

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form ([see an example](#)) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

TITLE (PROVISIONAL)	The timing of antibiotic administration in women undergoing caesarean section - a systematic review and meta-analysis
AUTHORS	Heesen, Michael; Klöhr, Sven; Rossaint, Rolf; Allegaert, Karel; Deprest, Jan; Straube, Sebastian

VERSION 1 - REVIEW

REVIEWER	Tim Pickles, Statistician, South East Wales Trials Unit, Cardiff University, Wales
REVIEW RETURNED	29-Oct-2012

GENERAL COMMENTS	<p>Quick summary:</p> <p>This systematic review and meta-analysis questions an existing result already reported by NICE. The paper is well written, and the statistical analyses are correctly undertaken and well reported. The discussion is fair given the findings, and notes any limitations.</p> <p>This paper is very close to publication standard but I would advise a few minor corrections and additions to build on what is already a very worthwhile piece of research. Some of these may be personal preference but I hope none are trivial.</p> <p>Abstract:</p> <ul style="list-style-type: none">• Insert 'skin' before 'incision'• 'More research is needed on this topic' is a null statement. Furthermore, this statement (thankfully) does not appear in the body of the paper so it should not appear in the abstract <p>(Assumed) Introduction:</p> <ul style="list-style-type: none">• Give this section a title <p>Methods:</p> <ul style="list-style-type: none">• MeSH undefined. It may be a common acronym for this topic but there is no harm in defining it <p>Results:</p> <ul style="list-style-type: none">• 'are given in Table 1', which shows ? What does it tell us? <p>Maternal Outcome:</p> <ul style="list-style-type: none">• Why is there no figure for the result of the 'preferred meta-analysis' of the five studies, or the 'supplementary meta-analysis' of seven studies?• Can the p-value for the result of the 'supplementary meta-analysis' of seven studies be removed? Most results presented in the text don't include them and they don't really add anything• Comma after 'For endometritis'• I don't see the want to re-do the endometritis meta-analysis with Nokiani et al. included. It doesn't add anything and the
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	<p>result is (reported) the same. If you choose to leave it then please remove the p-value from the report and this result.</p> <ul style="list-style-type: none"> • Report the wound infection result in the text, instead of just pointing to Figure 2c • The p-value reported from Witt et al. relating to UTIs does not serve a purpose here, as it is from a test comparing their antibiotic group (combined before and after) against their saline group. Please remove it <p>Neonatal outcome:</p> <ul style="list-style-type: none"> • There is no figure for the result of the NICU admission • There is no mention of which paper(s) provide the data for the NICU admission meta-analysis • Comma after 'receiving the antibiotic preoperatively' • 'The result of the meta-analysis showed', not 'The result of the meta-analysis was' • Space in '95%CI' • Why is there no figure for the infection result? • Why is there no figure for the neonatal sepsis result? • The result adding in Wax et al. is not interesting. It is obvious that it will give a similar (non-significant) result • Why is there no figure for the suspected sepsis result? <p>Discussion:</p> <ul style="list-style-type: none"> • 'high-quality' seems a little over-the-top when Nokiani et al. only scored 2 on the OQS! • Heterogeneity is only noted in Figure 2a. Given the lack of figures, or the report of I^2 in the text, I cannot tell if there is anymore. If there isn't then just note that the heterogeneity is in the result from Figure 2a. <p>Figure 1:</p> <ul style="list-style-type: none"> • Remove '# of' • Replace 'no RCTs' with 'trials, but not RCTs' <p>Checklist:</p> <ul style="list-style-type: none"> • Problems with page numbers from 'Introduction' onwards. For a start, the Introduction is on Page 5 • Is it acceptable for you to leave out items 12, 18 and 19? <ul style="list-style-type: none"> ◦ Study characteristics is partially held in Table 1 but could be so much more. For a large number of analyses (i.e., those without a figure), I don't know what numbers you have pulled from certain papers to create the result. A previously reviewed paper gave a whole section (within the methods) to this.
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REVIEWER	Kemal GUNGORDUK M.D.
	Istanbul Training and Research Hospital
REVIEW RETURNED	05-Nov-2012

GENERAL COMMENTS	This is a very well written clinical trial paper so it is suitable for the publication in the BMJ OPEN
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REVIEWER	Baha Sibai, M.d. professor of OB/ GYN , University of Texas at Houston
REVIEW RETURNED	21-Nov-2012

GENERAL COMMENTS	Since the findings reveal that giving antibiotics prior to cord clamping is associated with reduced rate of endometritis, the conclusions should recommend that it is advisable to use this method even though there are no differences in rates of wound infection.
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VERSION 1 – AUTHOR RESPONSE

2. Reviewer: Tim Pickles, Statistician, South East Wales Trials Unit, Cardiff University, Wales

Quick summary:

This systematic review and meta-analysis questions an existing result already reported by NICE. The paper is well written, and the statistical analyses are correctly undertaken and well reported. The discussion is fair given the findings, and notes any limitations.

This paper is very close to publication standard but I would advise a few minor corrections and additions to build on what is already a very worthwhile piece of research. Some of these may be personal preference but I hope none are trivial.

Reviewer:

Abstract:

- Insert 'skin' before 'incision'

Our response: Change performed.

- 'More research is needed on this topic' is a null statement. Furthermore, this statement (thankfully) does not appear in the body of the paper so it should not appear in the abstract

Our response: change performed.

(Assumed) Introduction:

- Give this section a title

Our response: Change performed.

Methods:

- MeSH undefined. It may be a common acronym for this topic but there is no harm in defining it

Our response: Change performed.

Results:

- 'are given in Table 1', which shows ? What does it tell us?

Our response: We added to the Results section: All five trials used cefazolin as the antibiotic but there was clinical heterogeneity between the studies, with regard to the dose of the antibiotic and with regard to the inclusion and exclusion criteria used in the studies.

Maternal Outcome:

- Why is there no figure for the result of the 'preferred meta-analysis' of the five studies, or the 'supplementary meta-analysis' of seven studies?

Our response: We omitted the supplementary analysis and focused only on randomized controlled double-blind trials!

- Can the p-value for the result of the 'supplementary meta-analysis' of seven studies be removed? Most results presented in the text don't include them and they don't really add anything

Our response: Change performed.

- Comma after 'For endometritis'

Our response: Change performed.

- I don't see the want to re-do the endometritis meta-analysis with Nokiani et al. included. It doesn't add anything and the result is (reported) the same. If you choose to leave it then please remove the p-value from the report and this result.

Our response: Change performed.

- Report the wound infection result in the text, instead of just pointing to Figure 2c

Our response: Change performed.

- The p-value reported from Witt et al. relating to UTIs does not serve a purpose here, as it is from a test comparing their antibiotic group (combined before and after) against their saline group. Please remove it

Our response: Change performed.

Neonatal outcome:

- There is no figure for the result of the NICU admission
- There is no mention of which paper(s) provide the data for the NICU admission meta-analysis

Our response: We now added a Figure 3 containing all analyses of neonatal outcome parameters.

- Comma after 'receiving the antibiotic preoperatively'

Our response: Change performed.

- 'The result of the meta-analysis showed', not 'The result of the meta-analysis was'

Our response: Change performed.

- Space in '95%CI'

Our response: Change performed.

- Why is there no figure for the infection result?
- Why is there no figure for the neonatal sepsis result?

Our response: We added a Figure 3 with all these data.

- The result adding in Wax et al. is not interesting. It is obvious that is will give a similar (non-significant) result

Our response: We omitted this phrase.

- Why is there no figure for the suspected sepsis result?

Our response: Change performed, a Figure was added to the new version.

Discussion:

- 'high-quality' seems a little over-the-top when Nokiani et al. only scored 2 on the OQS!

Our response: We omitted this phrase.

- Heterogeneity is only noted in Figure 2a. Given the lack of figures, or the report of I² in the text, I cannot tell if there is anymore. If there isn't then just note that the heterogeneity is in the result from Figure 2a.

Our response: Heterogeneity did not reach statistical significance. We added Figure 3 which now presents all meta-analyses including the corresponding I² values. Heterogeneity was present but never reached statistical significance. To deal with this issue we now wrote in the results section: All

five trials used cefazolin as the antibiotic but there was clinical heterogeneity between the studies, with regard to the dose of the antibiotic and with regard to the inclusion and exclusion criteria used in the studies.

Figure 1:

- Remove '# of'

Our response: Change performed.

- Replace 'no RCTs' with 'trials, but not RCTs'

Our response: Change performed.

Checklist:

- Problems with page numbers from 'Introduction' onwards. For a start, the Introduction is on Page 5

Our response: We deleted page numbering.

- Is it acceptable for you to leave out items 12, 18 and 19? Our response: Our literature list now ends with reference 13.

o Study characteristics is partially held in Table 1 but could be so much more. For a large number of analyses (i.e., those without a figure), I don't know what numbers you have pulled from certain papers to create the result. A previously reviewed paper gave a whole section (within the methods) to this.

Our response: We added the analyses in our new Figure 3 so that the data from the individual papers are also presented..

3. Reviewer: According to the suggestion raised by the referee Baha Sibai, M.d. professor of OB/GYN , University of Texas at Houston, we now wrote:

In conclusion, evidence provided by double blind RCTs suggests that only the risk for endometritis is reduced by antibiotic administration before skin incision; the corresponding NNT, i.e. 41, is quite high. No differences between the early administration versus the administration after cord clamping were observed for other maternal and neonatal outcome parameters. Nevertheless, it is advisable to administer antibiotics before skin incision.

4. Reviewer: We also responded to the issue of retrospective studies on antibiotic administration raised by the referee Mahmoud A Ismail, Professor Ob/GYN, University of Chicago by writing in our new version:

There are several studies with a large number of patients comparing pre-incisional antibiotic administration with administration after delivery. These studies found significant reductions in endometritis (12,13) and wound infection.(12,13,14) However, these studies were retrospective and not randomised. Thus they were more susceptible to bias. Furthermore, retrospective chart analyses are often flawed by the incomplete documentation of confounding factors.

This referee also criticized that "the ethics of pursuing a large randomized controlled trial may be questionable." Accordingly, we omitted this phrase in the new version.

VERSION 2 – REVIEW

REVIEWER	Mahmoud Ismail Professor Ob/Gyn University Of Chicago I have no competing interests.
REVIEW RETURNED	20-Mar-2013

- The reviewer completed the checklist but made no further comments.

Correction

Heesen M, Klöhr S, Rossaint R, *et al.* Concerning the timing of antibiotic administration in women undergoing caesarean section: a systematic review and meta-analysis. *BMJ Open* 2013;3:e002028. One of the authors' surnames is spelt incorrectly. 'Karel Allegeaert' should be 'Karel Allegaert'.

BMJ Open 2013;3:e002028corr1. doi:10.1136/bmjopen-2012-002028corr1