

WHO Surgical Site Infection Prevention Guidelines

Web Appendix 8

Summary of a systematic literature review on surgical site preparation

1. Introduction

Surgical site preparation refers to the preoperative treatment of the intact skin of the patient within the operating room. Preparation includes not only the immediate site of the intended surgical incision, but also a broader area of the patient's skin, and usually takes place when the patient is already positioned on the operating table. The aim of this procedure is to reduce the microbial load on the patient's skin as much as possible before incising the skin barrier. The most widely-used agents are chlorhexidine gluconate (CHG) and iodophors (for example, povidone iodine [PVP-I]) in alcohol-based solutions, which are effective against a wide range of bacteria, fungi and viruses. Aqueous solutions, particularly those containing iodophors, are also widely used, notably in developing countries.

Application techniques for preoperative surgical site preparation are also a topic of interest. However, 3 trials investigating the effect of the application technique with comparable antiseptic compounds showed no difference in surgical site infection (SSI) rates ¹⁻³. Despite current knowledge of the antimicrobial activity of many antiseptic agents and application techniques, it remains unclear what is the best approach to preoperative site preparation ^{4,5}.

Several guidelines, such as those published by the Society for Healthcare Epidemiology of America (SHEA)/Infectious Diseases Society of America (IDSA) ⁶, the United Kingdom (UK) National Institute for Health and Care Excellence (NICE) ⁷ or the Royal College of Physicians of Ireland ⁸, recommend the use of an alcohol-based solution for surgical site preparation. However, these recommendations are not based upon a systematic review of the literature and meta-analysis or a rigorous evaluation of the quality of the available evidence.

The objective of this systematic review is to assess the available evidence on the efficacy of solutions and antiseptic agents used for surgical site skin preparation.

2. PICO question

In surgical patients, should alcohol-based antiseptic or aqueous solutions be used for skin preparation and, more specifically, should CHG or PVP-I solutions be used?

- **Population:** patients of any age undergoing any type of surgical procedures
- **Intervention:** alcohol-based preparations
- **Comparator:** aqueous preparations
- **Outcome:** SSI, SSI-attributable mortality

3. Methods

The following databases were searched: Medline (PubMed); Excerpta Medica Database (EMBASE/Ovid), Cumulative Index to Nursing and Allied Health Literature (CINAHL); Cochrane Central Register of Controlled Trials (CENTRAL); and WHO regional medical databases. The time limit for the review was between 1 January 1960 and 15 August 2014. Language was restricted to English, French and Spanish. A comprehensive list of search terms was used, including Medical Subject Headings (MeSH) (Appendix 1).

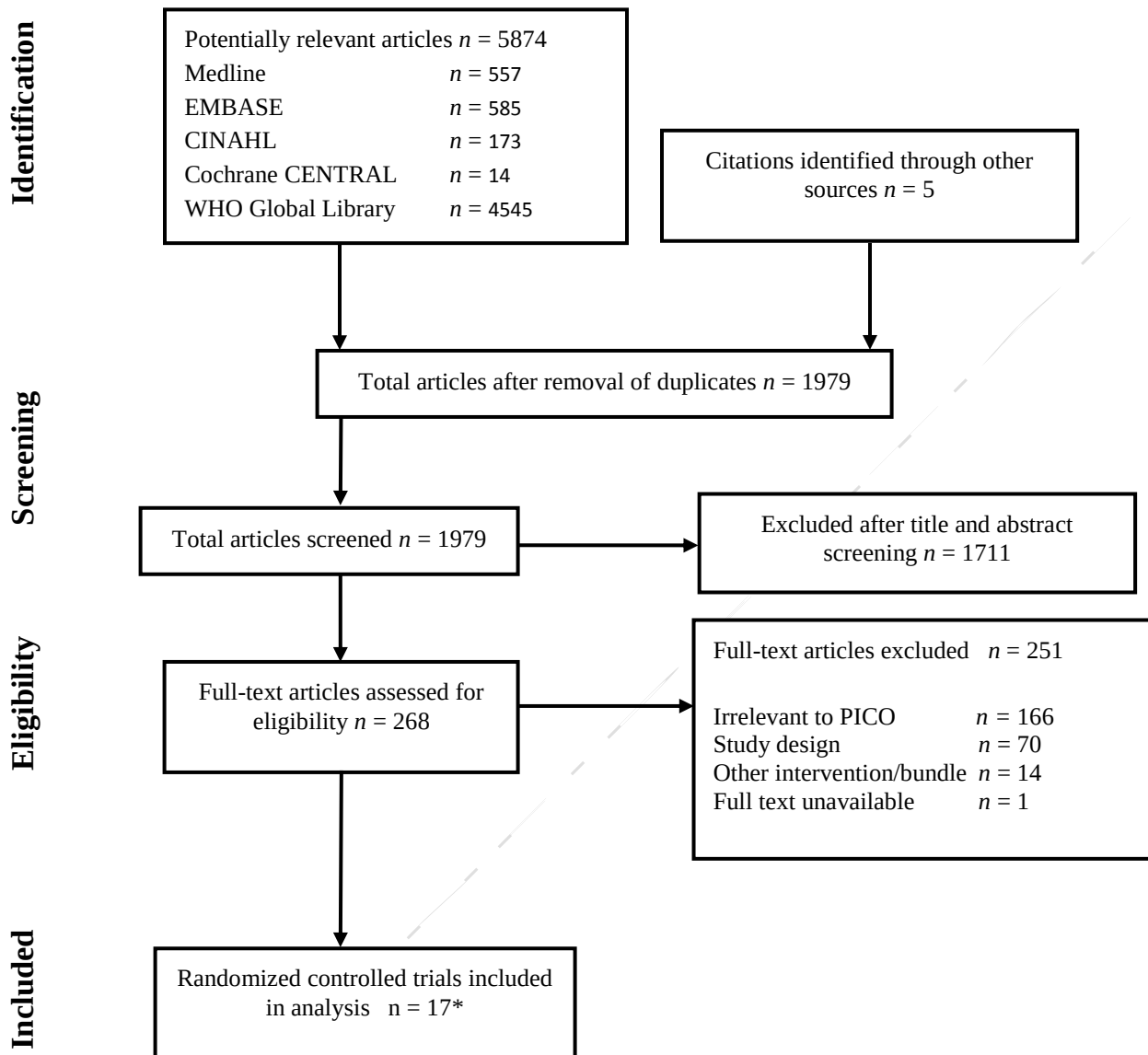
Two independent reviewers screened the titles and abstracts of retrieved references for potentially relevant studies. The full text of all potentially eligible articles was obtained. Two authors independently reviewed the full text articles for eligibility based on inclusion criteria. Duplicate studies were excluded.

Two authors extracted data in a predefined evidence table (Appendix 2) and critically appraised the retrieved studies using the Cochrane Collaboration tool to assess the risk of bias of randomized controlled trials (RCTs)⁹ (Appendix 3). Any disagreements were resolved through discussion or after consultation with the senior author, when necessary.

Meta-analyses of available comparisons were performed using Review Manager version 5.3 as appropriate¹⁰ (Appendix 4). Adjusted odds ratios (OR) and mean differences with 95% confidence intervals (CI) were extracted and pooled for each comparison with a random effects model. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology^{11,12} (GRADE Pro software; <http://gradepro.org/>) was used to assess the quality of the body of retrieved evidence (Appendix 5).

4. Study selection

Flow chart of the study selection process



* 16 studies were included from the original search (up to 15 August 2014) and one was exceptionally included later as this was a relevant trial published on 4 February 2016.

5. Summary of the findings

Overall, 17 RCTs^{2,13-28} comparing antiseptic agents (PVP-I and CHG) in aqueous and alcohol-based solutions with an SSI outcome were identified. Although the time limit for inclusion was set to a publication date of up to 15 August 2014, a relevant trial²⁸ published on 4 February 2016 was exceptionally included after discussion with the World Health Organization (WHO) Guidelines Review Committee and the Guidelines Development Group.

Included studies focused on adult patients and no study was available in the paediatric population. Most studies used isopropyl alcohol at a concentration of 70-74%. Concentrations of the iodophor compound ranged from 0.7-10% and from 0.5-4% for CHG. As there was heterogeneity among the included studies concerning the composition of the solution used for surgical site preparation, the research group decided to focus the evaluation on the following comparisons:

- PVP-I vs. CHG, both in alcohol-based solutions
- PVP-I in an aqueous solution vs. PVP-I in an alcohol-based solution
- CHG in an aqueous solution vs. CHG in an alcohol-based solution
- CHG vs. PVP-I, both in aqueous solutions.

However, a search of the literature did not identify any studies that compared CHG in an aqueous solution with CHG in an alcohol-based solution or CHG with PVP-I, both in aqueous solutions. The available studies included in the review made it possible to carry out the following comparisons:

1. Alcohol-based antiseptic solutions vs. aqueous solutions
 - a. CHG in an alcohol-based solution vs. PVP-I in an aqueous solution
 - b. PVP-I in an alcohol-based solution vs. PVP-I in an aqueous solution
2. CHG vs. PVP-I, both in alcohol-based solutions.

The results of the meta-analysis based on these comparisons are shown in Appendix 4.

1. Twelve RCTs^{2,13-23} compared alcohol-based vs. aqueous antiseptic solutions in preoperative surgical site preparation. Meta-analysis of these 12 studies (Appendix 4, comparison 1) showed that alcohol-based antiseptic solutions are more effective compared to aqueous solutions in reducing the risk of SSI (OR: 0.60; 95% CI: 0.45–0.78).

The overall quality of evidence of this comparison was moderate due to the risk of bias (Appendix 5).

- a. Among these 12 trials, 7⁸ RCTs compared CHG in an alcohol-based solution with PVP-I in an aqueous solution. Most trials found either no difference between the groups¹³⁻¹⁶ or there were no SSI events reported^{17,18}. One trial found an increased risk for SSI in the PVP-I group²³ (see Appendices 2 and 4). Meta-analysis of these 7 studies (Appendix 4, comparison 1a) showed a significant benefit in reducing the risk of SSI with CHG in

alcohol-based solutions compared to PVP-I in an aqueous solution (OR: 0.65; 95% CI: 0.47–0.90).

The quality of the evidence was moderate for this comparison due to the risk of bias (Appendix 5).

- b. Six[§] of the 12 RCTs compared alcohol-based vs. aqueous PVP-I. The trials found either no difference between the groups^{2,19,20} or there were no SSI events reported^{18,21,22}. Meta-analysis of these 6 studies (Appendix 4, comparison 1b) showed no significant difference between the groups (OR: 0.61; 95% CI: 0.19–1.92).

The quality of evidence was very low for this comparison due to the risk of bias and imprecision (Appendix 5).

2. Six RCTs compared CHG with PVP-I in alcohol-based solutions. Most trials found either no difference between the groups^{24,25} or there were no SSI events reported^{18,26}. Two trials^{27,28} found an increased risk for SSI in the PVP-I group. Meta-analysis of these studies (Appendix 4, comparison 2) showed a significant reduction of risk of SSI with the use of alcohol-based CHG compared to PVP-I in alcohol-based solutions (OR: 0.58; 95% CI: 0.42–0.80). However, 4 of the 6 trials^{18,24–26} reported no SSI events in at least one of the study arms and most studies reported the number of colony-forming units as the primary outcome and not SSI.

The quality of evidence was low for this comparison due to the risk of bias and imprecision (Appendix 5).

§ Numbers do not add up to 12 as some studies were included in multiple analyses.

In conclusion, the retrieved evidence can be summarized as follows:

Overall, there is a lack of robust, high-quality studies that evaluate the efficacy of alcohol-based vs. aqueous solutions or the antiseptic compound in the solutions.

1. Overall, a moderate quality of evidence shows that alcohol-based antiseptic solutions are more effective compared to aqueous solutions in reducing the risk of SSI.
 - a. Overall, a moderate quality of evidence shows a significant benefit in reducing the risk of SSI with alcohol-based CHG compared to PVP-I in an aqueous solution.
 - b. Overall, a very low quality of evidence shows that surgical site skin preparation with alcohol-based PVP-I is neither beneficial nor harmful in reducing SSI rates compared to aqueous PVP-I.
2. Overall, a low quality of evidence shows a significant benefit in reducing the risk of SSI with the use of alcohol-based CHG compared to alcohol-based PVP-I.

Several limitations can be observed in the available studies. The criteria for SSI were comparable, but the definitions of SSI were not identical between the studies. Most studies had a considerable risk of bias, particularly related to the blinding of outcome assessors. Although most included studies used isopropyl alcohol at a concentration of 70–74% in the alcohol-based solution, some authors^{13,27} did not specify the type of concentration used; one study¹⁴ used 70% ethanol. The concentration of antiseptic agent varied between the studies and the iodophor compound ranged from 0.7–10% and CHG from 0.5–4%. The study arms in the trials comparing aqueous vs. alcohol-based PVP-I had variations in the application method (aqueous “scrub and paint” vs. alcohol-based “paint”).

APPENDICES

Appendix 1. Search terms

Medline (via PubMed)

("surgical wound infection"[Mesh] OR surgical site infection* [TIAB] OR "SSI" OR "SSIs" OR surgical wound infection* [TIAB] OR surgical infection*[TIAB] OR post-operative wound infection* [TIAB] OR postoperative wound infection* [TIAB] OR wound infection*[TIAB]) OR (("preoperative care"[Mesh] OR "preoperative care" OR "pre-operative care" OR "perioperative care"[Mesh] OR "perioperative care" OR "peri-operative care" OR perioperative OR intraoperative OR "perioperative period"[Mesh] OR "intraoperative period"[Mesh]) AND ("infection"[Mesh] OR infection [TIAB])) AND ("skin preparation" [TIAB] OR "skin preparations" [TIAB] OR skin prep [TIAB] OR "baths"[Mesh] OR bath*[TIAB] OR (("povidone-iodine"[Mesh] OR povidone OR "iodophors"[Mesh] OR iodophor OR iodophors OR "iodine"[Mesh] OR iodine OR betadine OR "triclosan"[Mesh] OR triclosan OR "chlorhexidine"[Mesh] OR chlorhexidine OR hibiscrub OR hibisol OR alcohol OR alcohols OR Gel OR "soaps"[Mesh] OR soap [TIAB] OR soaps [TIAB]) AND skin AND (disinfectants OR "antiseptics"[Mesh] OR antiseptics OR antiseptics OR detergents OR cleaning OR cleansing)))

EMBASE and CINAHL

((ssi) OR (surgical site infection) OR (surgical site infections) OR (wound infection) OR (wound infections) OR (postoperative wound infection)) AND ("skin preparation" OR "skin preparations" OR skin prep OR "baths" OR bath* OR (("povidone-iodine" OR povidone OR "iodophors" OR iodophor OR iodophors OR "iodine" OR iodine OR betadine OR "triclosan" OR triclosan OR "chlorhexidine" OR chlorhexidine OR hibiscrub OR hibisol OR alcohol OR alcohols OR gel OR "soaps" OR soap OR soaps) AND skin AND (disinfectants OR "antiseptics" OR antiseptics OR antiseptics OR detergents OR cleaning OR cleansing)))

Cochrane CENTRAL

(wound infection or surgical wound infection) AND skin antiseptics

WHO Global Library

((ssi) OR (surgical site infection) OR (surgical site infections) OR (wound infection) OR (wound infections) OR (postoperative wound infection)) AND ("skin preparation" OR "skin preparations" OR skin prep

ti: title; ab: abstract

Appendix 2. Evidence table

Author, year, reference	Design, scope, setting, population	Objective	SSI definition	Type of surgery	Study methods	Intervention	Results (SSI)
Berry, 1982 ²⁷	Two-arm RCT May 1978-February 1980 Scotland, UK 542 patients Exclusion: sensitivity to solutions	To compare the effect of alcohol-based PVP-I alcohol-based CHG on the incidence of postoperative wound infection in a general surgical unit.	Presence of a wound abnormality: erythematous, serous, discharge or purulent. Follow-up: until discharge.	Elective, mostly clean.	Randomization allocation was done using a table of random numbers and recorded on a card. Each card was then placed in a sealed envelope. Skin shaving was routinely performed on hairy skin. Groups were allocated to bathe with the same scrub as their allocated intervention. (7.5% PVP-I or CHG 0.5% in methylated spirit).	Group A: 2 applications of CHG 0.5% in methylated spirit (n=286). Group B: 2 applications of (alcohol) paint 10% (n=256).	Group A: 18/286 Group B: 34/256 <i>P</i> =0.03

Bibbo, 2009 ¹⁷	RCT USA 127 patients Exclusion criteria eliminated patients with open wounds, skin ulcers and/or sores and active infection or who were on antibiotic therapy.	To determine the efficacy of CHG compared with PVP-I as a preoperative skin preparation agent in reducing bacterial skin contamination before clean, elective foot and ankle surgery.	NS	Clean, elective foot and ankle surgery.	Enrolled consecutively and randomly assigned into treatment groups. No special bathing instructions; patients followed usual personal hygiene routine on the day of surgery. Culture swabs were processed for aerobic, anaerobic, acid-fast and fungal cultures, as well as a routine qualitative sensitivity screening for antibiotic resistance. Culture results, demographic data, and infectious complications were recorded.	Group 1: patient skin was prepared preoperatively with a 7-minute scrub with PVP-I (7.5%) and painting of the foot and ankle with a PVP-I (10%) solution. Group 2: patient skin was prepared preoperatively with a 7-minute scrub with CHG (4%) and isopropyl alcohol (70%) paint.	SSI Group 1: 0/67 Group 2: 0/60 Microbial culture data also included. OR: NA CI: NA
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Cheng, 2009 ²⁶	RCT August 2007 to January 2008 UK 50 patients Exclusion criteria: open wounds, skin ulcers and/or sores, a history of onychomycosis, paronychia or nail deformity, poorly controlled diabetes mellitus or recent antibiotic use within 1 week of surgery.	To compare the effect of PVP-I or CHG with and without isopropyl alcohol on lowering the bacterial load. Also assessed whether any additional benefits were to be gained by an additional pre-scrub with a bristled surgical brush with either of these compounds.	NS	Foot surgery.	Patients were randomized via generation of random number tables to be prepared with either alcohol-based PVP-I or alcohol-based CHG. A sterile brush was used to generously apply the solution using the foam part of the brush. The bristled side was then used to scrub for a standardized 3 minutes. Feet were allowed to dry prior to draping. The same agent was used on the patient's other foot and then painted with solution (CFU data only) Specimens for bacterial cultures were obtained by one of the authors from 3 sites on the foot before and after skin preparation and transported for culture and quantitative analysis.	Group 1: alcohol-based betadine (10% PVP-I weight/weight). Group 2: CHG (0.5%) with 70% isopropyl alcohol.	SSI Group 1: 0/25 Group 2: 0/25 Microbial data also reported. OR: NA 95% CI: NA
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Darouiche, 2010 ²³	RCT April 2004-May 2008 USA 409 patients 6 university-affiliated hospitals	To compare the efficacy of CHG-alcohol with PVP-I for the prevention of SSI.	CDC criteria	Clean 70-73% abdominal. All procedures were similarly distributed between groups.	Randomization stratified by hospital using computer-generated randomization numbers without blocking. Preoperative shower with CHG, PVP-I or triclocarban soap was recorded in less than 30% of patients and was similar between groups. Patients and investigators who diagnosed SSI were unaware of group assignments. Outcome: SSI within 30 days after surgery; individual types of SSI.	Preoperatively scrubbed with an applicator containing CHG 2% and 70% isopropyl alcohol (ChloraPrep®; Care Fusion, San Diego, CA, USA) or preoperatively scrubbed and then painted with an aqueous solution of PVP-I 10%. More than one CHG-alcohol applicator was used if the coverage area exceeded 33x33cm.	Total SSI CHG/alcohol: 39/409 PVP-I: 71/440 RR: 0.59 95% CI: 0.41-0.85 P=0.004 Superficial CHG/alcohol: 17/409 PVP-I: 38/440 Deep CHG/alcohol: 4/409 PVP-I: 13/440 Organ/space CHG/alcohol: 18/409 PVP-I: 20/440
Gilliam, 1990 ²²	Two-arm RCT USA 60 patients	Not given	NS	Clean total joint surgery.	Hair removal was conducted just prior to skin preparation with a dry shave. Both groups bathed preoperatively with a CHG soap. Non-microbial drapes were also used.	Group A: 5-minute aqueous iodophor scrub followed by the application of iodophor paint (n=30). Group B: water insoluble iodophor-in-alcohol solution (iodophor 0.7% and isopropyl alcohol 74% (DuraPrep™; 3M, St Paul, MN, USA) (n=30).	Group A: 0/30 Group B: 0/30 OR: NA CI: NA

Hort, 2002 ²¹	Two-arm RCT USA 49 consecutive patients	To investigate the usefulness of a standard surgical preparation for the prevention of surgical site contamination.	NS	Foot and ankle surgery.	Patients were randomly assigned to an allocation group. The standard group was given 2 CHG scrub brushes with instructions to perform 2 separate self-scrubs several hours apart before bed. In the operating room, 10- minute scrub with PVP-I cleansing solution followed by PVP-I topical paint. The experimental group was supplemented with the addition of a 3-minute preoperative preparation of the area with alcohol 70%. All patients were draped by a blinded surgeon. Swabs were collected for CFU data.	Group A: PVP-I scrub + aqueous PVP-I paint. Group B: PVP-I scrub + PVP-I paint + alcohol.	Group A: 0/26 Group B: 0/23 OR: NA 95% CI: NA
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Howard, 1991 ²⁰	Two-arm RCT USA 159 patients over 18 years of age undergoing surgery with no known iodide allergy.	To compare the effectiveness of DuraPrep™ to standard iodophor scrub and paint.	Wounds were considered to be infected if: • they drained pus; • they developed significant erythema at the margins of the wound (erythema around a suture "stitch abscess" was not considered to be a wound infection); • the wound drained serous fluid and was opened by the surgeon; or • the wound was considered to be infected by the operating surgeon.	Clean and clean-contaminated operations	Patients randomized using a 1-to-1 basis. Cultures were taken and incubated for aerobic colonization; wounds were followed daily until discharge and then at clinic visits. Some patients who lived far from the medical centre were followed by their local physician and by telephone communication.	Group 1 (n=140) received a 10-minute scrub with an iodophor detergent followed by an aqueous iodophor paint. Group 2 (n=140) were prepared with a water-insoluble iodophor in isopropyl alcohol 70%.	Group 1: 2/75 Group 2: 2/84
Paocharoen, 2009 ¹⁶	RCT June 2006 to November 2008 Thailand 500 adult patients	To study the efficacy of the reduction of bacterial colonization and surgical wound infection among antiseptics.	Incisional SSI: if wound drained purulent material or if the surgeon judged it to be infected and opened it.	Clean, clean-contaminated and contaminated wounds and ASA class 1 and 2.	Randomization by "random assignment". Surgical wounds were examined twice a week in week 1 and every week thereafter up to 1 month. Outcomes were bacterial colonization following skin preparation and postoperative wound infection.	1) 5-minute scrub with PVP-1 scrub followed by PVP-1 paint. 2) 5-minute scrub with Hibitane® (RxMed scrub solution followed by Hibitane® paint (CHG 4% in 70% isopropyl alcohol 70%).	SSI: Group 1: 8/250 Group 2: 5/250 Allergic reaction: Group 1: 2/250 Group 2: 0/250 Microbial data also reported.

Roberts, 1995 ¹⁹	Two-arm RCT USA 200 adult patients		Purulent material drained from incision site.	Coronary artery bypass graft.	“Consenting adults were randomly assigned by a table of numbers.” Primary outcome was SSI.	Group A received aqueous iodophor scrub (5-10 minutes; n=96) followed by iodophor paint. Group B received iodophor-in-alcohol water-insoluble paint (7.5% iodine, isopropyl alcohol 74% weight/weight).	Group A: 10/104 Group B: 9/96
Rodrigues, 2013 ¹³	Randomized, longitudinal study Brazil 205 adult patients	To analyze the incidence of SSI when the pre-operative skin preparation was performed with PVP-I 10% and CHG-alcohol 0.5%.	NS	Clean and potentially contaminated operations.	Patients were divided into 2 groups according to the order of arrival to the operating room. Postoperative infection of the surgical site was inspected at postoperative days 3, 7 and 30.	Group 1: PVP-I 10% (n=102). Group 2: CHG 0.5% (n=103).	Group 1: 7/95 Group 2: 11/92 <i>P</i> =0.460

Saltzman, 2009¹⁸	RCT September 2007 to February 2008 USA 150 patients (age, 17-79 years) Patients were excluded if they had an open wound or current infection or were chronically immuno-suppressed.	To examine the native bacteria around the shoulder and to determine the efficacy of 3 different surgical skin preparation solutions on the eradication of bacteria from the shoulder.	NS	Shoulder surgery.	Randomized using randomly assigned sealed envelopes. All patients received preoperative antibiotics. Manufacturer's instructions were used for each preparation agent by the attending surgeon. Culture specimens were obtained for the first 20 patients from 3 different sites before and after the surgical preparation. The remaining 130 patients were cultured from two locations after skin preparation (aerobic and anaerobic microbiology). Assessment of infectious outcomes are not specified.	Each shoulder was prepared with one of 3 surgical skin preparation agents: 1. ChloraPrep® (CHG 2% with isopropyl alcohol 70%; n=50). 2. DuraPrep™ (iodophor 0.7% and isopropyl alcohol 74%; n=50). 3. PVP-I scrub and paint (iodine scrub 0.75% and iodine paint 1%; n=50).	Group 1: 0/50 Group 2: 0/50 Group 3: 0/50 OR: NA 95% CI: NA
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Savage, 2012 ²⁴	Two-arm RCT USA 100 patients	To identify the common bacterial flora on the skin overlying the lumbar spine and to evaluate the efficacy of 2 readily available skin preparation solutions for the elimination of bacterial pathogens from the surgical site following skin preparation.	NS	Elective lumbar spine surgery.	All patients were randomized using a randomly-assigned envelope method. Perioperative use of antibiotics in all patients. The site was prepared according to the manufacturer's instructions by the attending surgeon. Each solution was allowed to adequately dry for 3-5 minutes in order to minimize the recognized risk of fire associated with alcohol-based solutions. Assessment of rate of positive bacterial culture, wound infection.	Skin preparation with: Group 1: Chloraprep® (n=50; CHG 2% and isopropyl alcohol 70%). Group 2: DuraPrep™ (n=50; available iodine 0.7% and isopropyl alcohol 74%).	SSI Group 1: 1/50 Group 2: 0/50
Segal, 2002 ²	Four-arm RCT USA 209 patients	To investigate whether one method of skin preparation is better than another for reducing postoperative sternal SSIs in patients undergoing coronary artery bypass graft who are at high risk for developing SSIs.	CDC criteria	Coronary artery bypass graft (clean)	All patients were instructed to take an antimicrobial shower the evening before and the morning of surgery. All patients received prophylactic preoperative antibiotics.	Group A: 5-minute scrub with aqueous PVP-I paint (scrub 7.5% and paint 10% both aqueous) (n=52). Group B: aqueous PVP-I paint (10%) (n=56). Group C: iodophor in alcohol, film-forming antiseptic (n=50). Group D: iodophor in alcohol film-forming antiseptic with iodine-impregnated incise drape (not used).	Group A: 7/52 Group B: 7/56 Group C: 1/50 (Group D: 3/51) X ² between 4 groups = 5.889 P=0.117 NS between aqueous and alcohol-based solutions.

Sistla, 2010 ¹⁴	RCT India 400 adult patients	To test if CHG ethanol has a superior antimicrobial efficacy compared with PVP-I.	CDC criteria used to report SSI during the postoperative period; CFU counts from patients with SSI compared to those without SSI.	Elective inguinal hernia repair.	All patients fulfilling the inclusion criteria were prospectively randomized using a sealed envelope method. Antiseptics were applied in concentric circles beginning from the site of incision to the periphery and allowed to dry before the surgical site was draped. Incidence of SSI within 20 days following surgery, skin CFU counts pre/post-antisepsis. Patients undergoing prosthetic repair received a single dose of cefazolin 1 g intravenously 1 hour before surgery.	Group 1: PVP-I 10% group (n=285). Group 2: CHG 2.5% -ethanol 70% (n=271).	SSI Group 1:19/200 Group 2: 14/200 Grade 1 infection Group 1:7/200 Group 2: 5/200 Grade 2 infection Group 1:10/200 Group 2: 8/200 Grade 3 infection Group 1:2/200 Group 2: 1/200 (all) $P=0.364$
Srinivas, 2014 ¹⁵	RCT January 2011 to June 2012 India 342 adult patients	To compare the efficacy of CHG vs. PVI-I in preoperative skin preparation for the prevention of SSI in clean-contaminated upper abdominal surgeries	CDC criteria	Clean-contaminated upper abdominal surgeries.	Group A patients were painted 3 times around the site using an applicator containing CHG-alcohol (0.5% CHG in isopropyl 70% alcohol). Group B included those who were preoperatively painted with a PVP-I 5% solution 3 times. All patients received antibiotics preoperatively. SSI was assessed as the primary outcome with a 30-day follow-up period.	Group A: CHG-alcohol (n=163; 0.5% CHG in isopropyl alcohol 70%). Group B: PVP-I (n=188; 5%).	All SSI Group A: 17/158 Group B:33/184 $P=0.061$ Superficial SSI Group A: 17/158 Group B: 31/184 Deep SSI Group A: 0/158 Group B: 2/184 Organ/space SSI Group A: 0/158 Group B: 0/184

Tuuli 2016 ²⁸	RCT September 2011 to June 2015 USA 1147 pregnant women undergoing caesarean delivery	Patients were randomly assigned to preoperative skin antisepsis with CHG–alcohol or PVP-I–alcohol in a pragmatic trial to determine the comparative effectiveness of the 2 preoperative skin preparations for the prevention of SSI after caesarean delivery.	CDC	Caesarean delivery.	Skin preparation was performed by the circulating nurse according to the manufacturer’s instructions, which were similar for the two antiseptic agents. In brief, the prepackaged antiseptic applicator was opened and used to scrub the operative site. A wait time of 3 minutes was allowed between the 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.	Group A: CHG 2% with isopropyl alcohol 70%. Group B: PVP-I 8.3% with isopropyl alcohol 72.5%.	All SSI Group A: 23/572 Group B: 42/575 RR: 0.55 (0.34–0.90) P=0.02 Superficial SSI Group A: 17/572 Group B: 28/575 P=0.10 Deep SSI Group A: 0/572 Group B: 2/575 P=0.07
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Veiga, 2008 ²⁵	RCT Brazil 250 patients over 18 years undergoing elective plastic surgery	To compare PVP-I and chlorhexidine-ethanol-based solutions for skin antisepsis before plastic surgery procedures.	CDC criteria	Elective and clean plastic surgery procedures.	Antisepsis protocol was standardized to a vigorous scrub with antiseptic soap followed by sterile towel absorption and painting with an alcohol solution of PVP-I (10%) or chlorhexidine (0.5%). The solution was allowed to dry for 2 minutes after painting. Swabs were obtained from the operative field before the scrub, after painting and at the end of surgery for CFU data.	Group A: PVP-I 10% with alcohol. Group B: chlorhexidine 0.5% with alcohol.	Group A: 4/125* Group B: 0/125 *all classified as superficial SSI P=0.6
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SSI: surgical site infection; NA: not applicable; NS: not significant; ASA: American Anesthesiologists Association; CDC: Centers for Disease Control and Prevention; CFU: colony-forming unit; CHG: chlorhexidine gluconate; PVP-I: povidone-iodine; RCT: randomized controlled trial.

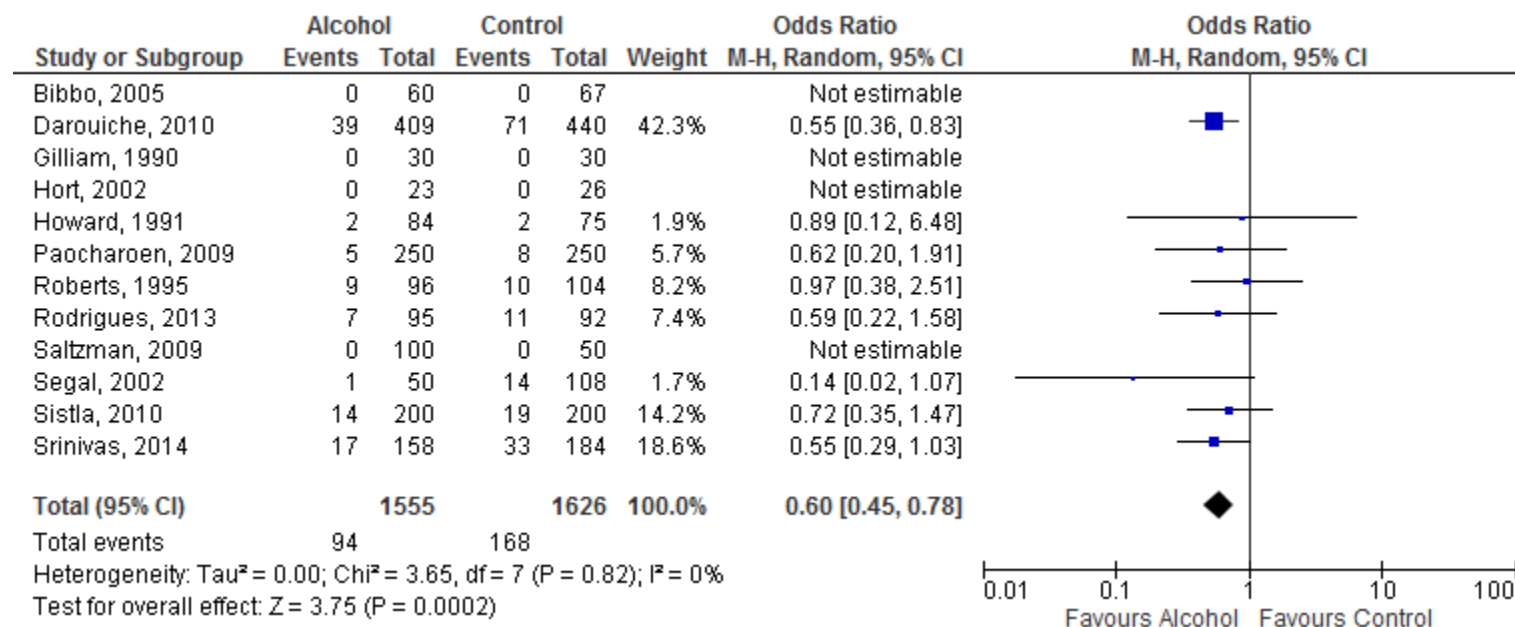
Appendix 3. Risk of bias assessment for included studies

RCT, author, year	Sequence generation	Allocation concealment	Participants and personnel blinded	Outcome assessors blinded	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Berry, 1982 ²⁷	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Bibbo, 2005 ¹⁷	UNCLEAR	UNCLEAR	LOW	LOW	LOW	LOW	UNCLEAR
Cheng, 2009 ²⁶	LOW	UNCLEAR	LOW	UNCLEAR	LOW	UNCLEAR	UNCLEAR
Darouiche, 2010 ²³	LOW	LOW	LOW	LOW	UNCLEAR	LOW	LOW
Gilliam, 1990 ²²	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR
Hort, 2002 ²¹	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW	LOW	UNCLEAR
Howard, 1991 ²⁰	HIGH	HIGH	UNCLEAR	UNCLEAR	LOW	LOW	UNCLEAR
Paocharoen, 2009 ¹⁶	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW	LOW	UNCLEAR
Roberts, 1995 ¹⁹	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW	LOW	UNCLEAR
Rodrigues, 2013 ¹³	HIGH	HIGH	UNCLEAR	UNCLEAR	LOW	LOW	UNCLEAR
Saltzman, 2009 ¹⁸	LOW	LOW	UNCLEAR	UNCLEAR	LOW	UNCLEAR	LOW
Savage, 2012 ²⁴	LOW	LOW	UNCLEAR	UNCLEAR	LOW	LOW	LOW
Segal, 2002 ²	LOW	UNCLEAR	UNCLEAR	UNCLEAR	LOW	LOW	UNCLEAR
Sistla, 2010 ¹⁴	LOW	LOW	LOW	LOW	UNCLEAR	UNCLEAR	UNCLEAR
Srinivas, 2014 ¹⁵	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW	LOW	LOW

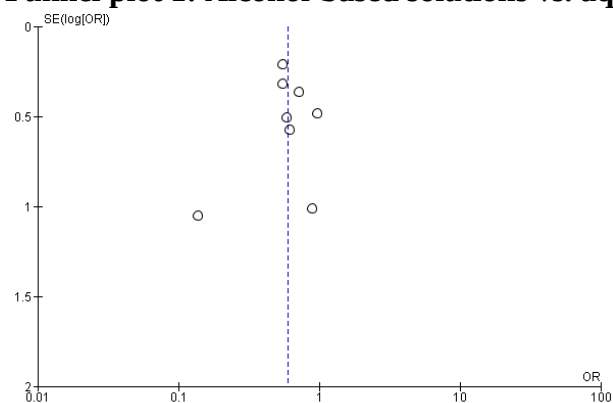
Veiga, 2008 ²⁵	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW	LOW	UNCLEAR
Tuuli, 2016 ²⁸	LOW	UNCLEAR	UNCLEAR	LOW	LOW	LOW	UNCLEAR

Appendix 4. Meta-analyses

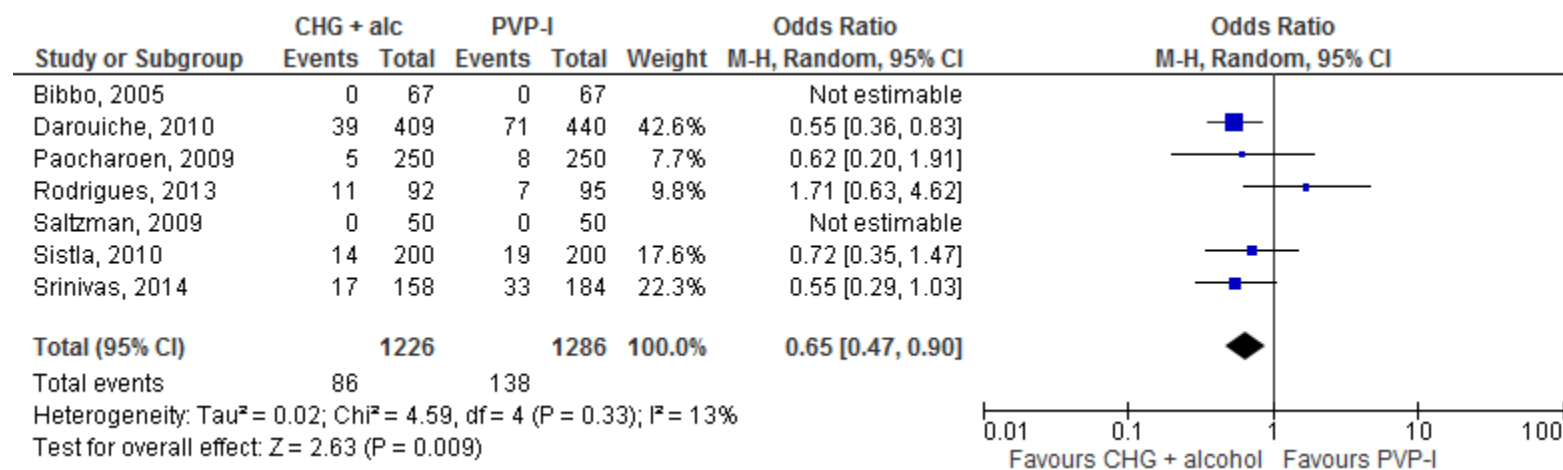
Comparison 1: Alcohol-based solutions vs. aqueous solutions - overall RCTs, outcome SSI



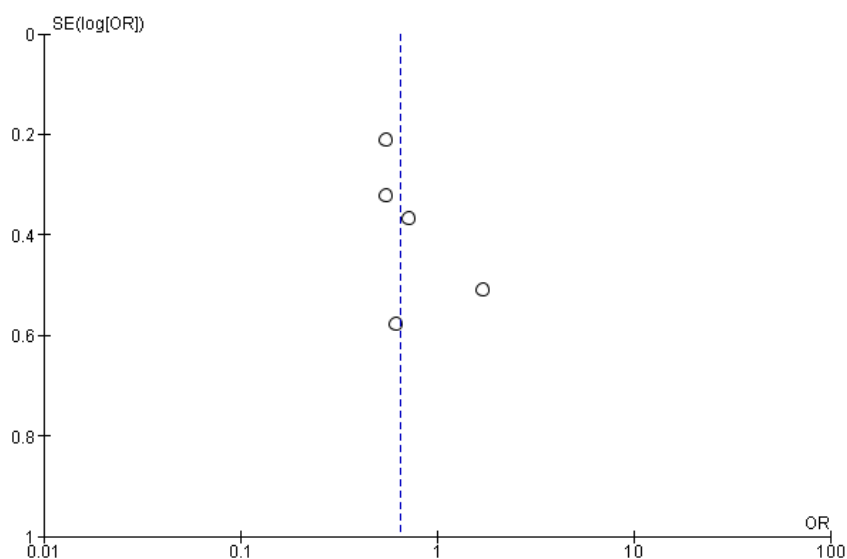
Funnel plot 1: Alcohol-based solutions vs. aqueous solutions - overall RCTs, outcome SSI



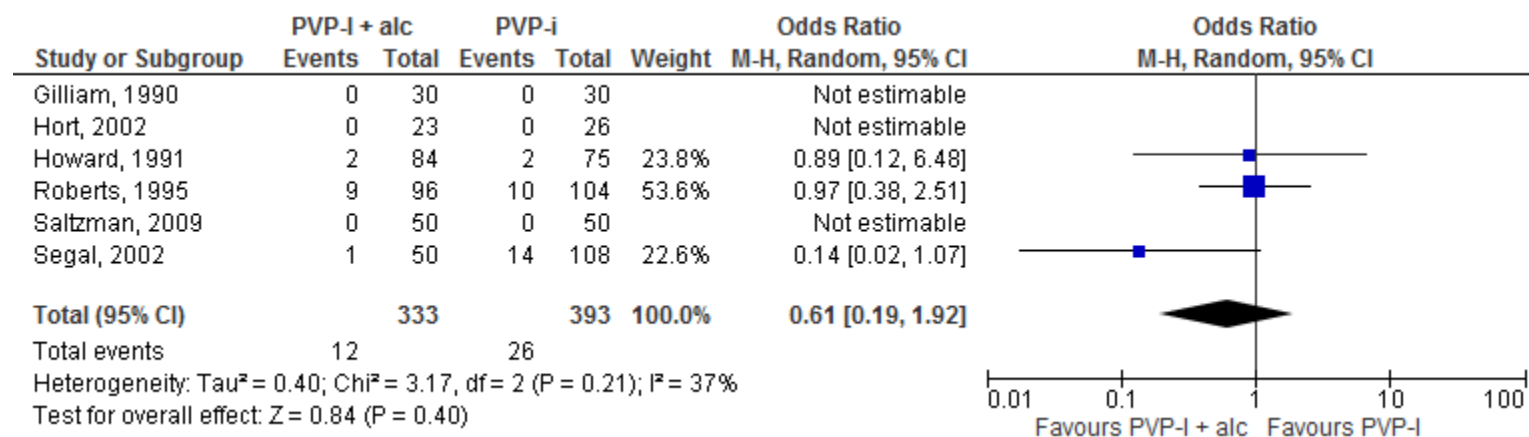
Comparison 1a: CHG + alcohol vs. aqueous PVP-I (as sub-analysis of comparison 1), outcome SSI



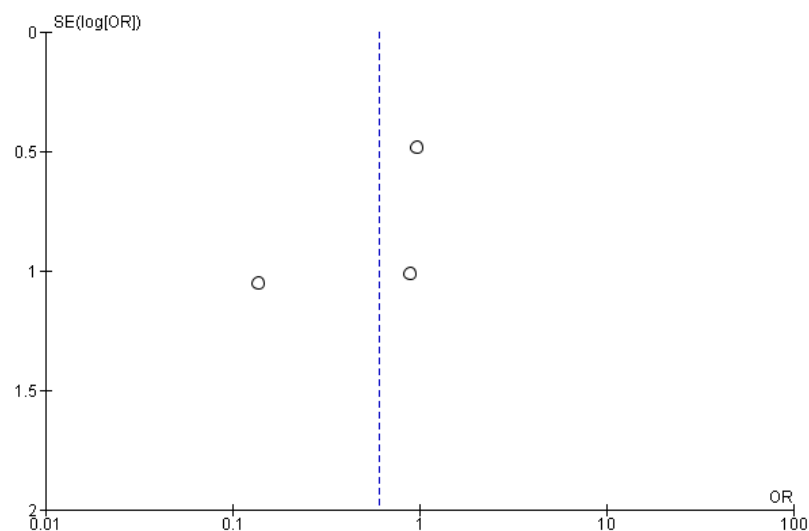
Funnel plot 1a: CHG + alcohol vs. aqueous PVP-I (as sub-analysis of comparison 1), outcome SSI



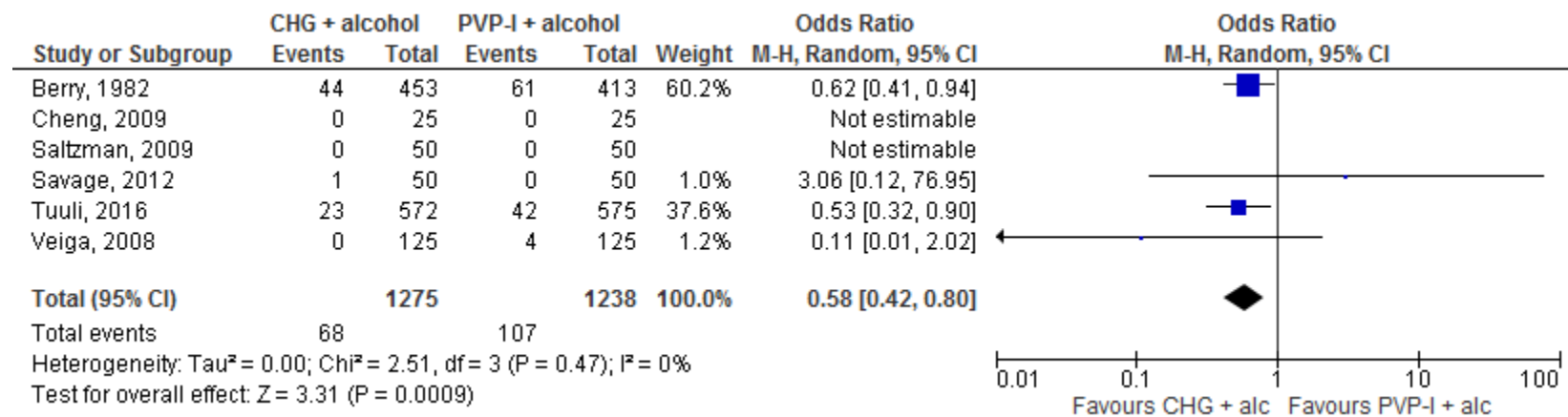
Comparison 1b: PVP-I + alcohol vs. aqueous PVP-I (as sub-analysis of comparison 1), outcome SSI



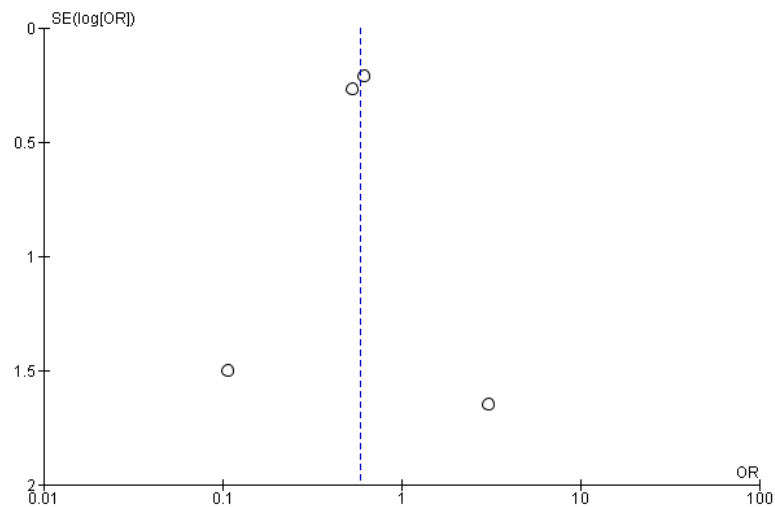
Funnel lot 1b: PVP-I + alcohol vs. aqueous PVP-I (as sub-analysis of comparison 1), outcome SSI



Comparison 2: CHG + alcohol vs. PVP-I + alcohol, outcome SSI



Funnel plot: CHG + alcohol vs. PVP-I + alcohol, outcome SSI



RCT: randomized controlled trial; SSI: surgical site infection; M-H: Mantel-Haenszel (test), CI: confidence interval; CHG: chlorhexidine gluconate; PVP-I: povidone-iodine.

Appendix 5. GRADE tables

Comparison 1: Alcohol-based solutions vs. aqueous solutions - all RCTs

Quality assessment							№ of patients		Effect		Quality
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Alcohol-based solutions	Aqueous solutions	Relative (95% CI)	Absolute (95% CI)	
Surgical site infection											
12	RCTs	serious ¹	not serious	not serious	not serious	none	94/1555 (6.0%)	168/1626 (10.3%)	OR: 0.60 (0.45-0.78)	39 fewer per 1000 (from 21 fewer to 54 fewer)	 MODERATE ¹

1. Risk of performance bias and detection bias

SSI: surgical site infection; CI: confidence interval; OR: odds ratio; RCT: randomized clinical trial

Comparison 1a: CHG in an alcohol-based solution vs. aqueous PVP-I (as sub-analysis of comparison 1)

Quality assessment							№ of patients		Effect		Quality
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CHG + alcohol	Aqueous PVP-I	Relative (95% CI)	Absolute (95% CI)	
Surgical site infection											
7	RCTs	serious ¹	not serious	not serious	not serious	none	86/1226 (7.0%)	138/1286 (10.7%)	OR: 0.65 (0.47-0.90)	35 fewer per 1000 (from 10 fewer to 54 fewer)	⊕⊕⊕○ MODERATE

1. Risk of performance and detection bias

CHG: chlorhexidine gluconate; PVP-I: iodine; CI: confidence interval; OR: odds ratio; RCT: randomized clinical trial

Comparison 1b: PVP-I in alcohol-based solution vs. aqueous PVP-I (as sub-analysis of comparison 1)

Quality assessment							№ of patients		Effect		Quality
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PVP-I + alcohol	Aqueous PVP-I	Relative (95% CI)	Absolute (95% CI)	
Surgical site infection											
6	RCTs	serious ¹	not serious	not serious	very serious ²	none	12/333 (3.6%)	26/393 (6.6%)	OR: 0.61 (0.19-1.92)	25 fewer per 1000 (from 53 fewer to 54 more)	⊕○○○ VERY LOW

1. Risk of performance and detection bias
2. Optimal information size not met and CI fails to exclude both appreciable benefit and harm (RR and RRR of 25%)

PVP-I: iodine; SSI: surgical site infection; CI: confidence interval; OR: odds ratio; RCT: randomized clinical trial.

Comparison 2: CHG in an alcohol-based solution vs. PVP-I in an alcohol-based solution

Quality assessment							№ of patients		Effect		Quality
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CHG alcohol	PVP-I alcohol	Relative (95% CI)	Absolute (95% CI)	
Surgical site infection											
6	RCTs	serious ¹	not serious	not serious	serious ²	none	68/1275 (5.3%)	107/1238 (8.6%)	OR: 0.58 (0.42-0.80)	34 fewer per 1000 (from 16 fewer to 48 fewer)	⊕⊕○○ LOW

1. Risk of performance bias and detection bias
2. Optimal information size criterion not met

CHG: chlorhexidine gluconate; PVP-I: iodine; SSI: surgical site infection; CI: confidence interval; RCT: randomized clinical trial; OR: odds ratio.

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