PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Cost-benefit analysis of surveillance for surgical site infection following caesarean section
AUTHORS	Wloch, Catherine; Van Hoek, Albert Jan; Green, Nathan; Conneely, Joanna; Harrington, Pauline; Sheridan, Elizabeth; Wilson, Jennie; Lamagni, Theresa

VERSION 1 – REVIEW

REVIEWER	John Posnett Parexel Access UK I am a consultant to Essity, makers of Leukomed Sorbact post-operative surgical dressing.
REVIEW RETURNED	27-Jan-2020

GENERAL COMMENTS	The objective of the study is important and the analysis is appropriate. However, this draft needs some further work. The distinction between excess LOS of 5 days and 2.6 days is not clearly explained (pg. 4 and 11 and various other places in the text). I am still not sure what the difference is. Similarly, details of the costing should be more detailed. For example, which HRG codes were applied and why? The methodology of the costing exercise is not clearly explained. My main comment is around the estimate of the mean cost of an SSI following cesarean surgery. The estimated total cost of £18,914 amounts to an average of £246 per case. This is a very small cost which is significantly less than other estimates in the literature. For example, Jenks PJ, Laurent M et al (2014) estimate the median SSI cost following caesarian surgery in the NHS at £3,716 (95% ci £894-£4,905) at 2010/12 prices. Other relevant sources include Badia J M, Casey AL (2017) who provide a review of SSI costs and outcomes in 6 European countries, including UK. I would recommend the authors update their literature search to include more recent papers, and provide a convincing explanation of the reason for differences between their cost estimates and others in the literature. Taken with the need to explain methods more clearly, the very low cost estimates raise questions about the generalisability of this study.

REVIEWER	Stuart Mealing York Health Economics Consortium United Kingdom

	I am currently working on a consultancy project for Public Health England but it is not related to caesarian sections.
REVIEW RETURNED	13-Feb-2020

GENERAL COMMENTS	This interesting paper covers a lot of ground and in great depth so the authors should be commended in this. The paper is well written and reads well and the conclusions follow on from the results, with the limitations of the work clearly laid out in a fair and balanced way. The paper highlights that there has been a large increase in the number of caesarean sections performed over a 30 year period, and that the SSI infection rate is relatively high. This, to me, as a non-clinical reader meant I was expecting to see a very high financial burden on the UK NHS because of these procedures. I found the data sources and the methods used by the authors to analyses information to be correct and of an appropriate standard for this journal. I was very pleased to see how they performed the cohort study and the case-controlled paired matching approach was ideal. I have no doubt from looking at figure 1 that surveillance is efficacious in reducing infection rates. All this said, I was very surprised when I got to the results to see that the financial impact was negligible in the grand scheme of things. If I understand table 1 correctly, the cost of £21,619 covers 800 procedures leading to a cost per procedure of about £27. From the introduction, I made a calculation that about 1% of all SSIs are deep infections of the muscle and fascial layer or organ/ space infections. As such, I was expecting a lot higher SSI associated cost per procedure. The downward trend seems to be driven by the twin assumptions that 55% of all infections being detected in the community (table 1) and that 100% of these community identified infections are managed in the community (table 2). This seems unrealistic. Can the authors really be sure there are no hospital cost in these patients? Apart from that, my only minor gripe relates to the cost years used. In one part of the paper it says they are using 2010 costs but in another it looks like they are using 2017 values. Either way, the paper is looking to be published in 2020 so an update to all of these is needed to the most recent year possible before publication.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name

John Posnett

Institution and Country

Parexel Access

UK

Please state any competing interests or state ‘None declared’:
I am a consultant to Essity, makers of Leukomed Sorbact post-operative surgical dressing.

Please leave your comments for the authors below

R.
The objective of the study is important and the analysis is appropriate. However, this draft needs some further work.

The distinction between excess LOS of 5 days and 2.6 days is not clearly explained (pg. 4 and 11 and various other places in the text). I am still not sure what the difference is.

A.
A simple comparison of median length of stay for patients with and without an SSI during their initial inpatient stay results in a median difference of 5 days for this study. Whilst this is a common approach used, it would overestimate the excess length of stay attributable to SSI as it would fail to account for an increased likelihood of detecting an infection with longer length of stay, and the fact that patients with complex clinical needs (who would be kept in for longer) would also be more likely to develop infection. This study improved on this method by assessing excess length of stay attributable to SSI through calculating the mean average of paired differences for patients with and without SSI matched on risk factors and the length of time during which an infection could have been detected (inpatient stay). This provides a more robust estimate of excess length of stay attributable to the SSI (2.6 days), a key strength of our study. We have reformulated the description of this in the manuscript to make it clearer (p8,12,19).

R.
Similarly, details of the costing should be more detailed. For example, which HRG codes were applied and why? The methodology of the costing exercise is not clearly explained.
My main comment is around the estimate of the mean cost of an SSI following cesarean surgery. The estimated total cost of £18,914 amounts to an average of £246 per case. This is a very small cost which is significantly less than other estimates in the literature.
For example, Jenks PJ, Laurent M et al (2014) estimate the median SSI cost following caesarian surgery in the NHS at £3,716 (95% ci £894-£4,905) at 2010/12 prices. Other relevant sources include Badia J M, Casey AL (2017) who provide a review of SSI costs and outcomes in 6 European countries, including UK.

I would recommend the authors update their literature search to include more recent papers, and provide a convincing explanation of the reason for differences between their cost estimates and others in the literature.

A.
One of the strengths of this study is that it incorporates not only costs to secondary care but also costs arising from treatment of SSI in the community (by midwives and primary care). This naturally reduces the average cost per SSI. To make comparisons with other studies, which base their costs on infections managed in secondary care, we have added average costs restricted to inpatient and readmission infections (see page 13). This equates to approximately £1,800 per infection.

We note that our estimate remains substantially lower than the median cost of £3,716 calculated by Jenks et al for inpatient and readmission infections. This disparity may be explained by the Jenks study being based on only one hospital rather than a multi-centre study. Also, our matching of patients with and without SSI on time at risk as well as risk factors enhanced the risk-adjusted method to assess excess length of stay attributable to SSI (a risk matching method was used by Jenks which estimated excess length of stay as 4 days versus 2.6 in this study). Further comment has been added to the discussion (p20).

We have added further details of the costing to the manuscript (p12-14). There are few papers on costs of SSI following caesarean section (see Bluebell study 2019 summary of costs https://www.journalslibrary.nihr.ac.uk/hta/hta23390#/scientific-summary and Stanirowski et al 2019 https://doi.org/10.12968/jowc.2019.28.4.222 which both use Jenks et al data) but updates have been made to the literature review.

R.
Taken with the need to explain methods more clearly, the very low cost estimates raise questions about the generalisability of this study.

Reviewer: 2

Reviewer Name

Stuart Mealing

Institution and Country

York Health Economics Consortium
United Kingdom

Please state any competing interests or state 'None declared':
I am currently working on a consultancy project for Public Health England but it is not related to caesarian sections.

Please leave your comments for the authors below
R.
This interesting paper covers a lot of ground and in great depth so the authors should be commended in this. The paper is well written and reads well and the conclusions follow on from the results, with the limitations of the work clearly laid out in a fair and balanced way.

A. Thank you for these positive comments.

R.
The paper highlights that there has been a large increase in the number of caesarean sections performed over a 30 year period, and that the SSI infection rate is relatively high. This, to me, as a non-clinical reader meant I was expecting to see a very high financial burden on the UK NHS because of these procedures.
I found the data sources and the methods used by the authors to analyses information to be correct and of an appropriate standard for this journal. I was very pleased to see how they performed the cohort study and the case-controlled paired matching approach was ideal. I have no doubt from looking at figure 1 that surveillance is efficacious in reducing infection rates.
All this said, I was very surprised when I got to the results to see that the financial impact was negligible in the grand scheme of things. If I understand table 1 correctly, the cost of £21,619 covers 800 procedures leading to a cost per procedure of about £27. From the introduction, I made a calculation that about 1% of all SSIs are deep infections of the muscle and fascial layer or organ/ space infections. As such, I was expecting a lot higher SSI associated cost per procedure.

A.
The costs of managing SSIs in hospital were based on 44 SSIs identified in the cohort study. Restricting the analysis to inpatient and readmission detected SSI would equate to approximately

£1,800 per infection. We have added the number of SSIs managed in hospital to the Results section (p13).

R.
The downward trend seems to be driven by the twin assumptions that 55% of all infections being detected in the community (table 1) and that 100% of these community identified infections are managed in the community (table 2). This seems unrealistic. Can the authors really be sure there are no hospital cost in these patients?

A.
The parameters used in our paper are not based on estimates of the proportion of SSIs managed in the community or in hospital settings but based on findings from our previous largescale cohort study (Wloch et al 2012). This utilised a hierarchical approach to assign detection method such that if a patient reported (community treated) infection was also identified by the community midwife or other outpatient visit then the SSI was reported as detection by midwife or other hospital healthcare professional respectively. Similarly, if the patient was readmitted, then detection was recorded as 'at readmission'. As such, we feel confident that the majority of secondary care costs were identified. We have added further details to the methods to make this clear (p6-7).

We note that a study in Scotland by Johnson et al 2006 found similar proportions of superficial SSI to our cohort study and also identified a majority of SSI through follow-up by midwives which would not have been detected by inpatient and readmission surveillance alone (90% superficial, 71% diagnosed by midwife, compared to the cohort study: superficial infections 88% and proportion detected by midwife 55%).

R.
Apart from that, my only minor gripe relates to the cost years used. In one part of the paper it says they are using 2010 costs but in another it looks like they are using 2017 values. Either way, the paper is looking to be published in 2020 so an update to all of these is needed to the most recent year possible before publication.

A.
We have inserted further information to clarify the year in which our costs were based on (p 10-14). At the time of the calculations, 2017 was the last full year available. To recalculate the costs up to 2019 is possible but would take longer than the 4 weeks allowed for this revision. As inflation in the UK remains low (<2%), we don't consider this update would greatly influence the interpretation of our findings.

VERSION 2 – REVIEW

REVIEWER	Stuart Mealing York Health Economics Consortium
REVIEW RETURNED	02-Apr-2020

GENERAL COMMENTS	Overall, this is a well written paper that documents a piece of research that seems to be of a general high quality, and is certainly of the standard I would expect to see in this journal. I liked the fact that the authors included community costs and really like the case matching approach used to quantify the impact of SSIs on length of stay. The variables they have controlled for in this approach seem appropriate to me. The use of a floor effect on the amount of residual infection is something I've not come across

	before but seems sensible and logical and I'll be carrying it forward to any infection models that I work on in the future. The results from the work seem internally consistent (i.e. the changes in strategy seem to have results move in the right direction). Minor gripes in the paper, and suggestions for amendments are around unit costs and distributions used in the modelling. It seems like the cost year is 2017 which, given it's not 2020 feels a little long in the tooth and so the authors could update all the costs and re-run the results to bring it up to date. This shouldn't take too long. In terms of the distributions, I'm not sure I agree with the choice of a binomial distribution for costs (normally a very skewed variable) and a normal distribution for LOS (unbounded in either direction) since LOS cannot go below zero. I'd be happy to see the authors justification in their response to this review. Overall though, these are minor gripes and I think this is a really good paper.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2

Reviewer Name

Stuart Mealing

Institution and Country

York Health Economics Consortium

Please state any competing interests or state 'None declared':
None

Please leave your comments for the authors below

R.
Overall, this is a well written paper that documents a piece of research that seems to be of a general high quality, and is certainly of the standard I would expect to see in this journal. I liked the fact that the authors included community costs and really like the case matching approach used to quantify the impact of SSIs on length of stay. The variables they have controlled for in this approach seem appropriate to me. The use of a floor effect on the amount of residual infection is something I've not come across before but seems sensible and logical and I'll be carrying it forward to any infection models that I work on in the future.
The results from the work seem internally consistent (i.e. the changes in strategy seem to have results move in the right direction).
A.
Thank you for your encouraging comments

R.
Minor gripes in the paper, and suggestions for amendments are around unit costs and distributions used in the modelling. It seems like the cost year is 2017 which, given it's not 2020 feels a little long in the tooth and so the authors could update all the costs and re-run the results to bring it up to date. This shouldn't take too long.

A.
The results have been re-run with costs inflated to 2019 (the last available full year). The manuscript has been updated together with Tables 2 and 3 and Figures 2-8.

R.
In terms of the distributions, I'm not sure I agree with the choice of a binomial distribution for costs (normally a very skewed variable) and a normal distribution for LOS (unbounded in either direction) since LOS cannot go below zero. I'd be happy to see the authors justification in their response to this review.
A.
The binomial distribution was not used as a distribution for costs. We used reference cost without uncertainty, and used the binomial distribution to estimate the uncertainty for the SSI detection rate – for which there is a number of positives and a sample size.

We would also like to clarify that for length of stay a non-parametric approach was used for matching patients, with a jack-knife error estimate and a normal approximation was used for the standard error on the expected length of stay.

The manuscript has been updated to more clearly reflect these two points.

R.
Overall though, these are minor gripes and I think this is a really good paper.
A.
Thank you