

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (Error! Hyperlink reference not valid.) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Reporting of adverse events, conflict of interest, and funding in randomised controlled trials of antibiotics: a secondary analysis.
AUTHORS	Bakhit, Mina; Jones, Mark; Baker, Jenalle; Nair, Ramil; Yan, Kylie; Del Mar, Chris; Scott, Anna Mae

VERSION 1 – REVIEW

REVIEWER	Pericas, Juan University of Barcelona
REVIEW RETURNED	27-Dec-2020

GENERAL COMMENTS	<p>Through a before-after study investigating the reporting of adverse events, COIs and funding in RCTs of penicillins, macrolides and cephalosporins, Bakhit and colleagues found that there were no significant differences in reporting of adverse events and funding before and after the publication of the 2001 CONSORT statement, whereas COIs were provided more frequently.</p> <p>The topic is interesting and timely, the methods are appropriate and the article is well-written.</p> <p>However, there are several aspects regarding which I would like the authors to comment and consider either introducing changes or mentioning as potential limitations of their study.</p> <p>1- Although the rationale to set the 2001 Consort as the reference to conduct the before/after study is clear, there are some nuances to be made. As the authors acknowledge in the introduction, in the 2001 version, neither funding nor COIs were clearly listed as requirements to be disclosed in all trials. Why then not using the 2010 version or at least consider a time series analysis with both the 2001 and 2010 as time reference points?</p> <p>2- Authors used articles from published RCTs, whereas they do not consider the potential impact of the lack of publication and potentially related items (type of sponsor, negative results, etc). Did the authors consider using Clinicaltrials.gov or EUDRA-CT as primary sources?</p> <p>3- Authors might consider clarifying whether RCTs in which the three classes of antibiotics investigated were also analyzed in case of combination therapy, either among them (e.g. ceftriaxone plus azythromycin for STD or pneumonia) or with other (e.g. with quinolones).</p>
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	<p>4- Although the bulk of RCTs is almost equally divided between the two time periods (before and after 2011), there might be a historical bias to be acknowledged in the 33 years period (1969-2001) compared to the 17 years (2002-2018).</p> <p>5- There are other aspects that might have provided insightful information regarding the outcomes, e.g, therapeutical vs. preventive trials, geographical scope, academic vs. industry sponsor, etc.</p>
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REVIEWER	Krleža-Jerić, Karmela Ottawa Group-IMPACT
REVIEW RETURNED	15-Jan-2021

GENERAL COMMENTS	<p>Overall, this is an important issue to study, that you for doing it.. Here are my comments and suggestions.</p> <p>1. Terminology: you use alternatively antimicrobial resistance AMR, and antibiotic resistance: suggest that you stick to one and provide the full name and acronym the first time used. They are not totally synonyms as explained by the WHO: https://www.who.int/news-room/q-a-detail/antimicrobial-resistance. By the way I suggest you defined the chosen term and cite the WHO. If various RCTs report different one, explain, or perhaps analyse separately.</p> <p>2. List of studies: the alphabetical list of all studies is not very useful. I suggest that you list original studies alphabetically but by the antibiotics/ syst review included in your sample, even by two subgroups for each group: prior and after CONSORT 2001.</p> <p>3. Clear/unclear/ non provided: Please explain why you put unclear in non provided group. It seems to me that unclear and not provided is not the same. Unclear is when they provide but not clearly. Pls consider to provide the number of those that provide "unclear" statement?</p> <p>4. COI: I suggest that you add additional analysis of reported COI and funding by journals and their policies/ requirements. Let me explain: as journals have essential role regarding declaration of the COI and funding, and as you included a variety of journals, it seems essential to analyse the COI and funding reporting by journals and by their policy/ requirement to report it. One can expect that having or not having the policy regarding declaration of COI and funding would influence the studies to include such info in their manuscript. Namely some journals might not require it while some journals would not accept the manuscript unless such statements are provided. You may wish to do such analysis separately for two periods to be comparable with the analysis you already did. By the way you obviously expect journals to influence this- as in the Conclusion you indicate that much work needs to be done regarding reporting of by journal editors, among others.</p> <p>5. McCullough systematic review issue</p>
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	<p>5.a. Please edit the citation of McCullough systematic review. The full citation should include a subtitle: intervention – protocol. Namely the review was not published, just the protocol. Please edit the abstract and the main body of the manuscript to reflect this issue.</p> <p>5.b. Please clarify and explain the manuscript: You indicated in your methods section that you used the info on adverse events as published in those three systematic reviews included in your analysis. As McCullough et al syst review was not published, and the original protocol published in 2016 was withdrawn, as indicated on the Cochrane database, please explain how you got the info for your reanalysis: how you learned which RCTs were to be included in that study and how you then analysed. Apparently, you could not use the info on adverse events as planned from the syst review as it was not published, but had to figure out which RCTs were to be included in that planned systematic review and analyse individual RCTs yourself.</p> <p>6. Additional analysis suggested. Based on your analysis you concluded that the COI reporting increased after 2001 but that is still under reported – as it was reported by only 55% of trials. It would be particularly useful to see whether the lack of COI and funding info were more present in RCT published in certain journals. I suggest that you analyse the reporting of COI and funding by journal and in the context of a journal having the policy -ie requires the COI and funding info as a prerequisite for submission of the manuscript esp after 2001. Pls note that ICMJE has been requiring COI statement since 2001. Following are my specific comments. Please note that I used the page number at the bottom right corner of the page.</p> <p>Page 5 line 33: Pls edit: comment “c” under Table 1 is not clear, the part of sentence starting with “If we could...”</p> <p>Pg 5 line 41 and 42: I already addressed this up front: the mentioned syst review on cephalosporins by McCullough is not published. Please explain how you got the adverse events data for those RCTs.</p> <p>Pg 5 line 44: Pls consider adding know how many, in each of systematic review ie antibiotic (group) had unclear reporting of adverse events.</p> <p>Duplicates. Page 5 line 10/11 and : Page 6 Figure 1: If I read well, you had a total of 2 duplicates that you excluded: $45 + 206 + 183 = 434 - 2 = 432$ Although this is a small number- pls explain how come there were two duplicate RCT if each of included systematic reviews analysed RCTs studying specific ie different antibiotics/ groups of antibiotics .</p> <p>P7 line 21 Please comment, and if possible, explain how come that COI was only 7%, considering that 45% were funded by the industry.</p> <p>P7 && starting with line 20 and 27. I suggest you add the number of those trials that did or did not report the adverse events? So</p>
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	<p>these sentences might read: line 20:” Among 266 trials that did report... “; line 27: “Of the 166 trials that did not ...”</p> <p>P7, Line 30: please edit the sentence starting with “ Thirty four of trials...”. If I read well the Table 2, 17 (34%) and not 34 trials that did not report any adverse provided the info on funders role. Thus this sentence should read something like: “Seventeen (34%) of these trials provided....”,</p> <p>P7 describing of findings on table 2 and P8 Table 2: If possible provide the info how many of those that indicated that they were funded by industry provided the info on funders role.</p> <p>P8, table 2: I suggest expanding the title and add the N, to read: “Reporting of adverse events, COI and funding by the included RCTs (N=432)”.</p> <p>page 9, line 3. Title of the Table 3. Suggest editing the title similarly to suggested edits of Table 2 title. It might read: “Reporting adverse events, COI and funding before and after Consort 2001 by included studies (N=237 and 195 respectively)”, or simply add the total N (N=432) to the expanded title.</p> <p>page 9 Table 3. Pls edit. The column Difference is not expressing difference but the significance of eventual difference. You might wish to indicate the trend/tendency: decrease-increase.</p> <p>P9 line 49 pl clarify /edit. I reckon that you wanted to say that your findings were consistent regarding COI, not all three. If so, please edit the sentence.</p> <p>P9. & line 54-59 in the & starting with “Our findings...”. add missing references for two mentioned studies- (on palliative and critical case): “Fewer than half of 848 studies in supportive and palliative oncology provided COI information, although there was an increase in reporting, from 39% of studies in 2004 to 55% in 2009..... However, funding information was provided in only 41% of the studies. An analysis of 374 studies in critical care also showed a trend towards increased reporting of...”</p> <p>P 10 line 25 -27: I already addressed this up front but let me repeat: You mention that one of included trials is not published. In the methods section you indicate that you used the info on adverse events presented in included systematic reviews. Please clarify/explain how you could use the adverse event reporting from the unpublished systematic review ie how you got that information. One might guess how you might have, but it is important that you clearly explain in the manuscript.</p> <p>P10: line 12: “...however our findings are consistent...”. Please edit/ reword as it is almost misleading. Namely of course your findings are consistent with findings in 2 published plus 1 unpublished systematic review that you reanalysed- that was your convenient sample, right?</p> <p>Page 10: Conclusion: Suggestion: you might wish to indicate that there is a positive trend regarding providing the COI statement although it is still underreported. If you add the analysis of reporting by journals and their policies, as I suggested up front, you might provide some explanation and perhaps even influence the improvement.</p>
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	P10 Conclusion line 52: “recent development of reporting checklist for ...” Please edit ie mention that several of co-authors of this secondary analysis developed this checklist. Checklist is a certainly helpful; please indicate whether this checklist has been (widely) accepted and by whom?
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REVIEWER	Cornelius, Victoria Imperial College London, Health and Social Care Research
REVIEW RETURNED	17-Jan-2021

GENERAL COMMENTS	<p>Authors have motivated the need to look at the reporting of trials of Antibiotics for three key aspects; AEs, Col and funding. Though the motivation</p> <p>It’s good to see more research with a focus towards reporting of AEs in RCTs – this with application in Antibiotics. I was really pleased to see this article but then subsequently really disappointed at the limited approach it has taken to review the AEs- only taking the outcome from the SRs - which reported them only at ‘reported, not reported or unclear’.</p> <p>Authors undertook a convenience sample of 3 SR and included 432 trials.</p> <p>Abstract: in order to put the low proportions for death and antimicrobial resistance reporting in to context it would be helpful to have some addition information on the trials involved such as the average duration (with IQR) as without this the reader has no feel for whether or not reporting of mortality would be appropriate. Also there is no information for the date of publication of these trials (how many before and after 2001?)</p> <p>While the authors have been able to detect large difference before and after 2001 due to the size of the difference, Its possible that if there were improvements before and after reporting guidelines were introduced that these would be gradual- did authors look at the pattern over time? For AEs I would also suggest that the consort 2004 reporting guidelines would likely be more influential on AE reporting.</p> <p>I have concern that the outcome used ‘ reporting of any AE’ is a rather broad brush and minimal bar for AE- and as a result whether is an outcome that is actually a measure of anything useful as it will not distinguish from one single report and comprehensive and appropriate reporting.</p> <p>Background. P4</p> <p>The applicants motivate this research by stating that little is known about quality of reporting of antibiotics trials- I was surprised by this. Do they mean quality of reporting in general or for the items they have raised? (AE, Col and funding?) could they summarise and cite what wok had been previously undertaken.</p> <p>Could they introduce why they chose the three antibiotic classes that they did (even if for pragmatic reasons such as they where one that had three large SR conducted with RCTs over time) or was is just that these were the most commonly used?</p> <p>As the use of antibiotics is disparate- could applicants provide some information on their interest or motivation on the three outcomes with regards to clinical setting ? the duration of studies</p>
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	<p>and severity of infection for example will have an impact on consideration for AE reporting</p> <p>Methods Really disappointing to get to this section and see the limited effort made for the AE data exploration- and that this was taken straight from the SR which reported them only at 'reported, not reported or unclear' . A real opportunity has been missed here.</p> <p>Results: Would want to see more characteristics of the RCTs in the SRs. There are three rather basic results and while these are interesting I do not think the extent of this re-analysis and the results warrants the need for a full article</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

2. **Through a before-after study investigating the reporting of adverse events, COIs and funding in RCTs of penicillins, macrolides and cephalosporins, Bakhit and colleagues found that there were no significant differences in reporting of adverse events and funding before and after the publication of the 2001 CONSORT statement, whereas COIs were provided more frequently. The topic is interesting and timely, the methods are appropriate and the article is well-written.**

Author response:

Thank you for your positive feedback, Dr Pericas.

3. **Although the rationale to set the 2001 Consort as the reference to conduct the before/after study is clear, there are some nuances to be made. As the authors acknowledge in the introduction, in the 2001 version, neither funding nor COIs were clearly listed as requirements to be disclosed in all trials. Why then not using the 2010 version or at least consider a time series analysis with both the 2001 and 2010 as time reference points?**

Author response:

We had originally considered doing the analysis as a pre-post 1997 CONSORT, however, none of the key items of interest (funding, COI, adverse events) were mentioned either in the checklist or in the accompanying article (Begg 1996), thus we abandoned this plan.

We also considered using the 2010 CONSORT as a cut-point, however, this would divide the study set into 98 studies (2011 and onwards) vs 334 studies, i.e. skew the set heavily towards older studies (approximately $\frac{1}{4}$ vs $\frac{3}{4}$). Moreover, whilst the 2010 checklist does mention harms/AEs (item 19) and funding (item 25), it does not mention COIs either in the text or in the checklist (Schultz 2010) and is therefore not a perfect solution.

As a pragmatic compromise, we settled on using the 2001 CONSORT as the cut-point, which does mention harms/AEs (item 19) and identify the reporting of funding for the trials as an item

“not considered essential [but] may well be highly desirable and still should be included in an RCT report even though they are not included in CONSORT. Such items include... sources of funding for the trial...” (page 1988, Moher 2001).

We are very grateful for the very interesting suggestion to conduct the time-series analysis, and will examine this when the original systematic reviews are due for updating (which will have the benefit of increasing the size of the RCT pool for the post-2010 CONSORT period).

Change:

No change.

4. **Authors used articles from published RCTs, whereas they do not consider the potential impact of the lack of publication and potentially related items (type of sponsor, negative results, etc). Did the authors consider using Clinicaltrials.gov or EUDRA-CT as primary sources?**

Author response:

Thank you very much for bringing this to our attention. We are aware of the problems stemming from non-publication of trials, and agree that this would be very interesting and important analysis, however it was outside the scope of our project, which focused on the published trails. We made this clearer to the readers of the manuscript.

Change:

Discussion; study limitations: page 10, lines 24, 26

5. **Authors might consider clarifying whether RCTs in which the three classes of antibiotics investigated were also analyzed in case of combination therapy, either among them (e.g. ceftriaxone plus azythromicin for STD or pneumonia) or with other (e.g. with quinolones).**

Author response:

The inclusion criteria for the original systematic reviews was to compare the adverse events of antibiotics within each class alone against a placebo arm, excluding combined therapy.

Change:

Methods; Data set: Page 5 lines 4-6

6. **Although the bulk of RCTs is almost equally divided between the two time periods (before and after 2011), there might be a historical bias to be acknowledged in the 33 years period (1969-2001) compared to the 17 years (2002-2018).**

Author response:

We are not sure what the peer reviewer means by “historical bias”. Does our response to comment 3, above, clarify the issue?

Change:

No changes

7. **There are other aspects that might have provided insightful information regarding the outcomes, e.g, therapeutical vs. preventive trials, geographical scope, academic vs. industry sponsor, etc.**

Author response:

Unfortunately, the original systematic reviews did not class trials by type (therapeutic vs preventative) or geographic scope whilst data-extracting. So, we are limited by the available data in the original systematic review. We agree that the information about sponsorship type is important in this context (which we categorised as industry vs non-industry), and have provided information about this (as well as the statement about the funder's role) in Table 2.

Change:

No changes. See Table 2 and Page 7 lines 10-11, & 15-16

Reviewer: 2

Overall, this is an important issue to study, that you for doing it

Author response:

Thank you very much for your positive feedback, Dr Krleža-Jerić.

1. **Terminology: you use alternatively antimicrobial resistance AMR, and antibiotic resistance: suggest that you stick to one and provide the full name and acronym the first time used. They are not totally synonyms as explained by the WHO: <https://www.who.int/news-room/q-a-detail/antimicrobial-resistance>. By the way I suggest you defined the chosen term and cite the WHO. If various RCTs report different one, explain, or perhaps analyse separately.**

Author response:

We agree – thank you very much for bringing this to our attention. We modified our manuscript and only used ‘antibiotic resistance,’ as our main focus is on bacterial resistance not viral or parasitic.

Change:

Highlighted changes across the whole manuscript

2. **List of studies: the alphabetical list of all studies is not very useful. I suggest that you list original studies alphabetically but by the antibiotics/ syst review included in your sample, even by two subgroups for each group: prior and after CONSORT 2001.**

Author response:

We made this modification and grouped the included RCTs by the systematic review (antibiotic class). Within each group, we sorted the studies by the year of publication, so that this is clearer.

Change:

Appendix 1

3. **Clear/unclear/ non provided: Please explain why you put unclear in non provided group. It seems to me that unclear and not provided is not the same. Unclear is**

when they provide but not clearly. Pls consider to provide the number of those that provide “unclear” statement?

Author response:

We agree that ‘unclear’ and ‘not provided’ are conceptually not identical, as ‘unclear’ means that (for example) a COI statement of some kind exists or is implied in the manuscript but is difficult to interpret, whilst ‘not provided’ means that a COI statement was simply not included in the RCT publication. However, the end result of both situations is the same – it is unclear whether a COI (for example) exists or not exists. This is why we amalgamated both types of cases under the ‘unclear’ category.

Change:

We removed the amalgamation in both types of cases. See changes in Table 2

4. **COI: I suggest that you add additional analysis of reported COI and funding by journals and their policies/requirements. Let me explain: as journals have essential role regarding declaration of the COI and funding, and as you included a variety of journals, it seems essential to analyse the COI and funding reporting by journals and by their policy/ requirement to report it. One can expect that having or not having the policy regarding declaration of COI and funding would influence the studies to include such info in their manuscript. Namely some journals might not require it while some journals would not accept the manuscript unless such statements are provided. You may wish to do such analysis separately for two periods to be comparable with the analysis you already did. By the way you obviously expect journals to influence this- as in the Conclusion you indicate that much work needs to be done regarding reporting of by journal editors, among others.**

Author response:

Thank you very much for this suggestion. We think it would be very difficult to do a retrospective analyse the COI and funding reporting by journals and their policy, as the journals’ policies evolve over the years (not always clearly), and it would be difficult to identify the policy in effect at each trial publishing year. We added this as a limitation in the discussion section.

Change:

Discussion Page 10 line 30-31

5. **a. Please edit the citation of McCullough systematic review. The full citation should include a subtitle: intervention – protocol. Namely the review was not published, just the protocol. Please edit the abstract and the main body of the manuscript to reflect this issue.**

Author response:

We modified the citation to reflect the current status of the cephalosporin review. We added a statement as well in the Methods section.

Change:

Page 5: line 7-11

b. Please clarify and explain the manuscript: You indicated in your methods section that you used the info on adverse events as published in those three systematic reviews included in your analysis. As McCullough et al syst review was not published, and the original protocol published in 2016 was withdrawn, as indicated on the Cochrane database, please explain how you got the info for your reanalysis: how you learned which RCTs were to be included in that study and how you then analysed. Apparently, you could not use the info on adverse events as planned from the syst review as it was not published, but had to figure out which RCTs were to be included in that planned systematic review and analyse individual RCTs yourself.

Author response:

Three authors of the present manuscript (AMS, MB, CDM) were involved in the cephalosporin review. The review was not completed due to personnel changes which resulted in an inability to commit to complete the review in the Cochrane required timeframe. The authors were able to retrieve the list of trials included in the cephalosporin review to be analysed for the present purposes. We provided a statement in the manuscript to clarify this.

Change:

Page 5: line 7-11

6. Additional analysis suggested. Based on your analysis you concluded that the COI reporting increased after 2001 but that is still under reported – as it was reported by only 55% of trials. It would be particularly useful to see whether the lack of COI and funding info were more present in RCT published in certain journals. I suggest that you analyse the reporting of COI and funding by journal and in the context of a journal having the policy -ie requires the COI and funding info as a prerequisite for submission of the manuscript esp after 2001. Pls note that ICMJE has been requiring COI statement since 2001.

Author response:

We agree that it's concerning that the COI reporting remains under-reported. As we note above (response to comment #4), this kind of an analysis would be very interesting but very difficult to execute, as journal policies change over time (and never in sync). We have, however, added this as a limitation in the discussion section.

Change:

Discussion Page 10 line 30-31

7. Page 5 line 33: Pls edit: comment “c” under Table 1 is not clear, the part of sentence starting with “If we could...”

Author response:

We made the sentence clearer “Macrolides SR included trials with more than two intervention arms if we could identify a macrolide arm and a placebo arm.”

Change:

Page 5 line 20

8. Pg 5 line 41 and 42: I already addressed this up front: the mentioned syst review on cephalosporins by McCullough is not published. Please explain how you got the adverse events data for those RCTs.

Author response:

We added a statement clarifying this in the manuscript.

Change:

Page 5 line 7-11

9. Pg 5 line 44: Pls consider adding know how many, in each of systematic review ie antibiotic (group) had unclear reporting of adverse events.

Author response:

Thanks for your comment. We made the requested changes

Change:

Table 2

10. Duplicates. Page 5 line 10/11 and : Page 6 Figure 1: If I read well, you had a total of 2 duplicates that you excluded: $45 + 206 + 183 = 434 - 2 = 432$ Although this is a small number- pls explain how come there were two duplicate RCT if each of included systematic reviews analysed RCTs studying specific ie different antibiotics/ groups of antibiotics .

Author response:

Thanks for your comment. These were 3 arm studies randomising participants to an amoxicillin, cephalosporin or placebo. They were included in each review as they are looking at a different antibiotic class comparing it to the placebo group. However, in our analysis they would be included one study as the COI and funding reporting would be the same (Mandel 1991 & Trehan 2013)

Change:

No change

11. P7 line 21 Please comment, and if possible, explain how come that COI was only 7%, considering that 45% were funded by the industry.

Author response:

We agree, this number is very low, but not surprising, since the COI statement was only provided in 26% of the trials. We emphasised this in the discussion section, as we expect other readers will also be wondering about this.

Change:

See Discussion, Page 9, lines 16-17

12. P7 && starting with line 20 and 27. I suggest you add the number of those trials that did or did not report the adverse events? So these sentences might read: line 20:” Among 266 trials that did report... “; line 27: “Of the 166 trials that did not ...”

Author response:

We made the requested changes

Change:

Page 7: lines 8 and 13

- 13. P7, Line 30: please edit the sentence starting with “ Thirty four of trials...”. If I read well the Table 2, 17 (34%) and not 34 trials that did not report any adverse provided the info on funders role. Thus this sentence should read something like: “Seventeen (34%) of these trials provided....”,**

Author response:

Thanks for pointing this out. We corrected the sentence

Change:

Page 7 lines 15-16

- 14. P7 describing of findings on table 2 and P8 Table 2: If possible provide the info how many of those that indicated that they were funded by industry provided the info on funders role.**

Author response:

We added the requested data to Table 2.

Change:

Table 2

- 15. P8, table 2: I suggest expanding the title and add the N, to read: “Reporting of adverse events, COI and funding by the included RCTs (N=432)”.**

Author response:

We made the recommended expansion of the title.

Change:

Table 2

- 16. page 9, line 3. Title of the Table 3. Suggest editing the title similarly to suggested edits of Table 2 title. It might read: “Reporting adverse events, COI and funding before and after Consort 2001 by included studies (N=237 and 195 respectively)”, or simply add the total N (N=432) to the expanded title.**

Author response:

We made the recommended expansion of the title.

Change:

Table 3

- 17. page 9 Table 3. Pls edit. The column Difference is not expressing difference but the significance of eventual difference. You might wish to indicate the trend/tendency: decrease-increase.**

Author response:

We provided clarification in the text just above table 3 (page 8/9) that the direction of changes was towards increase after 2001 (for COIs and funding). The difference pre-post 2001 for the reporting of AEs was not significant.

Change:

Clarifications added to text discussing Table 3 (page 8) about the direction of change.

18. P9 line 49 pl clarify /edit. I reckon that you wanted to say that your findings were consistent regarding COI, not all three. If so, please edit the sentence.

Author response:

We edited the sentence.

Change:

Page 10 line 4

19. P9. & line 54-59 in the & starting with “Our findings....”. add missing references for two mentioned studies- (on palliative and critical care): “Fewer than half of 848 studies in supportive and palliative oncology provided COI information, although there was an increase in reporting, from 39% of studies in 2004 to 55% in 2009..... However, funding information was provided in only 41% of the studies. An analysis of 374 studies in critical care also showed a trend towards increased reporting of....”

Author response:

Thanks for pointing this out. We added the references for the two mentioned studies.

Change:

Page 10 Lines 9 & 11

20. P 10 line 25 -27: I already addressed this up front but let me repeat: You mention that one of included trials is not published. In the methods section you indicate that you used the info on adverse events presented in included systematic reviews. Please clarify/explain how you could use the adverse event reporting from the unpublished systematic review ie how you got that information. One might guess how you might have, but it is important that you clearly explain in the manuscript.

Author response:

We added a statement clarifying this in the manuscript.

Change:

Page 5 line 7-11

21. P10: line 12: “...however our findings are consistent....”. Please edit/ reword as it is almost misleading. Namely of course your findings are consistent with findings in 2 published plus 1 unpublished systematic review that you reanalysed- that was your convenient sample, right?

Author response:

Indeed, it's circular reasoning – thank you for picking that up. We rephrased this in the manuscript

Change:

Page 10 line 17-18

22. Page 10: Conclusion: Suggestion: you might wish to indicate that there is a positive trend regarding providing the COI statement although it is still underreported. If you add the analysis of reporting by journals and their policies,

as I suggested up front, you might provide some explanation and perhaps even influence the improvement.

Author response:

We agree that this is important. Please see our responses to comment 4 by Reviewer 2. We added it to our limitations as well.

Change:

Page 5 lines 7-11 and Discussion Page 10 lines 28-29

- 23. P10 Conclusion line 52: “recent development of reporting checklist for ...” Please edit ie mention that several of coauthors of this secondary analysis developed this checklist. Checklist is a certainly helpful; please indicate whether this checklist has been (widely) accepted and by whom?**

Author response:

Although the uptake of our developed checklist has not yet been 'widely' used, we are hoping that highlighting the need of a better reporting through this study would help to make the checklist more known and tested by other researchers

Change:

Additional clarification page 11 lines 5-8

Reviewer: 3

- 1. Authors have motivated the need to look at the reporting of trials of Antibiotics for three key aspects; AEs, Col and funding. Though the motivation It's good to see more research with a focus towards reporting of AEs in RCTs – this with application in Antibiotics. I was really pleased to see this article but then subsequently really disappointed at the limited approach it has taken to review the AEs- only taking the outcome from the SRs - which reported them only at 'reported, not reported or unclear'. Authors undertook a convenience sample of 3 SR and included 432 trials.**

Author response:

Thank you very much for your feedback. We have made numerous changes to the manuscript at your, and other peer reviewers', suggestions, and hope this has improved the manuscript. Please see our responses to your comments below

- 2. Abstract: in order to put the low proportions for death and antimicrobial resistance reporting in to context it would be helpful to have some addition information on the trials involved such as the average duration (with IQR) as without this the reader has no feel for whether or not reporting of mortality would be appropriate.**

Author response:

Thanks for your comment. We are not able to extract the information regarding each trial average duration as it was not extracted in the original systematic reviews.

We provided an additional statement in our Discussion regarding the reporting of mortality. In CONSORT harms extension, authors highlight the need to report any serious adverse events.

Death is a serious adverse event and a mandatory outcome that need to be reported and it does not matter if the condition was acute, chronic, severe, or mild.

Change:

Discussion, Page 10 lines 14-17

3. **Also there is no information for the date of publication of these trials (how many before and after 2001?) While the authors have been able to detect large difference before and after 2001 due to the size of the difference, Its possible that if there were improvements before and after reporting guidelines were introduced that these would be gradual- did authors look at the pattern over time? For AEs I would also suggest that the consort 2004 reporting guidelines would likely be more influential on AE reporting.**

Author response:

We agree that where changes do occur, they tend to occur gradually, rather than immediately after an introduction of a guideline such as CONSORT. Dichotomisation into pre-post 2001 CONSORT is not a perfect solution, admittedly, although it is a pragmatic one, which implicitly takes this gradual diffusion into account.

We selected CONSORT 2001, because by the time of its publication, it had been 5 years since the introduction of CONSORT. And whilst admittedly, the 1996 version of CONSORT did not list any of the items of interest here (COI, funding, adverse events), we think it would have started to increase awareness amongst researchers about the importance of transparency and reporting in RCTs more generally. We had also considered using CONSORT 2010 as a cut-point (which does mention harms as item 19, and funding as item 25, but does not mention COIs), however, this would have skewed our study sample quite heavily towards earlier studies (about $\frac{3}{4}$ vs $\frac{1}{4}$). As a pragmatic compromise, we therefore settled on using the 2001 CONSORT as the cut-point, which does mention harms/AEs (item 19) and identify the reporting of funding for the trials as an item “not considered essential [but] may well be highly desirable and still should be included in an RCT report even though they are not included in CONSORT. Such items include... sources of funding for the trial...” (page 1988, Moher 2001). The CONSORT 2004-Harms checklist does not list either COIs or funding among its items, nor does it acknowledge the reporting of funding or COIs in the text, oddly enough.

Change:

No changes

4. **I have concern that the outcome used ‘ reporting of any AE’ is a rather broad brush and minimal bar for AE- and as a result whether is an outcome that is actually a measure of anything useful as it will not distinguish from one single report and comprehensive and appropriate reporting.**

Author response:

We agree that ‘any AE’ is a broad brush approach. However, we do separate out AEs into antibiotic resistance, deaths, and other AEs in Table 2. Given that 38% of all trials still did not report AEs in the ‘other AE’ category, we thought it worthwhile presenting this information.

Change:

No changes

5. The applicants motivate this research by stating that little is known about quality of reporting of antibiotics trials- I was surprised by this. Do they mean quality of reporting in general or for the items they have raised? (AE, CoI and funding?) could they summarise and cite what work had been previously undertaken.

Author response:

We mean quality of reporting in RCTs of antibiotics. We have made additional clarifications.

Change:

Page 4 lines 23-24

6. Could they introduce why they chose the three antibiotic classes that they did (even if for pragmatic reasons such as they were one that had three large SR conducted with RCTs over time) or was it just that these were the most commonly used?

Author response:

We chose these reviews as their main objective was to analyse the adverse events associated with the use of the most commonly used antibiotics.

Change:

Page 5, lines 3-4

7. As the use of antibiotics is disparate- could applicants provide some information on their interest or motivation on the three outcomes with regards to clinical setting ? the duration of studies and severity of infection for example will have an impact on consideration for AE reporting

Author response:

Because the systematic reviews themselves were focused on the clinical implications and issues, we felt it would have been duplicative to focus on these in the present manuscript. Our focus is therefore predominantly on issues around the reporting, rather than on issues around clinical implications.

Change:

No changes

8. Methods: Really disappointing to get to this section and see the limited effort made for the AE data exploration- and that this was taken straight from the SR which reported them only at 'reported, not reported or unclear' . A real opportunity has been missed here.

Author response:

Our main focus in this manuscript was in examining the patterns in the quality of reporting, in trials of Antibiotics, given the importance of CONSORT (and indeed, other reporting guidelines for other study types). There is a tremendous amount of detail in the systematic reviews themselves, about the individual AEs. For example, the Hansen (Macrolides) systematic review, categorises the identified AEs into 27 MedDRA categories, and includes over 30 meta-analyses for the various AE types. We felt that including all of this detail would have detracted from the focus of this manuscript.

Change:

No changes

- 9. Results: Would want to see more characteristics of the RCTs in the SRs. There are three rather basic results and while these are interesting I do not think the extent of this re-analysis and the results warrants the need for a full article**

Author response:

We do agree that readers may be interested in these data, however, as the data is already presented in the systematic reviews themselves, re-presenting it here would have been needlessly duplicative.

Change:

No changes

VERSION 2 – REVIEW

REVIEWER	Krleža-Jerić, Karmela Ottawa Group-IMPACT
REVIEW RETURNED	12-May-2021

GENERAL COMMENTS	<p>Thank you for thoroughly analysing and responding to all comments and for highlighting changes. As already mentioned, this is such an important issue, and you did a great job with your analysis and by pointing to the need to improve the reporting of antibiotic trials.</p> <p>I am asking you now to consider the minor revision. Let me explain: In your discussion you indicate the need for improvement of reporting and express expectations that the adoption and use of checklists “such as the check list developed by several authors of the present study” would influence reporting.</p> <p>As you are discussing what might lead to positive changes of reporting of these, and, allow me to add, other trial characteristics, I suggest you also indicate the role that SPIRIT (Standard Protocol Items for Randomized Trials) is expected to play in improvement of quality of studies and consequent reporting by providing a checklist of key items to be included in the trial protocol.</p> <p>As your study was based on trials that started and many were even completed and published before the launch of SPIRIT, you could not measure its impact on reporting of items of interest (adverse events, funding, COI,) but since then it was published and has been widely accepted and used.. For your convenience I am adding a link to SPIRIT website: https://www.spirit-statement.org/ and also, to its key publications that are by the way open access:</p> <p>the statement in Annals: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5114123/ and SPIRIT checklist in BMJ : https://www.bmj.com/content/346/bmj.e7586</p>
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VERSION 2 – AUTHOR RESPONSE

Reviewer: 2 Dr. Karmela Krleža-Jerić, Ottawa Group-IMPACT Comments to the Author:

1- Dear Authors, Thank you for thoroughly analysing and responding to all comments and for highlighting changes. As already mentioned, this is such an important issue, and you did a great job with your analysis and by pointing to the need to improve the reporting of antibiotic trials.

Author response:

Thank you very much for your positive feedback, Dr Krleža-Jerić.

2- I am asking you now to consider the minor revision. Let me explain: In your discussion you indicate the need for improvement of reporting and express expectations that the adoption and use of checklists “such as the check list developed by several authors of the present study” would influence reporting. As you are discussing what might lead to positive changes of reporting of these, and, allow me to add, other trial characteristics, I suggest you also indicate the role that SPIRIT (Standard Protocol Items for Randomized Trials) is expected to play in improvement of quality of studies and consequent reporting by providing a checklist of key items to be included in the trial protocol. As your study was based on trials that started and many were even completed and published before the launch of SPIRIT, you could not measure its impact on reporting of items of interest (adverse events, funding, COI,) but since then it was published and has been widely accepted and used.. For your convenience I am adding a link to SPIRIT website: <https://www.spirit-statement.org/> and also, to its key publications that are by the way open access:

the statement in Annals: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5114123/>

and SPIRIT checklist in BMJ : <https://www.bmj.com/content/346/bmj.e7586>

Author response:

Thank you for your comment. We have added the following sentence in our Discussion and cited the mentioned SPIRIT checklist publications: “The lack of change in reporting of adverse events, and the small decrease in reporting of antibiotic resistance are concerning, although may shift in the coming years by adequately reporting the protocols of clinical trials by using SPIRIT checklist (Standard Protocol Items for Randomised Trials),^{26, 27} and by the adoption of checklists specific to reporting antibiotic resistance in prospective studies of antibiotic use, such as the checklist developed by several authors of the present study.²⁸”