Region Västra Götaland, HTA-centrum
Regional activity-based HTA [Verksamhetsbaserad HTA]
Health Technology Assessment
HTA-report 2020:113

Update: Chlorhexidine wash prior to clean surgical procedures

Previous report: Chlorhexidine wash prior to clean surgical procedures. HTA. 2015:83

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VÄSTRA GÖTALANDSREGIONEN
SAHLGRENSKA UNIVERSITETSSJUKHUSET

Update: Chlorhexidine wash prior to clean surgical procedures [Uppdaterad: Preoperativ klorhexidintvätt]

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Published November 2015, and updated in March 2020: 2020:113
Suggested citation: Jivegård L, Petzold M, Stadig I, Svanberg T, Sjögren P. Update: Chlorhexidine wash prior to clean surgical procedures [Uppdaterad: Preoperativ klorhexidintvätt]. Göteborg: Västra Götalandsregionen, Sahlgrenska Universitetssjukhuset, HTA-centrum; 2020.
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1. Abstract

Background
Clean surgery is elective surgery, that does not enter the alimentary, respiratory or urinary tracts and without inflammation, infection or cellulitis in, or close to the operative field. Surgical site infection (SSI) following clean surgery occurs in from 1-3% after major joint implant surgery up to 10 - 38%, after, e.g., vascular and scrotal surgery respectively. Between 50 and 95 % of SSIs occur after discharge from the hospital. Serious SSI, usually implant infection, is a devastating complication with significant morbidity and mortality. Risk reducing strategies target environmental as well as patient related factors. Chlorhexidine gluconate (CHX) has a broad-spectrum activity and is known to reduce the risk for colonization of micro-organisms as well as nosocomial infections in high risk settings. The routine to recommend patients two or three double showers with CHX soap before clean surgery is well established but recently questioned. This update of our 2015 HTA report updates all parts except for background, intervention, objective, organisation and economy aspects.

Objective
To assess whether preoperative chlorhexidine whole body wash is better than no chlorhexidine wash prior to clean surgery through intact skin regarding mortality, serious SSI (sSSI), SSI: usually infection including implants or septicaemia, reintervention and length of hospital stay.

Methods
A systematic literature search was conducted in PubMed, Embase, the Cochrane Library, Cinahl and a number of HTA-databases. At least two persons independently screened titles, abstracts and full-text articles for inclusion and extracted data. The certainty of evidence was defined according to GRADE, first for RCTs and then for cohort studies and finally a combined GRADE.

Main results
The new literature search for this update identified one RCT and two cohort studies resulting, together with the studies identified in the previous HTA from 2015 (Rahm *et al.*, 2015), in a total of eight randomised controlled trials (RCT), and five cohort studies with 31,020 patients. There were three systematic reviews (SR) but the SRs included not only clean surgery patients as defined in the current HTA. Preoperative chlorhexidine wash was compared with five different comparators: placebo (C1), soap (C2), no wash (C3), local wash (C4) or no instructions (C5). The intervention varied between the studies from one double to three double preoperative washes.

Mortality and septicaemia were not reported by group in any study.

Serious SSI
Implant infection was reported in one RCT and two cohort studies. In the RCT, there was one implant infection in the CHX (0.4%) versus eight (2.9%, p< 0.05) in the soap group (C2) in patients with lower extremity total joint arthroplasties. In the two cohort studies (n=6,500) on arthroplasties, no difference was seen between the study groups in one and a lower implant infection rate in the CHX versus the “no instruction” group in the other.
Conclusion: There may be a lower sSSI implant infection rate after preoperative CHX compared with soap wash in lower extremity total joint arthroplasty patients (GRADE ⊕⊕◯◯)
It is uncertain whether there is any difference in the rate of sSSI after preoperative CHX wash versus “no instruction” (GRADE ⊕◯◯◯).

Surgical site infection (five different comparisons, C1 – C5)
CI: Chlorhexidine versus placebo was studied in four RCTs with n.s. intergroup differences. Meta-analysis showed an effect estimate of RR 0.85 (95%CI: 0.68 to 1.07, p=0.18).

Conclusion: Preoperative CHX wash compared with preoperative placebo wash (C1) may result in a moderate decrease to a slight increase in surgical site infection rate in mixed clean surgery patient populations. Low certainty of evidence (GRADE ⊕⊕◯◯).
C2: Chlorhexidine versus soap wash was studied in four RCTs and one cohort study with a lower SSI rate in the CHX group in one RCT and n.s. intergroup differences in the other RCTs and the cohort study. It is uncertain whether preoperative CHX wash affects SSI rates compared with preoperative soap wash. Very low certainty of evidence (GRADE ⊕◯◯◯).C3: Two RCTs and one cohort study compared preoperative CHX with no wash. One RCT found a significant difference in favour of CHX while the other did not. A meta-analysis did not reveal any intergroup differences (95%CI: 0.19 to 2.58, p=0.59). The cohort study (n= 3924) reported an *increased* risk of SSI (OR 1.49, 95%CI: 1.05 to 2.11, p< 0.05) in the CHX versus the no wash group for ventral hernia repair patients.
Conclusion: It is uncertain whether the surgical site infection rate is different after preoperative CHX compared with no wash. Very low certainty of evidence (GRADE ⊕◯◯◯).
C4: Chlorhexidine versus local wash was studied in one RCT with 1.7% versus 4.2% (p<0.05) SSI rates in the CHX and control groups respectively.
Conclusion: It is uncertain whether the surgical site infection rate is different after preoperative CHX compared with local wash. Very low certainty of evidence (GRADE ⊕◯◯◯).
C5: One RCT and three cohort studies compared preoperative CHX wash with no instruction. One cohort study (n=2,458) found a lower SSI rate in the CHX group, with 0.5% (p=0.043) and 0.6% infection rate among hip and knee surgery patients respectively compared with 1.7%, and 2.2% in the "no instruction" groups. The RCT (n=100) and the other two cohort studies (n=8,308) found no significant difference in SSI rates between the study groups.
Conclusion: It is uncertain whether the surgical site infection rate is different after preoperative CHX wash compared with no instructions. Very low certainty of evidence (GRADE ⊕◯◯◯).

Reinterventions was reported in one cohort study (n= 3,924) with no intergroup difference.

Length of stay was reported in two cohort studies with longer length of stay in the CHX versus the no wash group in one of the studies and no intergroup difference in the other.

Concluding remarks
In this update, one RCT and two cohort studies were added. This resulted in a total of eight RCTs and five cohort studies and a novel conclusion that there may be a lower implant infection rate after preoperative CHX compared with soap wash in lower extremity total joint arthroplasty patients (GRADE ⊕⊕◯◯). It is uncertain whether there is any difference in the rate of sSSI after preoperative CHX versus "no instruction" (GRADE ⊕◯◯◯). Regarding SSI, preoperative CHX compared with placebo wash may result in a moderate decrease to a slight increase in SSI rate in mixed clean surgery patient populations (GRADE ⊕⊕◯◯), whereas the certainty of evidence is very low (GRADE ⊕◯◯◯) for all other comparisons.

2. Svensk sammanfattning – Swedish summary

Bakgrund
Ren kirurgi definieras ofta som kirurgi som inte öppnar magtarmkanalen, andnings- eller urinvägarna och där det inte föreligger inflammation, infektion eller cellulit i, eller nära operationsfältet. Sårinfektion (SSI) efter ren kirurgi förekommer i från 1-3% efter ortopedisk proteskirurgi och i upp till 10 - 38% efter tex kärlkirurgi respektive scrotal kirurgi. Mellan 50 och 95% av SSI diagnosticeras efter utskrivning från sjukhuset. Allvarlig SSI, oftast implantatinfektion, är en mycket allvarlig komplikation med avsevärd morbiditet och mortalitet. Preoperativa riskreducerande strategier inkluderar optimering av den kirurgiska miljön samt av patienterna. Klorhexidin glukonat (CHX) har antibakteriell effekt med brett spektrum och har rapporterats reducera risken för koloniseringen av mikroorganismer och vårdrelaterad infektion i samband med operationer med hög infektionsrisk. Det är praxis att rekommendera patienter två eller tre dubbelduschar med CHX tvål innan ren kirurgi, men denna rutin har ifrågasatts. Denna uppdatering av vår HTA-rapport från 2015 uppdaterar alla delar utom bakgrund, intervention, syfte, organisation och ekonomiska aspekter.

Syfte
Att utvärdera huruvida preoperativ helkroppsdusch med klorhexidin är bättre än ingen klorhexidindusch vid ren kirurgi genom intakt hud, avseende mortalitet, allvarlig sårinfektion (sSSI): exempelvis implantatinfektion och/eller sepsis, sårinfektion (SSI), behov av reintervention och vårdtid.

Metod
Systematisk litteratursökning utfördes i PubMed, Embase, och the Cochrane Library, Cinahl samt ett antal HTA-databaser. Minst två av författarna granskade oberoende av varandra artiklarna på titel- och abstrakt nivå, samt fulltextartiklar, avseende inklusion och gjorde data extraktion. Vetenskapligt underlag bedömdes enligt GRADE, först för RCT, sedan för kohortstudier och till sist en kombinerad GRADE.

Resultat
Den nya litteratursökningen identifierade en ny RCT och två kohortstudier. Detta resulterande i totalt åtta RCT och fem kohortstudier med 31 020 patienter. Klorhexidindusch jämfördes mot placebo (C1), tvål (C2), ingen preoperativ tvätt (C3), lokal preoperativ tvätt (C4), eller inga preoperativa tvättinstruktioner (C5). Det fanns tre systematiska översikter (SR); samtliga inkluderade även icke ren kirurgi, till skillnad från denna HTA med endast ren kirurgi Interventionen varierade från en dubbel till tre dubbla preoperativa klorhexidinduschar.

Mortalitet och blodförgiftning rapporterades inte gruppvis i någon av de inkluderade studierna

Allvarlig SSI
Implantatinfektion rapporterades i en RCT och två kohortstudier. I RCT:n var det en implantatinfektion i CHX- (0,4%) versus åtta (2,9%, p< 0,05) i tvålgruppen (C2) hos patienter med ledprotesoperationer i nedre extremiteterna. I de två kohortstudierna (n= 6,500) med ledprotesoperationer sågs ingen skillnad mellan CHX och ”ingen instruktion” i den ena och lägre sSSI-frekvens i CHX-gruppen i den andra. Slutsats: Det kan vara en lägre frekvens av implantatinfektion efter preoperativ CHX jämfört med tvåltvätt hos patienter som genomgår ledprotesoperation i nedre extremiteterna (GRADE ⊕⊕◯◯). Det är osäkert huruvida det är någon skillnad i frekvensen implantatinfektion efter preoperativ CHX-tvätt jämfört med ”ingen instruktion” (GRADE ⊕◯◯).

SSI (fem olika jämförelser, C1 – C5)
CI: CHX versus placebo studerades i fyra RCT:er som inte visade några skillnader mellan grupperna. Meta-analys visade RR 0.85 (95% CI: 0.68 to 1.07, p=0,18).

Slutsats: Preoperativ CHX- jämfört med placebotvätt (C1) kan resultera i en måttlig sänkning till en mindre ökning i SSI-frekvens (GRADE ⊕⊕◯◯).
C2: CHX- jämfört tvåltvätt studerades i fyra RCT:er och en kohortstudie med lägre SSI-frekvens i en RCT och inga signifikanta skillnader i övriga RCT:er och kohortstudien. Slutsats: Det är osäkert huruvida preoperativ CHX- jämfört med tvåltvätt resulterar i någon skillnad i SSI-frekvens (GRADE ⊕◯◯◯).
C3: I två RCT:er och en kohortstudie jämfördes preoperative CHX med ingen preoperativ tvätt. En RCT visade signifikant lägre SSI-frekvens med CHX medan den andra inte visade någon skillnad. Meta-analys visade ingen skillnad (95% CI: 0,19 to 2,58, p=0,59). Kohortstudien (n= 3924) visade *ökad* SSI-frekvens efter CHX versus ingen tvätt (OR 1.49, 95%CI: 1.05 to 2.11, p< 0.05) vid ventral bråckoperation
Slutsats: Det är osäkert huruvida SSI-frekvensen påverkas av CHX- jämfört med ingen preoperativ tvätt (GRADE ⊕◯◯◯).
C4: CHX- versus lokal tvätt studerades i en RCT med 1,7% versus 4,2% SSI I CHX- respective lokal tvätt-gruppen Slutsats: Det är osäkert huruvida SSI-frekvensen påverkas efter preoperativ CHX- jämfört med lokal tvätt (GRADE ⊕◯◯◯).
C5: En RCT och tre kohortstudier jämförde preoperativ CHX-tvätt med ingen instruktion. En kohortstudie (n= 2 458) fann lägre SSI-frekvens i CHX- (0,5%, p= 0.043) och 0,6% SSI hos respektive höft- och knäprotesopererade jämfört med 1,7% och 2,2% i motsvarande ingen instruktions-grupp. RCT:n (n= 100) och de två andra kohortstudierna (n= 8 308) visade inga skillnader mellan grupperna.
Slutsats: Det är osäkert huruvida SSI-frekvensen påverkas av preoperativ CHX jämfört med ingen instruktion (GRADE ⊕◯◯◯).

Reintervention och vårdtid rapporterades i en kohortstudie (n= 3 924) utan skillnad mellan CHX- och ingen preoperativ tvätt-gruppen.

Vårddagar redovisades i två kohortstudier med längre vårdtid i CHX- jämfört med ingen preoperativ tvätt-gruppen i den ena och ingen skillnad mellan grupperna i den andra studien.

Komplikationer var sällsynt förekommande och bestod främst av lätt hudirritation.
and a novel conclusion that there may be a lower implant infection rate after preoperative CHX compared with soap wash in lower extremity total joint arthroplasty patients (GRADE ⊕⊕◯◯).

Sammanfattande slutsats
I denna uppdatering av vår HTA-rapport från 2015 tillkom en ny RCT samt två kohortstudier. Detta resulterade i totalt åtta RCT och fem kohortstudier och att för preoperativ CHX- jämfört med tvåltvätt skulle CHX kunna ge en lägre frekvens implantatinfektion efter ledprotesoperation i nedre extremiteterna [GRADE ⊕⊕◯◯). Sammanfattningsvis är det osäkert huruvida det är någon skillnad mellan preoperativ CHX jämfört med ingen instruktion (GRADE ⊕◯◯◯). Avseende SSI skulle CHX jämfört med placebotvätt kunna resultera i måttlig minskning till en lätt ökning i SSI-frekvens efter olika typer av rena operationer (GRADE ⊕⊕◯◯), medan ingen slutsats kunde dras avseende eventuella effekter av CHX för alla andra jämförelser (GRADE⊕◯◯◯).

The above summaries were written by HTA-centrum and approved by the Regional board for quality assurance of activity-based HTA. The Regional Health Technology Assessment Centre (HTA-centrum) Region Västra Götaland, Sweden has the task to make statements on HTA reports carried out in VGR. The English summary is a concise summary of similar outline as the summaries in the Cochrane systematic reviews.

The Swedish summary addresses the question at issue, results and quality of evidence regarding efficacy and risks, and economical and ethical aspects of the particular health technology that has been assessed in the report, and is ended with a final statement/concluding remark from HTA-centrum.

Christina Bergh, Professor, MD
Head of HTA-centrum of Region Västra Götaland, Sweden, February 26th 2020

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3. Summary of Findings (SoF-table)

Chlorhexidine wash prior to clean surgical procedures

Outcome	Study design Number of studies	Effect estimate	Certainty of evidence GRADE[1]
		Absolute effect	
I. Serious surgical site infection/Implant infection			
Chlorhexidine wash versus soap (C2)	RCT	Arthroplasties: 0.4% vs 2.9% p=0.0195	⊕⊕◯◯ Low [1]
Chlorhexidine wash versus no instruction (C5)	Cohort 2	Hip: 0.5% vs 1.7% (p=0.043) Knee: 0.6% vs 2.2% (p=0.021) Arthroplasties: 1.1% vs 0.9% (n.s.)	⊕◯◯◯ Very low [2]
		Relative effect (95%CI)	
II. Surgical site infection			
Chlorhexidine wash versus placebo (C1)	RCT 4	RR: 0.85 (CI: 0.68 to 1.07) p=0.18	⊕⊕◯◯ Low [3]
Chlorhexidine wash versus soap (C2)	RCT 4 1 Cohort	OR: 0.789 (0.326 to 1.910) p=0.599 I: 3.6% C: 4.0% (n.s.)	⊕◯◯◯ Very low [4]
Chlorhexidine wash versus no wash (C3)	RCT 2 Cohort 1	RR: 0.70 (0.19 to 2.58) p=0.59 OR: 1.49 (1.05 to 2.11) p< 0.05)	⊕◯◯◯ Very low [5]
		Absolute effect	
Chlorhexidine wash versus local wash (C4)	RCT 1	1.7% vs 4.2% (p<0.05)	⊕◯◯◯ Very low [6]
		Relative effect (95% CI)	
Chlorhexidine wash versus no instruction (C5)	RCT 1 Cohort 3	2% vs. 0% (n.s.)	⊕◯◯◯ Very low [7]

1: Serious study limitations (unblinded, uneven groups, per protocol analysis, industry sponsored), serious imprecision (few events), some indirectness (not enough to downgrade).
2: Study limitations (blinding, reporting of drop-outs, selection bias), Inconsistency (unclear reporting of confounders: baseline differences, socio economy, length of surgery), Imprecision (few events).
3: Study limitations (blinding, definitions of outcomes), Inconsistency, Indirectness, Imprecision across the studies (including unfavorable effects and few events).
4: Study limitations (blinding, reporting of drop-outs, very serious imprecision across the studies (including unfavorable effects). Heterogeneity.
5: Study limitations (randomization, blinding, selection bias, definition of outcomes), Indirectness.
6: Very serious study limitations (blinding, selection bias), Indirectness.
7: Serious study limitations (blinding, reporting of drop-outs, selection bias), Inconsistency, Some indirectness, Imprecision (few events).

Certainty of evidence:

High	⊕⊕⊕⊕	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	⊕⊕⊕◯	We aremoderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	⊕⊕◯◯	Confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low	⊕◯◯◯	We have very little confidence in the effect estimate: The true effect is likely to be substantiallydifferent from the estimate of effect.

4. Abbreviations

CHX	Chlorhexidine gluconate
RCT	Randomised controlled trial
SSI	Surgical site infection
sSSI	Serious SSI, which includes implant infections, deep (subfascial) infections and septicaemia

5. Background

A currently used clinical routine in Sweden to recommend patients two or three double showers with a CHX based soap before orthopaedic implant surgery is well established but has been questioned. The question whether preoperative CHX wash leads to a reduction in infections was studied in a systematic review and HTA report from HTA-centrum in 2015 (Rahm *et al.*, 2015). This is an update of that report.

Surgical site infections following clean surgery

A surgical site infection (SSI) is an infection that occurs after surgery in the part of the body where the surgery took place. Surgical site infections can sometimes be superficial infections involving the skin only. Other SSIs are more serious and can involve tissues under the skin, organs or implanted material (https://www.cdc.gov/hai/ssi/ssi.html). Different authors use varying definitions of SSI. The definitions of SSI used by the authors of the included articles in the present HTA are presented in Appendix 4.

In the present HTA, the term serious SSI (sSSI) is used for implant infections. Surgical site infections are preventable complications associated with increased postoperative length of hospital stay, costs, hospital re-admission rates, and the use of antimicrobial agents (Vogel *et al*., 2010). The adverse effects related to SSI vary depending on the category of surgery and type of SSI. Superficial incisional SSI is more common than deep organ/space SSI, and the cost and risks associated with SSI increase with the depth and extent of infection (Urban, 2006). De Lissovoy *et al*. (2009) examined cardiovascular, gynaecologic and orthopaedic surgery (with the exception of major joint surgery) with the aim to analyse the effect of SSI on length of hospital stay associated with SSI and cost. The greatest increase in length of hospital stay was observed for cardiovascular surgery, including 723,490 surgical procedures with an SSI rate at 1%, with a mean extension of 13.7 days. On average, any SSI extended the length of stay by 9.7 days and produced increased costs of USD 20,842 per hospital admission.

The Harvard Medical Practice Study II (Leape *et al*., 1991) found that surgical wound infections was the second-largest category of adverse events, after urinary tract infection, in hospitalised patients, and that hospital acquired Staphylococcal infections constituted a substantial risk for patients receiving surgical care.

The reported rates for SSI following clean surgery vary greatly from 1-3% after major joint implant procedures (Kurtz *et al*., 2012) to 2-9% following closed fracture surgery (Acklin *et al.*, 2011) and 1-20% after vascular and cardiac surgery (Bandyk, 2008). For scrotal surgery, SSI rates as high as 38% have been described (Randall *et al*., 1993). Moreover, between 50-95 % of the SSIs occur after discharge from the hospital (Berg *et al.*, 2011; Brown *et al*., 1987; Darle *et al*., 1997; Sands *et al*., 1996) and the true SSI rates are therefore most likely higher than often reported.

The most common causal infectious agents following clean and implant surgery are coagulase-negative staphylococci and *S. aureus,* followed by enterococci and, more rarely, streptococci and *Propionibacterium acnes* (Frei *et al*., 2011).

The route of transmission can be endogenous as well as exogenous. Whyte *et al*. (1982) concluded that the most consistent and important route of contamination in orthopaedic implant surgery is airborne. However, in patients with exceptionally high skin carriage of bacteria, gross wound contamination can occur. More recently, *S. aureus* carriage has been associated with postoperative and device related infections, with a reported 2 to 9-fold increased risk for infection (Perl, 2003).

Deep infection after implant surgery is a devastating complication associated with significant morbidity and mortality (Cayci *et al*., 2008; Salehi Omran *et al*., 2007), prolonged hospitalization, multiple re-operations, and long-term patient suffering (Swenne *et al*., 2007; Andersson *et al*., 2010). The need to find ways of minimizing the risk factors for infections is strong. Evidence based strategies include optimizing the surgical environment by the use of effective ventilation systems (Lidwell *et al*., 1983; Hansen *et al*., 2005), and surgical scrubs with low permeability (Tammelin *et al*., 2013). In addition, enhanced surgical techniques minimizing blood loss, thereby avoiding the need for (allogeneic) blood transfusions and eliminating postoperative hematoma, reduce the risks for SSI. Optimizing the patients by addressing risk factors associated with SSI (such as smoking, malnutrition, diabetes, infections and conditions that compromise the immunological defence systems) in combination with the timely distribution of antibiotic prophylaxis and to maintain perioperative normothermia can significantly improve postoperative outcomes (AlBuhairn *et al*., 2008; Lindstrom *et al*., 2008).

Chlorhexidine wash prior to surgery

The practice of skin preparation before surgery has been in use since Joseph Lister in 1867 scientifically tested, and reported, antiseptic methods for the reduction of wound infections (Lister, 1867).

Chlorhexidine gluconate (CHX) is widely used since the mid 1950's, and routinely for preoperative washes in Sweden since the 1980's. The antimicrobial effect on transient and resident skin microbes such as *S. aureus* is well documented. Chlorhexidine is safe for oral and topical use (Milstone *et al*., 2008). Severe adverse reactions are very rare, although there are reports on minor skin irritations (Milstone *et al*., 2008). Chlorhexidine gluconate has a broad spectrum activity that affects both gram positive and gram negative bacteria, yeast, facultative anaerobes and aerobes and some (lipid – enveloped) viruses like Human Immunodeficiency Virus (McDonnell and Russell, 1999). The effect is instant and cumulative with repeated applications. Moreover, CHX inhibits bacterial growth on the skin for several hours (Edmiston *et al*., 2007). The effect is dose dependent. In low concentrations the membrane integrity is affected, while high concentrations may lead to cell death (McDonnell and Russell, 1999).

Several studies have shown that bathing with soap containing CHX reduces the risk for colonization and cross transmission of microorganisms as well as nosocomial infections in high risk settings (Armellino *et al*., 2014; Petlin *et al*., 2014; Popp *et al*., 2014).

Does CHX lead to a reduction in SSIs? Some studies have demonstrated a positive effect while others have not (Colling *et al*., 2015; Webster and Osborne, 2015). Even so, the currently used clinical routine in Sweden to recommend patients two or three double showers with a CHX based soap before orthopaedic implant surgery is well established.

The normal pathway through the health care system

The information given to patients regarding how and when to take a double shower varies between hospitals and regions, there is no standardised procedure for this. The following instruction is only an approximate description of recommendations.

Patients undergoing elective surgery are often admitted to the hospital on the operation day. Only patients with special needs regarding, e.g., help with their activities of daily living are admitted the day before surgery. With regard to clean surgery the patient is often recommended two double showers before the admission to the hospital. The first double shower is taken the day before surgery.

The patient is recommended to put on clean clothes and sleep on clean sheets. The next double shower is taken the morning before surgery.

A double shower starts by thorough washing of the whole body with a soap containing CHX. The instructions include recommendations to give special attention to the area around the nose, the navel and the armpits followed by the groins and genital area. The soap should be rinsed off and the procedure repeated before drying the skin with a clean towel.

Number of patients per year who undergo preoperative chlorhexidine wash

The total number of patients undergoing preoperative CHX wash is unknown since there are no systematic records kept for the treatment. As an example, we have looked at the total number of patients undergoing knee and hip joint operations where a prosthetic implant is used as well as open abdominal aortic aneurysm operations, since these patient groups are recommended CXH wash. The number of patients was 4,718, during 2014 in Region Västra Götaland, which probably is a small proportion of the all patients undergoing “clean surgery”.

Present recommendations from medical societies or health authorities

A national group of experts representing Swedish Orthopaedic Association, Swedish Association of Infectious Disease Specialists, Orthopaedic Nurses Association in Sweden, National Association for Surgical Nursing, Swedish Association of Professional Physiotherapists and Swedish Association for Infection Control, has written best practice guidelines for the prevention of orthopaedic implant related infections within the PRISS project - a national, interdisciplinary collaboration for safer prosthetic knee and hip operations. The recommendations are “at least two full-body showers with soap containing CHX should be taken preoperatively” (PRISS, 2019).

6. Intervention: Preoperative chlorhexidine wash

Chlorhexidine is an antiseptic agent. It has been shown to decrease skin bacterial count. Preoperative CHX double wash is a procedure where the patient washes the whole body, including the hair, 2-3 times (depending on type of surgery) starting the day before surgery. The procedure is well established in Region Västra Götaland where every patient who will undergo elective surgery is recommended CHX double wash. It is used within all surgical fields with a particular attention in orthopaedic surgery.

7. Objective

The focused question
Prior to "clean surgery" through intact skin, is chlorhexidine whole body wash better than no chlorhexidine wash regarding mortality, serious surgical site infection (sSSI): implant infection, septicaemia, surgical site infection (SSI), reintervention and length of hospital stay?

PICO: P= Patients, I= Intervention, C= Comparison, O=Outcome

P	Patients undergoing so called "clean surgery" where the operation is performed through intact skin
I	Preoperative whole body wash with chlorhexidine
C	No chlorhexidine wash: C1: Placebo C2: Soap C3: No wash C4: Local wash C5: No instruction
O	Critical for decision making Mortality Implant infection (sSSI) Septicaemia (sSSI) Surgical site infection (SSI) Important but not critical for decision making Reintervention Number of days in hospital Not important for decision making (None)

8. Methods

The activity based HTA-process

Systematic literature search (Appendix 1)

This update of our 2015 HTA report (Rahm *et al.*, 2015) updates all parts except for background, intervention, objective, organisation and economy aspects. During August 2019 two authors (TS, IS) performed systematic searches in PubMed, Embase, the Cochrane Library and CINAHL to update the original HTA report from 2015, Chlorhexidine wash prior to clean surgical procedures. Reference lists of relevant articles were also scrutinised for additional references. Search strategies, eligibility criteria and a graphic presentation of the selection process are presented in Appendix 1. These authors conducted the literature searches, selected studies, and independently of one another assessed the obtained abstracts and made a first selection of full-text articles for inclusion or exclusion. Any disagreements were resolved in consensus. The remaining articles were sent to all authors. All authors read the articles independently of one another and it was finally decided in a consensus meeting which articles should be included in the assessment.

Critical appraisal and certainty of evidence

The included studies and their design and patient characteristics are presented in Appendix 2. The excluded studies and the reasons for exclusion are presented in Appendix 3. The included studies have been critically appraised using the checklists for assessment of randomised controlled trials (RCT) and cohort studies provided by the Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU). Meta-analyses were conducted using random effects model, using Review Manager (RevMan) [Computer program]. The results and the assessed quality of each article have been summarised per outcome in Appendix 4. A summary result per outcome and the associated certainty of evidence are presented in a Summary-of-findings table (page 9). The certainty of evidence was defined according to the GRADE system (Atkins *et al.*, 2004; GRADE Working group).

Ongoing research

A search in Clinicaltrials.gov (2019-10-25) using the search terms *(chlorhexidine AND (shower OR showers OR bath OR baths OR wash OR cleanse OR cleansing OR cloth OR cloths OR scrub OR soap) AND (infection OR infections OR infected OR preoperative OR pre-operative OR perioperative OR peri-operative OR preadmission))* and the criterion *First posted from 09/15/2015 to 10/25/2019* identified 55 trials.

A search in WHO ICTRP (2019-10-25) using the search terms: *chlorhexidine in the Title field AND (shower OR showers OR bath OR baths OR wash OR cleanse OR cleansing OR cloth OR cloths OR scrub OR soap) in the Intervention field*, and the criterion *Date of registration between 09/15/2015 to 10/25/2019* identified 104 trials.

9. Results

Literature search (Appendix 1)
The updated literature search (including the time period 21 May 2015 to 29 August 2019) identified 731 records after removal of duplicates. After reading the abstracts, 707 articles were excluded. Another 13 articles were excluded by two authors in consensus after reading the articles in full text. The remaining 11 articles were sent to all other authors, and 3 studies were finally included. Together with the 10 articles from the original HTA report, a total of 13 articles were included in the synthesis. A flowchart of the study selection process is presented in Appendix 1.

Results
The 13 studies included altogether 31,020 patients. All studies reported the outcome SSI, three of which also reported the outcome implant infection (sSSI). Mortality was reported in two, adverse events in five, length of hospital stay in two and reintervention in one study.
The three SRs, Chleblicki *et al*. (2013), Kamel *et al*. (2012), and Webster and Osborne (2015) included studies with patient populations from all kinds of surgical procedures, and not only clean surgery as defined in the current HTA. Chleblicki *et al*. (2013) concluded that there is no appreciable benefit of preoperative whole-body CHX bathing for prevention of SSI, and Kamel *et al*., (2012) concluded that the results regarding SSI were inconclusive. Webster and Osborne (2015) reported no significant difference in SSI rates between preoperative CHX wash compared with placebo (GRADE ⊕⊕⊕⊕), for all other comparisons the certainty of evidence was very low (GRADE ⊕◯◯◯), for patients undergoing clean as well as not clean surgery, thus allowing comparison of all kinds of surgical patients. Our current PICO was limited to patients undergoing "clean" surgery.

All included RCTs and cohort studies in the present SR had some or major limitations regarding blinding, definition of outcomes, length of follow up and heterogeneity of patient populations.
Chlorhexidine was compared with C1: placebo (four studies), C2: soap (five studies), C3: no wash (three studies), C4: local wash (one study) or C5: no instructions (four studies; Appendix 2).
The intervention varied between the studies from one double to three double preoperative washes, showers/baths. The concentration of CHX also varied between the studies.

Mortality
Only total mortality in the intervention and control groups combined was reported in two RCTs (Byrne, 1992; Earnshaw, 1989). One RCT reported 23 deaths in total (0.6%, n=3,733) (Byrne, 1992), and the other RCT reported two deaths (3.1%) among 64 high-risk vascular patients (Earnshaw, 1989).

Serious SSI
Chlorhexidine versus soap (C2) or no instruction (C5) (Appendix 4:1)
Implant infection (by group) was reported in one RCT comparing CHX wash with soap or with no instruction (Kapadia *et al*., 2016), and in two cohort studies comparing CHX with no instruction (Colling *et al*, 2015; Kapadia *et al*., 2013c). The RCT had no problems with directness, but serious problems with study limitations and imprecision. Both cohort studies had major study limitations. In the RCT there were eight implant infections (2.9%) in the soap group versus one in the CHX group (0.4%, $p< 0.05$). In one cohort study (n=4,042) on arthroplasties no significant difference was seen in the infection rate between the study groups with 1.1% implant infection rate in the preoperative CHX group versus 0.9% in the “no instruction” group (Colling *et al*., 2015). In the other cohort study (n=2,458) there was a significantly lower implant infection rate in the CHX group with 0.5% (p=0.043) infections among hip surgery patients and 0.6% (p=0.021) among knee surgery patients, compared with 1.7%, and 2.2% in the “no instruction” groups, respectively (Kapadia *et al*., 2013c).
Conclusion: The implant infection rate after lower extremity total joint arthroplasty may be lower after preoperative CHX compared with soap wash. Low certainty of evidence (GRADE ⊕⊕◯◯).

It is uncertain whether there is any difference in the rate of sSSI after preoperative CHX wash versus "no instruction" (GRADE ⊕◯◯◯).

Septicemia

The per group incidence of septicemia was not reported in any of the studies.

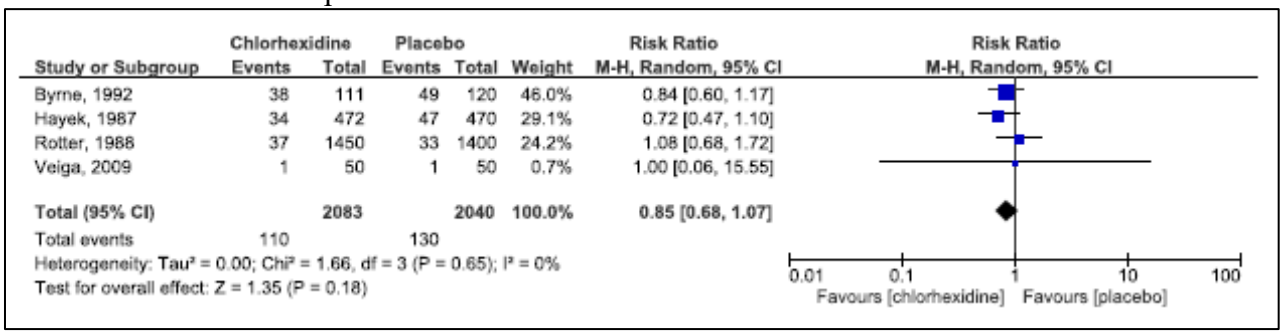
Surgical site infection (SSI)

C1: chlorhexidine versus placebo (Appendix 4:2)

Four RCTs compared preoperative CHX versus placebo wash with regard to SSI. None of the studies found any significant differences between the study groups. The SSI rates varied between two and 34% in the CHX groups, and between two and 41% in the placebo groups.

Based on a meta-analysis of the included RCTs the effect estimate was RR 0.85 (95%CI: 0.68 to 1.07, p=0.18) (Figure 1.)

Figure 1. Meta-analysis of the outcome surgical site infection from RCTs comparing preoperative chlorhexidine wash with placebo wash



Conclusion: Preoperative CHX wash compared with preoperative placebo wash (C1) may result in a moderate decrease to a slight increase in surgical site infection rate in mixed clean surgery patient populations. Low certainty of evidence (GRADE ⊕⊕◯◯).

C2: -chlorhexidine versus soap (Appendix 4:2)

Four RCTs and one cohort study compared preoperative CHX wash versus soap with regard to SSI. There were no significant differences between the study groups in three of the studies. In the most recent RCT, there were more SSIs (4.9%) in the soap versus the CHX group (0.7%, p= 0.0035) (Kapadia 2016).

A meta-analysis of the RCTs did not reveal significant difference between the studied interventions, with an overall OR of 0.789 (95%CI: 0.326 to 1.910, p=0.599) (Table 1).

Conclusion: It is uncertain whether preoperative CHX wash affects SSI rates compared with preoperative soap wash. Low certainty of evidence (GRADE ⊕◯◯◯).

Table 1.

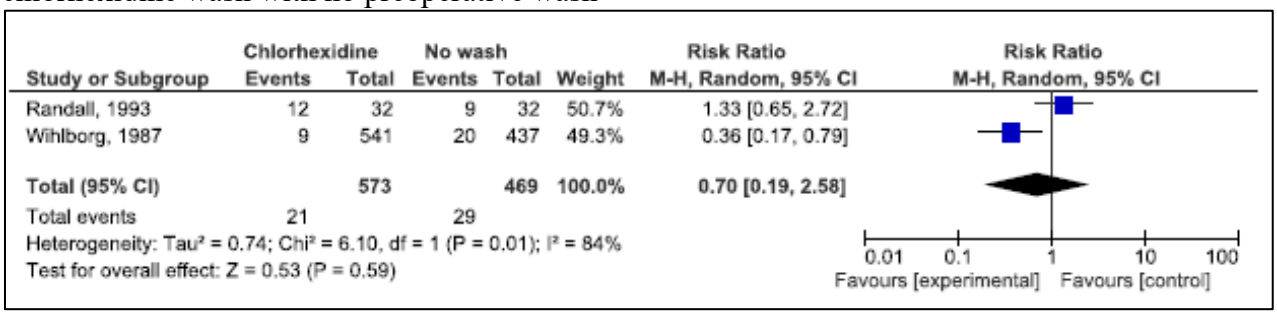
Meta-analysis of RCTs studying the outcome SSI for CHX wash compared with soap

Study	OR	[95% Conf.	Interval]	% Weight
Earnshaw, 1989	2.696	0.723	10.049	20.95
Hayek, 1987	0.682	0.429	1.084	35.31
Randall, 1993	1.200	0.423	3.406	25.32
Kapadia, 2016	0.145	0.032	0.648	18.42
D+L pooled OR	**0.789**	**0.326**	**1.910**	**100.00**

Heterogeneity chi-squared = 9.20 (d.f. = 3) p = 0.027
I-squared (variation in OR attributable to heterogeneity) = 67.4%
Estimate of between-study variance Tau-squared = 0.5204
Test of OR=1 : z= 0.53, p = 0.599

C3: Surgical site infection (SSI) - chlorhexidine versus no wash (Appendix 4:2)
Two RCTs and one cohort study compared preoperative CHX wash with no wash with regard to SSI . One RCT with very serious study limitations found a significant difference in favour of CHX, with 1.7% SSI in the CHX group compared with 4.6% (p<0.01) in the control group (Wihlborg, 1987). In the other RCT there was no significant difference between the study groups (37.5% vs. 28.1%, n.s.). The cohort study had some study limitations and problems with precision and reported an increased risk of SSI (OR 1.49, 95%CI: 1.05 to 2.11, p< 0.05) in the CHX (n= 2209 patients) versus the no wash group (n= 1,715 patients) for patients undergoing ventral hernia repair .
A meta-analysis of the two RCTs did not reveal any difference between the studied interventions, with an overall RR of 0.70 (95%CI: 0.19 to 2.58, p=0.59) (Figure 2).

Figure 2. Meta-analysis of the outcome surgical site infection from RCTs comparing preoperative chlorhexidine wash with no preoperative wash



Control: No wash, experimental: CHX

Conclusion: It is uncertain whether the surgical site infection rate is different after preoperative CHX wash compared with no preoperative wash.
Very low certainty of evidence (GRADE ⊕○○○).

C4: Surgical site infection - chlorhexidine versus local wash (Appendix 4:2)
One RCT, with very serious study limitations, as well as indirectness, compared preoperative CHX wash with local wash with regard to SSI. There was a significant difference in the surgical site infection rate with 1.7% infections in the CHX group and 4.2% (p<0.05) in the control group.
Conclusion: It is uncertain whether the surgical site infection rate is different after preoperative CHX wash compared with preoperative local wash.
Very low certainty of evidence (GRADE ⊕○○○).

C5: Surgical site infection - chlorhexidine versus no instruction (Appendix 4:2)
One RCT and three cohort studies compared preoperative CHX wash with no instruction with regard to SSI. The cohort study with implant infections (n=2,458) found a significantly lower SSI rate in the CHX group, with 0.5% (p=0.043) infection rate among hip surgery patients and 0.6% (p=0.021) among knee surgery patients, compared with 1.7%, and 2.2% in the corresponding "no instruction" groups, respectively. The RCT (n=100) and the two other cohort study (n=8,308) found no significant difference in SSI rates between the study groups, with 2%, 2% and 0.2% rates for CHX compared with 0%, 2% and 0.7% in the control groups, respectively.
Conclusion: It is uncertain whether the surgical site infection rate is different after preoperative CHX wash compared with no instructions.
Very low certainty of evidence (GRADE ⊕○○○).

Reintervention
Reintervention was reported in one cohort study (n= 3,924) with no difference between the CHX and the no wash groups (OR 1.07, 95%CI: 0.80 to 1.42).

Number of days in hospital

Length of stay was reported in two cohort studies including 8,190 patients comparing CHX wash with no instruction and no wash respectively. In one of the studies, length of stay was longer (3 days vs 2 days, $p< 0.001$) in the CHX versus the no wash group. In the other study, there was no difference between the groups (6.6 versus 6.3 days, n.s.).

Complications

Adverse events were reported in five RCTs. Only minor adverse events, such as skin irritation or reddening of the skin, were reported with frequencies of less than 1% in both CHX and control groups.

10. Ethical consequences

Ethical consequences

The widespread use of preoperative CHX wash, which is a relatively simple method with minor side effects should be considered in the context of the consequences of possible sSSI. There is low certainty of evidence that sSSI may be reduced by CHX versus soap wash in patients undergoing lower limb arthroplasty, while there is no evidence for a positive effect for other comparisons. Short term adverse effects such as skin rash are unusual. We could not identify any studies on the risk of long-term adverse effects. If CHX is effective in reducing SSI the benefits for the patient might exceed the risks and costs, especially looking at serious complications such as implant infections which may be life threatening. These serious complications should be included as outcomes in future studies. On the other hand, an ethical aspect is that CHX is paid for by the patient, at some hospitals/departments, and is not covered by the high-cost protection which creates an unequal care not available for everyone.

Time frame for putative introduction of preoperative chlorhexidine wash

Preoperative CHX washes are in use since many years.

Present use of preoperative chlorhexidine wash in Region Västra Götaland

Preoperative CHX washes are widely used in Region Västra Götaland.

Consequences of preoperative chlorhexidine wash for personnel

There is a need of personnel informing patients.

Consequences for other clinics or supporting functions at the hospital or in the Region Västra Götaland

None.

11. Economy aspects

The costs of preoperative chlorhexidine wash

At most hospitals/departments the patient has to cover the cost of CHX which is around 300 SEK for two preoperative washes. When looking at knee and hip joint operations as well as abdominal aortic aneurysm operations in Region Västra Götaland in 2014 (a small proportion of patients in the “clean surgery” category) the cost for this patient group alone would be 1.4 million SEK.

Preoperative washes are included in routine patient care procedures at the hospital ward. Thus, if the patient is admitted to hospital prior to surgery, and needs help with the procedure, there are no additional personnel costs associated with the preoperative washes/showers.

Expected costs of preoperative chlorhexidine wash
See above.

Total change of cost
The patients´ own expenses for the preoperative CHX washes could be saved.

Possibility to adopt and use preoperative chlorhexidine washing within the present budget
Usually the patient covers the cost of CHX.

Available analyses of health economy or cost advantages or disadvantages
The literature search identified two health economy articles (Kapadia *et al*., 2013b; Lynch *et al*., 1992). The more recent study from USA (Kapadia *et al*., 2013b), based the calculations on reports from National Healthcare Safety Network and previously published reports, reported a potential net saving with preoperative CHX washes per 1,000 knee arthroplasty patients of approximately USD 2.1 million. The earlier study, based on the years 1987-1989 in UK, reported a somewhat higher average hospital cost of both non-infected and infected patients in the CHX group, and concluded that preoperative whole-body disinfection with chlorhexidine was not cost-effective for reducing wound infection (Lynch *et al*., 1992).

12. Discussion
Our previous HTA report from 2015 (Rahm *et al.*, 2015) showed no evidence for a positive effect of chlorhexidine. The current update showed that, based on low certainty of evidence, the implant infection (sSSI) rate after lower extremity total joint arthroplasty may be lower after preoperative CHX compared with soap wash (GRADE ⊕⊕◯◯), and that preoperative showering/bathing with CHX compared with placebo may result in a moderate decrease to a slight increase in surgical site infection rate (GRADE ⊕⊕◯◯). However, it is uncertain whether preoperative CHX wash affects SSI rates compared with preoperative soap wash (GRADE ⊕◯◯◯). For all other comparisons the certainty of evidence was very low. The confidence intervals of all the pooled effect estimates, i.e. SSI rate for the comparisons CHX wash C1: placebo, C2: soap, and C3: no wash, included a negative effect and there is a need for further large studies.

In the included studies, preoperative CHX wash was compared with placebo (C1), regular soap (C2), no wash (C3), local CHX wash (C4), and no instruction (C5). Meta-analyses of RCTs were done for the outcome surgical site infection (SSI) for four different comparisons: CHX vs placebo (C1), CHX vs soap (C2), and CHX vs no wash (C3), for the comparison no instruction (C5) three cohort studies were pooled. The meta-analyses showed no significant differences in SSI rates between CHX and the control groups (e.g. Figures 1-3).

A majority of the included studies had some or serious problems with regard to directness, study limitations and/or precision. We defined the certainty of evidence lower than that reported (GRADE ⊕⊕⊕⊕) in a recent Cochrane review (Webster and Osborne, 2015). However, the latter review had a different PICO allowing comparison of all kinds of surgical patients. Our current PICO was limited to patients undergoing "clean" surgery. When both clean and potentially contaminated operations were included in a study, only the "clean" surgery patients were included in our analyses. Furthermore, we also included cohort studies, while the Cochrane analysis was confined to RCTs. In addition, we considered the quality of several of the studies somewhat lower than the Cochrane reviewers (Webster and Osborne, 2015).

A drawback of nearly all included studies in our present SR was the short time of follow-up, usually varying between two to six weeks. The length of follow-up was not adequately reported in some studies.

Only one RCT and two cohort studies investigated sSSI/implant infections after prosthetic implant surgery, which is a more critical outcome than SSI in general. The latter is usually defined as reddening of the operation scar and/or formation of pus. One RCT investigated CHX versus soap wash and reported a significantly reduced sSSI rate in the CHX group. Serious surgical site infectionsnfections after prosthetic surgery are often caused by low-virulence opportunistic bacteria, e.g. coagulase-negative staphylococci, and may appear many months or even years after surgery. Only two studies comparing CHX with no instruction investigated sSSI, A meta-analysis of the three cohort studies, identified in this update, did not reveal any significant difference between CHX wash compared with no instruction regarding SSI rate.

There is thus currently only low certainty of evidence that CHX, compared with soap wash, may reduce sSSI rates in lower limb arthroplasty patients but no evidence in favour of CHX for all other comparisons and outcomes. The widespread belief in the use of preoperative CHX showering to reduce SSI rate is likely to originate from an extrapolation of results in studies that have shown that this procedure significantly reduces the number of skin bacteria. However, such a reduction in bacterial numbers is no guarantee for a lowered risk of SSI, because 1) The bacteria causing SSI may not derive from the patient, but from the hospital staff, air or other sources, 2) The bacteria causing SSI may derive from the patient. Although the bacteria are reduced at the time of surgery, they might rebound in the area and cause infection at a later time-point. 3) Although CHX kills pathogens, it also kills normal commensal bacteria that might provide protection against infection.

The observed limited documentation in the current systematic review of available studies demonstrates a need for adequately powered well-conducted, randomised controlled double-blind studies, particularly investigating the potential benefit of CHX wash in relation to the most critical outcomes, including serious SSI/implant infections.

13. Future perspective

Scientific knowledge gaps

Regarding our focused question, there were no studies that had compared CHX with placebo (C1), regular soap (C2), no wash (C3), local wash (C4), and no instruction (C5) for the outcome mortality. Reintervention, and number of days in hospital were only reported in one and two studies respectively.
Only one RCT and two cohort studies had addressed the critical outcome implant infection, but only for the comparisons CHX vs soap (C2) and no instruction (C5) respectively. For the most frequently studied outcome SSI, covering all here issued comparisons the follow up periods in general were too short to evaluate late SSI. The identified knowledge gaps could be addressed in adequately powered RCTs with longer follow up periods, or validated large scale register studies.

Ongoing research 2015

A search in the Clinical trials database (clinicaltrials.gov) identified six RCTs potentially relevant for the current PICO:

NCT01090479: RCT comparing the CHX cloths with a control group which will be performing an ordinary shower prior to surgery. Primary Outcome Measure: clinically diagnosed infection. Status: completed. Published: Murray *et al*., (2011).

NCT02469311: RCT comparing 2% CHX-impregnated cloth skin wash the night before and the morning of surgical admission with bath with soap and water, in patients scheduled for total hip arthroplasty or total knee arthroplasty. Primary Outcome Measure: incidence of periprosthetic infection. Status: completed - last updated: June 12, 2015.

NCT02490631: RCT comparing 2% chlorhexidine skin preparation cloths for the prevention of SSI in spine patients with standard of care skin cleansing by nursing staff. Primary Outcome Measure: SSI. Status: recruiting.

NCT00130221: RCT comparing 2% CHX bath with soap and water bath. Primary Outcome Measure: Primary blood stream infections and culture negative sepsis. Status: completed. Published: not surgery patients, but medical intensive care unit patients (Bleasdale *et al*., 2007).

NCT01425697: RCT comparing 2% CHX cloths with standard of care preoperative preparation. Primary Outcome Measure: SSI. Status: completed. No study results posted.

NCT02385708: RCT comparing 2% CHX gluconate cloths with routine standard of care. Primary Outcome Measure: SSI. Status: recruiting.

Ongoing research - updated HTA, 2020:
A search in the Clinicaltrials.gov database (2019-10-25) and in the WHO ICTRP database (2019-10-25) resulted in 55 and 104 studies, respectively, two of which were relevant for the question at issue:

NCT03001102: "Preoperative Bath in Patients Submitted to Hip Arthroplasty". An RCT from Brazil comparing CHX wash with soap, primary outcome SSI. Status: Completed in March 2018. No results or publications attached to the record.

NCT03838575: "Reduction of Surgical Site Infection Using Several Novel Interventions (ROSSINI 2)". An international multi-centre RCT with several comparisons, but only with CHX vs. no wash comparison relevant for the here addressed PICO. Status: Recruiting, last update posted June 2019. Estimated completion Feb 2022.

14. Participants in the project

The question was nominated by

Anna Wallman, Head Office, Region Västra Götaland, Gothenburg, Sweden

Participants from the HTA-centrum

Lennart Jivegård, MD, PhD, Associate Professor of surgery, Senior University Lecturer, HTA-centrum, Region Västra Götaland, Gothenburg, Sweden
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Pernilla Rönnholm, project coordinator, Region Västra Götaland, Gothenburg, Sweden

External reviewer

Michael Breimer, MD, PhD, Professor/Consultant surgeon, Dept of Surgery, Sahlgrenska Academy at University of Gothenburg, Sweden

Conflicts of interest

None.

Project time

HTA was accomplished during the period of 2019-06-12 – 2020-02-26
Literature searches were made in August 2019.

Appendix 1: PICO, study selection, search strategies, and references

Question(s) at issue: Prior to "clean surgery" through intact skin, is chlorhexidine whole body wash better than no chlorhexidine wash regarding mortality, serious surgical site infection (sSSI): implant infection, septicaemia, surgical site infection (SSI), reintervention and length of hospital stay?

PICO: (*P=Patient I=Intervention C=Comparison O=Outcome*)

P	Patients undergoing so called "clean surgery" where the operation is performed through intact skin
I	Preoperative whole body wash with chlorhexidine
C	No chlorhexidine wash: C1: Placebo C2: Soap C3: No wash C4: Local wash C5: No instruction
O	<u>Critical for decision making</u> Mortality Implant infection Septicaemia Surgical site infection <u>Important but not critical for decision making</u> Reintervention Number of days in hospital <u>Not important for decision making</u> (None)

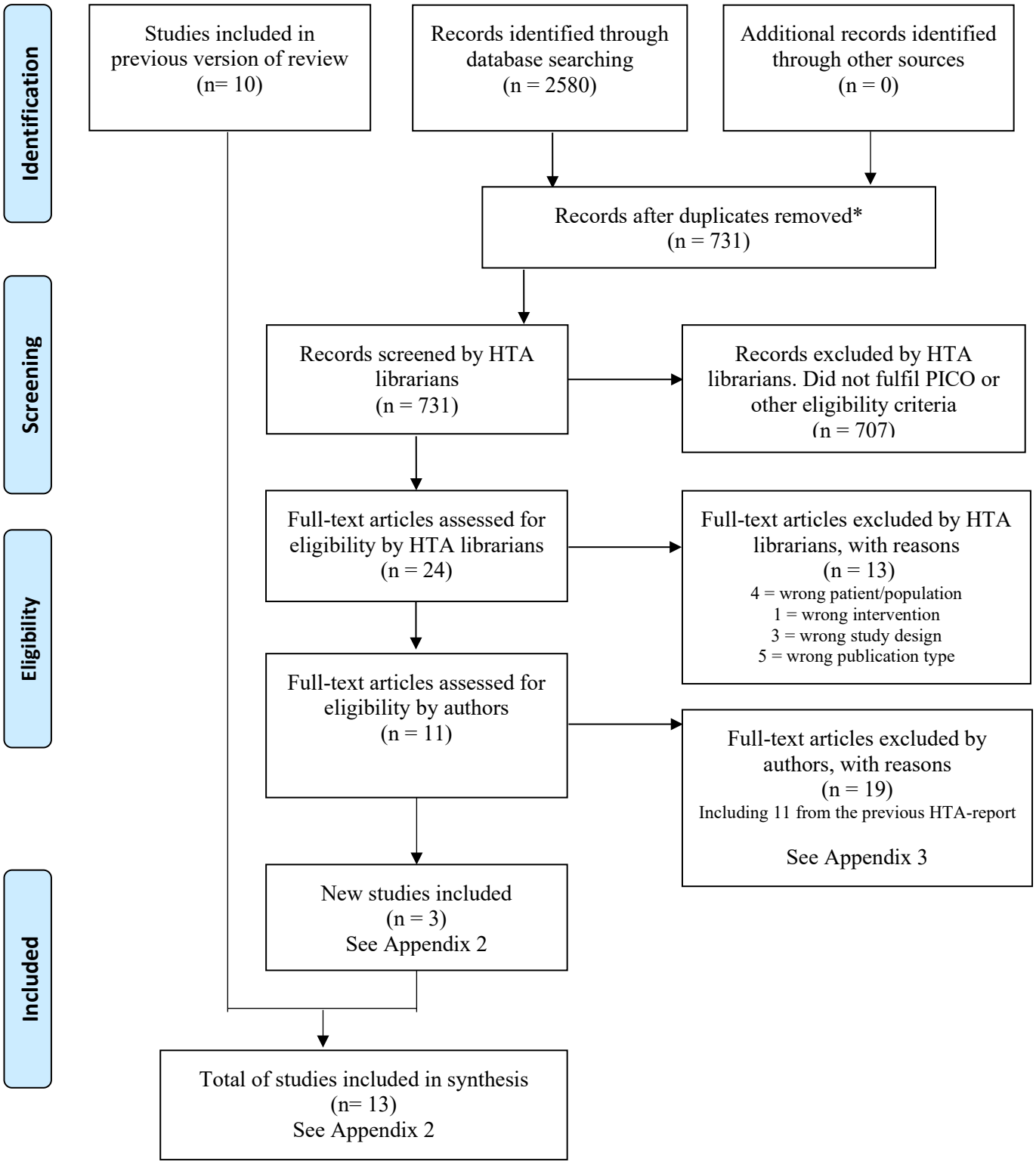
Eligibility criteria

Study design:
Systematic reviews
Randomised controlled trials
Non-randomised controlled studies if ≥ 1000 patients
Case series if ≥ 1000 patients

Language:
English, Swedish, Norwegian, Danish.

Publication date: 2015-
As this HTA is an update of a previous HTA-report (Rahm et al., 2015), literature searches were made with publication date from when the previous searches were made. Relevant articles from the previous report have also been included in this update.

Selection process – flow diagram



Modified from Moher et al., 2009

*Removal of duplicates also implicate removal of references retrieved in the previous searches made in May 2015

Search strategies

Database: PubMed
Date: 29 Aug 2019
No. of results: 757

Search	Query	Items found
#29	**Search #21 NOT #24 Filters: Danish; English; Norwegian; Swedish**	**757**
#25	Search #21 NOT #24	785
#24	Search #22 OR #23	6303944
#23	Search ((animals[mh]) NOT (animals[mh] AND humans[mh]))	4613038
#22	Search (Editorial[ptyp] OR Letter[ptyp] OR Comment[ptyp])	1756105
#21	Search #10 AND #18 AND #20	851
#20	Search #15 OR #19	1919471
#19	Search preadmission [tiab]	1417
#18	Search #16 OR #17	189653
#17	Search Baths[mesh]	5182
#16	Search shower*[tiab] OR bath*[tiab] OR wash*[tiab] OR cleans*[tiab] OR cloth[tiab] OR cloths[tiab] OR scrub[tiab] OR soap[tiab]	187967
#15	Search #11 OR #12 OR #13 OR #14	1918330
#14	Search preoperative [tiab] OR pre-operative [tiab] OR perioperative [tiab] OR peri-operative [tiab]	329958
#13	Search preoperative care [mesh] OR perioperative care [mesh]	145544
#12	Search infection[tiab] OR infections[tiab] OR infected[tiab]	1509981
#11	Search "Surgical Wound Infection"[Mesh]	35027
#10	Search chlorhexidine	11809

Database: Embase 1974 to 2019 August 28 (OvidSP)
Date: 29 Aug 2019
No. of results: 935

#	Searches	Results
1	exp chlorhexidine/ or exp chlorhexidine acetate/ or exp chlorhexidine gluconate/	20528
2	chlorhexidine.ti,ab,kw,tn,rn.	20031
3	1 or 2	21956
4	exp surgical infection/	42409
5	(infection or infections or infected).ti,ab,kw.	1872674
6	exp preoperative care/	37394
7	exp perioperative period/	46312
8	(preoperative or pre-operative or perioperative or peri-operative or preadmission).ti,ab,kw.	469681
9	4 or 5 or 6 or 7 or 8	2346083
10	(Shower$ or bath$ or wash$ or cleans$ or cloth or cloths or scrub or soap).ti,ab,kw.	238420
11	exp bath/	9870
12	10 or 11	240521
13	3 and 9 and 12	1491
14	**limit 13 to ((embase or medline) and (danish or english or norwegian or swedish) and (article or article in press or conference paper or note or "review"))**	**935**

Database: CINAHL (EBSCOhost)
Date: 29 Aug 2019
No. of results: 483

#	Undran	Resultat
S14	**S3 AND S9 AND S12** Avgränsare - Språk: Danish, English, Norwegian, Swedish Utökning - Sök med relaterade ord; Sök med likvärdiga ämnesord Sökinställningar - Hitta alla mina söktermer	**483**
S13	S3 AND S9 AND S12	488
S12	S10 OR S11	34,824
S11	(MH "Bathing and Baths")	2,736
S10	TI (shower* OR bath* OR wash* OR cleans* OR cloth OR cloths OR scrub OR soap) OR AB (shower* OR bath* OR wash* OR cleans* OR cloth OR cloths OR scrub OR soap)	33,640
S9	S4 OR S5 OR S6 OR S7 OR S8	276,891
S8	TI (infection OR infections OR infected) OR AB (infection OR infections OR infected)	198,400
S7	TI (preoperative or pre-operative or perioperative or peri-operative or preadmission) OR AB (preoperative or pre-operative or perioperative or peri-operative or preadmission)	65,915
S6	(MH "Perioperative Care")	9,444
S5	(MH "Preoperative Care+")	19,479
S4	(MH "Surgical Wound Infection")	9,442
S3	S1 OR S2	3,919
S2	TI chlorhexidine OR AB chlorhexidine	2,822
S1	(MH "Chlorhexidine")	3,050

Database: The Cochrane Library
Date: 29 Aug 2019
No. of results: 405
Cochrane Reviews 15
Cochrane Protocols 1
Trials 388
Clinical Answers 1

ID	Search	Hits
#1	(chlorhexidine):ti,ab,kw (Word variations have been searched)	4170
#2	MeSH descriptor: [Chlorhexidine] explode all trees	2029
#3	#1 OR #2	4170
#4	MeSH descriptor: [Surgical Wound Infection] explode all trees	3213
#5	(infection or infections or infected):ti,ab,kw (Word variations have been searched)	114541
#6	MeSH descriptor: [Preoperative Care] explode all trees	5730
#7	MeSH descriptor: [Perioperative Care] explode all trees	11759
#8	(preoperative or pre-operative or perioperative or peri-operative or preadmission):ti,ab,kw (Word variations have been searched)	51733
#9	#4 OR #5 OR #6 OR #7 OR #8	165804
#10	MeSH descriptor: [Baths] explode all trees	302
#11	(shower* or bath* or wash* or cleans* or cloth or cloths or scub or soap):ti,ab,kw (Word variations have been searched)	33709
#12	#10 OR #11	33709
#13	#3 AND #9 AND #12	524
#14	(clinicaltrials or trialsearch):so	262663
#15	**#13 NOT #14**	**405**

The web-sites of **SBU** and **Folkehelseinstituttet** were visited 29 Aug 2019
Nothing relevant to the question at issue was found

Reference lists
A comprehensive review of reference lists brought 0 new records

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Report: HTA Update: Chlorhexidine wash prior to surgical procedures
Appendix 2 – Characteristics of included studies alphabetically according to study design

Author, Year, Country	Study Design	Study Duration	Study Groups; Intervention vs control	Patients total (n)	Mean Age (years)	Men (%)	Outcome variables
Byrne, 1992	RCT	32 months	Chlorhexidine vs Placebo (C1)	1,754 1,753	Not stated	47% 48%	Mortality SSI Adverse events
Earnshaw, 1989	RCT	Not specified	Chlorhexidine vs Soap (C2)	31 35	66 (group median)	84%	Mortality SSI
Hayek, 1987	RCT	24 months	Chlorhexidine vs Placebo (C1) vs Soap (C2)	689 700 626	57 56 55	35%	SSI
Kapadia, 2016	RCT	9 months	Chlorhexidine vs Soap (C2)	307 275	61 62	37%	Implant infection SSI Adverse events
Randall, 1993	RCT	6 months	Chlorhexidine vs Soap (C2) vs No washing (C3)	32 30 32	Not specified	Not specified	SSI
Rotter, 1988	RCT	Not specified	Chlorhexidine vs Placebo (C1)	1,450 1,400	Not stated	52% 52%	SSI Adverse events
Veiga, 2009	RCT	16 months	Chlorhexidine vs Placebo (C1) vs No instruction (C5)	50 50 50	38 (group mean)	21% (alla)	SSI Adverse events
Wihlborg, 1987	RCT	6 years	Chlorhexidine vs Local wash (C4) vs No washing (C3)	541 552 437	> 60 years: 43% > 60 years: 45% > 60 years: 42%	Not specified	SSI Adverse events
Ayliffe, 1983	Cohort	15 months	Chlorhexidine vs Soap (C2)	2,703 2,833	Not specified	Not specified	SSI
Chan, 2018	Cohort	4 years	Chlorhexidine vs No instruction (C5)	2,541 1,725	58 59	51% 49%	SSI Length of hospital stay
Colling, 2015	Cohort	32 months	Chlorhexidine vs No instruction (C5)	2,349 1,693	62 (median) 66 (median)	39% 43%	Implant infection SSI
Kapadia, 2013c	Cohort	4 years	Chlorhexidine vs No instruction (C5)	557 1,901	Not specified	Not specified	Implant infection SSI
Prabhu, 2017	Cohort	4 years	Chlorhexidine vs No washing (C3)	2,209 1.715	58 57	46 46	SSI Reintervention Length of hospital stay

RCT = randomized controlled trial, SSI = Surgical site infection

Appendix 3
Excluded articles
HTA Update: Chlorhexidine wash prior to surgical procedures

Study **First author, publication year**	**Reason for exclusion**
Agarwal, 2018	Wrong Intervention
Bailey, 2011	Wrong O (only computer simulated outcomes)
Byrne, 1994	Duplicate publication (Byrne, 1992)
Chien,2014	Wrong I (mixed interventions)
Dizer, 2009	Wrong P (mixed abdominal surgery patients)
Hayek, 1988	Wrong O (no data on SSI for clean surgery)
Johnsson, 2010	Duplicate publication (Kapadia 2013c)
Johnson, 2013	Duplicate publication (Kapadia 2013c)
Garibaldi, 1988	Wrong outcome (no relevant SSI data)
Kapadia, 2013a	Duplicate publication (Kapadia, 2013c)
Kelley, 2018	Wrong Intervention
Kim, 2016	Wrong population
Kline, 2018	Wrong I, C and O
Rao, 2004	Wrong I (mixed interventions)
Savage, 2013	Wrong study design (case-control). No extractable data
Schaffzin, 2018	Wrong I (mixed interventions)
Schweizer, 2015	Wrong I (mixed interventions)
Smith, 2019	Wrong Intervention
Sporer, 2016	Wrong I (mixed interventions)

Appendix 4:1
HTA Update: Chlorhexidine wash prior to surgical procedures
Outcome variable: Implant infections
Abbreviations: Chx = Chlorhexidine, Pl = Placebo, S = Soap, NI = No instructions, NW = No wash, LW = Local wash

* + No or minor problems
? Some problems
- Major problems

Author, year, country	Study design	Number of patients n=	With drawals - dropouts	Results						Comments	* Directness	* Study limitations	* Precision
				Chlor-hexidine I	Placebo C1	Soap C2	No wash C3	Local wash C4	No Instruc-tion C5				
Kapadia, 2016	RCT	I = 307 C= 275	I = 35 C = 8	1 (0.4%)	NR	8 (2.9%) p= 0.0195	NR	NR	NR	Lower extremity total joint arthroplasty, 1 year follow up p-value calculated by Fisher's test, per protocol (n= I: 272 vs C: 267), 11.4% discontinued treatment in the intervention group, vs 2.9% in the control group.	?	?	?
Colling, 2015	Cohort	I = 2,349 C5 = 1,693	Not specified	1.1%	NR	NR	NR	NR	0.9% n.s.*	Arthroplasties, retrospective, 1 year follow up, control in different hospital, 2 showers, SSI = CDC definition * Calculated from data, Fischer's exact test	?	-	?
Kapadia, 2013c	Cohort	I = 557 C5 = 1,901	Not specified	0.5%* 0.6%≠	NR	NR	NR	NR	1.7%* p=0.043 2.2%≠ p=0.021	2 showers, 1 year follow up * Hip surgery ≠ Knee surgery	+	-	+/?

CDC = Centers for Disease Control and Prevention, NR = Not reported, RCT = randomised controlled trial, SSI = Surgical site infection.

Appendix 4:2
HTA Update: Chlorhexidine wash prior to surgical procedures
Outcome variable: SSI
Abbreviations: Chx = Chlorhexidine, Pl = Placebo, S = Soap, NI = No instructions, NW = No wash, LW = Local wash

* + No or minor problems
? Some problems
- Major problems

Author, year, country	Study design	Number of patients n=	With drawals - dropouts	Results						Comments	* Directness	* Study limitations	* Precision
				Chlor-hexidine I	Placebo C1	Soap C2	No wash C3	Local wash C4	No Instruc-tion C5				
Byrne, 1992	RCT	I = 111 C1= 120	NR	34.2%	40.8% n.s.	NR	NR	NR	NR	Mixed surgery (vascular surgery separated), 1 month follow up Pus, ASEPSIS score > 10 3 showers	?	?/+	+
Earnshaw, 1989	RCT	I = 31 C2 = 35	0	26%	NR	11% p=0.12	NR	NR	NR	Vascular reconstructive surgery SSI definition: pus discharge, cellulitis 1 month follow up 2 baths	-	-	-
Hayek, 1987	RCT	I = 472 C1 = 470 C2 = 450	?	7.2%	10.0% n.s.	10.2% n.s.	NR	NR	NR	Placebo had antimicrobial properties, 6 weeks follow up, 2 showers	-	-	-
Kapadia, 2016	RCT	I = 307 C= 275	I = 35 C = 8	2 (0.7%)	NR	13 (4.9%) p=0.0035	NR	NR	NR	Lower extremity total joint arthroplasty, 1 year follow up Deep + superficial infections p-value calculated by Fisher's test, per protocol (n= I: 272 vs C: 267), 11.4% discontinued treatment in the intervention group, vs 2.9% in the control group.	?	?	?
Randall, 1993	RCT	I = 32 C2 = 30 C3 = 32	?	37.5%	NR	33.3% n.s.	28.1% n.s.	NR	NR	Vasectomy, 7 days follow up, 1 single shower, SSI = open wound, purulent or serous discharge	?	-	?
Rotter, 1988	RCT	I = 1,450 C1 = 1,400	140 (group drop out)	2.62%	2.36% n.s.	NR	NR	NR	NR	”Clean surgery”, 21 days follow up, SSI = pus discharge 2 showers	+	+/?	?

Appendix 4:2
HTA Update: Chlorhexidine wash prior to surgical procedures
Outcome variable: SSI
Abbreviations: Chx = Chlorhexidine, Pl = Placebo, S = Soap, NI = No instructions, NW = No wash, LW = Local wash

* + No or minor problems
? Some problems
- Major problems

Author, year, country	Study design	Number of patients n=	With drawals - dropouts	Results						Comments	* Directness	* Study limitations	* Precision
				Chlor-hexidine I	Placebo C1	Soap C2	No wash C3	Local wash C4	No Instruc-tion C5				
Veiga, 2009	RCT	I = 50 C1 = 50 C5 = 50	0	2%	2% p=0.6	NR	NR	NR	0% n.s	Plastic surgery, 1 double shower, SSI = CDC classification, 30 days follow up	?	?	-
Wihlborg, 1987	RCT	I = 541 C3 = 437 C4 = 552	3 (group drop out)	1.7%	NR	NR	4.6% p<0.01	4.2% p<0.05	NR	Biliary, breast, inguinal hernia, , SSI definition: pus. 1 double shower Follow-up during hospital stay	?/+	?/-	?
Ayliffe, 1983	Cohort	I = 787 C2 = 750	Not specified	3.6%	NR	4.0% n.s.	NR	NR	NR	Mixed surgery, 1 shower, SSI = serous or purulent discharge, follow up not specified	+	-	-
Chan, 2018	Cohort	I = 2,541 C = 1,725	Not specified	0.2% (±0.1)	NR	NR	NR	NR	0.7% (±0.3) n.s	Spinal surgery 4,266 consecutive patients, historical controls. 90-days follow-up for SSI	?	-	?
Colling, 2015	Cohort	I = 2,349 C5 = 1,693	Not specified	1.96%	NR	NR	NR	NR	1.95% (n.s.)	Arthroplasties, retrospective, 1 year follow up, control in different hospital, 2 showers, SSI = CDC definition	?	-	?
Kapadia, 2013c	Cohort	I = 557 C5 = 1,901	Not specified	0.5%* 0.6%±	NR	NR	NR	NR	1.7%* p=0.043 2.2%± p=0.021	2 showers, 1 year follow up * Hip surgery ± Knee surgery Only periprosthetic infections reported	+	-	+/?
Prabhu, 2017	Cohort	I = 2,209 C = 1,715	Not specified	OR 1.49, (95%CI 1.05 to 2.11) p< 0.05	NR	NR	See I	NR	NR	Ventral hernia repair, 30-days follow up Reported only OR for CHX vs No wash: OR 1.49 95%CI (1.05 to 2.11), <0.05	+	?	?

CDC = Centers for Disease Control and Prevention, NR = Not reported, RCT = randomised controlled trial, SSI = Surgical site infection.

Appendix 4:3
Project: HTA Update: Chlorhexidine wash prior to surgical procedures
Outcome variable: Adverse events

Author, year, country	Study design	Number of patients n=	With drawals - dropouts	Results						Comments
				Chlorhex-idine I	Placebo C1	Soap C2	No wash C3	Local wash C4	No Instruc-tion C5	
Byrne, 1992	RCT	I = 1,754 C1= 1,753	23 (group dropout)	0.51% (n=9)	0.57% (n=10)	NR	NR	NR	NR	Skin irritation
Kapadia, 2016	RCT	I = 307 C= 275	I = 35 C = 8	1	NR	0	NR	NR	NR	Allergic skin reaction
Rotter, 1988	RCT	I = 1,450 C1 = 1,400	140 (group drop out)	0.34% (n=5)	0.36% (n=5)	NR	NR	NR	NR	Itching or reddening of skin
Veiga, 2009	RCT	I = 50 C1 = 50 C5 = 50	0	0	0	NR	NR	NR	0	No adverse events seen
Wihlborg, 1987	RCT	I = 541 C4 = 552 C5 = 437	3 (group drop out)	<1%	NR	NR	Not specified	Not specified	NR	Skin irritation

NR = Not reported, RCT = Randomised controlled trial.

Components of this Health Technology Assessment

- ☑ Description of methods
- ☑ PICO
- ☑ Full literature search
- ☑ Flowchart
- ☑ Selection based on relevance
- ☑ Quality assessment
- ☑ Data tabulation
- ☑ Evidence synthesis
- ☐ Meta-analysis
- ☑ Certainty of evidence by GRADE
- ☑ Summary
- ☑ Economical aspects
- ☑ Organisational aspects
- ☑ Ethical aspects
- ☑ Ongoing studies
- ☑ Excluded articles
- ☑ Participation of experts
- ☑ External review
- ☑ Knowledge gaps identified
- ☑ Conflict of interest reported

Region Västra Götaland, HTA-centrum

Health Technology Assessment
Regional activity-based HTA

HTA

Health technology assessment (HTA) is the systematic evaluation of properties, effects, and/or impacts of health care technologies, i.e. interventions that may be used to promote health, to prevent, diagnose or treat disease or for rehabilitation or long-term care. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in health care.

To evaluate the certainty of evidence the Centre of Health Technology Assessment in Region Västra Götaland is currently using the GRADE system, which has been developed by a widely representative group of international guideline developers. According to GRADE the level of evidence is graded in four categories:

High certainty of evidence	= (GRADE⊕⊕⊕⊕)
Moderate certainty of evidence	= (GRADE ⊕⊕⊕O)
Low certainty of evidence	= (GRADE ⊕⊕OO)
Very low certainty of evidence	= (GRADE ⊕OOO)

In GRADE there is also a system to rate the strength of recommendation of a technology as either “strong” or “weak”. This is presently not used by the Centre of Health Technology Assessment in Region Västra Götaland. However, the assessments still offer some guidance to decision makers in the health care system. If the level of evidence of a positive effect of a technology is of high or moderate quality it most probably qualifies to be used in routine medical care. If the level of evidence is of low quality the use of the technology may be motivated provided there is an acceptable balance between benefits and risks, cost-effectiveness and ethical considerations. Promising technologies, but a very low quality of evidence, motivate further research but should not be used in everyday routine clinical work.

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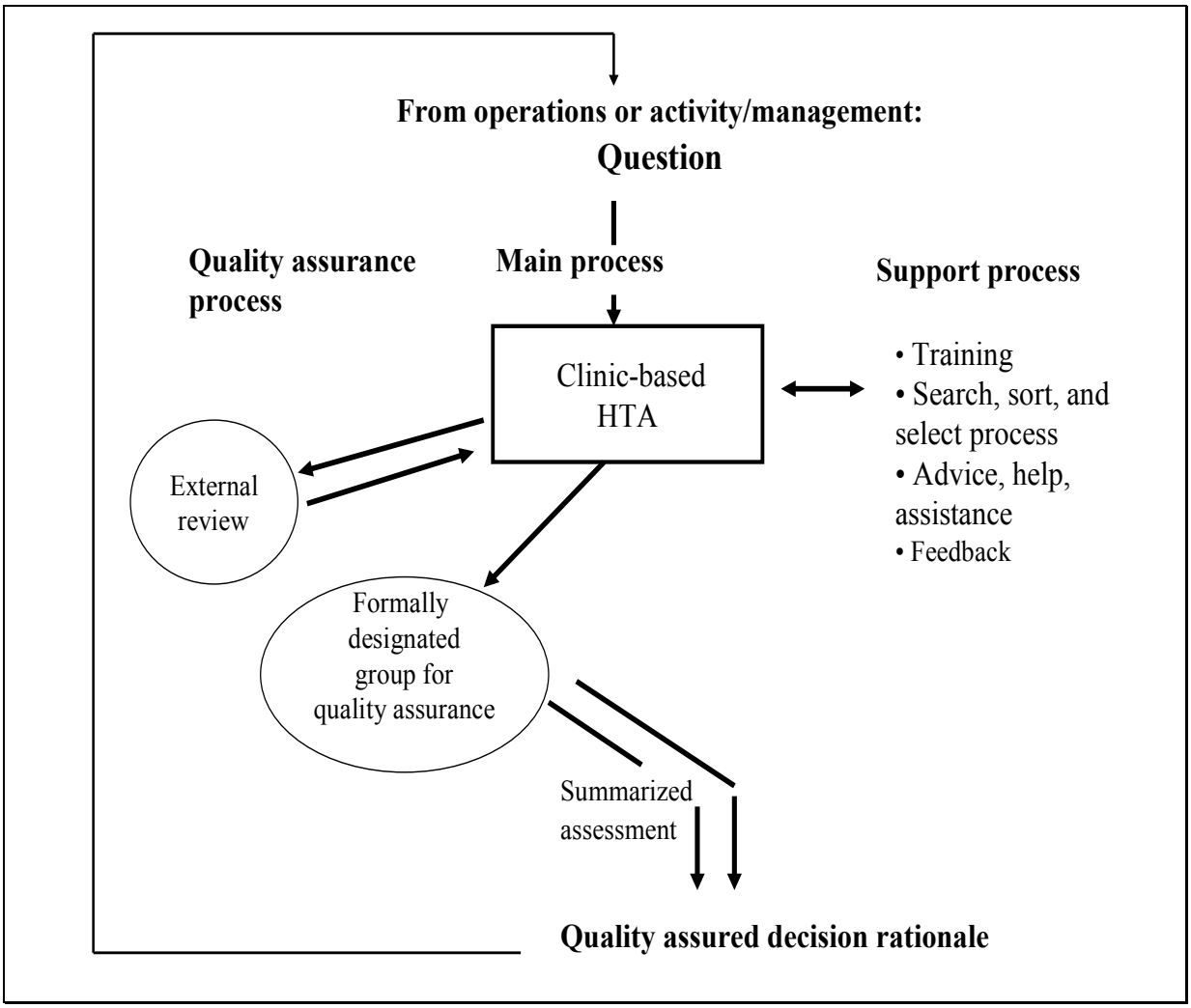
Head of HTA-centrum


From operations or activity/management:
Question
Quality assurance process
Main process
Support process
Clinic-based HTA
• Training
• Search, sort, and select process
• Advice, help, assistance
• Feedback
External review
Formally designated group for quality assurance
Summarized assessment
Quality assured decision rationale

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