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 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?

- Population: surgical team
- Intervention: SHP with antiseptic soap or ABHR using a specific technique and time duration
- Comparator: SHP with plain soap and other medicated soaps
- Outcome: 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,
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"[Mesh] OR duration OR "treatment outcome"[Mesh] OR technique OR "bacterial count"[Mesh] OR colonization OR transmission 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 '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 'soaps'/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
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 iodo phors 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 outcome] 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

64 studies

- 6 with a SSI outcome
  - 3 RCTs
  - 2 comparative
  - 1 before/after

- 58 with outcome as number of CFUs on participants' hands
  - 31 laboratory setting
    - 17 RCTs
    - 14 comparative
  - 27 hospital setting
    - 16 RCTs
    - 11 comparative

SSI: surgical site infection; RCT: randomized controlled trial; CFU: colony-forming units.
Appendix 3: Evidence table

3A. RCTs with SSI outcome

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

* RCT: randomized controlled trial; SSI: surgical site infection; ABHR: alcohol-based handrub; Sterilium®: 75% aqueous alcohol solution, propanol-1, propanol-2 and mecteronium; 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

<table>
<thead>
<tr>
<th>Authors, year, reference</th>
<th>Country/study period</th>
<th>Type of study/setting</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Primary outcome - SSI rate</th>
<th>Difference between groups</th>
<th>Cost analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight 2010 (22)</td>
<td>USA</td>
<td>Retrospective comparative study in a paediatric urology clinic</td>
<td>Handrubbing protocol with Avagard®* for 2 minutes (n=1800)</td>
<td>Hand scrubbing with antiseptic-impregnated hand brush for 6 minutes (n=1800)</td>
<td>0.11% handrub group; 0.17% hand scrub group</td>
<td>NS difference (<em>P &gt; .99</em>)</td>
<td>Avagard® costs US$ 0.59 per application; antiseptic-impregnated hand brushes cost US$ 1.04 per application.</td>
</tr>
<tr>
<td>Marchand 2008 (23)</td>
<td>Canada</td>
<td>Retrospective observational before/after study in a heart institute, cardiovascular surgery patients</td>
<td>Handrubbing with ethyl alcohol 70%/CHG 0.5% hand rub rinse (n=2174)</td>
<td>Hand scrubbing with antiseptic detergent (n=2084)</td>
<td>3.59% handrub group; 3.33% hand scrub group</td>
<td>NS difference**</td>
<td>Standard hand scrub = Can$ 6000/year for 2000 surgical procedures Handrub = Can$ 2531/year for an annual saving of approximately Can$ 3500.</td>
</tr>
<tr>
<td>Adjoussou 2009 (24)</td>
<td>Côte d'Ivoire</td>
<td>Comparative study in a university hospital, gynaecology patients</td>
<td>Handrubbing with Sterilium® (n=113)</td>
<td>Hand scrubbing with PVP-I (n=205)</td>
<td>11.5% handrub group; 13.2% traditional hand scrub group</td>
<td>NS difference (<em>P = 0.8</em>)</td>
<td>1 dose of PVP-I= € 0.2, 1 dose of ABHR= € 0.1</td>
</tr>
</tbody>
</table>

* 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

<table>
<thead>
<tr>
<th>Authors, year, reference</th>
<th>Country/type of study/ setting</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Sampling technique</th>
<th>Primary outcome - CFU on participants' hands</th>
<th>Difference between groups</th>
<th>Cost analysis</th>
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</thead>
<tbody>
<tr>
<td>Gupta 2007 (26)¹ 2007</td>
<td>USA RCT in hospital setting 18 participants</td>
<td>Handrubbing with Avagard®</td>
<td>Hand scrubbing with PVI*</td>
<td>Glove juice method 6 hours after scrub, on days 1, 2 and 5.</td>
<td>Mean CFU log reduction 0.8 ±0.21 with rub; 1.7± 0.87 with scrub</td>
<td>NS difference at any time</td>
<td></td>
</tr>
<tr>
<td>Hajipour 2006 (27)</td>
<td>UK RCT in hospital setting (orthopaedic surgeons) 41 procedures</td>
<td>Handrubbing: 5 minutes with CHG for their first case, then 3 minutes with alcohol-based gel</td>
<td>Hand scrubbing:5 minutes with CHG for their first case, then 3 minutes with CHG*</td>
<td>Fingerprints before/after surgery.</td>
<td>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).</td>
<td>Scrub&gt;rub (P =0.002)</td>
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<tr>
<td>Larson 2001 (28)¹ 2001</td>
<td>USA RCT in hospital setting 25 participants</td>
<td>Handrubbing with Avagard® for 2 minutes</td>
<td>Hand scrubbing with CHG 4% for 6 minutes</td>
<td>Glove juice method on days 1,5 and 19.</td>
<td>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).</td>
<td>NS difference except at the 2 specified times</td>
<td>Total cost per application time US$ 60.38-60.50 for scrub; US$ 20.40-20.52 for rub.</td>
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<tr>
<td>Ghorbani 2012 (29)¹ 2012</td>
<td>Iran RCT in hospital setting 33 participants</td>
<td>Handrubbing with ethanol 70% for 3 minutes</td>
<td>Hand scrubbing with PVI* for 6 minutes</td>
<td>Swab from the fingertips before and after wash and after 30 seconds of glove use.</td>
<td>Mean CFU log reduction 0.47 ±0.27 with rub; 0.5± 0.48 with scrub immediate effect.</td>
<td>NS difference P=0.53</td>
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<tr>
<td>Authors, year, reference</td>
<td>Country/type of study/setting</td>
<td>Intervention</td>
<td>Comparator</td>
<td>Sampling technique</td>
<td>Primary outcome - CFU on participants’ hands</td>
<td>Difference between groups</td>
<td>Cost analysis</td>
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<tr>
<td>Chen 2012 (&lt;sup&gt;30&lt;/sup&gt;)</td>
<td>Taiwan RCT in hospital setting 50+50 participants</td>
<td>Handrubbing with Avagard® for 3 minutes</td>
<td>Hand scrubbing with PVI or CHG in isopropyl 70% for 5 minutes</td>
<td>Fingerprints immediate after application.</td>
<td>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.</td>
<td>NS difference (OR: 1; 95% CI: 0.85-1.71; <em>P</em>=1.00)</td>
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<td>Pietsch 2001 (&lt;sup&gt;31&lt;/sup&gt;)</td>
<td>Switzerland RCT with cross-over design in hospital setting 60 participants</td>
<td>Handrubbing with Sterilium®</td>
<td>Hand scrubbing with CHG 4%</td>
<td>Bag broth technique followed by glove juice method pre- and post-surgery.</td>
<td>Mean CFU log reduction 2.4 ±0.13 with rub; 1.3± 0.12 with scrub immediate effect.</td>
<td>Rub&gt;scrub <em>P</em> &lt;0.001 immediate effect NS difference after surgery</td>
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<tr>
<td>Rotter 2006 (&lt;sup&gt;32&lt;/sup&gt;)</td>
<td>Austria, RCT multicentre laboratory setting 100 healthy volunteers</td>
<td>Handrubbing with propan-2-OL (70% by volume; isopropanol 70%) or ethanol 85% or propan-1-OL 60%</td>
<td>Hand scrubbing with CHG 4%</td>
<td>Fingerprints immediately after application.</td>
<td>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).</td>
<td>Rub&gt;scrub <em>P</em> ≤ 0.001</td>
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</table>

**LABORATORY SETTING**
<table>
<thead>
<tr>
<th>Authors, year, reference</th>
<th>Country/type of study/setting</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Sampling technique</th>
<th>Primary outcome - CFU on participants’ hands</th>
<th>Difference between groups</th>
<th>Cost analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mulberry 2001 (336)</td>
<td>USA RCT prospective, randomized, partially blinded, parallel group trial</td>
<td>52 healthy volunteers</td>
<td>Handrubbing with the CHG/ethanol hand preparation or CHG 4%</td>
<td>Hand scrubbing with CHG 4%</td>
<td>Glove juice technique at 1 minute, 3 hours, and 6 hours after application on days 1, 2 and 5.</td>
<td>Mean log CFU reduction immediate effect: rub 2.5; scrub 1.8.</td>
<td>Rub&gt;scrub at all times when 2 studies combined (P not provided)</td>
</tr>
<tr>
<td>Mulberry 2001 (335)</td>
<td>USA RCT prospective, randomized, partially blinded, parallel-group trial</td>
<td>33+30+20 healthy volunteers</td>
<td>Handrubbing with the CHG/ethanol hand preparation, or an ethanol 61% vehicle control</td>
<td>Hand scrubbing with CHG 4%</td>
<td>Glove juice technique at 1 minute, 3 hours and 6 hours after application on days 1.2 and 5.</td>
<td>Mean log CFU reduction immediate effect with CHG ethanol: 2.6 and 1.6 with scrub; 1.1 with vehicle.</td>
<td>Rub&gt;scrub when 2 studies combined (P not provided)</td>
</tr>
</tbody>
</table>

* CHG: chlorhexidine gluconate; Avagard®: 61% ethanol and 1% CHG; Sterilium®: 75% aqueous alcohol solution, propanol-1, propanol-2, and meccronium; 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

<table>
<thead>
<tr>
<th>Authors, year reference</th>
<th>Type of study/setting</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Sampling technique</th>
<th>Primary outcome - CFU on participants’ hands</th>
<th>Difference between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HOSPITAL SETTING</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Weber 2009 (&lt;sup&gt;[34]&lt;/sup&gt;) Switzerland</td>
<td>RCT with crossover design</td>
<td>Handrubbing with Sterilium® for 1.5 minutes</td>
<td>3 minutes</td>
<td>Fingerprints of both hands immediately after scrub and after surgery.</td>
<td>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).</td>
<td>NS difference</td>
</tr>
<tr>
<td><strong>LABORATORY SETTING</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suchomel 2009 (&lt;sup&gt;[35]&lt;/sup&gt;) Austria</td>
<td>RCT</td>
<td>Handrubbing with Sterilium® for 1.5 minutes</td>
<td>3 minutes</td>
<td>Fingerprints: one hand immediately, the other after 3 hours of glove use.</td>
<td>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.</td>
<td>NS difference P&gt;0.05</td>
</tr>
<tr>
<td>Suchomel 2009 (&lt;sup&gt;[36]&lt;/sup&gt;) Austria</td>
<td>RCT</td>
<td>Handrubbing with isopropanol 70% v/v or n-propanol 60% v/v for 1 minute</td>
<td>3 or 5 minutes</td>
<td>Fingerprints: one hand immediately, the other after 3 hours of glove use.</td>
<td>Immediate Mean log10 RFs with n-propanol or isopropanol were 1.05, 2.03 and 2.30 and 0.74, 1.48 and 2.12, 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.</td>
<td>Highly significant trend with increasing length of application P&lt;0.001</td>
</tr>
<tr>
<td>Authors, year reference</td>
<td>Type of study/setting</td>
<td>Intervention</td>
<td>Comparator</td>
<td>Sampling technique</td>
<td>Primary outcome - CFU on participants’ hands</td>
<td>Difference between groups</td>
</tr>
<tr>
<td>-------------------------</td>
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<td>---------------------------------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>Suchomel 2011 (37)</td>
<td>Austria, RCT</td>
<td>Rubbing with ethanol 85% for 3 minutes</td>
<td>5 minutes</td>
<td>Fingerprints: one hand immediately, the other after 3 hours of glove use</td>
<td>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.</td>
<td>NS difference P&gt;0.1</td>
</tr>
<tr>
<td>Babb 1991 (38)</td>
<td>UK, RCT cross-over design</td>
<td>Rubbing with isoproponol 70% for 30 seconds (after a 30-second hand wash with unmedicated soap)</td>
<td>2 minutes</td>
<td>Glove (with loose fitting gloves) juice method at baseline (3 times every 48 hours) after scrub and after 3 hours gloved</td>
<td>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.</td>
<td>NS difference (P not provided)</td>
</tr>
</tbody>
</table>

*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

<table>
<thead>
<tr>
<th>Author, year, reference</th>
<th>Sequence generation</th>
<th>Allocation concealment</th>
<th>Participants blinded*</th>
<th>Care providers blinded</th>
<th>Outcome assessors blinded</th>
<th>Incomplete outcome data</th>
<th>Selective outcome reporting</th>
<th>Other sources of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RCTs comparing handrubbing vs. hand scrubbing with SSI outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parienti 2002 (19)</td>
<td>Low risk</td>
<td>Low risk</td>
<td>High risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>-</td>
</tr>
<tr>
<td>Nthumba 2010 (20)</td>
<td>Low risk</td>
<td>Low risk</td>
<td>High risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>-</td>
</tr>
<tr>
<td>Al-Naami 2009 (21)</td>
<td>Low risk</td>
<td>Low risk</td>
<td>High risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>-</td>
</tr>
<tr>
<td><strong>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</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weber 2009 (34)</td>
<td>Low risk</td>
<td>Low risk</td>
<td>High risk</td>
<td>N/A</td>
<td>Unclear</td>
<td>Low risk</td>
<td>Low risk</td>
<td>**</td>
</tr>
<tr>
<td>Suchomel 2009 (35)</td>
<td>Low risk</td>
<td>Low risk</td>
<td>High risk</td>
<td>N/A</td>
<td>Unclear</td>
<td>Low risk</td>
<td>Low risk</td>
<td>**</td>
</tr>
</tbody>
</table>

*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?

<table>
<thead>
<tr>
<th>Nº of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Nº of patients</th>
<th>Effect</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MODERATE</td>
</tr>
<tr>
<td>Surgical site infection</td>
<td>3</td>
<td>RCTs</td>
<td>Not serious</td>
<td>Serious ¹</td>
<td>Not serious</td>
<td>Not serious</td>
<td>None</td>
<td>190/4061 (4.7%)</td>
<td>193/3959 (4.9%)</td>
</tr>
<tr>
<td>SSI</td>
<td>1</td>
<td>Observational studies, (before-after study)</td>
<td>Serious ²</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>None</td>
<td>78/2175 (3.6%)</td>
<td>69/2084 (3.3%)</td>
</tr>
<tr>
<td>SSI</td>
<td>2</td>
<td>Observational studies, (comparative cohorts)</td>
<td>Serious ³</td>
<td>Serious ⁴</td>
<td>Not serious</td>
<td>Not serious</td>
<td>None</td>
<td>15/1913 (0.8%)</td>
<td>30/2005 (1.5%)</td>
</tr>
</tbody>
</table>

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.
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?

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>№ of patients</th>
<th>Effect</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With handrubbing</td>
<td>With hand scrubbing</td>
<td>Relative (95% CI)</td>
</tr>
<tr>
<td><strong>Log reduction of CFUs on participants’ hands in a hospital setting (better indicated by higher values)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Log reduction of CFUs on participants’ hands in a laboratory setting (better indicated by higher values)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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.

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?

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Nº of patients</th>
<th>Effect</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With 1.5 minutes</td>
<td>With 3 minutes</td>
<td>Relative (95% CI)</td>
</tr>
<tr>
<td>Log reduction of CFUs on participants’ hands in a hospital setting (better indicated by higher values)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 ¹ RCTs</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Very serious</td>
</tr>
<tr>
<td>Log reduction of CFUs on participants’ hands in a laboratory setting (better indicated by higher values)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 ³ RCTs</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Very serious</td>
</tr>
</tbody>
</table>

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.
References


