

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	The use of triclosan coated sutures to prevent surgical site infections: a systematic review and meta-analysis of the literature
AUTHORS	Ahmed, Imran; Boulton, Adam; Rizvi, Sana; Carlos, William; Dickenson, Edward; Smith, NA; Reed, Mike

VERSION 1 – REVIEW

REVIEWER	Rick Nelson Epidemiology/Biometry Division University of Illinois School of Public Health Chicago USA
REVIEW RETURNED	09-Mar-2019

GENERAL COMMENTS	<p>The number of hits in the search is surprisingly small, though the included studies appear to be appropriate</p> <p>The risk of bias figure is a bit too green. If an author does not state specifically that he did something such as allocation concealment or blinding, then you must assume it was not done and give a red ball, such as in Baracs and Rasic. The "other" column in RoB can be deleted in Revman, but if included must specify what other parameter was assessed.</p> <p>Data were....</p> <p>Random effects. I would be a bit more specific. The clinical heterogeneity is primarily in the type of infection expected in each type of surgery. This would disappear in your subgroups and so a fixed effects model would be better there.</p> <p>SSI has three domains: superficial, deep and organ space. I presume no organ space infections were sought i this study.</p> <p>There is a study mentioned in the discussion, praised, of knee surgery but no citation, so it is not known which it was.</p> <p>Most important is that the overall quality of the evidence has not been evaluated. A GRADE description and evaluation is needed.</p>
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REVIEWER	Dr Laura Bonnett University of Liverpool, United Kingdom
REVIEW RETURNED	11-Mar-2019

GENERAL COMMENTS	<p>This systematic review and meta-analysis uses appropriate statistical methodology to combine existing evidence regarding the use of triclosan-coated sutures to prevent surgical site infections.</p> <p>My feedback is as follows:</p> <p>MAJOR</p>
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1. Having read the entire article it is clear that there are existing systematic reviews in this clinical area but that they include low-quality evidence and are outdated. However, this message is not explicitly described in the introduction and abstract.
2. It was also unclear (until the discussion) whether this was an update of the existing review or a completely new review. It appears to be the latter but this must be more explicit.
3. Additionally, it should be justified as to why it is not appropriate to update the existing review - I presume it is the inclusion of non-RCTs?
4. It is not appropriate to state "trends" for non-statistically significant results. These are just non-statistically significant results.
5. Additional summary information is required about each study i.e. age and gender as a minimum.

MINOR

1. There are occasional instances of missing words and grammatical errors - please check the article carefully before any future submission.
2. Explain each abbreviation in full the first time it is used (e.g. AMED, RCTs, PDS, CDC etc.)
3. Abstract - a discussion of how this review could inform guidelines would be informative.
4. The search was run nearly 1 year ago. It would be useful to run the searches again to see if further evidence is now available.
5. Data extraction - how were discrepancies resolved?
6. Statistical analysis - "predominant" is more accurately described as "pooled".
7. Statistical analysis - What is the criteria for heterogeneity? I.e. what percentage I-squared is considered "heterogeneous" and what reference supports that decision?
8. Patient and Public Involvement - (briefly) justify why patient and public members were not involved in the review.
9. Results - the authors state that "no other sources of records were identified". Given that the grey literature has not been searched where would these additional records have come from? The reference lists of included studies? If so, describe this in the methods. If not, delete this line.
10. Study characteristics - how many studies reported mean age? This should be included.
11. Study characteristics - when describing the duration of studies 12 studies was 30 days, 2 were 2 weeks, 1 was 6 weeks, 1 was 80 days, 1 was 1 year, 1 was until discharge and 1 did not report anything. However, 12+2+1+1+1+1+1=19 rather than 21 so add in details of the 2 missing studies.
12. Sub-group analysis - Add numerical results for each analysis (i.e. #### in the triclosan group and #### in the standard group for each analysis as per the first paragraph.)
13. Risk of bias - I think the reference should be to figure 2 rather than figure 1. A (brief) text description of the risk of bias results would be helpful.
14. Risk of bias - tau should be written as a mathematical symbol, and again indicate how you have decided that 22% is low heterogeneity (who's criteria and which reference?).
15. Conclusion - the authors suggest further work should consider the results on a speciality basis. Is there sufficient data to consider that in this review?
16. References - 38 & 39 have an unusual series of letters. Is this an acronym that has been scrambled by EndNote or similar?

	<p>17. References - 58 & 59 are missing the journal or similar.</p> <p>18. Figure 1: 242 records screened - 209 records excluded = 33 rather than 26 as mentioned in the following box.</p> <p>19. Figure 5 - add funnel-shaped lines to help the reader interpret the plot.</p> <p>20. PRISMA checklist - double check this table as the page numbers do not match up with the actual page numbers for some topics.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Rick Nelson

Institution and Country: Epidemiology/Biometry Division, University of Illinois School of Public Health, Chicago, USA

Please state any competing interests or state 'None declared': none

Please leave your comments for the authors below

The number of hits in the search is surprisingly small, though the included studies appear to be appropriate

Thank you for this comment. Having assessed the search strategy for previous reviews, our search strategy is more precise with more search terms. We believe this plays a role in the reduced number of hits. We agree the final number of full texts is appropriate.

The risk of bias figure is a bit too green. If an author does not state specifically that he did something such as allocation concealment or blinding, then you must assume it was not done and give a red ball, such as in Baracs and Rasic. The "other" column in RoB can be deleted in Revman, but if included must specify what other parameter was assessed.

Other sources of bias included sources of funding. Some studies were funded by Ethicon or Johnson and Johnson. Another source of bias was whether different antibiotics regimens were used between the treatment groups. Both the risk of bias and the text has been updated in response to your comment.

Data were....

Random effects. I would be a bit more specific. The clinical heterogeneity is primarily in the type of infection expected in each type of surgery. This would disappear in your subgroups and so a fixed effects model would be better there.

Thank you for this feedback. Our analysis has been changed to fixed effects model.

SSI has three domains: superficial, deep and organ space. I presume no organ space infections were sought in this study.

This is correct, for this review we only reported superficial and deep infections.

There is a study mentioned in the discussion, praised, of knee surgery but no citation, so it is not known which it was.

Thank you, this has been added.

Most important is that the overall quality of the evidence has not been evaluated. A GRADE description and evaluation is needed.

A GRADE description and evaluation has been added to the discussion.

Reviewer: 2

Reviewer Name: Dr Laura Bonnett

Institution and Country: University of Liverpool, United Kingdom

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

This systematic review and meta-analysis uses appropriate statistical methodology to combine existing evidence regarding the use of triclosan-coated sutures to prevent surgical site infections.

My feedback is as follows:

MAJOR

1. Having read the entire article it is clear that there are existing systematic reviews in this clinical area but that they include low-quality evidence and are outdated. However, this message is not explicitly described in the introduction and abstract.

This message has now been described in the introduction.

2. It was also unclear (until the discussion) whether this was an update of the existing review or a completely new review. It appears to be the latter but this must be more explicit.

Thank you, we have included a statement in the introduction and aim specifying that this is a new review.

3. Additionally, it should be justified as to why it is not appropriate to update the existing review - I presume it is the inclusion of non-RCTs?

This is a new review based on different search strategy and searching different databases. We have also included a different analysis plan by performing sub group analysis of superficial vs deep infections and different types of surgery. This has been stated in the methods and also in the discussion, highlighting how our study is different.

4. It is not appropriate to state "trends" for non-statistically significant results. These are just non-statistically significant results.

Thank you this has been corrected.

5. Additional summary information is required about each study i.e. age and gender as a minimum.

This has been updated in the text under study characteristics in the results section.

MINOR

1. There are occasional instances of missing words and grammatical errors - please check the article carefully before any future submission.

This has been done

2. Explain each abbreviation in full the first time it is used (e.g. AMED, RCTs, PDS, CDC etc.)

This has been done

3. Abstract - a discussion of how this review could inform guidelines would be informative.

We have adjusted the conclusion to provide a more informative statement.

4. The search was run nearly 1 year ago. It would be useful to run the searches again to see if further evidence is now available.

Thank you for this feedback, we have run the search again and updated the data included in this review. There were 4 further RCTs which we have incorporated in the meta-analysis.

5. Data extraction - how were discrepancies resolved?

Any discrepancies were then resolved following discussion between the two authors and a third author (ED).

6. Statistical analysis - "predominant" is more accurately described as "pooled".

This has been changed. Thank you.

7. Statistical analysis - What is the criteria for heterogeneity? I.e. what percentage I-squared is considered "heterogeneous" and what reference supports that decision?

This has been stated with a reference to the Cochrane handbook.

8. Patient and Public Involvement - (briefly) justify why patient and public members were not involved in the review.

PPI members were not involved in the conduct of this review due to the design of the study and the retrospective nature. We will endeavour to disseminate these results through lay summaries on social media.

9. Results - the authors state that "no other sources of records were identified". Given that the grey literature has not been searched where would these additional records have come from? The reference lists of included studies? If so, describe this in the methods. If not, delete this line.

This has been deleted.

10. Study characteristics - how many studies reported mean age? This should be included.

23/25 this has been included.

11. Study characteristics - when describing the duration of studies 12 studies was 30 days, 2 were 2 weeks, 1 was 6 weeks, 1 was 80 days, 1 was 1 year, 1 was until discharge and 1 did not report anything. However, $12+2+1+1+1+1+1=19$ rather than 21 so add in details of the 2 missing studies.

This has been corrected

12. Sub-group analysis - Add numerical results for each analysis (i.e. #### in the triclosan group and #### in the standard group for each analysis as per the first paragraph.)

This has been corrected

13. Risk of bias - I think the reference should be to figure 2 rather than figure 1. A (brief) text description of the risk of bias results would be helpful.

Thank you this has been corrected

14. Risk of bias - tau should be written as a mathematical symbol, and again indicate how you have decided that 22% is low heterogeneity (who's criteria and which reference?).

This has been updated.

15. Conclusion - the authors suggest further work should consider the results on a speciality basis. Is there sufficient data to consider that in this review?

The conclusion has been updated.

16. References - 38 & 39 have an unusual series of letters. Is this an acronym that has been scrambled by EndNote or similar?

This has been updated

17. References - 58 & 59 are missing the journal or similar.

This has been updated

18. Figure 1: 242 records screened - 209 records excluded = 33 rather than 26 as mentioned in the following box.

This has been updated with new search results

19. Figure 5 - add funnel-shaped lines to help the reader interpret the plot.

This has been updated

20. PRISMA checklist - double check this table as the page numbers do not match up with the actual page numbers for some topics.

This has been updated

VERSION 2 – REVIEW

REVIEWER	Rick Nelson University of Illinois School of Public Health, USA
REVIEW RETURNED	21-Jun-2019

GENERAL COMMENTS	<p>Thank you for the additional work. The biggest problem with SRs today is that there are way too many of them. Before this manuscript, 17 by my count, and that is excluding the copious dental literature. Which one should we read? Not all of them, since 2012, are discussed in the manuscript. Is there a way to present them with a bit more insight to demonstrate why this is more inclusive, more objectively analyzed? Study quality is still not well dealt with in most reviews, and strength of evidence almost never properly presented. GRADE? I don't see it. The funnel plot is also rather odd looking. There were certainly some fairly small studies. How did it get so bunched up at the top?</p> <p>I think a table of existing SRs with the key inclusion of RoB and GRADE would be very helpful to your reader. Also a bit more discussion of where Triclosan may do the most good (clean?) and the least (clean contaminated or dirty?)</p>
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REVIEWER	Dr Laura Bonnett University of Liverpool, UK
REVIEW RETURNED	24-Jun-2019

GENERAL COMMENTS	<p>Thank you for taking the time to update your article, particularly in light of my previous comments. I appreciate the extra effort required to re-run the searches and update the analyses. This article is now much improved in my opinion. In particular, the introduction is much easier to read and the need for your review is much better justified.</p> <p>There are still a few minor typos or grammatical errors but these are easily corrected. Importantly, some text has not been updated following the updated searches. Please ensure that the correct dates are inserted within the search methods section (the date that each database was searched up until), and ensure that the number of RCTs and patients described in the discussion/conclusion matches those in the results section.</p> <p>Thanks again for modifying your article in light of my comments.</p>
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VERSION 2 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name: Rick Nelson

Institution and Country: University of Illinois School of Public Health, USA

Please state any competing interests or state 'None declared': No competing interests

Please leave your comments for the authors below

Thank you for the additional work. The biggest problem with SRs today is that there are way too many of them. Before this manuscript, 17 by my count, and that is excluding the copious dental literature. Which one should we read? Not all of them, since 2012, are discussed in the manuscript. Is there a way to present them with a bit more insight to demonstrate why this is more inclusive, more objectively analysed? Study quality is still not well dealt with in most reviews, and strength of evidence almost never properly presented. GRADE? I don't see it. The funnel plot is also rather odd looking. There were certainly some fairly small studies. How did it get so bunched up at the top?

I think a table of existing SRs with the key inclusion of RoB and GRADE would be very helpful to your reader. Also a bit more discussion of where Triclosan may do the most good (clean?) and the least (clean contaminated or dirty?)

Thank you for reviewing the manuscript again. We have included a detailed GRADE assessment included reasons for downgrading in the discussion section. The evidence was 'graded' as moderate, reasons for downgrading were due to study limitations, importantly the issue of performance bias and detection bias secondary to issues surrounding blinding.

One potential reasons for the funnel plot is due to sample size of the included studies. The majority of the studies have similar patient numbers e.g 400-700, However there is a minority of studies where the total sample size is less than 100. This could explain where there appears to be more studies bunched at the top. However, we believe that the funnel plot remains symmetrical minimising the risk of publication bias.

We have added further discussion on where triclosan coated sutures may be more effective e.g. clean and contaminated surgery. We have also included potential reasons why it may not be as effective in dirty surgery.

Thank you for your suggestion on including a table. We have provided a table summarising the findings of the previous reviews including whether ROB or GRADE was used. As you can see, our review includes the largest number of RCTs and the quality of evidence was assessed using GRADE criteria.

Reviewer: 2

Reviewer Name: Dr Laura Bonnett

Institution and Country: University of Liverpool, UK

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

Thank you for taking the time to update your article, particularly in light of my previous comments. I appreciate the extra effort required to re-run the searches and update the analyses. This article is now much improved in my opinion. In particular, the introduction is much easier to read and the need for your review is much better justified.

There are still a few minor typos or grammatical errors but these are easily corrected. Importantly, some text has not been updated following the updated searches. Please ensure that the correct dates are inserted within the search methods section (the date that each database was searched up until), and ensure that the number of RCTs and patients described in the discussion/conclusion

matches those in the results section.
 Thanks again for modifying your article in light of my comments.

These changes have been made. Thank you for your feedback and providing us with a chance of substantially strengthening the article.

VERSION 3 – REVIEW

REVIEWER	Rick Nelson School of Public Health, University of Illinois at Chicago USA
REVIEW RETURNED	04-Aug-2019

GENERAL COMMENTS	<p>Only two points. One, a query about the search compared with one of the systematic reviews cited in his manuscript, Wu, et al, a 2018 study with 13 included studies. Yet this group, Ahmed,et al, have 25 RCTs. How did their searches differ?</p> <p>Second relates to the Risk of Bias paragraph. You suggest in your RoB paragraph that there were two domains in which significant concern might exist: allocation and blinding, yet only on step down in GRADE? This is a fairly minor point since there is some subjectivity in these categorizations, but I would have done 2.</p> <p>I felt his conclusions were a bit off as a result, but in fact these are minor points.</p>
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VERSION 3 – AUTHOR RESPONSE

Only two points. One, a query about the search compared with one of the systematic reviews cited in his manuscript, Wu, et al, a 2018 study with 13 included studies. Yet this group, Ahmed,et al, have 25 RCTs. How did their searches differ?

Second relates to the Risk of Bias paragraph. You suggest in your RoB paragraph that there were two domains in which significant concern might exist: allocation and blinding, yet only on step down in GRADE? This is a fairly minor point since there is some subjectivity in these categorizations, but I would have done 2.

We thank for again taking the time to review our manuscript and provide further comments. In response to the first point – Having reviewed the Wu search strategy, the two key differences are that our search strategy included the term ‘triclosan’ and perhaps most importantly our search ran until 2019. The Wu et al search strategy ran until 02/2015. As can be seen in our review since 2015 there have been a further 10 studies. This provides an explanation as to why our review included 25 RCTs and Wu et al included 13. The 10 additional studies included in our review are as follows:

- Arslan et al 2018
- Ichida et al 2018

- Karip et al 2016
- Lin et al 2018
- Mattavelli et al 2015
- Renko et al 2017
- Roy et al 2019
- Ruiz-Tovar et al 2015
- Sprowson et al 2018
- Tabrizi et al 2018

With regards to your comments on risk of bias and the impact on GRADE, this did indeed lead to some debate amongst the authors independently assessing the manuscripts, demonstrating the subjective nature of GRADE as you suggest. In this instance we referred to the GRADE handbook and recommendations to guide us. The GRADE handbook states that “One should be conservative in the judgment of rating down. That is, one should be confident that there is substantial risk of bias across most of the body of available evidence before one rates down for risk of bias.” Although there was concern over risk of bias in allocation and blinding, we did not feel that on global assessment of the manuscripts that downgrade by two points would be appropriate, based on the above recommendations.

We hope you can understand our decision to downgrade by one. We endeavoured to perform these GRADE assessments in as robust a fashion as possible, but as you say it is inherently a subjective assessment. The studies which provided the greatest weight to the meta-analysis – Diener et al (16.5%), Ichida et al (6.1%), Renko et al (7.3%) and Thimour-bergstom et al (6.5%) all had low risk of bias with regards to allocation concealment and blinding. As a result, we felt that although the results of the review may have been affected by risk of bias we did not feel it warranted downgraded by two. We agree that this is a minor point and believe our conclusions remain valid and important.

Many thanks again for taking the time to review our manuscript. We are very grateful for your input and your suggestions have helped to improve the quality of this manuscript considerably.