PEER REVIEW HISTORY

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ARTICLE DETAILS

Title (Provisional)

Cost savings of a nationwide project preventing healthcare-associated infections in adult, paediatric, and neonatal critical care settings in Brazil: a micro-costing study

Authors

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VERSION 1 - REVIEW

Reviewer	**1**
Name	**Kelson, Zoe**
Affiliation	**University of Exeter, Mathematics**
Date	**09-Jan-2025**
COI	**None**

This micro-costing study aims to evidence the cost savings of a project preventing HAIs in intensive care units (ICU, focusing on financial data related to a nationwide multicentric project in Brazil preventing three critical HAIs: central lineassociated bloodstream infection (CLABSI), ventilator-associated pneumonia (VAP), and catheter-associated urinary tract infection (CAUTI).

Reviewer comments:

"The cost savings were estimated using the HAIs prevented during the collaborative intervention period from September 2021 to December 2023." [Abstract]

Can the authors please summarise the modelling methodology applied to estimate HAIs prevented in the Abstract?

"Considering the prevented 7,443 HAIs for adult, pediatric, and neonatal ICUs, respectively: 1,647, 167, and 205 CLABSI; 3,775, 128, and 118 VAP; and 1,377 and 26 CAUTI, we estimated

a financial impact of Int$179 million to the Brazilian unified health system, leading to an estimated return on investment (ROI) of 973%." [Abstract]

Can uncertainty intervals please be reported alongside each point estimate in the Abstract?

"Participating institutions reported the number of patients with and without HAIs, accompanied by information on each HAI's aggregate average cost (AC), which was analyzed following the micro-costing study local guidelines." [Abstract]

and

"Thirty-one institutions out of 188 participating ICUs voluntarily completed and provided the requested financial data with 100% accuracy." [Abstract]

and

"Participating ICUs were from the five macro-regions of Brazil: South-east, North-east, South, Central-west, and North."

and

"An open call was made to all the participating institutions joining the SNM initiative. Participation was voluntary, and no financial incentive was provided, avoiding conflicts of interest."

Can the authors please further comment on whether the participating ICUs can be considered to be geographically and characteristically representative?

"The temporal framework for this evaluation was anchored to the SNM duration, spanning from September 2021 to December 2023. "

Can the authors please comment on whether infections prevented and/or costs may have changed since 2023?

Through a detailed internal checklist, we meticulously verified and detected conformity between the care, procedures, laboratory tests, materials and medications, and medical procedures directly dispensed to the patient. In cases of inconsistencies, the form was returned to the institution of origin for adjustments, and this procedure was repeated until the data were entirely consistent. Each participant was assigned a unique code, ensuring a distinct and accurate financial record for each hospital admission, preventing duplication or double-counting costs. "

The authors have undertaken rigorous data quality assurance procedures.

To clarify, was there no missing data?

"The potential for infection prevention attributable to the project was estimated as previously reported [11]. "

Can a summary in brief of this methodology please be provided here?

Can the authors please consider conducting a sensitivity analysis exploring different levels of infection prevention based on a range of scenarios and assumptions?

"Consequently, synthesizing aggregated AC data from before the intervention and quantifying HAIs averted through the project's implementation facilitated a robust assessment of the SNM initiative's economic impact. "

Can the authors please assess and quantify uncertainty in these estimations?

"The absorption model was used following the recommendations of the BMoH [15]. Results are presented in tables and figures summarizing the main findings. Additionally, a violin plot offers the aggregate AC for each ICU type regarding patients with and without HAIs. The main expenses by category are presented in a Tornado plot. The costs of each analyzed HAI are shown using a box-plot graphic, followed by a 3D plot including ICU type and mean LOS. After parametric assumptions were tested against normal plots, groups were contrasted using the U Mann-Whitney test. Aggregate AC was correlated with the mean LOS, and Spearman's rank test was calculated"

Suitable statistical methods have been applied for the types of data in hand.

Did the authors consider undertaking any mutlivariate analyses to adjust for potential confounders in the analysis?

For instance, 'Figure 3 shows the aggregated AC by ICU type with and with[out] HAI' might be influenced by age, gender, or comorbidity differences between HAI groups?

Can subgroup analyses please be explored by the authors?

"The financial impact resulting from the SNM implementation, based on 7,443 prevented HAIs, resulted in an estimated saving of BRL$436,821,480.76 million (Int$179.0 million) to SUS. The PROADI-SUS investment for the SNM project was BRL$44,876,978 (Int$18.3 million), leading to an estimated ROI of 973%."

In line with the above reviewer comments, can the authors please communicate uncertainty intervals for each point estimate reported throughout the Results?

"Table 2. Estimating the savings of (blind)"

and

"Figure 2. Financial indicators with clinical data to (blind) project"

Can the titles for Tables and Figures please be double checked and clarified?

"The sample size, covering 16% of participating ICUs, raises questions about the generalizability of the findings across Brazil's diverse healthcare settings. Additionally, the study's focus on the economic aspects of HAIs leaves room for further research on patient outcomes, quality of life post-HAI, and the long-term effects of HAIs on healthcare systems. The previous report [13] referred to additional limitations of our financial approach."

Can the discussion of the study limitations please be expanded on?

Thanks for providing the "Principles of the 'Reference Case for Estimating the Costs of Global Health Services and Interventions' proposed by the Global Health Cost Consortium. "

In addition to this, can the authors please consider adhering to formal guidelines for the reporting of this study, and provide a copy of the associated checklist?

Reviewer **2**

Name **Kairu, Angela**

Affiliation **KEMRI-Wellcome Trust Research Programme Nairobi, Health Economics Research Unit (HERU)**

Date **21-Jan-2025**

COI **None**

General

The authors conduct a financial costing of strategies to prevent HAIs. The study is relevant in cost and investments needed for clinical care of patients. With economic costing being more applicable and preferred in comparing the cost-effective strategies amongst various health priorities or interventions, the findings of the study may not fully inform such policy decisions. However, the authors can provided recommendations to be considered.

Specific

Introduction:

The authors highlight the relevance of strategies to prevent HAIs, however this section would benefit from more information or evidence of the types of strategies applied in the same or different contexts (paragraphs 2 and 3) and also brief descriptions/information on HAIs. The background information and context provided is not as comprehensive. For instance, the types of HAIs are mentioned in the abstract, but this is not clear in the background.

Methods:

Although the methods used are rigorous and comprehensive, there is no description of the project and activities being costed. This makes t unclear to follow exactly what is being costed. The abstract mentions a QI model with a multifaceted strategy which should be clearly explained in this section. If the costs of those with HAI and those without HAI was calculated based on this model, it may be clarified.

Results:

Although the costs are presented in the figures and tables it would be beneficial to mention the identified cost drivers. Authors may consider doing a sensitivity analysis to vary the different parameters and check for robustness of the results. The Supplementary table reporting on uncertainty doesn't capture clearly whether the sensitivity analysis performed or not

Discussion

Lines 22 to 26: ROI of investment may not necessarily mean cost effective because of the measure of outcomes needed to measure cost effectiveness. More appropriately would be the term cost saving.

The conclusion may benefit from possible recommendations from these findings relating to competing health priorities, and full investment of this may not be the country's health system priority for instance.

VERSION 1 - AUTHOR RESPONSE

Reviewer 1

This micro-costing study aims to evidence the cost savings of a project preventing HAIs in intensive care units (ICU, focusing on financial data related to a nationwide multicentric project in Brazil preventing three critical HAIs: central line-associated bloodstream infection (CLABSI), ventilator-associated pneumonia (VAP), and catheter-associated urinary tract infection (CAUTI).

Reviewer comments:

"The cost savings were estimated using the HAIs prevented during the collaborative intervention period from September 2021 to December 2023." [Abstract]
Can the authors please summarise the modelling methodology applied to estimate HAIs prevented in the Abstract?

A brief description was provided in the Abstract section, and a more detailed methodology was included in the Methods section.

"Considering the prevented 7,443 HAIs for adult, pediatric, and neonatal ICUs, respectively: 1,647, 167, and 205 CLABSI; 3,775, 128, and 118 VAP; and 1,377 and 26 CAUTI, we estimated a financial impact of Int$179 million to the Brazilian unified health system, leading to an estimated return on investment (ROI) of 973%." [Abstract]
Can uncertainty intervals please be reported alongside each point estimate in the Abstract?

IC 95% were now provided for each cost described.

"Participating institutions reported the number of patients with and without HAIs, accompanied by information on each HAI's aggregate average cost (AC), which was analyzed following the micro-costing study local guidelines." [Abstract] and "Thirty-one institutions out of 188 participating ICUs voluntarily completed and provided the requested financial data with 100% accuracy." [Abstract] and "Participating ICUs were from the five macro-regions of Brazil: South-east, North-east, South, Central-west, and North," and "An open call was made to all the participating institutions joining the SNM initiative. Participation was voluntary, and no financial incentive was provided, avoiding conflicts of interest."

Can the authors please further comment on whether the participating ICUs can be considered to be geographically and characteristically representative?

As the SNM is not an academic project and the participating ICUs were selected by convenience due to BMoH interests, we cannot state that our sample is representative of each macro-region. The inclusion of institutions from different regions aims to show potential differences due to local clinical-epidemiological and socio-economics features in the Brazilian public system, but further studies are necessary to assess representativity and specific characteristics such as size, resources, and administration type in different geographical settings. We include this in the Limitation section.

"The temporal framework for this evaluation was anchored to the SNM duration, spanning from September 2021 to December 2023. "

Can the authors please comment on whether infections prevented and/or costs may have changed since 2023?

We estimated the number using a forecast based on the baseline density incidence. As the intervention was implemented, we cannot assess the number of HAIs without intervention. Controlled studies, rather than pre-post and interrupted time-series studies, are necessary to evaluate this issue. We include this in the Limitations section.

We do not adjust the temporal variations for the temporal horizon of less than 5 years (we report this in Supplementary Table 1S).

Through a detailed internal checklist, we meticulously verified and detected conformity between the care, procedures, laboratory tests, materials and medications, and medical procedures directly dispensed to the patient. In cases of inconsistencies, the form was returned to the institution of origin for adjustments, and this procedure was repeated until the data were entirely consistent. Each participant was assigned a unique code, ensuring a distinct and accurate financial record for each hospital admission, preventing duplication or double-counting costs. "
The authors have undertaken rigorous data quality assurance procedures.
To clarify, was there no missing data?

No missing data was found. We include this Data Analysis section.

"The potential for infection prevention attributable to the project was estimated as previously reported [11]. "
Can a summary in brief of this methodology please be provided here?

We now include how the number of HAI that were prevented was estimated.

Can the authors please consider conducting a sensitivity analysis exploring different levels of infection prevention based on a range of scenarios and assumptions?

This proposal is exciting. We were worried about the volume of data regarding all the potential scenarios and assumptions, including variations on the baseline, estimation of infection prevented, cost per hospitalisation variations and cost per parameter variation. To assess the primary potential setting, we include a sensitivity analysis including the variation on the estimation of infections prevented (IC 95%), including a "worst" and "best" scenario based on the inferior and superior limit of prevented infection, respectively.

"Consequently, synthesizing aggregated AC data from before the intervention and quantifying HAIs averted through the project's implementation facilitated a robust assessment of the SNM initiative's economic impact. "
Can the authors please assess and quantify uncertainty in these estimations?

We provided the estimation and the IC95% of each HAI during the pre-intervention period (new Table 3). A sensitivity analysis is now offered for the cost parameters (new Figure 4).

"The absorption model was used following the recommendations of the BMoH [15]. Results are presented in tables and figures summarizing the main findings. Additionally, a violin plot offers the aggregate AC for each ICU type regarding patients with and without HAIs. The main expenses by category are presented in a Tornado plot. The costs of each analyzed HAI are shown using a box-plot graphic, followed by a 3D plot including ICU type and mean LOS. After parametric assumptions were tested against normal plots, groups were contrasted using the U Mann-Whitney test. Aggregate AC was correlated with the mean LOS, and Spearman's rank test was calculated"
Suitable statistical methods have been applied for the types of data in hand.
Did the authors consider undertaking any mutlivariate analyses to adjust for potential confounders in the analysis?

We performed the statistical analysis to have a better overview in terms of main comparators and well-known associations such as LOS and costs; however, we do not consider further statistical methods due to the complexity of the sample regarding unassessed factor such as age, weight (in neonatal), severity scores, and other clinical factor that may influence the costs. We include this discussion in the Limitation section.

For instance, 'Figure 3 shows the aggregated AC by ICU type with and with[out] HAI' might be influenced by age, gender, or comorbidity differences between HAI groups?

Can subgroup analyses please be explored by the authors?

Considering the nature of the initiative, clinico-assistance rather than research, we only used structured financial data without access to clinical records. To assess clinical features, the project should ethically and logistically organise a medical chart review and clinical data extraction. As our intention was only to evaluate the financial data and potential saving, this data was not included as mentioned in the Limitations sections.

"The financial impact resulting from the SNM implementation, based on 7,443 prevented HAIs, resulted in an estimated saving of BRL$436,821,480.76 million (Int$179.0 million) to SUS. The PROADI-SUS investment for the SNM project was BRL$44,876,978 (Int$18.3 million), leading to an estimated ROI of 973%."
In line with the above reviewer comments, can the authors please communicate uncertainty intervals for each point estimate reported throughout the Results?

IC 95% were now provided. We highlight that the PROADI-SUS investment is the exact amount expended (without variations).

"Table 2. Estimating the savings of (blind)"
and
"Figure 2. Financial indicators with clinical data to (blind) project"
Can the titles for Tables and Figures please be double checked and clarified?

Tables and Figures' legends were reviewed and updated.

"The sample size, covering 16% of participating ICUs, raises questions about the generalizability of the findings across Brazil's diverse healthcare settings. Additionally, the study's focus on the economic aspects of HAIs leaves room for further research on patient outcomes, quality of life post-HAI, and the long-term effects of HAIs on healthcare systems. The previous report [13] referred to additional limitations of our financial approach."
Can the discussion of the study limitations please be expanded on?

We include this in the Limitation section.

Thanks for providing the "Principles of the ‘Reference Case for Estimating the Costs of Global Health Services and Interventions’ proposed by the Global Health Cost Consortium. "

In addition to this, can the authors please consider adhering to formal guidelines for the reporting of this study, and provide a copy of the associated checklist?

The checklist and the description of each dimension are provided in Supplementary Table 1S.

Reviewer 2

The authors conduct a financial costing of strategies to prevent HAIs. The study is relevant in cost and investments needed for clinical care of patients. With economic costing being more applicable and preferred in comparing the cost-effective strategies amongst various health priorities or interventions, the findings of the study may not fully inform such policy decisions. However, the authors can provided recommendations to be considered.

Specific

Introduction:

The authors highlight the relevance of strategies to prevent HAIs, however this section would benefit from more information or evidence of the types of strategies applied in the same or different contexts (paragraphs 2 and 3) and also brief descriptions/information on HAIs. The background information and context provided is not as comprehensive. For instance, the types of HAIs are mentioned in the abstract, but this is not clear in the background.

We agree, and we updated the background section with a broader approach, including the QI model and the importance of the three critical HAIs analysed.

Methods:

Although the methods used are rigorous and comprehensive, there is no description of the project and activities being costed. This makes t unclear to follow exactly what

is being costed. The abstract mentions a QI model with a multifaceted strategy which should be clearly explained in this section. If the costs of those with HAI and those without HAI was calculated based on this model, it may be clarified.

We discussed this very relevant topic in our previous publication. Indeed, several authors have addressed this point regarding QI initiatives. We include this challenging topic in the Discussion section. If the reviewer agrees, we can provide the PROADI-SUS budget by generic items for a better overview of the expenses.

Results:

Although the costs are presented in the figures and tables it would be beneficial to mention the identified cost drivers. Authors may consider doing a sensitivity analysis to vary the different parameters and check for robustness of the results. The Supplementary table reporting on uncertainty doesn't capture clearly whether the sensitivity analysis performed or not.

We agreed. We are now including a univariate sensitivity analysis for the primary cost parameter. Please check our new Table 2 and Figure 4, which show the analysis results in a *tornado* diagram.

Discussion

Lines 22 to 26: ROI of investment may not necessarily mean cost effective because of the measure of outcomes needed to measure cost effectiveness. More appropriately would be the term cost saving.

We agreed, and the term was changed.

The conclusion may benefit from possible recommendations from these findings relating to competing health priorities, and full investment of this may not be the country's health system priority for instance

We believe that from our results, we cannot include conclusions related to these topics. The proposed recommendations depend on multiple factors,

and they are more specific among diverse services, systems, or countries than a statement or suggestion from our study.

VERSION 2 - REVIEW

Reviewer	**1**
Name	**Kelson, Zoe**
Affiliation	**University of Exeter, Mathematics**
Date	**17-Mar-2025**
COI	

Many thanks to the authors for responding to each reviewer comment in turn, providing clarification, and amending the article where required. The reporting of this study is strengthened as a result.