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► To cite this version:

V. Forget, O. Azzam, C. Khouri, C. Landelle. What is the benefit of preoperative washing with chlorhexidine gluconate-impregnated cloths on the incidence of surgical site infections? A systematic review and meta-analysis. *Infectious Diseases Now*, 2022, 52 (4), pp.185-192. <10.1016/j.idnow.2022.01.007>. <hal-04762583>

HAL Id: hal-04762583

<https://hal.science/hal-04762583v1>

Submitted on 13 Nov 2024

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What is the benefit of preoperative washing with chlorhexidine gluconate-impregnated cloths on the incidence of surgical site infections? A systematic review and meta-analysis

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An abstract containing partial data was presented at the *International Consortium for Prevention and Infection Control (ICPIC) 2019* (Geneva, Switzerland).

Declarations

- **Funding:** This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors
- **Declaration of interest:** None.

Key-words:

Preoperative washing; preoperative bathing; chlorhexidine cloths; surgical site infections; orthopaedic surgery

Abbreviations:

CENTRAL: Cochrane Central Register of Controlled Trials

CDC: Centres for Disease Control

CHG: chlorhexidine gluconate

CI: confidence interval

GRADE: Grading of Recommendations Assessment, Development and Evaluation

OR: Odds-Ratio

PICO: Population, Intervention, Comparison, Outcomes

RCT: Randomized controlled trials

RR: Relative Risk

SSI: surgical site infections

WHO: World Health Organisation

WOS: Web of science

1. Introduction

Worldwide, the incidence of surgical site infections (SSI) ranges from 1.2% to 23.6% in low- or middle-income countries, and from 1.2% to 5.2% in developed countries [1]. SSI can be responsible for a decrease in quality of life [2], a rise in mortality and a longer hospital stay, sequelae for the patient and additional financial costs [1–3].

In order to prevent these SSI, several preventive measures exist, including preoperative washing. According to the recommendations for the prevention of SSI by the World Health Organisation (WHO) [4], preoperative washing should be carried out before every surgical intervention. Regarding the kind of soap to use, the WHO suggests an ordinary or antimicrobial soap. Several literature reviews have assessed the benefit of preoperative washing with antiseptics to prevent SSI [5,6]. In our university hospital, we previously identify lack of preoperative antiseptic showers as a risk factor of *Staphylococcus aureus* SSI after orthopaedic surgery [7]. But the authors of previous literature reviews concluded that the benefit of preoperative washing with chlorhexidine gluconate (CHG) compared to other products, to a placebo or to ordinary soap, was not proven.

As a consequence, due to limited and very low-quality proof, the WHO scientific group has not formulated recommendations on the use of chlorhexidine-impregnated cloths with the aim of reducing SSI. Used without rinsing, CHG 2% cloths have shown a more significant lasting effect than CHG 4% soap. In fact, the average skin concentrations of CHG are significantly higher when using CHG 2% cloths compared to CHG 4% antiseptic soap [8]. Moreover, it has been shown that skin concentrations after the use of CHG 4% antiseptic soap are inferior to the minimum inhibitory concentration for staphylococci [8]; this is not found after using the cloths. CHG cloths without rinsing could be used for multiple trauma

patients, patients who experience pain when moved, or patients for whom a preoperative shower is difficult to carry out.

In this context, the objectives of this systematic review and meta-analysis were to assess the benefit of the preoperative washing of surgery patients with CHG-impregnated cloths, comparing to other preoperative washing or no preoperative washing, on the incidence of SSI, the mortality attributable to SSI, and skin bacterial colonisation.

2. Methods

The main objective of this study was to evaluate whether preoperative washing with CHG-impregnated cloths was more effective for reducing the incidence of SSI in surgical patients compared with washing with antiseptic soap, ordinary soap, with a placebo, or with no preoperative washing. The PICO (Population, Intervention, Comparison, Outcomes) methodology was followed:

- Population: The population consisted of patients who had undergone a surgical intervention (any type of procedure), as an inpatient or outpatient, aged over 18 years. Intensive care patients were excluded.
- Intervention: The intervention consisted in preoperative washing, without rinsing, with cloths impregnated with CHG 2%. Postoperative washings were excluded.
- Comparator: The comparator was the performance of preoperative washing with antiseptic soap, or ordinary soap, or a placebo, or no preoperative washing, or no washing instructions.
- Outcome: The main outcome was the occurrence of an SSI up to 30 days after the intervention or 1 year if material was implanted. Secondary outcomes were the mortality attributable to SSI and skin bacterial colonisation.

The databases searched were Medline (PubMed), Cochrane Central Register of Controlled Trials (CENTRAL), Web of science (WOS) and Clinical Trial, accessed on 30 June 2018. A discussion with the authors was scheduled if there was a need for more information on their work. The complete strategy for automated searching is available in Electronic Supplementary Material. Two independent reviewers (VF, OA) carried out the selection process, which consisted in identifying the references by searching databases or other sources, excluding references due to non-relevance of the title or of the abstract, deleting duplicates, and then including the articles in the review according to inclusion criteria. Disagreements were resolved by discussion or after consultation with the senior author if necessary.

Included studies were randomised controlled trials (RCT), case-control studies, cohort studies (with control group), and quasi-randomised trials without language restrictions.

Following which, the following variables were extracted: type of surgery, number of patients operated on, time of the preoperative washing with CHG-impregnated cloths, time and the product used as a comparator for the preoperative washing, number of SSIs, Relative Risk (RR) or Odds-Ratio (OR), definition of SSI applied, types of SSI, skin bacterial colonisation, and the mortality rate attributable to the SSI. The authors extracted the data in double reading into a predefined spreadsheet form.

The quality of the studies was evaluated by a single author (VF) using a tool from the Cochrane Collaboration for evaluation of the risk of bias in randomised controlled studies [9], and the Newcastle-Ottawa Quality Assessment Scale for cohort studies [10]. Publication bias was assessed by visual inspection of the funnel plot. Grading of Recommendations Assessment, Development and Evaluation (GRADE) was used to evaluate the overall quality of evidence [11]. Due to the low level of heterogeneity, the results were synthesised through

a meta-analysis using the inverse-variance fixed effect model,. Heterogeneity was evaluated according to I^2 , an $I^2 > 50\%$ reflecting a significant heterogeneity. The effect size chosen to synthesise the results were the crude OR and its Confidence Interval set at 95% (95%CI). The statistical analyses were carried out with Review Manager (RevMan) software version 5.3.

3. Results

A total of 1,108 publications were identified, all publications were in English language. A total of 26 references were selected according to the titles and abstracts, 15 after deleting duplicates, of which 9 were examined for the purposes of eligibility (Figure 1, Table 1). Among the 9 studies, 8 studies used SSI incidence as their main objective, 1 study was excluded from the meta-analysis since it did not deal with complete preoperative washing but rather with washing the operated area (shoulder) [12] and 4 studies [13–16] could be considered preliminary to the other studies retained because the authors published their results several times, including more patients. All in all, 3 were included in the meta-analysis, including 2 observational studies [17,18], and 1 RCT [19], all of which concerned orthopedic surgery.

In the Kapadia et al. RCT [19] on total hip or knee arthroplasty, whether primary or replacement, 275 patients were instructed to use CHG 2% cloths all over their bodies the evening before and the morning of the intervention (intervention group) and 279 patients were instructed to wash themselves with antibacterial soap and water the day before admission (control group). In the control group, 8 (2.9%) deep periprosthetic SSIs occurred versus 1 (0.4%) in the intervention group (OR=8.15 [95%CI 1.01-65.6]; p=0.049).

In the prospective cohort by Kapadia *et al.* [17] regarding total primary or replacement hip arthroplasty, 995 patients followed the instruction to use CHG 2% cloths all over their bodies

the evening before and the morning of the intervention and 2,846 were non-compliant i.e. these patients did not follow the protocol for using the cloths. Compliance was verified by asking patients to stick the cloths' packaging stickers on the instruction sheet given to them the day of the surgery, once they had been used. Patients were also surveyed the day of the surgery on proper use of the cloths. In the non-compliant group, which had not used the cloths, 46 (1.6%) deep infections occurred versus 6 (0.6%) in the group that used the cloths (RR=2.68 [95%CI 1.15-6.26]; p=0.02).

In the prospective cohort by Kapadia *et al.* 2016 [18] regarding total primary or replacement knee arthroplasty, 991 patients followed the instruction to use the CHG 2% cloths all over their bodies the evening before and the morning of the intervention and 2,726 were not compliant (same definition as before). In the non-compliant group, which had not used the cloths, 52 (1.9%) deep infections occurred versus 3 (0.3%) in the group that used the cloths (RR=6.3 [95%CI 1.9-20.1]; p=0.002).

The meta-analysis of the 2 included observational studies [17,18] comparing the effect of compliance with preoperative washing, without rinsing, with cloths impregnated with CHG 2% versus non-compliance on the incidence of SSI showed an OR of 0.25 [95%CI 0.13-0.50]; $I^2=0.29$. The estimated effect sizes and their confidence intervals were represented in a forest-plot (Figure 2).

The RCT [19] provided an OR of 0.12 [95%CI 0.02-1.00] in favour of the use of CHG 2% cloths on the incidence of SSI in comparison with washing with antibacterial soap the day before surgery (Figure 3).

Due to the small number of studies, it was not possible to evaluate risk of publication bias by funnel-plot. Evaluation of the risk of bias in the RCT [19], using the Cochrane Collaboration tool (Table 2), suggested low risks of randomisation and attrition bias

(incomplete data results). It was not clearly noted whether the staff performing the surgical intervention were blinded. The event report bias was unclear, not having been mentioned in the SSI detection strategy. Using the Newcastle-Ottawa Quality Assessment Scale (Table 3) evaluation of the risk of bias in the cohort studies [17,18] suggested that the 2 observational studies did not have any pronounced bias for representativeness of the cohort, for selection of the non-exposed cohort, for verification of exposure, for comparability of the cohorts, for evaluation of the event and for the follow-up period, all 6 of these items having a score of A*. However, there was a bias concerning the demonstration of the absence of the initial event, with a score of B. The study by Kapadia et al. [18] showed bias in the adequacy of cohort monitoring and a score of B* for this item. According to the GRADE methodology used to evaluate the overall quality of evidence (Table 4), the RCT [19] had significant bias (lack of blinding), and indirect evidence (population heterogeneity could not be assessed with a single trial); as a result, the RCT [19] was of moderate quality. The 2 observational studies [17,18] had no significant bias, no incoherence or heterogeneity, no significant imprecision or problem of indirect evidence. Moreover, according to additional considerations, the level of evidence of the 2 observational studies [17,18] could be increased by 1 level as they showed significant effects with $RR < 0.5$ ($RR = 0.26$) (increase of 1 level of quality), meaning that without significant limitation and with strong effects, they presented with higher quality. With these judgment criteria, the overall quality of evidence of this meta-analysis was moderate.

Regarding the secondary objective of mortality attributable to SSI, no study provided a result on this point.

Regarding skin colonisation, 2 studies were available [12,20]. Murray *et al.* [12] carried out a RCT on patients who were about to undergo shoulder surgery; 50 patients

were asked to take a shower with soap and water the evening before and use CHG 2% cloths 1 hour after the evening shower and the morning of the intervention (intervention group); 50 other patients were asked to take a shower with soap and water the evening before and the morning of the intervention (control group). Skin swabs were taken from the shoulder when the patients were in the preoperative area. Regarding the bacterial culture from the skin sample taken from the shoulder to be operated on, before surgery 94% were positive in the control group versus 66% in the intervention group ($p=0.0008$). There was no SSI in either of the 2 groups.

Makhni *et al.* [20] carried out a controlled prospective cohort study on 16 volunteers to simulate spinal surgery. The first skin samples from each side of the neck were taken on the intake day and acted as reference samples for skin colonisation before the surgery. The patients showered the day before the surgery (the type of soap was not specified), and used CHG 2% cloths the evening before and the morning of the intervention on the right side of their neck, but did not use any cloths on the left side, which was considered as the control. After having used the CHG cloths the day before and the morning of, each side of the neck was again sampled individually. A non-significant average decrease in the number of colonies/mL, from 790 colonies/mL on the right side of the intervention versus a decrease of 536 colonies/mL on the left side ($p=0.059$), was highlighted.

4. Discussion

Our systematic review has shown that only 3 studies could be included in a meta-analysis, and they all concerned hip or knee arthroplasties. These studies showed benefit from the use of cloths impregnated with CHG. The results of this literature review, including 2 observational studies [17,18] and only one RCT [19], were in favour of the use of CHG-

impregnated cloths the evening before and the morning of the intervention, in comparison with not using them or washing with antibacterial soap the day before the intervention, the objective being to decrease the incidence of SSI.

The evaluation of the risk of bias in the RCT suggested moderate risks of bias and did not suggest pronounced bias in the cohort studies. According to the GRADE methodology, the overall quality of evidence of this meta-analysis was moderate. No study was found on the effect of the use of CHG cloths for preoperative washing on mortality attributable to SSI. Two non-comparable studies were found, demonstrating a tendency for the use of CHG cloths for preoperative washing to decrease bacterial colonisation [12,20].

Due to limited and very low quality of evidence, the WHO scientific group [4] that developed the recommendations for SSI prevention did not formulate any recommendations on the preoperative use of CHG-impregnated cloths. To study the benefit of preoperative washing with CHG cloths versus other types of preoperative washing, the WHO included a prospective cohort study showing with moderate quality of evidence that washing with CHG cloths could be beneficial in comparison with CHG soap (OR=0.32, 95%CI [0.13–0.77]; $p=0.01$). This was a before-and-after study that we excluded from our meta-analysis. To compare the effect of preoperative washing with CHG cloths versus no washing, the WHO included 2 cohort studies in which the patients with no preoperative washing were the patients not compliant with preoperative washing with CHG cloths. The meta-analysis performed by the WHO showed benefit from the use of CHG cloths (OR=0.27, 95%CI [0.09–0.79]; $p=0.02$), but with very low quality of evidence. While limited in number, the studies included in our review are of a higher quality.

However, the 3 studies included in our meta-analysis have limitations. The SSI definition used was that of the Musculoskeletal Infection Society and the International

Consensus Group on Periprosthetic Infections and not that of the Centres for Disease Control (CDC) and Prevention [21], which are the most widely used for epidemiological purposes. It bears mentioning that the infections were monitored for 1 year, which is adequate and rarely done in practice. In only one study was use of CHG cloths in the evening and morning compared to a shower with antiseptic soap the day before [19], without the authors specifying the type of antiseptic soap used, and in 2 other studies, it was compared to non-use in non-compliant patients in [17,18]. It is not possible, based on a single study, to draw the conclusion that using CHG cloths is superior to the current practice (i.e. washing with antiseptic or ordinary soap) in the evening and/or morning before surgery. The 3 studies evaluating the decreased incidence of SSI revolved around orthopaedic surgery (knee and hip) alone; extrapolation to other surgeries, particularly in another Altemeier classification, remains to be further carried out.

The studies by Makhni *et al.* [20] and Murray *et al.* [12] were in favour of a shower the evening before the intervention (type of soap not specified in the study by Makhni *et al.* [20]; ordinary soap in the study by Murray *et al.* [12]) and of the use of CHG-impregnated cloths the evening before and the morning of the intervention in comparison with a shower the evening before the intervention [20], or with a shower using ordinary soap the evening before and the morning of the intervention [12], the objective being to reduce bacterial colonisation. Unfortunately, as the reduction in bacterial colonisation was measured non-homogeneously, it was not possible to group these studies and to perform a quantitative synthesis. More precisely, Murray *et al.* [12] measured the percentage of positive samples, whereas Makhni *et al.* [20] measured the average reduction in the number of colonies. In fact, the gold standard for the baseline measure of the effectiveness of an intervention on bacterial colonisation does not seem to have been defined. The study by Makhni *et al.* [20]

was carried out on healthy volunteers and on few participants, 16 in number, given that this headcount required was calculated to achieve a statistical power of results greater than 80% with an α risk of 0.05. Murray *et al.* [12] included 100 patients, with 50 patients in each intervention group. These two studies involved orthopaedic surgery [12] or spinal surgery [20] and did not involve others.

All in all, the concentration of CHG in the cloths used in these 5 studies was 2%, and we cannot guarantee similar results if cloths with different CHG concentrations are used. The studies were single-centre and mostly performed by a single team, which means that the results cannot be extrapolated to other hospitals. The time and the number of preoperative washes, to be carried out with CHG-impregnated cloths, remains to be defined. For all the hospitals receiving multiple trauma patients or those who experience pain when moved, the complete or localised preoperative washing described in the study by Murray *et al.* may or may not be advisable [12].

5. Conclusion

Only 3 studies are available, and 2 of them were non-randomized. While these studies show a benefit for CHG-cloths on SSI occurrence in orthopaedic surgery, there was no comparison with usual practices (antiseptic or plain soap washing the evening and/or the morning before surgery). In the current state of knowledge, it is not possible, for all surgeries, to recommend CHG cloths instead of preoperative showers. Since solid evidence remains limited, we strongly encourage further studies comparing use of these cloths to current practices. Furthermore, preliminary studies dealing first and foremost with skin colonisation are at once rare and necessary. Finally, most of the studies fail to recognize the potential benefit of an antiseptic as part of a comprehensive evidence-based care bundle. Preoperative CHG (2%

cloth or aqueous formulation) should never be viewed as a stand-alone intervention, but rather as part of a thought-out interventional effort.

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Figure 1. Flow chart for selection of studies

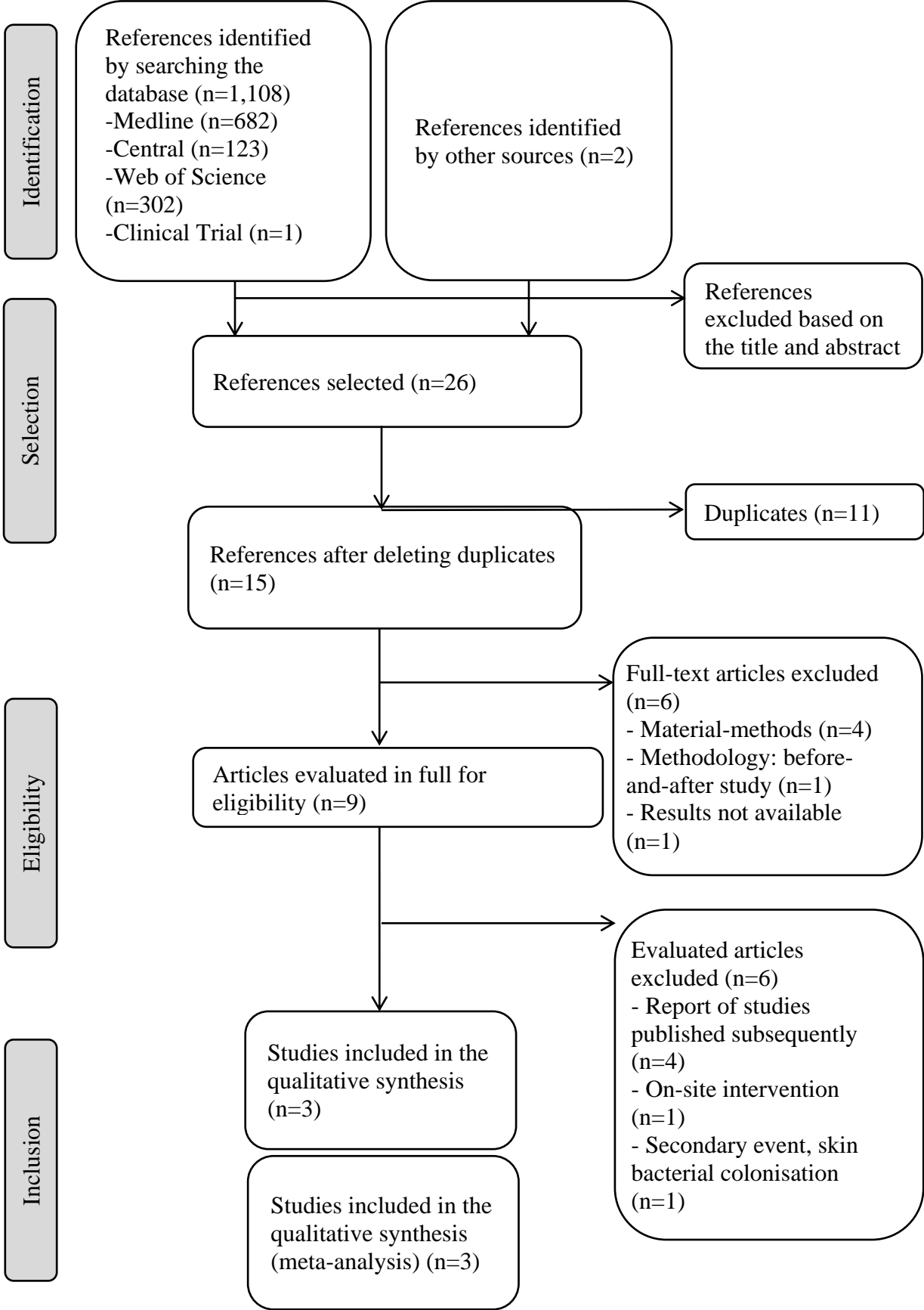


Figure 2. Comparison of the effect of compliance with preoperative washing with cloths impregnated with CHG 2% the evening before and the morning of surgery versus non-compliance, observational studies.

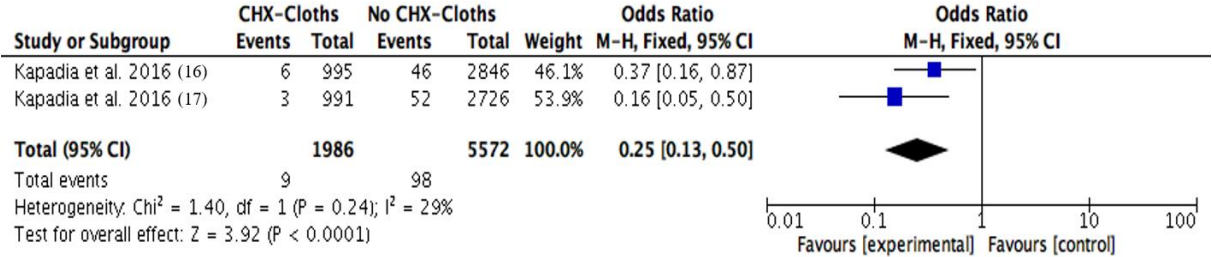


Figure 3. Comparison of the effect of preoperative washing with cloths impregnated with CHG 2% the evening before and the morning of surgery versus washing with antibacterial soap the evening before surgery, randomised controlled trial.

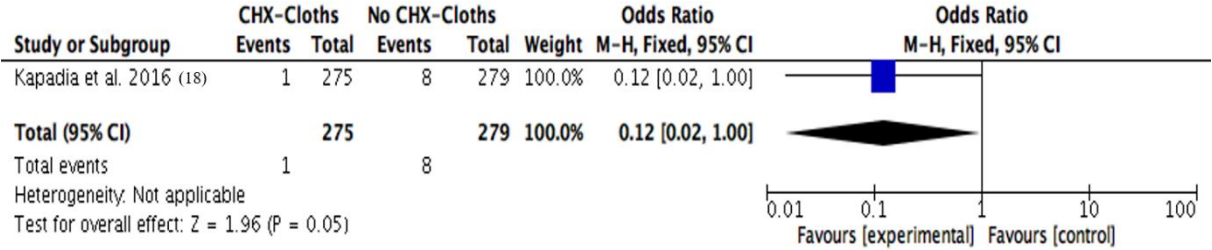


Table 1. Data extraction table

Study	Type of study	Type of surgery	Intervention (1) Comparator (2)	Number of patients	SSI definition	Number of SSI, n (%)	Secondary events	Included
[14] Johnson et al. 2010	Prospective cohort	Hip arthroplasty	1) CHG 2% cloths the evening before and the morning of surgery 2) non-compliant	1) 157 2) 897	Deep infection (fascia or joint space)	1) 0 2) 14 (1.6%) p=0.231	no	no
[13] Zywel et al. 2011	Prospective cohort	Knee arthroplasty , primary, replacement	1) CHG 2% cloths the evening before and the morning of surgery 2) non-compliant	1) 136 2) 711	Deep infection, CDC definition	1) 0 2) 21 (3%)	no	no
[15] Johnson et al. 2013	Prospective cohort	Total knee arthroplasty , primary, replacement	1) CHG 2% cloths the evening before and the morning of surgery 2) non-compliant	1) 478 2) 1,735	Deep infection (fascia or joint space) Definition from the <i>Musculoskeletal Infection Society</i> . Follow-up: 1 year	1) 3 (0.6%) 2) 38 (2.2%) p=0.02	no	no
[16] Kapadia et al. 2013	Prospective cohort	Total hip arthroplasty , primary, replacement	1) CHG 2% cloths the evening before and the morning of surgery	1) 557 2) 1,901	Deep or periprosthetic infection	1) 3 (0.5%) 2) 32 (1.7%) p=0.04	no	no

		t	2) non-compliant					
[20] Makhni et al. 2018	Case- controlled prospective cohort	Spinal surgery	1) right side of the neck: shower* the day before surgery + CHG 2% cloths the evening before and the morning of surgery 2) left side: shower the day before surgery	16 (the patient is their own control)	NA	NA	average decrease in colonies/m L 1) 790 2) 536 p=0.059	no
[12] Murray et al. 2011	Randomise d prospective study	Shoulder surgery	1) Shower with soap and water the evening before surgery + CHG 2% cloths around the shoulder 1 hour after the shower + cloths in the morning in the 2 hours before going to the hospital 2) Shower with soap and water the	1) 50 2) 50	Postoperative infection - 2 months	1) 0 2) 0	Positive bacterial cultures from the shoulder before surgery 1) 66% 2) 94% p=0.0008	no

			evening before and the morning of surgery					
[19] Kapadia et al. 2016	Randomised controlled study	Total hip or knee arthroplasty, primary or replacement	1) CHG 2% cloths the evening before and the morning of surgery 2) Antibacterial soap and water the evening before surgery**	1) 275 2) 279	Deep periprosthetic infection Definition from the <i>Musculoskeletal Infection Society</i> Follow-up: 1 year	1) 1 (0.4%) 2) 8 (2.9%) p=0.038 OR=8.15 for group 2 comparison vs 1, 95%CI [1.01-65.6]; p=0.049	no	yes
[17] Kapadia et al. 2016	Prospective cohort	Total hip arthroplasty, primary or replacement	1) CHG 2% cloths the evening before and the morning of surgery 2) non-compliant	1) 995 2) 2,846	Deep infection (fascia or joint space) Definition from the <i>Musculoskeletal Infection Society</i> Follow-up: 1 year	1) 6 (0.6%) 2) 46 (1.6%) RR=2.68 for group 2 comparison vs 1, 95%CI [1.15-6.26]; p=0.02	no	yes
[18] Kapadia et al. 2016	Prospective cohort	Total knee arthroplasty, primary or replacement	1) CHG 2% cloths the evening before and the morning of surgery 2) non-compliant	1) 991 2) 2,726	Deep infection (fascia or joint space) Definition from the <i>International Consensus Group on Periprosthetic</i>	1) 3 (0.3%) 2) 52 (1.9%) RR=6.3 for group 2 comparison	no	yes

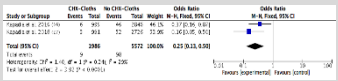
					<i>Infections</i> Follow-up: 1 year	vs 1, 95%CI [1.9-20.1]; p=0.002		
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CHG: Chlorhexidine; SSI: Surgical Site Infections; OR: Odds-ratio; RR: Relative Risk; 95%CI: Confidence Interval at 95%; CDC: Centres for Disease Control; NA: Not applicable

* Type of soap unknown, the request for information from the authors received no response.

** Behaviour in the morning not specified, type of antibacterial agent not specified, the request for information from the authors received no response.

Table 2. Cochrane Collaboration tool to evaluate the risk of bias

	Selection bias		Perform		Detection bias	Attrition bias	Relationship bias	Other biases	
									
Study	Randomisation	Allocation concealment	Double blind		Blind results reviewers	Incomplete results data	Event reporting		
			Personnel	Patient					
[19] Kapadia et al. 2016	Low risk	NA	Not clear	NA	Not clear	Low risk	Not clear	Unknown follow-up period SSI definition: Musculoskeletal Infection Society	

NA: Non-Applicable; SSI: Surgical Site Infection

Table 3. Risk of bias in the cohort studies included (Newcastle-Ottawa Quality Assessment Scale)

Study	Representativeness of the cohort	Selection of the non-exposed cohort	Verification of exposure	Demonstration of the absence of initial event	Comparability of the cohorts	Evaluation of the event	Sufficient monitoring period	Adequacy of cohort monitoring
[17] Kapadia et al. 2016	A*	A*	A*	B	A*	A*	A*	A*
[18] Kapadia et al. 2016	A*	A*	A*	B	A*	A*	A*	B-

Table 4. Comparison of the effect of compliance with preoperative washing with cloths impregnated with CHG 2% versus non-compliance on the incidence of SSI using the GRADE method.

Assessment of quality							Number of patients		Relative effect	Quality
Studies	Type of study	Bias	Heterogeneity /incoherence	Indirect evidence	Imprecision	Additional considerations	CHG cloths	No cloths		
[19] Kapadia et al. 2016	Randomised controlled trial	Significant ¹	Not significant	Significant ²	Not significant	RR<0.2 addition of 2 levels of quality	275	279	OR=0.12 95%CI [0.02-1.00]	Moderate
[17-18] Kapadia et al. 2016	Prospective cohorts	Not significant	Not significant	Not significant	Not significant	RR<0.5 addition of 1 level of quality	1986	5572	OR=0.25 95%CI [0.13-0.5]	High

CHG: Chlorhexidine; OR: Odd-Ratio; RR: Relative Risk; 95%CI: Confidence Interval at 95%

¹ Lack of blinding ² The population heterogeneity (differences in population, applicability) could not be judged with a single trial