

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Reappraisal of previously reported meta-analyses on antibiotic prophylaxis for low-risk laparoscopic cholecystectomy: An overview of systematic reviews
<b>AUTHORS</b>	Matsui, Yoichi; Sato, Sohei; Hirooka, Satoshi; Kosaka, Hisashi; Takayuki, Kawaura; Tomoki, Kitawaki

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Prof. Lukas Krähenbühl Department of Surgery Kantonsspital Glarus Senior Consultant University Hospital Zurich Switzerland
<b>REVIEW RETURNED</b>	07-Apr-2017

<b>GENERAL COMMENTS</b>	<p>This systematic review of reported meta-analyses on antibiotic prophylaxis in laparoscopic cholecystectomy is very important. However, the paper requires specialist statistical review. If this review confirms the results given in Figure 3 that SSI as well as systemic and overall infections are significantly less using prophylactic antibiotics for elective laparoscopic cholecystectomy compared to no antibiotics, this paper may be published without further revision.</p> <p>The results are so important that current guidelines (such as SAGES, EAES or National) would need major revision about the use on antibiotic prophylaxis in elective laparoscopic cholecystectomy.</p>
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<b>REVIEWER</b>	Robert Sutcliffe University Hospitals Birmingham NHS Foundation Trust, United Kingdom
<b>REVIEW RETURNED</b>	08-May-2017

<b>GENERAL COMMENTS</b>	<p>The authors have performed a systematic review of meta-analyses on the subject of prophylactic antibiotics in laparoscopic cholecystectomy, and found several miscounts in previous studies, and identified six RCTs which had been inappropriately included in previous meta-analyses. After correcting the miscounts and excluding the six RCTs, the authors concluded that antibiotic prophylaxis significantly reduced infections (opposite to all previous meta-analyses) and that the results were also affected whether a fixed-effects or random-effects model was used.</p> <p>The paper is very well written and the results have been presented</p>
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	<p>clearly. The topic is of clinical interest and is worthy of publication.</p> <p>Comment</p> <p>1. The authors noted that previous RCTs are limited by small sample size, and that 'large-scale well-conducted' RCTs are required. It would be helpful if the authors would also include a sample size/power calculation for such a trial in their discussion, based on their data.</p>
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<b>REVIEWER</b>	Richard Woodman Flinders University of South Australia Australia
<b>REVIEW RETURNED</b>	01-Jun-2017

<b>GENERAL COMMENTS</b>	<p>Given that the study concludes that differently to 7 previous meta-analyses, the results of this meta-analysis may have been influenced heavily by the 2 particular reviewers performing the review. Although the methods section describes how disagreements between the 2 assessors were managed, there are no results reporting the degree of agreement and/or disagreement between these 2 observers or the nature of the disagreements. It would be useful to see a table that lists each disagreement reported, the individual outcomes reported for each observer and a description of how consensus was reached. In addition it would be useful to know to what degree there was agreement between reporters on the observed discrepancies, and also agreement on the observed agreement with previous studies. Perhaps a kappa statistic could be calculated for:</p> <ol style="list-style-type: none"> <li>1) Agreement between the 2 observers</li> <li>2) Agreement for Observer 1 with previous studies</li> <li>3) Agreement for Observer 2 with previous studies</li> </ol> <p>There is a section in the discussion on "problems with meta-analysis" notably what the authors feel is a tendency for researchers to pick and choose between affixed and random effects approach. The section is however not referenced and is not tied to the results of the study in any way. I would therefore remove this section as it simply suggests that the authors themselves may be biased against the use of meta-analyses.</p> <p>Although a table is provided (S1 Appendix) to explain where the discrepancies occurred, there is nothing stated in the results as to which studies had the most influence in changing the previous findings. It would be helpful for the reader to know if there were any studies that were particularly influential in reversing the findings or were the changes in risk magnitude all similar across the mis-reported studies.</p> <p>The methods used for the statistical analysis are appropriate for this kind of data and the results well reported. The authors should however state which method (fixed effects or random effects) was their primary analysis and which their sensitivity analysis. At present they seem to have committed their own sin or reporting both and choosing that which suits to indicate evidence.</p> <p>There is no assessment of small study/publication bias</p> <p>The PRISMA checklist indicates that several items relating to assessment of bias were not assessed.</p>
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<b>REVIEWER</b>	Dr Safwaan Adam and Dr Shaishav S Dhage
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	University of Manchester, United Kingdom
<b>REVIEW RETURNED</b>	23-Aug-2017

<b>GENERAL COMMENTS</b>	<p>The authors appeared to have conducted a thorough meta-analysis of previous meta-analyses. I do however have some major concerns:</p> <p>1) Despite the authors mentioning in the introduction that they felt previous meta-analyses had RCTs with small sample sizes, it is not entirely otherwise clear what the motivation for this re-analysis was. In addition, if a re-analysis of existing meta-analyses with small sample sizes is done, that does not remove the sample size problem. Whereas a more thorough analysis of the existing reports might be done, the number of participants may only change marginally. Has clinical observation or a new clinical trial brought the old meta-analyses results into a new focus? This needs to be clarified in more detail with the introduction building more of a case for it.</p> <p>2) The obvious concern is selection bias and any 'super-analysis of analyses' is open to error and bias and it is clear that the authors, in their opinion, felt that previous meta-analyses have misrepresented the case for antibiotics. However, that in itself is not a reason not to do the work and I feel the authors have made a good effort of it. It is important though to list this as a limitation of the work.</p> <p>3) I would have liked, in addition to appraising older meta-analyses, for evidence since the publication of the last meta-analysis to be included in this study. For a clinician to derive complete benefit, it would be most useful if the latest evidence is reviewed in this new analysis as the publication of the last meta-analysis</p> <p>4) A more thorough inclusion and exclusion criteria section would be needed – in the results, the authors allude to 'after exclusions' though it is not clear what these are. Apart from English language, I cannot see any other firm criteria. Why were the 11 excluded?</p> <p>Minor Comments:</p> <p>1) The title should reflect that this meta-analysis pertains to only low risk or elective cholecystectomy.</p> <p>2) Try and substitute the word 'overdosage' with another one – though it is quite clear to me what the authors are alluding to, it can be interpreted differently by others.</p> <p>3) There is excessive use of the comma – I had initially made note of different places but given that this was a frequent issue, for brevity, I will not list these. Please review the use of the comma.</p> <p>4) The introduction refers to a healthcare burden of the ageing population (a point repeated in the discussion) – what relevance does this have?</p>
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<b>REVIEWER</b>	Giuseppe Biondi-Zoccai Sapienza University of Rome, Latina, Italy
<b>REVIEW RETURNED</b>	05-Oct-2017

<b>GENERAL COMMENTS</b>	<p>Matsui et al report an interesting overview of systematic reviews on antibiotic prophylaxis in laparoscopic cholecystectomy. Despite the work strengths, I recommend addressing the following comments:</p> <ol style="list-style-type: none"> <li>1. Clarify in the title or abstract that yours is an overview of systematic reviews.</li> <li>2. Appraise review validity.</li> <li>3. Add funnel plots and Egger tests.</li> <li>4. Add meta-regression analyses.</li> </ol>
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	<p>5. Add a trial-sequential analysis using date of publication in PubMed. It might be that earlier meta-analyses simply included few trials.</p> <p>6. Add correlation analyses (eg between funding/conflicts of interest and results/conclusions in included reviews).</p> <p>In addition, if you find it useful, you may exploit for reference the book I have recently edited on umbrella reviews, overview of reviews and meta-epidemiologic studies (ISBN 978-3-319-25653-5). It is just a suggestion and not a call to quote it.</p>
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## VERSION 1 – AUTHOR RESPONSE

### Point-by-point responses

#### Editor Comments to Author:

- Please include a colon in your title instead of a full stop, to ensure that the title remains as only one sentence.
  - A colon was inserted in the title.
- Please state which databases were search in the abstract.
  - Databases searched were added in the abstract.
- Please include any relevant quantitative results or statistics in the abstract results section.
  - Quantitative and statistic results were added in the abstract.
- Please discuss the limitations of the study in the discussion section.
  - The limitations were added Page 18, 2nd paragraph, in Discussion section.
- Please include an example of the full search strategy as a supplementary file.
  - The full search strategy was added as the supplementary S1 file.

#### Associate Editor Comments to Author:

On page 3, right after the abstract, in the section “Strengths and limitations of the study”, they say “(...) We reassessed all of these meta-analyses and their related RCTs, and found some issues (...)”, and “some issues” is a rather poor expression. Why not say instead, for example “(...) and found a number of miscounts of the number of outcomes as well as trials that were inappropriate for selection in the meta-analyses (...)”?

- The number of miscounts and the number of RCTs that were inappropriate for selection were shown in the “Strengths and limitations of the study”

#### Reviewer: 1

This systematic review of reported meta-analyses on antibiotic prophylaxis in laparoscopic cholecystectomy is very important. However, the paper requires specialist statistical review.

- Two statistical specialists reviewed the manuscript (T Kawaura, Dr. Eng. Librarian, T Kitawaki, Dr. Eng. P.E. Jp).

If this review confirms the results given in Figure 3 that SSI as well as systemic and overall infections are significantly less using prophylactic antibiotics for elective laparoscopic cholecystectomy compared to no antibiotics, this paper may be published without further revision.

The results are so important that current guidelines (such as SAGES, EAES or National) would need major revision about the use on antibiotic prophylaxis in elective laparoscopic cholecystectomy.

#### Reviewer: 2

The authors have performed a systematic review of meta-analyses on the subject of prophylactic antibiotics in laparoscopic cholecystectomy, and found several miscounts in previous studies, and identified six RCTs which had been inappropriately included in previous meta-analyses. After correcting the miscounts and excluding the six RCTs, the authors concluded that antibiotic prophylaxis significantly reduced infections (opposite to all previous meta-analyses) and that the results were also affected whether a fixed-effects or random-effects model was used.

The paper is very well written and the results have been presented clearly. The topic is of clinical interest and is worthy of publication.

#### Comment

1. The authors noted that previous RCTs are limited by small sample size, and that 'large-scale well-conducted' RCTs are required. It would be helpful if the authors would also include a sample size/power calculation for such a trial in their discussion, based on their data.

Results of the sample size/power calculation were added Page 18, 1st paragraph, lines 10-13, in Discussion section.

#### Reviewer: 3

Given that the study concludes that differently to 7 previous meta-analyses, the results of this meta-analysis may have been influenced heavily by the 2 particular reviewers performing the review. Although the methods section describes how disagreements between the 2 assessors were managed, there are no results reporting the degree of agreement and/or disagreement between these 2 observers or the nature of the disagreements. It would be useful to see a table that lists each disagreement reported, the individual outcomes reported for each observer and a description of how consensus was reached. In addition, it would be useful to know to what degree there was agreement between reporters on the observed discrepancies, and also agreement on the observed agreement with previous studies. Perhaps a kappa statistic could be calculated for:

1) Agreement between the 2 observers

2) Agreement for Observer 1 with previous studies

3) Agreement for Observer 2 with previous studies

The degree of agreement and disagreement between the 2 observers, and the nature of the disagreements were described Page 9, 2nd paragraph in Results section, and the supplementary S1 and S2 files.

There is a section in the discussion on "problems with meta-analysis" notably what the authors feel is a tendency for researchers to pick and choose between affixed and random effects approach. The section is however not referenced and is not tied to the results of the study in any way. I would therefore remove this section as it simply suggests that the authors themselves may be biased against the use of meta-analyses.

The discussion regarding the problem of the fixed-effect model and the random-effect model in meta-analysis was removed from Discussion section.

Although a table is provided (S1 Appendix) to explain where the discrepancies occurred, there is nothing stated in the results as to which studies had the most influence in changing the previous findings. It would be helpful for the reader to know if there were any studies that were particularly influential in reversing the findings or were the changes in risk magnitude all similar across the mis-reported studies.

The trial excluded from our analysis that was greatly influenced the reversal of previous findings was described Page 17, 2nd paragraph, in Discussion section.

The methods used for the statistical analysis are appropriate for this kind of data and the results well reported. The authors should however state which method (fixed effects or random effects) was their

primary analysis and which their sensitivity analysis. At present, they seem to have committed their own sin or reporting both and choosing that which suits to indicate evidence.

The fixed-effect model was used as a primary analysis because the results of our analysis had no heterogeneity. This was described Page 17, 3rd paragraph, in Discussion section, and shown in Table 2.

There is no assessment of small study/publication bias.

A funnel plot was added as Figure 4, and the small study/publication bias was mentioned Page 14, 2nd paragraph, in Results section.

The PRISMA checklist indicates that several items relating to assessment of bias were not assessed.

The PRISMA check list was altered.

Reviewer: 4

The authors appeared to have conducted a thorough meta-analysis of previous meta-analyses. I do however have some major concerns:

1) Despite the authors mentioning in the introduction that they felt previous meta-analyses had RCTs with small sample sizes, it is not entirely otherwise clear what the motivation for this re-analysis was. In addition, if a re-analysis of existing meta-analyses with small sample sizes is done, that does not remove the sample size problem. Whereas a more thorough analysis of the existing reports might be done, the number of participants may only change marginally. Has clinical observation or a new clinical trial brought the old meta-analyses results into a new focus? This needs to be clarified in more detail with the introduction building more of a case for it.

According to these comments, the last two sentences "In addition, the most --- RCTs examined by them." were added, Page 5, lines 21- Page 6, lines 4, in Introduction section.

2) The obvious concern is selection bias and any 'super-analysis of analyses' is open to error and bias and it is clear that the authors, in their opinion, felt that previous meta-analyses have misrepresented the case for antibiotics. However, that in itself is not a reason not to do the work and I feel the authors have made a good effort of it. It is important though to list this as a limitation of the work.

Above mentioned limitations were added Page 18, 2nd paragraph, in Discussion section.

3) I would have liked, in addition to appraising older meta-analyses, for evidence since the publication of the last meta-analysis to be included in this study. For a clinician to derive complete benefit, it would be most useful if the latest evidence is reviewed in this new analysis as the publication of the last meta-analysis

The latest evidence (ref. No. 37) was added and mentioned Page 5, lines 21-23, in Introduction section, and Page 19, lines 1, 2, in Discussion section.

4) A more thorough inclusion and exclusion criteria section would be needed – in the results, the authors allude to 'after exclusions' though it is not clear what these are. Apart from English language, I cannot see any other firm criteria. Why were the 11 excluded?

Precise inclusion and exclusion criteria was described Page 9, 2nd paragraph in Results section and Supplementary S1 and S2 files were provided.

Minor Comments:

1) The title should reflect that this meta-analysis pertains to only low risk or elective cholecystectomy.

The "low-risk" was inserted in the title.

2) Try and substitute the word 'overdosage' with another one – though it is quite clear to me what the authors are alluding to, it can be interpreted differently by others.

The word 'overdosage' was changed to 'over-dosage' through the manuscript.

3) There is excessive use of the comma – I had initially made note of different places but given that this was a frequent issue, for brevity, I will not list these. Please review the use of the comma.

Excessive use of the comma was improved.

4) The introduction refers to a healthcare burden of the ageing population (a point repeated in the discussion) – what relevance does this have?

The word 'healthcare burden' was changed to 'medical cost' in Introduction and Discussion section.

Reviewer: 5

Matsui et al report an interesting overview of systematic reviews on antibiotic prophylaxis in laparoscopic cholecystectomy. Despite the work strengths, I recommend addressing the following comments:

1. Clarify in the title or abstract that yours is an overview of systematic reviews.

The word 'overview' was inserted in the title.

2. Appraise review validity.

3. Add funnel plots and Egger tests.

4. Add meta-regression analyses.

5. Add a trial-sequential analysis using date of publication in PubMed. It might be that earlier meta-analyses simply included few trials.

6. Add correlation analyses (eg between funding/conflicts of interest and results/conclusions in included reviews).

The results of funnel plots and Egger tests were added as Figure 4, and the results of meta-regression analyses were shown in supplementary S5. The statistical results regarding above comments 2-6 was described Page 14, 2nd paragraph, in Results section.

In addition, if you find it useful, you may exploit for reference the book I have recently edited on umbrella reviews, overview of reviews and meta-epidemiologic studies (ISBN 978-3-319-25653-5). It is just a suggestion and not a call to quote it.

## VERSION 2 – REVIEW

<b>REVIEWER</b>	Giuseppe Biondi-Zoccai Sapienza University of Rome, Italy
<b>REVIEW RETURNED</b>	17-Nov-2017

<b>GENERAL COMMENTS</b>	NA
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<b>REVIEWER</b>	Robert Sutcliffe University Hospital Birmingham NHS Foundation Trust, UK
<b>REVIEW RETURNED</b>	20-Nov-2017

<b>GENERAL COMMENTS</b>	The authors have thoroughly considered all reviewers comments and amended the manuscript appropriately.
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<b>REVIEWER</b>	Prof. Lukas Krähenbühl Department of Surgery Spital Einsiedeln Spitalstrasse 28 Postfach 462 CH-8840 Einsiedeln Switzerland
<b>REVIEW RETURNED</b>	27-Nov-2017

<b>GENERAL COMMENTS</b>	After this revision the paper is well written and clear and also the statistical part is clear and gained the power needed. The paper is important and can now be suggested for publication without further revision
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<b>REVIEWER</b>	Safwaan Adam University of Manchester, United Kingdom Manchester University Hospitals NHS Foundation Trust, United Kingdom Salford Royal NHS Foundation Trust, United Kingdom
<b>REVIEW RETURNED</b>	09-Dec-2017

<b>GENERAL COMMENTS</b>	<p>Following the revision I do feel the authors have added clarity and more focus to this manuscript. It addresses an important question and is well presented.</p> <p>One very small change I would suggest in the "Results" section: "The reasons for these discrepancies were as follows; One observer had overlooked an inappropriate study design for Reference 23 and inappropriate outcome measures for Reference 28." Use a colon instead of a semi-colon and remove the capital letter from the word "One".</p> <p>Otherwise I would like to congratulate the authors of a well-written manuscript.</p>
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