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# Meta-Analysis of Prevention of Surgical Site Infections following Incision Closure with Triclosan-Coated Sutures: Robustness to New Evidence

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## Abstract

***Background:*** A systematic literature review (SLR) and meta-analysis of surgical site infections (SSIs) after surgical incision closure with triclosan-coated sutures (TS) compared with non-antibacterial coated sutures (NTS) previously published by the authors suggested that fewer SSIs occurred in the TS study arm. However, the results were vulnerable to the removal of one key randomized control trial (RCT) because of insufficient data. Furthermore, recently published RCTs highlighted the need for an update of the SLR to challenge the robustness of results.
***Methods:*** The protocol for the new SLR included more stringent tests of robustness than initially used and the meta-analysis was updated with the results of two new RCTs as well as the count of patients and SSIs by U.S. Centers for Disease Control and Prevention (CDC) incision class.
***Results:*** The updated SLR included 15 RCTs with 4,800 patients. No publication bias was suggested in the analysis. The predominant effect estimated a relative risk of 0.67 (95% CI: [0.54, 0.84], $p = 0.00053$) with an overall lower frequency of SSI in the TS arm than in the NTS arm. Results were robust to sensitivity analysis.
***Conclusions:*** The two additional peer-reviewed double-blind RCTs of this update confirmed the predominant effect found in the authors' previous meta-analysis and established the robustness of conclusions that were previously lacking. This SLR and meta-analysis showed that the use of triclosan antimicrobial sutures reduced the incidence of SSI after clean, clean-contaminated, and contaminated surgery. The Centre for Evidence-based Medicine (CEBM) evidence concentration Ia of this SLR was reinforced.

## Introduction

Triclosan (polychloro phenoxy phenol) is an antimicrobial biocide which exhibits broad-spectrum activity against Gram-positive and Gram-negative bacteria.[1,2] *In-vitro* studies have shown that microbial pathogens commonly associated with surgical site infections (SSIs) are inhibited from adhering to the surface of triclosan-coated polyglactin 910 braided sutures.[3] Animal studies have also documented the efficacy of polyglactin 910 with triclosan less than *in-vivo* conditions, and further *in-vitro* and *in-vivo* studies have shown the efficacy of triclosan when incorporated in polydioxanone sutures.[4,5] The triclosan dosage producing the intended biocidal effect in these absorbable sutures is a maximum of 2360 micrograms per meter in both polydioxanone and poliglecaprone 25; and 472 micrograms per meter in polyglactin 910.[6–8]

Tests and clinical trials have also shown that surgeons cannot differentiate the presence or absence of triclosan in braided or monofilament sutures, making it possible to design randomized double-blinded trials for clinical comparison.[9,10] Several randomized controlled clinical trials (RCTs) have compared the frequency of SSIs after closure of surgical incisions with triclosan coated sutures (TS) compared with non-triclosan sutures (NTS) in different clinical settings, and surgical procedures, to ensure the comparability of study arms, diagnostic criteria, suture materials, patient demographics, background diseases, and surgical operations. These clinical trials are the subject of this updated systematic literature review (SLR) and meta-analysis.

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An earlier SLR and meta-analysis published by the authors of this current article, was conducted according to a predefined written protocol, and identified 13 peer-reviewed eligible RCTs that compared TS vs. NTS in different clinical settings (different surgical operations, suture materials, underlying diseases, concentration of incision contamination, and methods to assess SSI occurrence).[9,11–23] The result was a lower risk of SSI in the TS arm with a point estimate relative risk (RR) of 0.69, and a 95% confidence interval (CI) of [0.52, 0.92; $p < 0.011$]. Sensitivity analysis showed that this result was vulnerable to the removal of one trial, resulting in a borderline p-value, suggesting that the conclusions of the meta-analysis depended on that trial alone.[16] This article reports an update of the prior SLR and meta-analysis with inclusion of new clinical trials as well as additional information about the study methods and patient characteristics communicated by the authors of the previously reported eligible trials. The primary objective was to determine if incision closure presented the same risk of SSI when triclosan was present or absent on the surface of the sutures. The secondary objectives were to assess potential bias or confounding factors that could invalidate the primary conclusion and to determine the extent to which the primary conclusion could be generalized to the various types of patients included in the pooled RCTs.

## Methods

The SLR protocol of the first meta-analysis previously reported was developed according to PRISMA recommendations and is repeated in the current communication with a number of differences described below.[24]

**Study Selection:** Embase/Medline, the Cochrane database (Central Register of Controlled Trials [CENTRAL], Cochrane Database of Systematic Reviews [CDRS], Health Economic Evaluations Database [HEED], and Database of Health Technology Assessments [HTA]) as well as www.clinicaltrials.gov were searched on July 30, 2013 using their own search engines with a syntax that combined the following keywords: triclosan AND sutur* AND (random* OR RCT). Clinicaltrials.gov was also searched with those keywords to identify potentially completed relevant RCTs. The ''*'' character at the end of keyword radicals indicated to search engines to include any character sequence that ended the keyword. This syntax differed from the previous meta-analysis by not searching broader keyword combinations that had proven to retrieve only non-randomized studies or irrelevant publications.

**Study Eligibility:** Study eligibility criteria were the same as previously reported.[11] The results of the clinicaltrials.gov search and the reference lists of all relevant publications were meticulously searched to ''catch back'' any potentially eligible RCTs that might have been missed by the electronic study extraction and filtering process.

**Data Extraction:** Data extraction was performed according to the same rules as previously described.[11] The four data items extracted from each study were the number of patients in the TS group (N_TS) with the number of patients presenting an SSI in the TS arm (n_TS), and their counterparts in the NTS arm (N_NTS, n_NTS).

Whenever a study reported outcomes on both an intention-to-treat (ITT) basis and a per protocol (PP) basis, ITT results were used. Whenever a study reported outcomes PP only, but indicated the number of randomized patients together with demographics on an ITT basis, the PP sample size was replaced by ITT sample size.

In the case of RCTs reporting outcomes of the closure of several incisions per patient, only outcomes of the incision defined with the primary endpoint were included. For example, when the primary endpoint was the occurrence of SSI in the closure of a leg incision, after venous graft harvesting for coronary artery bypass surgery (CABG), outcomes of chest closure in the same patient were reported as a secondary endpoint. Trials where the same patient was systematically used in the active arm and the control arm were excluded as these trials were not ''head-to-head'' comparison and did not provide independence of groups.

Compared with the previous protocol, the extraction also recorded the blinding method (double-blind, single-blind, open-label), the SSI diagnostic method used (Center for Disease Control ''CDC'' criteria or other) as well as the number of patients with and without SSI per treatment arm broken down by class of incision contamination (class I/clean, class II/clean-contaminated, class III/contaminated, class IV/dirty-infected).[25,26] Whenever these data were not reported in the publications and could not be deducted from the study context, the reviewers contacted the corresponding authors of the publications to obtain the missing information.

**Quality of Evidence:** As performed with the RCTs included in the previous SLR, newly published studies were tested against the eligibility criteria defined in this SLR, against the concentration of evidence criteria proposed by the Centre for Evidence-Based Medicine (CEBM) at the University of Oxford, and the Cochrane criteria for quality and low risk of bias.[27,28] Full publications of all new RCTs were acquired and reviewed.

**Statistical Analysis:** The data extracted from eligible RCTs was analyzed using meta-analytic techniques as previously, and the same CMA software (Comprehensive Meta-Analysis v2.2.027, Englewood, NJ, USA) and reproducibility of calculations was checked by running an auditable script in STATA 12 (StataCorp LP, College Station, TX, USA). A rigorous 13-step analytical strategy was formulated (Fig. 1) and implemented in order to include the additional questions to be compared to the meta-analysis. Subgroup meta-analysis was considered to be sufficiently powered if it pooled a minimum of five estimates. Similarly, the comparison of subgroups was considered sufficiently powered if all compared subgroups pooled a minimum of five estimates. Subgroups that pooled four estimates were considered only to describe the available evidence and to assess its internal validity, but not for generalization of conclusions.

**Step 1:** Calculated the risk ratio (RR) as the measure of effect between treatment arms in each RCT. $RR = (n\_TS/N\_TS)/(n\_NTS/N\_NTS)$, where in each treatment arm, n is the number of patients with SSI and N is the number patients treated.

**Step 2:** Tested the null hypothesis (H0) of absence of publication bias. H0 was rejected if the Egger intercept test (significant if $p < 0.05$) detected an asymmetric inverted funnel shape in the Funnel plot.[29–31]

**Step 3:** Tested the null hypothesis (H0) of no heterogeneity between trials, meaning that the RRs of all RCTs were

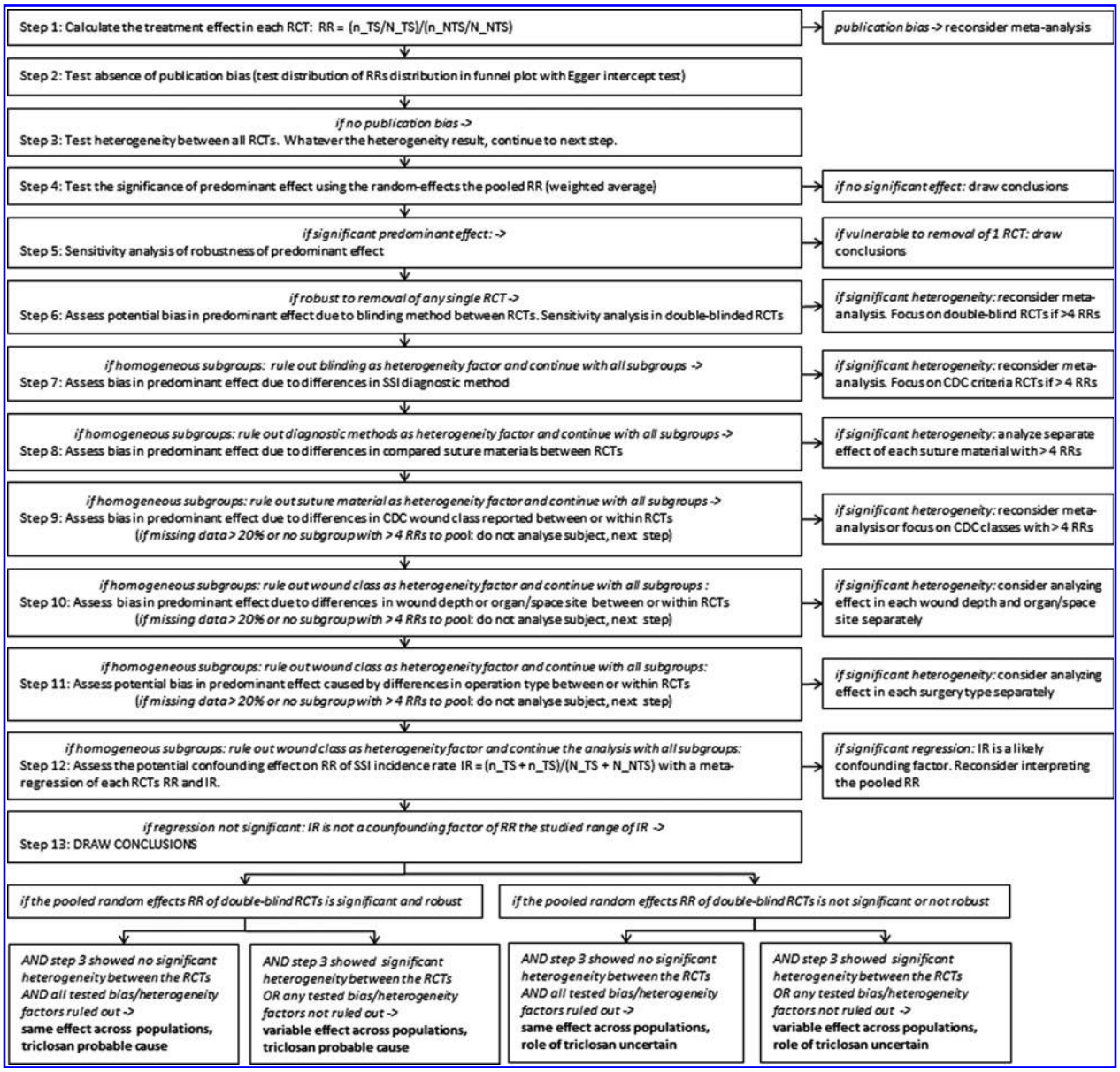


**FIG. 1.** Flowchart of the meta-analysis.

drawn from a common population with the same true mean. H0 was rejected if the Cochran's Q-test was significant (if $p < 0.05$).[32] The $I^2$ estimated the percentage of variability of study RRs that could not be explained by random error only.[33,34] Given differences between trials in terms of methods and clinical settings (blinding, diagnostic criteria, compared suture materials, types of operations, CDC incision classes, and site/organ location), the algorithm temporarily maintained the assumption of heterogeneity between study populations until all these factors would be ruled out further in the analysis.

**Step 4:** Tested the effect between treatment arms across studies by calculating the random effects pooled RR (weighted average).[36] This estimated the predominant effect among the populations from which the RCTs were drawn but not the true mean RR of any study population in particular. Under the null hypothesis (H0), the pooled RR is one, meaning the same frequency of SSIs between treatment arms. H0 would be rejected in favor of the alternative that the predominant effect was significant if the pooled RR's 95% CI included one.

**Step 5:** Sensitivity analysis of the robustness of meta-analysis was performed on all eligible RCTs. This consisted of repeating steps two, three, and four iteratively after removing one RCT at a time, then two RCTs at a time (any pair of RCTs), then three RCTs at a time, and so on, until 95% CI of the pooled RR reached one, thus non-significance. This process enabled to identify the RCTs upon which depended significance.

**Step 6:** Assessed the potential bias in the predominant effect potentially caused by differences in blinding method between RCTs (double-blind, single-blind, open-label). The pooled random effects RR and 95% CIs of each blinding subgroup with more than four individual RRs were

calculated. The null hypothesis (H0), that subgroups shared the same population mean RR, was rejected if $p < 0.05$, in favor of the alternative where subgroups had heterogeneous population means. Sensitivity analysis of robustness was planned similarly to step five in the double-blinded subgroup if the subgroup RR was significant and pooled more than four individual RRs.

**Step 7:** Assessed the potential bias in the predominant effect potentially caused by differences in SSI diagnostic method between RCTs (CDC criteria, other methods). The process was similar to step six but no sensitivity analysis was planned.

**Step 8:** Assessed potential bias in the predominant effect caused by differences in compared suture materials between RCTs (polyglactin 910, polydioxanone, poliglecaprone, combinations of various materials, silk sutures) as performed.[25] The process was similar to step six with sensitivity analysis.

**Step 9:** Assessed potential bias in the predominant effect caused by differences in CDC incision class reported either between RCTs or class of contamination. The process was similar to step six with sensitivity analysis.

**Step 10:** Assessment of the potential bias in the predominant effect caused by differences in incision depth or site, between RCTs or within RCTs, was planned if reviewers were able to extract that information from publications. Incisional and organ/space surgical site definitions were those proposed by the CDC.[37] The process was similar to step six with sensitivity analysis.

**Step 11:** Assessed potential bias in the predominant effect caused by differences in operation type as reported by RCT authors. The process was similar to step six with sensitivity analysis.

**Step 12:** Assessed the potentially confounding relationship between the RR and the SSI incidence rate (IR) in each RCT. Incidence rate is an outcome computed with the same inputs as RR but examines the frequency of SSI as an average, ignoring differences between treatment arms: $IR = (n\_TS + n\_NTS)/(N\_TS + N\_NTS)$. In order to enable a linear comparison of RR and IR, The Log(RR) of each RCT was plotted against the corresponding RCT's IR in a meta-regression. The null hypothesis (H0) that RR was independent of IR was tested by testing the slope of Log(RR) as a function of IR. The alternative hypothesis that RR did vary with IR was accepted if that slope was (i.e. $p < 0.05$) different from 0.

**Step 13:** Conclusion: If previous steps showed that the overall random-effects pooled RR was robust, and that RR did not dependent on the IR, four conclusion options were possible:

i. If the pooled RR of the double-blind RCTs subgroup was robust AND if no heterogeneity was found among all RRs, AND all tested potential bias/heterogeneity factors were ruled out: The conclusion was a similar treatment effect across study populations probably caused by triclosan.
ii. If the pooled RR of the double-blind RCTs subgroup was robust BUT heterogeneity was found among all RRs, OR any tested potential bias/heterogeneity factors was not ruled out: The conclusion was a significant but parameter treatment effect across study populations probably caused by triclosan.
iii. If the pooled RR of the double-blind RCTs subgroup was not robust BUT no heterogeneity was found among all RRs, AND all tested potential bias/heterogeneity factors were ruled out: The conclusion was a similar treatment effect across study populations but an uncertain role of triclosan in the effect.
iv. If the pooled RR of the double-blind RCTs subgroup was robust AND if heterogeneity was found among all RRs, OR if any tested potential bias/heterogeneity factors was not ruled out: The conclusion was a parameter treatment effect across study populations and an uncertain role of triclosan in the effect.

## Results

Seventy-six references were identified and one additional reference was caught back.[40] Forty-three duplicate references were removed, 34 references were screened and 15 were confirmed eligible RCTs (Fig. 2). The eligible trials included the 13 RCTs from the previous meta-analysis and two double-blind prospective RCTs published later.[11,38,39] The new RCTs met all eligibility criteria of this SLR protocol as well as CEBM and Cochrane criteria for quality and low risk of bias.[27,28] The 19 ineligible references included four abstracts of non-peer reviewed RCTs.[40–43] The eligibility of those four abstracts could not be determined because of insufficient methods descriptions or incomplete reporting of results reporting.

The SSI diagnostic method used and CDC incision class were reported in four RCTs and CDC incision class could be deducted as clean from the type of surgery in two others. Ten authors were contacted to obtain or confirm the count of patients with and without SSI by CDC class and the confirmation of the SSI diagnostic method when these were not specified in the publication. Seven authors responded, two of whom also added that SSI had been diagnosed using CDC criteria. The lead author of one trial on colorectal surgery, who did not use the CDC criteria, responded that all cases were clean or clean-contaminated so the reviewers assumed that all cases were clean-contaminated, as in other colorectal trials.[17] Three authors did not respond. Altogether outcomes were available by class of incision contamination in 12 RCTs. Table 1 summarizes the characteristics of the eligible RCTs obtained from publications and authors directly. Overall, the 15 RCTs enabled the extraction of outcomes in 4,800 patients; (TS: $N = 2{,}323$ and NTS: $N = 2{,}477$), with head-to-head comparisons of a single incision per patient. There were 453 patients who had an SSI (TS: $n = 180$ and NTS: $n = 273$). The 13-step analysis revealed the following:

The 15 trial RRs and their 95% CIs were calculated with data reported (Table 1) on an intention to treat (ITT) basis in nine RCTs, with data reported per protocol (PP) in four RCTs, and with the number of SSIs per protocol and the number of randomized patients according to ITT methods in two RCTs (**Step1**). The funnel plot (Fig. 3) and Egger intercept test (intercept $= -0.746$, standard error (SE) $= 0.647$, t-value $= 1.153$, degrees of freedom (df) $= 13$, 2-tailed $p = 0.269$) suggested no publication bias (**Step 2**). The Q-test (**Step 3**) showed no heterogeneity between the RRs of the 15 trials ($Q = 18.572$, $df = 14$, $p = 0.182$) and the $I^2$ estimated 24.6% of variability because of heterogeneity. Given the

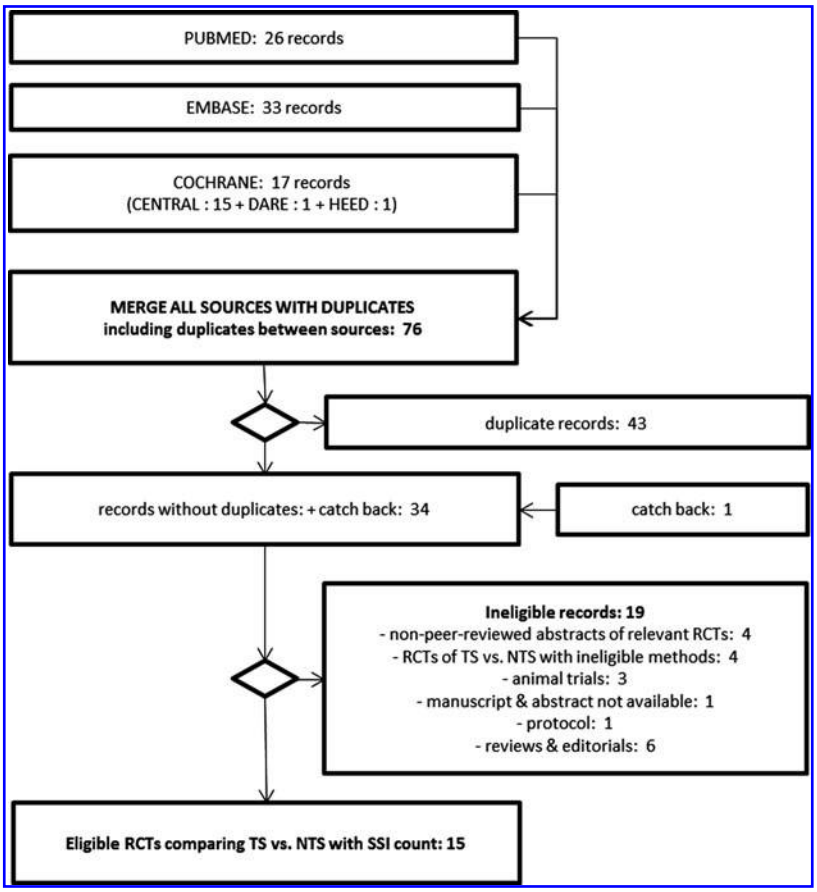


**FIG. 2.** PRISMA diagram of study extraction and eligibility selection.

heterogeneity between the 15 RCTs in terms of Incidence Rates (IR) of SSI ($Q = 123.97$, $df = 14$, $p < 0.00001$, $I^2 = 88.7\%$), the pooled RR continued to be estimated using a random-effects model until ruling out all identified potential confounders and factors of bias.

The overall pooled RR was 0.67, 95% CI: [0.54, 0.84], $p = 0.00053$ (**Step 4**). The Forrest plot (Fig. 4) showed the predominant effect to be a lower frequency of SSIs in the TS arm than in the NTS arm. Sensitivity analysis (**Step 5**) (Table 2) showed no indicator of publication bias and the predominant effect was robust to the iterative removal of any single RCT and any pair of RCTs. When removing three RCTs at a time, the only combination to result in the borderline $p = 0.045$ found during the previous meta-analysis was the joint removal of the Thimour-Bergström, Galal, and Justinger trials, with no indicator of associated publication bias.[38,26,39]

Pooled RR by blinding subgroup (**Step 6**), showed that nine RCTs were double-blind, four open-label, and two assessor single-blind (Fig. 5). Because of the low number of RRs in the open-label and assessor single-blind subgroups, the mixed-effects analysis ($Q = 2.688$, $df = 2$, $p = 0.261$) was underpowered to test the heterogeneity of the subgroups and to rule out potential bias because of the blinding method. However, the 95% CI of the pooled RR in the open-label subgroup included one, so open-label RCTs did not cause an overestimation of the predominant effect compared to double-blind RCTs. The assessor-blind subgroup consisted of the two RCTs comparing TS to silk sutures had a lower RR than the other subgroups, but their impact was small because of those RCTs' low relative weights of 1.88 and 0.63 respectively (Fig. 4).[14,15] The nine double-blind RCTs were the core subgroup that drove the overall pooled RR with no indicator of publication bias, a pooled RR of 0.65, 95% CI: [0.51, 0.82], $p < 0.00024$ (Table 3), and conclusions robust to sensitivity analysis with the removal of any single RCT and any pair of RCTs. That subgroup was vulnerable to the joint removal of three RCTs ($p = 0.107$).[16,38,39]

Pooled RR by diagnostic method subgroup (**Step 7**) demonstrated that 10 RCTs had used CDC criteria and five had used other methods. There were thus enough RRs per subgroup to test their heterogeneity with a mixed-effects analysis ($Q = 0.682$, $df = 1$, $p = 0.409$) but no heterogeneity was found. Diagnostic method was thus ruled out as a cause of bias and heterogeneity in the overall pooled RR. It should be noted that, the 95% CI of the pooled RR in the ''other methods'' subgroup included one, thus did not cause an overestimation of the predominant effect compared to RCTs using CDC criteria.

Pooled RR by suture material (**Step 8**) showed five suture-material subgroups: polyglactin with versus without triclosan in eight RCTs, polyglactin and poliglecaprone with versus without triclosan in three RCTs, polydioxanone with versus without triclosan in two RCTs, triclosan-polyglactin versus polydioxanone or versus silk in one RCT, and triclosan-polyglactin versus silk in one RCT. Because of the low

TABLE 1. CHARACTERISTICS OF ELIGIBLE RCTS

| *Study* | *Study design & population* | *Primary surgical procedures & population* | *CDCSurgical incision status* | *Compared sutures - Sutured incision depth -SSI definition* | *Reported Results Numbers used in meta-analysis* |
|---|---|---|---|---|---|
| Ford 2005, USA[9] | prospective, randomized, controlled, open-label with respect to SSI, comparative, single-center study<br>30-day follow-up | General surgery procedures<br>Patients: Children (151 randomized, 147 treated) | Not reported in publication but details disclosed by the author to reviewers. | -triclosan polyglactin 910, n = 98<br>-polyglactin 910, n = 49<br>SSI 2ndary endpoint. Defined as observed redness 3–5 mm from incision margins, edema, purulent discharge, pain, and increased skin temperature. Culture not required. SSI occurrence reported up to 80 days. | SSI reported cases PP:<br>TS: 3/98 NTS: 0/49<br>p-value not reported<br>SSI Meta-analysis PP |
| Rozzelle 2008, USA[12] | Single-center, prospective, randomized, double-blinded, and placebo-controlled study<br>6-month follow-up<br>Methodological issue: Data reported in relation to number of procedures | CSF shunt implantation or revision surgery<br>Patients: 61 children and adults, median age 6.3y, 84 randomized shunt procedures | Not reported in publication.<br>Reviewers' assumption: CSF shunt surgery, all CDC class I | - triclosan polyglactin 910, n = 46 procedures<br>- polyglactin 910, n = 38 procedures<br>Used in:<br>-galea closure &<br>- fascia closure<br>SSI 1mary endpoint. Defined as culture proven shunt infection from CSF or explanted shunt<br>84 shunt procedures: 40 implants & 44 reinterventions | SSI reported cases ITT:<br>TS: 2/46 NTS: 8/38<br>Reported p = 0.038<br>SSI Meta-analysis ITT |
| Mingmalairak 2009, Thailand[13] | Single-center, prospective, randomized, controlled, double blind, comparative trial<br>12-month follow-up | Appendectomy for acute appendicitis and ruptured appendix<br>Patients: 100, age 15–60y randomized | Not reported in publication but details disclosed by the author to reviewers. | - triclosan polyglactin 910, n = 50<br>- polyglactin 910, n = 50<br>Used in:<br>-closure not described<br>Per publication: SSI diagnostic criteria not described in publication.<br>Culture-proof *ad hoc*.<br>Author confirmed to reviewers using CDC diagnostic criteria | SSI reported cases ITT:<br>TS: 5/50 NTS: 4/50<br>Reported p = 0.727<br>SSI Meta-analysis ITT |

(*continued*)

TABLE 1. (CONTINUED)

| *Study* | *Study design & population* | *Primary surgical procedures & population* | *CDCSurgical incision status* | *Compared sutures - Sutured incision depth -SSI definition* | *Reported Results Numbers used in meta-analysis* |
|---|---|---|---|---|---|
| Zhuang 2009, China[14] | Single-center, prospective, randomized, controlled, assessor-blinded, comparative trial<br>12 to 14-month follow-up | Laparotomy (various abdominal operations)<br>Patients: 450 adults randomized | Not reported in publication. No response to reviewers' request. | -triclosan polyglactin 910, n = 150<br>-polydioxanone, n = 150<br>-silk, n = 150<br>Used in:<br>-abdominal wall closure: anadesma, muscle, and peritoneum.<br>-skin excluded in triclosan polyglactin and polydioxanone groups.<br>-Translation does not indicate differences in skin closure between group or differences in counting superficial incisional infections<br>SSI 2ndary endpoint. Diagnostic criteria not described. | SSI reported cases ITT:<br>TS polyglactin 910: 0/150<br>NTS polydioxanone, 3/150<br>NTS silk: 15/150<br>Reported lowest SSI rate in TS: $p < 0.01$<br>SSI Meta-analysis ITT |
| Zhang 2011, China[15] | Multi-center, prospective, randomized, controlled, assessor-blinded, comparative trial<br>90-day follow-up | Modified radical mastectomy<br>Patients: 101 adults randomized | Publication reports all CDC class I | -triclosan polyglactin 910, n = 50<br>-silk, n = 50<br>Used in:<br>-skin closure<br>SSI 2ndary endpoint. CDC diagnostic criteria & ASEPSIS score | CDC SSI reported cases PP:<br>TS: 2/46 NTS: 5/43<br>SSI Meta-analysis ITT |
| Galal 2011, Egypt[16] | Single-center, prospective, randomized, controlled, double-blinded, comparative trial<br>12-month follow-up:<br>SSI within 30 days or 1 year if prosthesis | Various surgeries<br>Patients: 450 adults randomized | Details reported in publication | - triclosan polyglactin 910, n = 230<br>- polyglactin 910, n = 220<br>Used in:<br>-broad range of surgical operation<br>SSI 1mary endpoint. CDC diagnostic criteria. | SSI reported cases ITT:<br>TS : 17/230 NTS : 33/220<br>Reported p = 0.011<br>SSI Meta-analysis ITT |
| Rasic 2011, Croatia[17] | Single-center, prospective, randomized, controlled, non-blinded, comparative trial<br>Follow-up (unspecified, apparently, minimum 14 days) | Colorectal surgery<br>Patients: 184 adults randomized | Not reported in publication.<br>Author confirmed to reviewers evaluated according to incision presentation but all patients were clean to clean-contaminated SSI.<br>Reviewers assumed all colorectal operations CDC class II | - triclosan polyglactin 910, n = 91<br>- polyglactin 910, n = 93<br>Used in:<br>-midline abdominal wall incision closed with continuous single-layer mass technique(peritoneum, muscle, and fascia)<br>-skin closure with polyamide suture<br>SSI part of 1mary endpoint. Diagnostic criteria not specified. | SSI reported cases ITT:<br>TS: 4/91 NTS: 12/93<br>Report p = 0.035<br>SSI Meta-analysis ITT |

(*continued*)

TABLE 1. (CONTINUED)

| *Study* | *Study design & population* | *Primary surgical procedures & population* | *CDCSurgical incision status* | *Compared sutures - Sutured incision depth -SSI definition* | *Reported Results Numbers used in meta-analysis* |
|---|---|---|---|---|---|
| Baracs 2011, Hungary[19] | Multi-center, prospective, randomized, controlled, comparative trial<br>Blinding not specified<br>30-day follow-up | Colorectal surgery<br>Patients: 485 adults randomized | Not reported in publication.<br>Author confirmed to reviewers: All CDC class II. | -triclosan polydioxanone, n = 188<br>-polydioxanone, n = 197<br>Used in:<br>- abdominal fascia closure with polydioxanone (TS or NTS depending on randomization)<br>-skin closure with triclosan poliglecaprone 25 in both arms<br>SSI 1mary endpoint.<br>Author confirmed to reviewers using CDC diagnostic criteria. | SSI reported cases ITT:<br>TS: 23/188 NTS: 24/197<br>p-value reported as non-significant<br>SSI Meta-analysis ITT |
| Williams 2011, UK[18] | Single-center, prospective, randomized, controlled, double-blinded, comparative trial<br>6-week follow-up duration | Skin closure after breast cancer surgery<br>Patients: 150 female adults randomized | Not reported in publication.<br>Author confirmed to reviewers: All CDC class I | -triclosan polyglactin 910 & triclosan poliglecaprone 25, n = 75<br>- polyglactin 910 & poliglecaprone 25 n = 75<br>Used in;<br>- deep tissue closure with polyglactin 910<br>-skin closure with poliglecaprone 25<br>SSI 1mary endpoint. CDC diagnostic criteria. | CDC SSI cases PP:<br>TS: 10/66 NTS: 14/61<br>p-value reported as non-significant<br>SSI Meta-analysis ITT |
| Turtiainen 2012, Finland[20] | Multi-center, prospective, randomized, controlled, double-blinded, comparative trial<br>1-month follow-up duration | Incision closure after lower limb revascularization surgery<br>Patients: 276 adults randomized | Not reported in publication. No response to reviewers' request. | -triclosan polyglactin 910 & triclosan poliglecaprone 25, n = 139<br>- polyglactin 910 & poliglecaprone 25 n = 137<br>Used in:<br>- subcutaneous closure with polyglactin 910<br>-intracutaneous closure with poliglecaprone 25<br>SSI 1mary endpoint. CDC diagnostic criteria. Culture-proof *ad hoc* | SSI reported ITT:<br>TS: 31/139 NTS: 30/137<br>Reported p = 0.94<br>SSI Meta-analysis ITT |
| Seim 2012, Norway[21] | Single-center, prospective, randomized, controlled, non-blinded, comparative trial<br>4-week follow-up duration | Leg incision after vein harvesting for CABG<br>Patients: 328 adults randomized | Not reported in publication. No response to reviewers' request. Reviewers' assumption CABG all CDC class I | - triclosan polyglactin 910, n = 160<br>- polyglactin 910, n = 163<br>Used in:<br>-leg incision closure without further details<br>Leg SSI 1mary endpoint. Diagnostic criteria not specified | SSI reported PP:<br>TS: 16/160 NTS: 17/163<br>p-value reported as NS<br>SSI Meta-analysis PP |

(*continued*)

TABLE 1. (CONTINUED)

| *Study* | *Study design & population* | *Primary surgical procedures & population* | *CDCSurgical incision status* | *Compared sutures - Sutured incision depth -SSI definition* | *Reported Results Numbers used in meta-analysis* |
|---|---|---|---|---|---|
| Isik 2012, Turkey[22] | Single-center, prospective, randomized, controlled, double-blinded, comparative trial<br>30-day follow-up duration | Sternal incision in cardiac surgery.<br>Patients: 510 adults randomized | Not reported in publication.<br>Author confirmed to reviewers: All CDC class I | - triclosan polyglactin 910, n = 170<br>- polyglactin 910, n = 340<br>Used in:<br>-sternal incision closure without further detail<br>Sternal SSI 1mary endpoint. CDC diagnostic criteria. | SSI reported sternal incision ITT:<br>TS: 4/170 NTS: 12/340<br>Reported p = 0.516<br>SSI sternal Meta-analysis ITT |
| Nakamura 2013, Japan[23] | Single-center, prospective, randomized, controlled, double-blinded, comparative trial<br>30-day follow-up duration | Colorectal surgery<br>Patients: 410 adults randomized | Reported in publication. | - triclosan polyglactin 910, n = 206<br>- polyglactin 910, n = 204<br>Used in:<br>-colorectal incision closure without further detail<br>SSI 1mary endpoint. CDC diagnostic criteria. | SSI reported ITT:<br>TS: 9/206 NTS: 19/204<br>Report p = 0.047<br>SSI Meta-analysis ITT |
| Thimour-Bergstöm 2013, Sweden[38] | Single-center, prospective, randomized, controlled, double-blinded, comparative trial<br>60-day follow-up duration | Leg incision after vein harvesting for CABG<br>Patients: 392 adults randomized | Not reported in publication.<br>Author confirmed to reviewers: All CDC class I | -triclosan polyglactin 910 & triclosan poliglecaprone 25, n = 184<br>- polyglactin 910 & poliglecaprone 25 n = 190<br>Used in:<br>- subcutaneous closure with polyglactin 910<br>-intracutaneous closure with poliglecaprone 25<br>SSI 1mary endpoint. CDC criteria. Bacterial culture proof in some patients. | SSI reported PP:<br>TS :23/184 NTS: 38/190<br>Reported p = 0.0497<br>SSI Meta-analysis PP |
| Justinger 2013, Germany[39] | Single-center, prospective, randomized, controlled, double-blinded, comparative trial<br>2-week follow-up duration<br>Only the primary incision was evaluated. | Laparotomy (various abdominal operations)<br>Patients: 856 adults randomized | Reported in publication | -triclosan polydioxanone, n = 485<br>-polydioxanone, n = 371<br>Used in:<br>-abdominal fascia closure.<br>CDC diagnostic criteria. | SSI reported ITT:<br>TS: 31/485 NTS: 42/371<br>reported p < 0.05<br>SSI Meta-analysis ITT |

RCT = randomized controlled trial; TS = triclosan-coated sutures; NTS = non-triclosan-coated sutures; n = number of patients, SSI = surgical site infections; ITT = intention to treat; PP = per protocol.

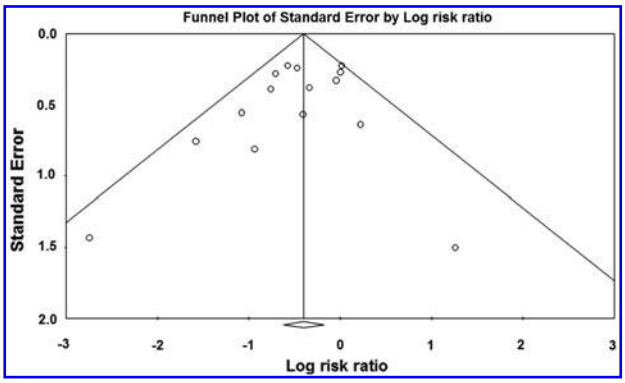


**FIG. 3.** Funnel plot of the risk ratios of eligible RCTs.

number of RRs in all but the first subgroup, the mixed-effects analysis (Q = 4.661, df = 4, p = 0.324) was underpowered to test the heterogeneity of the subgroups and to rule out potential bias or heterogeneity in the overall pooled RR because of comparisons of different suture materials. The 11 RCTs of the two first subgroups studying polyglactin, with versus without triclosan, had no indicator of publication bias (Egger test: p = 0.66), yielded a pooled RR = 0.68, 95% CI [0.52, 0.88], p = 0.003 and sensitivity analysis showed robustness to the iterative removal of any single RCT. Those results were vulnerable to the joint removal of the Thimour-Bergström and Galal trials (p = 0.066).[16,38]

Pooled RR by incision contamination (**Step 9**) showed five subgroups (Fig. 6). Given only clean and clean-contaminated incisions had at least five RRs to pool, the mixed-effects analysis (Q = 6.560, df = 4, p = 0.161) was underpowered to test the heterogeneity of the five subgroups and to rule out potential bias or heterogeneity in the overall pooled RR because of pooling studies with different incision contamination. However, the 95% CI of the pooled RR in clean, clean-contaminated, and contaminated incisions (borderline number of observations with four RRs to pool) were all significant with p-values ranging from 0.001 in clean incisions, 0.010 in clean-contaminated incision and 0.026 in contaminated incisions. The clean incision subgroup presented no indicator of publication bias (Egger test: p = 0.158) and sensitivity analysis showed conclusions to be robust to the removal of any single RCT, and borderline vulnerable to the joint removal of the Thimour-Bergström and Justinger trials (p = 0.046).[38,39] The clean-contaminated and contaminated subgroups were not robust to the iterative removal of one RCT at a time.

Pooled RR by incision depth and organ/space infection (**Step 10**) could not be conducted because of the inability to extract the data. Pooled RR by operation type (**Step 11**) was performed using all published data and resulted in 13 subgroups but only 12 could be analyzed because no SSI was reported in either arm in the abdominal vascular surgery subgroup (Fig. 7). Appendectomy was grouped together with colorectal surgery and the resulting subgroup was the only one pooling at least five RRs, with a pooled RR of 0.698, 95% CI [0.476, 1.002], p = 0.0536. Because of the low number of RRs in all but that subgroup, the mixed-effects analysis (Q = 10.233, df = 11, p = 0.510) was underpowered to test the heterogeneity of the subgroups and to rule out potential bias or heterogeneity in the overall pooled RR because of pooling studies with different operation types.

The heterogeneity of average incidence rate (IR) of SSI in treatment arms described in step three was visible on the Forrest plot (Fig. 8). The meta-regression was conducted using the mixed effects method of moments on the 15 RCTs with the IR as independent parameter and Log(RR) as dependent parameter. The regression slope was 3.35, 95% CI

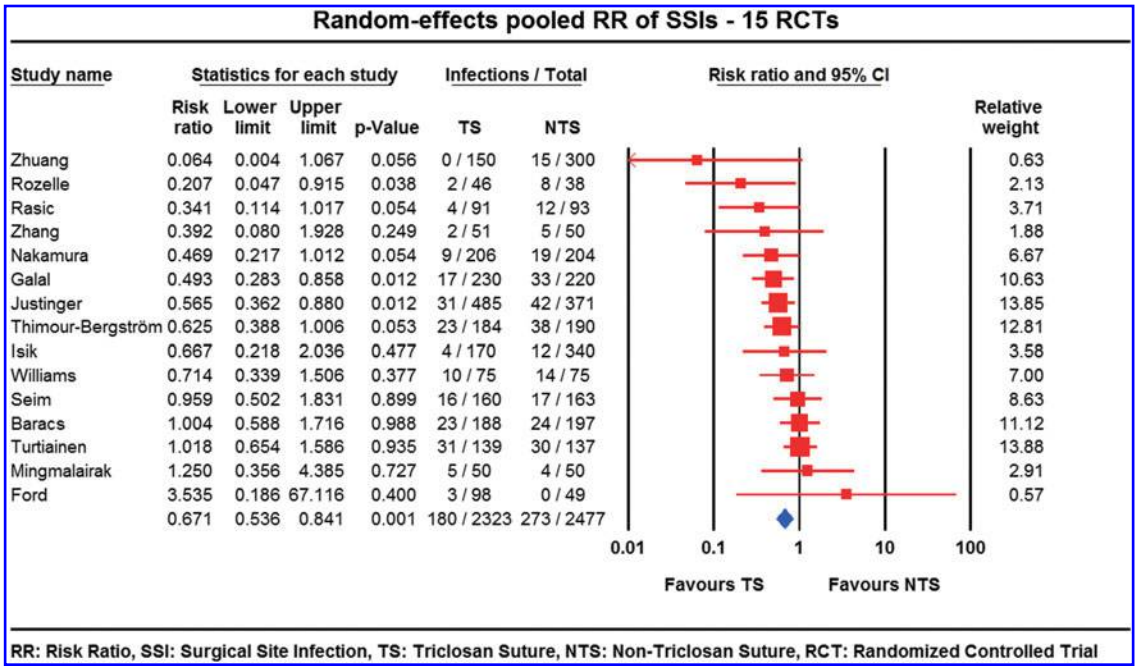


**FIG. 4.** Forrest plot of the risk ratios – Overall.

Table 2. Sensitivity Analysis: Meta-Analysis of All Eligible RCTs

| *Number of RCTs removed* | *RCT removed* | *RR* | *95% CI LL* | *95% CI UL* | *p-value* | *Publication bias Egger p-value* | *N SSI/N TS* | *N SSI/N NTS* | *IR N SSI/N total & % SSI* |
|---|---|---|---|---|---|---|---|---|---|
| 0 | None | 0.671 | 0.536 | 0.841 | 0.001 | 0.269 | 180/2323 | 273/2477 | 450/4653, 9.5% [7.2%, 12.5%] |
| 1 | Zhuang | 0.685 | 0.555 | 0.846 | 0.000 | 0.578 | 180/2173 | 258/2177 | 437/4290, 9.8% [7.5%, 12.6%] |
| 1 | Rozelle | 0.691 | 0.558 | 0.857 | 0.001 | 0.476 | 178/2277 | 265/2439 | 438/4350, 9.7% [7.4%, 12.6%] |
| 1 | Rasic | 0.690 | 0.551 | 0.865 | 0.001 | 0.388 | 176/2232 | 261/2384 | 425/4390, 9.2% [6.8%, 12.3%] |
| 1 | Zhang | 0.677 | 0.537 | 0.854 | 0.001 | 0.353 | 178/2272 | 268/2427 | 446/4699, 9.1% [6.8%, 12.2%] |
| 1 | Nakamura | 0.688 | 0.543 | 0.871 | 0.002 | 0.317 | 171/2117 | 254/2273 | 380/3944, 9.0% [6.6%, 12.2%] |
| 1 | Galal | 0.696 | 0.549 | 0.884 | 0.003 | 0.232 | 163/2093 | 240/2257 | 437/4616, 9.0% [6.7%, 12.1%] |
| 1 | Justinger | 0.686 | 0.534 | 0.883 | 0.003 | 0.155 | 149/1838 | 231/2106 | 444/4700, 9.0% [6.7%, 12.0%] |
| 1 | Thimour-Bergström | 0.673 | 0.521 | 0.870 | 0.002 | 0.248 | 157/2139 | 235/2287 | 420/4477, 8.9% [6.5%, 12.0%] |
| 1 | Isik | 0.669 | 0.526 | 0.849 | 0.001 | 0.278 | 176/2153 | 261/2137 | 403/4350, 8.8% [6.4%, 11.9%] |
| 1 | Williams | 0.665 | 0.520 | 0.849 | 0.001 | 0.283 | 170/2248 | 259/2402 | 443/4716, 8.8% [6.6%, 11.8%] |
| 1 | Seim | 0.648 | 0.511 | 0.823 | 0.000 | 0.265 | 164/2163 | 256/2314 | 406/4415, 8.7% [6.4%, 11.8%] |
| 1 | Baracs | 0.640 | 0.507 | 0.808 | 0.000 | 0.315 | 157/2135 | 249/2280 | 429/4650, 8.6% [6.4%, 11.5%] |
| 1 | Turtiainen | 0.631 | 0.505 | 0.788 | 0.000 | 0.447 | 149/2184 | 243/2340 | 392/4426, 8.6% [6.3%, 11.5%] |
| 1 | Mingmalairak | 0.658 | 0.523 | 0.829 | 0.000 | 0.163 | 175/2273 | 269/2427 | 392/4524, 8.4% [6.5%, 10.9%] |
| 1 | Ford | 0.666 | 0.532 | 0.833 | 0.000 | 0.079 | 177/2225 | 273/2428 | 450/4653, 9.5% [7.2%, 12.5%] |
| 2-RCTs removal: C(15, 2) = 105 possible cominbations tested. Combinations with the largest effect displayed. | | | | | | | | | |
| 2 | Justinger & Thimour-Bergström | 0.689 | 0.516 | 0.920 | 0.012 | 0.138 | 126/1654 | 193/1916 | 319/3570, 8.5% [6.0%, 11.8%] |
| 2 | Justinger & Galal | 0.721 | 0.553 | 0.940 | 0.016 | 0.124 | 132/1608 | 198/1886 | 330/3494, 8.8% [6.2%, 12.4%] |
| 2 | Thimour-Bergström & Galal | 0.702 | 0.534 | 0.923 | 0.011 | 0.197 | 140/1909 | 202/2067 | 342/3976, 8.3% [5.9%, 11.5%] |
| 3-RCTs removal: C(15, 3) = 455 possible cominbations tested. Combination with the largest effect displayed. | | | | | | | | | |
| 3 | Thimour-Bergström & Justinger & Galal | 0.730 | 0.538 | 0.992 | 0.045 | 0.069 | 109/1424 | 160/1696 | 269/3120, 8.2% [5.6%, 12.0%] |

RR = risk ratio; CI = confidence interval; LL = lower limit; UL = upper limit; dF = degrees of freedom; TS = triclosan sutures; NTS = non-triclosan sutures; N = number of patients; SSI = surgical site infections; IR = incidence rate.

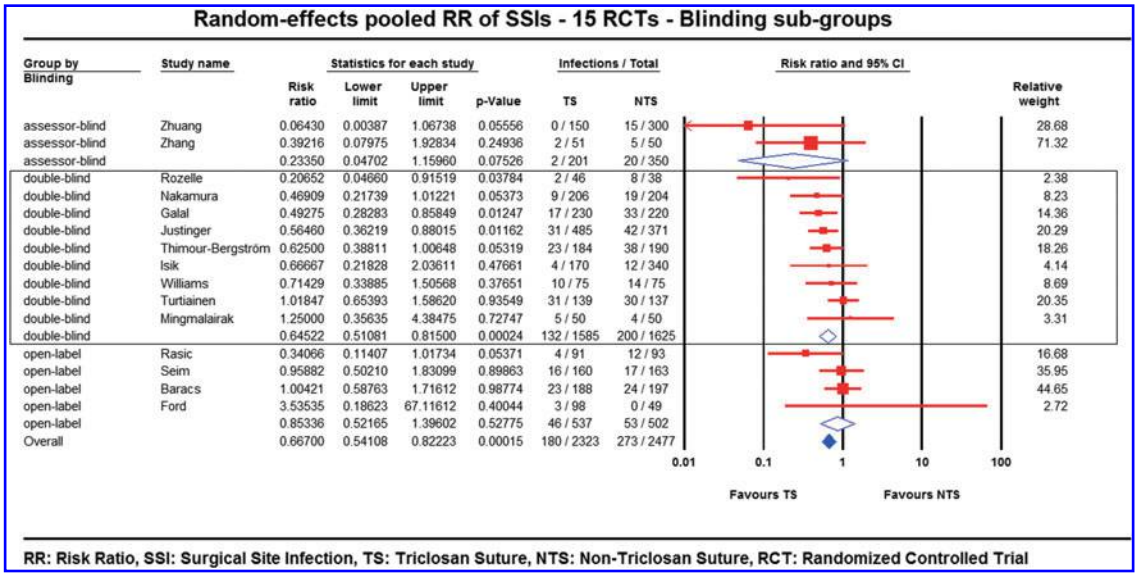


**FIG. 5.** Forrest plot of risk ratios – Blinding subgroup.

[−0.60, 7.31], p = 0.096, thus non-significant (Fig. 9). The null hypothesis that the RR is independent of IR was therefore not rejected (**Step 12**). IR was ruled out as a potential confounding factor for RR in the studied ranges. One RCT presented a 22.1% IR (61 SSI in 276 patients), which was an outlier according to Tukey's rule.[20,44] That outlier IR had a negligible effect on the meta-regression of the 15 RCTs, but led to a borderline significance in the meta-regression of the nine double-blind RCTs (slope 3.74, 95% CI [0.068, 7.41], p < 0.046). Sensitivity analysis with the removal of the outlier IR resulted in a meta-regression of the eight other double-blind RCTs (271 SSI in 2836 patients) with a non-significant slope (slope 3.05, 95% CI [-4.83, 7.11], p = 0.710).

Given the above results, it was concluded that results were significant with robust conclusions, and that triclosan was the only known cause of difference in SSI frequency between treatment arms (**Step 13**). Certain risk factors could not be ruled out as potential factors of heterogeneity and bias, so effect size should continue to be regarded as potentially heterogeneous across study populations.

## Discussion

### *Internal validity*

The two newly included trials increased the number of double-blind RCTs to nine studies compared with seven in the previous meta-analysis.[11] The double-blind RCTs, being designed to ensure equipoise of the patient sample and comparability of study arms from baseline through follow-up completion (given TS and NTS made of the same material), could not be distinguished. All double-blinded RCTs used CDC criteria of SSI except the Rozelle trial which used microbiological culture proof of shunt infection.[12] The core of double-blind studies yielded a highly robust predominant effect, with a small proportion of heterogeneity ($I^2$ close to 0), no indicator of publication bias and robustness of results to the removal of up to three RCTs.

Certain potential heterogeneity factors that could have affected the pooled RR were not ruled out owing to an insufficient number of estimates per subgroup. Such was the case with suture material and operation type. However, the proportion of heterogeneity among the nine double-blind RCTs was close to zero (percentage calculated using the $I^2$ statistic). The incidence rate of SSI, which is the expression of the differences in risk through the trials' clinical settings, was ruled out as factor of bias in the double-blind RCTs below outlier IR of 22% and in the 15 RCTs including the outlier.[20] Finally, the pooled RR was significant throughout three incision classes, clean, clean-contaminated, and contaminated classes, both among the double-blind RCTs and all 15 RCTs, which included approximately 80% of enrolled patients. This distribution of a predominant effect throughout the incision contamination class case-mix indicated that the overall predominant effect was not biased by that case-mix. Therefore, the core of double-blind RCTs enabled this updated SLR to meet the many rigorous criteria of internal validity that were not met by previous SLRs on this topic. In addition, no indicator suggested that the conclusions of double-blind RCTs should not apply to the entire set of 15 RCTs.[11,45,46]

The results of this analysis highly suggest that the presence of triclosan coated sutures within the surgical incision bed appears to be the predominant factor associated with a reduction in the incidence of SSIs reported in the 15 RCTs included in this meta-analysis. Given the insufficient number of trials which included the size of effect according to operation type, definition of SSI incisional and organ/space sites, it would be prudent to continue to report the predominant effect size obtained with a random-effects model, to account for potentially underestimated heterogeneity across study populations.

The two trials where RR was calculated with the number of SSIs reported per protocol and the number of randomized patients for whom demographics were also reported, according to ITT method avoided decreasing the sample size by 11.9% (12 in 101 patients) yielding an RR of 0.39 ITT instead of 0.37 PP in the Zhang trial, and avoided decreasing the sample size by 15.3% (23 in 150 patients) yielding an RR of

Table 3. Sensitivity Analysis: Meta-Analysis of the Double-Blind RCTs

| *Number of RCTs removed* | *RCT removed* | *RR* | *95% CI LL* | *95% CI UL* | *p-value* | *Publication bias Egger p-value* | *N SSI/N TS* | *N SSI/N NTS* | *IR N SSI/N total & % SSI* |
|---|---|---|---|---|---|---|---|---|---|
| | None | 0.645 | 0.511 | 0.815 | 0.00024 | 0.521 | 132 / 1585 | 200 / 1625 | 332/3210, 10.6% [7.4%, 15.0%] |
| 1 | Galal | 0.675 | 0.523 | 0.870 | 0.002 | 0.504 | 115 / 1355 | 167 / 1405 | 282/2760, 10.5% [6.8%, 15.7%] |
| 1 | Isik | 0.641 | 0.495 | 0.829 | 0.001 | 0.498 | 128 / 1415 | 188 / 1285 | 316/2700, 12.2% [8.9%, 16.4%] |
| 1 | Justinger | 0.662 | 0.500 | 0.876 | 0.004 | 0.403 | 101 / 1100 | 158 / 1254 | 259/2354, 10.9% [7.2%, 16.1%] |
| 1 | Mingmalairak | 0.631 | 0.498 | 0.800 | 0.00015 | 0.204 | 127 / 1535 | 196 / 1575 | 323/3110, 10.7% [7.3%, 15.5%] |
| 1 | Nakamura | 0.663 | 0.516 | 0.853 | 0.001 | 0.644 | 123 / 1379 | 181 / 1421 | 304/2800, 11.2% [7.6%, 16.1%] |
| 1 | Rozelle | 0.666 | 0.539 | 0.822 | 0.00016 | 0.926 | 130 / 1539 | 192 / 1587 | 322/3126, 10.4% [7.1%, 15.2%] |
| 1 | Thimour-Bergström | 0.644 | 0.484 | 0.857 | 0.003 | 0.523 | 109 / 1401 | 162 / 1435 | 271/2836, 9.9% [6.6%, 14.7%] |
| 1 | Turtiainen | 0.574 | 0.454 | 0.726 | 0.000004 | 0.941 | 101 / 1446 | 170 / 1488 | 271/2934, 9.5% [6.8%, 13.2%] |
| 1 | Williams | 0.635 | 0.487 | 0.828 | 0.001 | 0.515 | 122 / 1510 | 186 / 1550 | 308/3060, 10.0% [6.7%, 14.7%] |
| 2-RCTs removal C(9, 2) = 36 possible combinations tested. Combinations with the largest effect displayed. | | | | | | | | | |
| 2 | Justinger & Galal | 0.707 | 0.521 | 0.960 | 0.026 | 0.331 | 84 / 870 | 125 / 1034 | 209/1904, 10.8% [6.5%, 17.3%] |
| 2 | Thimour-Bergström & Justinger | 0.661 | 0.464 | 0.943 | 0.022 | 0.362 | 78 / 916 | 120 / 1064 | 198/1980, 10.1% [6.2%, 16.2%] |
| 2 | Thimour-Bergström & Galal | 0.680 | 0.493 | 0.938 | 0.019 | 0.482 | 92 / 1171 | 129 / 1215 | 221/2386, 9.7% [5.9%, 15.6%] |
| 3-RCTs removal: C(9, 3) = 84 possible combinations tested. Combination with the largest effect displayed. | | | | | | | | | |
| 3 | Thimour-Bergström & Justinger & Galal | 0.721 | 0.484 | 1.073 | 0.107 | 0.214 | 109/1424 | 160/1696 | 148/1530, 9.9% [5.2%, 18.0%] |

RR = risk ratio; CI = confidence interval; LL = lower limit; UL = upper limit; dF = degrees of freedom; TS = triclosan sutures; NTS = non-triclosan sutures; N = number of patients; SSI = surgical site infections; IR = incidence rate.

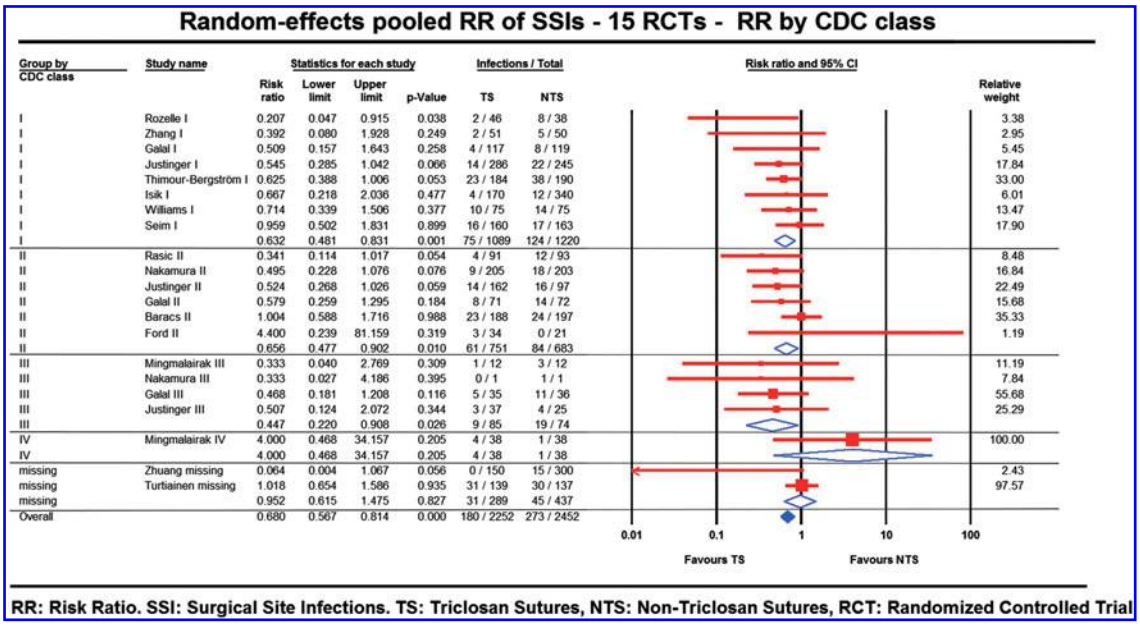


**FIG. 6.** Forrest plot of risk ratios – CDC incision class subgroup

0.71 ITT instead of 0.66 PP in the Williams trial.[15,18] This approach thus maintained sample size without overestimating treatment effect.

### *External validity*

The applicability of these pooled results to future patient care depends on the similarity of the case-mix of future surgical patient populations based upon the case-mix reported in the 15 RCTs, where case-mix is defined in terms of incision contamination class. External validity should be quantifiable when examining patients with incisions classified as clean, clean-contaminated, and contaminated, with high confidence that the risk reduction of SSIs found in clean incisions should apply, given the robustness of that subgroup but with a lower confidence for clean-contaminated and contaminated incisions. External validity could not be established for the effect of triclosan coated sutures to close dirty incisions or for operations where incision contamination was not described.

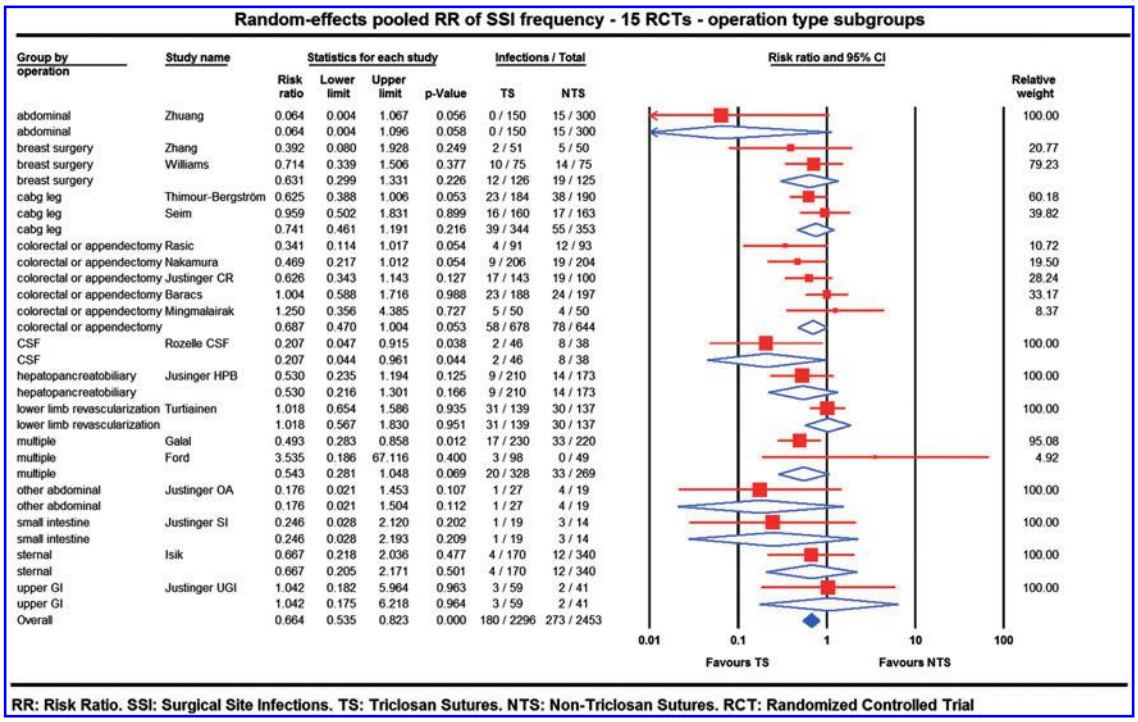


**FIG. 7.** Forrest plot of risk ratios – Operation type subgroup.

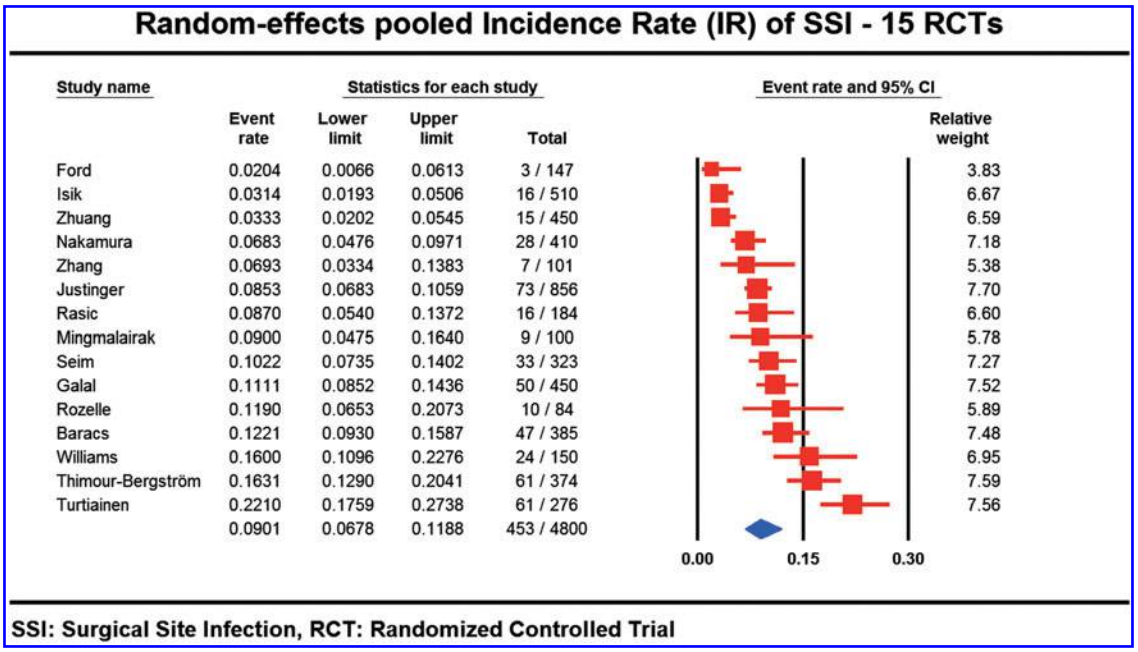


**FIG. 8.** Forrest plot of the incidence rates of SSI – Overall.

## Conclusion

This systematic literature review (SLR) and meta-analysis identified 15 randomized controlled trials and produced a risk ratio of 0.67, 95% CI: [0.54, 0.84], p = < 0.00053, demonstrating a highly statistically significant, lower risk of SSI following operative procedures in incisions which were closed with triclosan coated sutures compared to non-antimicrobial closure technology. This result was robust to the removal of up to three trials. Similar results, yielded by the core of nine double-blind randomized controlled trials, supported the hypothesis that triclosan coated sutures were responsible for the reported reduction in SSI.

Trials comparing triclosan polyglactin to polyglactin demonstrated a robust risk ratio in favor of triclosan. Subgroup analysis was underpowered to determine heterogeneity between studies comparing different suture materials.

Diagnostic method was ruled out as a cause of bias and the incidence of SSIs, which ranged between 2% and 22%, had no significant effect on risk reduction effect of the triclosan coated sutures and was therefore ruled out as a cause of bias. Based upon this analysis there was a high concentration of confidence that a 20% to 50% reduction in SSIs should be expected in surgical procedures involving clean surgical incisions. A smaller and statistically significant reduction could be expected in clean-contaminated and contaminated incisions but these results were not robust when considered separately from the clean incisions. No conclusions could be drawn based upon this analysis on the impact of triclosan sutures as a risk reduction strategy for SSIs involving dirty incisions or surgical procedures where the composite incidence rate of infections exceeded 17%. The two additional peer-reviewed double-blind RCTs reinforced the evidence concentration of this SLR as CEBM evidence concentration Ia.

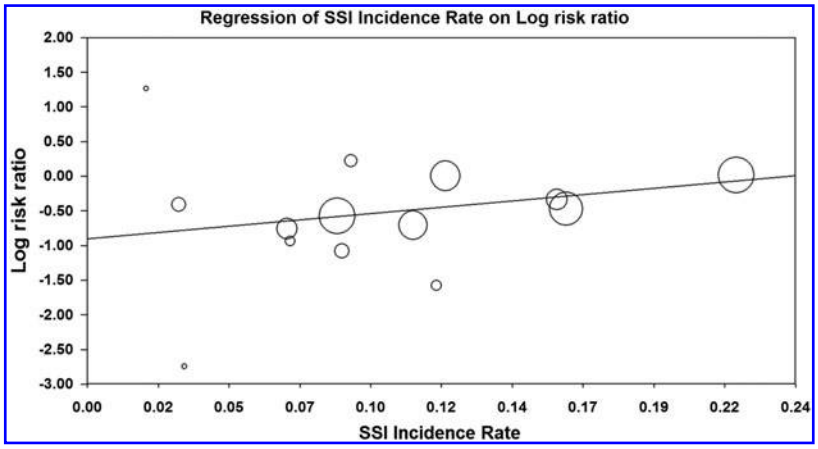


**FIG. 9.** Meta-regression of (Log) risk ratio depending on incidence rate.

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### Author Disclosure Statement

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