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)	The cost of hospitalised patients due to complicated urinary tract infections – A retrospective observational study in countries with high prevalence of multidrug resistant Gram-negative bacteria: the COMBACTE-MAGNET, RESCUING study
AUTHORS	Vallejo Torres, Laura; Pujol, Miquel; Shaw, Evelyn; Wiegand, Irith; Vigo, Joan Miquel; Stoddart, Margaret; Grier, Sally; Gibbs, Julie; Vank, Christiane; Cuperus, Nienke; van den Heuvel, Leo; Eliakim-Raz, Noa; Carratala, Jordi; Vuong, Cuong; MacGowan, Alasdair; Babich, Tanya; Leibovici, Leonard; Addy, Ibironke; Morris, Stephen

VERSION 1 – REVIEW

REVIEWER	Marya Zilberberg EviMed Research Group, LLC, USA I have published studies related to cUTI and antimicrobial resistance
REVIEW RETURNED	20-Nov-2017

GENERAL COMMENTS	This is a secondary analysis of a primary retrospective international cohort study aiming to define multidrug resistance in the setting of cUTI. The study is fairly well done and reported completely. My one observation is that there is an awful lot of complicated statistical discussion when the main aim of the study was simply to report out an unadjusted cost of hospitalization with cUTI as the principal diagnosis. Granted, a secondary aim was to model what factors increase this cost, but the fact remains that the primary aim was quite simple, though important. The simplicity of this aim gets somewhat lost in the cumbersome description of all the methods, which can be cut substantially. The more complex parts of the study should be called out and discussed in greater detail; namely, the components of costs, regional variations (it may be of interest for the authors to actually look into the different models of care to explain the vast differences in the LOS, etc. between participant nations). The factors that contribute to higher costs are not altogether surprising, but do require some contextualizing in the discussion -- other literature that has found this, compare and contrast? Finally, though the authors make a point of hedging the generalizability of their results (applies only to principal dx cUTI), they fail to put that into any kind of a context. For example, what proportion of all cUTI does this represent? What are the implications of this being community-onset cUTI for the prevalence of MDR pathogens?

	Just as a note, in the US I am able to get at a very accurate and generalizable estimate for hospital costs of cUTI hospitalizations (based on all the ICD-9-CM codes utilized in the paper) with just a few keystrokes at the HCUPNet web site, where I learned that cUTI as the principal diagnosis comprises only about 1/6th of all cUTI hospitalizations. The average cost, by the way, was $6,600 per case in 2014, with a LOS of 4 days. In short, I believe the data are of interest, but the paper can be shortened substantially to focus on some of the points I suggested above.

REVIEWER	Andrew Stewardson Monash University, Australia
REVIEW RETURNED	22-Nov-2017

GENERAL COMMENTS	The authors perform a multinational retrospective observational study to estimate the cost of admission for complicated urinary tract infection in several European countries and Israel. This study is reported clearly and provides valuable information which could be used to inform future cost-effectiveness models. The fact that unit cost data is derived from three hospitals in Spain is a limitation, however this is clearly described and resource consumption data is clearly presented. It's interesting to note the variation in length of stay between the different countries. Could I ask the authors to consider the following points: - Page 9, Line 23: Cost of day in hospital is challenging to estimate and the authors report difficulty in obtaining this information (and other unit cost data) for countries other than Spain. Did the authors consider using the WHO-CHOICE health service delivery 'hotel' costs (http://www.who.int/choice/cost-effectiveness/inputs/health_service/en/), which was used for similar purpose by the BURDEN study (https://doi.org/10.1371/journal.pmed.1001104)? This may assist in capturing the heterogeneity of 'bed day' unit cost between different participating countries. - Page 10: Regarding cohort characteristics, is it possible to provide further information about the reasons that the cases were classified as 'complicated'. e.g. functional abnormality, structural abnormality, male, pregnancy etc. Also, could a brief comment be made about relative frequency of causative organisms? - Page 11, Line 32: "We also adjust for clustering at the site level and control for the patient episode number." How was this done? Random effect? - What definition was used for MDR? - Page 11, Table 1: It would be useful for future studies that wish to use these results to inform cost-effectiveness studies (and characterise uncertainty) to include 95% confidence intervals for the marginal effects. - Page 10, Line 58: Could the authors please clarify how 'source of infection' is defined? Urinary catheterisation and pyelonephritis don't seem to me to be mutually exclusive. - Page 11, Line 22: "Values between 5 and 10% are regarded as weakly significant." Is this accepted practice for economic evaluation? Could I suggest it would be more useful to report 95% confidence intervals for marginal estimates (see above) rather than p-values.

	- Page 14, Line 38: Interesting to note that 80% of cost is driven by length of stay, which means that the result is sensitive to changes in the unit price of a bed-day. There is an argument that when looking at bed-day cost from a short term hospital perspective, that an accounting cost (which appears to be used here) overestimates the value of a bed-day. This is because most hospital costs are fixed and cannot be recouped even if the admission is avoided. One alternative is an opportunity cost i.e. the value of a bed day if freed up for use for other purposes e.g. elective surgery (PMID: 25203185). Did the author consider this approach? Minor - Table 1: 9% of admissions for cUTI are "elective". How can an admission for cUTI be elective? Is this a coding error?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Marya Zilberberg
Institution and Country: EviMed Research Group, LLC, USA
Competing Interests: I have published studies related to cUTI and antimicrobial resistance

Comment: This is a secondary analysis of a primary retrospective international cohort study aiming to define multidrug resistance in the setting of cUTI. The study is fairly well done and reported completely. My one observation is that there is an awful lot of complicated statistical discussion when the main aim of the study was simply to report out an unadjusted cost of hospitalization with cUTI as the principal diagnosis. Granted, a secondary aim was to model what factors increase this cost, but the fact remains that the primary aim was quite simple, though important. The simplicity of this aim gets somewhat lost in the cumbersome description of all the methods, which can be cut substantially.

Response: We have cut the description of the methods in the paper and we now provide the statistical details as supplementary material.

Comment: The more complex parts of the study should be called out and discussed in greater detail; namely, the components of costs, regional variations (it may be of interest for the authors to actually look into the different models of care to explain the vast differences in the LOS, etc. between participant nations).

Response: We now discuss in greater detail the findings regarding cost components and regional variations in the Discussion section.

Comment: The factors that contribute to higher costs are not altogether surprising, but do require some contextualizing in the discussion -- other literature that has found this, compare and contrast?

Response: We have included in the Discussion section a comparison with other studies looking at the factors contributing to higher costs in these patient group.

Comment: Finally, though the authors make a point of hedging the generalizability of their results (applies only to principal dx cUTI), they fail to put that into any kind of a context. For example, what proportion of all cUTI does this represent? What are the implications of this being community-onset cUTI for the prevalence of MDR pathogens?

Response: We now indicate the proportion of cUTI that are principal dx for hospital admission and the prevalence of causative pathogens in this sample.

Comment: Just as a note, in the US I am able to get at a very accurate and generalizable estimate for hospital costs of cUTI hospitalizations (based on all the ICD-9-CM codes utilized in the paper) with just a few keystrokes at the HCUPNet web site, where I learned that cUTI as the principal diagnosis comprises only about 1/6th of all cUTI hospitalizations. The average cost, by the way, was $6,600 per case in 2014, with a LOS of 4 days.

Response: We thank the reviewer for checking and sharing this information.

Comment; In short, I believe the data are of interest, but the paper can be shortened substantially to focus on some of the points I suggested above.

Response: As mentioned above, we have shortened the explanation about the statistical methods to focus more on the discussion about cost components, regional variations and placing into context the findings of this study. We were unable to shorten the paper overall following the changes that were required to address the comments made by the other Reviewer, as described below.

Reviewer: 2
Reviewer Name: Andrew Stewardson
Institution and Country: Monash University, Australia
Competing Interests: None declared.

The authors perform a multinational retrospective observational study to estimate the cost of admission for complicated urinary tract infection in several European countries and Israel. This study is reported clearly and provides valuable information which could be used to inform future cost-effectiveness models. The fact that unit cost data is derived from three hospitals in Spain is a limitation, however this is clearly described and resource consumption data is clearly presented. It's interesting to note the variation in length of stay between the different countries.
Could I ask the authors to consider the following points:

- Page 9, Line 23: Cost of day in hospital is challenging to estimate and the authors report difficulty in obtaining this information (and other unit cost data) for countries other than Spain. Did the authors consider using the WHO-CHOICE health service delivery 'hotel' costs (http://www.who.int/choice/cost-effectiveness/inputs/health_service/en/), which was used for similar purpose by the BURDEN study (https://doi.org/10.1371/journal.pmed.1001104)? This may assist in capturing the heterogeneity of 'bed day' unit cost between different participating countries.

Response: We now further explore the heterogeneity between countries based on data from the WHO-CHOICE health service delivery costs in the Discussion section. We planned to but could not use this dataset to estimate costs per case in our analysis as unit costs values from this tool are only available for inpatient and outpatient visits, and for 2007-08.

- Page 10: Regarding cohort characteristics, is it possible to provide further information about the reasons that the cases were classified as 'complicated'. e.g. functional abnormality, structural abnormality, male, pregnancy etc. Also, could a brief comment be made about relative frequency of causative organisms?

Response: We now describe the inclusion criteria and definition for cUTI in the paper, and indicate the most common causative pathogens

- Page 11, Line 32: "We also adjust for clustering at the site level and control for the patient episode number." How was this done? Random effect?

Response: We clarify that we adjust for clustering at the site level by computing robust standard errors, and control for the patient episode number by including this indicator as an explanatory variable in the models. This information is now in Supplementary material 2 following the comments from Reviewer #1.

- What definition was used for MDR?

Response: We specify in the paper that MDR was defined as non-susceptibility to at least one agent in three or more antimicrobial categories.

- Page 11, Table 1: It would be useful for future studies that wish to use these results to inform cost-effectiveness studies (and characterise uncertainty) to include 95% confidence intervals for the marginal effects.

Response: We have now included 95% confidence intervals for the marginal effects in Table 1.

- Page 10, Line 58: Could the authors please clarify how 'source of infection' is defined? Urinary catheterisation and pyelonephritis don't seem to me to be mutually exclusive.

Response: We now clarify in the paper the definition of source of infection in the Methods section.

- Page 11, Line 22: "Values between 5 and 10% are regarded as weakly significant." Is this accepted practice for economic evaluation? Could I suggest it would be more useful to report 95% confidence intervals for marginal estimates (see above) rather than p-values.

Response: We now report 95% confidence intervals for the marginal effects in Table 1.

- Page 14, Line 38: Interesting to note that 80% of cost is driven by length of stay, which means that the result is sensitive to changes in the unit price of a bed-day. There is an argument that when looking at bed-day cost from a short term hospital perspective, that an accounting cost (which appears to be used here) overestimates the value of a bed-day. This is because most hospital costs are fixed and cannot be recouped even if the admission is avoided. One alternative is an opportunity cost i.e. the value of a bed day if freed up for use for other purposes e.g. elective surgery (PMID: 25203185). Did the author consider this approach?

Response: We now discuss the limitation of using accounting costs rather than opportunity costs in the Discussion section.

Minor
- Table 1: 9% of admissions for cUTI are "elective". How can an admission for cUTI be elective? Is this a coding error?

Response: We agree that cUTI admissions are most often urgent rather than elective. However, in our sample 59 patients from 6 different countries had an elective admission due to cUTI. Most of these patients had anatomical urinary tract modifications or indwelling urinary catheterizations at admission, and some were referred from a different health care facility.

VERSION 2 – REVIEW

REVIEWER	Andrew Stewardson Monash University, Australia
REVIEW RETURNED	11-Dec-2017

GENERAL COMMENTS	Thanks for this revised version which addresses all points raised. I have no further comments.