Alcoholic chlorhexidine skin preparation or triclosan-coated sutures to reduce surgical site infection: a systematic review and meta-analysis of high-quality randomised controlled trials

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Summary

Background WHO and the UK's National Institute for Health and Care Excellence recommend alcoholic chlorhexidine skin preparation and triclosan-coated sutures to prevent surgical site infections (SSIs). Existing meta-analyses that include studies at high risk of bias, combined with the recent publication of large, randomised trials, justify an updated meta-analysis of high-quality randomised controlled trials (RCTs). We aimed to test the rates of SSI according to skin preparation solutions (ie, alcoholic chlorhexidine *vs* aqueous povidone-iodine) and types of sutures (ie, coated *vs* uncoated).

Methods In this systematic review and meta-analysis, we searched MEDLINE, Embase, Pubmed, and Cochrane Library databases, with no language restrictions, to identify high-quality RCTs testing either alcoholic chlorhexidine skin preparation (*vs* aqueous povidone-iodine) or triclosan-coated sutures (*vs* uncoated sutures), or both, published from database inception to Sept 1, 2021. Patients who received clean-contaminated, contaminated, or dirty surgery were included. We predefined the characteristics of a high-quality trial through an expert consensus process to develop an enhanced Cochrane risk of bias-2 tool specifically for RCTs with a primary outcome of SSI. Data were extracted from published reports. Meta-analysis was performed using a random-effects model and heterogeneity was assessed using the I^2 statistic. This systematic review and meta-analysis was prospectively registered in PROSPERO, CRD42021267220.

Findings Of 942 studies identified, 933 were excluded. Four high-quality RCTs (n=7467 patients) were included that tested alcoholic chlorhexidine. No significant difference in SSI rates was noted between alcoholic chlorhexidine and aqueous povidone-iodine (17·9% [667 of 3723 patients] *vs* 19·8% [740 of 3744 patients]; odds ratio 0·84 [95% CI 0·65–1·06]; p=0·21, I^2=53·1%). Five high-quality RCTs were included that tested triclosan-coated sutures (n=8619 patients), with no significant difference noted between triclosan-coated and uncoated sutures (16·8% [733 of 4360 patients] *vs* 18·4% [784 of 4259 patients]; OR 0·90 [95% CI 0·74–1·09]; p=0·29, I^2=36·4%).

Interpretation Contrary to previous meta-analyses, this study did not show a benefit from either alcoholic chlorhexidine skin preparation or triclosan-coated sutures, both of which are more expensive than other readily available alternatives. Global and national guidance should be reconsidered to remove recommendations for their routine use.

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Introduction

Surgical site infection (SSI) is the most common complication after surgery worldwide, affecting up to one in five patients across all surgical specialties.[1] Patients in lower-income countries are disproportionately affected by infections and antimicrobial resistance.[2] Treatment frequently requires prolonged courses of antibiotics, contributing to antimicrobial resistance. Antibiotics and dressings are costly to patients and providers. In low-income and middle-income countries (LMICs), SSIs are a contributor to catastrophic expenditure.

In 2016, WHO recommended 29 interventions to prevent SSIs, although most of the included trials within the evidence review were at best of moderate quality, with

little data from LMICs and paediatric populations.[3] The FALCON randomised trial[4] was designed to further investigate recommended interventions by WHO and included 5788 adults and children from seven LMICs. The trial addressed two interventions—alcoholic chlorhexidine skin preparation and triclosan-coated sutures to close the abdominal fascia—for which frontline collaborators felt that the highest levels of clinical equipoise existed.[5] Although these interventions are both recommended by WHO in their 2018 guidelines[3] and the UK's National Institute for Health and Care Excellence (NICE) in their 2019 guidelines[6] on the basis of data from a meta-analysis,[7] the majority of supporting trials were at high risk of bias through methodological weaknesses

Research in context

Evidence before this study
Triclosan-coated sutures and alcoholic chlorhexidine skin preparation are recommended by WHO in their 2018 guidelines and the UK's National Institute for Health and Care Excellence in their 2019 guidelines to mitigate against surgical site infection (SSI), on the basis of meta-analyses. However, the numerous meta-analyses performed to date, including those done as part of the guideline creation process, contain studies at high risk of bias. Further limitations of current data include very few trials based in lower-income countries or addressing high-risk surgery (eg, contaminated or dirty surgery, or emergency surgery). Concerns around conflicts of interest, inconsistent definitions of SSIs, and methodological rigour cast further doubt over the apparently conclusive results. The 2021 FALCON trial is one of the largest trials to date to compare both skin preparation (alcoholic chlorhexidine *vs* aqueous povidone-iodine) and suture type (triclosan-coated *vs* uncoated). FALCON was pragmatic, conducted to a high quality, performed in low-income and middle-income countries, included contaminated or dirty surgery and emergency surgery, and was at low risk of bias. Given that no meta-analysis has exclusively examined rigorously conducted randomised controlled trials (RCTs), a meta-analysis of only high-quality studies is urgently warranted.

Added value of this study
This study re-defined high quality and low risk of bias, using an expert consensus process that was focussed specifically towards RCTs on SSI. Using those criteria, we also included data from the newly published FALCON trial, meaning patients from low-income, middle-income, and high-income

countries were included. The overall rates of SSI were 12·8% (1428/11182) in clean-contaminated and 30·0% (1418/4722) in contaminated or dirty surgery. Four high-quality RCTs (n=7467 patients) were included that tested alcoholic chlorhexidine, with no significant difference in SSI rates between alcoholic chlorhexidine and aqueous povidone-iodine. Five high quality RCTs (n=8619 patients) were included that tested triclosan-coated sutures, with no significant differences in rates of SSI between coated and uncoated sutures. Stratified analyses by clean-contaminated, contaminated, and dirty surgery showed a similar lack of benefit. One study analysed the use of both interventions simultaneously and found no significant cumulative effects.

Implications of all the available evidence
Contrary to previous meta-analyses, we did not find a significant benefit from either 2% alcoholic chlorhexidine skin preparation or triclosan-coated sutures, which are both more expensive than other readily available alternatives. The difference between our analysis and previous analyses is the inclusion of only rigorously conducted RCTs, including the 2021 FALCON trial. Global and national guidance should be revised to reflect this higher quality evidence, and recommendations for routine use of both interventions should be revisited. Further high-quality randomised trials are warranted for these and other interventions to deal with SSI, which occurs at unacceptably high rates after surgery and is a driver of costs and antimicrobial resistance. We recommend that our enhanced risk of bias-2 tool should be used in future SSI-specific meta-analyses, and when planning new studies, to ensure complete reporting can take place.

that are inherent to trials of SSI. Generic assessments of risk of bias in previous meta-analyses might have overlooked some of the most salient threats to the validity of randomised trials of interventions to reduce SSI, including definitions of outcomes (SSI diagnosis is subjective and a structured, concealed assessment method is needed), timing of assessment (SSIs can be diagnosed after discharge from hospital, so a 30-day assessment is optimum), and differential dropouts (patients without SSIs are less likely to attend follow-up, so high loss to follow-up rates introduce bias). Furthermore, there is little evidence in LMIC settings for the clinical effectiveness of alcoholic chlorhexidine skin preparation and triclosan-coated sutures in patients with heavily contaminated wounds.

Within the past 5 years publication of large, randomised trials, including the FALCON trial,[1,4] and the moderate quality of evidence justify the need for an updated meta-analysis. The unique requirements needed for the conduct of SSI trials mean that a bespoke quality assessment process is needed that identifies only the most rigorous, high-quality randomised controlled trials (RCTs). A

specific analysis focused on patients receiving clean-contaminated, contaminated, or dirty surgery, which together represent operation types with the highest burden of infection, has also not been done. The aim of this study was to provide a rapid, efficient systematic review and meta-analysis of both interventions that included a bespoke quality assessment specific to SSI RCTs.

Methods

Development of a bespoke study quality assessment tool

SSI trials have certain challenges regarding design and conduct; as such, they warrant a specialised modification of the Cochrane risk of bias-2 tool[8] to optimise assessment in this context. We developed an expert-led definition of a high-quality randomised SSI trial. A four-staged process was used to define the criteria of a high-quality randomised SSI trial with a group of surgeons and methodologists with expertise in international SSI trials who adapted the risk of bias tool using a nominal group consensus method.[9,10] A detailed description of the

four-staged process and expert group is in the appendix (p 19). This final list of qualifying domains constituted the enhanced Cochrane risk of bias-2 tool. The protocol is listed in the appendix (pp 20–22).

Search strategy and selection criteria

This systematic review and meta-analysis was conducted in accordance with the recommendations of the Cochrane Library and Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[11,12] We searched MEDLINE, Embase, Pubmed, and Cochrane Library databases for studies published from database inception to Sept 1, 2021, with no language restrictions. A summary of the search terms used is presented in the appendix (p 3). Data were extracted from published reports. Any relevant citations from search results were explored and authors were contacted when queries or discrepancies were encountered.

Studies were included according to the following criteria: (1) high quality (table 1 shows criteria for assessment of study quality from the expert consensus process); (2) randomised; (3) assessing different forms of skin preparation (ie, alcoholic chlorhexidine *vs* aqueous povidone-iodine) or types of sutures (ie coated *vs* uncoated); and (4) data regarding the contamination level of surgery is extractable, relating specifically to patients who received clean-contaminated, contaminated, or dirty surgery. Studies were excluded if they were RCTs evaluating clean surgery only or if data on contamination strata for clean-contaminated, contaminated, or dirty surgery were not available, or they were of low quality.

Four authors (SK, EL, JS, and ET) extracted the data, and any discrepancies were discussed with all authors together and any conflict was resolved by discussion with the senior author (AB). Type of data extracted were number of centres, number of patients, interventions used, SSI rates by each intervention, and degree of contamination. Duplicates were excluded.

Outcome

The primary outcome of this review was to examine the rates of SSI between skin preparation (ie, alcoholic chlorhexidine *vs* aqueous povidone-iodine) or types of sutures (ie, coated *vs* uncoated). Sensitivity analysis was also performed on studies that contained an explicit statement of conflict of interest.

Statistical analysis

We generated a random-effects estimate of the pooled odds of each outcome with use of the hybrid Mantel-Haenszel methods. The rates of SSIs described in the RCTs reported in the articles were used directly in the quantitative meta-analysis. Funnel plots were used to visually assess publication bias of included studies. Heterogeneity between studies was assessed using the I^2 statistic to determine the degree of variation not attributable to chance alone. I^2 values were considered to

represent low, moderate, and high degrees of heterogeneity when values were less than 25%, 25–75%, and more than 75%, respectively. Funnel plot asymmetry was assessed using the Egger test. A p value of less than 0·05 was considered statistically significant. Data analysis was done using R Foundation Statistical software, with packages such as meta, finalfit, and tidyverse,[13] (R 3.2.1).

Subgroup analyses were performed by the degree of contamination (ie, clean-contaminated, contaminated, and dirty) for both skin preparation and suture type. A further sensitivity post-hoc analysis was performed in studies for which conflicts of interest were reported transparently (ie, the conflict of interest statement was present).

This systematic review and meta-analysis was prospectively registered in PROSPERO, CRD42021267220.

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

The nominal group consensus process identified ten domains containing ten areas of bias, mapped out from the Cochrane risk of bias-2 tool for randomised trials,[8] in which SSI-specific quality criteria were included where possible (figure 1). Of the ten domains, one was new (quality assurance of outcome assessment) and nine were adapted from different aspects of the Cochrane tool through a four-stage process (appendix pp 4–6). From these ten, eight were prioritised as essential and taken forward into the final adapted risk-of-bias tool (table 1). The eight essential key domains are listed in the appendix (pp 22–24).

Two domains were classed as desirable, which were blinding of surgeons and blinding of patients, because they were non-discriminatory towards a high-quality or low-quality assessment. Although desirable for all RCTs, blinding of the surgeon delivering an intraoperative intervention is difficult (ie, because they are performing the index operation);[14] to lower the risk of bias in SSI trials, ideally, the unblinded surgeon will not perform the outcome assessment. Although blinding of patients to the intervention is useful, it might not be possible in all interventions in reducing SSI and, therefore, not pragmatic for future conduct of SSI trials.

Of the 942 studies identified from the literature search, 40 studies received full-text review and 31 were excluded (figure 2). Reasons for exclusion of studies are presented in the appendix (p 7). Results on the enhanced Cochrane risk of bias-2 tool for each included study are presented in table 2 and the appendix (p 8). Baseline study and patient characteristics of the included studies are presented in table 3 and the appendix (pp 9–11). In the final analysis, four high-quality RCTs[4,15–17] (n=7467 patients; patient numbers differed from totals given in table 3

	Type of bias	Definition of low risk	Assessment	Essential
Random sequence generation	Selection	Randomisation of patients using validated methodology, which included centralised, computer-based, or web-based sequence generation but excluded mechanical methods that could potentially be manipulated, such as shuffling of cards; quasi-randomisation or randomisation based on surgeons' judgment, preference, or availability were excluded	Low risk: valid randomisation methodology; high risk: none or unclear randomisation methodology	Yes
Allocation concealment	Selection	Acceptable method for assigning participants to comparison groups without risk of previous knowledge of an upcoming allocation; low-risk methods include central allocation and randomly mixed block sizes	Low risk: valid allocation methodology; high risk: none or unclear allocation methodology	Yes
Baseline differences between intervention groups	Selection	No significant differences between the baseline demographics of the intervention and control groups; recognition, analysis, and control of baseline differences between groups	Low risk: analysis and appropriate control for baseline differences; high risk: little or no recognition or control for baseline differences, or both	Yes
Blinding of surgeons	Performance	Blinding of surgeons performing the procedure is not possible and unlikely to be a source of bias, as long as unblinded surgeons do not also perform outcome assessment	Low risk: independent blinded surgeon delivering intervention; high risk: no independent blinded surgeon delivering intervention	No
Blinding of patients	Performance	Blinding of patients to sutures is possible, and therefore an important method of reducing performance bias	Low risk: patients blinded; high risk: patients not blinded	No
Analysis of groups to which they were randomly assigned	Attrition	Complete reporting of follow-up of all patients, including protocol deviations, deaths, and loss to follow-up; an intention-to-treat analysis is highly desirable; modification for loss to follow-up (ie, patients who did not complete 30-day follow-up) or in those for whom a wound could not be assessed, or in those who did not have surgery after randomisation, was still considered low risk; exclusion of patients in whom wounds could be assessed (eg, incorrect allocation) and per-protocol only analysis without adequate description of patients lost to follow-up were considered to be high risk	Low risk: intention-to-treat analysis performed, or full reporting of protocol deviations and loss to follow-up; high risk: no intention-to-treat analysis performed or incomplete reporting	Yes
Missing outcome data	Loss to follow-up	Acceptable level of loss to follow-up is <20% in patients who survived at 30 days; sensitivity analysis around missing outcome data is preferable to demonstrate that missing results do not affect the overall outcome of the analysis	Low risk: loss to follow-up <20%; high risk: loss to follow-up ≥20%	Yes
Blinding of outcome assessors	Detection	As diagnosis of SSI is a structured but subjective assessment, and blinding of outcome assessors is essential, appropriate training of the outcome assessor should also be provided	Low risk: blinded outcome assessor; high risk: unblinded, untrained outcome assessor	Yes
Quality assurance of outcome assessment	Outcome definition	A formal definition of SSI was used	Low risk: valid definition stated; high risk: definition not stated, or invalid	Yes
Quality assurance of outcome assessment	Follow-up period pre-defined	Follow-up intervals were pre-defined and standardised for each participant	Low risk: follow-up defined; high risk: follow-up not defined	Yes
Quality assurance of outcome assessment	Post-discharge surveillance	A process for wound assessment was established for post-discharge assessment at time of primary outcome evaluation; reliance on ad-hoc re-admissions or notes-only reviews were considered at high risk of bias	Low risk: prespecified post discharge wound assessment plan; high risk: no prespecified post discharge wound assessment plan	Yes
Reporting	Selective reporting	Reporting of the primary outcome matched the pre-published or registered protocol	Low risk: complete, prespecified primary outcome reporting; high risk: incomplete, prespecified primary outcome reporting	Yes
Reporting	Protocol registration	The study protocol should have been published or registered on a recognised trials registry in the public domain	Low risk: protocol published or registered; high risk: protocol not published or registered	Yes

We defined a high-quality randomised controlled trial as one that was at low risk of bias across all of the domains stated above. When the assessment was unclear, this constituted a risk of bias. SSI=surgical site infection.

Table 1: Quality assessment of randomised controlled trials adapted from the domains of the Cochrane risk of bias-2 tool, modified for interventions to reduce SSIs

because clean procedures were excluded from analysis) on skin preparation (ie, alcoholic chlorhexidine and aqueous povidone-iodine) and five high-quality RCTs[4,18–21] (n=8619 patients; patient numbers differed from totals given in table 3 because clean procedures were excluded from analysis) on suture type (ie, triclosan-coated and uncoated) were included.

Regarding skin preparation solutions, the NICE 2019 guidelines included 28 studies, 14 of which were originally rated as high quality by the authors of the NICE guidelines, and two of which were included in the current review. WHO 2018 guidelines included 17 studies,

five of which were originally rated as high quality by the authors of the WHO guidelines according to the Cochrane risk of bias, and one of which was included in the current review. Detailed reasons for exclusions are reported in the appendix (p 15).

In the overall analysis, no significant differences were reported in the rates of SSI between alcoholic chlorhexidine and aqueous povidone-iodine (17·9% [667 of 3723 patients] vs 19·8% [740 of 3744 patients]; odds ratio [OR] 0·84 [95% CI 0·65–1·10]; p=0·21; figure 3, appendix p 12). There was moderate heterogeneity across trials (I^2=53% [95% CI 0·0–84·5]).
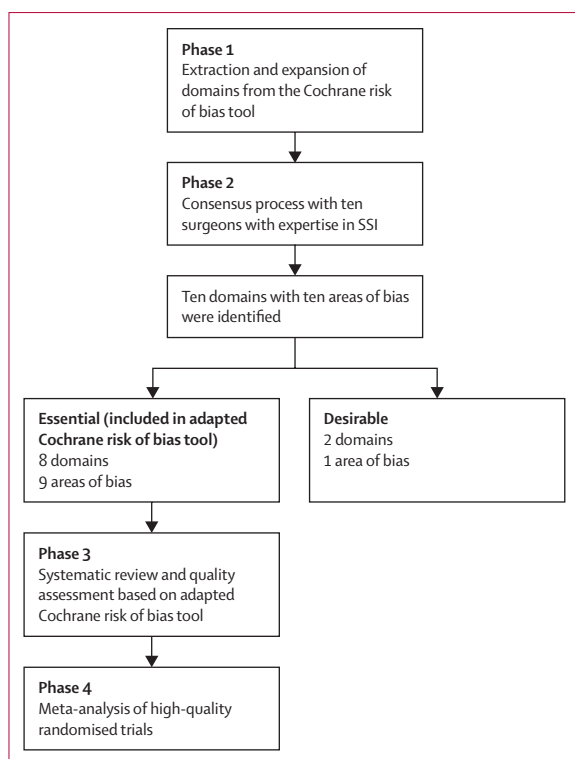
Figure 1: Flow diagram of consensus process and systematic review of high-quality randomised controlled trials
SSI=surgical site infection.
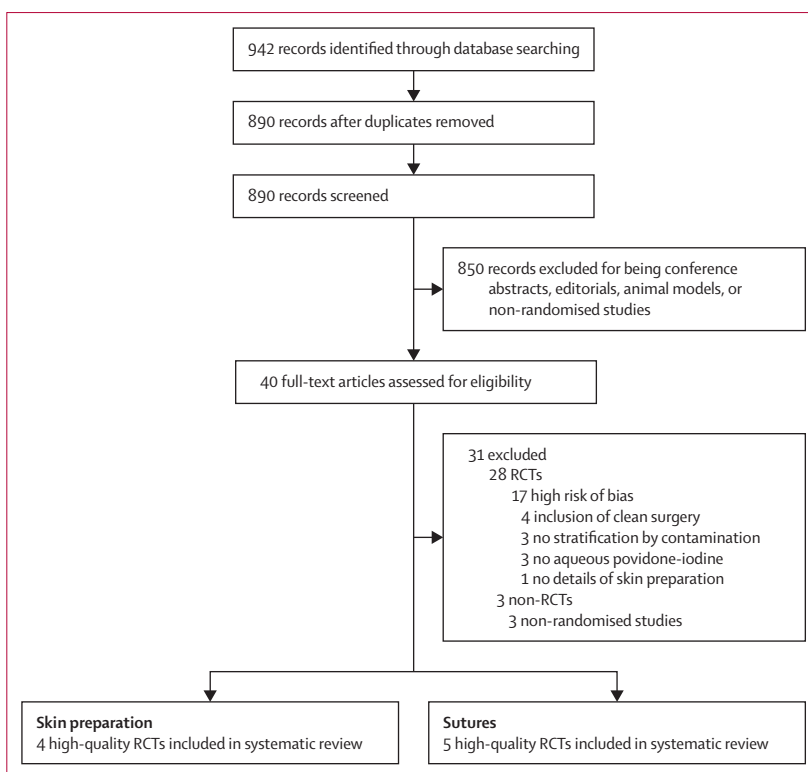
Figure 2: Preferred Reporting Items for Systematic Reviews and Meta-analysis flow chart of included studies in the systematic review and meta-analysis
RCT=randomised controlled trial.

Stratified analyses by degree of contamination showed no significant difference in patients who received clean-contaminated surgery (OR 0·86 [95% CI 0·64–1·16]; p=0·32; figure 3, appendix p 12), with moderate heterogeneity across trials (I^2=57% [95% CI 0·0–85·8]). Only one high-quality trial reported rates of SSI in contaminated or dirty surgery, which showed no significant difference between interventions (OR 0·85 [95% CI 0·71–1·01]); when this analysis was adjusted within the original trial report, there remained no significant difference (adjusted OR 0·97 [95% CI 0·81–1·02]; figure 3, appendix p 12).

A sensitivity analysis was performed for RCTs that clearly reported conflicts of interest. Three RCTs were included in this part of the analysis, comprising 6557 patients. No overall significant differences in SSI rates were observed, which remained consistent in stratified analysis by degree of contamination for clean-contaminated surgery and for contaminated or dirty surgery (appendix pp 12–15).

A summary of other types of skin preparation solutions is presented the appendix (pp 10–11). Only three (n=2872 patients) RCTs[22–24] were deemed to be of high quality. These RCTs compared alcoholic chlorhexidine with alcoholic povidone-iodine, all of which were in clean-contaminated settings. There was no significant difference between the rates of SSI between these

interventions (OR 0·75 [95% CI 0·55–1·03]; p=0·070; appendix p 14).

With regard to suture types, NICE 2019 guidelines included 14 studies, nine of which were deemed high quality by the authors of the NICE guidelines, four of which were included in the current review. WHO 2018 guidelines included 18 studies, 13 of which were originally rated as high quality by the authors of the WHO guidelines according to the Cochrane risk of bias, two of which were included in the current review. Detailed reasons for exclusions are shown in the appendix (p 16).

In the overall analysis, there were no significant differences in rates of SSI between coated (16·8% [733 of 4360 patients]) and uncoated sutures (18·4% [784 of 4259 patients]; OR 0·90 [95% CI 0·74–1·09; p=0·29; figure 3, appendix p 17). There was moderate heterogeneity across trials (I^2=36% [95% CI 0·0–76·2]).

Stratified analyses by degree of contamination showed no significant difference in patients receiving clean-contaminated surgery (OR 0·91 [95% CI 0·75–1·10]; p=0·32; figure 3, appendix p 17). Only one high-quality trial reported rates of SSI in contaminated or dirty surgery, and it found no significant difference between interventions (figure 3, appendix p 17).

A sensitivity analysis was performed for RCTs that clearly reported conflicts of interest. Four RCTs were

	Random sequence generation (selection)	Allocation concealment (selection)	Baseline differences between intervention groups (selection)	Blinding of patients (performance)	Analysis of groups to which they were randomly assigned (attrition)	Missing outcome data (loss to follow-up)	Blinding of outcome assessors (detection)	Blinding of outcome assessors (outcome definition)	Quality assurance of outcome assessment (follow-up period pre-defined)	Quality assurance of outcome assessment (post-discharge surveillance plan)	Reporting (selective reporting)	Reporting (protocol publication or registration)
Skin preparation												
Springel et al (2017)[15]	Low risk: computer-generated 1:1 simple randomisation	Low risk: sequentially numbered opaque envelopes, which remained sealed until after consent	Low risk: no significant differences between groups	Low risk	Low risk: ITT analysis, complete reporting of protocol deviations and loss to follow-up	Low risk: 2%	Low risk: assessed by blinded, trained member of infection control team	Low risk: CDC	Low risk: 30-day pre-defined	Low risk: monitoring of electronic medical records and face-to-face	Low risk: SSI primary outcome	Complete: NCT02202577
Darouiche et al (2010)[16]	Low risk: computer-generated 1:1 randomisation stratified by hospital	Low risk: computer-generated randomisation stratified by hospital, without blocks	Low risk: no significant differences between groups	Low risk	Low risk: ITT analysis, complete reporting of protocol deviations and loss to follow-up	Low risk: 0%	Low risk: blinded assessor, using pre-set criteria	Low risk: CDC	Low risk: 30-day pre-defined	Low risk: mixed (telephone and face-to-face)	Low risk: SSI primary outcome	Complete: NCT00290290
Dior et al (2020)[17]	Low risk: computer-generated 1:1:1 randomisation	Low risk: computer-generated randomisation	Low risk: no significant differences between groups	Low risk	Low risk: ITT analysis, complete reporting of protocol deviations and loss to follow-up	Low risk: 3%	Low risk: blinded assessor, using pre-set criteria	Low risk: CDC	Low risk: 7-day and 30-day pre-defined	Low risk: face-to-face	Low risk: SSI primary outcome	Complete: ACTRN12617000475347
FALCON (2021)[4]*	Low risk: centralised computer-generated randomisation	Low risk: computerised stratified randomisation just before operation	Low risk: no significant differences between groups	Low risk	Low risk: ITT analysis, complete reporting of protocol deviations and loss to follow-up	Low risk: 10%	Low risk: blinded outcome assessor trained on pre-set criteria	Low risk: CDC	Low risk: 30-day pre-defined	Low risk: mixed (telephone and face-to-face)	Low risk: SSI primary outcome	Complete: NCT01602380

(Table 2 continues on next page)

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Suture type

	Random sequence generation (selection)	Allocation concealment (selection)	Baseline differences between intervention groups (selection)	Blinding of patients (performance)	Analysis of groups to which they were randomly assigned (attrition)	Missing outcome data (loss to follow-up)	Blinding of outcome assessors (detection)	Blinding of outcome assessors (outcome definition)	Quality assurance of outcome assessment (follow-up period pre-defined)	Quality assurance of outcome assessment (post-discharge surveillance plan)	Reporting (selective reporting)	Reporting (protocol publication or registration)
Justinger et al (2013)[18]	Low risk: randomisation into mixed block sizes	Low risk: mixed block sizes ranged from 50 patients to 100 patients	Low risk: no significant differences between groups	Low risk	Low risk: per-protocol analysis, complete reporting of protocol deviations and loss to follow-up	Low risk: 0%	Low risk: blinded assessor, using pre-set criteria	Low risk: CDC	Low risk: 14-days (pre-defined)	Low risk: face-to-face	Low risk: SSI primary outcome	Complete: NCT00998907
Diener et al (2014)[19]	Low risk: central web-based permuted block randomisation	Low risk: permuted block randomisation, 1:1 allocation ratio, block size 4	Low risk: no significant differences between groups	Low risk	Low risk: modified ITT analysis, complete reporting of protocol deviations and loss to follow-up	Low risk: 0%	Low risk: blinded assessor, using pre-set criteria	Low risk: CDC	Low risk: 30-day pre-defined	Low risk: face-to-face	Low risk: SSI primary outcome	Complete: DRKS00000390
Mattavelli et al (2015)[20]	Low risk: computer-generated 1:1 randomisation	Low risk: sealed, opaque, numbered envelopes	Low risk: no significant differences between groups	Low risk	Low risk: per-protocol analysis, complete reporting of protocol deviations and loss to follow-up	Low risk: 7%	Low risk: blinded assessor, pre-set criteria	Low risk: CDC	Low risk: 30-day pre-defined	Low risk: face-to-face	Low risk: SSI primary outcome	Complete: NCT01869257
Ichida et al (2018)[21]	Low risk: permuted block randomisation, 1:1 allocation ratio	Low risk: sealed, opaque, sequential envelopes, with a block size of 2	Low risk: no significant differences between groups	Low risk	Low risk: modified ITT analysis, complete reporting of protocol deviations and loss to follow-up	Low risk: 0%	Low risk: blinded assessor, pre-set criteria	Low risk: CDC	Low risk: daily up to 30 days pre-defined	Low risk: face-to-face	Low risk: SSI primary outcome	Complete: UMIN000013054
FALCON (2021)*	Low risk: centralised computer randomisation	Low risk: computerised stratified randomisation just before surgery	Low risk: no significant differences between groups	Low risk	Low risk: ITT analysis, complete reporting of protocol deviations and loss to follow-up	Low risk: 10%	Low risk: blinded outcome assessor trained on pre-set criteria	Low risk: CDC	Low risk: 30-day pre-defined	Low risk: mixed (telephone and face-to-face)	Low risk: SSI primary outcome	Complete: NCT01602380

CDC=Centre for disease control. ITT=intention-to-treat. SSI=surgical site infection.

Table 2: **High-quality randomised controlled trials, assessed using the enhanced Cochrane risk of bias-2 tool**

	Study period	Centres	Surgery type	Patients, n	Preoperative antibiotic, n (%)	SSI (n, %)	Clean-contaminated, n (%)	Contaminated or dirty, n (%)	Follow-up, days
Skin preparation									
Springel et al (2017)[15]	Feb, 2013–May, 2016	Single	Abdominal (caesarean section)	932	902 (99%)	62 (6%)	932 (100%)	0 (0%)	30
Darouiche et al (2010)[16]	April, 2004–May, 2008	Multiple	Abdominal and thoracic	897	200 (24%)	110 (13%)	897 (100%)	0 (0%)	30
Dior et al (2020)[17]	Feb, 2017–Nov, 2018	Single	Abdominal (gynaecological)	426	418 (99%)	72 (17%)	424 (100%)	0 (0%)	30
FALCON (2021)[4]*	Nov, 2018–July, 2020	Multiple	Abdominal (mixed)	5788	5134 (97%)	1163 (22%)	3091 (53%)	2697 (47%)	30
Suture type									
Justinger et al (2013)[18]	Sept, 2009–Sept, 2011	Single	Abdominal (mixed)	856	..	73 (9%)	790 (92%)	66 (8%)	14
Diener et al (2014)[19]	April, 2010–Oct, 2012	Multiple	Abdominal (mixed)	1185	238 (20%)	183 (15%)	880 (74%)	23 (2%)	30
Mattavelli et al (2015)[20]	Jan, 2010–March, 2013	Multiple	Abdominal (colorectal)	281	237 (84%)	33 (12%)	281 (100%)	0 (0%)	30
Ichida et al (2018)[21]	March, 2014–March, 2017	Single	Abdominal (mixed)	1023	173 (17%)	65 (6%)	990 (97%)	14 (1%)	30
FALCON (2021)[4]*	Nov, 2018–July, 2020	Multiple	Abdominal (mixed)	5788	5234 (99%)	1163 (22%)	3091 (53%)	2697 (47%)	30

*Only study in the review that included centres from low-income and middle-income countries.

Table 3: Study characteristics of included high-quality randomised controlled trials

included in this part of the analysis, comprising 7606 patients. No overall significant differences were reported in SSI rates, which remained consistent in stratified analysis by degree of contamination for clean-contaminated, contaminated, or dirty surgery (appendix pp 19, 20).
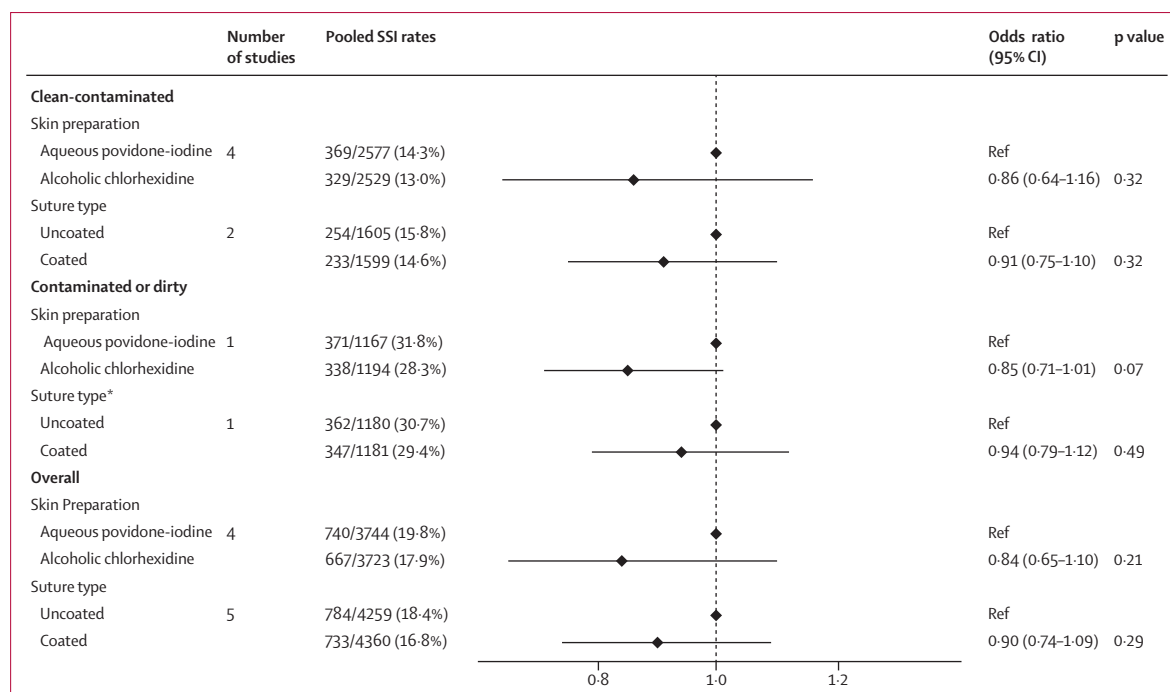
Discussion

NICE 2019 and WHO 2018 guidelines recommend the use of triclosan-coated sutures and alcoholic chlorhexidine to reduce SSI rates, yet these recommendations are based on a meta-analysis[7] of small RCTs showing positive results that were deemed predominately low or very low quality according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) by the guidelines' authors. This systematic review and meta-analysis of only high-quality RCTs showed no significant differences between type of sutures (ie, coated *vs* uncoated sutures) or skin preparation (ie, alcoholic chlorhexidine *vs* aqueous povidone-iodine) on rates of SSI. We included more recent high-quality trials, contributing larger numbers. To our knowledge, our systematic review and meta-analysis is the first to include high-quality randomised data from LMICs. Based on our findings, global guidance should be reconsidered and potentially changed to remove recommendations for the routine use or alcoholic chlorhexidine and coated sutures.

The differences observed in effect estimates between our updated meta-analysis and previous meta-analyses are explained by inclusion of only very high-quality studies. Although our inclusion criteria risk the exclusion of well conducted studies that might not have been reported at a high quality, the expert panel decided that this approach was superior to drawing conclusions from a data pool of mixed or unknown quality. We hope that this approach encourages debate around the conduct of SSI trials and on these interventions, especially given the cost differences that must be realised when compared with alternatives. Previous meta-analyses included trials that were of low-to-moderate quality and thus had poor standardisation, conduct, and reporting. For example, only five of 11 meta-analyses on coated sutures included a quality assessment.[25–29] Through consensus with experts, we developed an enhanced risk-of-bias tool based on the Cochrane risk of bias-2 tool to assess SSI trials for quality; the tool was developed ahead of literature searches and then applied during quality assessment to prevent any selection bias during the inclusion of studies. By doing so and by updating searches, only truly high-quality RCTs were selected and included, and those at high risk of bias were excluded. Full details of excluded studies have been provided, allowing a detailed understanding of this process. Our enhanced risk of bias-2 tool can be used by other researchers in future SSI meta-analyses.

The high SSI rates reported in this meta-analysis show that SSI remains a major global problem that is contributing to antimicrobial consumption and resistance, as well as excessive patient costs. These high rates are consistent with the highest published rates found when SSIs are collected as a primary rather than

	Number of studies	Pooled SSI rates		Odds ratio (95% CI)	p value
Clean-contaminated					
Skin preparation					
Aqueous povidone-iodine	4	369/2577 (14·3%)		Ref	
Alcoholic chlorhexidine		329/2529 (13·0%)		0·86 (0·64–1·16)	0·32
Suture type					
Uncoated	2	254/1605 (15·8%)		Ref	
Coated		233/1599 (14·6%)		0·91 (0·75–1·10)	0·32
Contaminated or dirty					
Skin preparation					
Aqueous povidone-iodine	1	371/1167 (31·8%)		Ref	
Alcoholic chlorhexidine		338/1194 (28·3%)		0·85 (0·71–1·01)	0·07
Suture type*					
Uncoated	1	362/1180 (30·7%)		Ref	
Coated		347/1181 (29·4%)		0·94 (0·79–1·12)	0·49
Overall					
Skin Preparation					
Aqueous povidone-iodine	4	740/3744 (19·8%)		Ref	
Alcoholic chlorhexidine		667/3723 (17·9%)		0·84 (0·65–1·10)	0·21
Suture type					
Uncoated	5	784/4259 (18·4%)		Ref	
Coated		733/4360 (16·8%)		0·90 (0·74–1·09)	0·29

Figure 3: **Summary forest plots of meta-analysis comparing effects of skin preparation (alcoholic chlorhexidine *vs* aqueous povidone-iodine) and suture types (triclosan-coated *vs* uncoated) on SSI rates in high-quality randomised controlled trials, stratified by degree of contamination**
SSI=surgical site infection. *The adjusted relative risk within the original published paper (adjusted for trial minimisation factors) was RR 0·97 (95% CI 0·81–1·02).

secondary outcome measure in trials of wound class II–IV.[30] This disparity in SSI rates reinforces that only high-quality trials with low risk of bias in ascertainment of SSIs were included in this process. Although combining data from heterogenous settings could hide marginal benefits in specific situations, the benefits of combining global data and the subsequent generalisable results are broadly relevant.

This study has some limitations that should be considered when interpreting its results, which are detailed in full in the appendix (pp 25–26). First, the definitions of low risk of bias might have led to the exclusion of some studies that were well conducted but poorly reported. Second, the studies included heterogeneous care that theoretically might have masked certain effects. For instance, routine antibiotic prophylaxis is likely to have varied in agent and timing. Third, the use of triclosan-coated sutures varied from use in full thickness closure of the abdominal wall to use only in the superficial layers. Fourth, an investigation is required into the potential effects of using sutures in different anatomical layers of the wound, although our study results suggest that any potential benefit will be slight. Fifth, the benefits of clean surgery, for which infection rates are low, might be marginal at best, and are beyond the scope of this study. Finally, there were too few studies included in either the comparison of suture types or skin preparation to assess publication bias.[31] We also did not exclude any older studies, as search was performed from database inception.[32]

Our analysis identifies areas in which more research is needed, especially in contaminated and dirty surgery, for which the need is greatest and only data from the FALCON RCT were available. We identify (through a 2×2 factorial design using two different in theatre interventions) that the combination of multiple interventions warrants further attention in prospective trials, which would allow for a multifactorial approach. Further, the relative effects of different skin preparation solutions and different suture formats (coated and uncoated polydioxanone or Vicryl) could be assessed through a network meta-analysis when higher quality trials are available. When planning new SSI RCTs, research teams could use our enhanced risk of bias-2 tool to reinforce trial design. By addressing these issues upfront, the conduct of such trials will be at low risk of bias, leading to high-quality outputs that are specific to the needs of SSI trials.

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Declaration of interests

Data sharing

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