

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.

This paper was submitted to the JECH but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Cost effectiveness of a quality improvement programme to reduce central line-associated bloodstream infections in intensive care units in the United States
AUTHORS	Herzer, Kurt; Niessen, Louis; Constenla, Dagna; Ward, William; Pronovost, Peter

VERSION 1 - REVIEW

REVIEWER	Derek S. Wheeler Cincinnati Children's Hospital Medical Center Cincinnati, OH, U.S.A.
REVIEW RETURNED	27-Jul-2014

GENERAL COMMENTS	<p>Thank you for the opportunity to review your manuscript - overall, this is a very well written manuscript describing the findings of an in-depth analysis of the cost effectiveness of a Quality Improvement program (analagous to the Keystone ICU project/CUSP program) to reduce central line-associated bloodstream infections in ICU's in the United States.</p> <p>As the study investigators point out, there are few (if any) studies analyzing the potential return on investment for hospitals for reducing hospital-acquired infections. This is an excellent study and provides a nice outline of how to conduct this kind of analysis. While the results are applicable to CLA-BSI specifically, a similar kind of analysis using the same methodology could be performed for VAP, CA-UTI, SSI, etc.</p> <p>The manuscript is appropriate in length and the conclusions made seem very reasonable given the data provided by the study. The number of references is appropriate (more importantly, the key references are included).</p> <p>This will be an important study - congratulations to the study investigators!</p>
-------------------------	---

REVIEWER	Patricia W Stone Columbia University School of Nursing, Center for Health Policy
REVIEW RETURNED	28-Jul-2014

GENERAL COMMENTS	<p>Thank you for the opportunity to review this interesting report on a decision analytic model estimating the cost-effectiveness of a quality improvement program to reduce central line-associated bloodstream infections in US ICUS. There are many strengths to the paper including the basic model and including the CHEERS checklist. There are areas in which I think there could be increased clarity in the presentation of the methods, results and limitations.</p> <p>In the introduction it is argued that there are no formal economic evaluations of the Keystone Project. Yet, the authors reference Waters et al (reference 29 in article) to estimate their costs from. I would argue that a business case is a formal economic evaluation (see Perencevich, E., Stone, P. W., Wright, S., Carmeli, Y., Fisman, D.N, & Cosgrove, S. (2007). Raising Standards While Watching the Bottom Line Making a Business Case for Infection Control Intervention. <i>Infection Control and Hospital Epidemiology</i>, 28:1121-1133). Perhaps the point is that to your knowledge there is no formal cost-effectiveness analyses.</p> <p>As the authors point out the “On the CUSP: Stop BSI program” is officially in over 1,200 hospitals. However, they don’t recognize that additionally more are probably using checklists in ICUs and have multifaceted infection prevention programs that are similar to the CUSP program, making this the standard of care. In the discussion section the authors cite Wise et al. (reference 46) stating over 800 hospitals continue to have high CLABSI rates. It is true that Wise et al conducted a Monte Carlo simulation and using data from 2010, estimated that there were still 15,000 preventable CLABSI annually; however they concluded that these likely occurred in fewer than 800 hospitals. It has also been reported in the HAI Action Plan (see http://www.health.gov/hai/prevent_hai.asp) that the CLABSI rate continued to decrease in the US from 2010-2013. I believe the introduction could be improved upon and stating that multifaceted infection prevention programs have become the standard in the majority of hospitals in the US.</p> <p>Because this is a patient level analysis, the assumptions regarding the estimation of hospital based costs to an individual (based on an average of 423 patients in the ICU at risk for CLABSI per year) is very important and should not be buried in the appendix.</p> <p>The discussion of measures of effectiveness and outcomes could be quite a bit clearer. In this analysis effectiveness is operationalized by two outcomes, infection prevented and live saved (or death averted). The estimation of effectiveness comes from an appropriate study. It is not clear what the degree of uncertainty was in this point estimate. Perhaps if this was in a Table or something it would be</p>
-------------------------	---

	<p>more readily apparent.</p> <p>In presenting Figure 2, it may be helpful to readers that do not know CEA methods to describe the cost-effectiveness planes more clearly. Additionally, there seems to be a typo or something in the text around Figure 2. From Figure 2 a reader cannot see the difference in costs is -\$249,000. This data comes from Table 3. Figure shows sensitivity analyses.</p> <p>There are published data that demonstrate the long-term out of hospital costs associated with bloodstream infections (see Dick AW, Liu H, Zwanzinger J, Perencevich E, Furuya YE, Larson E, Pogorzelska-Maziarz M, Stone PW. (2012). Longterm survival and healthcare utilization outcomes attributable to sepsis and pneumonia. <i>BMC Healthservices Research</i>) While it might not be in the scope of this analysis, the limitation of not including these costs should be recognized.</p> <p>Minor problems</p> <p>Multiple times it is stated that “all costs were adjusted to 2013 US Dollars”</p> <p>The use of acronyms is inconsistent (eg ICU, intensive care unit) and it is not clear why other acronyms such as CLABSI (which is the CDC preferred acronym isn’t used).</p>
--	---

REVIEWER	Victor D Rosenthal International Nosocomial Infection Control Consortium (INICC)
REVIEW RETURNED	29-Jul-2014

VERSION 1 – AUTHOR RESPONSE

Reviewer Name: Derek S. Wheeler

Institution and Country: Cincinnati Children's Hospital Medical Center
Cincinnati, OH, U.S.A.

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

Thank you for the opportunity to review your manuscript - overall, this is a very well written manuscript describing the findings of an in-depth analysis of the cost effectiveness of a Quality Improvement program (analogous to the Keystone ICU project/CUSP program) to reduce central line-associated bloodstream infections in ICU's in the United States.

As the study investigators point out, there are few (if any) studies analyzing the potential return on investment for hospitals for reducing hospital-acquired infections. This is an excellent study and provides a nice outline of how to conduct this kind of analysis. While the results are applicable to CLA-BSI specifically, a similar kind of analysis using the same methodology could be performed for VAP, CA-UTI, SSI, etc.

The manuscript is appropriate in length and the conclusions made seem very reasonable given the data provided by the study. The number of references is appropriate (more importantly, the key references are included).

This will be an important study - congratulations to the study investigators!

RESPONSE: Thank you very much for the positive feedback. We agree that similar analyses can and should be conducted for other nosocomial infections that are currently the target of intervention.

Reviewer Name: Patricia W Stone

Institution and Country Columbia University School of Nursing, Center for Health Policy

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

Thank you for the opportunity to review this interesting report on a decision analytic model estimating the cost-effectiveness of a quality improvement program to reduce central line-associated bloodstream infections in US ICUS. There are many strengths to the paper including the basic model and including the CHEERS checklist. There are areas in which I think there could be increased clarity in the presentation of the methods, results and limitations.

In the introduction it is argued that there are no formal economic evaluations of the Keystone Project. Yet, the authors reference Waters et al (reference 29 in article) to estimate their costs from. I would argue that a business case is a formal economic evaluation (see Perencevich, E., Stone, P. W., Wright, S., Carmeli, Y., Fisman, D.N, & Cosgrove, S. (2007). Raising Standards While Watching the Bottom Line Making a Business Case for Infection Control Intervention. *Infection Control and Hospital Epidemiology*, 28:1121-1133). Perhaps the point is that to your knowledge there is no formal cost-effectiveness analyses.

RESPONSE: Thank you for identifying this important opportunity to provide greater clarity. We have revised this sentence on page 5 to read: 'Reporting of economic data in quality improvement studies is uncommon, and there are few formal cost effectiveness analyses of quality improvement

programmes.'

As the authors point out the "On the CUSP: Stop BSI program" is officially in over 1,200 hospitals. However, they don't recognize that additionally more are probably using checklists in ICUs and have multifaceted infection prevention programs that are similar to the CUSP program, making this the standard of care.

RESPONSE: To address this point, we have amended the text (on page 5) as follows: 'Over 1,200 US hospitals are currently participating in this multifaceted quality improvement programme through On the CUSP: Stop BSI, a national collaborative, and many others are likely using checklists and multifaceted infection prevention programmes in their ICUs as standard practice.'

In the discussion section the authors cite Wise et al. (reference 46) stating over 800 hospitals continue to have high CLABSI rates. It is true that Wise et al conducted a Monte Carlo simulation and using data from 2010, estimated that there were still 15,000 preventable CLABSI annually; however they concluded that these likely occurred in fewer than 800 hospitals. It has also been reported in the HAI Action Plan (see http://www.health.gov/hai/prevent_hai.asp) that the CLABSI rate continued to decrease in the US from 2010-2013. I believe the introduction could be improved upon and stating that multifaceted infection prevention programs have become the standard in the majority of hospitals in the US.

RESPONSE: We have modified the manuscript to remove the qualifier "over" in terms of the 800 medium and large hospitals that continue to have high CLABSI rates. As mentioned previously, we have revised the introduction to indicate that multifaceted infection prevention programs have become a standard practice.

Because this is a patient level analysis, the assumptions regarding the estimation of hospital based costs to an individual (based on an average of 423 patients in the ICU at risk for CLABSI per year) is very important and should not be buried in the appendix.

RESPONSE: Thank you for raising this point. Our goal was to present a succinct manuscript and to provide additional detail for interested readers in the supplementary appendix. As the reviewer described, the assumptions underlying this calculation are indeed important. As such, we have elaborated on how the per patient cost of the programme was derived in the main text (pages 10-11). The appendix includes the actual calculations used.

The discussion of measures of effectiveness and outcomes could be quite a bit clearer. In this analysis effectiveness is operationalized by two outcomes, infection prevented and lives saved (or death averted). The estimation of effectiveness comes from an appropriate study. It is not clear what the degree of uncertainty was in this point estimate. Perhaps if this was in a Table or something it would be more readily apparent.

RESPONSE: Thank you for these points. We used the confidence interval of the effectiveness point estimate (from Marsteller et al), as a measure of uncertainty in the programme's effectiveness. The confidence interval was used to define the distribution of the effectiveness parameter for the probabilistic sensitivity analysis. We report the standard deviation of the point estimate in Table 1. We improved this explanation in the Effectiveness subsection of the Methods (page 11) and we believe this is more clear. We have also improved the description of the uncertainty incorporated into the probabilistic sensitivity analysis on page 13.

In presenting Figure 2, it may be helpful to readers that do not know CEA methods to describe the cost-effectiveness planes more clearly. Additionally, there seems to be a typo or something in the text

around Figure 2. From Figure 2 a reader cannot see the difference in costs is -\$249,000. This data comes from Table 3. Figure shows sensitivity analyses.

RESPONSE: We have described the cost effectiveness planes more clearly for readers who are less familiar with cost effectiveness analysis methods by discussing the axes of the figures, what the data points mean, and what the distribution of data points suggests. We have also made the Results more concise. In addition, we have corrected the reference to Table 3 rather than Figure 2.

There are published data that demonstrate the long-term out of hospital costs associated with bloodstream infections (see Dick AW, Liu H, Zwanzinger J, Perencevich E, Furuya YE, Larson E, Pogorzelska-Maziarz M, Stone PW. (2012). Longterm survival and healthcare utilization outcomes attributable to sepsis and pneumonia. BMC Healthservices Research) While it might not be in the scope of this analysis, the limitation of not including these costs should be recognized.

RESPONSE: Thank you for calling attention to this paper. We do identify as a limitation in the Discussion that we did not include long term and/or post acute care costs in our model. We have elaborated on the importance of future research or economic evaluations taking into account long term costs and outcomes and included the reference to the suggested paper.

Minor problems

Multiple times it is stated that "all costs were adjusted to 2013 US Dollars"

RESPONSE: Thank you for identifying this; we have resolved this and it is only stated once now, on page 11.

The use of acronyms is inconsistent (eg ICU, intensive care unit) and it is not clear why other acronyms such as CLABSI (which is the CDC preferred acronym isn't used).

RESPONSE: We have amended the text to include "ICU" in place of "intensive care unit" and "CLABSI" in place of "central line-associated bloodstream infection" in all instances. This should improve consistency and readability.

Reviewer Name Victor D Rosenthal

Institution and Country International Nosocomial Infection Control Consortium (INICC)

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

Reviewer replied 'No' to the following questions:

Are the methods described sufficiently to allow the study to be repeated?

RESPONSE: We have amended sections of the Methods based on feedback from other reviewers that we believe improves clarity and facilitates replication of our study. In addition, we provide significant additional detail in the included appendices to walk interested readers through our calculations.

Are the outcomes clearly defined?

RESPONSE: We have improved the description of the outcomes, making it clear that we were interested in two outcomes: CLABSIs prevented and deaths averted.

Are the references up-to-date and appropriate?

RESPONSE: We have referenced a wide array of papers related to economic analysis in the ICU setting, and specific to healthcare associated infections. We have also incorporated additional references in this revision in accordance with the recommendations of another reviewer. The references contained in this revision are up-to-date and appropriate.

Are they [the results] presented clearly?

RESPONSE: We have amended the Results significantly based on the specific recommendations of another reviewer. The Results as presented in the revised manuscript are much clearer (and more concise). We have endeavored to describe the cost effectiveness analysis results in a manner that should be accessible to any reader, including those less familiar with CEA methods.

VERSION 2 – REVIEW

REVIEWER	Patricia W Stone Columbia University School of Nursing, USA
REVIEW RETURNED	03-Sep-2014