic joint infections	• Review article but not a systematic review
Benson (2014)	Dual application versus single application of povidone-iodine in reducing surgical site contamination during strabismus surgery	• Does not contain a population of interest
Bredemeyer (2011)	Randomised controlled trial of two strengths of topical aqueous chlorhexidine for	• Conference abstract

Short Title	Title	New column
	prevention of nosocomial infection in neonates born before 29 weeks	
Brooks (2001)	Bacterial recolonization during foot surgery: a prospective randomized study of toe preparation techniques	• Study not relevant to RQ. Study compared technique of application.
Cai (2017)	Preoperative chlorhexidine reduces the incidence of surgical site infections in total knee and hip arthroplasty: A systematic review and meta-analysis	• Systematic review did not contain new relevant papers
Culligan (2005)	A randomized trial that compared povidone iodine and chlorhexidine as antiseptics for vaginal hysterectomy	• Study does not contain any of the outcomes of interest
Davies (2016)	Does chlorhexidine and povidone-iodine preoperative antisepsis reduce surgical site infection in cranial neurosurgery?	• Not a relevant study design
Davies (2016)	Systematic Review and Meta-Analysis of Preoperative Antisepsis with Combination Chlorhexidine and Povidone-Iodine	• Systematic review did not contain new relevant papers
Djozic (2016)	Efficiency of Local Antiseptic Alkosol (Ethanol, Isopropanol-30g and Ortophenilphenol) and Povidone Iodide on the Incidence Of Surgical Site Infection After Inguinal Hernioplasty	• Study does not contain any relevant interventions
Dumville (2013)	Preoperative skin antiseptics for preventing surgical wound infections after clean surgery	• More recent systematic review included that covers the same topic
Eason (2004)	Antisepsis for abdominal hysterectomy: a randomised controlled trial of povidone-iodine gel	• Comparator in study does not match that specified in protocol
Edmiston (2007)	Comparative of a new and innovative 2% chlorhexidine gluconate-impregnated cloth with 4% chlorhexidine gluconate as topical antiseptic for preparation of the skin prior to surgery	• Study does not contain any of the outcomes of interest
Edwards (2004)	Preoperative skin antiseptics for preventing surgical wound infections after clean surgery	• More recent systematic review included that covers the same

Short Title	Title	New column
		topic
Fournel (2010)	Meta-analysis of intraoperative povidone-iodine application to prevent surgical-site infection	• Systematic review did not contain new relevant papers
Galland (1983)	Topical antiseptics in addition to peroperative antibiotics in preventing post-appendicectomy wound infections	• Comparator in study does not match that specified in protocol
Geelhoed (1983)	A comparative study of surgical skin preparation methods	• Study does not contain any of the outcomes of interest
George (2017)	Use of Chlorhexidine Preparations in Total Joint Arthroplasty	• Review article but not a systematic review
Ghobrial (2018)	Preoperative skin antisepsis with Chlorhexidine gluconate versus povidone-iodine: A prospective analysis of 6959 consecutive spinal surgery patients	• Not a relevant study design
Guzel (2009)	Evaluation of the skin flora after chlorhexidine and povidone-iodine preparation in neurosurgical practice	• Study does not contain any relevant interventions
Haas (2010)	Vaginal preparation with antiseptic solution before cesarean section for preventing postoperative infections	• Systematic review did not contain new relevant papers
Haas (2013)	Vaginal preparation with antiseptic solution before cesarean section for preventing postoperative infections	• Systematic review did not contain new relevant papers
Haas (2014)	Vaginal preparation with antiseptic solution before cesarean section for preventing postoperative infections	• Systematic review did not contain new relevant papers
Hadiati (2012)	Skin preparation for preventing infection following caesarean section	• Systematic review did not contain new relevant papers
Hadiati (2014)	Skin preparation for preventing infection following caesarean section	• Systematic review did not contain new relevant papers
Hagen (1995)	A comparison of two skin preps used in cardiac surgical procedures	• Review article but not a systematic review

Short Title	Title	New column
Hanedan (2014)	Comparison of two different skin preparation strategies for open cardiac surgery	• Study does not contain any relevant interventions
Harnoss (2018)	Comparison of chlorhexidine-isopropanol with isopropanol skin antisepsis for prevention of surgical-site infection after abdominal surgery	• Not a relevant study design
Hort (2002)	Residual bacterial contamination after surgical preparation of the foot or ankle with or without alcohol	• Study does not contain any relevant interventions
Hsieh (2014)	Effect of 4% chlorhexidine gluconate predisinfection skin scrub prior to hepatectomy: a double-blinded, randomized control study	• Comparator in study does not match that specified in protocol
Hunter (2016)	Randomized, Prospective Study of the Order of Preoperative Preparation Solutions for Patients Undergoing Foot and Ankle Orthopedic Surgery	• Not a relevant study design
Jacobson (2005)	Prevention of wound contamination using DuraPrep solution plus Ioban 2 drapes	• Study does not contain any of the outcomes of interest
Jeng (2001)	A new, water-resistant, film-forming, 30-second, one-step application iodophor preoperative skin preparation	• Study does not contain any of the outcomes of interest
Kalantar-Hormozi (2005)	No need for preoperative antiseptics in elective outpatient plastic surgical operations: a prospective study	• Not a relevant study design
Kamel (2012)	Preoperative skin antiseptic preparations for preventing surgical site infections: a systematic review	• Systematic review did not contain new relevant papers
Keblish (2005)	Preoperative skin preparation of the foot and ankle: bristles and alcohol are better	• Study does not contain any of the outcomes of interest
Kothuis (1981)	The effect of povidone-iodine on postoperative wound infection in abdominal surgery	• Not a relevant study design
Leclair (1988)	Effect of preoperative shampoos with chlorhexidine or iodophor on emergence of resident scalp flora in neurosurgery	• Study not relevant to RQ Study assessed effectiveness of antiseptic shampoos.
Lee (2010)	Systematic review and cost analysis comparing use of	• Systematic review did not

Short Title	Title	New column
	chlorhexidine with use of iodine for preoperative skin antisepsis to prevent surgical site infection	contain new relevant papers
Lefebvre (2015)	Is surgical site scrubbing before painting of value? Review and meta-analysis of clinical studies	• Systematic review did not contain new relevant papers
Lim (2008)	Chlorhexidine--pharmacology and clinical applications	• Review article but not a systematic review
Lorenz (1988)	Skin preparation methods before cesarean section. A comparative study	• Study not relevant to RQ Study examined effectiveness of preoperative adhesive film
Magann (1993)	Preoperative skin preparation and intraoperative pelvic irrigation: impact on post-cesarean endometritis and wound infection	• Study does not contain any relevant interventions
Maiwald (2012)	The forgotten role of alcohol: a systematic review and meta-analysis of the clinical efficacy and perceived role of chlorhexidine in skin antisepsis	• Systematic review did not contain new relevant papers
Malhotra (2011)	One vs two applications of chlorhexidine/ethanol for disinfecting the skin: Implications for regional anaesthesia	• Study not relevant to RQ Study did not report incidence of SSI
Meier (2001)	Prospective randomized comparison of two preoperative skin preparation techniques in a developing world country	• Comparator in study does not match that specified in protocol
Moon (2010)	Chlorhexidine-alcohol antiseptic reduces surgical site infections	• Review article but not a systematic review
Morrison (2016)	Single vs Repeat Surgical Skin Preparations for Reducing Surgical Site Infection After Total Joint Arthroplasty: A Prospective, Randomized, Double-Blinded Study	• Study not relevant to RQ Study examined reapplication of preparation solutions after draping.
Nishihara (2012)	A comparative clinical study focusing on the antimicrobial efficacies of chlorhexidine gluconate alcohol for patient skin preparations	• Does not contain a population of interest
Nishihara (2012)	Evaluation with a focus on both the antimicrobial efficacy and cumulative skin irritation potential of chlorhexidine	• Does not contain a population of interest

Short Title	Title	New column
	gluconate alcohol-containing preoperative skin preparations	
Noorani (2010)	Systematic review and meta-analysis of preoperative antisepsis with chlorhexidine versus povidone-iodine in clean-contaminated surgery	• Systematic review did not contain new relevant papers
Odedra (2014)	Chlorhexidine: an unrecognised cause of anaphylaxis	• Systematic review did not match review protocol
Ostrander (2003)	Bacterial skin contamination after surgical preparation in foot and ankle surgery	• Study does not contain any of the outcomes of interest
Ostrander (2005)	Efficacy of surgical preparation solutions in foot and ankle surgery	• Not a relevant study design
Patrick (2017)	Antisepsis of the skin before spinal surgery with povidone iodine-alcohol followed by chlorhexidine gluconate-alcohol versus povidone iodine-alcohol applied twice for the prevention of contamination of the wound by bacteria: a randomised controlled trial	• Study not relevant to RQ Study compared the use of povidone iodine and chlorhexidine with povidone iodine alone
Peel (2014)	Alcoholic Chlorhexidine or Alcoholic Iodine Skin Antisepsis (ACAISA): protocol for cluster randomised controlled trial of surgical skin preparation for the prevention of superficial wound complications in prosthetic hip and knee replacement surgery	• Not a relevant study design
Poirot (2018)	Skin preparation for abdominal surgery	• Systematic review did not match review protocol
Poulin (2014)	Preoperative skin antiseptics for preventing surgical site infections: what to do?	• Study not reported in English
Privitera (2017)	Skin antisepsis with chlorhexidine versus iodine for the prevention of surgical site infection: A systematic review and meta-analysis	• Systematic review did not contain new relevant papers
Rodrigues (2013)	Incidence of surgical site infection with pre-operative skin preparation using 10% polyvidone-iodine and 0.5% chlorhexidine-alcohol	• Not a relevant study design
Rogers (2011)	The effect of surgical preparation technique on the	• Study not relevant to RQ

Short Title	Title	New column
	bacterial load of surgical needles and suture material used during strabismus surgery	Study examined suture and needle contamination rates
Scowcroft (2012)	A critical review of the literature regarding the use of povidone iodine chlorhexidine gluconate for preoperative surgical skin preparation	• Review article but not a systematic review
Sharp (2016)	Chlorhexidine-induced anaphylaxis in surgical patients: a review of the literature	• Systematic review did not match review protocol
Shirahatti (1993)	Effect of pre-operative skin preparation on post-operative wound infection	• Comparator in study does not match that specified in protocol
Sidhwa (2015)	Skin preparation before surgery: options and evidence	• Review article but not a systematic review
Silva (2013)	An evidence based protocol for preoperative skin preparation	• Review article but not a systematic review
Silva (2014)	The right skin preparation technique: a literature review	• Review article but not a systematic review
Sullivan (2008)	An assessment of skin preparation in upper limb surgery	• Study not relevant to RQ Study examined the influence of staining properties of skin preparation, timing allowed to complete preparation and the grade of the surgeon.
Taneja (2012)	Can surgical site infection after joint arthroplasty be reduced?	• Conference abstract
Veiga (2008)	Influence of povidone-iodine preoperative showers on skin colonization in elective plastic surgery procedures	• Study not relevant to RQ Study focused on preoperative showering
Vinkomin (1995)	Vaginal scrub prophylaxis in abdominal hysterectomy	• Study not relevant to RQ Study examined effectiveness of vaginal cleansing.
Wistrand (2011)	Effects and experiences of warm versus cold skin disinfection	• Study not relevant to RQ

Short Title	Title	New column
		Study compared warm and cold skin disinfection
Wistrand (2015)	The effect of preheated versus room-temperature skin disinfection on bacterial colonization during pacemaker device implantation: a randomized controlled non-inferiority trial	• Study not relevant to RQ Study compared preheated and room temperature skin disinfection
Yasuda (2015)	Optimal Timing of Preoperative Skin Preparation with Povidone-Iodine for Spine Surgery: A Prospective, Randomized Controlled Study	• Study not relevant to RQ Study examined timing of skin preparation
Yeung (2013)	A comparison of chlorhexidine-alcohol versus povidone-iodine for eliminating skin flora before genitourinary prosthetic surgery: a randomized controlled trial	• Study does not contain any of the outcomes of interest
Zhang (2017)	Preoperative chlorhexidine versus povidone-iodine antisepsis for preventing surgical site infection: A meta-analysis and trial sequential analysis of randomized controlled trials	• Systematic review did not contain new relevant papers
Zinn (2010)	Intraoperative patient skin prep agents: is there a difference?	• Review article but not a systematic review

Economic studies

Study	Full title	Primary reason for exclusion
Bailey 2011	Bailey, R.R., Stuckey, D.R., Norman, B.A., Duggan, A.P., Bacon, K.M., Connor, D.L., Lee, I., Muder, R.R. and Lee, B.Y., 2011. Economic value of dispensing home-based preoperative chlorhexidine bathing cloths to prevent surgical site infection. Infection Control & Hospital Epidemiology, 32(5), pp.465-471.	Not a cost-utility analysis.
Ellenhorn 2006	Ellenhorn, J.D., Smith, D.D., Schwarz, R.E., Kawachi, M.H., Wilson, T.G., McGonigle, K.F., Wagman, L.D. and Paz, I.B., 2005. Paint-only is equivalent to scrub-and-paint in preoperative preparation of abdominal surgery sites. Journal of the American College of Surgeons, 201(5), pp.737-741.	Not a cost-utility analysis.
Gillespie 2017	Gillespie, B.M., Chaboyer, W., Erichsen-Andersson, A., Hettiarachchi, R.M. and Kularatna, S., 2017. Economic case for intraoperative interventions to prevent surgical-site infection. British Journal of Surgery, 104(2), pp.e55-e64.	Not a cost-utility analysis.

Study	Full title	Primary reason for exclusion
Hagen 1995	Hagen, K.S. and Treston-Aurand, J., 1995. A comparison of two skin preps used in cardiac surgical procedures. AORN journal, 62(3), pp.393-402.	Not a cost-utility analysis.
Jacobson 2005	Morrey, B. F. "Prevention of Wound Contamination Using DuraPrep™ Solution Plus Ioban™ 2 Drapes Jacobson C, Osmon DR, Hanssen A, et al (3M Company, St Paul, Minn; Mayo Clinic, Rochester, Minn; P-Value Statistical Consulting, Moab, Utah) Clin Orthop 439: 32–37, 2005." Year Book of Orthopedics 2006 (2006): 114-115.	Not a cost-utility analysis.
Kapadia 2013	Kapadia, B.H., Johnson, A.J., Issa, K. and Mont, M.A., 2013. Economic evaluation of chlorhexidine cloths on healthcare costs due to surgical site infections following total knee arthroplasty. The Journal of arthroplasty, 28(7), pp.1061-1065.	Not a cost-utility analysis.
Sutton 1999	Sutton, C.D., White, S.A., Edwards, R. and Lewis, M.H., 1999. A prospective controlled trial of the efficacy of isopropyl alcohol wipes before venesection in surgical patients. Annals of the Royal College of Surgeons of England, 81(3), p.183.	Not a cost-utility analysis.
Starr 1995	Starr, M.B. and Lally, J.M., 1996. Antimicrobial prophylaxis for ophthalmic surgery. Ophthalmic Literature, 1(49), p.60.	Not a cost-utility analysis.

Appendix L – Research recommendations

1. What is the clinical and cost effectiveness of a double application of antiseptics to the skin at the surgical site compared with a single application?

Limited evidence of very low quality was identified which demonstrated that there was no significant difference between double application of antiseptics compared to single application. Further up-to-date research is needed using a robust study design to explore the clinical effectiveness of number of applications of different antiseptics in the reduction in the incidence of SSI. These studies should ideally compare single application of the same antiseptic to double application of the same antiseptic. These should be UK based studies and should take into account different surgical procedures. Research in this area can help improve services therefore improving patient outcomes.

PICO	**Population:** People of any age undergoing any surgery, including minimally invasive surgery (arthroscopic, thoracoscopic and laparoscopic surgery) **Interventions:** Repeated applications of different antiseptics **Comparator:** Single application of same intervention compared to double application of same intervention **Outcomes:** • Surgical site infections (superficial, deep and organ/space SSI), including SSIs up to 30 days and 1 year, defined using appropriate criteria such as CDC SSI criteria • Mortality post-surgery • Length of hospital stay • Postoperative antibiotic use • Hospital readmission • Infectious complications such as septicaemia or septic shock • Adverse events such as: antimicrobial resistance, anaphylaxis and skin and other allergic reactions • Resource implications
Current evidence base	3 RCTs of low power
Study design	Randomised controlled trial
Other comments	These studies should take into account different surgery types and should be conducted within the UK with an adequate sample size.

2. What is the clinical and cost effectiveness of chlorhexidine in alcohol at different concentrations in the prevention of surgical site infection when applied to the skin before incision?

In the current review, evidence was identified which examined alcoholic preparations of chlorhexidine at different concentrations such as 0.5%, 2%, 2.5% and 4% chlorhexidine. Only 1 study was identified which conducted a head to head comparison of 2% chlorhexidine with 70% alcohol and 0.5% chlorhexidine with 70% alcohol. While this study demonstrated that 2% chlorhexidine reduced the incidence of superficial SSI, the result was not statistically significant. Further research is needed using a robust study design to explore the clinical effectiveness and cost effectiveness of chlorhexidine in alcohol at different concentrations. These should be UK based studies and should take into account different surgical procedures. Research in this area is essential to inform future updates of key recommendations in this guidance which in turn can help improve patient outcomes.

PICO	**Population:** People of any age undergoing any surgery, including minimally invasive surgery (arthroscopic, thoracoscopic and laparoscopic surgery) **Interventions:** • 0.5% chlorhexidine in alcohol • 2% chlorhexidine in alcohol • Chlorhexidine in alcohol at different concentrations **Comparator:** Different chlorhexidine concentrations compared to each other **Outcomes:** • Surgical site infections (superficial, deep and organ/space SSI), including SSIs up to 30 days and 1 year, defined using appropriate criteria such as CDC SSI criteria • Mortality post-surgery • Length of hospital stay • Postoperative antibiotic use • Hospital readmission • Infectious complications such as septicaemia or septic shock • Adverse events such as: antimicrobial resistance, anaphylaxis and skin and other allergic reactions • Resource implications
Current evidence base	1 RCT of low power
Study design	Randomised controlled trial
Other comments	These studies should take into account different surgery types and should be conducted within the UK with an adequate sample size.

3. What is the clinical and cost effectiveness of different modes of applying skin antiseptic before incision in the prevention of surgical site infection?

In the current review interventions with different modes of application such as sponge, swabs and sprays were identified. However, the aim of this review did not include the comparison of mode of antiseptic application. However, it was identified that mode of application can be a confounding factor with regards to SSI. Research is required, which utilises a robust study design, to assess the clinical and cost effectiveness of different modes of antiseptic application prior skin incision and incidence of SSI. These should be UK based studies and should take into account different surgical procedures. Research in this area can help improve services therefore improving patient outcomes.

PICO	**Population:** People of any age undergoing any surgery, including minimally invasive surgery (arthroscopic, thoracoscopic and laparoscopic surgery) **Interventions:** Application of different skin antiseptics using different mechanical methods including: • Sponge • Swabs • Any other mechanical method • Non mechanical methods such as spray **Comparator:** Different mechanical or non-mechanical methods compared to each other **Outcomes:** • Surgical site infections (superficial, deep and organ/space SSI), including SSIs up to 30 days and 1 year, defined using appropriate criteria such as CDC SSI criteria • Mortality post-surgery • Length of hospital stay • Postoperative antibiotic use • Hospital readmission • Infectious complications such as septicaemia or septic shock • Adverse events such as: antimicrobial resistance, anaphylaxis and skin and other allergic reactions • Resource implications
Current evidence base	Not examined part of current analysis
Study design	Randomised controlled trial
Other comments	These studies should take into account different surgery types and should be conducted within the UK with an adequate sample size.

Appendix M – References

Included Studies

Systematic review

Dumville Jo C, McFarlane Emma, Edwards Peggy, Lipp Allyson, Holmes Alexandra, and Liu Zhenmi (2015) Preoperative skin antiseptics for preventing surgical wound infections after clean surgery. The Cochrane database of systematic reviews (4), CD003949

Randomised controlled trial

Abreu Diego, Campos Enrique, Seija Veronica, Arroyo Carlos, Suarez Ruben, Rotemberg Pablo, Guillama Fernanda, Carvalhal Gustavo, Campolo Horacio, Machado Miguel, and Decia Ricardo (2014) Surgical site infection in surgery for benign prostatic hyperplasia: comparison of two skin antiseptics and risk factors. Surgical infections 15(6), 763-7

Alexander J W, Aerni S, and Plettner J P (1985) Development of a safe and effective one-minute preoperative skin preparation. Archives of surgery (Chicago, and Ill. : 1960) 120(12), 1357-61

Berry AR, Watt B, Goldacre MJ, Thomson JW, and McNair TJ (1982) A comparison of the use of povidone-iodine and chlorhexidine in the prophylaxis of postoperative wound infection.. The Journal of hospital infection 3(1), 55-63

Bibbo Christopher, Patel Dipak V, Gehrmann Robin M, and Lin Sheldon S (2005) Chlorhexidine provides superior skin decontamination in foot and ankle surgery: a prospective randomized study. Clinical orthopaedics and related research 438, 204-8

Bibi Safia, Shah Syed Aslam, Qureshi Shamim, Siddiqui Taranum Ruba, Soomro Iftikhar Ahmed, Ahmed Waquaruddin, and Alam Syed Ejaz (2015) Is chlorhexidine-gluconate superior than Povidone-Iodine in preventing surgical site infections? A multicenter study. JPMA. The Journal of the Pakistan Medical Association 65(11), 1197-201

Broach Robyn B, Paulson Emily C, Scott Charles, and Mahmoud Najjia N (2017) Randomized Controlled Trial of Two Alcohol-based Preparations for Surgical Site Antisepsis in Colorectal Surgery. Annals of surgery 266(6), 946-951

Brown T R, Ehrlich C E, Stehman F B, Golichowski A M, Madura J A, and Eitzen H E (1984) A clinical evaluation of chlorhexidine gluconate spray as compared with

iodophor scrub for preoperative skin preparation. Surgery, and gynecology & obstetrics 158(4), 363-6

Casey Anna, Itrakjy Abdul, Birkett Chrissie, Clethro Alan, Bonser Robert, Graham Tim, Mascaro Jorge, Pagano Domenico, Rooney Stephen, Wilson Ian, Nightingale Peter, Crosby Cynthia, and Elliott Thomas (2015) A comparison of the efficacy of 70% v/v isopropyl alcohol with either 0.5% w/v or 2% w/v chlorhexidine gluconate for skin preparation before harvest of the long saphenous vein used in coronary artery bypass grafting. American journal of infection control 43(8), 816-20

Charles Daniel, Heal Clare F, Delpachitra Meth, Wohlfahrt Michael, Kimber Debbie, Sullivan Julie, Browning Sheldon, Saednia Sabine, Hardy Alexandra, Banks Jennifer, and Buttner Petra (2017) Alcoholic versus aqueous chlorhexidine for skin antisepsis: the AVALANCHE trial. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne 189(31), E1008-E1016

Cheng Kenneth, Robertson Hannah, St Mart , Jean Pierre, Leanord Alistair, and McLeod Ian (2009) Quantitative analysis of bacteria in forefoot surgery: a comparison of skin preparation techniques. Foot & ankle international 30(10), 992-7

Darouiche Rabih O, Wall Matthew J, Jr , Itani Kamal M. F, Otterson Mary F, Webb Alexandra L, Carrick Matthew M, Miller Harold J, Awad Samir S, Crosby Cynthia T, Mosier Michael C, Alsharif Atef, and Berger David H (2010) Chlorhexidine-Alcohol versus Povidone-Iodine for Surgical-Site Antisepsis. The New England journal of medicine 362(1), 18-26

Ellenhorn Joshua D. I, Smith David D, Schwarz Roderich E, Kawachi Mark H, Wilson Timothy G, McGonigle Kathryn F, Wagman Lawrence D, and Paz I Benjamin (2005) Paint-only is equivalent to scrub-and-paint in preoperative preparation of abdominal surgery sites. Journal of the American College of Surgeons 201(5), 737-41

Gilliam D L, and Nelson C L (1990) Comparison of a one-step iodophor skin preparation versus traditional preparation in total joint surgery. Clinical orthopaedics and related research (250), 258-60

Howard R (1991) Comparison of a 10 minute aqueous iodophor and 2 minute wa ter-insoluble iodophor in alcoholpreoperative skin preparation. . Complications in Surgery 10(7), 43–5

Kunkle Cynelle M, Marchan Jennifer, Safadi Sara, Whitman Stephanie, and Chmait Ramen H (2015) Chlorhexidine gluconate versus povidone iodine at cesarean delivery: a randomized controlled trial. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, and the International Society of Perinatal Obstetricians 28(5), 573-7

Ngai Ivan M, Van Arsdale , Anne , Govindappagari Shravya, Judge Nancy E, Neto Nicole K, Bernstein Jeffrey, Bernstein Peter S, and Garry David J (2015) Skin Preparation for Prevention of Surgical Site Infection After Cesarean Delivery: A Randomized Controlled Trial. Obstetrics and gynecology 126(6), 1251-7

Paocharoen Veeraya, Mingmalairak Chatchai, and Apisarnthanarak Anucha (2009) Comparison of surgical wound infection after preoperative skin preparation with 4% chlorhexidine [correction of chlohexidine] and povidone iodine: a prospective randomized trial. Journal of the Medical Association of Thailand = Chotmaihet thangphaet 92(7), 898-902

Park H M, Han S S, Lee E C, Lee S D, Yoon H M, Eom B W, Kim S H, Ryu K W, Park S J, Kim Y W, and Park B (2017) Randomized clinical trial of preoperative skin antisepsis with chlorhexidine gluconate or povidone-iodine. The British journal of surgery 104(2), e145-e150

Roberts A, Wilcox K, Devineni R, Harris R, and Osevala M (1995) Skin preparation in CA BG surgery: A prospective randomized trial. Complications in Surgery 14(6), 724,741-4, 747

Saltzman Matthew D, Nuber Gordon W, Gryzlo Stephen M, Marecek Geoffrey S, and Koh Jason L (2009) Efficacy of surgical preparation solutions in shoulder surgery. The Journal of bone and joint surgery. American volume 91(8), 1949-53

Savage Jason W, Weatherford Brian M, Sugrue Patrick A, Nolden Mark T, Liu John C, Song John K, and Haak Michael H (2012) Efficacy of surgical preparation solutions in lumbar spine surgery. The Journal of bone and joint surgery. American volume 94(6), 490-4

Segal Cynthia G, and Anderson Jacqueline J (2002) Preoperative skin preparation of cardiac patients. AORN journal 76(5), 821-8

Sistla Sarath Chandra, Prabhu Ganesh, Sistla Sujatha, and Sadasivan Jagdish (2010) Minimizing wound contamination in a 'clean' surgery: comparison of chlorhexidine-ethanol and povidone-iodine. Chemotherapy 56(4), 261-7

Springel Edward H, Wang Xiao-Yu, Sarfoh Vanessa M, Stetzer Bradley P, Weight Steven A, and Mercer Brian M (2017) A randomized open-label controlled trial of chlorhexidine-alcohol vs povidone-iodine for cesarean antisepsis: the CAPICA trial. American journal of obstetrics and gynecology 217(4), 463.e1-463.e8

Srinivas Anirudh, Kaman Lileswar, Raj Prithivi, Gautam Vikas, Dahiya Divya, Singh Gurpreet, Singh Rajinder, and Medhi Bikash (2015) Comparison of the efficacy of chlorhexidine gluconate versus povidone iodine as preoperative skin preparation for

the prevention of surgical site infections in clean-contaminated upper abdominal surgeries. Surgery today 45(11), 1378-84

Tuuli Methodius G, Liu Jingxia, Stout Molly J, Martin Shannon, Cahill Alison G, Odibo Anthony O, Colditz Graham A, and Macones George A (2016) A Randomized Trial Comparing Skin Antiseptic Agents at Cesarean Delivery. The New England journal of medicine 374(7), 647-55

Xu Peter Z, Fowler John R, and Goitz Robert J (2017) Prospective Randomized Trial Comparing the Efficacy of Surgical Preparation Solutions in Hand Surgery. Hand (New York, and N.Y.) 12(3), 258-264

Zdeblick T A, Lederman M M, Jacobs M R, and Marcus R E (1986) Preoperative use of povidone-iodine. A prospective, randomized study. Clinical orthopaedics and related research (213), 211-5

Excluded studies

Afonso Elsa, Llaurado Mireia, and Gallart Elisabeth (2013) The value of chlorhexidine gluconate wipes and prepacked washcloths to prevent the spread of pathogens--a systematic review. Australian critical care : official journal of the Confederation of Australian Critical Care Nurses 26(4), 158-66

Ahmed Magdy R, Aref Nisreen K, Sayed Ahmed, Waleed A, and Arain Farzana R (2016) Chlorhexidine vaginal wipes prior to elective cesarean section: does it reduce infectious morbidity? A randomized trial. Journal of Maternal-Fetal & Neonatal Medicine 29(17), 1-4

Ahmed Magdy R, Aref Nisreen K, Sayed Ahmed, Waleed A, and Arain Farzana R (2017) Chlorhexidine vaginal wipes prior to elective cesarean section: does it reduce infectious morbidity? A randomized trial. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, and the International Society of Perinatal Obstetricians 30(12), 1484-1487

Anggrahita T, Wardhana A, and Sudjatmiko G (2017) Chlorhexidine-alcohol versus povidone-Iodine as preoperative skin preparation to prevent surgical site infection: A meta-analysis. Medical Journal of Indonesia 26(1), 54-61

Art Greg (2005) Combination povidone-iodine and alcohol formulations more effective, more convenient versus formulations containing either iodine or alcohol alone: a review of the literature. Journal of infusion nursing : the official publication of the Infusion Nurses Society 28(5), 314-20

Ayoub F, Quirke M, Conroy R, and Hill A (2015) Chlorhexidine-alcohol versus povidone-iodine for pre-operative skin preparation: A systematic review and meta-analysis. International Journal of Surgery Open 1, 41-46

Bajaj Tarun Inder, Loh Cecilia, and Borgstrom David (2014) Diluting chlorhexidine gluconate: one scrub or two?. Surgical infections 15(5), 544-7

Banerjee Samik, Kapadia Bhaveen H, and Mont Michael A (2014) Preoperative skin disinfection methodologies for reducing prosthetic joint infections. The journal of knee surgery 27(4), 283-8

Benson C E, Rogers K L, and Suh D W (2014) Dual application versus single application of povidone-iodine in reducing surgical site contamination during strabismus surgery. Journal of AAPOS 18(4), 347-350

Bredemeyer Sl, Reid S, Evans N, and Gibbons E (2011) Randomised controlled trial of two strengths of topical aqueous chlorhexidine for prevention of nosocomial infection in neonates born before 29 weeks. Journal of paediatrics and child health 47, 64-65

Brooks R A, Hollinghurst D, Ribbans W J, and Severn M (2001) Bacterial recolonization during foot surgery: a prospective randomized study of toe preparation techniques. Foot & ankle international 22(4), 347-50

Cai Yuanzhen, Xu Ke, Hou Weikun, Yang Zhi, and Xu Peng (2017) Preoperative chlorhexidine reduces the incidence of surgical site infections in total knee and hip arthroplasty: A systematic review and meta-analysis. International journal of surgery (London, and England) 39, 221-228

Culligan Patrick J, Kubik Kari, Murphy Miles, Blackwell Linda, and Snyder James (2005) A randomized trial that compared povidone iodine and chlorhexidine as antiseptics for vaginal hysterectomy. American journal of obstetrics and gynecology 192(2), 422-5

Davies B M, and Patel H C (2016) Does chlorhexidine and povidone-iodine preoperative antisepsis reduce surgical site infection in cranial neurosurgery?. Annals of the Royal College of Surgeons of England 98(6), 405-8

Davies Benjamin M, and Patel Hiren C (2016) Systematic Review and Meta-Analysis of Preoperative Antisepsis with Combination Chlorhexidine and Povidone-Iodine. Surgery journal (New York, and N.Y.) 2(3), e70-e77

Djozic Harun, Pandza Haris, Hasukic Sefik, Custovic Samir, Pandza Berina, Krupalija Amina, and Beciragic Edin (2016) Efficiency of Local Antiseptic Alkosol (Ethanol, Isopropanol-30g and Ortophenilphenol) and Povidone Iodide on the Incidence Of

Surgical Site Infection After Inguinal Hernioplasty. Medical archives (Sarajevo, and Bosnia and Herzegovina) 70(2), 108-11

Dumville Jo C, McFarlane Emma, Edwards Peggy, Lipp Allyson, and Holmes Alexandra (2013) Preoperative skin antiseptics for preventing surgical wound infections after clean surgery. The Cochrane database of systematic reviews (3), CD003949

Eason E, Wells G, Garber G, Hemmings R, Luskey G, Gillett P, Martin M, Vaginal Antisepsis For Abdominal Hysterectomy Study, and Group (2004) Antisepsis for abdominal hysterectomy: a randomised controlled trial of povidone-iodine gel. BJOG : an international journal of obstetrics and gynaecology 111(7), 695-9

Edmiston Charles E, Jr , Seabrook Gary R, Johnson Christopher P, Paulson Daryl S, and Beausoleil Christopher M (2007) Comparative of a new and innovative 2% chlorhexidine gluconate-impregnated cloth with 4% chlorhexidine gluconate as topical antiseptic for preparation of the skin prior to surgery. American journal of infection control 35(2), 89-96

Edwards P S, Lipp A, and Holmes A (2004) Preoperative skin antiseptics for preventing surgical wound infections after clean surgery. The Cochrane database of systematic reviews (3), CD003949

Fournel I, Tiv M, Soulias M, Hua C, Astruc K, Aho Glele, and L S (2010) Meta-analysis of intraoperative povidone-iodine application to prevent surgical-site infection. The British journal of surgery 97(11), 1603-13

Galland R B, Karlowski T, Midwood C J, Madden M V, and Carmalt H (1983) Topical antiseptics in addition to peroperative antibiotics in preventing post-appendicectomy wound infections. Annals of the Royal College of Surgeons of England 65(6), 397-9

Geelhoed G W, Sharpe K, and Simon G L (1983) A comparative study of surgical skin preparation methods. Surgery, and gynecology & obstetrics 157(3), 265-8

George Jaiben, Klika Alison K, and Higuera Carlos A (2017) Use of Chlorhexidine Preparations in Total Joint Arthroplasty. Journal of bone and joint infection 2(1), 15-22

Ghobrial G M, Wang M Y, Green B A, Levene H B, Manzano G, Vanni S, Starke R M, Jimsheleishvili G, Crandall K M, Dididze M, and Levi A D (2018) Preoperative skin antisepsis with Chlorhexidine gluconate versus povidone-iodine: A prospective analysis of 6959 consecutive spinal surgery patients. Journal of Neurosurgery: Spine 28(2), 209-214

Guzel Aslan, Ozekinci Tuncer, Ozkan Umit, Celik Yusuf, Ceviz Adnan, and Belen Deniz (2009) Evaluation of the skin flora after chlorhexidine and povidone-iodine preparation in neurosurgical practice. Surgical neurology 71(2), 207-210

Haas David M, Morgan Al Darei, Sarah , and Contreras Karenrose (2010) Vaginal preparation with antiseptic solution before cesarean section for preventing postoperative infections. The Cochrane database of systematic reviews (3), CD007892

Haas David M, Morgan Sarah, and Contreras Karenrose (2013) Vaginal preparation with antiseptic solution before cesarean section for preventing postoperative infections. The Cochrane database of systematic reviews (1), CD007892

Haas David M, Morgan Sarah, and Contreras Karenrose (2014) Vaginal preparation with antiseptic solution before cesarean section for preventing postoperative infections. The Cochrane database of systematic reviews (12), CD007892

Hadiati Diah R, Hakimi Mohammad, and Nurdiati Detty S (2012) Skin preparation for preventing infection following caesarean section. The Cochrane database of systematic reviews (9), CD007462

Hadiati Diah R, Hakimi Mohammad, Nurdiati Detty S, and Ota Erika (2014) Skin preparation for preventing infection following caesarean section. The Cochrane database of systematic reviews (9), CD007462

Hagen K S, and Treston-Aurand J (1995) A comparison of two skin preps used in cardiac surgical procedures. AORN journal 62(3), 393-402

Hanedan Muhammet Onur, Unal Ertekin Utku, Aksoyek Aysen, Basar Veysel, Tak Sercan, Tutun Ufuk, Isik Hasan, and Birincioglu Cemal Levent (2014) Comparison of two different skin preparation strategies for open cardiac surgery. Journal of infection in developing countries 8(7), 885-90

Harnoss J C, Assadian O, Kramer A, Probst P, Muller-Lantzsch C, Scheerer L, Bruckner T, Diener M K, Buchler M W, and Ulrich A B (2018) Comparison of chlorhexidine-isopropanol with isopropanol skin antisepsis for prevention of surgical-site infection after abdominal surgery. The British journal of surgery 105(7), 893-899

Hort Kurtis R, and DeOrio James K (2002) Residual bacterial contamination after surgical preparation of the foot or ankle with or without alcohol. Foot & ankle international 23(10), 946-8

Hsieh Ching-Shui, Cheng Hsiu-Chi, Lin Jen-Shiou, Kuo Shou-Jen, and Chen Yao-Li (2014) Effect of 4% chlorhexidine gluconate predisinfection skin scrub prior to

hepatectomy: a double-blinded, randomized control study. International surgery 99(6), 787-94

Hunter Joshua G, Dawson Laura K, Soin Sandeep P, and Baumhauer Judith F (2016) Randomized, Prospective Study of the Order of Preoperative Preparation Solutions for Patients Undergoing Foot and Ankle Orthopedic Surgery. Foot & ankle international 37(5), 478-82

Jacobson Cassie, Osmon Douglas R, Hanssen Arlen, Trousdale Robert T, Pagnano Mark W, Pyrek Janine, Berbari Elie, and Naessens James (2005) Prevention of wound contamination using DuraPrep solution plus Ioban 2 drapes. Clinical orthopaedics and related research 439, 32-7

Jeng D K (2001) A new, water-resistant, film-forming, 30-second, one-step application iodophor preoperative skin preparation. American Journal of Infection Control 29(6), 370-376

Kalantar-Hormozi A J, and Davami Babak (2005) No need for preoperative antiseptics in elective outpatient plastic surgical operations: a prospective study. Plastic and reconstructive surgery 116(2), 529-31

Kamel Chris, McGahan Lynda, Polisena Julie, Mierzwinski-Urban Monika, and Embil John M (2012) Preoperative skin antiseptic preparations for preventing surgical site infections: a systematic review. Infection control and hospital epidemiology 33(6), 608-17

Keblish Dj, Zurakowski D, Wilson Mg, and Chiodo Cp (2005) Preoperative skin preparation of the foot and ankle: bristles and alcohol are better. Journal of bone and joint surgery. American volume 87(5), 986-992

Kothuis B J (1981) The effect of povidone-iodine on postoperative wound infection in abdominal surgery. The Netherlands journal of surgery 33(4), 186-9

Leclair J M, Winston K R, Sullivan B F, O'Connell J M, Harrington S M, and Goldmann D A (1988) Effect of preoperative shampoos with chlorhexidine or iodophor on emergence of resident scalp flora in neurosurgery. Infection control : IC 9(1), 8-12

Lee Ingi, Agarwal Rajender K, Lee Bruce Y, Fishman Neil O, and Umscheid Craig A (2010) Systematic review and cost analysis comparing use of chlorhexidine with use of iodine for preoperative skin antisepsis to prevent surgical site infection. Infection control and hospital epidemiology 31(12), 1219-29

Lefebvre A, Saliou P, Mimoz O, Lucet J C, Le Guyader , A , Bruyere F, Roche P H, Astruc K, Tiv M, Lepelletier D, Aho-Glele L S, French Study Group for the Pre-

operative Prevention of Surgical, and Infections (2015) Is surgical site scrubbing before painting of value? Review and meta-analysis of clinical studies. The Journal of hospital infection 89(1), 28-37

Lim K S, and Kam P C. A (2008) Chlorhexidine--pharmacology and clinical applications. Anaesthesia and intensive care 36(4), 502-12

Lorenz R P, Botti J J, Appelbaum P C, and Bennett N (1988) Skin preparation methods before cesarean section. A comparative study. The Journal of reproductive medicine 33(2), 202-4

Magann E F, Dodson M K, Ray M A, Harris R L, Martin J N, Jr , and Morrison J C (1993) Preoperative skin preparation and intraoperative pelvic irrigation: impact on post-cesarean endometritis and wound infection. Obstetrics and gynecology 81(6), 922-5

Maiwald Matthias, and Chan Edwin S. Y (2012) The forgotten role of alcohol: a systematic review and meta-analysis of the clinical efficacy and perceived role of chlorhexidine in skin antisepsis. PloS one 7(9), e44277

Malhotra S, Dharmadasa A, and Yentis S M (2011) One vs two applications of chlorhexidine/ethanol for disinfecting the skin: Implications for regional anaesthesia. Anaesthesia 66(7), 574-578

Meier D E, Nkor S K, Aasa D, OlaOlorun D A, and Tarpley J L (2001) Prospective randomized comparison of two preoperative skin preparation techniques in a developing world country. World journal of surgery 25(4), 441-3

Moon K T (2010) Chlorhexidine-alcohol antiseptic reduces surgical site infections. American Family Physician 81(11), 1369

Morrison Tiffany N, Chen Antonia F, Taneja Mayank, Kucukdurmaz Fatih, Rothman Richard H, and Parvizi Javad (2016) Single vs Repeat Surgical Skin Preparations for Reducing Surgical Site Infection After Total Joint Arthroplasty: A Prospective, Randomized, Double-Blinded Study. The Journal of arthroplasty 31(6), 1289-94

Nishihara Y, Kajiura T, Katsuhiro Y, Kobayashi H, and Okubo T (2012) A comparative clinical study focusing on the antimicrobial efficacies of chlorhexidine gluconate alcohol for patient skin preparations. Journal of Infusion Nursing 35(1), 44-50

Nishihara Yutaka, Kajiura Takumi, Yokota Katsuhiro, Kobayashi Hiroyoshi, and Okubo Takashi (2012) Evaluation with a focus on both the antimicrobial efficacy and cumulative skin irritation potential of chlorhexidine gluconate alcohol-containing preoperative skin preparations. American journal of infection control 40(10), 973-8

Noorani A, Rabey N, Walsh S R, and Davies R J (2010) Systematic review and meta-analysis of preoperative antisepsis with chlorhexidine versus povidone-iodine in clean-contaminated surgery. The British journal of surgery 97(11), 1614-20

Odedra Katy Mara, and Farooque Sophie (2014) Chlorhexidine: an unrecognised cause of anaphylaxis. Postgraduate medical journal 90(1070), 709-14

Ostrander Roger V, Botte Michael J, and Brage Michael E (2005) Efficacy of surgical preparation solutions in foot and ankle surgery. The Journal of bone and joint surgery. American volume 87(5), 980-5

Ostrander Roger V, Brage Michael E, and Botte Michael J (2003) Bacterial skin contamination after surgical preparation in foot and ankle surgery. Clinical orthopaedics and related research (406), 246-52

Patrick S, McDowell A, Lee A, Frau A, Martin U, Gardner E, McLorinan G, and Eames N (2017) Antisepsis of the skin before spinal surgery with povidone iodine-alcohol followed by chlorhexidine gluconate-alcohol versus povidone iodine-alcohol applied twice for the prevention of contamination of the wound by bacteria: a randomised controlled trial. The bone & joint journal 99-B(10), 1354-1365

Peel T N, Cheng A C, Buising K L, Dowsey M M, and Choong P F. M (2014) Alcoholic Chlorhexidine or Alcoholic Iodine Skin Antisepsis (ACAISA): protocol for cluster randomised controlled trial of surgical skin preparation for the prevention of superficial wound complications in prosthetic hip and knee replacement surgery. BMJ open 4(5), e005424

Poirot K, Le Roy , B , Badrikian L, and Slim K (2018) Skin preparation for abdominal surgery. Journal of visceral surgery ,

Poulin Paule, Chapman Kelly, McGahan Lynda, Austen Lea, and Schuler Trevor (2014) Preoperative skin antiseptics for preventing surgical site infections: what to do?. ORNAC journal 32(3), 12-9

Privitera Gaetano Pierpaolo, Costa Anna Laura, Brusaferro Silvio, Chirletti Piero, Crosasso Paola, Massimetti Gabriele, Nespoli Angelo, Petrosillo Nicola, Pittiruti Mauro, Scoppettuolo Giancarlo, Tumietto Fabio, and Viale Pierluigi (2017) Skin antisepsis with chlorhexidine versus iodine for the prevention of surgical site infection: A systematic review and meta-analysis. American journal of infection control 45(2), 180-189

Rodrigues Ana Luzia, and Simoes Maria de Lourdes Pessole Biondo (2013) Incidence of surgical site infection with pre-operative skin preparation using 10% polyvidone-iodine and 0.5% chlorhexidine-alcohol. Revista do Colegio Brasileiro de Cirurgioes 40(6), 443-8

Rogers David L, Chheda Lena, Ford Carla, Marcon Mario, Fellows Rae R, Rogers Gary L, Bremer Don L, McGregor Mary Lou, Golden Richard P, and Cassady Cybil Bean (2011) The effect of surgical preparation technique on the bacterial load of surgical needles and suture material used during strabismus surgery. Journal of AAPOS : the official publication of the American Association for Pediatric Ophthalmology and Strabismus 15(3), 230-3

Scowcroft Tammy (2012) A critical review of the literature regarding the use of povidone iodine chlorhexidine gluconate for preoperative surgical skin preparation. Journal of perioperative practice 22(3), 95-9

Sharp Gary, Green Sarah, and Rose Michael (2016) Chlorhexidine-induced anaphylaxis in surgical patients: a review of the literature. ANZ journal of surgery 86(4), 237-43

Shirahatti R G, Joshi R M, Vishwanath Y K, Shinkre N, Rao S, Sankpal J S, and Govindrajulu N K (1993) Effect of pre-operative skin preparation on post-operative wound infection. Journal of postgraduate medicine 39(3), 134-6

Sidhwa Feroze, and Itani Kamal M. F (2015) Skin preparation before surgery: options and evidence. Surgical infections 16(1), 14-23

Silva Pedro (2013) An evidence based protocol for preoperative skin preparation. Journal of Perioperative Practice 23(4), 87-90

Silva Pedro (2014) The right skin preparation technique: a literature review. Journal of perioperative practice 24(12), 283-5

Sullivan P J, Healy C E, Hirpara K M, Hussey A J, Potter S M, and Kelly J L (2008) An assessment of skin preparation in upper limb surgery. The Journal of hand surgery, and European volume 33(4), 513-4

Taneja M, Purtill J, Rothman R, Austin M, and Parvizi J (2012) Can surgical site infection after joint arthroplasty be reduced?. Surgical infections. 13, S10

Veiga Daniela F, Damasceno Carlos A. V, Veiga Filho, Joel , Silva Rivalino V, Jr , Cordeiro Daniel L, Vieira Antonio M, Andrade Carlos H. V, and Ferreira Lydia M (2008) Influence of povidone-iodine preoperative showers on skin colonization in elective plastic surgery procedures. Plastic and reconstructive surgery 121(1), 115-20

Vinkomin V (1995) Vaginal scrub prophylaxis in abdominal hysterectomy. The Southeast Asian journal of tropical medicine and public health 26(1), 188-92

Wistrand Camilla, and Nilsson Ulrica (2011) Effects and experiences of warm versus cold skin disinfection. British journal of nursing (Mark Allen Publishing) 20(3), 148-1

Wistrand Camilla, Soderquist Bo, Magnusson Anders, and Nilsson Ulrica (2015) The effect of preheated versus room-temperature skin disinfection on bacterial colonization during pacemaker device implantation: a randomized controlled non-inferiority trial. Antimicrobial resistance and infection control 4, 44

Yasuda Tatsuya, Hasegawa Tomohiko, Yamato Yu, Kobayashi Sho, Togawa Daisuke, Arima Hideyuki, and Matsuyama Yukihiro (2015) Optimal Timing of Preoperative Skin Preparation with Povidone-Iodine for Spine Surgery: A Prospective, Randomized Controlled Study. Asian spine journal 9(3), 423-6

Yeung Lawrence L, Grewal Shaun, Bullock Arnold, Lai H Henry, and Brandes Steven B (2013) A comparison of chlorhexidine-alcohol versus povidone-iodine for eliminating skin flora before genitourinary prosthetic surgery: a randomized controlled trial. The Journal of urology 189(1), 136-40

Zhang Dan, Wang Xi-Chen, Yang Zeng-Xi, Gan Jian-Xin, Pan Jie-Bin, and Yin Lan-Ning (2017) Preoperative chlorhexidine versus povidone-iodine antisepsis for preventing surgical site infection: A meta-analysis and trial sequential analysis of randomized controlled trials. International journal of surgery (London, and England) 44, 176-184

Zinn Jennifer, Jenkins Jeanne B, Swofford Vangela, Harrelson Beverly, and McCarter Sharon (2010) Intraoperative patient skin prep agents: is there a difference?. AORN journal 92(6), 662-74