BMJ Open

Cost effectiveness of a quality improvement programme to reduce central line-associated bloodstream infections in intensive care units in the United States

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-006065
Article Type:	Research
Date Submitted by the Author:	09-Jul-2014
Complete List of Authors:	Herzer, Kurt; Johns Hopkins School of Medicine, Medical Scientist Training Program Niessen, Louis; University of Warwick, Liverpool School of Tropical Medicine, Centre for Applied Health Research and Delivery (CAHRD) Constenla, Dagna; Johns Hopkins Bloomberg School of Public Health, International Vaccine Access Center Ward, William; Johns Hopkins Bloomberg School of Public Health, Health Policy and Management Pronovost, Peter; The Johns Hopkins University School of Medicine, Anesthesiology and Critical Care Medicine
Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Health services research, Health policy, Infectious diseases
Keywords:	Health economics < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Health & safety < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Infection control < INFECTIOUS DISEASES, Adult intensive & critical care < INTENSIVE & CRITICAL CARE

Cost effectiveness of a quality improvement programme to reduce central line-associated bloodstream infections in intensive care units in the United States

Kurt R Herzer, Louis Niessen, Dagna O Constenla, William J Ward Jr, Peter J Pronovost

Medical Scientist Training Program, Johns Hopkins School of Medicine, 1830 East Monument Street, Baltimore, MD 21205, USA

Kurt R Herzer

MD-PhD student

Centre for Applied Health Research and Delivery (CAHRD), Liverpool School of Tropical Medicine, University of Warwick, Coventry, CV4 7AL, United Kingdom

Louis Niessen

Professor

International Vaccine Access Center, Johns Hopkins Bloomberg School of Public Health, 855 North Wolfe Street, Baltimore, MD 21205, USA

Dagna O Constenla

Associate Scientist

Department of Health Policy and Management, Johns Hopkins Bloomberg School of Public Health, 624 North Broadway Street, Baltimore, MD 21205, USA

William J Ward Jr

Associate Professor

Armstrong Institute for Patient Safety and Quality, Johns Hopkins Medicine, 750 East Pratt Street, Baltimore, MD 21202, USA

Peter J Pronovost

Professor

Correspondence to: Kurt Herzer, 1830 East Monument Street, Baltimore, MD 21205, USA; kherzer@jhmi.edu; 443-900-2415

Keywords: quality improvement, cost effectiveness, nosocomial infections, health policy, checklists

Word Count: 3,349

Abstract

Objective: To assess the cost effectiveness of a multifaceted quality improvement programme focused on reducing central line-associated bloodstream infections in intensive care units.

Design: Cost effectiveness analysis using a decision tree model to compare programme to non-programme intensive care units.

Setting: United States (US).

Population: Adult patients in the intensive care unit.

Costs: Economic costs of the programme and of central line-associated bloodstream infections were estimated from the perspective of the hospital and presented in 2013 US dollars.

Main outcome measures: Central line-associated bloodstream infections prevented, deaths averted due to central line-associated bloodstream infections prevented, and incremental cost effectiveness ratios. Probabilistic sensitivity analysis was performed.

Results: Compared to current practice, the programme is strongly dominant and reduces bloodstream infections and deaths at no additional cost. The probabilistic sensitivity analysis showed that there was an almost 80% probability that the programme reduces bloodstream infections and the infections' economic costs to hospitals. The opportunity cost of a bloodstream infection to a hospital was the most important model parameter in these analyses.

Conclusions: This multifaceted quality improvement programme, as it is currently implemented by hospitals on an increasingly large scale in the US, likely reduces the economic costs of central line-associated bloodstream infections for US hospitals. Awareness among hospitals about the programme's benefits should enhance implementation. The programme's implementation has the potential to substantially reduce morbidity, mortality, and economic costs associated with central line-associated bloodstream infections.

Article summary

Strengths and limitations of this study

- This study was conducted according to best practices in cost effectiveness analysis and demonstrates that a multifaceted quality improvement programme can reduce the economic costs of central line-associated bloodstream infections for hospitals.
- We used nationally representative data sources to increase generalisability and performed a probabilistic sensitivity analysis to quantify the uncertainty in our cost effectiveness estimates.
- Due to data limitations we were unable to assess the impact of patient heterogeneity, such as demographics and clinical characteristics, on baseline risk, treatment effect, or resource utilisation. We did not evaluate costs outside the acute hospital setting, such as rehabilitation costs or productivity losses for delays returning to work.

INTRODUCTION

Central line-associated bloodstream infections are common, expensive to payers and patients, and potentially fatal.[1 2] Each year, nearly 80,000 Americans develop central line-associated bloodstream infections in the intensive care unit, and more than 25,000 of these patients die.[3] A single infection can cost payers as much as $56,000, culminating in over $2 billion in related costs per year in the United States.[4] Central line-associated bloodstream infections in intensive care unit patients have an estimated attributable mortality rate of 14 to 40%, with a prolonged length of stay of 7.5 to 25 days.[5 6]

The Keystone ICU (intensive care unit) project, first launched in Michigan in 2004 and since scaled across the United States, Spain, Peru, Pakistan, and the United Kingdom, has captured the interest and attention of patients, payers, and policymakers for its substantial, sustained, and scalable reductions in preventable nosocomial infections. Over 1,200 US hospitals are currently participating in this multifaceted quality improvement programme through *On the CUSP: Stop BSI,* a national collaborative. The programme has been evaluated through prospective cohort studies,[7-10] retrospective observational studies using claims data,[11] and both cluster nonrandomised[12] and randomised controlled trials.[13] When viewed collectively, this evidence suggests that the programme is associated with substantial reductions in both central line-associated bloodstream infections and mortality in intensive care unit patients.

In spite of commendable investment in this programme to manage the undesirable consequences of central line-associated bloodstream infections, an important question remains unanswered: compared with current practice, is this programme cost effective for US hospitals? Reporting of economic data in quality improvement studies is uncommon, and there are few formal economic evaluations of quality improvement programmes.[14-16] Similarly, because the

estimated gross costs of central line-associated bloodstream infections to the healthcare system are very high, the conclusion that expanding infection control efforts will be cost saving (relative to the costs incurred by expanded efforts) is accepted without rigorous analysis.[17] This paper examines the cost changes and effectiveness of the Keystone ICU project from the perspective of the hospital using nationally representative data sources from the United States.

METHODS

Overview of the analysis

We developed a decision tree model to address the choice faced at an individual hospital about implementing the programme (Figure 1). The use of a decision tree approach is justified by the short-term progression of central line-associated bloodstream infections. The model assumes that patients do not experience other adverse effects of catheterisation, such as catheter colonisation leading to local infection, hypersensitivity reactions, or mechanical complications such as pneumothorax. The Keystone ICU project instead focused on infectious complications, because they are more common, more costly, and often fatal.[18] Consistent with other economic evaluations of central line-associated bloodstream infections in the intensive care unit setting, we assumed that the consequences of infection are independent of age, patient disease severity, and the causative organism.[18 19] These assumptions are congruent with the programme itself, which does not discriminate between subgroups of patients based on these factors.

The comparator was current practice as the most realistic alternative faced by organisations seeking to implement the programme. Current practice encompasses on-going or existing activities that might influence the risk of infection amongst patients, such as the use of anti-infective central venous catheters.

The target population consisted of adult (18 years or older) intensive care unit patients in accordance with studies of the Keystone ICU project and its subsequent replications.[13] Because costs and benefits only accrue while the programme is implemented, the time frame and analytic horizon are fundamentally the same. We used a time horizon of five years. This analysis was performed from the hospital's perspective. Our study aims to address the following question: is implementation of this quality improvement programme to decrease central line-associated bloodstream infections in the intensive care unit a cost-effective approach when compared with current practice in US hospitals?

Quality improvement programme

Details of the programme and its conceptual approach have been described elsewhere.[20-22] In brief, this multifaceted programme employed clinician communication tools, teamwork, and safety culture assessment and improvement tools (known as the Comprehensive Unit-based Safety Program [CUSP]), and a five-item, evidence-based checklist for correctly inserting central venous catheters. The five components of the checklist included using basic hand hygiene, exercising full barrier precautions, cleaning the skin with chlorhexidine, avoiding the femoral site when possible, and removing any unnecessary catheters. A model for translating evidence into practice identified and mitigated local barriers to implementation of the checklist.[22]

Quarterly infection rates measured at the intensive care unit level were used to monitor progress toward the goal of reducing central line-associated bloodstream infections. The remainder of this paper uses the phrase "bloodstream infection" to refer to central line-associated bloodstream infection.

Model inputs

Table 1 shows the key parameters used in the decision tree model, such as probabilities and cost inputs as well as the effectiveness of the programme, which are described in detail in the following sections.

Table 1 | Parameters used in the decision tree model

Parameter	Distribution	Source
Probability of bloodstream infection*	Beta: 0.052 (SD 0.0074)	18,25
Death attributable to bloodstream infection	Beta: 0.15 (SD 0.056)	3,6
Incidence rate ratio of programme versus non-programme ICUs	Lognormal based on normal mean 0.19 (SD 0.13)	13
Total cost ($):		
Bloodstream infection (per patient)†	Lognormal based on normal mean 18,793 (SD 5,533)	39
Programme (per patient)†	Lognormal based on normal mean 540 (SD 120)	29

ICU = intensive care unit
*Conditional probability of a bloodstream infection given exposure to a central venous catheter, assumes standard (non-antimicrobial) catheter.
†Discounted costs presented

Risk of bloodstream infection and death

Estimates of the risk of bloodstream infection given exposure to a central venous catheter varied from 3.0% to as much as 16.0%.[23 24] We used a probability estimate of 5.2% for a standard catheter, derived from a meta analysis of 13 randomised controlled trials from a previous economic evaluation.[18 25] Estimates of the attributable mortality of bloodstream infections ranged from 14 to 40%.[5 6 26 27] We used a point estimate of 15%.

Costs

Estimates of payer costs attributable to bloodstream infections varied widely, from as little as $6,000 to over $56,000.[4 6 18 28] The reasons for this variation can be attributed to the

small sample sizes of studies, challenges allocating inpatient costs, perspectives used, the types of cost categories included, and the methodology used for estimation.[29] Existing studies have largely focused on financial costs (or hospital charges or payer costs) rather than opportunity costs and so they may incorrectly estimate the economic cost of bloodstream infections to hospitals. We considered the economic cost of bloodstream infections in terms of the increased length of stay and variable costs associated with that occurrence.[30] Given that a significant amount of hospital costs are fixed in the short run, the economic viability of quality improvement programmes that reduce bloodstream infections rests on two things: deploying the bed-days freed by shorter lengths of stay for new admissions and reducing utilization of medications and supplies. The value of the new admissions, (the potential incremental net revenue opportunity per prevented infection) represents the economic cost of infection and accordingly, the potential economic cost avoidance resulting from infection prevention.[31] Using this approach, we estimated that the discounted cost of a bloodstream infection was $18,793 (see the appendix for details of this calculation).

Start-up costs and recurring costs associated with the quality improvement programme were assigned using an activity-based micro-costing of the programme performed in six hospitals in Michigan.[29] We assumed that start-up costs occurred in the first year of implementation and did not discount them. Capital items, such as bloodstream infection line carts, were annualised assuming a five-year useful life and 3% discount rate. We included the opportunity costs of key personnel whose time was committed to the programme even though a hospital may not incur any financial costs related to personnel who are already on staff. We estimated this cost by multiplying each staff person's percentage effort committed to the programme by an estimate of that position's annual compensation. We used the Society of Critical Care Medicine's annual

compensation estimates from 2009 for critical care physicians, nurses, pharmacists, and respiratory therapists.[32] The salary for infection control preventionists was based on the Bureau of Labor Statistics's 2011 Occupational Employment Statistics and we added 30% benefits. All compensation figures were adjusted to 2013 US dollars using the Consumer Price Index for medical care services. Table 2 presents a detailed itemisation of the start-up costs and recurring costs of the programme. Start-up costs were approximately $80,000 and recurring costs were approximately $192,000 per hospital per year. Personnel costs were the largest contributor, comprising 95% of start-up costs and 89% of recurring costs.

Table 2 | Itemisation of programme costs (per hospital)

Cost category	Start-up costs	Recurring costs*
Personnel ($)		
Critical care physicians (2 on average per hospital)	26,004	71,953
Nurses (8 on average per hospital)	44,406	75,306
Respiratory therapists	4,605	7,923
Infection control preventionists	1,981	7,855
Pharmacists	2,725	7,962
Education and Training ($)		
Education and training expenses	3,579	
Capital Items ($)		
BSI line cart/central line insertion cart (annual equivalent cost)	426	426
Materials ($)		
Chlorohexidine		2,378
Oral care kits		6,933
Sterile central line dressing kits		11,555
Total ($)	83,725	192,292

BSI = bloodstream infection
*Recurring costs occur each year that the intervention is in place; as such, this total represents the annual recurring cost (not discounted as presented here).

We estimated a per patient cost of the programme by deriving an average number of intensive care unit patients per hospital who had central venous catheters (the patients most

likely to benefit from the programme's prevention efforts) based on published estimates and the American Hospital Association's Annual Survey of Hospitals, yielding $540 per patient (see the appendix for details of this calculation).[33 34]

All costs were adjusted to 2013 US dollars. Recurring costs were discounted by 3% annually. In separate sensitivity analyses, we examined the effect of not discounting costs and of discounting costs by 5%.

Effectiveness

We based our estimate of the programme's effectiveness on a cluster randomised controlled trial that found an 81% reduction in bloodstream infection rates comparing programme intensive care units to control intensive care units.[13] This effectiveness parameter was measured at the intensive care unit level but in our model we assumed that it applied to individual patients (considering all intensive care unit patients together). This ecological assumption is necessary because there are no patient level effectiveness estimates available from the Keystone ICU project. Its uncertainty range captures the heterogenic reality among intensive care unit patients that the intervention benefit is not uniform. The base case probability of a bloodstream infection in the programme arm of the decision tree is adjusted by multiplying by the incidence rate ratio (0.19) from the trial. We assumed that by the end of the first year of implementation, programme intensive care units achieve this reduction. The original intensive care units that implemented the programme maintained the reduction for the subsequent 10 years (Sam Watson, written communication, August 18, 2013). We assumed this to be true for the five-year period used in this evaluation.[35]

The number of annual intensive care unit admissions requiring catheters, the probability of infection, and the attributable mortality parameters were assumed not to change during the five-year period.

Outcome measures

The outcomes of interest were bloodstream infections prevented and deaths averted due to bloodstream infections prevented. We calculated the number of bloodstream infections prevented by determining the difference in the number of bloodstream infections between programme and non-programme intensive care units. Deaths averted were calculated similarly. We did not discount bloodstream infections or deaths in the base case analysis to avoid making the ethically challenging assumption that infections or deaths prevented in the future are worth less than they are in the present. We explored the effect of discounting bloodstream infections and deaths by 3% in a sensitivity analysis.

We calculated incremental cost effectiveness ratios as the additional cost divided by the additional health benefit comparing the programme to current practice.

Probabilistic sensitivity analyses

We conducted a probabilistic sensitivity analysis to account for uncertainty in the model's input parameters. We used Monte Carlo simulation to perform 10,000 iterations of the model, simultaneously sampling each parameter from an underlying distribution that reflects the degree of uncertainty in the parameter estimate. Table 1 presents the uncertainty ranges applied to key model parameters. All analyses were performed using Microsoft Excel (Microsoft Corporation; Redmond, WA) with @Risk (Palisade Corporation; Ithaca, NY).

RESULTS

The quality improvement programme reduces bloodstream infections and deaths at no additional cost in the base case analysis and represents a dominant strategy when compared with current practice. Table 3 compares programme and non-programme intensive care unit costs and outcomes for bloodstream infections prevented and deaths prevented.

Table 3 | Comparison of costs and outcomes between programme and non-programme intensive care units (ICUs)

	Mean	Median	2.5th – 97.5th Percentile
Non-programme ICU			
Bloodstream infections	52	52	39 – 66
Deaths	8	8	2 – 14
Costs (S)*	987,000	937,000	488,000 – 1,760,000
Programme ICU			
Bloodstream infections	10	9	3 – 29
Deaths	2	1	0 – 5
Costs ($)*	738,000	710,000	453,000 – 1,190,000
Benefit of programme†			
Bloodstream infections prevented	42	42	23 – 58
Deaths prevented	6	6	2 – 12
Net costs ($)	-249,000	-221,000	-976,000 – 300,000
Incremental cost effectiveness ratio (Prob.)			
Cost per infection prevented	Strongly dominant (0.80)‡		
Cost per death prevented	Strongly dominant (0.80)‡		

Mean, median, 2.5% and 97.5% centile estimates for outputs from probabilistic sensitivity analysis of 10,000 model runs representing uncertainty in epidemiologic and economic parameters are reported. All mean, median, and percentile values are expressed per 1,000 patients to make the scale easier to interpret. Values have been rounded to 3 significant digits at most.

*Costs are not presented separately for each outcome (bloodstream infection and death) because no additional cost was assumed to occur for death; discounted at 3%.

†Benefit of programme determined by subtracting programme ICU estimates from non-programme ICU estimates within the model

‡Probability that the programme is more effective and less costly than current practice

Figure 2 and online supplementary Figure S3 show the cost effectiveness planes comparing the joint density of incremental costs and incremental effects for 10,000 model iterations. Incremental refers to the difference in costs or effects between programme and non-programme intensive care units. The scatterplot illustrates the uncertainty surrounding the estimates of expected incremental cost and expected incremental effect (bloodstream infections prevented or deaths prevented) associated with the quality improvement programme compared to current practice.

Figure 2 shows that the mean point estimate for the difference in costs and effects between the programme and current practice is -$249,000 with 42 infections prevented per 1,000 patients. The location of the incremental cost-effect pairs indicates that there is limited uncertainty regarding the effectiveness of the programme, yet there is uncertainty regarding the number of infections prevented. For costs, the location and spread of points indicate uncertainty in the existence and magnitude of economic cost savings. In Figure S3, the mean point estimate for the difference in costs and effects between the programme and current practice is -$249,000 with 6 deaths prevented per 1,000 patients. There is similar uncertainty in the magnitude of deaths prevented and the existence and magnitude of cost savings. For both bloodstream infections prevented and deaths prevented, about 80% of the incremental cost-effect pairs fall below the horizontal axis, indicating that the programme is incrementally less costly and more effective than current practice (base case). The remaining 20% of points fall above the horizontal axis, indicating that the programme is incrementally more costly and more effective. The 95% confidence ellipses are calculated assuming a bivariate normal distribution and display the uncertainty surrounding incremental costs and effects. The ellipses cross the horizontal axis, indicating less than 95% confidence that the intervention is dominant.

Online supplementary figures S4 and S5 display tornado diagrams of the results of the probabilistic sensitivity analysis. The opportunity cost of bloodstream infections exerted the largest influence on the cost effectiveness of the programme for preventing bloodstream infections and deaths. As such, hospitals implementing the programme should know the opportunity costs they face due to bloodstream infections. The opportunity cost is calculated as the potential incremental net revenue opportunity per prevented infection. We provide an example of how to perform this calculation in the appendix. Discounting bloodstream infections or deaths at 3% in addition to costs, does not change the interpretation of our results. Similarly, discounting costs at 0% or 5% does not change the interpretation of our findings (see supplementary Table D).

DISCUSSION

This study represents the first formal cost effectiveness analysis of a nationally implemented quality improvement programme (the Keystone ICU project) in the US to decrease bloodstream infections in critically ill patients. One of the few large scale quality improvement projects to demonstrate long term sustainability, this programme has the potential to reduce bloodstream infections and deaths at no additional cost to US hospitals.

Comparison with other studies

Previous studies highlight both the importance and difficulty of developing a business case for quality improvement. A business case exists if healthcare organisations investing in an intervention reap a return on their investment.[36] Many prevention initiatives have suffered from a lack of evidence supporting a positive return on investment for hospitals and payers.[37] Incentive misalignment results in hospitals incurring costs to implement quality improvement

programmes while payers accrue the subsequent cost savings. A financial analysis of a replication of the Keystone ICU project in one tertiary hospital in Hawaii demonstrated that reducing bloodstream infections actually resulted in lower profit margins, thus creating a perverse incentive to provide a lower quality of care.[38] A different study calculated that, for every bloodstream infection prevented, the programme costs $5,404,[29] and suggested that it is cost saving when compared to the cost of an infection (which ranges from $6,000 to over $56,000[4 6 39-41]). However, both studies used inaccurate cost analyses that focused on the financial rather than the economic costs of bloodstream infections. These studies also did not account for uncertainty in the cost or effect estimates.

Our evaluation offers several improvements to these existing studies. First, whenever possible we used nationally representative data to determine provider salary and compensation costs, so as to increase the ability to generalise our findings. Second, we performed a probabilistic sensitivity analysis to quantify the uncertainty in our cost effectiveness estimates. Third, we considered the opportunity costs of bloodstream infections rather than financial costs. Our estimate of the cost of a bloodstream infection is based on the foregone hospital revenue that results whenever an infection occurs. From the perspective of the hospital, reducing the cost of bloodstream infections is tantamount to reducing this foregone revenue by redeploying intensive care unit beds for new admissions. Finally, we extended the evaluation to consider deaths prevented as an additional outcome because of its interest to clinicians and patients.

Limitations of the study

This evaluation has several limitations. First, the impact of patient heterogeneity, such as demographics and clinical characteristics on baseline risk, treatment effect, or resource

utilisation was not fully explored.[42] This evaluation sought instead to represent an average intensive care unit experience, in part because the data needed to explore subgroups are not available, but more importantly because the intervention applies to patients irrespective of these differences. It would be impractical—and possibly unethical—to only use this programme in subgroups of patients for whom greater benefit is expected. The programme is based on evidence-based practices for inserting central venous catheters—practices that should apply equally to all patients. Second, we did not evaluate costs outside the hospital setting, such as rehabilitation costs or productivity losses for delays returning to work incurred by patients suffering bloodstream infections. However, doing so would further support the cost effectiveness of the programme. We chose to examine costs from the perspective of the hospital because hospitals bear the greatest burden of nosocomial infection costs in the prospective payer system and demonstrating a business case is important for the dissemination of effective quality improvement programmes. Finally, this evaluation did not explore the use of antimicrobial catheters as an comparator because systematic reviews have come to differing conclusions about the extent of their effectiveness in preventing bloodstream infections, and many of the trials have been small and of a low quality.[43 44] In addition, the choice facing hospital decision makers is not necessarily a mutually exclusive choice between the Keystone ICU project or the use of antimicrobial catheters. The results of Keystone ICU project already reflect the use of various types of catheters because the programme itself did not specify catheter type. The parameter estimate for effectiveness of the programme used in this evaluation was derived from a cluster randomised controlled trial. In this setting it can be expected that the utilisation of antimicrobial catheters should be balanced between the intervention and control arms of the trial (though this was not explicitly measured), and the effectiveness estimate is attributable to the quality

improvement programme itself. The Keystone ICU project quality improvement programme is also a complex social intervention. Comparing it directly to technology or a device understates its broader effects, which may include reductions in sepsis and ventilator-associated pneumonia or reduced staff turnover resulting from an improved safety culture.[21] Data for these effects are limited in comparison to the data available for bloodstream infections, but recent evidence suggests that the Keystone ICU project significantly reduced rates of ventilator associated pneumonia in Michigan ICUs.[9] Inclusion of these additional beneficial effects for the same set of costs would further support the cost effectiveness of the programme.

Conclusions and implications of study findings

These findings have important implications for health care. Broad implementation of the Keystone ICU project in the US healthcare system could substantially reduce the morbidity and mortality associated with bloodstream infections and their economic costs to hospitals. Although the Centers for Disease Control and Prevention has demonstrated that significant reductions in bloodstream infections are indeed being realised for intensive care patients in the US,[45] over 800 medium and large hospitals continue to have high bloodstream infection rates.[46] Further dissemination of cost effective quality improvement programmes is needed. Although our analysis adopted a hospital perspective, payers also stand to benefit from the programme and can support dissemination efforts. Hospitals and payers should partner to reform the incentive structure facing hospitals in order to better support patient safety and quality. Payer support, such as covering or funding some intervention costs and imposing financial penalties on hospitals when patients develop bloodstream infections, could encourage uptake and dissemination of the programme. Future evaluations of this quality improvement programme in non-US settings can

incorporate country specific costs or extend the evaluation to consider additional outcomes, such as cases of ventilator-associated pneumonia prevented.

To conclude, this multifaceted quality improvement programme, currently being implemented by thousands of hospitals in the US, likely reduces unnecessary morbidity, mortality, and economic costs associated with central line-associated bloodstream infections.

Acknowledgements: We thank Susan M. Turley for her assistance in editing the manuscript.

Contributors: KRH is the guarantor and had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All the authors were involved in preparing this manuscript. KRH was responsible for the overall study design, data analysis, and interpretation of data, and wrote the initial draft of the manuscript. All other authors contributed to the study design, analysis and interpretation of data, and critical revision of the manuscript. LN, DOC, WJW, and PJP also provided supervision.

The study guarantor affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Funding: This study was conducted as part of KRH's doctoral training at the Johns Hopkins Bloomberg School of Public Health. KRH is supported by the Harry S. Truman Scholarship Foundation and by a training grant from the National Institutes of Health under award number T32 GM007309. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. All of the researchers were independent of the sponsors, and neither sponsor had any influence over the study design; collection, analysis, or interpretation of the data; writing of the manuscript; or decision to submit it for publication.

Role of the Sponsors: The Truman Scholarship Foundation and the National Institutes of Health had played no direct role in any aspect of this study. The researchers were independent of the sponsors and neither sponsor had any influence over the study design, collection, analysis or interpretation of the data, writing of the manuscript, or decision to submit it for publication.

Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that they had (1) No financial support for the submitted work. (2) PJP reports: receiving grant or contract support from the Agency for Healthcare Research and Quality, the Gordon and Betty Moore Foundation (research related to patient safety and quality of care), the National Institutes of Health (acute lung injury research), and the American Medical Association Inc. (improve blood pressure control); honoraria from various healthcare organizations for speaking on patient safety and quality (the Leigh Bureau manages most of these engagements); and book royalties from the Penguin Group for his book *Safe Patients, Smart Hospitals*. Dr. Pronovost is a paid strategic advisor to the Gordon and Betty Moore Foundation; receives stock and fees to serve as a director for Cantel Medical; and is a founder of *Patient Doctor Technologies*, a startup company that seeks to enhance the partnership between patients and clinicians with an application called Doctella; (3) No spouses, partners, or children with relationships with commercial entities that might have an interest in the submitted work and (4) No non-financial interests that may be relevant to the submitted work.

Ethics approval: Not required.

Data sharing: Data used for this study are available by emailing kherzer@jhmi.edu.

Figure legends

Figure 1 | Decision tree model. Decision tree model depicting programme versus no programme and its effects on outcomes in intensive care unit (ICU) patients. “Bloodstream infections” refers to central line-associated bloodstream infection.

Figure 2 | Cost effectiveness plane for bloodstream infections prevented with 95% confidence ellipses. Values on both axes have been multiplied by 1,000 to yield incremental costs and effects expressed per 1,000 patients to aid interpretation. Incremental refers to the difference in costs or effects between programme and non-programme intensive care units. Cost values in US dollars. Boxes in the plot region display the percentage of the distribution of incremental cost-effectiveness ratios falling above or below $0.

References

1. Mermel LA. Prevention of intravascular catheter-related infections. *Ann Intern Med* 2000;132(5):391-402.

2. Burke JP. Infection control - a problem for patient safety. *N Engl J Med* 2003;348(7):651-6. doi: 10.1056/NEJMhpr020557.

3. Klevens RM, Edwards JR, Richards CL, Jr., *et al.* Estimating health care-associated infections and deaths in U.S. hospitals, 2002. *Public Health Rep* 2007;122(2):160-6.

4. O'Grady NP, Alexander M, Dellinger EP, *et al.* Guidelines for the prevention of intravascular catheter-related infections. *Infect Control Hosp Epidemiol* 2002;23(12):759-69. doi: 10.1086/502007.

5. Digiovine B, Chenoweth C, Watts C, *et al.* The attributable mortality and costs of primary nosocomial bloodstream infections in the intensive care unit. *Am J Respir Crit Care Med* 1999;160(3):976-81. doi: 10.1164/ajrccm.160.3.9808145.

6. Pittet D, Tarara D, Wenzel RP. Nosocomial bloodstream infection in critically ill patients. Excess length of stay, extra costs, and attributable mortality. *JAMA* 1994;271(20):1598-601.

7. Pronovost P, Needham D, Berenholtz S, *et al.* An intervention to decrease catheter-related bloodstream infections in the ICU. *N Engl J Med* 2006;355(26):2725-32. doi: 10.1056/NEJMoa061115.

8. Berenholtz SM, Pronovost PJ, Lipsett PA, *et al.* Eliminating catheter-related bloodstream infections in the intensive care unit. *Crit Care Med* 2004;32(10):2014-20. doi: 10.1097/01.ccm.0000142399.70913.2f.

9. Berenholtz SM, Pham JC, Thompson DA, *et al.* Collaborative cohort study of an intervention to reduce ventilator-associated pneumonia in the intensive care unit. *Infect Control Hosp Epidemiol* 2011;32(4):305-14. doi: 10.1086/658938.

10. Lin DM, Weeks K, Bauer L, *et al.* Eradicating central line-associated bloodstream infections statewide: the Hawaii experience. *Am J Med Qual* 2012;27(2):124-9. doi: 10.1177/1062860611414299.

11. Lipitz-Snyderman A, Steinwachs D, Needham DM, *et al.* Impact of a statewide intensive care unit quality improvement initiative on hospital mortality and length of stay: retrospective comparative analysis. *BMJ* 2011;342:d219. doi: 10.1136/bmj.d219.

12. Bion J, Richardson A, Hibbert P, *et al.* 'Matching Michigan': a 2-year stepped interventional programme to minimise central venous catheter-blood stream infections in intensive care units in England. *BMJ Qual Saf* 2013;22(2):110-23. doi: 10.1136/bmjqs-2012-001325.

13. Marsteller JA, Sexton JB, Hsu YJ, *et al.* A multicenter, phased, cluster-randomized controlled trial to reduce central line-associated bloodstream infections in intensive care units. *Crit Care Med* 2012;40(11):2933-9. doi: 10.1097/CCM.0b013e31825fd4d8.

14. Niessen LW, Grijseels EW, Rutten FF. The evidence-based approach in health policy and health care delivery. *Soc Sci Med* 2000;51(6):859-69.

15. Grimshaw JM, Thomas RE, MacLennan G, *et al.* Effectiveness and efficiency of guideline dissemination and implementation strategies. *Health Technol Assess* 2004;8(6):iii-iv, 1-72.

16. Hoomans T, Evers SM, Ament AJ, *et al.* The methodological quality of economic evaluations of guideline implementation into clinical practice: a systematic review of

empiric studies. *Value Health* 2007;10(4):305-16. doi: 10.1111/j.1524-4733.2007.00175.x.

17. Graves N, Harbarth S, Beyersmann J*, et al.* Estimating the cost of health care-associated infections: mind your p's and q's. *Clin Infect Dis* 2010;50(7):1017-21. doi: 10.1086/651110.

18. Veenstra DL, Saint S, Sullivan SD. Cost-effectiveness of antiseptic-impregnated central venous catheters for the prevention of catheter-related bloodstream infection. *JAMA* 1999;282(6):554-60.

19. Halton KA, Cook DA, Whitby M*, et al.* Cost effectiveness of antimicrobial catheters in the intensive care unit: addressing uncertainty in the decision. *Crit Care* 2009;13(2):R35. doi: 10.1186/cc7744.

20. Pronovost P, Weast B, Rosenstein B*, et al.* Implementing and validating a comprehensive unit-based safety program. *J Patient Saf* 2005;1(1):33-39.

21. Pronovost PJ, Berenholtz SM, Goeschel C*, et al.* Improving patient safety in intensive care units in Michigan. *J Crit Care* 2008;23(2):207-21. doi: 10.1016/j.jcrc.2007.09.002.

22. Pronovost PJ, Berenholtz SM, Needham DM. Translating evidence into practice: a model for large scale knowledge translation. *BMJ* 2008;337:a1714. doi: 10.1136/bmj.a1714.

23. Fletcher S. Catheter-related bloodstream infection. *Contin Educ Anaesth Crit Care Pain* 2005;5(2):49-51. doi: 10.1093/bjaceaccp/mki011.

24. Brun-Buisson C. New technologies and infection control practices to prevent intravascular catheter-related infections. *Am J Respir Crit Care Med* 2001;164(9):1557-8. doi: 10.1164/ajrccm.164.9.2109051.

25. Veenstra DL, Saint S, Saha S, *et al.* Efficacy of antiseptic-impregnated central venous catheters in preventing catheter-related bloodstream infection: a meta-analysis. *JAMA* 1999;281(3):261-7.

26. Martin MA, Pfaller MA, Wenzel RP. Coagulase-negative staphylococcal bacteremia. Mortality and hospital stay. *Ann Intern Med* 1989;110(1):9-16.

27. Smith RL, Meixler SM, Simberkoff MS. Excess mortality in critically ill patients with nosocomial bloodstream infections. *Chest* 1991;100(1):164-7.

28. Arnow PM, Quimosing EM, Beach M. Consequences of intravascular catheter sepsis. *Clin Infect Dis* 1993;16(6):778-84.

29. Waters HR, Korn R, Jr., Colantuoni E, *et al.* The business case for quality: economic analysis of the Michigan Keystone Patient Safety Program in ICUs. *Am J Med Qual* 2011;26(5):333-9. doi: 10.1177/1062860611410685.

30. Graves N, Weinhold D, Tong E, *et al.* Effect of healthcare-acquired infection on length of hospital stay and cost. *Infect Control Hosp Epidemiol* 2007;28(3):280-92. doi: 10.1086/512642.

31. Graves N. Economics and preventing hospital-acquired infection. *Emerg Infect Dis* 2004;10(4):561-6. doi: 10.3201/eid1004.020754.

32. Society of Critical Care Medicine. *Compensation of Critical Care Professionals*: Society of Critical Care Medicine, 2009.

33. Wunsch H, Angus DC, Harrison DA, *et al.* Variation in critical care services across North America and Western Europe. *Crit Care Med* 2008;36(10):2787-93, e1-9. doi: 10.1097/CCM.0b013e318186aec8.

34. American Hospital Association. *AHA Hospital Statistics. 2013 ed*: American Hospital Association, 2012.

35. Pronovost PJ, Goeschel CA, Colantuoni E*, et al.* Sustaining reductions in catheter related bloodstream infections in Michigan intensive care units: observational study. *BMJ* 2010;340:c309. doi: 10.1136/bmj.c309.

36. Leatherman S, Berwick D, Iles D*, et al.* The business case for quality: case studies and an analysis. *Health Aff (Millwood)* 2003;22(2):17-30.

37. Galvin RS, Delbanco S, Milstein A*, et al.* Has the leapfrog group had an impact on the health care market? *Health Aff (Millwood)* 2005;24(1):228-33. doi: 10.1377/hlthaff.24.1.228.

38. Hsu E, Lin D, Evans SJ*, et al.* Doing well by doing good: assessing the cost savings of an intervention to reduce central line-associated bloodstream infections in a Hawaii hospital. *Am J Med Qual* 2014;29(1):13-9. doi: 10.1177/1062860613486173.

39. Warren DK, Quadir WW, Hollenbeak CS*, et al.* Attributable cost of catheter-associated bloodstream infections among intensive care patients in a nonteaching hospital. *Crit Care Med* 2006;34(8):2084-9. doi: 10.1097/01.CCM.0000227648.15804.2D.

40. Halton K, Graves N. Economic evaluation and catheter-related bloodstream infections. *Emerg Infect Dis* 2007;13(6):815-23. doi: 10.3201/eid1306.070048.

41. Dimick JB, Pronovost PJ, Heitmiller RF*, et al.* Intensive care unit physician staffing is associated with decreased length of stay, hospital cost, and complications after esophageal resection. *Crit Care Med* 2001;29(4):753-8.

42. Grutters JP, Sculpher M, Briggs AH*, et al.* Acknowledging patient heterogeneity in economic evaluation : a systematic literature review. *Pharmacoeconomics* 2013;31(2):111-23. doi: 10.1007/s40273-012-0015-4.

43. Niel-Weise BS, Stijnen T, van den Broek PJ. Anti-infective-treated central venous catheters: a systematic review of randomized controlled trials. *Intensive Care Med* 2007;33(12):2058-68. doi: 10.1007/s00134-007-0897-3.

44. Hockenhull JC, Dwan K, Boland A*, et al.* The clinical effectiveness and cost-effectiveness of central venous catheters treated with anti-infective agents in preventing bloodstream infections: a systematic review and economic evaluation. *Health Technol Assess* 2008;12(12):iii-iv, xi-xii, 1-154.

45. Center for Disease Control and Prevention. *National and State Healthcare Association Infections Progress Report*. Atlanta, 2014.

46. Wise ME, Scott RD, 2nd, Baggs JM*, et al.* National estimates of central line-associated bloodstream infections in critical care patients. *Infect Control Hosp Epidemiol* 2013;34(6):547-54. doi: 10.1086/670629.

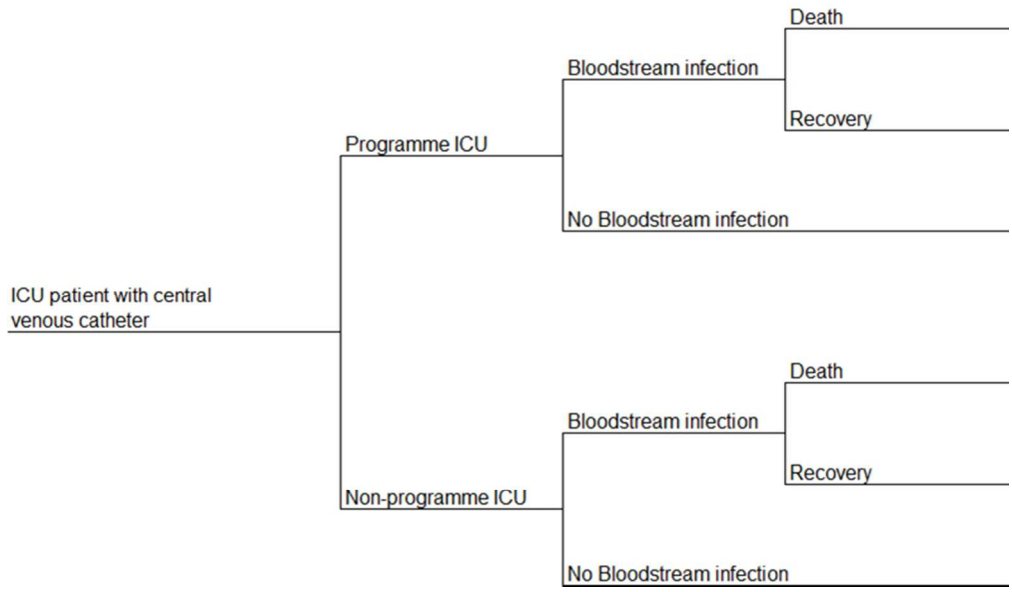


Figure 1 | Decision tree model depicting programme versus no programme and its effects on outcomes in intensive care unit (ICU) patients. "Bloodstream infections" refers to central line-associated bloodstream infection.
233x136mm (86 x 86 DPI)

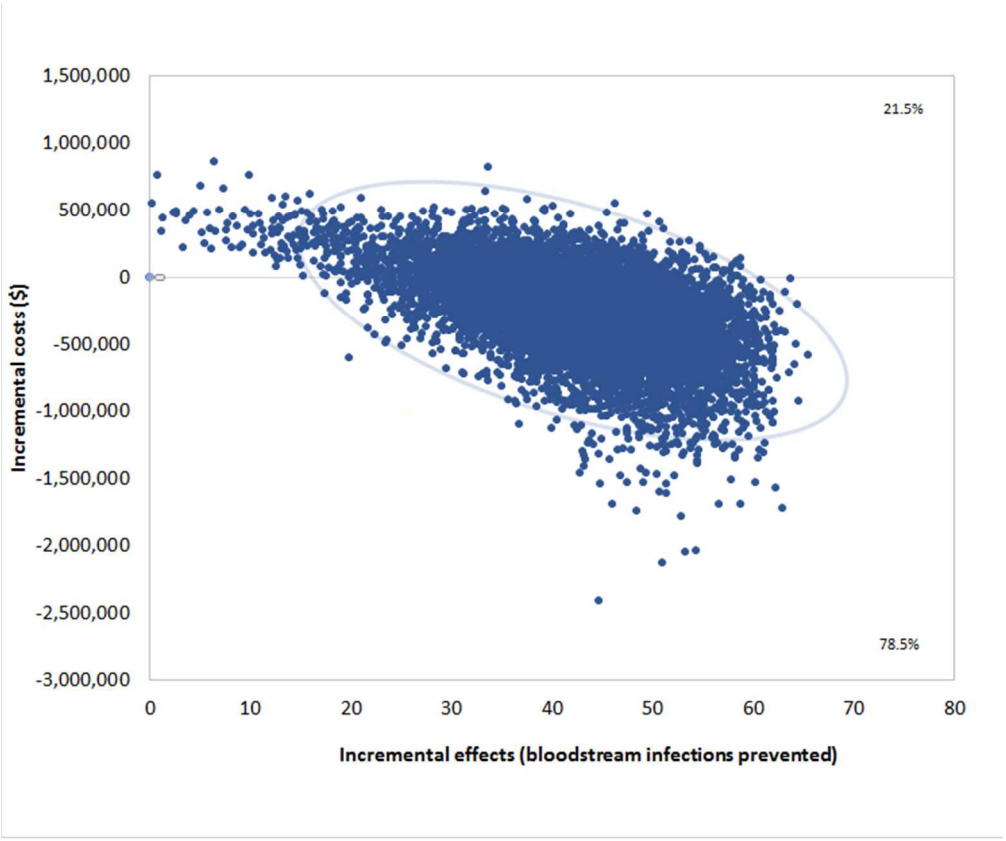


Figure 2 | Cost effectiveness plane for bloodstream infections prevented with 95% confidence ellipses. Values on both axes have been multiplied by 1,000 to yield incremental costs and effects expressed per 1,000 patients to aid interpretation. Incremental refers to the difference in costs or effects between programme and non-programme intensive care units. Cost values in US dollars. Boxes in the plot region display the percentage of the distribution of incremental cost-effectiveness ratios falling above or below $0.
196x163mm (96 x 96 DPI)

Web only appendices and tables

Calculation of the economic cost of a bloodstream infection

As described in the main text, determining the economic cost of a bloodstream infection requires estimating the opportunity costs and variable costs associated with infection.[1] In this analysis, we do not consider the variable costs (e.g., medications and supplies) because they contribute less to the total economic cost than do the opportunity costs. In addition, the probabilistic sensitivity analysis accounts for the variability in the economic cost over a wide range.

The follow steps were taken to estimate the opportunity cost of bloodstream infection. Based on a recent meta analysis, the average attributable excess hospital length of stay for bloodstream infections is 10.4 days.[2] Dividing by the average length of stay for all discharges in acute care hospitals in the United States yields the potential incremental case throughput. Multiplying this potential case throughput per infection prevented by the national average net revenue per equivalent discharge results in a point estimate of $19,617 (Table A). Using an economic interpretation, this represents the opportunity cost of lost revenue for a single infection. The results of the probabilistic analysis incorporating uncertainty in several of the parameters are displayed in Table 2. We then calculated the 5-year discounted cost of a bloodstream infection, which is the value used in the decision tree model described in the main text.

Table A. Calculation of economic (opportunity) cost of a bloodstream infection

	Value	Calculation	Uncertainty	Source
Average length of stay—all discharges (days)	4.8	A		CDC—NHDS
Excess total average length of stay attributable to bloodstream infection, i.e., the potential reduction in total length of stay per prevented infection (days)	10.4	B	6.9 to 15.2	Zimlichman
Potential incremental case throughput	2.17	C = B/A		
Median net revenue per equivalent discharge ($)	9,054	D	7,896 to 10,327 (25^{th} and 75^{th} percentile, respectively)	Cleverley and Associates
Potential incremental net revenue opportunity per prevented infection, i.e., economic opportunity cost per infection ($)	19,617	E = C x D		

Table B. Results of probabilistic analysis

Mean	19,951
Standard Deviation	5,978

Abbreviations: CDC=Centers for Disease Control and Prevention, NHDS=National Hospital Discharge Survey

Approach for estimating an average per patient cost of the quality improvement programme

Given that the Keystone ICU project is implemented at the ICU level—and its costs have been estimated at the intensive care unit level—but the decision tree model is implemented at a patient level, a per patient cost of the programme must be determined. Ultimately, this depends on the cost of the programme to a hospital and the number of intensive care unit patients receiving central venous catheters in that hospital (patients who represent the population that stands to benefit from the bloodstream infection prevention effort). It can be argued that all intensive care unit patients in a hospital stand to benefit (regardless of whether they receive a central venous catheter or not) because of the culture change components of the programme, but the approach used here is more conservative.

We estimated a per patient cost of the programme by first deriving a national annual cohort of intensive care unit patients exposed to central venous catheters. To do this, we multiplied 4.85 million estimated annual intensive care unit admissions in the US by an estimate of the proportion of patients admitted to an intensive care unit who receive a central venous catheter,[3] yielding 1.8 million patients who had catheters. We then divided the estimate of 1.8 million patients by the number of hospitals that reported having adult intensive care units in the American Hospital Association Annual Survey of Hospitals.[4] This provided an average number of "exposed" patients per hospital (Table 3). Finally, we divided total costs of the programme per hospital by the number of patients per hospital to yield an average cost for the programme per patient.

Table C. Calculation of the average number of ICU patients with CVCs

	Base case	**Low value**†	**High value**†
Number of annual ICU admissions in US	4,850,000*	4,000,000	5,700,000
X % of ICU admissions receiving CVCs	38%	17%	48%
= Number of ICU patients receiving CVCs	**1,843,000**		
Number of US hospitals with adult ICUs	4,355		
Average number of ICU patients with CVCs per hospital per year	**423**		

*Midpoint between the lowest and highest values identified in the literature
†The low value and the high value were used in the probabilistic model to capture the uncertainty in the calculation.
Abbreviation: ICU—intensive care unit, CVC—central venous catheter

Based on this calculation there is an average of 423 intensive care unit patients with central venous catheters per hospital per year in the United States (the average does not distinguish between small hospitals or large hospitals). Multiplying this by 5 to reflect the 5-year period used in this cost effectiveness analysis yields 2,115 patients. Diving this by the discounted cost of the quality improvement programme for a single hospital over 5 years ($990,340) results in a per patient cost of the programme of $468. For the main analysis presented in the paper, we implemented these calculations using Monte Carlo simulation to capture the uncertainty in the

base case parameter values. Doing so results in different estimates than the basic arithmetic used here. As such, we calculated that the mean per patient cost of the programme was $540 with a standard deviation of $120 and we applied a distribution that was lognormal based on normal mean.

This approach has several limitations. First, deriving a patient cost estimate of the programme was limited by a lack of appropriate individual-based national data on central line utilisation among intensive care unit patients. We consulted experts to inquire about less apparent sources of data to aid in the estimation of this parameter but consensus emerged that we would need to make several assumptions to derive this estimate. These assumptions were based on published data in the critical care literature and reputable national surveys.[4 5] To address the uncertainty in our estimate we tested a large standard deviation for the parameter in the probabilistic sensitivity analysis. The estimate is intended to reflect an average. It is likely that hospitals with more intensive care unit beds benefit from economies of scale when implementing the programme, providing a lower programme cost per patient.

Table D. Full numerical results from all analyses

	Incremental cost effectiveness ratio					
Model	**Mean**	**Median**	**2.5th Percentile**	**97.5th Percentile**	**Prob. Negative**	**Prob. Positive**
Main Analyses						
Bloodstream infections prevented	-4,401	-5,204	-20,169	10,758	0.79	0.21
Deaths prevented	-36,724	-34,149	-215,592	90,695	0.79	0.21
Sensitivity Analyses						
Bloodstream infections discounted	-3,866	-5,442	-20,912	10,921	0.79	0.21
Deaths discounted	-38,191	-36,784	-220,378	92,979	0.79	0.21
0% discounting of costs, infections prevented	-5,019	-5,578	-21,467	10,923	0.79	0.21
0% discounting of costs, deaths prevented	-40,289	-36,855	-216,212	93,041	0.79	0.21
5% discounting of costs, infections prevented*	-4,503	-4,821	-19,512	10,268	0.78	0.22
5% discounting of costs, deaths prevented*	-32,925	-32,605	-196,368	80,484	0.79	0.21

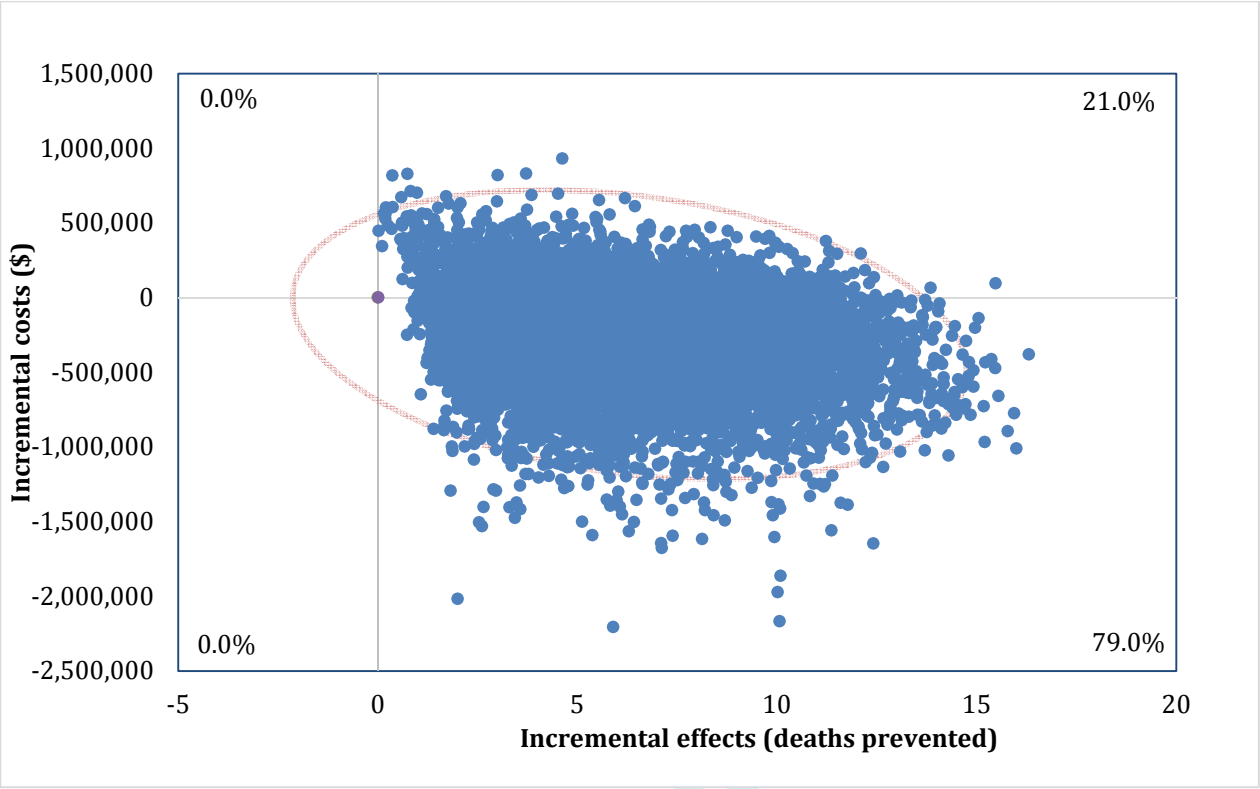
*The average of the 5-year stream of discounted costs was used.

References

1. Graves N, Halton K, Lairson D. Economics and preventing hospital-acquired infection: broadening the perspective. *Infect Control Hosp Epidemiol* 2007;28(2):178-84. doi: 10.1086/510787.
2. Zimlichman E, Henderson D, Tamir O*, et al.* Health care-associated infections: a meta-analysis of costs and financial impact on the US health care system. *JAMA Intern Med* 2013;173(22):2039-46. doi: 10.1001/jamainternmed.2013.9763.
3. Warren DK, Quadir WW, Hollenbeak CS*, et al.* Attributable cost of catheter-associated bloodstream infections among intensive care patients in a nonteaching hospital. *Crit Care Med* 2006;34(8):2084-9. doi: 10.1097/01.CCM.0000227648.15804.2D.
4. American Hospital Association. *AHA Hospital Statistics. 2013 ed*: American Hospital Association, 2012.
5. Wunsch H, Angus DC, Harrison DA*, et al.* Comparison of medical admissions to intensive care units in the United States and United Kingdom. *Am J Respir Crit Care Med* 2011;183(12):1666-73. doi: 10.1164/rccm.201012-1961OC.

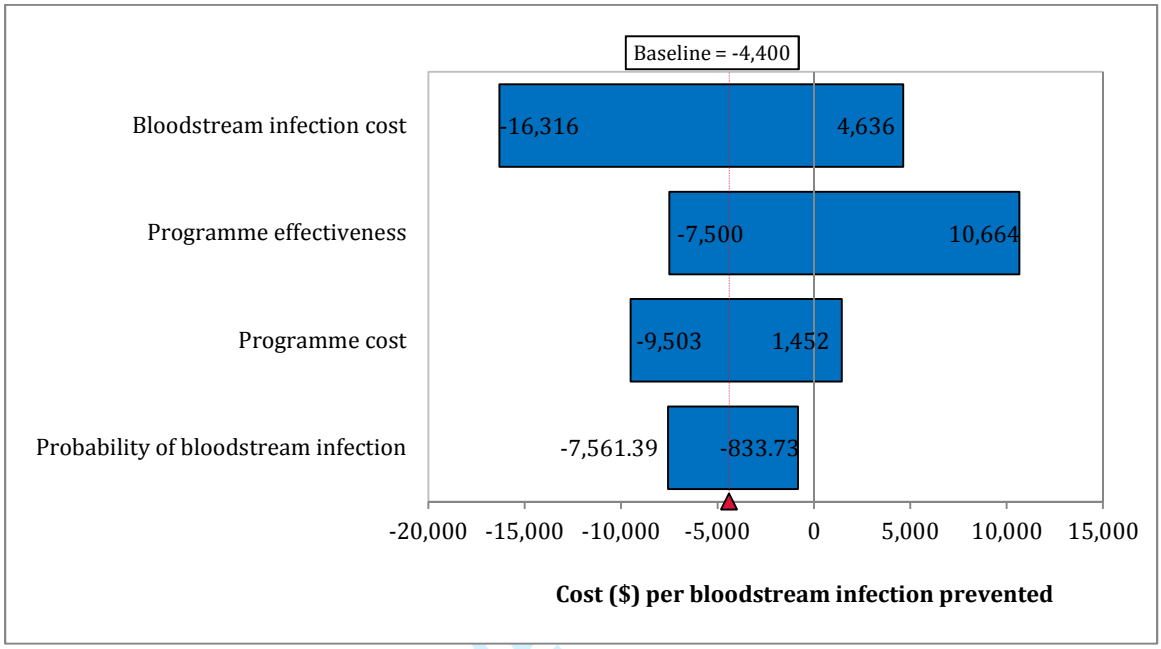
Web only figures

Figure S3 | Cost effectiveness plane for deaths averted due to bloodstream infections prevented



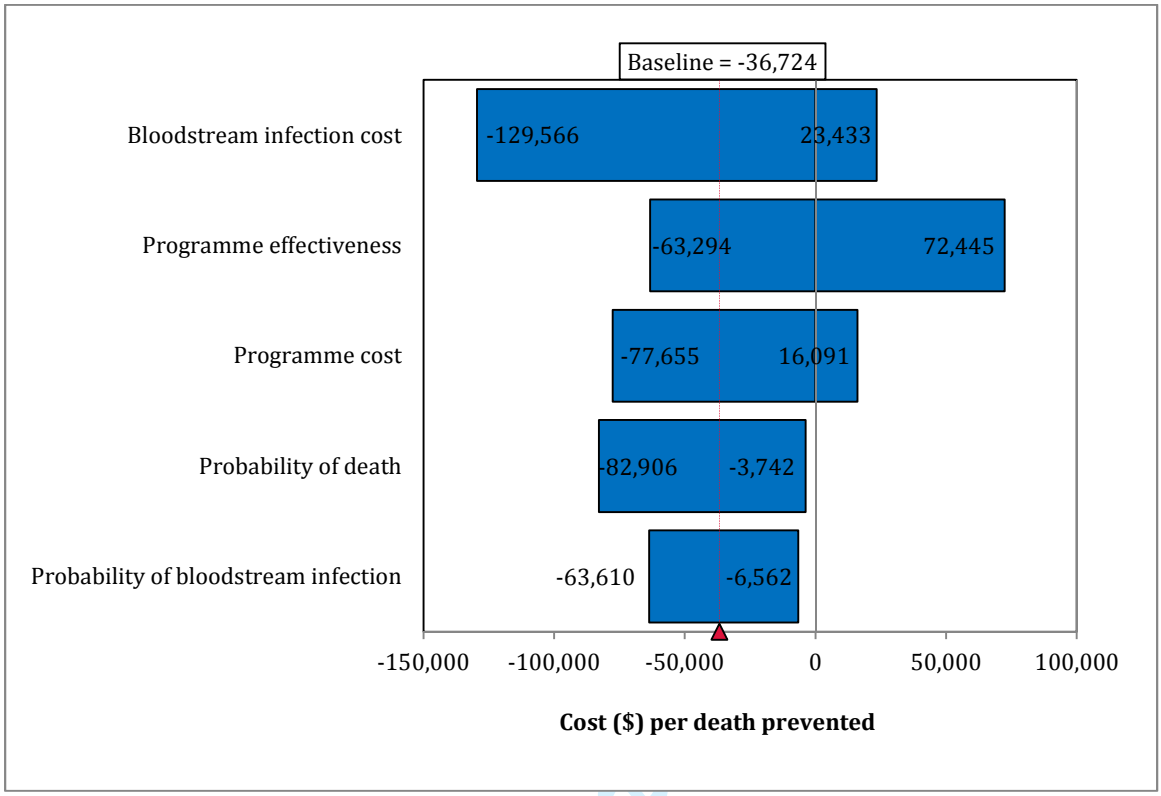
Cost effectiveness plane for deaths averted due to bloodstream infections prevented with 95% confidence ellipses. Values on both axes have been multiplied by 1,000 to yield incremental costs and effects expressed per 1,000 patients to aid interpretation. Incremental refers to the difference in costs or effects between programme and non-programme intensive care units. Cost values in US dollars. Boxes in the plot region display the percentage of the distribution of incremental cost effectiveness ratios falling in each quadrant.

Figure S4 | Tornado diagram for bloodstream infections prevented



Tornado diagram of model inputs ranked by effect on the mean cost per bloodstream infection prevented. Each parameter was simultaneously sampled 10,000 times from an underlying distribution that reflects uncertainty in the parameter estimate. Cost values are in US dollars.

Figure S5 | Tornado diagram for deaths averted due to bloodstream infections prevented



Tornado diagram of model inputs ranked by effect on the mean cost per death prevented. Each parameter was simultaneously sampled 10,000 times from an underlying distribution that reflects uncertainty in the parameter estimate. Cost values are in US dollars.

Table

Table 1| CHEERS checklist—Items to include when reporting economic evaluations of health interventions Nos. refer to pages

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	3
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	5-6
		Present the study question and its relevance for health policy or practice decisions.	5-6
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	7
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	7
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	7
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	6
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	7
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	11, 12
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	12
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	11
	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	NA
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	8-11
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	11
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	6; Fig
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	6
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	12
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	8
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	13-15
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	

(continued)

Section/item	Item No	Recommendation	Reported on page No/ line No
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	13-15
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	NA
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	15-19
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	20
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	21

For consistency, the CHEERS statement checklist format is based on the format of the CONSORT statement checklist

BMJ Open

Cost effectiveness of a quality improvement programme to reduce central line-associated bloodstream infections in intensive care units in the United States

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-006065.R1
Article Type:	Research
Date Submitted by the Author:	15-Aug-2014
Complete List of Authors:	Herzer, Kurt; Johns Hopkins School of Medicine, Medical Scientist Training Program Niessen, Louis; University of Warwick, Liverpool School of Tropical Medicine, Centre for Applied Health Research and Delivery (CAHRD) Constenla, Dagna; Johns Hopkins Bloomberg School of Public Health, International Vaccine Access Center Ward, William; Johns Hopkins Bloomberg School of Public Health, Health Policy and Management Pronovost, Peter; The Johns Hopkins University School of Medicine, Anesthesiology and Critical Care Medicine
Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Health economics, Health services research, Health policy, Intensive care, Infectious diseases
Keywords:	Health economics < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Health & safety < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Infection control < INFECTIOUS DISEASES, Adult intensive & critical care < INTENSIVE & CRITICAL CARE

Cost effectiveness of a quality improvement programme to reduce central line-associated bloodstream infections in intensive care units in the United States

Kurt R Herzer, Louis Niessen, Dagna O Constenla, William J Ward Jr, Peter J Pronovost

Medical Scientist Training Program, Johns Hopkins School of Medicine, 1830 East Monument Street, Baltimore, MD 21205, USA

Kurt R Herzer

MD-PhD student

Centre for Applied Health Research and Delivery (CAHRD), Liverpool School of Tropical Medicine, University of Warwick, Coventry, CV4 7AL, United Kingdom

Louis Niessen

Professor

International Vaccine Access Center, Johns Hopkins Bloomberg School of Public Health, 855 North Wolfe Street, Baltimore, MD 21205, USA

Dagna O Constenla

Associate Scientist

Department of Health Policy and Management, Johns Hopkins Bloomberg School of Public Health, 624 North Broadway Street, Baltimore, MD 21205, USA

William J Ward Jr

Associate Professor

Armstrong Institute for Patient Safety and Quality, Johns Hopkins Medicine, 750 East Pratt Street, Baltimore, MD 21202, USA

Peter J Pronovost

Professor

Correspondence to: Kurt Herzer, 1830 East Monument Street, Baltimore, MD 21205, USA; kherzer@jhmi.edu; 443-900-2415

Keywords: quality improvement, cost effectiveness, nosocomial infections, health policy, checklists

Word Count: 3,424

Abstract

Objective: To assess the cost effectiveness of a multifaceted quality improvement programme focused on reducing central line-associated bloodstream infections in intensive care units.

Design: Cost effectiveness analysis using a decision tree model to compare programme to non-programme intensive care units.

Setting: United States (US).

Population: Adult patients in the intensive care unit.

Costs: Economic costs of the programme and of central line-associated bloodstream infections were estimated from the perspective of the hospital and presented in 2013 US dollars.

Main outcome measures: Central line-associated bloodstream infections prevented, deaths averted due to central line-associated bloodstream infections prevented, and incremental cost effectiveness ratios. Probabilistic sensitivity analysis was performed.

Results: Compared to current practice, the programme is strongly dominant and reduces bloodstream infections and deaths at no additional cost. The probabilistic sensitivity analysis showed that there was an almost 80% probability that the programme reduces bloodstream infections and the infections' economic costs to hospitals. The opportunity cost of a bloodstream infection to a hospital was the most important model parameter in these analyses.

Conclusions: This multifaceted quality improvement programme, as it is currently implemented by hospitals on an increasingly large scale in the US, likely reduces the economic costs of central line-associated bloodstream infections for US hospitals. Awareness among hospitals about the programme's benefits should enhance implementation. The programme's implementation has the potential to substantially reduce morbidity, mortality, and economic costs associated with central line-associated bloodstream infections.

Article summary

Strengths and limitations of this study

- This study was conducted according to best practices in cost effectiveness analysis and demonstrates that a multifaceted quality improvement programme can reduce the economic costs of central line-associated bloodstream infections for hospitals.
- We used nationally representative data sources to increase generalisability and performed a probabilistic sensitivity analysis to quantify the uncertainty in our cost effectiveness estimates.
- Due to data limitations we were unable to assess the impact of patient heterogeneity, such as demographics and clinical characteristics, on baseline risk, treatment effect, or resource utilisation. We did not evaluate costs outside the acute hospital setting, such as rehabilitation costs or productivity losses for delays returning to work.

INTRODUCTION

Central line-associated bloodstream infections (CLABSI) are common, expensive to payers and patients, and potentially fatal.[1 2] Each year, nearly 80,000 Americans develop CLABSIs in the intensive care unit (ICU), and more than 25,000 of these patients die.[3] A single infection can cost payers as much as $56,000, culminating in over $2 billion in related costs per year in the United States.[4] CLABSIs in ICU patients have an estimated attributable mortality rate of 14 to 40%, with a prolonged length of stay of 7.5 to 25 days.[5 6]

The Keystone ICU project, first launched in Michigan in 2004 and since scaled across the United States, Spain, Peru, Pakistan, and the United Kingdom, has captured the interest and attention of patients, payers, and policymakers for its substantial, sustained, and scalable reductions in preventable nosocomial infections. 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 infection prevention programmes in their ICUs as standard practice. The programme has been evaluated through prospective cohort studies,[7-10] retrospective observational studies using claims data,[11] and both cluster nonrandomised[12] and randomised controlled trials.[13] When viewed collectively, this evidence suggests that the programme is associated with substantial reductions in both CLABSIs and mortality in ICU patients.

In spite of commendable investment in this programme to manage the undesirable consequences of CLABSIs, an important question remains unanswered: compared with current practice, is this programme cost effective for US hospitals? Reporting of economic data in quality improvement studies is uncommon, and there are few formal cost effectiveness analyses of quality improvement programmes.[14-16] Similarly, because the estimated gross costs of

CLABSIs to the healthcare system are very high, the conclusion that expanding infection control efforts will be cost saving (relative to the costs incurred by expanded efforts) is accepted without rigorous analysis.[17] This paper examines the cost changes and effectiveness of the Keystone ICU project from the perspective of the hospital using nationally representative data sources from the United States.

METHODS

Overview of the analysis

We developed a decision tree model to address the choice faced at an individual hospital about implementing the programme (Figure 1). The use of a decision tree approach is justified by the short-term progression of CLABSIs. The model assumes that patients do not experience other adverse effects of catheterisation, such as catheter colonisation leading to local infection, hypersensitivity reactions, or mechanical complications such as pneumothorax. The Keystone ICU project instead focused on infectious complications, because they are more common, more costly, and often fatal.[18] Consistent with other economic evaluations of CLABSIs in the ICU setting, we assumed that the consequences of infection are independent of age, patient disease severity, and the causative organism.[18 19] These assumptions are congruent with the programme itself, which does not discriminate between subgroups of patients based on these factors.

The comparator was current practice as the most realistic alternative faced by organisations seeking to implement the programme. Current practice encompasses on-going or existing activities that might influence the risk of infection amongst patients, such as the use of anti-infective central venous catheters.

The target population consisted of adult (18 years or older) ICU patients in accordance with studies of the Keystone ICU project and its subsequent replications.[13] Because costs and benefits only accrue while the programme is implemented, the time frame and analytic horizon are fundamentally the same. We used a time horizon of five years. This analysis was performed from the hospital's perspective. Our study aims to address the following question: is implementation of this quality improvement programme to decrease CLABSIs in the ICU a cost-effective approach when compared with current practice in US hospitals?

Quality improvement programme

Details of the programme and its conceptual approach have been described elsewhere.[20-22] In brief, this multifaceted programme employed clinician communication tools, teamwork, and safety culture assessment and improvement tools (known as the Comprehensive Unit-based Safety Program [CUSP]), and a five-item, evidence-based checklist for correctly inserting central venous catheters. The five components of the checklist included using basic hand hygiene, exercising full barrier precautions, cleaning the skin with chlorhexidine, avoiding the femoral site when possible, and removing any unnecessary catheters. A model for translating evidence into practice identified and mitigated local barriers to implementation of the checklist.[22] Quarterly infection rates measured at the ICU level were used to monitor progress toward the goal of reducing CLABSIs.

Model inputs

Table 1 shows the key parameters used in the decision tree model, such as probabilities and cost inputs as well as the effectiveness of the programme, which are described in detail in the following sections.

Table 1 | Parameters used in the decision tree model

Parameter	Distribution	Source
Probability of CLABSI*	Beta: 0.052 (SD 0.0074)	18,25
Death attributable to CLABSI	Beta: 0.15 (SD 0.056)	6
Incidence rate ratio of programme versus non-programme ICUs	Lognormal based on normal mean 0.19 (SD 0.13)	13
Total cost ($):		
CLABSI (per patient)†	Lognormal based on normal mean 18,793 (SD 5,533)	33
Programme (per patient)†	Lognormal based on normal mean 540 (SD 120)	29

CLABSI = central-line associated bloodstream infection, ICU = intensive care unit
*Conditional probability of a CLABSI given exposure to a central venous catheter, assumes standard (non-antimicrobial) catheter.
†Discounted costs presented

Risk of CLABSI and death

Estimates of the risk of CLABSI given exposure to a central venous catheter varied from 3.0% to as much as 16.0%.[23 24] We used a probability estimate of 5.2% for a standard catheter, derived from a meta analysis of 13 randomised controlled trials from a previous economic evaluation.[18 25] Estimates of the attributable mortality of CLABSI ranged from 14 to 40%.[5 6 26 27] We used a point estimate of 15%.

Costs

Estimates of payer costs attributable to CLABSI varied widely, from as little as $6,000 to over $56,000.[4 6 18 28] The reasons for this variation can be attributed to the small sample

sizes of studies, challenges allocating inpatient costs, perspectives used, the types of cost categories included, and the methodology used for estimation.[29] Existing studies have largely focused on financial costs (or hospital charges or payer costs) rather than opportunity costs and so they may incorrectly estimate the economic cost of CLABSIs to hospitals. We considered the economic cost of CLABSIs in terms of the increased length of stay and variable costs associated with that occurrence.[30] Given that a significant amount of hospital costs are fixed in the short run, the economic viability of quality improvement programmes that reduce CLABSIs rests on two things: deploying the bed-days freed by shorter lengths of stay for new admissions and reducing utilization of medications and supplies. The value of the new admissions, (the potential incremental net revenue opportunity per prevented infection) represents the economic cost of infection and accordingly, the potential economic cost avoidance resulting from infection prevention.[31] Using this approach, we estimated that the discounted cost of a CLABSI was $18,793 (see appendix Tables A and B for details of this calculation).

Start-up costs and recurring costs associated with the quality improvement programme were assigned using an activity-based micro-costing of the programme performed in six hospitals in Michigan.[29] We assumed that start-up costs occurred in the first year of implementation and did not discount them. Capital items, such as bloodstream infection line carts, were annualised assuming a five-year useful life and 3% discount rate. We included the opportunity costs of key personnel whose time was committed to the programme even though a hospital may not incur any financial costs related to personnel who are already on staff. We estimated this cost by multiplying each staff person's percentage effort committed to the programme by an estimate of that position's annual compensation. We used the Society of Critical Care Medicine's annual compensation estimates from 2009 for critical care physicians, nurses, pharmacists, and

respiratory therapists.[32] The salary for infection control preventionists was based on the Bureau of Labor Statistics's 2011 Occupational Employment Statistics and we added 30% benefits. Table 2 presents a detailed itemisation of the start-up costs and recurring costs of the programme. Start-up costs were approximately $80,000 and recurring costs were approximately $192,000 per hospital per year. Personnel costs were the largest contributor, comprising 95% of start-up costs and 89% of recurring costs.

Table 2 | Itemisation of programme costs (per hospital)

Cost category	Start-up costs	Recurring costs*
Personnel ($)		
Critical care physicians (2 on average per hospital)	26,004	71,953
Nurses (8 on average per hospital)	44,406	75,306
Respiratory therapists	4,605	7,923
Infection control preventionists	1,981	7,855
Pharmacists	2,725	7,962
Education and Training ($)		
Education and training expenses	3,579	
Capital Items ($)		
CLABSI line cart/central line insertion cart (annual equivalent cost)	426	426
Materials ($)		
Chlorohexidine		2,378
Oral care kits		6,933
Sterile central line dressing kits		11,555
Total ($)	83,725	192,292

CLABSI = central line-associated bloodstream infection
*Recurring costs occur each year that the intervention is in place; as such, this total represents the annual recurring cost (not discounted as presented here).

We estimated a per patient cost of the programme by deriving an average number of ICU patients per hospital who had central venous catheters (the patients most likely to benefit from the programme's prevention efforts). To calculate this, we first derived a national annual cohort of ICU patients exposed to central venous catheters by multiplying the total annual ICU

admissions in the US by an estimate of the proportion of patients admitted to an ICU that receive central venous catheters.[33] We then divided this group of ICU admissions with central venous catheters by the number of hospitals that reported having adult ICUs in the American Hospital Association Annual Survey of Hospitals,[34] yielding an average number of "exposed" patients per hospital. Finally, we divided the total costs of the programme per hospital by the number of patients per hospital to yield an average cost for the programme per patient of $540 (standard deviation, 120). Appendix Table C contains additional details of this calculation, including the uncertainty ranges incorporated into the estimate.

All costs were adjusted to 2013 US dollars using the Consumer Price Index for medical care services. Recurring costs were discounted by 3% annually. In separate sensitivity analyses, we examined the effect of not discounting costs and of discounting costs by 5%.

Effectiveness

We based our estimate of the programme's effectiveness on a cluster randomised controlled trial that found an 81% reduction in CLABSI rates comparing programme ICUs to control ICUs (incidence rate ratio, 0.19; 95% confidence interval, 0.06–0.57).[13] We used the confidence interval of this point estimate, a measure of uncertainty in the programme's effectiveness, to derive a standard deviation of the estimate for probabilistic sensitivity analysis. This effectiveness parameter was measured at the ICU level but in our model we assumed that it applied to individual patients. This ecological assumption was necessary because there are no patient level effectiveness estimates available from the Keystone ICU project. The standard deviation of the estimate captures the heterogenic reality that the intervention benefit is not uniform among ICU patients.

To calculate the base case probability of a CLABSI in the programme arm of the decision tree, we multiplied the probability of CLABSI by the incidence rate ratio (0.19) from the trial. We assumed that by the end of the first year of implementation, programme ICUs achieve this reduction. The original ICUs that implemented the programme maintained the reduction for the subsequent 10 years (Sam Watson, written communication, August 18, 2013). We assumed this to be true for the five-year period used in this evaluation.[36]

The number of annual ICU admissions requiring catheters, the probability of infection, and the attributable mortality parameters were assumed not to change during the five-year period.

Outcome measures

The two outcomes of interest were CLABSIs prevented and deaths averted (lives saved). We calculated the number of CLABSIs prevented as the difference in the number of CLABSIs between programme and non-programme ICUs. Deaths averted were calculated similarly. We did not discount CLABSIs or deaths in the base case analysis to avoid making the ethically challenging assumption that infections or deaths prevented in the future are worth less than they are in the present. We explored the effect of discounting CLABSIs and deaths by 3% in a sensitivity analysis.

We calculated incremental cost effectiveness ratios as the additional cost divided by the additional health benefit (CLABSIs prevented or deaths averted) comparing the programme to current practice.

Probabilistic sensitivity analyses

We conducted a probabilistic sensitivity analysis to account for uncertainty in the

model's input parameters. We used Monte Carlo simulation to perform 10,000 iterations of the model, simultaneously sampling each parameter from an underlying distribution that reflects the degree of uncertainty in the parameter estimate. Uncertainty in parameter estimates was obtained from the confidence intervals or standard deviations published with the point estimates. Table 1 presents the modelled distributions, point estimates, and standard deviations for the key model parameters. All analyses were performed using Microsoft Excel (Microsoft Corporation; Redmond, WA) with @Risk (Palisade Corporation; Ithaca, NY).

RESULTS

Table 3 compares programme and non-programme ICU costs and outcomes for CLABSIs prevented and deaths averted. The quality improvement programme prevents 42 CLABSIs per 1,000 patients and averts 6 deaths per 1,000 patients at no additional cost in the base case analysis, representing a dominant strategy when compared with current practice.

Table 3 | Comparison of costs and outcomes between programme and non-programme intensive care units (ICUs)

	Mean	Median	2.5th – 97.5th Percentile
Non-programme ICU			
CLABSIs	52	52	39 – 66
Deaths	8	8	2 – 14
Costs (S)*	987,000	937,000	488,000 – 1,760,000
Programme ICU			
CLABSIs	10	9	3 – 29
Deaths	2	1	0 – 5
Costs ($)*	738,000	710,000	453,000 – 1,190,000
Benefit of programme†			
CLABSIs prevented	42	42	23 – 58
Deaths averted	6	6	2 – 12
Net costs ($)	-249,000	-221,000	-976,000 – 300,000
Incremental cost effectiveness ratio (Prob.)			

Cost per CLABSI prevented	Strongly dominant (0.80)‡
Cost per death prevented	Strongly dominant (0.80)‡

CLABSI = central line-associated bloodstream infection
Mean, median, 2.5% and 97.5% centile estimates for outputs from probabilistic sensitivity analysis of 10,000 model runs representing uncertainty in epidemiologic and economic parameters are reported.
All mean, median, and percentile values are expressed per 1,000 patients to make the scale easier to interpret. Values have been rounded to 3 significant digits at most.
*Costs are not presented separately for each outcome (CLABSI and death) because no additional cost was assumed to occur for death; discounted at 3%.
†Benefit of programme determined by subtracting programme ICU estimates from non-programme ICU estimates within the model
‡Probability that the programme is more effective and less costly than current practice

Figure 2 and online supplementary Figure S1 show the cost effectiveness planes comparing the joint density of incremental costs and incremental effects for 10,000 model iterations. Incremental refers to the difference in costs or effects between programme and non-programme ICUs. The X-axis represents the incremental level of effectiveness of an outcome and the Y-axis represents the additional total cost of achieving this outcome. Each data point in the scatterplot represents an estimated incremental cost effectiveness ratio for the outcome; as such, the scatterplot illustrates the distribution of incremental cost effectiveness ratios over a sample population. Points falling to the right of the Y-axis demonstrate that the programme is effective for preventing CLABSIs and averting deaths. Points falling above the X-axis represent the additional costs of the programme and points falling below the X-axis represent the economic cost savings from the programme. In Figure 2, because 80% of the points fall below the X-axis, there is an 80% probability that the programme reduces bloodstream infections and the infections' economic costs to hospitals compared with current practice. Figure 2 also demonstrates the presence of few extreme values (outlier incremental cost effectiveness ratios) in the model, indicating little uncertainty in the estimates of the quality improvement programme's cost effectiveness compared to current practice. Outliers add variability and uncertainty to the overall

cost effectiveness results and the existence of few such outliers in the cost effectiveness plane supports the robustness of the programme as a dominant strategy.

Online supplementary figures S2 and S3 display tornado diagrams of the results of the probabilistic sensitivity analysis. The opportunity cost of CLABSIs exerted the largest influence on the cost effectiveness of the programme for preventing CLABSIs and deaths. As such, hospitals implementing the programme should know the opportunity costs they face due to CLABSIs. The opportunity cost is calculated as the potential incremental net revenue opportunity per prevented CLABSI. We provide an example of how to perform this calculation in the appendix. Discounting CLABSIs or deaths at 3% in addition to costs, does not change the interpretation of our results. Similarly, discounting costs at 0% or 5% does not change the interpretation of our findings (see appendix Table D).

DISCUSSION

This study represents the first formal cost effectiveness analysis of a nationally implemented quality improvement programme (the Keystone ICU project) in the US to decrease CLABSIs in critically ill patients. One of the few large scale quality improvement projects to demonstrate long term sustainability, this programme has the potential to reduce CLABSIs and deaths at no additional cost to US hospitals.

Comparison with other studies

Previous studies highlight both the importance and difficulty of developing a business case for quality improvement. A business case exists if healthcare organisations investing in an intervention reap a return on their investment.[37] Many prevention initiatives have suffered from a lack of evidence supporting a positive return on investment for hospitals and payers.[38]

Incentive misalignment results in hospitals incurring costs to implement quality improvement programmes while payers accrue the subsequent cost savings. A financial analysis of a replication of the Keystone ICU project in one tertiary hospital in Hawaii demonstrated that reducing CLABSIs actually resulted in lower profit margins, thus creating a perverse incentive to provide a lower quality of care.[39] A different study calculated that, for every CLABSI prevented, the programme costs $5,404,[29] and suggested that it is cost saving when compared to the cost of an infection (which ranges from $6,000 to over $56,000[4 6 33 40 41]). However, both studies used inaccurate cost analyses that focused on the financial rather than the economic costs of CLABSIs. These studies also did not account for uncertainty in the cost or effect estimates.

Our evaluation offers several improvements to these existing studies. First, whenever possible we used nationally representative data to determine provider salary and compensation costs, so as to increase the ability to generalise our findings. Second, we performed a probabilistic sensitivity analysis to quantify the uncertainty in our cost effectiveness estimates. Third, we considered the opportunity costs of CLABSIs rather than financial costs. Our estimate of the cost of a CLABSI is based on the foregone hospital revenue that results whenever an infection occurs. From the perspective of the hospital, reducing the cost of CLABSIs is tantamount to reducing this foregone revenue by redeploying ICU beds for new admissions. Finally, we extended the evaluation to consider deaths prevented as an additional outcome because of its interest to clinicians and patients.

Limitations of the study

This evaluation has several limitations. First, the impact of patient heterogeneity, such as demographics and clinical characteristics on baseline risk, treatment effect, or resource utilisation was not fully explored.[42] This evaluation sought instead to represent an average ICU experience, in part because the data needed to explore subgroups are not available, but more importantly because the intervention applies to patients irrespective of these differences. It would be impractical—and possibly unethical—to only use this programme in subgroups of patients for whom greater benefit is expected. The programme is based on evidence-based practices for inserting central venous catheters—practices that should apply equally to all patients. Second, we did not evaluate costs outside the acute hospital setting, such as rehabilitation costs or productivity losses for delays returning to work incurred by patients suffering CLABSIs. However, doing so would further support the cost effectiveness of the programme. We chose to examine costs from the perspective of the hospital because hospitals bear the greatest burden of nosocomial infection costs in the prospective payer system and demonstrating a business case is important for the dissemination of effective quality improvement programmes. Finally, this evaluation did not explore the use of antimicrobial catheters as an comparator because systematic reviews have come to differing conclusions about the extent of their effectiveness in preventing CLABSIs, and many of the trials have been small and of a low quality.[43 44] In addition, the choice facing hospital decision makers is not necessarily a mutually exclusive choice between the Keystone ICU project or the use of antimicrobial catheters. The results of Keystone ICU project already reflect the use of various types of catheters because the programme itself did not specify catheter type. The parameter estimate for effectiveness of the programme used in this evaluation was derived from a cluster randomised controlled trial. In this setting it can be expected that the utilisation of antimicrobial catheters should be balanced between the

intervention and control arms of the trial (though this was not explicitly measured), and the effectiveness estimate is attributable to the quality improvement programme itself. The Keystone ICU project quality improvement programme is also a complex social intervention. Comparing it directly to technology or a device understates its broader effects, which may include reductions in sepsis and ventilator-associated pneumonia or reduced staff turnover resulting from an improved safety culture.[21] Data for these effects are limited in comparison to the data available for CLABSIs, but recent evidence suggests that the Keystone ICU project significantly reduced rates of ventilator associated pneumonia in Michigan ICUs.[9] Inclusion of these additional beneficial effects for the same set of costs would further support the cost effectiveness of the programme.

Conclusions and implications of study findings

These findings have important implications for health care. Broad implementation of the Keystone ICU project in the US healthcare system could substantially reduce the morbidity and mortality associated with CLABSIs and their economic costs to hospitals. Although the Centers for Disease Control and Prevention has demonstrated that significant reductions in CLABSIs are indeed being realised for intensive care patients in the US,[45] 800 medium and large hospitals continue to have high CLABSIs rates.[46] Further dissemination of cost effective quality improvement programmes is needed. Although our analysis adopted a hospital perspective, payers also stand to benefit from the programme and can support dissemination efforts. Hospitals and payers should partner to reform the incentive structure facing hospitals in order to better support patient safety and quality. Payer support, such as covering or funding some intervention costs and imposing financial penalties on hospitals when patients develop CLABSIs, could encourage uptake and dissemination of the programme. Future evaluations of this quality

improvement programme in non-US settings can incorporate country specific costs or extend the evaluation to consider additional outcomes, such as cases of ventilator-associated pneumonia prevented. As more data and evidence emerges regarding the long-term costs and outcomes for patients with CLABSI and other healthcare associated infections,[47] future economic evaluations can incorporate this information to gauge the cost effectiveness of prevention and quality improvement efforts.

To conclude, this multifaceted quality improvement programme, currently being implemented by thousands of hospitals in the US, likely reduces unnecessary morbidity, mortality, and economic costs associated with CLABSIs.

Acknowledgements: We thank Susan M. Turley for her assistance in editing the manuscript.

Contributors: KRH is the guarantor and had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All the authors were involved in preparing this manuscript. KRH was responsible for the overall study design, data analysis, and interpretation of data, and wrote the initial draft of the manuscript. All other authors contributed to the study design, analysis and interpretation of data, and critical revision of the manuscript. LN, DOC, WJW, and PJP also provided supervision.

The study guarantor affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Funding: This study was conducted as part of KRH's doctoral training at the Johns Hopkins Bloomberg School of Public Health. KRH is supported by the Harry S. Truman Scholarship Foundation and by a training grant from the National Institutes of Health under award number T32 GM007309. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. All of the researchers were independent of the sponsors, and neither sponsor had any influence over the study design; collection, analysis, or interpretation of the data; writing of the manuscript; or decision to submit it for publication.

Role of the Sponsors: The Truman Scholarship Foundation and the National Institutes of Health had played no direct role in any aspect of this study. The researchers were independent of the sponsors and neither sponsor had any influence over the study design, collection, analysis or interpretation of the data, writing of the manuscript, or decision to submit it for publication.

Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that they had (1) No financial support for the submitted work. (2) PJP reports: receiving grant or contract support from the Agency for Healthcare Research and Quality, the Gordon and Betty Moore Foundation (research related to patient safety and quality of care), the National Institutes of Health (acute lung injury research), and the American Medical Association Inc. (improve blood pressure control); honoraria from various healthcare organizations for speaking on patient safety and quality (the Leigh Bureau manages most of these engagements); and book royalties from the Penguin Group for his book *Safe Patients, Smart Hospitals*. Dr. Pronovost is a paid strategic advisor to the Gordon and Betty Moore Foundation; receives stock and fees to serve as a director for Cantel Medical; and is a founder of *Patient Doctor Technologies*, a startup company that seeks to enhance the partnership between patients and clinicians with an application called Doctella; (3) No spouses, partners, or children with relationships with commercial entities that might have an interest in the submitted work and (4) No non-financial interests that may be relevant to the submitted work.

Ethics approval: Not required.

Data sharing: No additional data available.

Figure legends

Figure 1 | Decision tree model. Decision tree model depicting programme versus no programme and its effects on outcomes in intensive care unit (ICU) patients. “Bloodstream infections” refers to central line-associated bloodstream infection.

Figure 2 | Cost effectiveness plane for central line-associated bloodstream infections prevented with 95% confidence ellipses. Values on both axes have been multiplied by 1,000 to yield incremental costs and effects expressed per 1,000 patients to aid interpretation. Incremental refers to the difference in costs or effects between programme and non-programme intensive care units. Cost values in US dollars. Boxes in the plot region display the percentage of the distribution of incremental cost-effectiveness ratios falling above or below $0. The 95% confidence ellipses overlaid on the figure are calculated assuming a bivariate normal distribution and display the uncertainty in the incremental costs effectiveness ratios.

References

1. Mermel LA. Prevention of intravascular catheter-related infections. *Ann Intern Med* 2000;132(5):391-402.

2. Burke JP. Infection control - a problem for patient safety. *N Engl J Med* 2003;348(7):651-6. doi: 10.1056/NEJMhpr020557.

3. Klevens RM, Edwards JR, Richards CL, Jr.*, et al.* Estimating health care-associated infections and deaths in U.S. hospitals, 2002. *Public Health Rep* 2007;122(2):160-6.

4. O'Grady NP, Alexander M, Dellinger EP*, et al.* Guidelines for the prevention of intravascular catheter-related infections. *Infect Control Hosp Epidemiol* 2002;23(12):759-69. doi: 10.1086/502007.

5. Digiovine B, Chenoweth C, Watts C*, et al.* The attributable mortality and costs of primary nosocomial bloodstream infections in the intensive care unit. *Am J Respir Crit Care Med* 1999;160(3):976-81. doi: 10.1164/ajrccm.160.3.9808145.

6. Pittet D, Tarara D, Wenzel RP. Nosocomial bloodstream infection in critically ill patients. Excess length of stay, extra costs, and attributable mortality. *JAMA* 1994;271(20):1598-601.

7. Pronovost P, Needham D, Berenholtz S*, et al.* An intervention to decrease catheter-related bloodstream infections in the ICU. *N Engl J Med* 2006;355(26):2725-32. doi: 10.1056/NEJMoa061115.

8. Berenholtz SM, Pronovost PJ, Lipsett PA*, et al.* Eliminating catheter-related bloodstream infections in the intensive care unit. *Crit Care Med* 2004;32(10):2014-20. doi: 10.1097/01.ccm.0000142399.70913.2f.

9. Berenholtz SM, Pham JC, Thompson DA, *et al.* Collaborative cohort study of an intervention to reduce ventilator-associated pneumonia in the intensive care unit. *Infect Control Hosp Epidemiol* 2011;32(4):305-14. doi: 10.1086/658938.

10. Lin DM, Weeks K, Bauer L, *et al.* Eradicating central line-associated bloodstream infections statewide: the Hawaii experience. *Am J Med Qual* 2012;27(2):124-9. doi: 10.1177/1062860611414299.

11. Lipitz-Snyderman A, Steinwachs D, Needham DM, *et al.* Impact of a statewide intensive care unit quality improvement initiative on hospital mortality and length of stay: retrospective comparative analysis. *BMJ* 2011;342:d219. doi: 10.1136/bmj.d219.

12. Bion J, Richardson A, Hibbert P, *et al.* 'Matching Michigan': a 2-year stepped interventional programme to minimise central venous catheter-blood stream infections in intensive care units in England. *BMJ Qual Saf* 2013;22(2):110-23. doi: 10.1136/bmjqs-2012-001325.

13. Marsteller JA, Sexton JB, Hsu YJ, *et al.* A multicenter, phased, cluster-randomized controlled trial to reduce central line-associated bloodstream infections in intensive care units. *Crit Care Med* 2012;40(11):2933-9. doi: 10.1097/CCM.0b013e31825fd4d8.

14. Niessen LW, Grijseels EW, Rutten FF. The evidence-based approach in health policy and health care delivery. *Soc Sci Med* 2000;51(6):859-69.

15. Grimshaw JM, Thomas RE, MacLennan G, *et al.* Effectiveness and efficiency of guideline dissemination and implementation strategies. *Health Technol Assess* 2004;8(6):iii-iv, 1-72.

16. Hoomans T, Evers SM, Ament AJ, *et al.* The methodological quality of economic evaluations of guideline implementation into clinical practice: a systematic review of

empiric studies. *Value Health* 2007;10(4):305-16. doi: 10.1111/j.1524-4733.2007.00175.x.

17. Graves N, Harbarth S, Beyersmann J*, et al.* Estimating the cost of health care-associated infections: mind your p's and q's. *Clin Infect Dis* 2010;50(7):1017-21. doi: 10.1086/651110.

18. Veenstra DL, Saint S, Sullivan SD. Cost-effectiveness of antiseptic-impregnated central venous catheters for the prevention of catheter-related bloodstream infection. *JAMA* 1999;282(6):554-60.

19. Halton KA, Cook DA, Whitby M*, et al.* Cost effectiveness of antimicrobial catheters in the intensive care unit: addressing uncertainty in the decision. *Crit Care* 2009;13(2):R35. doi: 10.1186/cc7744.

20. Needham DM, Scales DC, Laupacis A*, et al.* A systematic review of the Charlson comorbidity index using Canadian administrative databases: a perspective on risk adjustment in critical care research. *J Crit Care* 2005;20(1):12-9.

21. Pronovost PJ, Berenholtz SM, Goeschel C*, et al.* Improving patient safety in intensive care units in Michigan. *J Crit Care* 2008;23(2):207-21. doi: 10.1016/j.jcrc.2007.09.002.

22. Pronovost PJ, Berenholtz SM, Needham DM. Translating evidence into practice: a model for large scale knowledge translation. *BMJ* 2008;337:a1714. doi: 10.1136/bmj.a1714.

23. Fletcher S. Catheter-related bloodstream infection. *Contin Educ Anaesth Crit Care Pain* 2005;5(2):49-51. doi: 10.1093/bjaceaccp/mki011.

24. Brun-Buisson C. New technologies and infection control practices to prevent intravascular catheter-related infections. *Am J Respir Crit Care Med* 2001;164(9):1557-8. doi: 10.1164/ajrccm.164.9.2109051.

25. Veenstra DL, Saint S, Saha S, *et al.* Efficacy of antiseptic-impregnated central venous catheters in preventing catheter-related bloodstream infection: a meta-analysis. *JAMA* 1999;281(3):261-7.

26. Martin MA, Pfaller MA, Wenzel RP. Coagulase-negative staphylococcal bacteremia. Mortality and hospital stay. *Ann Intern Med* 1989;110(1):9-16.

27. Smith RL, Meixler SM, Simberkoff MS. Excess mortality in critically ill patients with nosocomial bloodstream infections. *Chest* 1991;100(1):164-7.

28. Arnow PM, Quimosing EM, Beach M. Consequences of intravascular catheter sepsis. *Clin Infect Dis* 1993;16(6):778-84.

29. Waters HR, Korn R, Jr., Colantuoni E, *et al.* The business case for quality: economic analysis of the Michigan Keystone Patient Safety Program in ICUs. *Am J Med Qual* 2011;26(5):333-9. doi: 10.1177/1062860611410685.

30. Graves N, Weinhold D, Tong E, *et al.* Effect of healthcare-acquired infection on length of hospital stay and cost. *Infect Control Hosp Epidemiol* 2007;28(3):280-92. doi: 10.1086/512642.

31. Graves N. Economics and preventing hospital-acquired infection. *Emerg Infect Dis* 2004;10(4):561-6. doi: 10.3201/eid1004.020754.

32. Society of Critical Care Medicine. *Compensation of Critical Care Professionals*: Society of Critical Care Medicine, 2009.

33. Warren DK, Quadir WW, Hollenbeak CS, *et al.* Attributable cost of catheter-associated bloodstream infections among intensive care patients in a nonteaching hospital. *Crit Care Med* 2006;34(8):2084-9. doi: 10.1097/01.CCM.0000227648.15804.2D.

34. American Hospital Association. *AHA Hospital Statistics. 2013 ed*: American Hospital Association, 2012.

35. Wunsch H, Angus DC, Harrison DA*, et al.* Variation in critical care services across North America and Western Europe. *Crit Care Med* 2008;36(10):2787-93, e1-9. doi: 10.1097/CCM.0b013e318186aec8.

36. Pronovost PJ, Goeschel CA, Colantuoni E*, et al.* Sustaining reductions in catheter related bloodstream infections in Michigan intensive care units: observational study. *BMJ* 2010;340:c309. doi: 10.1136/bmj.c309.

37. Leatherman S, Berwick D, Iles D*, et al.* The business case for quality: case studies and an analysis. *Health Aff (Millwood)* 2003;22(2):17-30.

38. Galvin RS, Delbanco S, Milstein A*, et al.* Has the leapfrog group had an impact on the health care market? *Health Aff (Millwood)* 2005;24(1):228-33. doi: 10.1377/hlthaff.24.1.228.

39. Hsu E, Lin D, Evans SJ*, et al.* Doing well by doing good: assessing the cost savings of an intervention to reduce central line-associated bloodstream infections in a Hawaii hospital. *Am J Med Qual* 2014;29(1):13-9. doi: 10.1177/1062860613486173.

40. Halton K, Graves N. Economic evaluation and catheter-related bloodstream infections. *Emerg Infect Dis* 2007;13(6):815-23. doi: 10.3201/eid1306.070048.

41. Dimick JB, Pronovost PJ, Heitmiller RF*, et al.* Intensive care unit physician staffing is associated with decreased length of stay, hospital cost, and complications after esophageal resection. *Crit Care Med* 2001;29(4):753-8.

42. Grutters JP, Sculpher M, Briggs AH*, et al.* Acknowledging patient heterogeneity in economic evaluation : a systematic literature review. *Pharmacoeconomics* 2013;31(2):111-23. doi: 10.1007/s40273-012-0015-4.

43. Niel-Weise BS, Stijnen T, van den Broek PJ. Anti-infective-treated central venous catheters: a systematic review of randomized controlled trials. *Intensive Care Med* 2007;33(12):2058-68. doi: 10.1007/s00134-007-0897-3.

44. Hockenhull JC, Dwan K, Boland A*, et al.* The clinical effectiveness and cost-effectiveness of central venous catheters treated with anti-infective agents in preventing bloodstream infections: a systematic review and economic evaluation. *Health Technol Assess* 2008;12(12):iii-iv, xi-xii, 1-154.

45. Center for Disease Control and Prevention. *National and State Healthcare Association Infections Progress Report*. Atlanta, 2014.

46. Wise ME, Scott RD, 2nd, Baggs JM*, et al.* National estimates of central line-associated bloodstream infections in critical care patients. *Infect Control Hosp Epidemiol* 2013;34(6):547-54. doi: 10.1086/670629.

47. Dick A, Liu H, Zwanziger J*, et al.* Long-term survival and healthcare utilization outcomes attributable to sepsis and pneumonia. *BMC Health Serv Res* 2012;12:432. doi: 10.1186/1472-6963-12-432.

Cost effectiveness of a quality improvement programme to reduce central line-associated bloodstream infections in intensive care units in the United States

Kurt R Herzer, Louis Niessen, Dagna O Constenla, William J Ward Jr, Peter J Pronovost

Medical Scientist Training Program, Johns Hopkins School of Medicine, 1830 East Monument Street, Baltimore, MD 21205, USA

Kurt R Herzer

MD-PhD student

Centre for Applied Health Research and Delivery (CAHRD), Liverpool School of Tropical Medicine, University of Warwick, Coventry, CV4 7AL, United Kingdom

Louis Niessen

Professor

International Vaccine Access Center, Johns Hopkins Bloomberg School of Public Health, 855 North Wolfe Street, Baltimore, MD 21205, USA

Dagna O Constenla

Associate Scientist

Department of Health Policy and Management, Johns Hopkins Bloomberg School of Public Health, 624 North Broadway Street, Baltimore, MD 21205, USA

William J Ward Jr

Associate Professor

Armstrong Institute for Patient Safety and Quality, Johns Hopkins Medicine, 750 East Pratt Street, Baltimore, MD 21202, USA

Peter J Pronovost

Professor

Correspondence to: Kurt Herzer, 1830 East Monument Street, Baltimore, MD 21205, USA; kherzer@jhmi.edu; 443-900-2415

Keywords: quality improvement, cost effectiveness, nosocomial infections, health policy, checklists

Word Count: 3,424

Abstract

Objective: To assess the cost effectiveness of a multifaceted quality improvement programme focused on reducing central line-associated bloodstream infections in intensive care units.

Design: Cost effectiveness analysis using a decision tree model to compare programme to non-programme intensive care units.

Setting: United States (US).

Population: Adult patients in the intensive care unit.

Costs: Economic costs of the programme and of central line-associated bloodstream infections were estimated from the perspective of the hospital and presented in 2013 US dollars.

Main outcome measures: Central line-associated bloodstream infections prevented, deaths averted due to central line-associated bloodstream infections prevented, and incremental cost effectiveness ratios. Probabilistic sensitivity analysis was performed.

Results: Compared to current practice, the programme is strongly dominant and reduces bloodstream infections and deaths at no additional cost. The probabilistic sensitivity analysis showed that there was an almost 80% probability that the programme reduces bloodstream infections and the infections' economic costs to hospitals. The opportunity cost of a bloodstream infection to a hospital was the most important model parameter in these analyses.

Conclusions: This multifaceted quality improvement programme, as it is currently implemented by hospitals on an increasingly large scale in the US, likely reduces the economic costs of central line-associated bloodstream infections for US hospitals. Awareness among hospitals about the programme's benefits should enhance implementation. The programme's implementation has the potential to substantially reduce morbidity, mortality, and economic costs associated with central line-associated bloodstream infections.

Article summary

Strengths and limitations of this study

- This study was conducted according to best practices in cost effectiveness analysis and demonstrates that a multifaceted quality improvement programme can reduce the economic costs of central line-associated bloodstream infections for hospitals.
- We used nationally representative data sources to increase generalisability and performed a probabilistic sensitivity analysis to quantify the uncertainty in our cost effectiveness estimates.
- Due to data limitations we were unable to assess the impact of patient heterogeneity, such as demographics and clinical characteristics, on baseline risk, treatment effect, or resource utilisation. We did not evaluate costs outside the acute hospital setting, such as rehabilitation costs or productivity losses for delays returning to work.

INTRODUCTION

Central line-associated bloodstream infections (CLABSI) are common, expensive to payers and patients, and potentially fatal.[1 2] Each year, nearly 80,000 Americans develop CLABSIs in the intensive care unit (ICU), and more than 25,000 of these patients die.[3] A single infection can cost payers as much as $56,000, culminating in over $2 billion in related costs per year in the United States.[4] CLABSIs in ICU patients have an estimated attributable mortality rate of 14 to 40%, with a prolonged length of stay of 7.5 to 25 days.[5 6]

The Keystone ICU project, first launched in Michigan in 2004 and since scaled across the United States, Spain, Peru, Pakistan, and the United Kingdom, has captured the interest and attention of patients, payers, and policymakers for its substantial, sustained, and scalable reductions in preventable nosocomial infections. 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 infection prevention programmes in their ICUs as standard practice. The programme has been evaluated through prospective cohort studies,[7-10] retrospective observational studies using claims data,[11] and both cluster nonrandomised[12] and randomised controlled trials.[13] When viewed collectively, this evidence suggests that the programme is associated with substantial reductions in both CLABSIs and mortality in ICU patients.

In spite of commendable investment in this programme to manage the undesirable consequences of CLABSIs, an important question remains unanswered: compared with current practice, is this programme cost effective for US hospitals? Reporting of economic data in quality improvement studies is uncommon, and there are few formal cost effectiveness analyses of quality improvement programmes.[14-16] Similarly, because the estimated gross costs of

CLABSIs to the healthcare system are very high, the conclusion that expanding infection control efforts will be cost saving (relative to the costs incurred by expanded efforts) is accepted without rigorous analysis.[17] This paper examines the cost changes and effectiveness of the Keystone ICU project from the perspective of the hospital using nationally representative data sources from the United States.

METHODS

Overview of the analysis

We developed a decision tree model to address the choice faced at an individual hospital about implementing the programme (Figure 1). The use of a decision tree approach is justified by the short-term progression of CLABSIs. The model assumes that patients do not experience other adverse effects of catheterisation, such as catheter colonisation leading to local infection, hypersensitivity reactions, or mechanical complications such as pneumothorax. The Keystone ICU project instead focused on infectious complications, because they are more common, more costly, and often fatal.[18] Consistent with other economic evaluations of CLABSIs in the ICU setting, we assumed that the consequences of infection are independent of age, patient disease severity, and the causative organism.[18 19] These assumptions are congruent with the programme itself, which does not discriminate between subgroups of patients based on these factors.

The comparator was current practice as the most realistic alternative faced by organisations seeking to implement the programme. Current practice encompasses on-going or existing activities that might influence the risk of infection amongst patients, such as the use of anti-infective central venous catheters.

The target population consisted of adult (18 years or older) ICU patients in accordance with studies of the Keystone ICU project and its subsequent replications.[13] Because costs and benefits only accrue while the programme is implemented, the time frame and analytic horizon are fundamentally the same. We used a time horizon of five years. This analysis was performed from the hospital's perspective. Our study aims to address the following question: is implementation of this quality improvement programme to decrease CLABSIs in the ICU a cost-effective approach when compared with current practice in US hospitals?

Quality improvement programme

Details of the programme and its conceptual approach have been described elsewhere.[20-22] In brief, this multifaceted programme employed clinician communication tools, teamwork, and safety culture assessment and improvement tools (known as the Comprehensive Unit-based Safety Program [CUSP]), and a five-item, evidence-based checklist for correctly inserting central venous catheters. The five components of the checklist included using basic hand hygiene, exercising full barrier precautions, cleaning the skin with chlorhexidine, avoiding the femoral site when possible, and removing any unnecessary catheters. A model for translating evidence into practice identified and mitigated local barriers to implementation of the checklist.[22] Quarterly infection rates measured at the ICU level were used to monitor progress toward the goal of reducing CLABSIs. ~~The remainder of this paper uses the phrase "bloodstream infection" to refer to central line-associated bloodstream infection.~~

Model inputs

Table 1 shows the key parameters used in the decision tree model, such as probabilities and cost inputs as well as the effectiveness of the programme, which are described in detail in the following sections.

Table 1 | Parameters used in the decision tree model

Parameter	Distribution	Source
Probability of CLABSI*	Beta: 0.052 (SD 0.0074)	18,25
Death attributable to CLABSI	Beta: 0.15 (SD 0.056)	6
Incidence rate ratio of programme versus non-programme ICUs	Lognormal based on normal mean 0.19 (SD 0.13)	13
Total cost ($):		
CLABSI (per patient)†	Lognormal based on normal mean 18,793 (SD 5,533)	33
Programme (per patient)†	Lognormal based on normal mean 540 (SD 120)	29

CLABSI = central-line associated bloodstream infection, ICU = intensive care unit
*Conditional probability of a CLABSI given exposure to a central venous catheter, assumes standard (non-antimicrobial) catheter.
†Discounted costs presented

Risk of CLABSI and death

Estimates of the risk of CLABSI given exposure to a central venous catheter varied from 3.0% to as much as 16.0%.[23 24] We used a probability estimate of 5.2% for a standard catheter, derived from a meta analysis of 13 randomised controlled trials from a previous economic evaluation.[18 25] Estimates of the attributable mortality of CLABSI ranged from 14 to 40%.[5 6 26 27] We used a point estimate of 15%.

Costs

Estimates of payer costs attributable to CLABSI varied widely, from as little as $6,000 to over $56,000.[4 6 18 28] The reasons for this variation can be attributed to the small sample

sizes of studies, challenges allocating inpatient costs, perspectives used, the types of cost categories included, and the methodology used for estimation.[29] Existing studies have largely focused on financial costs (or hospital charges or payer costs) rather than opportunity costs and so they may incorrectly estimate the economic cost of CLABSIs to hospitals. We considered the economic cost of CLABSIs in terms of the increased length of stay and variable costs associated with that occurrence.[30] Given that a significant amount of hospital costs are fixed in the short run, the economic viability of quality improvement programmes that reduce CLABSIs rests on two things: deploying the bed-days freed by shorter lengths of stay for new admissions and reducing utilization of medications and supplies. The value of the new admissions, (the potential incremental net revenue opportunity per prevented infection) represents the economic cost of infection and accordingly, the potential economic cost avoidance resulting from infection prevention.[31] Using this approach, we estimated that the discounted cost of a CLABSI was $18,793 (see ~~the~~ appendix Tables A and B for details of this calculation).

Start-up costs and recurring costs associated with the quality improvement programme were assigned using an activity-based micro-costing of the programme performed in six hospitals in Michigan.[29] We assumed that start-up costs occurred in the first year of implementation and did not discount them. Capital items, such as bloodstream infection line carts, were annualised assuming a five-year useful life and 3% discount rate. We included the opportunity costs of key personnel whose time was committed to the programme even though a hospital may not incur any financial costs related to personnel who are already on staff. We estimated this cost by multiplying each staff person's percentage effort committed to the programme by an estimate of that position's annual compensation. We used the Society of Critical Care Medicine's annual compensation estimates from 2009 for critical care physicians, nurses, pharmacists, and

respiratory therapists.[32] The salary for infection control preventionists was based on the Bureau of Labor Statistics's 2011 Occupational Employment Statistics and we added 30% benefits. ~~All compensation figures were adjusted to 2013 US dollars using the Consumer Price Index for medical care services.~~ Table 2 presents a detailed itemisation of the start-up costs and recurring costs of the programme. Start-up costs were approximately $80,000 and recurring costs were approximately $192,000 per hospital per year. Personnel costs were the largest contributor, comprising 95% of start-up costs and 89% of recurring costs.

Table 2 | Itemisation of programme costs (per hospital)

Cost category	Start-up costs	Recurring costs*
Personnel ($)		
Critical care physicians (2 on average per hospital)	26,004	71,953
Nurses (8 on average per hospital)	44,406	75,306
Respiratory therapists	4,605	7,923
Infection control preventionists	1,981	7,855
Pharmacists	2,725	7,962
Education and Training ($)		
Education and training expenses	3,579	
Capital Items ($)		
CLABSI line cart/central line insertion cart (annual equivalent cost)	426	426
Materials ($)		
Chlorohexidine		2,378
Oral care kits		6,933
Sterile central line dressing kits		11,555
Total ($)	83,725	192,292

CLABSI = central line-associated bloodstream infection
*Recurring costs occur each year that the intervention is in place; as such, this total represents the annual recurring cost (not discounted as presented here).

We estimated a per patient cost of the programme by deriving an average number of ICU patients per hospital who had central venous catheters (the patients most likely to benefit from the programme's prevention efforts). To calculate this, we first derived a national annual cohort

of ICU patients exposed to central venous catheters by multiplying the total annual ICU admissions in the US by an estimate of the proportion of patients admitted to an ICU that receive central venous catheters.[33] We then divided this group of ICU admissions with central venous catheters by the number of hospitals that reported having adult ICUs in the American Hospital Association Annual Survey of Hospitals,[34] yielding an average number of "exposed" patients per hospital. Finally, we divided the total costs of the programme per hospital by the number of patients per hospital to yield an average cost for the programme per patient of $540 (standard deviation, 120). Appendix Table C contains additional details of this calculation, including the uncertainty ranges incorporated into the estimate. ~~based on published estimates and the American Hospital Association's Annual Survey of Hospitals, yielding $540 per patient (see the appendix for details of this calculation).~~[34 35]

All costs were adjusted to 2013 US dollars using the Consumer Price Index for medical care services. Recurring costs were discounted by 3% annually. In separate sensitivity analyses, we examined the effect of not discounting costs and of discounting costs by 5%.

Effectiveness

We based our estimate of the programme's effectiveness on a cluster randomised controlled trial that found an 81% reduction in CLABSI rates comparing programme ICUs to control ICUs (incidence rate ratio, 0.19; 95% confidence interval, 0.06–0.57).[13] We used the confidence interval of this point estimate, a measure of uncertainty in the programme's effectiveness, to derive a standard deviation of the estimate for probabilistic sensitivity analysis. This effectiveness parameter was measured at the ICU level but in our model we assumed that it applied to individual patients ~~(considering all patients together)~~. This ecological assumption was

necessary because there are no patient level effectiveness estimates available from the Keystone ICU project. ~~Its~~ The ~~uncertainty range~~standard deviation of the estimate captures the heterogenic reality ~~among patients~~ that the intervention benefit is not uniform among ICU patients.

To calculate the base case probability of a CLABSI in the programme arm of the decision tree, we multiplied the probability of CLABSI by the incidence rate ratio (0.19) from the trial. We assumed that by the end of the first year of implementation, programme ICUs achieve this reduction. The original ICUs that implemented the programme maintained the reduction for the subsequent 10 years (Sam Watson, written communication, August 18, 2013). We assumed this to be true for the five-year period used in this evaluation.[36]

The number of annual ICU admissions requiring catheters, the probability of infection, and the attributable mortality parameters were assumed not to change during the five-year period.

Outcome measures

The two outcomes of interest were CLABSIs prevented and deaths averted (lives saved) ~~due to prevented~~. We calculated the number of CLABSIs prevented ~~by determining~~ as the difference in the number of CLABSIs between programme and non-programme ICUs. Deaths averted were calculated similarly. We did not discount CLABSIs or deaths in the base case analysis to avoid making the ethically challenging assumption that infections or deaths prevented in the future are worth less than they are in the present. We explored the effect of discounting CLABSIs and deaths by 3% in a sensitivity analysis.

We calculated incremental cost effectiveness ratios as the additional cost divided by the additional health benefit (CLABSIs prevented or deaths averted) comparing the programme to current practice.

Probabilistic sensitivity analyses

We conducted a probabilistic sensitivity analysis to account for uncertainty in the model's input parameters. We used Monte Carlo simulation to perform 10,000 iterations of the model, simultaneously sampling each parameter from an underlying distribution that reflects the degree of uncertainty in the parameter estimate. Uncertainty in parameter estimates was obtained from the confidence intervals or standard deviations published with the point estimates. Table 1 presents the modelled distributions, point estimates, and standard deviations ~~uncertainty ranges applied to~~for the key model parameters. All analyses were performed using Microsoft Excel (Microsoft Corporation; Redmond, WA) with @Risk (Palisade Corporation; Ithaca, NY).

RESULTS

Table 3 compares programme and non-programme ICU costs and outcomes for CLABSIs prevented and deaths averted. The quality improvement programme ~~reduces~~ prevents 42 CLABSIs per 1,000 patients and averts 6 deaths per 1,000 patients at no additional cost in the base case analysis, ~~and~~ representings a dominant strategy when compared with current practice. ~~Table 3 compares programme and non-programme costs and outcomes for prevented and deaths prevented.~~

Table 3 | Comparison of costs and outcomes between programme and non-programme intensive care units (ICUs)

	Mean	Median	2.5th – 97.5th Percentile
Non-programme ICU			
CLABSIs	52	52	39 – 66
Deaths	8	8	2 – 14
Costs (S)*	987,000	937,000	488,000 – 1,760,000
Programme ICU			

CLABSIs	10	9	3 – 29
Deaths	2	1	0 – 5
Costs ($)*	738,000	710,000	453,000 – 1,190,000
Benefit of programme†			
CLABSIs prevented	42	42	23 – 58
Deaths averted	6	6	2 – 12
Net costs ($)	-249,000	-221,000	-976,000 – 300,000
Incremental cost effectiveness ratio (Prob.)			
Cost per CLABSI prevented	Strongly dominant (0.80)‡		
Cost per death prevented	Strongly dominant (0.80)‡		

CLABSI = central line-associated bloodstream infection

Mean, median, 2.5% and 97.5% centile estimates for outputs from probabilistic sensitivity analysis of 10,000 model runs representing uncertainty in epidemiologic and economic parameters are reported. All mean, median, and percentile values are expressed per 1,000 patients to make the scale easier to interpret. Values have been rounded to 3 significant digits at most.

*Costs are not presented separately for each outcome (CLABSI and death) because no additional cost was assumed to occur for death; discounted at 3%.

†Benefit of programme determined by subtracting programme ICU estimates from non-programme ICU estimates within the model

‡Probability that the programme is more effective and less costly than current practice

Figure 2 and online supplementary Figure S1 show the cost effectiveness planes comparing the joint density of incremental costs and incremental effects for 10,000 model iterations. Incremental refers to the difference in costs or effects between programme and non-programme ICUs. The X-axis represents the incremental level of effectiveness of an outcome and the Y-axis represents the additional total cost of achieving this outcome. Each data point in the scatterplot represents an estimated incremental cost effectiveness ratio for the outcome; as such, the scatterplot illustrates the distribution of incremental cost effectiveness ratios over a sample population. Points falling to the right of the Y-axis demonstrate that the programme is effective for preventing CLABSIs and averting deaths. Points falling above the X-axis represent the additional costs of the programme and points falling below the X-axis represent the economic cost savings from the programme. In Figure 2, because 80% of the points fall below the X-axis, there is an 80% probability that the programme reduces bloodstream infections and the infections'

economic costs to hospitals compared with current practice. Figure 2 also demonstrates the presence of few extreme values (outlier incremental cost effectiveness ratios) in the model, indicating little uncertainty in the estimates of the quality improvement programme's cost effectiveness compared to current practice. Outliers add variability and uncertainty to the overall cost effectiveness results and the existence of few such outliers in the cost effectiveness plane supports the robustness of the programme as a dominant strategy.

~~The scatterplot illustrates the uncertainty surrounding the estimates of expected incremental cost and expected incremental effect (prevented or deaths prevented) associated with the quality improvement programme compared to current practice.~~

~~Figure 2 shows that the mean point estimate for the difference in costs and effects between the programme and current practice is -$249,000 with 42 prevented per 1,000 patients. The location of the incremental cost-effect pairs indicates that there is limited uncertainty regarding the effectiveness of the programme, yet there is uncertainty regarding the number of prevented. For costs, the location and spread of points indicate uncertainty in the existence and magnitude of economic cost savings. In Figure S3, the mean point estimate for the difference in costs and effects between the programme and current practice is -$249,000 with 6 deaths prevented per 1,000 patients. There is similar uncertainty in the magnitude of deaths prevented and the existence and magnitude of cost savings. For both prevented and deaths prevented, about 80% of the incremental cost-effect pairs fall below the horizontal axis, indicating that the programme is incrementally less costly and more effective than current practice (base case). The remaining 20% of points fall above the horizontal axis, indicating that the programme is incrementally more costly and more effective. The 95% confidence ellipses are calculated assuming a bivariate normal distribution and display the uncertainty surrounding incremental costs and effects. The~~

~~ellipses cross the horizontal axis, indicating less than 95% confidence that the intervention is dominant.~~

Online supplementary figures S24 and S35 display tornado diagrams of the results of the probabilistic sensitivity analysis. The opportunity cost of CLABSIs exerted the largest influence on the cost effectiveness of the programme for preventing CLABSIs and deaths. As such, hospitals implementing the programme should know the opportunity costs they face due to CLABSIs. The opportunity cost is calculated as the potential incremental net revenue opportunity per prevented CLABSI. We provide an example of how to perform this calculation in the appendix. Discounting CLABSIs or deaths at 3% in addition to costs, does not change the interpretation of our results. Similarly, discounting costs at 0% or 5% does not change the interpretation of our findings (see ~~supplementary~~ appendix Table D).

DISCUSSION

This study represents the first formal cost effectiveness analysis of a nationally implemented quality improvement programme (the Keystone ICU project) in the US to decrease CLABSIs in critically ill patients. One of the few large scale quality improvement projects to demonstrate long term sustainability, this programme has the potential to reduce CLABSIs and deaths at no additional cost to US hospitals.

Comparison with other studies

Previous studies highlight both the importance and difficulty of developing a business case for quality improvement. A business case exists if healthcare organisations investing in an intervention reap a return on their investment.[37] Many prevention initiatives have suffered from a lack of evidence supporting a positive return on investment for hospitals and payers.[38]

Incentive misalignment results in hospitals incurring costs to implement quality improvement programmes while payers accrue the subsequent cost savings. A financial analysis of a replication of the Keystone ICU project in one tertiary hospital in Hawaii demonstrated that reducing CLABSIs actually resulted in lower profit margins, thus creating a perverse incentive to provide a lower quality of care.[39] A different study calculated that, for every CLABSI prevented, the programme costs $5,404,[29] and suggested that it is cost saving when compared to the cost of an infection (which ranges from $6,000 to over $56,000[4 6 33 40 41]). However, both studies used inaccurate cost analyses that focused on the financial rather than the economic costs of CLABSIs. These studies also did not account for uncertainty in the cost or effect estimates.

Our evaluation offers several improvements to these existing studies. First, whenever possible we used nationally representative data to determine provider salary and compensation costs, so as to increase the ability to generalise our findings. Second, we performed a probabilistic sensitivity analysis to quantify the uncertainty in our cost effectiveness estimates. Third, we considered the opportunity costs of CLABSIs rather than financial costs. Our estimate of the cost of a CLABSI is based on the foregone hospital revenue that results whenever an infection occurs. From the perspective of the hospital, reducing the cost of CLABSIs is tantamount to reducing this foregone revenue by redeploying ICU beds for new admissions. Finally, we extended the evaluation to consider deaths prevented as an additional outcome because of its interest to clinicians and patients.

Limitations of the study

This evaluation has several limitations. First, the impact of patient heterogeneity, such as demographics and clinical characteristics on baseline risk, treatment effect, or resource utilisation was not fully explored.[42] This evaluation sought instead to represent an average ICU experience, in part because the data needed to explore subgroups are not available, but more importantly because the intervention applies to patients irrespective of these differences. It would be impractical—and possibly unethical—to only use this programme in subgroups of patients for whom greater benefit is expected. The programme is based on evidence-based practices for inserting central venous catheters—practices that should apply equally to all patients. Second, we did not evaluate costs outside the acute hospital setting, such as rehabilitation costs or productivity losses for delays returning to work incurred by patients suffering CLABSIs. However, doing so would further support the cost effectiveness of the programme. We chose to examine costs from the perspective of the hospital because hospitals bear the greatest burden of nosocomial infection costs in the prospective payer system and demonstrating a business case is important for the dissemination of effective quality improvement programmes. Finally, this evaluation did not explore the use of antimicrobial catheters as an comparator because systematic reviews have come to differing conclusions about the extent of their effectiveness in preventing CLABSIs, and many of the trials have been small and of a low quality.[43 44] In addition, the choice facing hospital decision makers is not necessarily a mutually exclusive choice between the Keystone ICU project or the use of antimicrobial catheters. The results of Keystone ICU project already reflect the use of various types of catheters because the programme itself did not specify catheter type. The parameter estimate for effectiveness of the programme used in this evaluation was derived from a cluster randomised controlled trial. In this setting it can be expected that the utilisation of antimicrobial catheters should be balanced between the

intervention and control arms of the trial (though this was not explicitly measured), and the effectiveness estimate is attributable to the quality improvement programme itself. The Keystone ICU project quality improvement programme is also a complex social intervention. Comparing it directly to technology or a device understates its broader effects, which may include reductions in sepsis and ventilator-associated pneumonia or reduced staff turnover resulting from an improved safety culture.[21] Data for these effects are limited in comparison to the data available for CLABSIs, but recent evidence suggests that the Keystone ICU project significantly reduced rates of ventilator associated pneumonia in Michigan ICUs.[9] Inclusion of these additional beneficial effects for the same set of costs would further support the cost effectiveness of the programme.

Conclusions and implications of study findings

These findings have important implications for health care. Broad implementation of the Keystone ICU project in the US healthcare system could substantially reduce the morbidity and mortality associated with CLABSIs and their economic costs to hospitals. Although the Centers for Disease Control and Prevention has demonstrated that significant reductions in CLABSIs are indeed being realised for intensive care patients in the US,[45] 800 medium and large hospitals continue to have high CLABSIs rates.[46] Further dissemination of cost effective quality improvement programmes is needed. Although our analysis adopted a hospital perspective, payers also stand to benefit from the programme and can support dissemination efforts. Hospitals and payers should partner to reform the incentive structure facing hospitals in order to better support patient safety and quality. Payer support, such as covering or funding some intervention costs and imposing financial penalties on hospitals when patients develop CLABSIs, could encourage uptake and dissemination of the programme. Future evaluations of this quality

improvement programme in non-US settings can incorporate country specific costs or extend the evaluation to consider additional outcomes, such as cases of ventilator-associated pneumonia prevented. As more data and evidence emerges regarding the long-term costs and outcomes for patients with CLABSI and other healthcare associated infections,[47] future economic evaluations can incorporate this information to gauge the cost effectiveness of prevention and quality improvement efforts.

To conclude, this multifaceted quality improvement programme, currently being implemented by thousands of hospitals in the US, likely reduces unnecessary morbidity, mortality, and economic costs associated with CLABSIs.

Acknowledgements: We thank Susan M. Turley for her assistance in editing the manuscript.

Contributors: KRH is the guarantor and had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All the authors were involved in preparing this manuscript. KRH was responsible for the overall study design, data analysis, and interpretation of data, and wrote the initial draft of the manuscript. All other authors contributed to the study design, analysis and interpretation of data, and critical revision of the manuscript. LN, DOC, WJW, and PJP also provided supervision.

The study guarantor affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Funding: This study was conducted as part of KRH's doctoral training at the Johns Hopkins Bloomberg School of Public Health. KRH is supported by the Harry S. Truman Scholarship Foundation and by a training grant from the National Institutes of Health under award number T32 GM007309. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. All of the researchers were independent of the sponsors, and neither sponsor had any influence over the study design; collection, analysis, or interpretation of the data; writing of the manuscript; or decision to submit it for publication.

Role of the Sponsors: The Truman Scholarship Foundation and the National Institutes of Health had played no direct role in any aspect of this study. The researchers were independent of the sponsors and neither sponsor had any influence over the study design, collection, analysis or interpretation of the data, writing of the manuscript, or decision to submit it for publication.

Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that they had (1) No financial support for the submitted work. (2) PJP reports: receiving grant or contract support from the Agency for Healthcare Research and Quality, the Gordon and Betty Moore Foundation (research related to patient safety and quality of care), the National Institutes of Health (acute lung injury research), and the American Medical Association Inc. (improve blood pressure control); honoraria from various healthcare organizations for speaking on patient safety and quality (the Leigh Bureau manages most of these engagements); and book royalties from the Penguin Group for his book *Safe Patients, Smart Hospitals*. Dr. Pronovost is a paid strategic advisor to the Gordon and Betty Moore Foundation; receives stock and fees to serve as a director for Cantel Medical; and is a founder of *Patient Doctor Technologies*, a startup company that seeks to enhance the partnership between patients and clinicians with an application called Doctella; (3) No spouses, partners, or children with relationships with commercial entities that might have an interest in the submitted work and (4) No non-financial interests that may be relevant to the submitted work.

Ethics approval: Not required.

Data sharing: No additional data available.

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, a worldwide licence to the Publishers and its licensees in perpetuity, in all forms, formats and media (whether known now or created in the future), to i) publish, reproduce, distribute, display and store the Contribution, ii) translate the Contribution into other languages, create adaptations, reprints, include within collections and create summaries, extracts and/or, abstracts of the Contribution, iii) create any other derivative work(s) based on the Contribution, iv) to exploit all subsidiary rights in the Contribution, v) the inclusion of electronic links from the Contribution to third party material where-ever it may be located; and, vi) licence any third party to do any or all of the above

Figure legends

Figure 1 | Decision tree model. Decision tree model depicting programme versus no programme and its effects on outcomes in intensive care unit (ICU) patients. “Bloodstream infections” refers to central line-associated bloodstream infection.

Figure 2 | Cost effectiveness plane for central line-associated bloodstream infections prevented with 95% confidence ellipses. Values on both axes have been multiplied by 1,000 to yield incremental costs and effects expressed per 1,000 patients to aid interpretation. Incremental refers to the difference in costs or effects between programme and non-programme intensive care units. Cost values in US dollars. Boxes in the plot region display the percentage of the distribution of incremental cost-effectiveness ratios falling above or below $0. The 95% confidence ellipses overlaid on the figure are calculated assuming a bivariate normal distribution and display the uncertainty in the incremental costs effectiveness ratios.

References

1. Mermel LA. Prevention of intravascular catheter-related infections. *Ann Intern Med* 2000;132(5):391-402.

2. Burke JP. Infection control - a problem for patient safety. *N Engl J Med* 2003;348(7):651-6. doi: 10.1056/NEJMhpr020557.

3. Klevens RM, Edwards JR, Richards CL, Jr.*, et al.* Estimating health care-associated infections and deaths in U.S. hospitals, 2002. *Public Health Rep* 2007;122(2):160-6.

4. O'Grady NP, Alexander M, Dellinger EP*, et al.* Guidelines for the prevention of intravascular catheter-related infections. *Infect Control Hosp Epidemiol* 2002;23(12):759-69. doi: 10.1086/502007.

5. Digiovine B, Chenoweth C, Watts C*, et al.* The attributable mortality and costs of primary nosocomial bloodstream infections in the intensive care unit. *Am J Respir Crit Care Med* 1999;160(3):976-81. doi: 10.1164/ajrccm.160.3.9808145.

6. Pittet D, Tarara D, Wenzel RP. Nosocomial bloodstream infection in critically ill patients. Excess length of stay, extra costs, and attributable mortality. *JAMA* 1994;271(20):1598-601.

7. Pronovost P, Needham D, Berenholtz S*, et al.* An intervention to decrease catheter-related bloodstream infections in the ICU. *N Engl J Med* 2006;355(26):2725-32. doi: 10.1056/NEJMoa061115.

8. Berenholtz SM, Pronovost PJ, Lipsett PA*, et al.* Eliminating catheter-related bloodstream infections in the intensive care unit. *Crit Care Med* 2004;32(10):2014-20. doi: 10.1097/01.ccm.0000142399.70913.2f.

9. Berenholtz SM, Pham JC, Thompson DA, *et al.* Collaborative cohort study of an intervention to reduce ventilator-associated pneumonia in the intensive care unit. *Infect Control Hosp Epidemiol* 2011;32(4):305-14. doi: 10.1086/658938.

10. Lin DM, Weeks K, Bauer L, *et al.* Eradicating central line-associated bloodstream infections statewide: the Hawaii experience. *Am J Med Qual* 2012;27(2):124-9. doi: 10.1177/1062860611414299.

11. Lipitz-Snyderman A, Steinwachs D, Needham DM, *et al.* Impact of a statewide intensive care unit quality improvement initiative on hospital mortality and length of stay: retrospective comparative analysis. *BMJ* 2011;342:d219. doi: 10.1136/bmj.d219.

12. Bion J, Richardson A, Hibbert P, *et al.* 'Matching Michigan': a 2-year stepped interventional programme to minimise central venous catheter-blood stream infections in intensive care units in England. *BMJ Qual Saf* 2013;22(2):110-23. doi: 10.1136/bmjqs-2012-001325.

13. Marsteller JA, Sexton JB, Hsu YJ, *et al.* A multicenter, phased, cluster-randomized controlled trial to reduce central line-associated bloodstream infections in intensive care units. *Crit Care Med* 2012;40(11):2933-9. doi: 10.1097/CCM.0b013e31825fd4d8.

14. Niessen LW, Grijseels EW, Rutten FF. The evidence-based approach in health policy and health care delivery. *Soc Sci Med* 2000;51(6):859-69.

15. Grimshaw JM, Thomas RE, MacLennan G, *et al.* Effectiveness and efficiency of guideline dissemination and implementation strategies. *Health Technol Assess* 2004;8(6):iii-iv, 1-72.

16. Hoomans T, Evers SM, Ament AJ, *et al.* The methodological quality of economic evaluations of guideline implementation into clinical practice: a systematic review of

empiric studies. *Value Health* 2007;10(4):305-16. doi: 10.1111/j.1524-4733.2007.00175.x.

17. Graves N, Harbarth S, Beyersmann J*, et al.* Estimating the cost of health care-associated infections: mind your p's and q's. *Clin Infect Dis* 2010;50(7):1017-21. doi: 10.1086/651110.

18. Veenstra DL, Saint S, Sullivan SD. Cost-effectiveness of antiseptic-impregnated central venous catheters for the prevention of catheter-related bloodstream infection. *JAMA* 1999;282(6):554-60.

19. Halton KA, Cook DA, Whitby M*, et al.* Cost effectiveness of antimicrobial catheters in the intensive care unit: addressing uncertainty in the decision. *Crit Care* 2009;13(2):R35. doi: 10.1186/cc7744.

20. Needham DM, Scales DC, Laupacis A*, et al.* A systematic review of the Charlson comorbidity index using Canadian administrative databases: a perspective on risk adjustment in critical care research. *J Crit Care* 2005;20(1):12-9.

21. Pronovost PJ, Berenholtz SM, Goeschel C*, et al.* Improving patient safety in intensive care units in Michigan. *J Crit Care* 2008;23(2):207-21. doi: 10.1016/j.jcrc.2007.09.002.

22. Pronovost PJ, Berenholtz SM, Needham DM. Translating evidence into practice: a model for large scale knowledge translation. *BMJ* 2008;337:a1714. doi: 10.1136/bmj.a1714.

23. Fletcher S. Catheter-related bloodstream infection. *Contin Educ Anaesth Crit Care Pain* 2005;5(2):49-51. doi: 10.1093/bjaceaccp/mki011.

24. Brun-Buisson C. New technologies and infection control practices to prevent intravascular catheter-related infections. *Am J Respir Crit Care Med* 2001;164(9):1557-8. doi: 10.1164/ajrccm.164.9.2109051.

25. Veenstra DL, Saint S, Saha S, *et al.* Efficacy of antiseptic-impregnated central venous catheters in preventing catheter-related bloodstream infection: a meta-analysis. *JAMA* 1999;281(3):261-7.

26. Martin MA, Pfaller MA, Wenzel RP. Coagulase-negative staphylococcal bacteremia. Mortality and hospital stay. *Ann Intern Med* 1989;110(1):9-16.

27. Smith RL, Meixler SM, Simberkoff MS. Excess mortality in critically ill patients with nosocomial bloodstream infections. *Chest* 1991;100(1):164-7.

28. Arnow PM, Quimosing EM, Beach M. Consequences of intravascular catheter sepsis. *Clin Infect Dis* 1993;16(6):778-84.

29. Waters HR, Korn R, Jr., Colantuoni E, *et al.* The business case for quality: economic analysis of the Michigan Keystone Patient Safety Program in ICUs. *Am J Med Qual* 2011;26(5):333-9. doi: 10.1177/1062860611410685.

30. Graves N, Weinhold D, Tong E, *et al.* Effect of healthcare-acquired infection on length of hospital stay and cost. *Infect Control Hosp Epidemiol* 2007;28(3):280-92. doi: 10.1086/512642.

31. Graves N. Economics and preventing hospital-acquired infection. *Emerg Infect Dis* 2004;10(4):561-6. doi: 10.3201/eid1004.020754.

32. Society of Critical Care Medicine. *Compensation of Critical Care Professionals*: Society of Critical Care Medicine, 2009.

33. Warren DK, Quadir WW, Hollenbeak CS, *et al.* Attributable cost of catheter-associated bloodstream infections among intensive care patients in a nonteaching hospital. *Crit Care Med* 2006;34(8):2084-9. doi: 10.1097/01.CCM.0000227648.15804.2D.

34. American Hospital Association. *AHA Hospital Statistics. 2013 ed*: American Hospital Association, 2012.

35. Wunsch H, Angus DC, Harrison DA*, et al.* Variation in critical care services across North America and Western Europe. *Crit Care Med* 2008;36(10):2787-93, e1-9. doi: 10.1097/CCM.0b013e318186aec8.

36. Pronovost PJ, Goeschel CA, Colantuoni E*, et al.* Sustaining reductions in catheter related bloodstream infections in Michigan intensive care units: observational study. *BMJ* 2010;340:c309. doi: 10.1136/bmj.c309.

37. Leatherman S, Berwick D, Iles D*, et al.* The business case for quality: case studies and an analysis. *Health Aff (Millwood)* 2003;22(2):17-30.

38. Galvin RS, Delbanco S, Milstein A*, et al.* Has the leapfrog group had an impact on the health care market? *Health Aff (Millwood)* 2005;24(1):228-33. doi: 10.1377/hlthaff.24.1.228.

39. Hsu E, Lin D, Evans SJ*, et al.* Doing well by doing good: assessing the cost savings of an intervention to reduce central line-associated bloodstream infections in a Hawaii hospital. *Am J Med Qual* 2014;29(1):13-9. doi: 10.1177/1062860613486173.

40. Halton K, Graves N. Economic evaluation and catheter-related bloodstream infections. *Emerg Infect Dis* 2007;13(6):815-23. doi: 10.3201/eid1306.070048.

41. Dimick JB, Pronovost PJ, Heitmiller RF*, et al.* Intensive care unit physician staffing is associated with decreased length of stay, hospital cost, and complications after esophageal resection. *Crit Care Med* 2001;29(4):753-8.

42. Grutters JP, Sculpher M, Briggs AH*, et al.* Acknowledging patient heterogeneity in economic evaluation : a systematic literature review. *Pharmacoeconomics* 2013;31(2):111-23. doi: 10.1007/s40273-012-0015-4.

43. Niel-Weise BS, Stijnen T, van den Broek PJ. Anti-infective-treated central venous catheters: a systematic review of randomized controlled trials. *Intensive Care Med* 2007;33(12):2058-68. doi: 10.1007/s00134-007-0897-3.

44. Hockenhull JC, Dwan K, Boland A*, et al.* The clinical effectiveness and cost-effectiveness of central venous catheters treated with anti-infective agents in preventing bloodstream infections: a systematic review and economic evaluation. *Health Technol Assess* 2008;12(12):iii-iv, xi-xii, 1-154.

45. Center for Disease Control and Prevention. *National and State Healthcare Association Infections Progress Report*. Atlanta, 2014.

46. Wise ME, Scott RD, 2nd, Baggs JM*, et al.* National estimates of central line-associated bloodstream infections in critical care patients. *Infect Control Hosp Epidemiol* 2013;34(6):547-54. doi: 10.1086/670629.

47. Dick A, Liu H, Zwanziger J*, et al.* Long-term survival and healthcare utilization outcomes attributable to sepsis and pneumonia. *BMC Health Serv Res* 2012;12:432. doi: 10.1186/1472-6963-12-432.

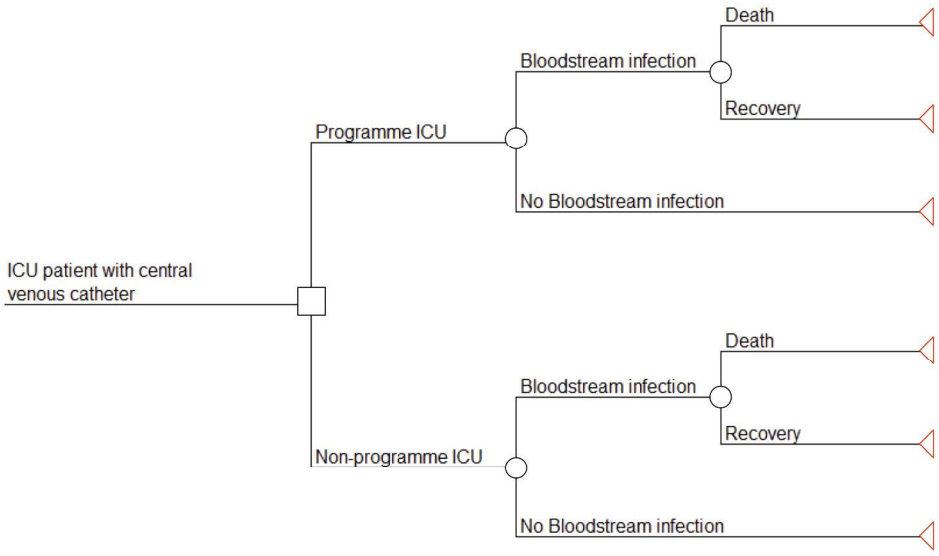


Figure 1 | Decision tree model. Decision tree model depicting programme versus no programme and its effects on outcomes in intensive care unit (ICU) patients. "Bloodstream infections" refers to central line-associated bloodstream infection.
254x190mm (300 x 300 DPI)

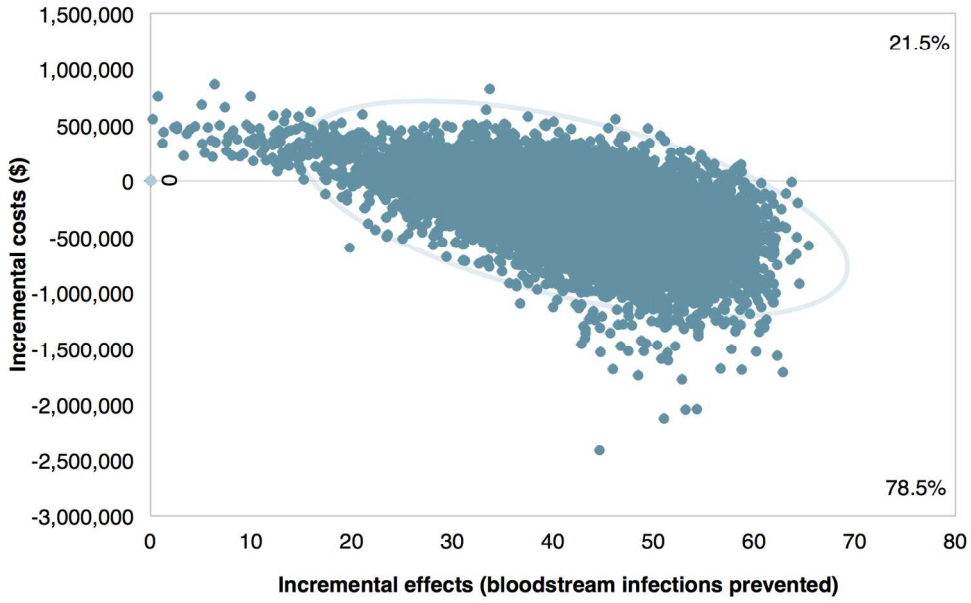


Figure 2 | Cost effectiveness plane for central line-associated bloodstream infections prevented with 95% confidence ellipses. Values on both axes have been multiplied by 1,000 to yield incremental costs and effects expressed per 1,000 patients to aid interpretation. Incremental refers to the difference in costs or effects between programme and non-programme intensive care units. Cost values in US dollars. Boxes in the plot region display the percentage of the distribution of incremental cost-effectiveness ratios falling above or below $0. The 95% confidence ellipses overlaid on the figure are calculated assuming a bivariate normal distribution and display the uncertainty in the incremental costs effectiveness ratios.
164x113mm (300 x 300 DPI)

Web only appendices and tables

Calculation of the economic cost of a bloodstream infection

As described in the main text, determining the economic cost of a bloodstream infection requires estimating the opportunity costs and variable costs associated with infection.[1] In this analysis, we do not consider the variable costs (e.g., medications and supplies) because they contribute less to the total economic cost than do the opportunity costs. In addition, the probabilistic sensitivity analysis accounts for the variability in the economic cost over a wide range.

The follow steps were taken to estimate the opportunity cost of bloodstream infection. Based on a recent meta analysis, the average attributable excess hospital length of stay for bloodstream infections is 10.4 days.[2] Dividing by the average length of stay for all discharges in acute care hospitals in the United States yields the potential incremental case throughput. Multiplying this potential case throughput per infection prevented by the national average net revenue per equivalent discharge results in a point estimate of $19,617 (Table A). Using an economic interpretation, this represents the opportunity cost of lost revenue for a single infection. The results of the probabilistic analysis incorporating uncertainty in several of the parameters are displayed in Table 2. We then calculated the 5-year discounted cost of a bloodstream infection, which is the value used in the decision tree model described in the main text.

Table A. Calculation of economic (opportunity) cost of a bloodstream infection

	Value	Calculation	Uncertainty	Source
Average length of stay—all discharges (days)	4.8	A		CDC—NHDS
Excess total average length of stay attributable to bloodstream infection, i.e., the potential reduction in total length of stay per prevented infection (days)	10.4	B	6.9 to 15.2	Zimlichman
Potential incremental case throughput	2.17	C = B/A		
Median net revenue per equivalent discharge ($)	9,054	D	7,896 to 10,327 (25^{th} and 75^{th} percentile, respectively)	Cleverley and Associates
Potential incremental net revenue opportunity per prevented infection, i.e., economic opportunity cost per infection ($)	19,617	E = C x D		

Table B. Results of probabilistic analysis

Mean	19,951
Standard Deviation	5,978

Abbreviations: CDC=Centers for Disease Control and Prevention, NHDS=National Hospital Discharge Survey

Approach for estimating an average per patient cost of the quality improvement programme

Given that the Keystone ICU project is implemented at the ICU level—and its costs have been estimated at the intensive care unit level—but the decision tree model is implemented at a patient level, a per patient cost of the programme must be determined. Ultimately, this depends on the cost of the programme to a hospital and the number of intensive care unit patients receiving central venous catheters in that hospital (patients who represent the population that stands to benefit from the bloodstream infection prevention effort). It can be argued that all intensive care unit patients in a hospital stand to benefit (regardless of whether they receive a central venous catheter or not) because of the culture change components of the programme, but the approach used here is more conservative.

We estimated a per patient cost of the programme by first deriving a national annual cohort of intensive care unit patients exposed to central venous catheters. To do this, we multiplied 4.85 million estimated annual intensive care unit admissions in the US by an estimate of the proportion of patients admitted to an intensive care unit who receive a central venous catheter,[3] yielding 1.8 million patients who had catheters. We then divided the estimate of 1.8 million patients by the number of hospitals that reported having adult intensive care units in the American Hospital Association Annual Survey of Hospitals.[4] This provided an average number of "exposed" patients per hospital (Table 3). Finally, we divided total costs of the programme per hospital by the number of patients per hospital to yield an average cost for the programme per patient.

Table C. Calculation of the average number of ICU patients with CVCs

	Base case	**Low value**†	**High value**†
Number of annual ICU admissions in US	4,850,000*	4,000,000	5,700,000
X % of ICU admissions receiving CVCs	38%	17%	48%
= Number of ICU patients receiving CVCs	**1,843,000**		
Number of US hospitals with adult ICUs	4,355		
Average number of ICU patients with CVCs per hospital per year	**423**		

*Midpoint between the lowest and highest values identified in the literature
†The low value and the high value were used in the probabilistic model to capture the uncertainty in the calculation.
Abbreviation: ICU—intensive care unit, CVC—central venous catheter

Based on this calculation there is an average of 423 intensive care unit patients with central venous catheters per hospital per year in the United States (the average does not distinguish between small hospitals or large hospitals). Multiplying this by 5 to reflect the 5-year period used in this cost effectiveness analysis yields 2,115 patients. Diving this by the discounted cost of the quality improvement programme for a single hospital over 5 years ($990,340) results in a per patient cost of the programme of $468. For the main analysis presented in the paper, we implemented these calculations using Monte Carlo simulation to capture the uncertainty in the

base case parameter values. Doing so results in different estimates than the basic arithmetic used here. As such, we calculated that the mean per patient cost of the programme was $540 with a standard deviation of $120 and we applied a distribution that was lognormal based on normal mean.

This approach has several limitations. First, deriving a patient cost estimate of the programme was limited by a lack of appropriate individual-based national data on central line utilisation among intensive care unit patients. We consulted experts to inquire about less apparent sources of data to aid in the estimation of this parameter but consensus emerged that we would need to make several assumptions to derive this estimate. These assumptions were based on published data in the critical care literature and reputable national surveys.[4 5] To address the uncertainty in our estimate we tested a large standard deviation for the parameter in the probabilistic sensitivity analysis. The estimate is intended to reflect an average. It is likely that hospitals with more intensive care unit beds benefit from economies of scale when implementing the programme, providing a lower programme cost per patient.

Table D. Results from sensitivity analyses

	Incremental cost effectiveness ratio					
Model	**Mean**	**Median**	**2.5th Percentile**	**97.5th Percentile**	**Prob. Negative**	**Prob. Positive**
Sensitivity Analyses						
Bloodstream infections discounted	-3,866	-5,442	-20,912	10,921	0.79	0.21
Deaths discounted	-38,191	-36,784	-220,378	92,979	0.79	0.21
0% discounting of costs, infections prevented	-5,019	-5,578	-21,467	10,923	0.79	0.21
0% discounting of costs, deaths prevented	-40,289	-36,855	-216,212	93,041	0.79	0.21
5% discounting of costs, infections prevented*	-4,503	-4,821	-19,512	10,268	0.78	0.22
5% discounting of costs, deaths prevented*	-32,925	-32,605	-196,368	80,484	0.79	0.21

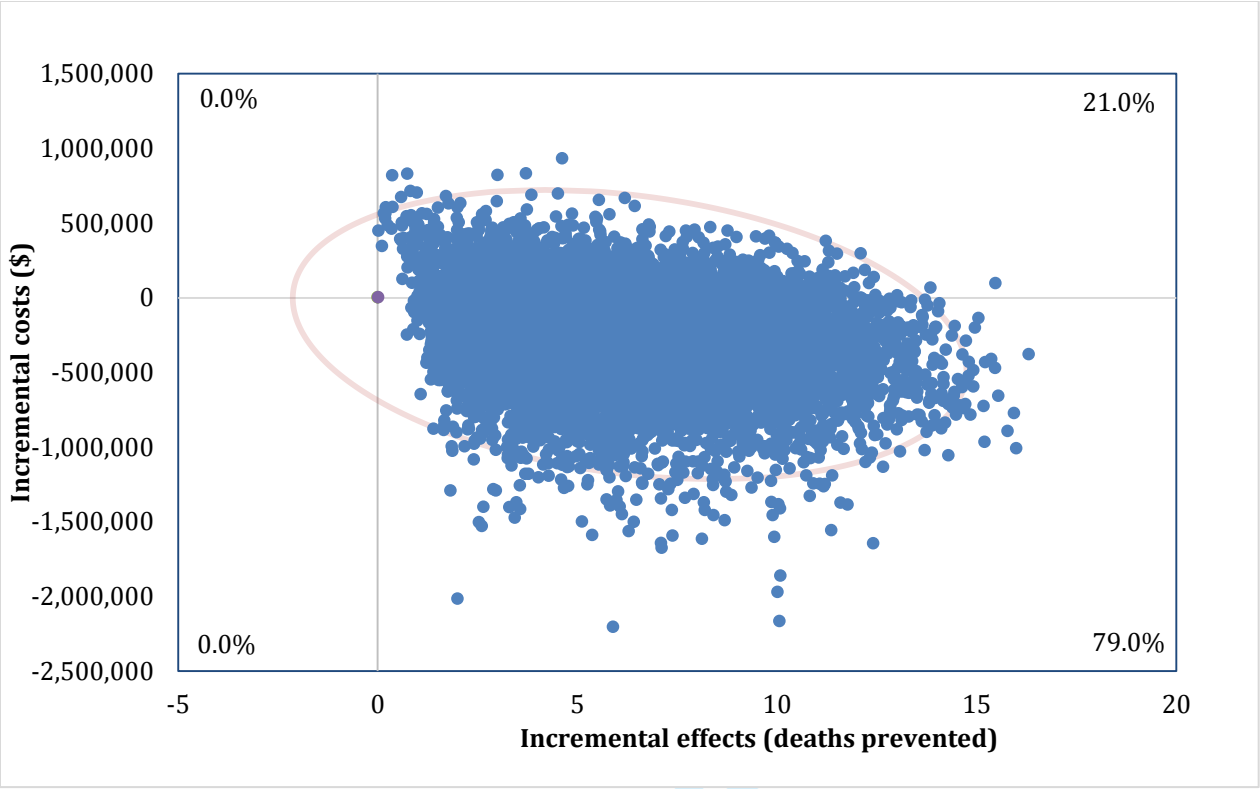
*The average of the 5-year stream of discounted costs was used.

References

1. Graves N, Halton K, Lairson D. Economics and preventing hospital-acquired infection: broadening the perspective. *Infect Control Hosp Epidemiol* 2007;28(2):178-84. doi: 10.1086/510787.
2. Zimlichman E, Henderson D, Tamir O, *et al.* Health care-associated infections: a meta-analysis of costs and financial impact on the US health care system. *JAMA Intern Med* 2013;173(22):2039-46. doi: 10.1001/jamainternmed.2013.9763.
3. Warren DK, Quadir WW, Hollenbeak CS, *et al.* Attributable cost of catheter-associated bloodstream infections among intensive care patients in a nonteaching hospital. *Crit Care Med* 2006;34(8):2084-9. doi: 10.1097/01.CCM.0000227648.15804.2D.
4. American Hospital Association. *AHA Hospital Statistics. 2013 ed*: American Hospital Association, 2012.
5. Wunsch H, Angus DC, Harrison DA, *et al.* Comparison of medical admissions to intensive care units in the United States and United Kingdom. *Am J Respir Crit Care Med* 2011;183(12):1666-73. doi: 10.1164/rccm.201012-1961OC.

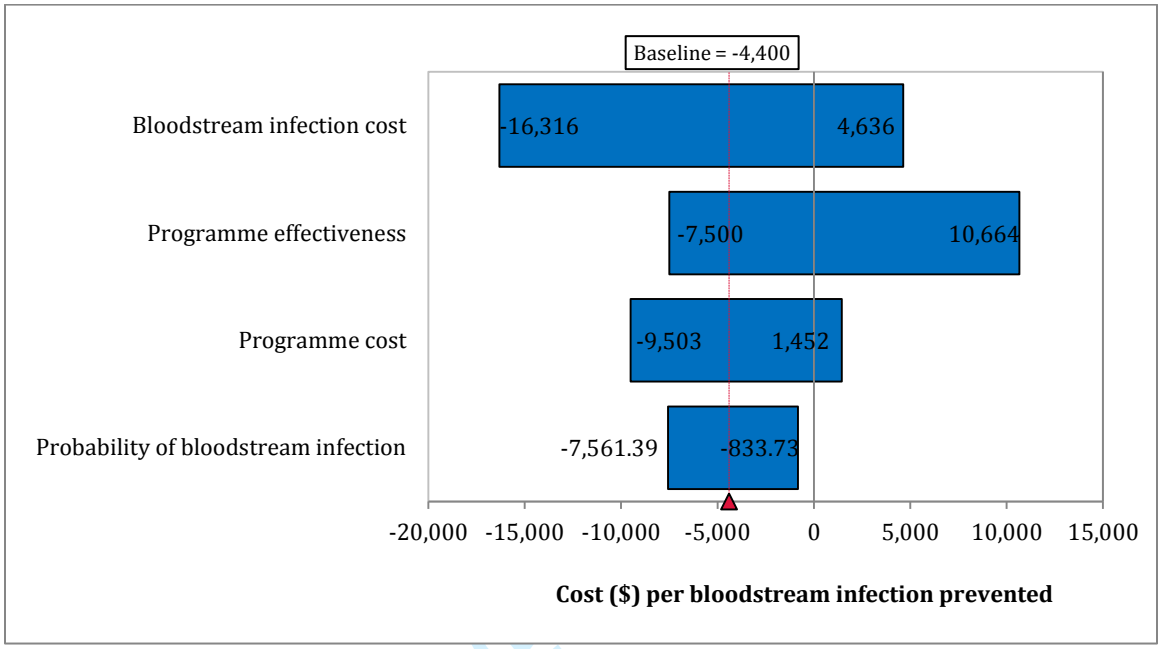
Web only figures

Figure S1 | Cost effectiveness plane for deaths averted due to bloodstream infections prevented



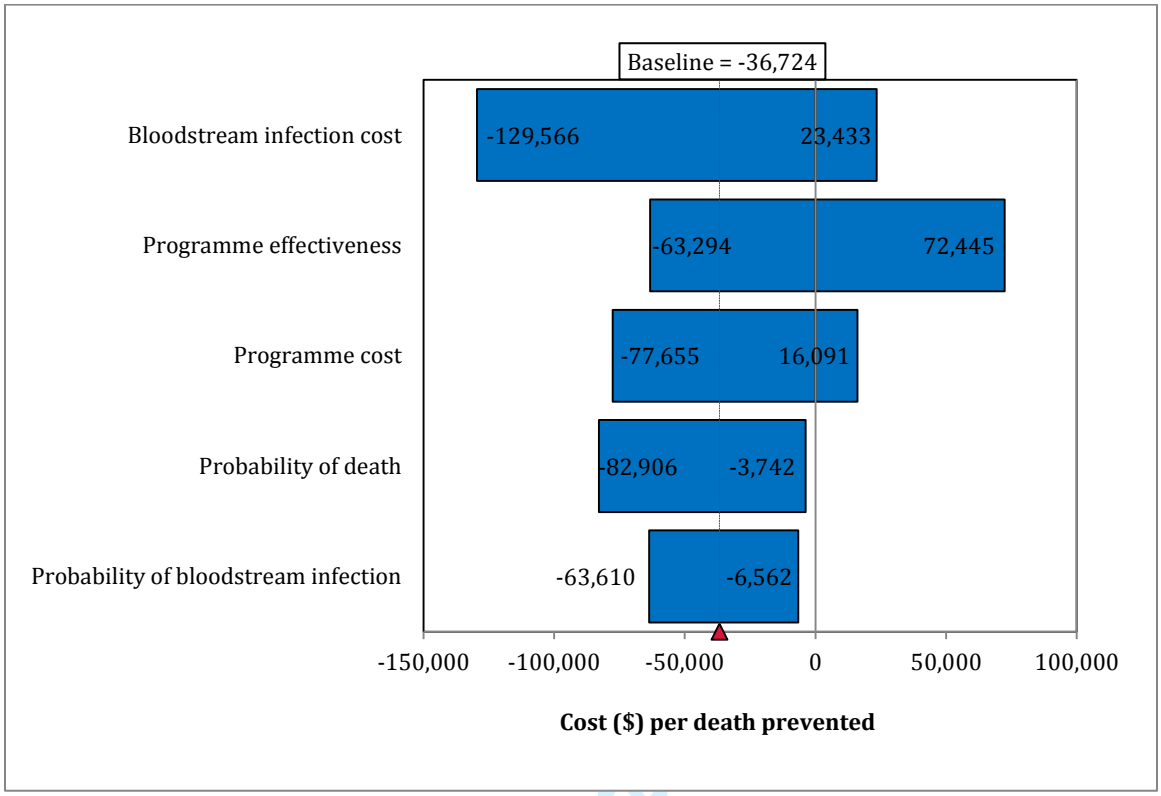
Cost effectiveness plane for deaths averted due to bloodstream infections prevented with 95% confidence ellipses. Values on both axes have been multiplied by 1,000 to yield incremental costs and effects expressed per 1,000 patients to aid interpretation. Incremental refers to the difference in costs or effects between programme and non-programme intensive care units. Cost values in US dollars. Boxes in the plot region display the percentage of the distribution of incremental cost effectiveness ratios falling in each quadrant.

Figure S2 | Tornado diagram for bloodstream infections prevented



Tornado diagram of model inputs ranked by effect on the mean cost per bloodstream infection prevented. Each parameter was simultaneously sampled 10,000 times from an underlying distribution that reflects uncertainty in the parameter estimate. Cost values are in US dollars.

Figure S3 | Tornado diagram for deaths averted due to bloodstream infections prevented



Tornado diagram of model inputs ranked by effect on the mean cost per death prevented. Each parameter was simultaneously sampled 10,000 times from an underlying distribution that reflects uncertainty in the parameter estimate. Cost values are in US dollars.

Table

Table 1| CHEERS checklist—Items to include when reporting economic evaluations of health interventions Nos. refer to pages

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	3
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	5-6
		Present the study question and its relevance for health policy or practice decisions.	5-6
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	7
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	7
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	7
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	6
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	7
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	11, 12
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	12
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	11
	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	NA
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	8-11
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	11
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	6; Fig
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	6
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	12
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	8
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	13-15
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	

(continued)

Section/item	Item No	Recommendation	Reported on page No/ line No
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	13-15
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	NA
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	15-19
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	20
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	21

For consistency, the CHEERS statement checklist format is based on the format of the CONSORT statement checklist