RESEARCH ARTICLE

Single dose ceftriaxone and metronidazole versus multiple doses for antibiotic prophylaxis at elective caesarean section in Mulago hospital: A randomized clinical trial [version 1; referees: 1 approved, 1 approved with reservations]

Gideon Alex Mugisa¹, Paul Kiondo², Imelda Namagembe¹ ¹,²

¹Department of Obstetrics and Gynecology, Mulago National Referral Hospital, Kampala, Uganda
²Department of Obstetrics and Gynaecology, Makerere University College of Health Sciences, Kampala, Uganda

Abstract

Objective: To compare the incidence of post-operative infections among mothers who received single dose pre-operative ceftriaxone and metronidazole compared to multiple doses after delivery by elective caesarean section.

Methods: This was (parallel, balanced randomization, 1:1) open label randomized controlled trial conducted Mulago Hospital, Department of Obstetrics and Gynaecology. Participants included in this study were pregnant women who had been admitted for elective caesarean section. The mothers were randomized to receive single dose of ceftriaxone and metronidazole minutes before the operation or multiple doses 30-60 during the operation and postoperatively. The primary outcome was post-operative wound infection. Secondary outcomes were clinical endometritis and febrile morbidity. The 174 eligible participants were randomized into one of the two treatment arms in a ratio of 1:1. The research assistants who collected the outcomes were blinded to the study allocation.

Results: Of the 174 eligible participants who recruited; 87 were randomized to the single dose group while 87 to the multiple doses group. The participants were recruited from 17th September 2015 up to 29th February 2016. All the participants were followed up for two weeks after delivery. Outcome data was available for 79 women in the single dose group and 81 women in the multiple dose group. There were no differences in the incidence of post-operative wound infections between the single dose arm versus the multiple dose arm (RR 1.895; 95% CI (0.2-21.4). There was no clinical endometritis and febrile morbidity observed during the 14 days of follow up.

Conclusion: Single dose pre-operative antibiotic prophylactic with ceftriaxone and metronidazole is as effective as multiple doses in prevention of post-operative infectious morbidity in women who undergo elective caesarean section. We recommend the use of single dose ceftriaxone and metronidazole in women undergoing elective caesarean section in our setting.

Trial registration: NCT02736682. Registration date, 7th April, 2016.

Keywords

Single dose antibiotic prophylaxis, elective caesarean section
Corresponding authors: Gideon Alex Mugisa (gideonmugisa@gmail.com), Imelda Namagembe (imeldanamagembe@gmail.com)

Author roles: Mugisa GA: Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Project Administration, Resources, Writing – Original Draft Preparation, Writing – Review & Editing; Kiondo P: Conceptualization, Methodology, Supervision, Writing – Review & Editing; Namagembe I: Conceptualization, Methodology, Supervision, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

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The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Introduction
The single most important risk factor for postpartum maternal infection is caesarean section. Women undergoing caesarean section have a 5-20-fold greater risk of infection and infectious morbidity compared with a vaginal delivery. (Gibbs, 1980; Smaill & Gyte, 2010)

Provision of single dose or combination broad spectrum intravenous antibiotics 30–60 minutes before the caesarean section has been found to reduce post-operative infections (Classen et al., 1992; Costantine et al., 2008; Kaimal et al., 2008). A review by Cochrane collaboration 2010 showed that prophylactic antibiotics reduced the incidence of endometritis and wound infection following either elective or emergency caesarean section by two thirds to three quarters. The purpose of antibiotic prophylaxis in surgical procedures not to sterilize tissues, but instead to reduce the colonization pressure of microorganisms introduced during surgery to a level that the patient’s immune system is able to overcome (Mugford et al., 1989). Prophylaxis does not prevent infection caused by postoperative contamination. (American College of Obstetricians and Gynecologists, 2003).

Rational use of prophylactic antibiotics prevents post-operative infections, reduces costs, saves nursing time, and development of antibiotic drug resistance (Seni et al., 2013; van Buul et al., 2012). Single dose pre-operative antibiotic prophylaxis has been demonstrated to be as effective as multiple antibiotic treatments in prevention of post-operative infections (Classen et al., 1992; Kaimal et al., 2008; Lyimo et al., 2013). Currently in Mulago hospital it is common practice for mothers for both elective and emergency caesarean section to receive post-operative treatment rather than pre-operative prophylaxis with multiple doses of antibiotics for three to seven days post-operation where otherwise a single dose may have been as effective. Single dose is cheaper than multiple doses, would save on staff time to attend to more sick patients and increase on availability of supplies to use such as sterile syringes and needles especially in low income settings.

The effectiveness of single dose pre-operative antibiotic prophylaxis for prevention of post operative infections such as wound infection, endometritis, and febrile morbidity among mothers delivered by elective caesarean section in Mulago hospital for a period after discharge has not been evaluated. In this study single dose ceftriaxone and metronidazole was compared with multiple doses.

The objective of this study was to compare the incidence of wound infection, clinical endometritis and febrile morbidity among mothers who received single dose versus multiple dose of ceftriaxone and metronidazole.

Methods
Trial registration: NCT02736682. This trial was registered on 7th April 2016.

This study has been reported according to the CONSORT checklist (Supplementary File 1)

Study design
This was a parallel, balanced randomisation, 1:1, randomized clinical trial (RCT) involving 174 women who delivered their pregnancy by elective caesarean section from 17th September 2015 to the 29th of February 2016.

Participants
Women recruited in the study were those that delivered by elective caesarean section for various reasons such as one previous scar with a contracted pelvis, two previous scars or more, major type placenta. Previous mothers were excluded from the study if they had a history of allergy to any of the drugs in the study, had infection at any site or elevated body temperature before going to theatre, had rupture of membranes, were in labour, had use of antibiotics in the last 7 days or were in WHO Clinical HIV/AIDS stage III and IV disease.

All the mothers were counselled and consented to participate in the study. After obtaining written informed consent, complete histories of the participants were taken using a structured questionnaire (Supplementary File 2).

Study setting
This study was conducted at Mulago National Referral Hospital Foetal Maternal Unit. Mulago hospital is a National Referral hospital for Uganda, and a teaching Hospital for Makerere University College of Health Sciences. Mulago hospital delivers 32,000 women annually, with a caesarean section rate of 26.14% (Department of Obstetrics and Gynecology annual report, 2013), and about 7–10% of caesarean sections are elective operations.

Interventions
The mothers were randomly assigned to one of the two treatment arms in a ratio of 1:1 using computer generated numbers. The mothers in the single dose arm (SD) received intravenous ceftriaxone at a dose of 2g and intravenous metronidazole 500mg 30–60 minutes before the caesarean section. Mothers in the multiple dose arm (MD) received intravenous ceftriaxone at a dose of 1g and intravenous metronidazole 500mg during the caesarean section, and there after received intravenous ceftriaxone 1g once daily and 500 mgs metronidazole every 8 hours for 3 days, and following discharge received metronidazole 400mgs 8 hourly and ampiclox 500 mgs 8 hourly for 5 days. The drugs used were EPICEFIN brand of ceftriaxone made by E.I.P.I.CO (Cairo, Egypt) and METROGYL brand of metronidazole made by Alphapharm Pty Limited (Brisbane, QLD, Australia).

Study procedure
Eligible mothers were identified from the wards by the research assistants who were trained midwives. The mothers were
conducted through an informed consent procedure and gave written informed consent. The Principal Investigator G.A.M confirmed the eligibility and conducted a clinical and obstetric examination.

Follow up
The mothers were reviewed by the principle investigator and research assistants within the first 6 hours after they returned from theatre and twice daily on post-operative day 1, 2, and 3 and thereafter on day 7 and 14. During the first 2–3 post-operative days, the mothers were reviewed twice daily for indicators of infection (temperature, pulse, blood pressure and respiratory rate), the size of the uterus, state of the incision wound, presence of tenderness, amount colour and smell of the lochia. On the 7th and 14th day post operatively the mothers returned to the postnatal ward and were examined again for presence of wound infection, abdominal tenderness and abnormal lochia.

Outcomes
The primary outcome was wound infection and the secondary outcomes were clinical endometritis and febrile morbidity.

Wound infection was defined as partial or total dehiscence, presence of purulent or serous discharge from the wound with indurations, warmth and tenderness. Clinical endometritis was defined as the presence of fever (38°C or above) in association with one or more of the following; uterine tenderness or foul smelling lochia. Febrile morbidity was defined as temperature above 38°C at least 4 hours apart on two or more occasions excluding the first 24 hours after delivery.

Once wound infection, clinical endometritis or febrile morbidity was identified a blood sample was taken for complete blood count and blood cultures as well as pus swabs for microscopy, culture, and sensitivity patterns. The patient was treated first empirically with broad spectrum antibiotics. When we received the culture and sensitivity results the treatment was then adjusted.

Sample size
We assumed that the proportion of participants in the multiple drug combination arm expected to develop wound infection to be 85.1% and 65.9% the single dose arm based on previous evidence from the literature (Dlamini et al., 2015). With these estimates a sample size of 174 participants would give a power of 80% at confidence level of 95%.

Randomization
Sequence generation: an independent pharmacist allocated the single dose or multiple dose regimens according to the computer generated randomization list. The women received the treatment at the time of operation.

Type: the randomisation sequence of ratio of 1:1 was generated using STATA 12 software package. Block sizes of 4 to 6 were used and these were randomly varied.

Allocation concealment: the single dose and multiple dose regimens were put in identical sealed packs. The packs were consecutively numbered for each participant by a researcher who was not involved in the clinical care and recruitment.

Implementation: an independent statistician who was not involved in the study did the randomization. The randomization list which was sent to the pharmacy was generated by computer randomization codes.

The eligible participants were allocated a study number by the research assistants who recorded the enrolment date and escorted the women to the pharmacy to receive the treatment assignment code and received the treatment package.

Blinding: those who assessed the outcomes were blinded to the study allocation.

Data analysis
Data were cleaned, coded and double entered into EPIDATA version 3.1 Software. It was then exported to STATA version 12.0 for analysis. Analyses were done using the intention-to-treat principle. All the mothers were analysed in the groups in which they were allocated. A midterm analysis was done when data from 50% of the sample size was collected. The results showed no evidence of greater than 10% difference in the two arms. Results were shared with the safety monitoring board.

The mothers who were lost to follow up were not included in the analysis of outcomes. Categorical variables were compared between groups using Chi squared test. Risks of outcomes were calculated and compared between the two treatment groups. The results are presented as risk ratios with their 95% confidence intervals.

Ethical considerations
The study was approved by Makerere University College of Health Sciences Ethics committee (# REC REF 2015-124). The participants gave written informed consent.

There were no adverse events that occurred as a result of the drugs used during the study. However in the event that it occurred an adverse event reporting form would be filled and patient treated.

Results
In total, 186 women were screened, of which 174 were eligible and were randomized: 87 (50%) to the single dose arm and 87 (50%) to the multiple doses arm. Loses to follow up were 6 (6.9%) in the single dose arm and 8 (9.2%) in the multiple doses arm. Some of the participants phones could not be reached while others had changed the residence (Figure 1). Figure 1, the flow chart suggested by the Consolidated Standards of Reporting Trials (CONSORT) of 2010 (Schulz et al., 2010), shows the enrolment and randomization of the women. The baseline
The characteristics of the participants is shown in Table 1. The two groups did not differ significantly in their baseline characteristics (maternal age, marital status, level of education, parity, number of previous scars and HIV status). There were no significant differences in the type of abdominal incision, duration of surgery and suture type used for skin closure.

The analysis was by intention-to-treat in that participants were analysed in the groups in which they were randomized. Six women in the single dose arm were lost to follow up and 81 women were available for the analysis of the final outcome and 8 women were lost to follow up the multiple doses arm and 79 were available for the final analysis. There were no significant differences in the mothers who were lost to follow up between groups regarding their baseline characteristics and there were no significant differences between the mothers who were lost to follow up and those who stayed in the study.

The primary outcome was post-operative wound infection. The incidence of post-operative wound infection in the single dose arm was 1.3% and in the multiple dose arm was 2.4% (RR: 1.895; 95% CI 0.2-21.4) (Table 2). There were no cases
Table 1. Socio demographic characteristics of mothers delivered by elective caesarean section in both arms.

<table>
<thead>
<tr>
<th></th>
<th>Single dose arm N=79 Count (%)</th>
<th>Multiple dose arm N=81 Count (%)</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>9(11)</td>
<td>12(15)</td>
<td>0.523</td>
</tr>
<tr>
<td>Married</td>
<td>70(87)</td>
<td>69(85)</td>
<td></td>
</tr>
<tr>
<td>Level of Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>none/primary</td>
<td>21(26)</td>
<td>33(41)</td>
<td></td>
</tr>
<tr>
<td>secondary/tertiary</td>
<td>58(74)</td>
<td>48(59)</td>
<td>0.06</td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>41(52)</td>
<td>34(43)</td>
<td></td>
</tr>
<tr>
<td>Formal employment</td>
<td>8(10)</td>
<td>12(15)</td>
<td>0.247</td>
</tr>
<tr>
<td>Business</td>
<td>30(38)</td>
<td>35(43)</td>
<td>0.316</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>3(4)</td>
<td>3(4)</td>
<td></td>
</tr>
<tr>
<td>20–30</td>
<td>54(68)</td>
<td>50(62)</td>
<td>0.927</td>
</tr>
<tr>
<td>&gt;=30</td>
<td>22(28)</td>
<td>28(35)</td>
<td>0.78</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;=2</td>
<td>16(20)</td>
<td>27(33)</td>
<td></td>
</tr>
<tr>
<td>3–4</td>
<td>46(58)</td>
<td>38(47)</td>
<td>0.063</td>
</tr>
<tr>
<td>&gt;4</td>
<td>17(22)</td>
<td>16(20)</td>
<td>0.214</td>
</tr>
<tr>
<td>Number of previous sections</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;=1</td>
<td>22(28)</td>
<td>35(43)</td>
<td></td>
</tr>
<tr>
<td>2 sections</td>
<td>28(35)</td>
<td>25(31)</td>
<td>0.136</td>
</tr>
<tr>
<td>&gt;=3</td>
<td>29(37)</td>
<td>21(26)</td>
<td>0.046</td>
</tr>
<tr>
<td>HIV status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>6(8)</td>
<td>11(14)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>73(92)</td>
<td>70(86)</td>
<td>0.225</td>
</tr>
</tbody>
</table>

Table 2. Summary of the outcomes in the two study arms of single dose (SD) and multiple dose (MD).

<table>
<thead>
<tr>
<th></th>
<th>SD- Count (%)</th>
<th>MD-Count (%)</th>
<th>RR (95%CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound infection</td>
<td>1(1.3)</td>
<td>2(2.4)</td>
<td>1.895(0.2-21.4)</td>
<td>0.605</td>
</tr>
<tr>
<td>Clinical endometritis</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Febrile morbidity</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

clinical endometritis or febrile morbidity in the single drug group or in the multiple drugs group.

The social demographics and pre-operative characteristics of the two groups were comparable (p-values have been incorporated too).

There was no evidence of clinical endometritis or febrile morbidity during the follow up period.

However there was superficial wound infection but the difference was not statistically significant in the two groups.

Discussion
This study was a randomized clinical trial in which single dose therapy of ceftriaxone and metronidazole was compared to multiple doses in women who were undergoing elective caesar-ean section on the incidence of postoperative wound infection.
Single dose therapy of metronidazole and ceftriaxone was as effective as multiple doses in the prevention of postoperative wound infection. There was no clinical endometritis and febrile morbidity observed.

This is in contrast with a study by Sullivan and Smith in a randomized controlled trial among both elective and emergency caesarean section. The total infectious morbidity and endometritis was found to be lower in the preoperative antibiotic group although there was no difference in the wound infection. This could be because this study included women with emergency caesarean section who are more likely to have bacterial contamination during labour and therefore preoperative administration of antibiotics are more beneficial. They found that the rates of endometritis of 1% versus 5% and wound infection of 3% versus 5% were less in the preoperative dose study arm compared to the perioperative dose arm and the difference for endometriosis was statistically significant. This was comparable to our study with wound infection of 1.3% in the intervention arm with single dose arm (study arm) and 2.4% in the control arm (standard practice using multiple doses) RR 95%CI 1.89(0.2-21.4) P value of 0.605 however no cases of clinical endometritis were observed.

However, the findings in our study were in agreement with a study by Alekwe and Kuti in Nigeria who compared single dose Ceftriaxone to multiple dose ampiclox, gentamycin and metronidazole among mothers delivered by elective caesarean section and found that the single dose was as effective as multiple doses for antibiotic prophylaxis. In that study, the incidence of endometritis (14% versus 15%), wound infections (7% versus 8%) and febrile morbidity (7% versus 6%) were higher than in our study as they used microbiology criteria rather than clinical criteria to confirm the diagnosis by doing endo-cervical wound swabs and mid stream urine sample on day 3 and 5 for culture and microscopy. They also found higher incidence of febrile morbidity which we did not find in any participant in our study. This differs from a study done by Sekikubo et al., 2005 in Mulago and Kawoolo hospitals comparing single dose ceftriaxone versus multiple doses of X-pen and gentamycin among mothers delivered by both emergency and elective caesarean section which found no wound infection in the single dose arm and 8.3% of wound infection in the multiple dose arm on the fourth day of discharge. In the single dose arm incidence of no post operative infections was comparable to the low incidence of 1.3% in my study for the single dose arm.

There was no clinical endometritis observed among these mothers in both arms as evidenced by no temperature of greater than 38°C in association of one or more of the following; foul smelling lochia or abdominal tenderness. The absence of endometritis in both arms may be because mothers delivered by elective caesarean section.

The absence of clinical endometritis in this study is comparable to other studies by Shakya & Sharma, 2010 where no cases of endometritis were seen in both the single dose and multiple dose arms among mothers delivered by elective caesarean section. Other studies, however, noted endometritis as one of the significant out comes (Alekwe et al., 2008) (Sullivan et al., 2007). In a non published RCT at Nairobi hospital comparing single dose versus multiple doses in elective caesarean section showed no evidence of endometritis as well as wound infection at 14 days of follow up (Unpublished study, Macharia et al., 2010).

There was absence of temperature greater than 38°C among mothers in both arms with a mean temperature of 36.4°C standard deviation of 0.5. This could have been a result of mothers taking antipyretics as part of their pain management. Other studies among mothers delivered by elective caesarean section however showed significant incidences of febrile morbidity of 4% and 6% in single and multiple dose arms (Shakya & Sharma, 2010) while in a non published study in Nairobi University by Martin Macharia showed that febrile morbidity was noted in 8.3% in both study arms.

The limitation in this study was that it was not possible to blind after randomization however at the time of follow up there was blinding of the research assistant.

In conclusion single dose preoperative antibiotic prophylactic dose of ceftriaxone and metronidazole gives as much protection from post-operative infections in elective caesarean section as multiple doses.

It is recommended that the use of single dose IV Ceftriaxone 2gm and 500mg of IV Metronidazole should be implemented as routine practice for elective caesarean section at Mulago Hospital.

Data availability
Data underlying this study are available on OSF: http://doi.org/10.17605/OSF.IO/W4JTR (Mugisa et al., 2018).

Data are available under the terms of the Creative Commons Zero “No rights reserved” data waiver (CC0 1.0 Public domain dedication).

Competing interests
No competing interests were declared.
Grant Information
Wide Spectrum Enterprise Uganda who provided the ceftriaxone for the study, and trainee Imelda Namagembe who supervised Mugisa Gideon during the writing, and conduct of this research up working on the manuscript is supported buy DELTAS Africa Initiative THRiVE-2 [DEL-15-011].

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Acknowledgments
First and foremost I would like to acknowledge God my Father the almighty for bringing me to this point. Special thanks to the research assistants Walabyeki, Shifa and Ashaba and colleagues who supported in one way or another. Last but not least, I would like to thank the dear study participants without whom this study would not take place and furthermore thanks to THRiVE-2 support for the skills offered to my research mentor Dr Imelda Namagembe to ensure we write this manuscript to disseminate the findings.

Supplementary Material
Supplementary File 1: CONSORT checklist.

Click here to access the data.

Supplementary File 2: Questionnaire to collect complete histories of participants.

Click here to access the data.

References


Department of Obstetrics and Gynaecology annual report: Mulago Hospital Data. 2013.


Open Peer Review

Current Referee Status: ✔️❓

Version 1

Referee Report 15 May 2018

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Ashraf Nabhan 1,2
1 Department of Obstetrics and Gynecology, Ain Shams University, Cairo, Egypt
2 Egyptian Center for Evidence Based Medicine, Heliopolis, Cairo, Egypt

1. Query the timing of the first dose in the multiple dose group.

2. The assumptions for sample size calculation are not accurate (revise the risk of wound infection in the cited study), based on infection in emergency CS, and markedly exaggerated. This renders the current study under-powered to detect a difference between groups. This is actually clearly shown in the analysis of all outcomes.

3. Query the method of analysis, was it an intention to treat? Please note that the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate.

4. Query the use of a third-generation cephalosporin for surgical prophylaxis.

5. Please cite the updated Cochrane reviews regarding timing of antibiotics, regimens, route of administration. These reviews are in the heart of your study.

6. Please do not use P values in baseline characteristics table (CONSORT compliance).

7. The trial registration needs some corrections for example this is not a cross over trial.

8. Query the new knowledge to gain from this study.

Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Partly

**Competing Interests:** No competing interests were disclosed.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

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**Fiona M Smaill**
Department of Pathology and Molecular Medicine, Faculty of Health Sciences, McMaster University, Hamilton, ON, Canada

In this study, the combination of ceftriaxone and metronidazole given pre-incision for elective cesarean section is compared with multiple doses started, I think, during the procedure and continued for a total of 8 days (3 days IV followed by 5 days po). Please confirm that the first dose given for the multiple dose group was given DURING the procedure, rather than before the incision.

Overall the study design is appropriate, definitions used for fever, wound infection and endometritis appropriate, and the methods adequately described. The method of randomization was adequate and although the study was not blinded, an attempt was made to ensure the assessment for infection was done independently of knowledge of the allocated group.

The numbers needed to calculate the sample size were based on a study done also at Mulago Hospital, comparing pre-incision or after the incision antibiotics in women undergoing EMERGENCY cesarean section. The rates of wound infection (according to my calculations) were 108/211 (51%) and 136/221 (62%), so I am unclear where the numbers quoted in this paper came from. Also these were rates in emergency cesarean section, which would have been higher, so the current study is very underpowered to detect a difference between groups. Ideally in the sample size calculation I think there should have been a comment about what difference between the two groups would have been clinically important (usually <10%) and possibly power the study for equivalence, using incidence rates for infection relating to elective c-section relevant to an African setting. Although then the study would have needed to be so large (with updated incidence numbers) it likely would have no longer been feasible. An interim analysis would likely have confirmed they were unlikely even with full enrolment to meet their goals, although this would have further complicated the power calculations. I would suggest a statistician be involved next time.

Hopefully, however, this study may have achieved its goal of changing practise locally, despite these limitations. It would be great if the authors could include in the methods and results what they did for knowledge translation and how the results have been implemented in changing practice. Including this
could be a very important outcome of the study and relevant likely in many other similar settings. Otherwise the results of the study do not add much to what is already known.

It is stated that the analysis was by intent to treat, but those women who were lost to follow-up were not included in the analysis, so it was not a true intent to treat analysis (when all lost to follow-up would have been treated as failures). It is however reasonable to only include those women in the analysis. Follow-up was for two weeks; while this will pick up many infections, infections occurring later would have been missed.

The way the inclusion criteria were written was unclear. Rather than saying "scar" refer to it as a previous cesarean section (or two). Similarly the term "major type placenta" is not familiar to me - I think we would refer to this as placenta praevia.

The rationale for choosing the combination of metronidazole and ceftriaxone for prophylaxis is not justified. While it is an effective regimen, it is relatively expensive and the metronidazole may be associated with more side-effects. Most guidelines recommend the use of a first generation cephalosporin. If there were data on the type and antibiotic resistance of bacteria isolated from post-cesarean infections usually seen at Mulago Hospital that informs this choice of antibiotic regimen, this could be included as justification.

Although there were only three infections, were there any culture results available? In the methods it is stated that cultures would be taken if infection occurred. This could provide useful information to know if infection occurred with a resistant organism.

It is commented that "there were no adverse events". In studies were antibiotics are given prior to the cord clamping (i.e. before the incision) and continued postpartum (during breast feeding), it would have been helpful to have included infant outcomes, although very few studies do this well. Were any data collected?

The references cited could include all the relevant Cochrane systematic reviews regarding timing of antibiotics (Mackeen et al) and regimens (Gyte et al), although ceftriaxone and metronidazole have not been specifically compared and it is unclear whether the broader spectrum regimen is indicated.

References

Is the work clearly and accurately presented and does it cite the current literature? Partly

Is the study design appropriate and is the work technically sound? Partly

Are sufficient details of methods and analysis provided to allow replication by others? Yes
If applicable, is the statistical analysis and its interpretation appropriate?  
Partly

Are all the source data underlying the results available to ensure full reproducibility?  
Yes

Are the conclusions drawn adequately supported by the results?  
Partly

**Competing Interests:** No competing interests were disclosed.

**Referee Expertise:** Infectious Diseases, Medical Microbiology, systematic reviews, infections in pregnancy

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.