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)	MODELLING THE ANNUAL NHS COSTS AND OUTCOMES ATTRIBUTABLE TO HEALTHCARE ASSOCIATED INFECTIONS IN ENGLAND
AUTHORS	Guest, Julian F.; Keating, Tomas; Gould, Dinah; Wigglesworth, Neil

VERSION 1 – REVIEW

REVIEWER	Carlos Magno Castelo Branco Fortaleza São Paulo State University, Brazil
REVIEW RETURNED	30-Aug-2019

GENERAL COMMENTS	This is a valuable study that addresses the financial impact and mortality of healthcare-associated infections in the UK. This issue is relevant to direct public health policies of infection prevention and control. Modelling parameters are well explained, though a relevant proportion of those parameters are based on assumptions (a topic that should be stressed among study limitations). The discussion, including limitation statements and conclusion, are generally appropriate and supported by results. Nevertheless, there are minor aspects that deserve correction or clarification. I list those topics bellow: 1. Though the study is described in the abstract as based on published data and clinical practice, most of data were obtained by systematic review of scientific and "gray" literature. This should be clearly stated in the abstract. 2. The discussion about hand hygiene in the introduction does not seem relevant to the focus of the paper, and could be suppressed. 3. In page 9 (data sources), a more detailed description of inclusion and exclusion criteria for articles found in searchs would improve clarity of the text. 4. In the same page, the search results should be placed in a PRISMA-oriented flowchart. 5. In page 10, the authors should explain their assumption that patients remain in ICU for average of 4 days. The same applies to assumptions about absenteims from work and others. 6. In the results, numbers provided for 2016/2017 seem to be "incidence", not "prevalence" data. 7. The discussion is generally clear, but I emphasize that other limitations, such as lots of data based on assumption 8. The authors state in the conclusion that "This study provides the best estimate available of NHS resource use and costs with which to inform policy and budgetary decisions pertaining to preventing and managing HCAIs." Not necessarily denying that no recent study had a similar approach, I think that those self-referent compliments may be prone to errors, especially given the amount of

	publications focusing on the clinical and financial impact of HCAIs. I suggest that authors tone down that statement, possibly by starting with "To our knowledge etc...". Those are minor aspects. I belive that this paper provides invaluable information for public health in the UK.

REVIEWER	Yara Halasa-Rappel Brandeis University, USA
REVIEW RETURNED	31-Aug-2019

GENERAL COMMENTS	I would like to thank the authors for this interesting manuscript. It addresses a very important and costly topic. My main concern is with the simplicity of the model you have used. Please see my comments below. Comment 1. Page 9 (10 pdf) line 60. What is the base of the assumption that 90% of HCP will stay home and 10% will continue to work or “attend”? Later in the manuscript, page 11 (12pdf) line 52, you mentioned hospitalization of HCPs. The assumption and sources used to justify this are not clear in the methods. Comment 2. Page 10 (11 pdf) line 14: Can you please justify the assumption made regarding the proportion of HCPs replaced by bank staff compared to agency staff? Why this allocation of 70% bank staff compared to 30% agency staff? And how does this vary across the different setting you have studied? Comment 3. Page 12 (13 pdf) lines 21-36: The sensitivity analysis results introduced a new level of the analysis; this should be covered in the methods and if needed could have its own subtitle in the results. I am assuming the authors included specialized hospitals as additional parameters to the sensitivity analysis which affect the volume and cost. The addition of specialized hospital is not uncertainty in the parameters, it is an additional level of the analysis. Comment 4. Page 27 (28pdf): Table 4 can you please explain the two numbers you presented and used in the analysis; in the columns following base case value column? Are they ranges, confidence intervals or what? This is not clear in the methods or the table. Comment 5. Page 16 (17 pdf) line 57: Simplicity is good, but it might hurt precision, Is there any reason why you didn’t breakdown your analysis by ward and type of infection? What is your justification for using averages? This is not clear to me

REVIEWER	Sarkis Manoukian Glasgow Caledonian University
REVIEW RETURNED	09-Sep-2019

GENERAL COMMENTS	This is a modelling study which attempts to estimate the cost of HAI to NHS England in 2016/2017. Unfortunately I cannot give my consent for this study to be published in its present form due to methodological issues that this study has. The authors do not take into account known biases when estimating the excess cost due to health care associated infections. This modelling study has the

	potential to confuse policymakers by inflating the cost of HAI. The mortality estimate seems extremely high given the number of deaths across Europe in a calendar year are estimated to be in the low 30 thousands. You can see in the following list the main problems I had with this study. 1) HAI is an umbrella term that describes many different infections which have different epidemiological attributes and differential impact on patients. For example HAIs can be resistant to antibiotics and this has a large impact on costs and mortality but this is not addressed in this paper. Taking average estimates from fairly old sources and uniformly applying those to all HAIs will inflate the costs due to infection. 2) I have problems with certain estimates that the authors used. Probability of death is based on a paper that used prevalence data across Europe in 2011-2012. Not sure how this translates to England. I'm not sure if it is a good idea to use an estimate from a modelling study to inform another modelling study and call that evidence. A key parameter in this study is coming from a good source use but still that good source is a modelling study in a different period with big limitations. What is the uncertainty around this number, we are given no information about this key parameter from the authors. 3) 9 Mean length of ward stay as a result of acquiring a HCAI. The authors claim that every HAI on average will add 9 days to length of stay and they give us NHS digital as the source. There has been a lot of research in this literature about how many excess days we expect for HAIs and we also know the methodological limitations of this research. For example see Graves N, et al. Estimating the cost of health-care infections: mind your p's and q's. Clin Infect Dis (2010); 50:1017-1021, and also Beyersmann J, et al Nosocomial infection, length of stay, and time-dependent bias. Infect Control Hosp Epidemiol (2009); 30:273-276. There is evidence to suggest that the majority of HAIs add no extra days to hospital stay. It is very difficult to accept a study that is basing the cost to a 9 day excess stay when no information is given about this number. Did you use a distribution and how did you come up with that. Where is the sensitivity analysis around this number? You can also read reference 10 in your manuscript that makes similar points. 4) In page 3 you call this an economic evaluation. Are you evaluating an intervention in your model? Is this an economic evaluation? I don't think your study is an economic evaluation and you shouldn't call it as such. This is modelling study that estimating the cost of HAI on the health sector. 5) We don't know anything about the model. What is the modelling approach? What kind of software did you use? How did you do the sensitivity analysis? I have seen many modelling papers but this is one of the very few that reports so little about the model. Have you used the Philips checklist as you should have done? If yes why not report it? 6) Issues with using reference costs to count the cost of HAI. By using reference costs you introduce bias in your estimates since reference costs do not reflect opportunity costs that should be used in economic analysis. If we prevent one infection do we actually save the cost of the bed day (times 9) that you report? That is very unlikely since we will still be paying for the staff and the buildings. If we had zero infections in a year we would not have an extra £2.1 billion to spend on the NHS as your study suggests. I would have liked to see a discussion of these issues.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1
Reviewer Name: Carlos Magno Castelo Branco Fortaleza Institution and Country: São Paulo State University, Brazil Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below This is a valuable study that addresses the financial impact and mortality of healthcare-associated infections in the UK. This issue is relevant to direct public health policies of infection prevention and control. Modelling parameters are well explained, though a relevant proportion of those parameters are based on assumptions (a topic that should be stressed among study limitations). The discussion, including limitation statements and conclusion, are generally appropriate and supported by results. Nevertheless, there are minor aspects that deserve correction or clarification. I list those topics bellow:
1. Though the study is described in the abstract as based on published data and clinical practice, most of data were obtained by systematic review of scientific and "gray" literature. This should be clearly stated in the abstract. The abstract has been amended. However, to the Authors' knowledge there is little unpublished work in relation to infection prevention and we do not know of any additional policy documents would add anything.
2. The discussion about hand hygiene in the introduction does not seem relevant to the focus of the paper, and could be suppressed. The Introduction has been amended accordingly.
3. In page 9 (data sources), a more detailed description of inclusion and exclusion criteria for articles found in searches would improve clarity of the text. The text has now been expanded.
4. In the same page, the search results should be placed in a PRISMA-oriented flowchart. That has now been included as a Supplementary Figure.
5. In page 10, the authors should explain their assumption that patients remain in ICU for average of 4 days. The same applies to assumptions about absenteeism from work and others. The references for these estimates (cited in Table 1) have now been incorporated into the text. Additionally, one of the clinical authors is a Director of Infection Prevention and Control at a large London-based hospital and another is a Professor of Nursing who works across several Trusts. It is NHS policy that any member of staff with an infection should remain absent from work until they are no longer infectious. However, in practice these authors estimated that 10% of staff members with an infection would attend work.
6. In the results, numbers provided for 2016/2017 seem to be "incidence", not "prevalence" data. This is not correct. The results report the annual number in the year. Notwithstanding this, in all probability prevalence becomes synonymous with incidence because the infections are successfully treated within a couple of weeks.
7. The discussion is generally clear, but I emphasize that other limitations, such as lots of data based on assumption This has already been stated in the study limitations section.
8. The authors state in the conclusion that "This study provides the best estimate available of NHS resource use and costs with which to inform policy and budgetary decisions pertaining to preventing and managing HCAIs." Not necessarily denying that no recent study had a similar approach, I think that those self-referent compliments may be prone to errors, especially given the amount of publications focusing on the clinical and financial impact of HCAIs. I suggest that authors tone down that statement, possibly by starting with "To our knowledge etc...". The Conclusion has been amended accordingly.

Those are minor aspects. I believe that this paper provides invaluable information for public health in the UK.

Reviewer: 2
Reviewer Name: Yara Halasa-Rappel

Institution and Country: Brandeis University, USA Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below I would like to thank the authors for this interesting manuscript. It addresses a very important and costly topic. My main concern is with the simplicity of the model you have used. Please see my comments below.

1. Page 9 (10 pdf) line 60. What is the base of the assumption that 90% of HCP will stay home and 10% will continue to work or "attend"? Later in the manuscript, page 11 (12pdf) line 52, you mentioned hospitalization of HCPs. The assumption and sources used to justify this are not clear in the methods. One of the clinical authors is a Director of Infection Prevention and Control at a large London-based hospital and the other is a Professor of Nursing who works across several Trusts. It is NHS policy that any member of staff with an infection should remain absent from work until they are no longer infectious. However, in practice these authors estimated that 10% of staff members with an infection would attend work. The sources for the assumptions (in Table 1) have now been incorporated into the text.
2. Page 10 (11 pdf) line 14: Can you please justify the assumption made regarding the proportion of HCPs replaced by bank staff compared to agency staff? Why this allocation of 70% bank staff compared to 30% agency staff? And how does this vary across the different setting you have studied? One of the clinical authors is a Director of Infection Prevention and Control at a large London-based hospital and the other is a Professor of Nursing who works across several Trusts. This estimate is based on practice at their respective hospitals. Nevertheless, changing this estimate has negligible affect o the results since the cost of absent HCPs being replaced by bank or agency staff accounts for <0.5% of the total annual cost attributable to HCAIs.
3. Page 12 (13 pdf) lines 21-36: The sensitivity analysis results introduced a new level of the analysis; this should be covered in the methods and if needed could have its own subtitle in the results. I am assuming the authors included specialized hospitals as additional parameters to the sensitivity analysis which affect the volume and cost. The addition of specialized hospital is not uncertainty in the parameters, it is an additional level of the analysis. The Methods and Results have been re-structured accordingly.
4. Page 27 (28pdf): Table 4 can you please explain the two numbers you presented and used in the analysis; in the columns following base case value column? Are they ranges, confidence intervals or what? This is not clear in the methods or the table. This omission has now been clarified in both the Methods and Results.
5. Page 16 (17 pdf) line 57: Simplicity is good, but it might hurt precision, Is there any reason why you didn't breakdown your analysis by ward and type of infection? What is your justification for using averages? This is not clear to me It was not possible to stratify the results by ward and type of infection due to the lack of granular data required to perform such an analysis. To have attempted to perform such an analysis with the available data would have resulted in considerable uncertainty in such findings.

Reviewer: 3
Reviewer Name: Sarkis Manoukian
Institution and Country: Glasgow Caledonian University Please state any competing interests or state 'None declared': No competing interests

Please leave your comments for the authors below This is a modelling study which attempts to estimate the cost of HAI to NHS England in 2016/2017. Unfortunately I cannot give my consent for this study to be published in its present form due to methodological issues that this study has. The authors do not take into account known biases when estimating the excess cost due to health care associated infections. This modelling study has the potential to confuse policymakers by inflating the

cost of HAI. The mortality estimate seems extremely high given the number of deaths across Europe in a calendar year are estimated to be in the low 30 thousands. You can see in the following list the main problems I had with this study.

1. HAI is an umbrella term that describes many different infections which have different epidemiological attributes and differential impact on patients. For example HAIs can be resistant to antibiotics and this has a large impact on costs and mortality but this is not addressed in this paper. Taking average estimates from fairly old sources and uniformly applying those to all HAIs will inflate the costs due to infection. This has now been addressed in the Study Limitations section.
2. I have problems with certain estimates that the authors used. Probability of death is based on a paper that used prevalence data across Europe in 2011-2012. Not sure how this translates to England. I'm not sure if it is a good idea to use an estimate from a modelling study to inform another modelling study and call that evidence. A key parameter in this study is coming from a good source use but still that good source is a modelling study in a different period with big limitations. What is the uncertainty around this number, we are given no information about this key parameter from the authors. The Authors are aware of the points raised by the reviewer but in the absence of more updated estimates, this pan-European estimate was used. Furthermore, there is no evidence to suggest that HCAI-related mortality in England would be any different to that of the other EU countries. Nevertheless, the impact of changing this value is shown in the sensitivity analysis in Table 4.
3. Mean length of ward stay as a result of acquiring a HCAI. The authors claim that every HAI on average will add 9 days to length of stay and they give us NHS digital as the source. There has been a lot of research in this literature about how many excess days we expect for HAIs and we also know the methodological limitations of this research. For example see Graves N, et al. Estimating the cost of health-care infections: mind your p's and q's. Clin Infect Dis (2010); 50:1017-1021, and also Beyersmann J, et al Nosocomial infection, length of stay, and time-dependent bias. Infect Control Hosp Epidemiol (2009); 30:273-276. There is evidence to suggest that the majority of HAIs add no extra days to hospital stay. It is very difficult to accept a study that is basing the cost to a 9 day excess stay when no information is given about this number. Did you use a distribution and how did you come up with that. Where is the sensitivity analysis around this number? You can also read reference 10 in your manuscript that makes similar points. The Authors are aware of the limitations surrounding estimates of extra length of stay due to HCAIs. Nevertheless, the limitations reported by Graves et al and Beyersmann et al are based on algorithms that are now more than 10 years old and patient pathways and resource use have changed considerably during that period. The reviewer states "There is evidence to suggest that the majority of HAIs add no extra days to hospital stay" but this may be anecdotal and not consistent with the meta-analysis by Manoukian et al (Reference 10) to which the reviewer referred. This meta-analysis calculated the number of excess days of hospital stay based on multistate modelling, group comparisons, matching samples, time-matched studies and regression analyses. The mean of each appears to be around 8-10 days with the exception of the regression analysis and the group comparison which appears to be around a mean of 3 and 16 days respectively. The matched samples comparisons are consistent with our own estimate of 9 days derived from hospital admissions statistics obtained from NHS digital. The impact of changing this value is reported in the sensitivity analyses in Table 4. The Discussion has now been expanded to incorporate this issue.
4. In page 3 you call this an economic evaluation. Are you evaluating an intervention in your model? Is this an economic evaluation? I don't think your study is an economic evaluation and you shouldn't call it as such. This is modelling study that estimating the cost of HAI on the health sector. This has been changed to economic study.
5. We don't know anything about the model. What is the modelling approach? What kind of software did you use? How did you do the sensitivity analysis? I have seen many modelling papers but this is one of the very few that reports so little about the model. Have you used the Philips checklist as you should have done? If yes why not report it? The Authors have attempted to be very transparent about

the model. The model structure and inputs have been reported in Figure 1 and Tables 1 and 2 and the sensitivity analyses have been explained in the text. Some of the text has now been expanded to enhance clarity.

6. Issues with using reference costs to count the cost of HAI. By using reference costs you introduce bias in your estimates since reference costs do not reflect opportunity costs that should be used in economic analysis. If we prevent one infection do we actually save the cost of the bed day (times 9) that you report? That is very unlikely since we will still be paying for the staff and the buildings. If we had zero infections in a year we would not have an extra £2.1 billion to spend on the NHS as your study suggests. I would have liked to see a discussion of these issues. The Authors have calculated costs in accordance with the guidance provided by the National Institute for Health and Care Excellence (NICE), which recommends the use of the National Schedule of Reference Costs. We would therefore prefer to leave our costs unchanged. Moreover, this is a burden of illness study and the Authors are reporting estimates of the annual cost of managing HCAIs. Consequently, the analysis does not address the consequences of preventing infections and the corresponding opportunity costs. Nevertheless, if one infection could be prevented then a mean of 9 bed days would be released for alternative use (by other patients). Whether money is saved or not depends on the new patient who occupies the bed and a discussion of this issue is beyond the remit of the article.

VERSION 2 – REVIEW

REVIEWER	Sarkis Manoukian Glasgow Caledonian University
REVIEW RETURNED	11-Oct-2019

GENERAL COMMENTS	I have now assessed the revised manuscript. The authors have made improvements and have responded to the reviewer's comments. However, significant problems remain and I still cannot give my consent for the paper to be published in it's current form due to methodological and other problems. See for specific details below: 1. Even though the authors have mentioned the issue of HAI being an umbrella term I would like to see a distribution of the main HAIs in the English NHS. For example, what is the proportion of UTIs out of the total? This information should be easily available and it will strengthen the paper. I'd like to see the main HAI types: BSI, CDI, SSI, UTI etc and the rest grouped in other. 2. We know that the majority of HAIs are UTIs and gastrointestinal infections (around 50% of the total). The meta-analysis that you refer to does not include UTIs but only focuses on CDI and BSI. This meta-analysis should not be used in this way as it was conducted to show that the methodology (time-dependent bias) has a big impact on excess length of stay estimates and not to be used as a standard meta-analysis. If you would like to use some figures from the meta-analysis then you should focus on CDI where the estimates in the matching (time) and multistate modelling are 3.66 and 2.32 excess days respectively. I would not recommend using the BSI estimates since these are based on heterogeneous studies based on different organisms unless you want to focus on individual studies. UTI has also been estimated in other studies to add between 0 and 2 excess days. CDI is one of the most common and serious gastrointestinal HAI. Therefore, the best estimates of excess LOS for about 50% of HAIs are less than 4 days. In your paper you take 9.1 days as the average excess LOS across all HAIs. This number greatly exceeds the above figures and in your sensitivity analysis you take values from 6.8 to 11.4 days which again are much higher to what we would expect to see. The most serious HAIs that would add around

	9 excess days are also the most uncommon (less than 10% of the total) but in your analysis you do not weight by type of HAI. I think it would be straightforward in your model to allow for different types of HAIs that have differential excess LOS rather than a 9.1 fits all number. If the most common HAIs add 2 or 3 days how can we accept a paper that is basing everything on 9 days? There is also good evidence that SSIs and pneumonias add approximately 5 days on average which means that more than 80% of infections would add much less than the 9.1 days you claim in your paper. I think you have to very seriously reconsider the 9.1 number. 3. Table 4: This table is slightly confusing. Did you vary simultaneously all variables by ±25% and report the results? Can we see the impact of individual variables? For example what happens if we vary incidence and keep everything else the same? I'd like to see this for 3 key variables: Incidence, Excess LOS and mortality. 4. I accept the fact that you need to use reference costs however you need to recognise the limitations of these costs when used for economic analysis. Economic analysis has a different purpose than accounting and this needs to be recognised and communicated to the reader. It would be good to refer to this paper A.J. Stewardson, S. Harbarth, N. Graves, T.S. Group Valuation of hospital bed-days released by infection control programs: a comparison of methods Infect Control Hosp Epidemiol, 35 (2014) when discussing valuation of bed-days. Occupied bed-days are much more important than what you call "cost" in your paper especially in a system such as the NHS. I'm personally more interested in the occupied bed-days lost due to HAI but it's important to make sure we use excess LOS estimates that do not suffer from time-dependent bias.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 3

Reviewer Name: Sarkis Manoukian

Institution and Country: Glasgow Caledonian University, UK Please state any competing interests or state 'None declared': None declared

I have now assessed the revised manuscript. The authors have made improvements and have responded to the reviewer's comments. However, significant problems remain and I still cannot give my consent for the paper to be published in it's current form due to methodological and other problems. See for specific details below:

1. Even though the authors have mentioned the issue of HAI being an umbrella term I would like to see a distribution of the main HAIs in the English NHS. For example, what is the proportion of UTIs out of the total? This information should be easily available and it will strengthen the paper. I'd like to see the main HAI types: BSI, CDI, SSI, UTI etc and the rest grouped in other.

Public Health England (PHE) makes reference to 2016/17 data but this information has never been made public. The most recent English data (that are published) are the 2011 estimates by the Health Protection Agency (HPA). These estimates indicate that within NHS England respiratory tract infections (pneumonia and other respiratory infections) account for 22.8% of all HCAIs; urinary tract infections (UTI) for 17.2%; surgical site infections (SSI) for 15.7%; clinical sepsis for 10.5%; gastrointestinal infections for 8.8% and bloodstream infections (BSI) for 7.3%. C. difficile infections account for 5.6% of all infections within NHS England. The Introduction has now been made clearer.

2. We know that the majority of HAIs are UTIs and gastrointestinal infections (around 50% of the total).

This is not correct. The most recent estimates (above) suggest that these infections account for only 30% of the total.

The meta-analysis that you refer to does not include UTIs but only focuses on CDI and BSI. This meta-analysis should not be used in this way as it was conducted to show that the methodology (time-dependent bias) has a big impact on excess length of stay estimates and not to be used as a standard meta-analysis. If you would like to use some figures from the meta-analysis then you should focus on CDI where the estimates in the matching (time) and multistate modelling are 3.66 and 2.32 excess days respectively. I would not recommend using the BSI estimates since these are based on heterogeneous studies based on different organisms unless you want to focus on individual studies. UTI has also been estimated in other studies to add between 0 and 2 excess days. CDI is one of the most common and serious gastrointestinal HAI. Therefore, the best estimates of excess LOS for about 50% of HAIs are less than 4 days. In your paper you take 9.1 days as the average excess LOS across all HAIs. This number greatly exceeds the above figures and in your sensitivity analysis you take values from 6.8 to 11.4 days which again are much higher to what we would expect to see. The most serious HAIs that would add around 9 excess days are also the most uncommon (less than 10% of the total) but in your analysis you do not weight by type of HAI. I think it would be straightforward in your model to allow for different types of HAIs that have differential excess LOS rather than a 9.1 fits all number. If the most common HAIs add 2 or 3 days how can we accept a paper that is basing everything on 9 days? There is also good evidence that SSIs and pneumonias add approximately 5 days on average which means that more than 80% of infections would add much less than the 9.1 days you claim in your paper. I think you have to very seriously reconsider the 9.1 number.

With all due respect to the Reviewer, his percentages are not consistent with those reported by the HPA. Additionally, the incremental length of hospital stay due to infections has been reported to be a mean of 9.1 days in NHS England's Hospital Episode Statistics on admitted diagnosis 2016-17. Notwithstanding this, we have performed sensitivity analysis showing the impact on the results of changing the length of stay.

3. Table 4: This table is slightly confusing. Did you vary simultaneously all variables by ±25% and report the results? Can we see the impact of individual variables? For example what happens if we

vary incidence and keep everything else the same? I'd like to see this for 3 key variables: Incidence, Excess LOS and mortality.

In the Methods section, it states: "Deterministic sensitivity analyses were undertaken to examine the effect of independently varying the values of individual parameters within the model. The parameter estimates were individually varied over plausible ranges by altering them to ±25% around the base case value. However, the percentages were bounded by 0% and 100%. The Results section has now been amended to include this. The sensitivity analysis already includes Incidence, Excess LOS and mortality.

4. I accept the fact that you need to use reference costs however you need to recognise the limitations of these costs when used for economic analysis. Economic analysis has a different purpose than accounting and this needs to be recognised and communicated to the reader. It would be good to refer to this paper A.J. Stewardson, S. Harbarth, N. Graves, T.S. Group Valuation of hospital bed-days released by infection control programs: a comparison of methods Infect Control Hosp Epidemiol, 35 (2014) when discussing valuation of bed-days. Occupied bed-days are much more important than what you call "cost" in your paper especially in a system such as the NHS. I'm personally more interested in the occupied bed-days lost due to HAI but it's important to make sure we use excess LOS estimates that do not suffer from time-dependent bias.

The Sensitivity Analysis has been expanded to show the impact of changing the daily cost of bed occupancy. This analysis already showed the impact of changing the number of occupied bed days lost due to HCAIs. Additionally, the Study Limitations section now includes a reference to the disparity between accounting and economic costing of hospital beds.

Notwithstanding this, the article by Stewardson et al referred to by the reviewer focussed on eleven European public hospitals, all of which were tertiary hospitals, except one secondary hospital in Italy. Furthermore only two hospitals were from the UK. Stewardson et al recognised that one limitation of their study is that it measured purchase intention rather than real payment. Additionally, they found that the WTP values they estimated were significantly higher among hospitals with DRG-based reimbursement, but this was not the case among the accounting values. Consequently, the actual economic value of occupied bed days in district general hospitals in the UK is unknown.

VERSION 3 – REVIEW

REVIEWER	Sarkis Manoukian Glasgow Caledonian University, School of Health and Life Sciences
REVIEW RETURNED	18-Nov-2019

GENERAL COMMENTS	On page 2 in the limitations of the study you say: The results may be confounded by assumptions around the epidemiology of HCAIs, excess length of hospital stay and outpatient appointments. However, there is no discussion in the limitations section in the end about the issues around your excess length of stay estimates. Your limitations sections at the end of the text should include a statement similar to the following: This study does not take into account time-

	dependent bias and is based on time-fixed excess length of stay due to HAI estimates. Your sensitivity analysis shows that varying length of stay due to HAI has a very big impact on your results. There is one billion pounds difference between the low and high estimate which is very substantial. However, you have the following statement on page 13: "Varying the other model inputs and assumptions appeared to have a minimal impact on the results." Change this statement and be clear about the impact of the "LOS due to HAI" sensitivity analysis on your results. Right now you do not mention LOS due to HAI at all in the sensitivity analysis paragraph when it is having a massive impact. This is very misleading for the reader. Be specific about reference 15. Where exactly on that page, or excel file, the reader can find the 9.1 days figure you reference? Reference that specific file or pdf rather than the generic page. Can you say something about the methodology NHS England used to calculate the 9.1 figure on the main text?

VERSION 3 – AUTHOR RESPONSE

Reviewer's Comments to Author:

Reviewer: 3
Reviewer Name: Sarkis Manoukian
Institution: GCU
Please state any competing interests or state ‘None declared’: None declared

On page 2 in the limitations of the study you say: The results may be confounded by assumptions around the epidemiology of HCAIs, excess length of hospital stay and outpatient appointments. However, there is no discussion in the limitations section in the end about the issues around your excess length of stay estimates. Your limitations sections at the end of the text should include a statement similar to the following: This study does not take into account time-dependent bias and is based on time-fixed excess length of stay due to HAI estimates.
This has now been included in the limitations section on Page 2.

Your sensitivity analysis shows that varying length of stay due to HAI has a very big impact on your results. There is one billion pounds difference between the low and high estimate which is very substantial. However, you have the following statement on page 13: "Varying the other model inputs and assumptions appeared to have a minimal impact on the results." Change this statement and be clear about the impact of the "LOS due to HAI" sensitivity analysis on your results. Right now you do not mention LOS due to HAI at all in the sensitivity analysis paragraph when it is having a massive impact. This is very misleading for the reader.
Length of stay arising from HCAIs was included in this section, but the text has been amended to clarify this.

Be specific about reference 15. Where exactly on that page, or excel file, the reader can find the 9.1 days figure you reference? Reference that specific file or pdf rather than the generic page. Can you say something about the methodology NHS England used to calculate the 9.1 figure on the main text?
What the reviewer is asking for is not so easy. The mean of 9.1 days is our estimated mean derived from 95 ICD 10 classification codes pertaining to 1.66 million Finished Consultant Episodes of patients with an infection in the Hospital Episode Statistics for England for 2016/17. However, to corroborate this we analysed excess length of hospital stay documented in a difference source, i.e.

the NHS Reference Costs for England. Analysis of the NHS Reference Costs suggested that the length of hospital stay for patients with a code for an infection was a mean of 9 days per patient in 2016/17. However, the excess length of hospital stay for patients with the same code was a mean of 29.4 days per patient in 2016/17. Clearly, there is uncertainty surrounding the excess length of hospital stay arising from infection. However, most Hospital Directors of Infection Control in England would confirm that hospital bed-occupancy arising from an HCAI has become very problematic. Page 9 in the Methods and page 14 in the Discussion have been amended accordingly.

VERSION 4 – REVIEW

REVIEWER	Sarkis Manoukian Glasgow Caledonian University
REVIEW RETURNED	09-Dec-2019

GENERAL COMMENTS	Page 2 Strengths and limitations: Change to "does not take into account time-dependent bias" .Do not use article "a" before time-dependent bias. Repeat the above statement in the limitations section of the study on page 18 of the revised manuscript. Say something similar to: "it was not possible to estimate excess LOS using a time-varied methodology with the available data. We recognise that our estimates of excess LOS may suffer from time-dependent bias and therefore could be overestimated. Deterministic analysis showed that our results were sensitive to the excess LOS estimate and caution should be exercised when interpreting our results" Add an appropriate reference: #10 from your list of references and this study which makes a similar argument and although focusing on CDI still is relevant to your work: "Heister T, Wolkewitz M, Hehn P, Wolff J, Dettenkofer M, Grundmann H, Kaier K. Costs of hospital-acquired Clostridium difficile infections: an analysis on the effect of time-dependent exposures using routine and surveillance data. Cost Eff Resour Alloc. 2019 Aug 1;17:16. doi: 10.1186/s12962-019-0184-5."

VERSION 4 – AUTHOR RESPONSE

Reviewer's Comments to Author:

Reviewer: 3
Reviewer Name: Sarkis Manoukian
Institution and Country: Glasgow Caledonian University, UK Please state any competing interests or state ‘None declared’: None declared

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This change has been made.

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