WHO Surgical Site Infection Prevention Guidelines

Web Appendix 10

Summary of a systematic review on surgical hand preparation

1. Introduction

Surgical site infections (SSI) are the result of multiple risk factors related to the patient, the surgeon and the health care environment. Microorganisms that cause SSI come from a variety of sources in the operating room environment, including the hands of the surgical team. Historically, surgical hand preparation (SHP) has been used to prevent SSI *(1, 2)*.

The introduction of sterile gloves does not render SHP unnecessary. Sterile gloves contribute to preventing surgical site contamination and reduce the risk of bloodborne pathogen transmission from patients to the surgical team *(3)*. However, 18% (range, 5–82%) of gloves have tiny punctures after surgery and more than 80% of cases go unnoticed by the surgeon *(4)*. In addition, even unused gloves do not fully prevent bacterial hand contamination *(5)*. Several reported outbreaks have been traced to contaminated hands from the surgical team, despite wearing sterile gloves *(6-11)*. In contrast to hygienic handwash or handrub, SHP must eliminate the transient flora and reduce the resident flora *(1)*. The aim of this preventive measure is to reduce the release of skin bacteria from the hands of the surgical team to the open wound for the duration of the procedure in case of an unnoticed puncture of the surgical glove *(12)*.

The United Kingdom (UK)-based National Institute for Health and Clinical Excellence (NICE) 2008 guideline on SSI prevention recommends that the operating team should wash their hands prior to the first operation on the list using an aqueous antiseptic surgical solution and ensure that hands and nails are visibly clean with a single-use brush or pick for the nails,. Before subsequent operations, hands should be washed using either an alcohol-based handrub (ABHR) or an antiseptic surgical solution. If hands are visibly soiled, they should be washed again with an antiseptic surgical solution. A revised version of this guideline was published in 2013 and repeats the same SHP recommendation with the addition of ensuring the removal of any hand jewellery, artificial nails and nail polish before starting surgical hand decontamination *(13, 14)*.

The Society for Healthcare Epidemiology of America (SHEA)/Infectious Diseases Society of America (IDSA) practice recommendation guideline for preventing SSIs in acute care settings was updated in 2014 and suggests using an appropriate antiseptic agent to perform the preoperative surgical scrub. For most products, scrubbing of the hands and forearms was recommended to be performed for 2–5 minutes *(15)*. However, none of the current guidelines is based on a systematic evaluation of the evidence.

A Cochrane systematic review was published in 2008 and very recently updated and published in 2016. The update included 14 randomized controlled trials (RCTs). Four trials reported SSI rates as the primary outcome, while the remaining studies

measured the numbers of colony-forming units (CFUs) on participants' hands. The main finding was that that there is no firm evidence that one type of hand antisepsis (either ABHRs or aqueous scrubs) is better than another in reducing SSI, but the quality of the evidence was considered low to very low. However, moderate or very low quality evidence showed that ABHRs with additional antiseptic ingredients may be more effective to reduce CFUs compared with aqueous scrubs *(16)*.

Given these controversial results, we decided to conduct a systematic review to identify any new evidence that would change these recommendations in terms of technique, duration and/or the product of choice.

2. PICO questions

1. What is the most effective type of product for SHP to prevent SSI?

2. What is the most effective technique and the ideal duration for SHP?

- **P**opulation: surgical team
- **I**ntervention: SHP with antiseptic soap or ABHR using a specific technique and time duration
- **C**omparator: SHP with plain soap and other medicated soaps
- **O**utcome: SSI, SSI-attributable mortality

3. Methods

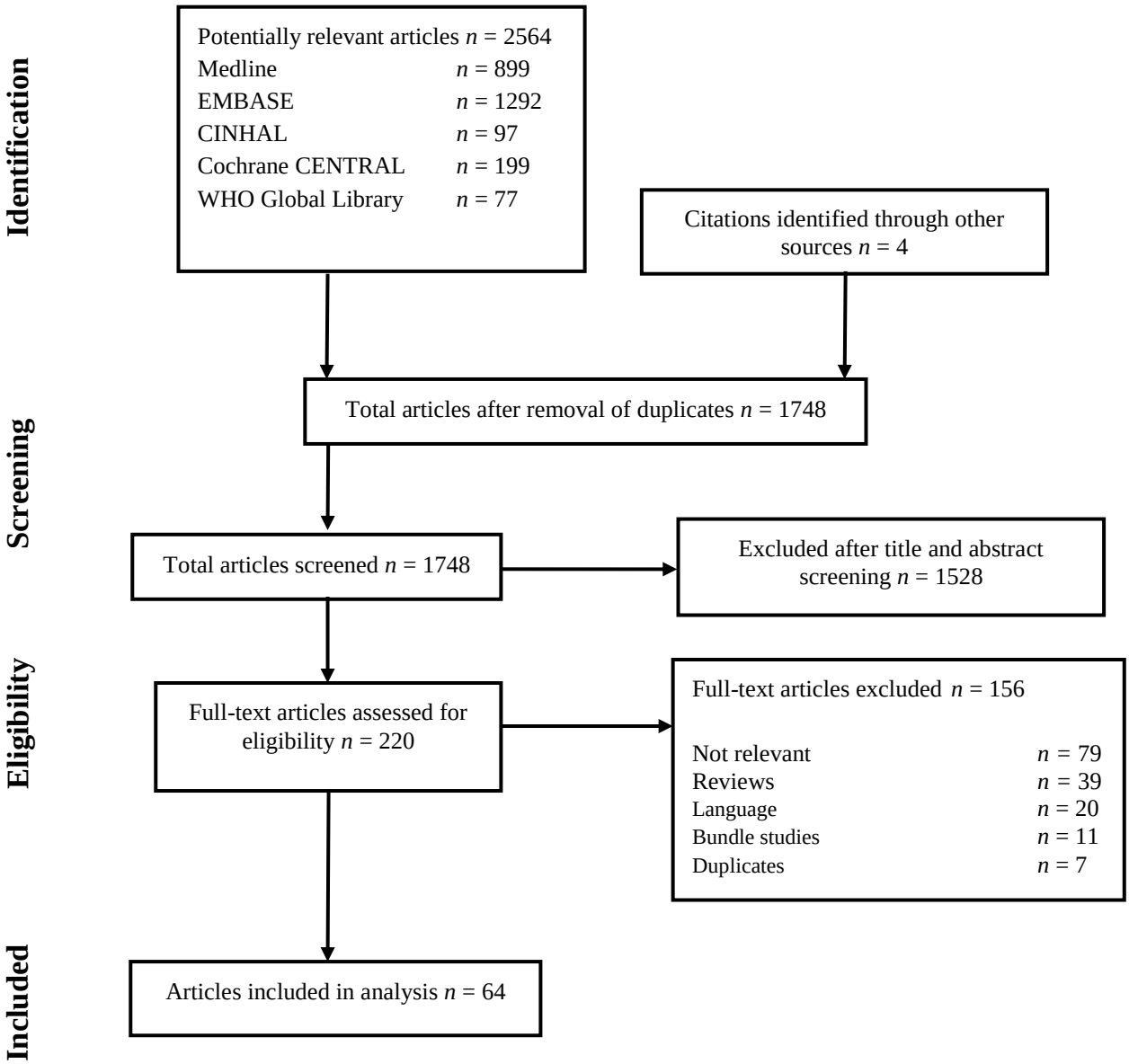
The following databases were searched: Medline (PubMed); Excerpta Medica database (EMBASE); Cumulative Index to Nursing and Allied Health Literature (CINAHL); Cochrane Central Register of Controlled Trials (CENTRAL); and the World Health Organization (WHO) Global Health Library. The time limit for the review was between 1 January 1990 and 24 April 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 (Appendix 2).

Two authors extracted data in a predefined evidence table (Appendix 3A-D) and critically appraised the retrieved studies. Quality was assessed using the Cochrane Collaboration tool to assess the risk of bias of RCTs *(17)* (Appendix 4). Any disagreements were resolved through discussion or after consultation of the senior author, when necessary. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (GRADE Pro software)*(18)* was used to assess the quality of the body of retrieved evidence (Appendix 5).

4. Study selection

Flow chart of the study selection process



5. Summary of the findings

Among the 64 studies (Appendix 2) identified, there were only 6 studies *(19-24)* with SSI as the primary outcome, including 3 RCTs *(19-21)* and 3 observational *(22-24)* (one before-after study *(23)* and 2 comparative cohorts *(22, 24)*). All 6 studies compared handrubbing to hand scrubbing for SHP. Handrubbing was performed by using either Sterilium® (Bode Chemie GmbH, Hamburg-Stellingen, Germany; 75% aqueous alcohol solution containing propanol-1, propanol-2 and mecetronium), the WHO-recommended formulation II (75% (volume/volume [v/v]) isopropyl alcohol, 1.45% (v/v) glycerol, 0.125% (v/v) hydrogen peroxide), Avagard® (3M, Maplewood,

MN, USA; 61% ethanol + 1% chlorhexidine gluconate [CHG] solution) or Purell® (Gojo Industries Inc., Akron, OH, USA; 62% ethyl alcohol as an active ingredient and water, aminomethyl propanol, isopropyl myristate, propylene glycol, glycerine, tocopheryl acetate, carbomer and fragrance as inactive ingredients). Hand scrubbing products containing either CHG or povidone-iodine (PVP-I) and/or plain soap. Five studies comparing ABHR to hand scrubbing with an antimicrobial soap containing either PVP-I 4% or CHG 4% showed no significant difference in SSI. The same result was found in a cluster, randomized, cross-over trial comparing ABHR to hand scrubbing with plain soap *(20)*. It was not possible to perform any meta-analysis of these data as the products used for handrubbing and/or hand scrubbing were different. (Appendix 3A-3B).

The primary outcome in the remaining studies (58/64) was the number of CFUs on participants' hands. The evaluation of this outcome demonstrated a great variety in terms of measurement (that is, log reduction, percentage or decrease in numbers) and/or different sampling techniques (that is, glove juice method or sampling the fingertips) and/or sampling times (that is, before and after surgery or at specific time points to evaluate the immediate and sustained effect). We identified 17 of 58 studies comparing handrub vs. hand scrub: 13 in a hospital setting and 4 in a laboratory setting. Only RCTs were included. Of a total of 8 RCTs, 6 were conducted in a hospital setting and 2 in a laboratory setting. Varying results were reported at different sampling times (that is immediate effect, sustained effect). Most studies in the hospital setting showed no significant difference, whereas the 2 RCTs in the laboratory setting showed that handrubbing was more effective than hand scrubbing in reducing the number of CFUs on participants' hands (Appendix 3C).

The only comparison we were able to make was to investigate the efficacy of a shorter duration of application than usually recommended when the same formulation and technique were used. Twelve studies addressed this question: 3 in the hospital setting and 9 in the laboratory setting. Only RCTs were included. Of a total of 5 RCTs (one in a hospital setting and 4 in a laboratory setting), all reported varying results. Although all studies used an ABHR, the product formulations differed, including the alcohol percentages (Appendix 4D). There were only 2 RCTs (one in the hospital setting and one in the laboratory setting) comparing exactly the same formulation (Sterilium®). Both studies showed an equivalence of 1.5 minutes to 3 minutes in decreasing CFUs on participants' hands (Appendix 3D).

As the product concentrations differed across the studies, a meta-analysis comparing the effectiveness of their duration could not be performed due to substantial heterogeneity and no conclusion could be drawn from these findings. There were only 2 RCTs comparing exactly the same formulations, but they were performed in different settings (one in the laboratory and the one in the hospital setting). Given the variability of the products, sampling techniques, settings and/or outcome measures, none of the identified studies was eligible for meta-analysis.

In conclusion, evidence from RCTs with an SSI outcome only was taken into account for this systematic review and was rated as moderate due to inconsistency. The overall evidence shows no difference between handrubbing and hand scrubbing in reducing SSI.

However, there are a number of limitations related to these studies. Although the systematic review also identified 58 studies conducted either in laboratory or hospital settings and evaluating participants' hand microbial colonization following SHP with different products and techniques, there was a high variability in the study setting, microbiological methods used, type of product and time of sampling. The authors decided not to take this indirect evidence into consideration when formulating the recommendation.

6. Other factors considered in the review

The systematic review team identified the following other factors to be considered.

Values and preferences

No study was found on patient values and preferences with regards to this intervention. Given that SHP is considered as best clinical practice since almost 200 years and is recommended in all surgical guidelines, the Guidelines Development Group is confident that the typical values and preferences of the target population would favour the intervention.

Studies of surgeon preferences indicate a primary preference for ABHRs. Most studies show that ABHRs are better tolerated and more acceptable to surgeons than hand scrubbing, mainly due to the decrease in time required for SHP and less skin reactions. The included studies provided some data on the acceptability and tolerability of the formulations. According to a user survey in a study conducted in Kenya *(20)*, operating room staff showed a preference for ABHR as it was quicker to use, independent of the water supply and quality and did not require drying hands with towels. No skin reactions were reported with either ABHR or plain soap and water. Parienti and colleagues *(19)* assessed 77 operating room staff for skin tolerance and found that skin dryness and irritation was significantly better in the handrubbing periods of the study. Although Al- Naami and colleagues *(21)* failed to show a significant difference, a survey of operating room staff in a Canadian SHP intervention study *(23)* showed that 97% of responders approved of the switch to handrubbing and 4 persons even noted an improvement in their skin condition. All studies reported fewer (one or none) cases of substantial dermatitis with ABHR compared to hand scrubbing. In one study, some surgeons noted occasional reversible bleaching of the forearm hair after the repeated use of handrub *(20)*.

Resource implications

Observational studies with SSI outcome showed a significant cost benefit of handrubbing. A Canadian study *(23)* showed that the standard hand scrub-related costs of direct supplies were evaluated to be approximately Can$ 6000 per year for 2000 surgical procedures, not including the cost of cleaning and sterilizing surgical towels. The actual expenses incurred after a full year of handrub use were Can$ 2531 for an annual saving of approximately Can$ 3500. A dramatic decrease in surgical towel usage (an average of 300 fewer towels per week or 1200 per period) added to the savings. Two other studies *(22, 24)* from the United States of America and the Côte d'Ivoire showed lower costs with Avagard® and Sterilium® when compared to using antiseptic-impregnated hand brushes and a PVP-I product, respectively. One of

the RCTs *(20)* included in this review also supported these findings and showed that the approximate total weekly cost of a locally-produced ABHR according to the modified WHO formula was even cheaper than plain soap and water (€ 4.60 compared to € 3.30; cost ratio 1:1.4).

Despite this evidence of the cost-effectiveness of ABHRs, they may still be very expensive with limited availability in low- and middle-income countries (LMICs), even if local production is promoted. The barriers to local production include the difficulty to identify staff with adequate skills, the need for staff training, constraints related to ingredient and dispenser procurement and a lack of adequate quality control. However, the Guidelines Development Group strongly emphasized that local production is a promising option in these circumstances. A WHO survey *(25)* in 39 health facilities from 29 countries demonstrated that the WHO ABHR formulations can be easily produced locally at low cost and are very well tolerated and accepted by health care workers. The contamination of alcohol-based solutions has seldom been reported, but the GDG highlighted the concern that top-up dispensers, which are more readily available, impose a risk for microbial contamination, particularly in LMICs. According to the WHO survey, the reuse of dispensers at several sites helped overcome difficulties caused by local shortages and the relatively high costs of new dispensers. However, such reuse may lead to handrub contamination, especially when empty dispensers are reprocessed by simple washing before being refilled. In addition, the "empty, clean, dry, then refill" strategy to avoid this risk may require extra resources.

The feasibility and costs related to the standard quality control of locally-produced products is another consideration. In the WHO survey *(25)*, 11 of 24 sites were unable to perform quality control locally due to the lack of equipment and costs. However, most sites were able to perform basic quality control with locally-purchased alcoholmeters.

The use of soap and water will require disposable towels, which add to the cost. Cloth towel reuse is not recommended in the health care setting and towels should be changed between health care workers, if necessary, thus resulting in resource implications.

7. Key uncertainties and future research priorities

The Guidelines Development Group noted that there are major research gaps and heterogeneity in the literature regarding comparisons of product efficacy and the technique and duration of scrubbing methods with SSI as the primary outcome. In particular, it would be useful to conduct RCTs in the clinical setting to compare the effectiveness of various antiseptic products with sustained activity to reduce SSI vs. ABHR or antimicrobial soap with no sustained effect. Furthermore, well-designed studies on cost-effectiveness and the tolerability/acceptability of locally-produced formulations in LMICs would be helpful. Further research is also needed to assess the interaction between products used for SHP and the different types of surgical gloves in relation to SSI outcome.

APPENDICES

Appendix 1: Search strategies

Medline (via PubMed)

#1 "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])
#2 "hand hygiene"[MeSH] OR "hand hygiene" OR "hand washing" OR handwashing OR" hand rubbing" OR handrubbing OR "hand disinfection"[Mesh] OR "hand disinfection" OR "hand antisepsis" OR "scrubbing" OR scrub OR "hand preparation" OR "alcohol-based hand rub" OR "alcohol-based handrub" 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 hand AND (disinfectants OR "antisepsis"[Mesh] OR antisepsis OR antiseptics OR detergents))
#3 Step 1 AND Step 2
#4 ("surgical procedures, operative"[Mesh] OR surgery OR surgical)
#5 "time factors"[Mesh] OR duration OR "treatment outcome"[Mesh] OR technique OR "colony count, microbial"[Mesh] or colonization [TIAB] OR transmission [TIAB] OR contamination [TIAB]
#6 Step 4 AND Step 2 AND Step 5
#7 Step 3 OR Step 6

EMBASE

#1 'surgical infection'/exp OR 'surgical site infection':ti,ab OR 'surgical site infections':ti,ab OR ssis OR 'surgical infection wound':ti,ab OR 'surgical infection wounds':ti,ab OR 'surgical infection':ti,ab OR 'postoperative wound infection':ti,ab OR 'postoperative wound infections':ti,ab OR 'post-operative wound infection':ti,ab OR 'post-operative wound infections':ti,ab OR 'wound infection':ti,ab OR 'wound infections':ti,ab
#2 'hand washing'/exp OR 'hand hygiene' OR 'hand washing' OR 'handwashing' OR 'hand rubbing' OR 'handrubbing' OR 'hand disinfection' OR 'hand antisepsis' OR 'scrubbing' OR 'scrub' OR 'hand preparation' OR 'alcohol based hand rub' OR 'alcohol based handrub' OR (('povidone iodine'/exp OR povidone OR 'iodophor'/exp OR iodophor OR iodophors OR 'iodine'/exp OR iodine OR betadine OR 'triclosan'/exp OR triclosan OR 'chlorhexidine'/exp OR chlorhexidine OR hibiscrub OR hibisol OR alcohol OR alcohols OR gel OR 'soap'/exp OR soap*:ti,ab) AND hand AND (disinfectants OR 'antisepsis'/exp OR antisepsis OR antiseptics OR detergents))
#3 'surgery'/exp OR surgery;ti,ab OR surgical:ti,ab
#4 'time'/exp OR duration OR 'treatment outcome'/exp OR technique:ti,ab OR 'bacterial count'/exp OR colonization:ti,ab OR colonisation:ti,ab OR transmission:ti,ab OR contamination:ti,ab
#5 #2 AND #3 AND #4

#6 #1 AND #2
#7 #5 OR #6

CINAHL

#1 (MH surgical wound infection) OR (AB surgical site infection* OR AB SSI OR AB SSIs OR AB surgical wound infection* OR AB surgical infection* OR AB post-operative wound infection* OR AB postoperative wound infection* OR AB wound infection*)
#2 (MH handwashing+) OR AB hand hygiene OR AB hand washing OR AB handwashing OR AB hand rubbing OR AB handrubbing OR AB disinfection OR AB antisepsis OR AB **scrubbing OR** AB **scrub OR** AB **hand preparation** OR AB alcohol-based hand rub OR AB alcohol-based handrub OR (((MH povidone-iodine) OR AB povidone OR (MH iodophors) OR AB iodophor OR AB iodophors OR (MH iodine) OR AB iodine OR AB betadine OR (MH triclosan) OR AB triclosan OR (MH chlorhexidine) OR AB chlorhexidine OR AB hibiscrub OR AB hibisol OR AB alcohol OR AB alcohols OR AB Gel OR (MH soaps) OR AB soap OR AB soaps) AND AB hand AND (AB disinfectants OR (MH antiinfective agents+) OR AB antisepsis OR AB antiseptics OR AB detergents))
#3 Step 1 AND Step 2
#4 (MH surgery, operative+) OR AB surgery OR AB surgical)
#5 (MH time factors) OR AB duration OR (MH treatment outcomes+) OR AB technique OR (MH colony count, microbial) or AB colonization OR AB transmission OR AB contamination
#6 Step 4 AND Step 2 AND Step 5
#7 Step 3 OR Step 6

Cochrane CENTRAL

#1 MeSH descriptor: [surgical wound infection] explode all trees
#2 surgical site infections or SSI or SSIs or surgical wound infection* or surgical infection* or post-operative wound infection* or postoperative wound infection* or wound infection*:ti,ab,kw (word variations have been searched)
#3 #1 or #2
#4 MeSH descriptor: [hand hygiene] explode all trees
#5 hand hygiene or hand washing or handwashing or hand rubbing or handrubbing or hand disinfection or hand antisepsis or scrub* or hand preparation or alcohol-based hand rub or alcohol-based handrub:ti,ab,kw (word variations have been searched
#6 #4 or #5
#7 MeSH descriptor: [povidone-iodine] explode all trees
#8 MeSH descriptor: [iodine] explode all trees
#9 MeSH descriptor: [iodophors] explode all trees
#10 MeSH descriptor: [chlorhexidine] explode all trees
#11 MeSH descriptor: [alcohols] explode all trees
#12 MeSH descriptor: [soaps] explode all trees
#13 MeSH descriptor: [triclosan] explode all trees

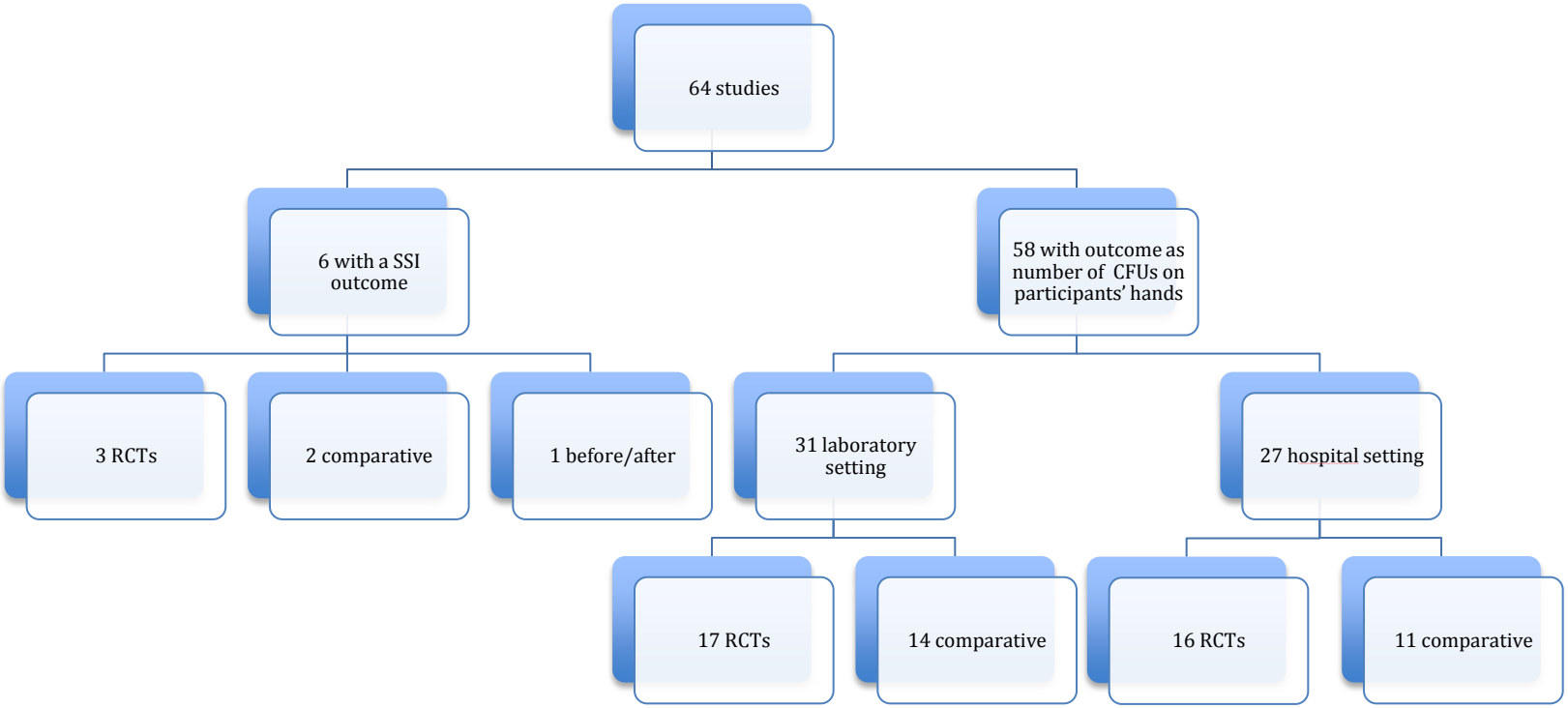
#14 povidone or iodophor or iodophors or iodine or betadine or triclosan or chlorhexidine or hibiscrub or hibisol or alcohol or alcohols or gel or soap or soaps:ti,ab,kw (word variations have been searched)
#15 MeSH descriptor: [detergents] explode all trees
#16 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15
#17 hand:ti,ab,kw
#18 MeSH descriptor: [disinfectants] explode all trees
#19 MeSH descriptor: [antisepsis] explode all trees
#20 disinfect* or antisepsis or antiseptic* or detergent*:ti,ab,kw (word variations have been searched)
#21 #18 or #19 or #20
#22 #16 and #17 and #21
#23 #6 or #22
#24 #3 and #23
#25 MeSH descriptor: [general surgery] explode all trees
#26 surgery or surgical:ti,ab,kw (word variations have been searched)
#27 #25 or #26
#28 MeSH descriptor: [colony count, microbial] explode all trees
#29 MeSH descriptor: [time factors] explode all trees
#30 MeSH descriptor: [treatment uutcome] explode all trees
#31 duration or technique or colonization or transmission or contamination:ti,ab,kw (word variations have been searched)
#32 #28 or #29 or #30 or #31
#33 #23 and #27 and #32
#34 #24 or #33

WHO Global Health Library

((ssi) OR (surgical site infection) OR (surgical site infections) OR (wound infection) OR (wound infections)) AND ((hand) OR (scrub) OR (scrubbing))

ti: title; ab: abstract;

Appendix 2: Distribution of the selected studies



SSI: surgical site infection; RCT: randomized controlled trial; CFU: colony-forming units.

Appendix 3: Evidence table

3A. RCTs with SSI outcome

Author, year, reference	Country/ study period	Type of study/ setting	Intervention	Comparator	Primary outcome - SSI rate	Difference between groups	Cost analysis
Parienti 2002 [19]	France, 16 months	Multicentre randomized equivalence trial	Handrubbing protocol with ABHR (Sterilium®) for 5 minutes (n=2252)	Hand scrubbing with PVI 4% or CHG 4% for 5 minutes (n=2135)	2.44% handrub group; 2.48% hand scrub group	OR: 0.04% (95% CI: 0.88-0.96) **NS difference**	
Nthumba 2010 [20]	Kenya, 11 months	Longitudinal comparative cluster randomized cross-over trial in a rural hospital	ABHR procedure with WHO formula II for 3 minutes (n=1537)	Hand scrubbing with plain soap and water for 4-5 minutes (n=1596)	8.3% in ABHR (95% CI: 6.7-9.5) 8.0% plain soap & water group (95% CI: 6.9-9.8)	Crude OR: 1.03 (95% CI: 0.80-1.33; *P*=0.804) **NS difference**	The approximate total weekly cost of ABHR was € 4.60 compared with € 3.30 for plain soap and water (cost ratio: 1:1·4).
Al-Naami 2009 [21]	Saudi Arabia, 9 months	Randomized equivalence trial in a university hospital	Handrubbing with alcohol-based hand gel (Purell ®) (n=272)	Hand scrubbing with PVP-I 4% or CHG 4% 3-5 minutes (n=228)	2.94% in ABHR; 5.26% in traditional hand scrub group	OR: 1.833, (95% CI 0.683-5.007; *P*= 0.275) **NS difference**	

* RCT: randomized controlled trial; SSI: surgical site infection; ABHR: alcohol-based handrub; Sterilium®: 75% aqueous alcohol solution, propanol-1, propanol-2 and mecetronium; WHO-recommended formulation II: 75% (v/v) isopropyl alcohol, 1.45% (v/v) glycerol, 0.125% (v/v) hydrogen peroxide); Purell ®: 62% ethyl alcohol as an active ingredient; water, aminomethyl propanol, isopropyl myristate, propylene glycol, glycerine, tocopheryl acetate, carbomer and fragrance (perfume) as inactive ingredients; PVI: povidone-iodine; CHG: chlorhexidine gluconate; CI: confidence interval; OR: odds ratio; NS: not significant.

3B: Observational studies with SSI outcome

Authors, year, reference	Country/ study period	Type of study/ setting	Intervention	Comparator	Primary outcome - SSI rate	Difference between groups	Cost analysis
Weight 2010 [22]	USA Study period not stated	Retrospective comparative study in a paediatric urology clinic	Handrubbing protocol with Avagard®* for 2 minutes (n=1800)	Hand scrubbing with antiseptic-impregnated hand brush for 6 minutes (n=1800)	0.11% handrub group; 0.17% hand scrub group	**NS difference (*P*>.99)**	Avagard® costs US$ 0.59 per application; antiseptic-impregnated hand brushes cost US$ 1.04 per application.
Marchand 2008 [23]	Canada 2 years	Retrospective observational before/after study in a heart institute, cardiovascular surgery patients	Handrubbing with ethyl alcohol 70%/ CHG 0.5% hand rub rinse (n=2174)	Hand scrubbing with antiseptic detergent (n=2084)	3.59% handrub group 3.33 % hand scrub group	**NS difference****	Standard hand scrub = Can$ 6000/year for 2000 surgical procedures Handrub = Can$ 2531/year for an annual saving of approximately Can$ 3500.
Adjoussou 2009 [24]	Côte d'Ivoire 5 months	Comparative study in a university hospital, gynaecology patients	Handrubbing with Sterilium® (n=113)	Hand scrubbing with PVP-I (n=205)	11.5% handrub group 13.2% traditional hand scrub group	**NS difference (*P*=0.8)**	1 dose of PVP-I= € 0.2, 1 dose of ABHR= € 0.1

* Avagard®: 61% ethanol and 1% CHG ; ** *P* not provided.
SSI: surgical site infection; CHG: chlorhexidine gluconate; PVI: povidone iodine. ABHR: alcohol-based handrub; NS: not significant.

3C: RCTs: handrub vs. hand scrub with the number of CFUs on participants' hands as outcome

Authors, year, reference	Country/type of study/ setting	Intervention	Comparator	Sampling technique	Primary outcome - CFU on participants' hands	Difference between groups	Cost analysis
HOSPITAL SETTING							
Gupta 2007 *(26)* ¥ 2007	USA RCT in hospital setting 18 participants	Handrubbing with Avagard®	Hand scrubbing with PVI*	Glove juice method 6 hours after scrub, on days 1, 2 and 5.	Mean CFU log reduction 0.8 ±0.21 with rub; 1.7± 0.87 with scrub	**NS difference at any time**	
Hajipour 2006 *(27)*	UK RCT in hospital setting (orthopaedic surgeons) 41 procedures	Handrubbing: 5 minutes with CHG for their first case, then 3 minutes with **alcohol-based gel**	Hand scrubbing:5 minutes with CHG for their first case, then 3 minutes with **CHG***	Fingerprints before/after surgery.	34% (n=19) in the ABHR group. 8% (n=4) were contaminated in the CHG group (positive CFUs after 48 hours). Average CFU count: ABHR 20; CHG 5 (*P* not provided).	**Scrub>rub (*P* =0.002)**	
Larson 2001 *(28)*¥	USA RCT in hospital setting 25 participants	Handrubbing with Avagard® for 2 minutes	Hand scrubbing with CHG 4% for 6 minutes	Glove juice method on days 1,5 and 19.	Post-scrub mean log CFU reduction: 3.09± 0.54 on day 5; 3.43± 0.98 on day 19 with rub; 3.68± 0.8 on day 5; 4.09± 1.29 on day 19 with scrub (*P*=0.002 and *P*=0.02 respectively).	**NS difference except at the 2 specified times**	Total cost per application time US$ 60.38-60.50 for scrub; US$ 20.40-20.52 for rub.
Ghorbani 2012 *(29)* ¥	Iran RCT in hospital setting 33 participants	Handrubbing with ethanol 70% for 3 minutes	Hand scrubbing with PVI* for 6 minutes	Swab from the fingertips before and after wash and after 30 seconds of glove use.	Mean CFU log reduction 0.47 ±0.27 with rub; 0.5± 0.48 with scrub immediate effect.	**NS difference *P*=0.53**	

Authors, year, reference	Country/type of study/ setting	Intervention	Comparator	Sampling technique	Primary outcome - CFU on participants' hands	Difference between groups	Cost analysis
Chen 2012 *(30)*	Taiwan RCT in hospital setting 50+50 participants	Handrubbing with Avagard® for 3 minutes	Hand scrubbing with PVI or CHG in isopropyl 70% for 5 minutes	Fingerprints immediate after application.	Microorganism CFU counts of 1-9 CFU were detected in 7/50 plates in the rub group, and counts of 1-5 CFU were detected in 7/50 plates in the scrub group.	**NS difference** (OR: 1; 95% CI: 0.85-1.71; *P*=1.00)	
Pietsch 2001 *(31)*	Switzerland RCT with cross-over design in hospital setting 60 participants	Handrubbing with Sterilium®	Hand scrubbing with CHG 4%	Bag broth technique followed by glove juice method pre- and post-surgery.	Mean CFU log reduction 2.4 ±0.13 with rub; 1.3± 0.12 with scrub immediate effect.	**Rub>scrub** ***P* <0.001 immediate effect** **NS difference after surgery**	
LABORATORY SETTING							
Rotter 2006 *(32)*¥	Austria, RCT multicentre laboratory setting 100 healthy volunteers	Handrubbing with propan-2-OL (70% by volume; ispropanol 70%) or ethanol 85% or propan-1-OL 60%	Hand scrubbing with CHG 4%	Fingerprints immediately after application.	Mean log CFU reduction (that is, the mean of the mean values for all laboratories and both hands) was obtained with the CHG-containing product (1.1 ± 0.3 CFU/mL), isopropanol 70% (1.7 ±0.3 CFU/mL) and ethanol 85% (2.1 ± 0.3 CFU/mL) and with propan-1-OL 60% (2.4 ±0.4 CFU/mL).	**Rub>scrub** ***P* ≤ 0.001**	

Authors, year, reference	Country/type of study/ setting	Intervention	Comparator	Sampling technique	Primary outcome - CFU on participants' hands	Difference between groups	Cost analysis
Mulberrry 2001 *(33)*¥ **STUDY A**	USA RCT prospective, randomized, partially blinded, parallel group trial 52 healthy volunteers	Handrubbing with the CHG/ethanol hand preparation or CHG 4%	Hand scrubbing with CHG 4%	Glove juice technique at 1 minute, 3 hours, and 6 hours after application on days 1, 2 and 5.	Mean log CFU reduction immediate effect: rub 2.5; scrub 1.8.	**Rub>scrub at all times when 2 studies combined (*P* not provided)**	
Mulberry 2001 *(33)* **STUDY B**	USA RCT prospective, randomized, partially blinded, parallel-group trial 33+30+20 healthy volunteers	Handrubbing with the CHG/ethanol hand preparation, or an ethanol 61% vehicle control	Hand scrubbing with CHG 4%	Glove juice technique at 1 minute, 3 hours and 6 hours after application on days 1,2 and 5.	Mean log CFU reduction immediate effect with CHG ethanol: 2.6 and 1.6 with scrub; 1.1 with vehicle.	**Rub>scrub when 2 studies combined (*P* not provided)**	

* CHG: chlorhexidine gluconate; Avagard®: 61% ethanol and 1% CHG; Sterilium®: 75% aqueous alcohol solution, propanol-1, propanol-2, and mecetronium; RCT: randomized controlled trial; UK: United Kingdom; USA: United States of America; CFU: colony-forming unit; PVP-I: povidone iodine; NS: not significant.

¥The studies included in the grade tables with the same outcome measure and NS results. Individual studies have not been graded.

3D: RCTs comparing different application times with the number of CFUs on participants' hands as outcome

Authors, year reference	Type of study/ setting	Intervention	Comparator	Sampling technique	Primary outcome - CFU on participants' hands	Difference between groups
HOSPITAL SETTING						
Weber 2009 *(34)*¥	Switzerland RCT with crossover design 32 participants	Handrubbing with Sterilium® for 1.5 minutes	3 minutes	Fingerprints of both hands immediately after scrub and after surgery.	Mean (±SD) log10 CFU RFs immediately after application were **2.66±1.13 for the 1.5-minute group 3.01±1.06 for the 3-minute group (***P*= 0.204). Sustained effect values were a mean (±SD) increase of 1.08 ± 1.13 log10 CFU in the 1.5-minute group; 0.95±1.27 log10 CFU in the 3-minute group (*P* =0.708).	**NS difference**
LABORATORY SETTING						
Suchomel 2009 *(35)*¥	Austria RCT 21 healthy volunteers	Handrubbing with Sterilium® for 1.5 minutes	3 minutes	Fingerprints: one hand immediately, the other after 3 hours of glove use.	Mean (±SD) log10 CFU RF immediately after application were 2**.86±1.3 for the 1.5-minute group; 3.43±1.23 for the 3-minute** group. Sustained effect values: log10 CFU RF of 1.66 ± 0.79 in the 1.5-minute group; 2.16±1.23 log10 CFU in the 3-minute group.	**NS difference *P*>0.05**
Suchomel 2009 *(36)*	Austria RCT 21 healthy volunteers	Handrubbing with isopropanol 70% v/v or n-propanol 60% v/v for 1 minute	3 or 5 minutes	Fingerprints: one hand immediately, the other after 3 hours of glove use.	**Immediate** mean log10 RFs with n-propanol or isopropanol were **1.05, 2.03 and 2.30** and **0.74, 1.48 and 2.1**2, respectively, when applied for **1, 3 or 5 minutes**, respectively. After 3 hours, the respective mean log10 RFs were 0.45, 1.01 and 1.60 and 0.19, 0.79 and 1.03.	**Highly significant trend with increasing length of application *P*<0.001**

Authors, year reference	Type of study/ setting	Intervention	Comparator	Sampling technique	Primary outcome - CFU on participants' hands	Difference between groups
Suchomel 2011 [37]	Austria, RCT 20 healthy volunteers	Rubbing with ethanol 85% for 3 minutes	5 minutes	Fingerprints: one hand immediately, the other after 3 hours of glove use	3- and 5-minute log 10 RFs: 2.90±1.07 and 3.12±0.87, for 3 and 5 minutes, respectively, for immediate effect. Sustained effect: 1.78± 0.79 and 1,35 ± 0.82, respectively.	NS difference *P*>0.1
Babb 1991 [38]	UK, RCT cross-over design 24 healthy volunteers	Rubbing with isoproponol 70% for 30 seconds (after a 30-second hand wash with unmedicated soap)	2 minutes	Glove (with loose fitting gloves) juice method at baseline (3 times every 48 hours) after scrub and after 3 hours gloved	A 2-minute application of isopropyl alcohol 70% - log10 CFU reductions for immediate effect: 1.65 and 1.50 for 2 minutes and 30 seconds, respectively. Prolonged effect: 1.58 and 1.24, respectively.	NS difference (*P* not provided)

¥The studies comparing exactly the same product with the same outcome measure are included in the grade tables.
RCT: randomized controlled trial; CFU: colony-forming units; RF: reduction factor; NS: not significant; SD: standard deviation; v/v: volume/volume; UK: United Kingdom

Appendix 4: Risk of bias assessment

Author, year, reference	Sequence generation	Allocation concealment	Participants blinded*	Care providers blinded	Outcome assessors blinded	Incomplete outcome data	Selective outcome reporting	Other sources of bias
RCTs comparing handrubbing vs. hand scrubbing with SSI outcome								
Parienti 2002 *(19)*	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk	-
Nthumba 2010 *(20)*	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk	-
Al-Naami 2009 *(21)*	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk	-
RCTs comparing an application of 1.5 minute vs. 3 minutes of the same ABHR with the number of CFUs on participants' hands as outcome								
Weber 2009 *(34)*	Low risk	Low risk	High risk	N/A	Unclear	Low risk	Low risk	**
Suchomel 2009 *(35)*	Low risk	Low risk	High risk	N/A	Unclear	Low risk	Low risk	**

*Blinding participants is impossible in these studies as the intervention and comparator are significantly different in nature (that is, ABHR vs. soap or PVP-I or CHG and different durations of the same ABHR)

**Potential reporting bias was suspected as both studies tested Sterilium®, which was the commercially available product at the time. However; they clearly state a conflict of interest in the studies. First (Weber), was funded partially by the University of Basel and Bode Chemie, but they clearly state that industry had no role in any aspect of the study, and the second (Suchomel) was not funded at all. Of note, neither of the studies are a superiority trial as they tested the efficacy of different durations of the same product. Therefore, reporting bias is highly unlikely.

RCT: randomized controlled trial; SSI: surgical site outcome; PVP-I: povidone-iodine; CHG: chlorhexidine gluconate; ABHR: alcohol-based hand rub; CFU: colony-forming units; N/A: not applicable.

Appendix 5: Grade tables

Studies with SSI outcome

Should handrubbing or hand scrubbing be used to reduce SSI?

Quality assessment							№ of patients		Effect		Quality
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**With handrubbing**	**With handscrubbing**	**Relative (95% CI)**	**Absolute (95% CI)**	
Surgical site infection											
3	RCTs	Not serious	Serious [1]	Not serious	Not serious	None	190/4061 (4.7%)	193/3959 (4.9%)	Not pooled	See comment	⊕⊕⊕◯ MODERATE
SSI											
1	Observational studies, (before-after study)	Serious [2]	Not serious	Not serious	Not serious	None	78/2175 (3.6%)	69/2084 (3.3%)	Not pooled	See comment	⊕◯◯◯ VERY LOW
SSI											
2	Observational studies , (comparative cohorts)	Serious [3]	Serious [4]	Not serious	Not serious	None	15/1913 (0.8%)	30/2005 (1.5%)	Not pooled	See comment	⊕◯◯◯ VERY LOW

1. Sampling technique, time and primary outcome measure are all extremely variable.
2. Marchand (2008): the data before the intervention were collected retrospectively and serious confounding was suspected.
3. Weight (2010): retrospective design and selection of groups based on availability of the product - serious confounding suspected; no clear follow-up period. Adjoussou (2009): reporting bias suspected.
4. One study from the USA with a very low SSI rate, the other is from Africa with a higher SSI rate, but a very small sample size.

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

Studies with CFU outcome

Should handrubbing or hand scrubbing be used to reduce CFUs on participants' hands for an immediate or sustained effect?

Quality assessment							№ of patients		Effect		Quality
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**With handrubbing**	**With hand scrubbing**	**Relative (95% CI)**	**Absolute (95% CI)**	
Log reduction of CFUs on participants' hands in a hospital setting (better indicated by higher values)											
3 [1]	RCTs	Not serious	Serious [2]	Very serious [3]	Not serious	none	60	58	-	Mean ranged from 0.47 to 3.43 higher	⨁◯◯◯ VERY LOW
Log reduction of CFUs on participants' hands in a laboratory setting (better indicated by higher values)											
2 [4]	RCTs	Not serious	Serious	Very serious [3]	Not serious	none	170	100	-	Mean ranged from 1.7 to 2.6 higher	⨁◯◯◯ VERY LOW

1. Included studies are Gupta (2007), Larson (2009) and Ghorbani (2012).
2. Sampling technique, time and primary outcome measure are all extremely variable.
3. All studies measured CFU on participants' hands (surrogate outcome) whereas our primary outcome measure is the SSI rate. The association between the reduction in CFUs and SSI rate has not been shown yet.
4. Included studies are Rotter (2006) and Mulberry (2001).

CFU: colony-forming unit; RCT: randomized controlled trial; OR: odds ratio; CI: confidence interval.

Should 1.5 minutes vs. 3 minutes be used for handrubbing to reduce CFUs on participants' hands for an immediate or sustained effect?

Quality assessment							№ of patients		Effect		Quality
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**With 1.5 minutes**	**With 3 minutes**	**Relative (95% CI)**	**Absolute (95% CI)**	
Log reduction of CFUs on participants' hands in a hospital setting (better indicated by higher values)											
1 [1]	RCTs	Not serious	Not serious	Very serious [2]	Not serious	None	32	32	-	Mean ranged from 1.53 to 3.79 higher	⨁⨁◯◯ LOW
Log reduction of CFUs on participants' hands in a laboratory setting (better indicated by higher values)											
1 [3]	RCTs	Not serious	Not serious	Very serious [2]	Not serious	None	21	21	-	Mean ranged from 1.56 to 4.16 higher	⨁⨁◯◯ LOW

1. Included study is Weber (2009).
2. Surrogate outcome.
3. Included study is Suchomel (2009).

CFU: colony-forming unit; RCT: randomized controlled trial; OR: odds ratio; CI: confidence interval; CFU: colony-forming unit.

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