PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Maternal Morbidity and Mortality from Severe Sepsis: A National Cohort Study
AUTHORS	Acosta, Colleen; Harrison, David; Rowan, Kathryn; Lucas, D. Nuala; Kurinczuk, Jenny; Knight, Marian

VERSION 1 - REVIEW

REVIEWER	Melissa E Bauer, D.O. Assistant Professor of Anesthesiology Director of Obstetric Anesthesiology Research University of Michigan Health System United States of America I have no specific conflicts of interest to declare. However, I also do research in maternal sepsis.
REVIEW RETURNED	06-May-2016

GENERAL COMMENTS	This work is from a well-respected group of researchers who have published multiple articles on maternal sepsis and have greatly expanded our knowledge of this disease as it pertains to maternal mortality and morbidity. The paper is well written and provides an important piece of data that fills a void in the literature about risk factors for death from maternal sepsis. My questions and comments are below. 1) Abstract- the abstract well summarizes the manuscript. 2) Introduction- It may be helpful to inform the reader about the difficulty of diagnosis of maternal sepsis due to physiologic changes of pregnancy. 3) Methods- Can you please expand upon further on how “deprivation” is determined and graded within the database? 4) Methods- Can you please explain why you chose to exclude ICU readmissions during the same hospital stay? There has been literature to suggest higher mortality with ICU readmissions in the general population. 5) Methods- As far as reporting hospitals, how is it determined which hospitals are reporting? Are they chosen to make up a representative sample of the population? Or is it voluntary? If voluntary, does it require certain resources in order to be a reporting hospital? Could there be disparities in poorer settings among which hospitals are reporting? 6) Table 2. Is there organism information in the database? Could the most common organism cultures be included here as well? 7) Table 3. Does the database have maternal comorbidity information as well? It may be interesting to see if certain immunocompromised disease states have an effect on mortality. 8) Discussion- Why do you think the sepsis admission rates were

	highest in women aged 16 to 19 years of age? It may be worth mentioning that although they had the highest rate of admission in that age group, the mortality was the lowest among all age groups for women less than 25 years of age. 9) Discussion- Why do you think socioeconomic status was a risk factor? Although there is socialized medicine available for all in the UK, are there still disparities in access to care? 10) Discussion- The paragraph explaining about educating pregnant and recently pregnant women about the symptoms and seeking early medical care is among the most important in the article. Could the authors please suggest how clinicians should educate patients more specifically as well as the importance of influenza vaccination? Overall, the manuscript provides very important information about this important cause of maternal mortality, and I look forward to future work from this group.

REVIEWER	Karen Orr and Esther Davis Department of Anaesthetics Antrim Area Hospital Northern Ireland
REVIEW RETURNED	19-May-2016

GENERAL COMMENTS	Overall it is a well presented paper that highlights clear issues and is easy to follow. Our feeling is that it presents more questions than answers which could be highlighted further. We have a few suggestions for consideration: 1. As well as the missing units and Scottish patients, potentially an additional source of missing patients includes those managed directly in labour ward in a high dependency area. Inclusion of these patients in future work would potentially be beneficial although not covered by ICNARC recording. 2. Some information regarding the demographics of the units not contributing data would be helpful i.e. number of deliveries, tertiary referral centre etc. This would aid the reliability of the data extrapolation the authors undertook if the missing units were broadly representative of the included units 3. Is any information available regarding the type of obstetric unit and outcome measures? I.e. does the size of the unit or tertiary referral status alter the observed effects? 4. Given the greatly increased risk of sepsis associated with caesarean section, it is correct, as has been done in the discussion section, that this is highlighted as an area of future work to attempt to elucidate cause and effect if possible. 5. Acknowledgement of the possibility of coding errors in ICNARC data from which the information was obtained. This may be of particular importance with regard to the low numbers of H1N1 infections seen in the study and the slight discrepancy with the published data in the CMACE report 6. Interesting comments regarding the relationship between affluence and mortality highlighting the need for future work to

	determine causative and potentially modifiable factors amongst the most deprived. 7. Although not appropriate for the years studied, acknowledgement of the recently updated sepsis definitions should be made. Reference 22 is used to define septic shock and given it is not a mainstream paper and is from 1984, a more updated paper should be identified. It isn't clear from the paper what the criteria were for either severe sepsis or septic shock in this study

REVIEWER	LJ Schlapbach University of Queensland, Australia
REVIEW RETURNED	30-May-2016

GENERAL COMMENTS	The authors provide an estimate of the incidence of maternal sepsis, using the ICNARC database of 198 ICUs in the UK from 2008-2010. They estimate that maternal sepsis results in 1.8 maternal deaths/100,000maternities, which is very similar to a previous UK study (UKOSS). Their data suggest that 1:6 maternal ICU admsissions is due to sepsis, with the highest risk in teenage pregnancies, and lower socioeconomic status. Comments: The paper demonstrates impact of social deprivation on increased risk of infection (as a striking example of health inequities within high income countries). The authors may consider putting this more into context in the discussion section (see for example Marmot. Lancet Volume 365, No. 9464, p1099–1104, 19 March 2005). Do the authors have data that would allow to compare their classification into severe sepsis/septic shock, with the recent Sepsis-3 update? Does the % ICU coverage report to the proportion of all UK ICUs contributing to the database, or to the % coverage of reporting amongst contributing ICUs? Does the database including private hospitals? Pathogen-specific causes of infection, including bacterial and viral causes, should be provided. In view of the predominance of respiratory infections, it would be interesting to know how many of these had viral pathogens identified.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

This work is from a well-respected group of researchers who have published multiple articles on maternal sepsis and have greatly expanded our knowledge of this disease as it pertains to maternal mortality and morbidity. The paper is well written and provides an important piece of data that fills a void in the literature about risk factors for death from maternal sepsis. My questions and comments are below.

1) Abstract- the abstract well summarizes the manuscript.
Thank you – no response required.

2) Introduction- It may be helpful to inform the reader about the difficulty of diagnosis of maternal sepsis due to physiologic changes of pregnancy.
We have added the following sentence as suggested:
Studies of maternal sepsis are also made more challenging due to the normal physiologic changes of pregnancy, which overlap with some of the pathophysiological changes of sepsis.

3) Methods- Can you please expand upon further on how “deprivation” is determined and graded within the database?
We have clarified this in the methods section:
Data on maternal age, deprivation (measured using the Index of Multiple Deprivation (IMD)), multiple births and stillbirths were obtained from the Office for National Statistics for England and Wales (ONS)[13], and the Northern Ireland Statistics and Research Agency.

4) Methods- Can you please explain why you chose to exclude ICU readmissions during the same hospital stay? There has been literature to suggest higher mortality with ICU readmissions in the general population.
We apologise for any confusion. Readmissions were excluded to avoid counting the same woman twice, however, all women, including those readmitted to ICU were followed up to final hospital discharge or death, so these women are all included in the assessment of mortality. We have clarified this in the paper.

5) Methods- As far as reporting hospitals, how is it determined which hospitals are reporting? Are they chosen to make up a representative sample of the population? Or is it voluntary? If voluntary, does it require certain resources in order to be a reporting hospital? Could there be disparities in poorer settings among which hospitals are reporting?
Reporting to the CMP is voluntary, but is not related to hospital resources in the UK where all hospitals are publicly funded, and thus it is unlikely that there are disparities in poorer settings among which hospitals are reporting. As we note in the limitations section, data on the characteristics of non-reporting hospitals were not available so we are unfortunately unable to compare them formally.

6) Table 2. Is there organism information in the database? Could the most common organism cultures be included here as well?
Unfortunately the infective organisms were not available for the purposes of this study and we have added this as a limitation.

7) Table 3. Does the database have maternal comorbidity information as well? It may be interesting to see if certain immunocompromised disease states have an effect on mortality.
The reviewer raises an interesting point. Unfortunately we do not have any further information on maternal comorbidity. We have, however, included a history of immunosuppression in table 3 to investigate immunocompromise from this perspective.

8) Discussion- Why do you think the sepsis admission rates were highest in women aged 16 to 19 years of age? It may be worth mentioning that although they had the highest rate of admission in that age group, the mortality was the lowest among all age groups for women less than 25 years of age.
The reviewer raises an important point. As individual level population data are not available we were unable to perform an adjusted analysis; it is therefore possible that the observed association with younger maternal age is confounded by deprivation, as this group are known to be more deprived that older women. We have added this to the discussion and highlighted that their mortality is lower.

9) Discussion- Why do you think socioeconomic status was a risk factor? Although there is socialized medicine available for all in the UK, are there still disparities in access to care?

The reviewer is correct. Although there is universally available healthcare in the UK, there are still socioeconomic differences in access. Women from lower socioeconomic groups, for example, are known to access care later that women living in less deprived areas. We have highlighted this as an area for future research as suggested by reviewer 2.

10) Discussion- The paragraph explaining about educating pregnant and recently pregnant women about the symptoms and seeking early medical care is among the most important in the article. Could the authors please suggest how clinicians should educate patients more specifically as well as the importance of influenza vaccination?
We have added, as suggested, the symptoms and signs the 2014 Confidential Enquiry into Maternal Death suggested women should be aware of, as well as emphasising the importance of influenza vaccination.

Overall, the manuscript provides very important information about this important cause of maternal mortality, and I look forward to future work from this group.
Thank you. No response required.

Reviewer: 2

Overall it is a well presented paper that highlights clear issues and is easy to follow. Our feeling is that it presents more questions than answers which could be highlighted further.

We have a few suggestions for consideration:

1. As well as the missing units and Scottish patients, potentially an additional source of missing patients includes those managed directly in labour ward in a high dependency area. Inclusion of these patients in future work would potentially be beneficial although not covered by ICNARC recording.
Thank you for this helpful suggestion. These women would have been included in the national study conducted through maternity units in 2011-12, but are not, as the reviewers point out, currently always captured through ICNARC. We have added a comment to this effect in the limitations.

2. Some information regarding the demographics of the units not contributing data would be helpful i.e. number of deliveries, tertiary referral centre etc. This would aid the reliability of the data extrapolation the authors undertook if the missing units were broadly representative of the included units
Unfortunately, as we note in the limitations, these data are not available, so we are unable to provide this.

3. Is any information available regarding the type of obstetric unit and outcome measures? I.e. does the size of the unit or tertiary referral status alter the observed effects?
This is an interesting point, however, we do not have any detail on the obstetric unit of origin of the women admitted to ICU (noting that not all women would have been admitted via an obstetric unit).

4. Given the greatly increased risk of sepsis associated with caesarean section, it is correct, as has been done in the discussion section, that this is highlighted as an area of future work to attempt to elucidate cause and effect if possible.
Thank you, no further response needed.

5. Acknowledgement of the possibility of coding errors in ICNARC data from which the information was obtained. This may be of particular importance with regard to the low numbers of H1N1 infections seen in the study and the slight discrepancy with the published data in the CMACE report.
We do not believe the observed data on H1N1 show a discrepancy with the MBRRACE-UK report

(the collaborator organisation which now runs the Confidential Enquiry into Maternal Death following the closure of CMACE), which described all the recent maternal deaths from H1N1 (32 women died from confirmed or probable H1N1 between 2009 and 2012). CMACE produced an interim report describing only 12 cases in 2010. Not all of these women survived to be admitted to ICU and would thus not all be captured within the ICNARC data. We have, however, noted in paragraph 2 on page 14, as suggested, that reporting of H1N1 may be incomplete in the ICNARC data.

6. Interesting comments regarding the relationship between affluence and mortality highlighting the need for future work to determine causative and potentially modifiable factors amongst the most deprived.
We have added this to the discussion as suggested.

7. Although not appropriate for the years studied, acknowledgement of the recently updated sepsis definitions should be made. Reference 22 is used to define septic shock and given it is not a mainstream paper and is from 1984, a more updated paper should be identified. It isn't clear from the paper what the criteria were for either severe sepsis or septic shock in this study.
As we note in the methods section, page 6, severe sepsis was defined according to a modified version of the PROWESS clinical trial definition [21]. Septic shock was defined as severe sepsis with cardiovascular organ system dysfunction [22]. As that was the definition we used, we cannot change the reference to a more recent one. As the reviewers quite rightly note, the most recent proposed changes to the sepsis definitions, published in 2016, are not appropriate to this study. The WHO is currently conducting a project to better define maternal sepsis, and we await the results of this project to further inform future research on maternal sepsis.

Reviewer: 3

The authors provide an estimate of the incidence of maternal sepsis, using the ICNARC database of 198 ICUs in the UK from 2008-2010. They estimate that maternal sepsis results in 1.8 maternal deaths/100,000maternities, which is very similar to a previous UK study (UKOSS). Their data suggest that 1:6 maternal ICU admissions is due to sepsis, with the highest risk in teenage pregnancies, and lower socioeconomic status.

Comments:
The paper demonstrates impact of social deprivation on increased risk of infection (as a striking example of health inequities within high income countries). The authors may consider putting this more into context in the discussion section (see for example Marmot. Lancet Volume 365, No. 9464, p1099–1104, 19 March 2005).
We have highlighted this further, and added a suggestion for further research as recommended by reviewer 2.

Do the authors have data that would allow to compare their classification into severe sepsis/septic shock, with the recent Sepsis-3 update?
Unfortunately we do not have these data, since the data for this study were collected several years before this new definition was proposed. See also response to reviewer 2 concerning the current WHO project to produce a definition appropriate for maternal sepsis.

Does the % ICU coverage report to the proportion of all UK ICUs contributing to the database, or to the % coverage of reporting amongst contributing ICUs? Does the database including private hospitals?
This refers to the percentage of all ICUs contributing data (page 6, third paragraph). In 2008, 2009 and 2010, 65.0%, 75.2% and 80.2% respectively of critical care units in England, Wales and Northern

Ireland reported to the database. There is only one private maternity hospital in the UK, and this does not have an ICU, thus private healthcare is not relevant in our context.

Pathogen-specific causes of infection, including bacterial and viral causes, should be provided. In view of the predominance of respiratory infections, it would be interesting to know how many of these had viral pathogens identified.
Unfortunately, as noted above, we do not have details of the pathogen-specific causes of infection and we have added this as a limitation. We did, however, have information on women with identified H1N1 infection, which we have included. As discussed above, however, the data on H1N1 may be incomplete.

VERSION 2 – REVIEW

REVIEWER	Melissa E Bauer D.O. Director of Obstetric Anesthesiology Research Assistant Professor of Anesthesiology University of Michigan Health System
REVIEW RETURNED	10-Jun-2016

GENERAL COMMENTS	The concerns I addressed with the initial review have been addressed to my satisfaction.

REVIEWER	Karen Orr Antrim Area Hospital, Northern Ireland
REVIEW RETURNED	21-Jun-2016

GENERAL COMMENTS	Many thanks for your replies to our and other reviewers comments with modifications as appropriate. Most of our questions were addressed however we feel that the reader would benefit from a fuller description of how severe sepsis and septic shock were defined for the purposes of study inclusion. This would allow easier applicability to the reader's own population

REVIEWER	Luregn Schlapbach University of Queensland, Australia
REVIEW RETURNED	01-Jul-2016

GENERAL COMMENTS	The authors have expanded the discussion section as suggested by the reviewers. Limitations in the dataset used are now clearly discussed.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Melissa E Bauer D.O.
Institution and Country: Director of Obstetric Anesthesiology Research, Assistant Professor of Anesthesiology, University of Michigan Health System, USA
Competing Interests: None declared

The concerns I addressed with the initial review have been addressed to my satisfaction.
Thank you. No response required.

Reviewer: 2
Reviewer Name: Karen Orr
Institution and Country: Antrim Area Hospital, Northern Ireland
Competing Interests: None declared

Many thanks for your replies to our and other reviewers comments with modifications as appropriate. Most of our questions were addressed however we feel that the reader would benefit from a fuller description of how severe sepsis and septic shock were defined for the purposes of study inclusion. This would allow easier applicability to the reader's own population.

We apologise that the definition was insufficiently detailed. We have expanded as follows:

Severe sepsis was defined according to a modified version of the PROWESS clinical trial definition[21]: diagnosis of infection as primary or secondary reason for critical care unit admission or laboratory confirmed/strongly suspected infection within the first 24 hours of critical care unit admission AND at least three Systemic Inflammatory Response Syndrome (SIRS) criteria AND evidence of at least one organ-system dysfunction. Septic shock was defined as severe sepsis with cardiovascular organ system dysfunction[22] (systolic blood pressure <90mmHg or mean arterial pressure <70mmHg or the use of vasoactive drugs for ≥1 hour in the first 24 hours).

Reviewer: 3
Reviewer Name: Luregn Schlapbach
Institution and Country: University of Queensland, Australia
Competing Interests: None declared

The authors have expanded the discussion section as suggested by the reviewers. Limitations in the dataset used are now clearly discussed.

Thank you. No response required.