PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Global incidence of surgical-site infection after appendectomy: a systematic review and meta-analysis
AUTHORS	Danwang, Celestin; Bigna, Jean Joel; Tochie, Joel Noutakdie; Mbonda, Aimé; Mbanga, Clarence; Nzalie, Rolf; Guifo, Marc Leroy; Essomba, Arthur

VERSION 1 – REVIEW

REVIEWER	Siv Fonnes CPO, Department of Surgery, Herlev Hospital
REVIEW RETURNED	01-Oct-2019

GENERAL COMMENTS	The authors have conducted a systematic review with an impressive number of included studies from all over the world with allows them to estimate the global prevalence of sugerical site infection after appendectomy. The vast number of included studies also results in the review's greatest limitation, that individual data of the included studies, the heterogeneity of the included studies definitions and outcomes, and the bias assessment of the individual studies are not reported. This was planned in the protocol and is recommended by PRISMA guidelines. Therefore, the quality of the estimate for global prevalence comes with major limitations, which cannot be assessed from the review. 1. Methods: Please follow the PRISMA guideline in your reporting as stated in your protocol. 1a. It is recommended that details on registration and protocol at the beginning of the method section. 1b. Please add details on eligibility criteria or where to find these. 1c. Please move the information on the risk of bias, so it comes before data analysis. In your protocol, you state two tools will be used, but you only report on one of these tools. 2. Flowchart, all of the 226 studies could be included in the meta-analysis. There were no heterogeneity of the definition of procedures (single incision, multiple incisions, different open surgeries) or definition of the outcome (SSI definition, follow-up method, time for follow-up), which limited the number of studies that could be included in the meta-analysis? 3. Results, line 168-169: please add "overall characteristics" as you do not present the individual data for each of the included studies. PRISMA guideline recommends that each study is presented. I understand that you have included >200 studies and the table would be huge and not provide an overview, so I do understand why you have chosen not to present all data. However, I would recommend that you add more information in the suppl table 1 e.g. median(range) or mean(SD) where appropriate or proportions for e.g. year 2000-2002, region etc., so the actual distribution of data is

	easier to grasp. Please revise suppl table 1. 4. Table 1, please define all abbreviations used in the table. 5. Risk of bias is not presented for each study as planned in the protocol and as recommended by PRISMA. 6. Limitations: The use of antibiotics was not used assessed in you meta-analysis though you discuss its importance in the discussion section. 7. As the individual data from the included studies are not presented in the review, it is difficult for the reader to assess the heterogeneity on definitions and outcomes (not the statistical) of the included studies. Can you give an overview of more of the individual data from the included studies, so the possible limitations of the estimate can be deduced by the readers? 8. Please review your manuscript and reference list for spelling errors.

REVIEWER	Lifeng Lin Florida State University, USA
REVIEW RETURNED	22-Oct-2019

GENERAL COMMENTS	This manuscript presents a meta-analysis of observational studies on the global prevalence of surgical-site infection after appendectomy. I have focused on reviewing the statistical analyses. A strength of this study is that it is the first to summarize such evidence in all WHO regions, and the meta-analysis contains a large number of studies. Due to the nature of observational studies, however, the studies included in this meta-analysis are highly heterogeneous. It's good to report the prediction intervals so that researchers will know the uncertainty of this meta-analysis conclusion when generalizing it to a future study. The authors tried to partially adjust for the high heterogeneity by subgroup analyses and meta-regression, but many potential confounders still could not be ruled out. I have several questions as follows. On page 7, "For multinational studies, data was disaggregated, with the results shown within individual country". If I understand correctly, the data from individual countries from a single multinational study were treated as multiple separate studies in the meta-analysis, right? I was wondering how many multinational studies exist in this meta-analysis? Based on the flow chart (Supplementary Figure 1), a total of 226 studies were eventually included in the meta-analysis. Is this the number of studies before or after the disaggregation? Please clarify these. The authors conducted meta-analyses to quantitatively summarize the incidence of SSIs. I was wondering if the synthesis was conducted on the original scale of the incidence, or a properly transformed scale (say the log transformation)? The conventional meta-analysis models (including the DerSimonian and Laird method used by the authors) make the normality assumption at both within-study and between-study levels. However, from the forest plots in Figures 1-3, the within-study CIs do not look symmetric, and thus the individual studies' incidences are unlikely normal. If the data are not normal, it may be also inappropriate to use the funnel plot or the associated Egger's regression to test for publication bias, as the funnel plot is expected to be asymmetric even if no publication bias is present. As shown in the current funnel plot in Supplementary Figure 2, all studies' incidences must be above 0, and the asymmetry may be just due to the nature that incidences must be nonnegative.

	On page 7, please remove “Cochrane’s” before “Q statistic”; see, e.g., Hoaglin DC (2016). Misunderstandings about Q and ‘Cochran’s Q test’ in meta-analysis. Statistics in Medicine, 35(4), 485-495. Also, please cite the original papers by Higgins et al. (2002, Statistics in Medicine or 2003, BMJ) when mentioning the I^2 statistic, instead of just citing Huedo-Medina et al. (ref 33). Please also indicate which statistical software package is used in the methods section, and indicate its version.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Siv Fonnes
CPO, Department of Surgery, Herlev Hospital

The authors have conducted a systematic review with an impressive number of included studies from all over the world with allows them to estimate the global prevalence of sugerical site infection after appendectomy. The vast number of included studies also results in the review's greatest limitation, that individual data of the included studies, the heterogeneity of the included studies definitions and outcomes, and the bias assessment of the individual studies are not reported. This was planned in the protocol and is recommended by PRISMA guidelines. Therefore, the quality of the estimate for global prevalence comes with major limitations, which cannot be assessed from the review.

Authors: We thank the reviewer for the comments and suggestions. We considered all suggestions and we hope that the manuscript was greatly improved.

1. Methods: Please follow the PRISMA guideline in your reporting as stated in your protocol.
1a. It is recommended that details on registration and protocol at the beginning of the method section.

Authors: Thank you dear reviewer. We moved information on registration and published protocol at the beginning of the Methods section. We now considered the MOOSE guidelines as suggested by the Editor.

1b. Please add details on eligibility criteria or where to find these.

Authors: Dear reviewer, we have added a paragraph to describe eligibility criteria.

1c. Please move the information on the risk of bias, so it comes before data analysis. In your protocol, you state two tools will be used, but you only report on one of these tools.

Authors: Thank you for highlighting this. As this is a review of incidence data, we finally only considered the tool by Hoy and colleagues. The tool recommended by the Cochrane group is more adequate for a systematic review and meta-analysis of randomized controlled trial. We have updated the protocol in PROSPERO to reflect that. We have also moved the section on risk of bias as suggested.

2. Flowchart, all of the 226 studies could be included in the meta-analysis. There were no heterogeneity of the definition of procedures (single incision, multiple incisions, different open

surgeries) or definition of the outcome (SSI definition, follow-up method, time for follow-up), which limited the number of studies that could be included in the meta-analysis?

Authors: Thank you for this important comment. The characteristics of the study population and the types of surgical procedure (Supplementary Table 3. Individual characteristics of included studies) were inconsistently reported across studies. In addition, most of studies did not describe the characteristics you mentioned above. Therefore, we were not able to fully explore the sources of heterogeneity. We have now revised the Limitations section to highlight that: "*Secondly, few studies reported on the participants' characteristics and details on the surgical procedure since this can modify the risk for developing SSIs. We were not therefore able to measure the impact on our outcome of interest.*"

3. Results, line 168-169: please add "overall characteristics" as you do not present the individual data for each of the included studies. PRISMA guideline recommends that each study is presented. I understand that you have included >200 studies and the table would be huge and not provide an overview, so I do understand why you have chosen not to present all data. However, I would recommend that you add more information in the suppl table 1 e.g. median(range) or mean(SD) where appropriate or proportions for e.g. year 2000-2002, region etc., so the actual distribution of data is easier to grasp. Please revise suppl table 1./span>

Authors: Thank you for the suggestion. We have now added the Supplementary Table 3 with individual characteristics of included studies.

4. Table 1, please define all abbreviations used in the table.

Authors: We now defined and explained all abbreviations.

5. Risk of bias is not presented for each study as planned in the protocol and as recommended by PRISMA.

Authors: We have added this information in the Supplementary Table 3 (3rd column).

6. Limitations: The use of antibiotics was not used assessed in you meta-analysis though you discuss its importance in the discussion section.

Authors: We have now performed a meta-regression analysis and we have added the outputs at the end of the Results section. We have also revised the Discussion section when necessary. We thank the reviewer for this valuable comment.

7. As the individual data from the included studies are not presented in the review, it is difficult for the reader to assess the heterogeneity on definitions and outcomes (not the statistical) of the included studies. Can you give an overview of more of the individual data from the included studies, so the possible limitations of the estimate can be deduced by the readers?

Authors: Dear reviewer, we have added the Supplementary Table 3. Thank you for the suggestion.

8. Please review your manuscript and reference list for spelling errors.

Authors: Thank you the suggestion. We have proofread the manuscript.

Reviewer: 2
Lifeng Lin
Florida State University, USA

This manuscript presents a meta-analysis of observational studies on the global prevalence of surgical-site infection after appendectomy. I have focused on reviewing the statistical analyses. A strength of this study is that it is the first to summarize such evidence in all WHO regions, and the meta-analysis contains a large number of studies. Due to the nature of observational studies, however, the studies included in this meta-analysis are highly heterogeneous. It's good to report the prediction intervals so that researchers will know the uncertainty of this meta-analysis conclusion when generalizing it to a future study. The authors tried to partially adjust for the high heterogeneity by subgroup analyses and meta-regression, but many potential confounders still could not be ruled out. I have several questions as follows.

Authors: We thank the reviewer for the comments and suggestions. We considered all suggestions and we hope that the manuscript was greatly improved.

On page 7, "For multinational studies, data was disaggregated, with the results shown within individual country". If I understand correctly, the data from individual countries from a single multinational study were treated as multiple separate studies in the meta-analysis, right? I was wondering how many multinational studies exist in this meta-analysis? Based on the flow chart (Supplementary Figure 1), a total of 226 studies were eventually included in the meta-analysis. Is this the number of studies before or after the disaggregation? Please clarify these.

Authors: Thank you for this comment. We have removed this sentence. This was planned in the protocol, however we have disaggregated any prevalence data.

The authors conducted meta-analyses to quantitatively summarize the incidence of SSIs. I was wondering if the synthesis was conducted on the original scale of the incidence, or a properly transformed scale (say the log transformation)? The conventional meta-analysis models (including the DerSimonian and Laird method used by the authors) make the normality assumption at both within-study and between-study levels. However, from the forest plots in Figures 1-3, the within-study CIs do not look symmetric, and thus the individual studies' incidences are unlikely normal. If the data are not normal, it may be also inappropriate to use the funnel plot or the associated Egger's regression to test for publication bias, as the funnel plot is expected to be asymmetric even if no publication bias is present. As shown in the current funnel plot in Supplementary Figure 2, all studies' incidences must be above 0, and the asymmetry may be just due to the nature that incidences must be nonnegative.

Authors: Dear reviewer, thank you for the comment. The synthesis was done after Freeman-Tukey double-arcsine transformation as recommended by Barendregt and colleagues. (*Barendregt JJ, Doi SA, Lee YY, Norman RE, Vos T. Meta-analysis of prevalence. J Epidemiol Community Health. 2013 Nov 1;67(11):974–8.*). In the forest plots, we back-transformed prevalence to show the original scale (before Freeman-Tukey double arcsine transformation). In the funnel plot, prevalence data were the Freeman-Tukey double arcsine transformed form.

On page 7, please remove "Cochrane's" before "Q statistic"; see, e.g., Hoaglin DC (2016). Misunderstandings about Q and 'Cochran's Q test' in meta-analysis. Statistics in Medicine, 35(4),

485-495. Also, please cite the original papers by Higgins et al. (2002, Statistics in Medicine or 2003, BMJ) when mentioning the I^2 statistic, instead of just citing Huedo-Medina et al. (ref 33).

Authors: Thank you for this valuable suggestions. We revised as suggested.

Please also indicate which statistical software package is used in the methods section, and indicate its version.
Authors: We have added this information: "*Data were analysed using the 'meta' package in R, version 3.6.1.*"

VERSION 2 – REVIEW

REVIEWER	Siv Fonnes CPO, Department of Surgery, Herlev Hospital
REVIEW RETURNED	08-Dec-2019

GENERAL COMMENTS	Thank you for revising your manuscript accordingly. Below are the mentioned the number of the comment where questions or new comments have arisen after reviewing the changes to the manuscript. 1a. I would recommend that you report both according to MOOSE (after editors request) and according to PRISMA (as planned in your protocol) as you already have as all the subheadings of PRISMA has remained in the manuscript file. Please add information on the reporting guideline(s) in the first paragraph of the method section, design. 2. According to your answer and suppl. table 3, there is considerable heterogeneity of the definition of the outcome and the procedure used. Furthermore, there was limited information on the included participants of the studies. Though there are many sources of heterogeneity, yet you have chosen to include all studies in the meta-analysis. Therefore, the estimates of meta-analysis come with great limitations, which is also evident from the broad confidence intervals. I would recommend that you highlight this even further in your limitations section. 3. Thank you for the overview of all the included studies, this is very valuable to include in the review. Would you please add references in the table, so all the included studies can be safely identified. 6. Please add to the results section that the extra analysis was done post hoc.

REVIEWER	Lifeng Lin Florida State University
REVIEW RETURNED	25-Nov-2019

GENERAL COMMENTS	I thank the authors for addressing my previous comments. I do not have further comments on the revised version.

VERSION 2 – AUTHOR RESPONSE

Reviewer #1
Siv Fonnes
CPO, Department of Surgery, Herlev Hospital

Thank you for revising your manuscript accordingly. Below are the mentioned the number of the comment where questions or new comments have arisen after reviewing the changes to the manuscript.

1a. I would recommend that you report both according to MOOSE (after editors request) and according to PRISMA (as planned in your protocol) as you already have as all the subheadings of PRISMA has remained in the manuscript file. Please add information on the reporting guideline(s) in the first paragraph of the method section, design.
Authors: Thank you for the suggestion. We have revised as requested.

2. According to your answer and suppl. table 3, there is considerable heterogeneity of the definition of the outcome and the procedure used. Furthermore, there was limited information on the included participants of the studies. Though there are many sources of heterogeneity, yet you have chosen to include all studies in the meta-analysis. Therefore, the estimates of meta-analysis come with great limitations, which is also evident from the broad confidence intervals. I would recommend that you highlight this even further in your limitations section.
Authors: Thank you for the suggestion. We have revised as suggested.

3. Thank you for the overview of all the included studies, this is very valuable to include in the review. Would you please add references in the table, so all the included studies can be safely identified.
Authors: Thank you for the suggestion. We have added references.

6. Please add to the results section that the extra analysis was done post hoc.
Authors: Added as suggested.

Reviewer #2
Lifeng Lin
Florida State University

I thank the authors for addressing my previous comments. I do not have further comments on the revised version.
Authors: We thank the reviewer for the valuable comments that helped to improve the quality of the manuscript.

VERSION 3 – REVIEW

REVIEWER	Siv Fonnes CPO, Department of Surgery, Herlev Hospital
REVIEW RETURNED	06-Jan-2020

GENERAL COMMENTS	The authors have added all suggestions and I have no further comments.