Efficacy of different preoperative skin antiseptics on the incidence of surgical site infections: a systematic review, GRADE assessment, and network meta-analysis

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Summary

Background Surgical site infection (SSI) is the most common postoperative complication and substantially increases health-care costs. Published meta-analyses and international guidelines differ with regard to which preoperative skin antiseptic solution and concentration has the highest efficacy. We aimed to compare the efficacy of different skin preparation solutions and concentrations for the prevention of SSIs, and to provide an overview of current guidelines.

Methods This systematic review and network meta-analysis compared different preoperative skin antiseptics in the prevention of SSIs in adult patients undergoing any wound classification. We searched for randomised controlled trials (RCTs) in MEDLINE, Embase, and Cochrane CENTRAL, published up to Nov 23, 2021, that directly compared two or more antiseptic agents (ie, chlorhexidine, iodine, or olanexidine) or concentrations in aqueous and alcohol-based solutions. We excluded paediatric, animal, and non-randomised studies, and studies not providing standard preoperative intravenous antibiotic prophylaxis. Studies with no SSIs in both groups were excluded from the quantitative analysis. Two reviewers screened and reviewed eligible full texts and extracted data. The primary outcome was the occurrence of SSI (ie, superficial, deep, and organ space). We conducted a frequentist random effects network meta-analysis to estimate the network effects of the skin preparation solutions on the prevention of SSIs. A risk-of-bias and Grading of Recommendations, Assessment, Development, and Evaluation assessment were done to determine the certainty of the evidence. This study is registered with PROSPERO, CRD42021293554.

Findings Overall, 2326 articles were identified, 33 studies were eligible for the systematic review, and 27 studies with 17735 patients reporting 2144 SSIs (overall incidence of 12·1%) were included in the quantitative analysis. Only 2·0–2·5% chlorhexidine in alcohol (relative risk 0·75, 95% CI 0·61–0·92) and 1·5% olanexidine (0·49, 0·26–0·92) significantly reduced the rate of SSIs compared with aqueous iodine. For clean surgery, we found no difference in efficacy between different concentrations of chlorhexidine in alcohol. Seven RCTs were at high risk of bias, 24 had some concerns, and two had low risk of bias. Heterogeneity across the studies was moderate (P=27·5%), and netsplitting did not show inconsistencies between direct and indirect comparisons. Five of ten studies that mentioned adverse events related to the skin preparation solutions reported no adverse events, and five reported a total of 56 mild events (mainly erythema, pruritus, dermatitis, skin irritation, or mild allergic symptoms); none reported a substantial difference in adverse events between groups.

Interpretation For adult patients undergoing a surgical procedure of any wound classification, skin preparation using either 2·0–2·5% chlorhexidine in alcohol or 1·5% olanexidine is most effective in the prevention of SSIs. For clean surgery, no specific concentration of chlorhexidine in alcohol can be recommended. The efficacy of olanexidine was established by a single randomised trial and further investigation is needed.

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was based on findings from studies published up until 2017 and made recommendations on the basis of their network meta-analysis. It is notable that none of these guidelines give a recommendation on what concentration of the recommended antiseptic should be used.

Another network meta-analysis, reported by Wade and colleagues in 2021, included randomised trials and non-randomised studies and focused only on clean surgery. The authors misclassified and wrongly analysed three of the included studies as 4-0–5-0% chlorhexidine in alcohol, which could have led to unjust results.

Evidence before this study
Evidence from previous randomised trials and meta-analyses suggests that alcohol-based preoperative skin antiseptics reduce the risk of surgical site infections (SSIs). We searched PubMed for systematic reviews, meta-analyses, and current international guidelines for the prevention of SSIs with the search terms “surgical site infection”, “post-operative wound infection”, “pre-operative care”, “povidone-iodine”, “chlorhexidine”, “antiseptic”, and “perioperative care”. The US Centers for Disease Control and Prevention recommend surgical skin antisepsis with any alcohol-based solution, whereas the UK National Institute for Health and Care Excellence (NICE) and WHO guidelines specifically recommend the use of chlorhexidine in alcohol as a surgical site preparation for the prevention of SSIs. None of these guidelines give an evidence-based recommendation on which concentration of chlorhexidine is most effective. Several (network) meta-analyses have been conducted, including those undertaken for the development of the NICE and WHO guidelines, but they have been inconsistent in both study and data selection. Wade and colleagues’ network meta-analysis (published in 2021) concluded 4-0% chlorhexidine in alcohol to be the most effective concentration for the prevention of SSIs, but their research focused on clean surgery only. In addition, some studies in this network meta-analysis were wrongly classified as 4-0–5-0% chlorhexidine in alcohol, which could have led to unjust results.

Implications of all the available evidence
In line with previous research, we found a benefit of chlorhexidine in alcohol over both aqueous iodine and iodine in alcohol for the prevention of SSIs in all wound classifications, particularly 2-0–2-5% chlorhexidine in alcohol. In contrast to a previous network meta-analysis, we found no additional benefit from 4-0% chlorhexidine in alcohol. 1-5% olanexidine showed benefit, but results were based on only one randomised controlled trial with some methodological limitations and further investigation is needed.

Research in context
Added value of this study
We provide an updated systematic review and network meta-analysis of the current evidence comparing efficacy of antiseptic solutions, including comparisons of different concentrations of chlorhexidine in alcohol. In adult patients undergoing a surgical procedure of any wound classification, a skin preparation using either 2-0–2-5% chlorhexidine in alcohol or 1-5% olanexidine is most effective in the prevention of SSIs compared with aqueous iodine. For clean surgery, the efficacy of prevention of SSIs by different concentrations of chlorhexidine in alcohol is equivalent to both aqueous iodine and iodine in alcohol. Furthermore, we provide an accurate, unbiased updated overview of the recommendations on surgical site preparation compared with available international guidelines and published (network) meta-analyses.

A network meta-analysis provides an effective and suitable solution to combine all the available evidence from RCTs with different comparisons and allows these RCTs to be simultaneously analysed. All different skin antiseptic solutions and different concentrations can be compared through direct and indirect comparisons. Direct effect estimates are calculated comparably to a regular pairwise meta-analysis with all studies that directly compare two treatments. Indirect effect estimates are calculated from all indirect paths in the network through common comparators. For comparisons in which both direct and indirect evidence are available, a network estimate is calculated by combining both direct and indirect effect estimates. When only indirect evidence is available for a comparison, the network estimate is the same as the indirect effect estimate of that comparison. The network meta-analysis utilises more information in the network than a regular pairwise meta-analysis.

Skin preparation is an important and highly relevant topic for daily surgical practice and needs an unambiguous recommendation of the type and concentration of a skin antiseptic, made on the basis of all available evidence. Therefore, the aim of this study was to give an overview and comparison of different guidelines on the prevention of SSIs and to do a systematic review and network meta-analysis of published RCTs comparing two or more antiseptic skin solutions, including comparisons of different concentrations of chlorhexidine in alcohol.
preparation agents. In addition, we aimed to provide an accurate, unbiased update of the efficacy of different skin antiseptic solutions and concentrations for the prevention of SSIs in adult patients undergoing any kind of surgery, with a recommendation for clinical practice.

Methods

Search strategy and selection criteria

This systematic review and network meta-analysis is reported according to the Preferred Reporting Items for Systematic Reviews and Network Meta-analysis statement. The summarised protocol is available on the PROSPERO database (CRD42021293554).

We included RCTs comparing two or more antiseptic skin preparation agents (chlorhexidine, iodine, or olenaxidine) or concentrations in aqueous and alcohol-based solutions in adults (aged ≥18 years) undergoing surgical procedures in the operating theatre that reported SSI rates. Studies investigating paediatric patients, animal studies, non-randomised studies, and studies not providing standard preoperative intravenous antibiotic prophylaxis were excluded. There were no restrictions on language or the year of publication.

A systematic literature search of Embase, PubMed, and Cochrane CENTRAL was conducted for articles published up to Nov 23, 2021. Search terms included: “surgical site infection”, “post-operative wound infection”, “pre-operative care”, “povidone-iodine”, “chlorhexidine”, “antiseptic”, and “perioperative care”. We based our search strategy on the one used during the development of the WHO guideline. Additional articles were identified by backward and forward citation tracking of previously published (network) meta-analyses and included studies. The complete search strategy can be found in the appendix (p 2).

Two reviewers (HJ and HG) independently executed title and abstract screening and full text review of potential eligible studies. Discrepancies between the two reviewers were resolved through discussion and, if necessary, the senior author (MAB) was consulted.

Data analysis

The following data were extracted using a prespecified form: author, year, country, primary outcomes, secondary outcomes, number of patients in each study group, type of surgery, number of SSIs, type of SSIs, adverse events, definition of SSI, and surgical wound classification. Authors were contacted for additional information if data were incomplete or unclear (eg, unknown concentration of the antiseptic solution).

The primary outcome was the occurrence of SSIs (ie, superficial, deep, and organ-space SSI), defined by the authors of the original publication. Secondary outcomes were adverse effects of the intervention (eg, allergic reactions).

Assessment of the risk of bias within individual studies was performed by two authors (HJ and HG)
See Online for appendix

### Table 2: Comparison of the inclusion of studies on only clean surgery in different systematic reviews and (network) meta-analyses

| Reason for exclusion from our review and network meta-analysis |
|---------------------------------------------------------------|
| Ritter et al (2020)                                      |
| Shadid et al (2019)                                       |
| Xu et al (2017)                                         |
| Bili et al (2015)                                        |
| Casey et al (2015)                                       |
| Perek et al (2013)                                       |
| Savage et al (2012)                                      |
| Sistla et al (2010)                                      |
| Cheng et al (2009)                                       |
| Paucharoen et al (2009)                                   |
| Saltzman et al (2009)                                     |
| Veiga et al (2008)                                       |
| Ellenhorn et al (2005)                                    |
| Bibbo et al (2005)                                       |
| Ostrander et al (2005)                                    |
| Segal and Anderson (2002)                                 |
| Meier et al (2001)                                       |
| Roberts et al (1995)                                     |
| Shirahatti et al (1993)                                   |
| Howard (1991)                                            |
| Gilliam and Nelson (1990)                                 |
| Alexander et al (1983)                                   |
| Berry et al (1982)                                       |

*Studies with no events in both groups were not included in our network meta-analysis.

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individually using the Cochrane risk-of-bias tool, version 2. A comparison-adjusted funnel plot was used to judge small-study effects. The certainty of evidence was assessed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology.

Relative risks (RRs), corresponding 95% CIs, and SEs were calculated for the individual studies. Studies with no SSIs in both groups were excluded from the quantitative analysis.

A network meta-analysis was performed using the frequentist method and a random effects model. A p value of less than 0.05 was considered statistically significant. Heterogeneity was assessed by the I² statistic. We assessed transitivity of the treatment modalities and inconsistency to see whether the direct and indirect effect estimates were similar. The node-splitting method used to evaluate inconsistency was the Separate Indirect from Direct Design Evidence approach. We present the results of the network meta-analysis in pooled RRs with 95% CI, shown in league tables with all the network RRs. We also calculated P-scores to rank the different treatment modalities; a P-score is a ranking metric for network meta-analyses that ranges between 0 and 1 (a treatment with a higher score is suggested to be more effective than a treatment with a lower score).

A subgroup analysis was conducted on the basis of the US CDC wound classification (ie, clean, clean-contaminated, contaminated, or dirty). For this subgroup analysis we performed an additional analysis clustering all concentrations of chlorhexidine in alcohol. Because there is uncertainty as to whether skin antiseptics affect the incidence of organ-space infections, we performed an additional analysis excluding organ-space infection. Furthermore, two sensitivity analyses were done—one on the basis of the risk-of-bias tool, excluding studies scored as high risk of bias, and another one where studies published before the year 2000 were excluded, because these studies might not adhere to the current standards of perioperative clinical care comprising other SSI-prevention measures.

We did a quantitative analysis using R, version 4.0.3, using the packages netmeta, metafor, meta, and tidyverse. This study is registered with PROSPERO, CRD42021293554.

### Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

### Results

An overview of included studies, compared with previously published systematic reviews and (network) meta-analyses, is listed in table 1 (any type of surgery) and table 2 (only clean surgery). Reasons for exclusion of full texts are listed in the appendix (pp 3–4). In total, 2326 abstracts were screened and 13 additional articles were identified by backward and forward citation tracking. From these reports, 67 full texts were reviewed (figure 1). We included 33 RCTs in the systematic review, of which 27 RCTs with 17735 patients were included in the network meta-analysis. This systematic review includes 37 comparisons. Six studies reported no SSIs in the study groups and were not included in the quantitative analysis.

The study characteristics of the 33 included RCTs are listed in the appendix (pp 5–7). One RCT compared 0·5% chlorhexidine in alcohol with 2·0–2·5% chlorhexidine in alcohol, three RCTs compared 0·5% chlorhexidine in alcohol with aqueous iodine, four RCTs compared 0·5% chlorhexidine in alcohol with iodine in alcohol, four RCTs compared 0·2–0·5% chlorhexidine in alcohol with iodine in alcohol, 11 RCTs compared 2·0–2·5% chlorhexidine in alcohol with aqueous iodine, seven RCTs compared 2·0–2·5% chlorhexidine in alcohol in iodine in alcohol, three RCTs compared...
4·0% chlorhexidine in alcohol with aqueous iodine, one RCT compared aqueous chlorhexidine with aqueous iodine, six RCTs compared aqueous iodine and iodine in alcohol, and one RCT compared aqueous iodine with 1·5% aqueous olanexidine. The network graphs of direct comparisons between the 27 studies included in the network meta-analysis are shown in figure 2A.

27 different solutions were used as skin antiseptics. For our quantitative analysis, we combined the studies assessing these antiseptic agents into seven groups on the basis of type and concentration. RCTs assessing 2·0% and 2·5% chlorhexidine in 70% isopropyl alcohol, alcohol, or ethanol were included in the 2·0–2·5% chlorhexidine in alcohol group. Those assessing 0·5% chlorhexidine in 70% isopropyl alcohol, alcohol, or ethanol were included in the 0·5% chlorhexidine in alcohol group. The 4·0% chlorhexidine in alcohol group consisted of studies assessing 4·0% chlorhexidine in 70% isopropyl alcohol or alcohol. All RCTs assessing formulations of aqueous iodine, aqueous povidone-iodine, or aqueous iodophor were combined into one group (the aqueous iodine group), as were those assessing iodine in alcohol, povidone-iodine in alcohol, and iodophor in alcohol (the iodine in alcohol group). The one RCT that assessed olanexidine and the one RCT that assessed 4·0% aqueous chlorhexidine were included in their own separate groups.

In total, 17735 patients were included in the systematic review, and 2144 SSIs were reported, corresponding to an overall SSI rate of 12·1%. The forest plot representing the efficacy of a preoperative skin antiseptic compared with aqueous iodine for any type of surgery is presented in figure 3A; the league table of these data is presented in the appendix (p 8). Compared with aqueous iodine in any type of surgery, 2·0–2·5% chlorhexidine in alcohol and 1·5% olanexidine had the highest efficacy (figure 3A). The efficacy of iodine in alcohol was similar to aqueous iodine. There are no data available on olanexidine compared with iodine in alcohol. The results of the net-ranking, expressed in P-scores, are presented in the appendix (p 8).

Adverse events of the skin related to the skin preparation solutions were mentioned in ten RCTs. Five studies reported no events, the other five studies reported a total of 56 mild adverse events.
**Articles**

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### Figure 3: Forest plots

The forest plots show the efficacy of different skin preparation solutions and concentrations in the prevention of SSIs compared with aqueous iodine. Data are RR with corresponding 95% CI. (A) Efficacy for any type of surgery. (B) Efficacy for clean surgery. (C) Efficacy for clean surgery, clustering of chlorhexidine in alcohol. (D) Efficacy for non-clean surgery, excluding studies looking at only clean surgical procedures (ie, wound class 1). US CDC=US Centers for Disease Control and Prevention. RR-relative risk. SSIs=surgical site infections.

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The 16 studies that investigated exclusively clean procedures, ten of which had events and six of which had no events, none of the skin preparation solutions had a higher efficacy than aqueous iodine. The RR for 4·0% chlorhexidine in alcohol compared with 0·5% chlorhexidine in alcohol in clean procedures was 0·51 (0·05–5·04).

When clustering the different concentrations of chlorhexidine in alcohol into one group we found a non-significant benefit when compared with iodine in alcohol (RR 0·54 [95% CI 0·27–1·07]) and a significant benefit when compared with aqueous iodine (0·60 [0·36–0·99]) in clean surgeries (figure 3C; appendix p 9).

We performed a subgroup analysis excluding studies that investigated exclusively clean surgical procedures (figure 3D; appendix p 9). The 20 studies included in this analysis did include clean surgical procedures, in addition to non-clean surgeries. The proportion of patients who had an SSI in this group was 13·1% (2044 SSIs in 15562 patients). For this cohort, we found that the efficacy of 2·0–2·5% chlorhexidine in alcohol was higher than the efficacy of aqueous iodine and was similar to that found in the overall analysis. The RR for 1·5% olanexidine compared with aqueous iodine was 0·49 (0·27–0·88).

The results of the sensitivity analysis of the 20 high-quality studies (excluding studies at high risk of bias, appendix p 12) were similar to those of the overall analysis, with both 2·0–2·5% chlorhexidine in alcohol and 1·5% olanexidine having significantly higher efficacy than aqueous iodine. A detailed risk-of-bias assessment can be found in the appendix (p 16). There were seven RCTs at high risk of bias, and two had low risk of bias. The sensitivity analysis that excluded the three studies reported before the year 2000 showed similar results to the overall analysis (appendix p 13). Furthermore, after excluding organ-space infections, results of the 21 included studies closely resembled those of the overall analysis (appendix p 14). The comparison-adjusted funnel plot showed no signs of small-study effects (appendix p 17).

The GRADE assessment for SSIs is shown in the appendix (pp 18–22). Starting certainty of evidence was high because all included studies were RCTs. Of the 27 studies included in the network meta-analysis, six had an overall high risk of bias. Due to the nature of a network meta-analysis, this risk of bias could affect all the network estimates of all comparisons. We performed a sensitivity analysis excluding studies with high risk of bias (appendix p 12). The results closely resembled the results from the main analysis, which meant that downgrading for risk of bias was not needed. In addition, some comparisons were also downgraded because of imprecision. Overall, the certainty of the treatment effects was deemed moderate, except for one comparison, which was deemed high (2·0–2·5% chlorhexidine in alcohol vs aqueous iodine).
We compared overall recommendations from our network meta-analysis with leading recommendations.\textsuperscript{2–4,44,45} The results of our network meta-analysis led to the following recommendations. For any type of surgery, the use of 2.0–2.5% chlorhexidine in alcohol is recommended for preoperative skin preparation in any type of surgery. If this concentration is not available, 0.5% or 4.0% chlorhexidine in alcohol could be used. For clean surgery, the use of chlorhexidine in alcohol is recommended for skin preparation before clean surgical procedures. For clean surgery, no specific concentration of chlorhexidine in alcohol can be recommended. Table 3 lists our study recommendations, compared with the recommendations of the three most important (international) guidelines\textsuperscript{2–4} and two additional (network) meta-analyses.\textsuperscript{44,45}

Discussion

This systematic review and network meta-analysis investigated the efficacy of different preoperative skin antiseptic solutions and concentrations on theSSI rate for adult patients undergoing any type of surgical procedure. Furthermore, we provide an accurate, unbiased updated overview of our recommendations for surgical site preparation compared with the available guidelines and previous (network) meta-analyses (tables 1, 2).

We hypothesised that a higher concentration of chlorhexidine in alcohol would be most effective in the prevention of SSIs. However, we found a significant benefit of the use of either 2.0–2.5% chlorhexidine in alcohol or 1.5% olanexidine (evidence from only one RCT) for the reduction of SSIs compared with aqueous iodine in any type of surgery. The results of 0.5% chlorhexidine in alcohol and 4.0% chlorhexidine in alcohol also suggested a beneficial effect but remain non-significant with a wide CI. These non-significant results might be due to the scarcity of evidence for the effects of 0.5% chlorhexidine in alcohol and 4.0% chlorhexidine in alcohol. Aqueous chlorhexidine and iodine in alcohol showed similar effects when compared with aqueous iodine. Olanexidine, an antiseptic solution that has been available since 2015, was found to be the most effective agent for the reduction of SSIs. However, olanexidine was only investigated in one RCT due to its novelty.\textsuperscript{4}

In clean surgery only, we found a potential benefit of the different concentrations of chlorhexidine in alcohol over aqueous iodine. These effects were not significant due to a wide CI, possibly because of the low incidence of SSIs and a relatively small number of patients in the included studies. The incidence of SSIs in studies that only investigated clean surgery was 4.8% (158 SSIs in 3301 patients), whereas after excluding these studies, we found an SSI incidence of 13.1% (204 SSIs in 15562 patients). When clustering the different concentrations of chlorhexidine in alcohol into one group, chlorhexidine in alcohol was significantly more effective than aqueous iodine, whereas iodine in alcohol was not significantly more effective than aqueous iodine.

It could be assumed that skin antisepsis would be equally effective in clean and non-clean surgery when SSIs originate from only the skin. However, in non-clean surgery, spillage from contaminated surgical areas to the wound surface, wound edges, and surrounding skin also plays a role. Antiseptics are toxic to bacteria and therefore aid their mechanical removal. Alcohol-based antiseptic solutions have durable effects for more than 6 h after skin preparation,\textsuperscript{42} with broad-spectrum antimicrobial activity after surgical spillage.

The overall level of evidence was graded as moderate (downgraded because of imprecision) and, in one comparison, was graded as high.

Our study is substantially more comprehensive than earlier studies on this subject. Our finding that chlorhexidine in alcohol as a surgical site preparation is more effective than aqueous chlorhexidine, iodine in

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**Table 3: Comparison of current recommendations of different network meta-analyses**

| Analysis | Recommendation |
|----------|----------------|
| Benito-Torres (2017)\textsuperscript{4} | Multiple meta-analyses | Perform intraoperative skin preparation with an alcohol-based antiseptic agent unless contraindicated. |
| WHO (2018)\textsuperscript{4} | Multiple meta-analyses | The panel recommends alcohol-based antiseptic solutions based on chlorhexidine for surgical site skin preparation in patients undergoing surgical procedures. |
| NICE (2019)\textsuperscript{3} | Network meta-analysis | First choice of skin preparation is alcohol-based solution of chlorhexidine, alternative is aqueous solution of chlorhexidine if surgical site is not to a mucous membrane. If chlorhexidine is contraindicated, alcohol-based solution of povidone-iodine can be used as an alternative. If both an alcohol-based solution and chlorhexidine are unsuitable, aqueous solution of povidone-iodine can be used. |
| Our study | Network meta-analysis | Use chlorhexidine in alcohol in a concentration of 2.0–2.5% for skin preparation before any surgical procedures; if this concentration is not available, 0.5% or 4.0% chlorhexidine in alcohol can be used. |

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Wade et al (2021)\textsuperscript{46} | Network meta-analysis | Alcohol concentrations of 4.0–5.0% chlorhexidine seem to be safe and twice as effective as povidone iodine (alcoholic or aqueous solutions) in preventing infection after clean surgery in adults. These findings concur with the literature on contaminated and clean-contaminated surgery, and endorse guidelines worldwide which advocate the use of alcoholic chlorhexidine for preoperative skin antisepsis. |

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Dumville et al (2015)\textsuperscript{44} | Multiple meta-analyses | A comprehensive review of current evidence found some evidence that preoperative skin preparation with 0.5% chlorhexidine in methylated spirits was associated with lower rates of SSIs following clean surgery than alcohol-based povidone iodine paint. However this single study was poorly reported. Practitioners may therefore elect to consider other characteristics such as costs and potential side effects when choosing between alternatives. |

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Our study | Network meta-analysis | Use chlorhexidine in alcohol for skin preparation before clean surgical procedure (no specific concentration of chlorhexidine plus alcohol). |

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NICE=National Institute for Health and Care Excellence. SSIs=surgical site infections.
alcohol, and aqueous iodine in preventing SSIs is in line with previous research. However, in contrast to previous recommendations and research we showed that 2.0–2.5% chlorhexidine in alcohol is superior to other concentrations of chlorhexidine in alcohol. The US CDC recommends alcohol-based solutions, whereas the NICE and WHO guidelines recommend explicitly chlorhexidine in alcohol as an antiseptic for the reduction of SSIs. Since the publication of these important guidelines, many new RCTs have been conducted investigating various types of antiseptic solutions. We included seven additional studies, all published since 2019, that were not included in the NICE guideline.1 We also included 11 additional studies, published since 2016, that were not included in the WHO guideline.2

A 2021 systematic review and network meta-analysis by Wade and colleagues45 showed that 4.0% chlorhexidine in alcohol was the most effective antiseptic for reducing SSIs, but this network meta-analysis focused only on clean surgery and unfortunately misclassified three studies in the 4.0–5.0% chlorhexidine in alcohol group that should have been classified in the 0.5%26 and 2.0–2.5% chlorhexidine in alcohol groups.28,31 In our analyses, we partly reproduced the results of the study by Wade and colleagues45 when looking at the analysis of exclusively clean surgical procedures (figure 3B). We saw a potential benefit of 4.0% chlorhexidine in alcohol compared with aqueous iodine (RR 0.36 [95% CI 0.06–2.44]), but the CI is much wider than the results reported by Wade and colleagues (0.49 [0.24–1.02]),45 making us wary of drawing hard conclusions in favour of 4.0% chlorhexidine in alcohol for clean surgery. Additionally, the main analysis of Wade and colleagues45 included both randomised and non-randomised studies, although it is recommended that randomised and non-randomised studies should not be combined in one meta-analysis, and subsequently not in one network meta-analysis. Also, we made methodological choices that considered the current high standard of clinical care to answer our research question. For example, we excluded two studies because they used a setting outside the operating theatre and did not use preoperative intravenous antibiotic prophylaxis if indicated. Results from studies without adequate preoperative antibiotic prophylaxis would be hard to interpret in current standard practice. In addition, we only included RCTs and therefore excluded all quasi-randomised trials.

Our study found an overall SSI rate of 12.1%, which is higher than the rates reported in the literature on SSI across all types of surgery.1 This discrepancy can be explained by the SSI rate of 20% reported by the largest included RCT6 conducted in seven low-income and middle-income countries. This RCT, reported by the UK National Institute for Health and Care Research in 2021,6 found SSIs in 1163 (20.1%) of 5788 patients undergoing abdominal surgery (US CDC wound classification 2, 3, or 4) with a skin incision of 5 cm or greater. Excluding this RCT, all other included studies reported that a total of 981 (8.2%) of 11947 patients had an SSI.

We also aimed to investigate the potential adverse effects of the different antiseptic solutions. Only ten of the 33 included studies reported adverse skin reactions, with five of the studies reporting actual events. These five studies found no substantial difference in the incidence of adverse events between the different antiseptic solutions, although, there is some evidence suggesting a high concentration (4.0%) of chlorhexidine in alcohol should be avoided because it is known to cause irritation in high concentrations.35,64 However, the evidence was too scarce to analyse this effect properly.

Our study has several limitations. Only three RCTs examined 4.0% chlorhexidine in alcohol as an antiseptic solution and aqueous chlorhexidine and 1.5% olanexidine were both investigated by only one RCT. With the scarcity of available data for these antiseptic solutions, effects shown by the treatment ranking might be overvalued.35,66 Olanexidine was ranked highest in the net-ranking, but was ranked on the basis of only one RCT. Therefore, we put more emphasis on the network RR with 95% CI, instead of the net-rankings.

To our knowledge, except for a randomised trial by Obara and colleagues,4 only non-randomised studies have been conducted on olanexidine.67,68 Furthermore, the study by Obara and colleagues has an important methodological limitation. In the published protocol, an adjusted RR (ARR) with 95% CI was planned, but the final analysis was done by calculating an ARR with 90% CI.65 We used the original number of events and number of patients of individual studies to conduct our network meta-analysis. Therefore, our network meta-analysis was not hampered by the RR and 90% CI that Obara and colleagues reported in their RCT. Additionally, a large proportion of the SSIs (29 of 58) in Obara and colleagues’ study were organ-space infections. It is debatable whether skin flora affect the number of organ-space infections. More RCTs regarding the efficacy of olanexidine are needed to be able to draw more reliable conclusions and before implementation in daily practice is possible. Furthermore, we categorised the great variety of different concentrations and types of iodine used in individual studies into two clinical applicable groups, which was necessary to pursue interpretable results. We also did not do a cost-effective analysis. SSIs are a costly complication and therefore, in our opinion, the prevention of SSIs contributes more to cost reduction than the difference in costs between individual antiseptic solutions.

Additionally, skin preparation is not the only preventive measure for SSIs. Other measures, such as timing and dosing of surgical antimicrobial prophylaxis, normovolaemia, and irrigation of the operative wound are of equal importance. Most of the included studies adhere to best practice guidelines, but not all included studies mention these guidelines, and the heterogeneity of other preventive measures is inevitable.
This network meta-analysis provides evidence for a benefit of all different chlorhexidine in alcohol concentrations, 2.0–2.5% chlorhexidine in alcohol in particular, compared with iodine for the prevention of SSIs in adult patients undergoing a surgical procedure. However, we found no difference in efficacy between different concentrations of chlorhexidine in alcohol for clean surgery, although when clustering the different concentrations into one group we found a benefit when compared with aqueous iodine. 1.5% olanexidine also shows a potential benefit compared with iodine for the prevention of SSIs in clean-contaminated surgery. However, this benefit was observed in a single randomised trial and further investigation is needed.

**Contributors**
HJ and HG contributed equally to this study. MAB, HJ, HG, and NW were responsible for the conceptualisation and were actively involved in planning the methodology. HJ and HG contributed equally to the formal analysis, investigation, project administration, and visualisation and writing of the original draft. NW and MAB provided critical advice. All authors reviewed, edited, and approved the final version of the manuscript. HJ and HG verified the underlying data reported in the manuscript. All authors had full access to all the data in the study and responsibility for the decision to submit for publication.

**Declaration of interests**
MAB reports receiving institutional grants from Johnson & Johnson/Ethicon, KC/3M, Bard, and New Coplean; and being a speaker or instructor for 3M/KCI, Johnson & Johnson/Ethicon, Allergan/LifeCell, BD Bard, Gore, Smith & Nephew, GDM, and Medtronic. All other authors declare no competing interests.

**Data sharing**
All data is published in this manuscript, the cited manuscripts, or the supplementary appendix. Data can be provided upon request to corresponding authors, and in agreement of terms. No individual participant data was used; we used raw data presented in the cited manuscripts.

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