

A Model to Evaluate the Impact of Hospital-Based Interventions Targeting False-positive Blood Cultures on Economic and Clinical Outcomes

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Structured Summary

Background: Blood culture contamination (BCC) increases length of stay (LOS) and leads to unnecessary anti-microbial therapy and/or hospital-acquired conditions (HACs).

Aim: We sought to quantify the magnitude of the additional LOS, costs to hospitals and society as well as the harm to patients attributable to BCC.

Methods: A retrospective matched survival analysis was performed involving hospitalized patients with septicaemia-compatible symptoms. BCC costs, hospital-acquired conditions (HACs), and potential savings were calculated based on the primary LOS data, a modified Delphi process, and published sources. The cost analysis compared standard care to interventions for reducing BCC, and estimated annual economic and clinical consequences for a typical hospital and for the entire U.S.

Findings: Patients with BCC experienced mean prolonged hospital stays of 2.35 days ($p=0.0076$). Avoiding BCCs would decrease costs by \$6,463 (\$4,818 from inpatient care, of which 53% was from reduced length of stay, and 26% was from reduced antibiotic use). Annually, in a typical 250- to 400-bed hospital, employing phlebotomists would save \$1.3 million and prevent 24 HACs (including 2 *C. difficile* cases); based on clinical efficacy evidence, using the studied Initial Specimen Diversion Device (ISDD) would save \$ 1.9 million and prevent 34 HACs (including 3 *C. difficile* cases). In the United States, the respective strategies would prevent 69,300 and 102,900 HACs (including 6,000 and 8,900 *C. difficile* cases) and costs of \$5 and \$7.5 billion.

Conclusion: Costs and clinical burdens associated with false-positive cultures are substantial and can be reduced by available interventions, including phlebotomists and ISDD use.

Key Words: Blood Culture[MeSH]; Contamination; False-positive; Quality of Health Care[MeSH]; Costs and Cost Analysis[MeSH]

Abbreviations

CCR: cost-to-charge ratio

BCC: Blood culture contamination

HAC: hospital-acquired conditions

ISDD: Initial Specimen Diversion Device

LOS: length of stay

Introduction

Blood culture is the current gold standard for the diagnosis of bacteraemia, for bacterial species identification, and for antibiotic susceptibility testing [1]. However, contamination of blood cultures with commensal skin flora leads to increased costs and longer hospital stays and causes harm to patients. Unnecessary hospitalization can lead to hospital-acquired conditions (HACs), including infection with *Clostridium difficile* [2].

Most studies estimate that around half of all positive blood cultures become contaminated during phlebotomy [3-11]. Across most healthcare settings, the largest proportion of false-positive blood cultures (50% to 85%) result from contamination with coagulase-negative staphylococci [3, 7, 8, 10-21].

Researchers have previously studied several approaches to reducing the rate of false-positive blood cultures, including optimized skin antisepsis [22], the use of sterile collection kits [23], and implementation of dedicated phlebotomy teams [24], and, more recently, a device-based option [3].

Previous efforts to quantify the economic impact of such strategies have been conducted outside the United States [25], mostly before 2012 [5, 8, 10, 21, 25], and have failed to comprehensively compare the strategies under study [10, 23].

The objective of the present study was to quantify the potential for cost savings and patient harm reduction—for a typical hospital and for the U.S. healthcare system as a whole—by adopting interventions suited to decrease the rate of false-positive blood cultures.

Methods

Overview

Clinical event and treatment rate projections were combined with an analysis of related costs and adopted both a hospital and societal perspective. Length of stay (LOS) data were compared between patients with false-positive and true-negative cultures. Clinical utilization data were estimated utilizing a modified Delphi process. Unit costs were obtained from literature, internet searches, and manufacturer queries.

Outcome measures were the incremental costs resulting from a false-positive blood culture, costs per all cultures (i.e., incremental costs resulting from all false-positive blood cultures, divided by the total number of cultures obtained), and HACs resulting from false-positive blood cultures. From the cost of an individual culture, assuming typical contamination rates and utilization patterns, we explored extrapolations to a small- to medium-sized hospital and to the United States-national level. We performed comprehensive sensitivity analyses to quantify the effects of varied input parameters on the results.

False-positive Rate and Comparator Effect Sizes

The false-positive rate was estimated by pooling proportions identified in a systematic review (Appendix). As comparators we chose implementation of dedicated phlebotomists and a more recently evaluated, device-based treatment. The relative risk of reducing BCC by using phlebotomists of 0.41 was estimated in a random-effects meta-analysis (Appendix). The device for the other comparator was Steripath. This Initial Specimen Diversion Device (ISDD, Magnolia Medical Technologies, Inc., Seattle, Washington) diverts and sequesters an initial portion of blood prior to collection of the subsequent specimen for culture, and in a single-centre, prospective, controlled, open-label trial has been shown to be associated with a relative risk of 0.12 for BCC [3].

Length of Stay

We obtained data for 270 true-negative and false-positive patients from a 281-bed university-affiliated hospital in the greater Seattle area. We searched the hospital's electronic medical records for calendar year 2013 to identify patients with suspected sepsis and potentially false-positive blood cultures. We verified that an organism typically found in contaminated cultures was detected in only a single culture bottle and that all follow-up cultures remained negative.

Each of the 135 patients thus identified as having a false-positive blood culture was then matched with a patient having a true-negative blood culture, based on the following criteria:

symptoms compatible with septicaemia, same hospital unit, similar severity of illness and risk of mortality scores, and nearest time proximity to the false-positive case.

To avoid outliers, we excluded patients whose LOS exceeded 30 days. Based on Kaplan-Meier estimates, we then plotted survival curves with discharge as the outcome of interest, and we performed a log-rank test using Stata (Stata Corp., College Station, TX).

Adverse Events and Resource Utilization

Based on literature estimates and differences in the LOS between patients with true-negative blood cultures and those with false-positive blood cultures, we calculated the additional incidence of the following HACs: catheter-associated urinary tract infection, *C. difficile*, delirium, falls, hospital-acquired pneumonia, and venous thromboembolism [26-29]. For our model, we assumed HAC incidence rates similar to—but not higher than—those reported in the literature (Table 1 and Appendix).

The distribution of blood culture contaminants was taken from a recent controlled clinical trial [3]. Based on these distributions, some patients were subsequently treated with antibiotics, following current guidelines and clinical routines. We conducted a modified-Delphi survey about utilization patterns among 19 infectious disease physicians (Appendix).

Unit Costs, Cost Analysis, and Perspectives

We derived unit costs from the medical literature; if cost estimates were not available, we used the payment amounts allowed by Medicare as a proxy for true costs (see Table 1 and Appendix). We performed cost analyses considering only the costs that a single hospital would incur ('hospital perspective') or all direct medical costs ('societal perspective'), including charges related to the primary team and any infectious disease consultations, but excluding all outpatient costs and physician compensation for proceduralists. We calculated the hospital perspective to provide economic insights for members of the hospital team, as they are ultimately responsible for deciding what interventions or programs should be adopted to reduce false-positive rates. Moreover, most inpatient stays are reimbursed according to diagnosis-related groups, meaning that payers make a single lump sum payment for an entire hospitalization. Consequently, the costs related to complications—including additional LOS—are typically borne by the hospitals, creating financial incentives to reduce any avoidable costs.

Endpoints, Projections, and Sensitivity Analysis

The primary endpoint was the incremental costs resulting from a false-positive blood culture. Other endpoints considered were the incidence of HACs attributable to a false-positive blood culture, and the incremental costs per all cultures. For the hospital perspective, the costs per all cultures were further delineated into imminent savings related to the cost of materials in the microbiological laboratory not used in patient care (e.g. reagents, kits and other materials), antibiotics and other savings related to all remaining cost categories.

For the hospital perspective, we assumed a typical, medium-sized hospital with 250–400 beds and an annual volume of 10,000 blood cultures (range: 8,500 to 13,600). For the societal perspective, we further assumed that 30 million cultures are drawn annually in the United States (see Appendix). Reduction through the studied ISDD was assumed to be similar as in a recent trial [3].

To assess robustness and to quantify the impact of LOS, incidence of clinical events, and cost components, we performed sensitivity analyses by varying the input parameters by at least $\pm 30\%$, the interquartile range for primary data, and a 2% to 8% false-positive rate.

Results

After excluding patients with hospitalization periods longer than 30 days, the mean LOS for the matched true-negative blood culture group was 6.67 days (95% CI: 1; 22), while patients with a false-positive blood culture stayed in the hospital for 9.02 days (95% CI: 1; 30). The mean difference of 2.35 days was statistically significant ($p=0.0076$, Figure 1 and Appendix).

A medium-sized hospital would annually experience approximately 39 HACs attributable to contaminated blood cultures (range: 15 to 87). The hospital-associated adverse event associated most frequently by incremental LOS due to false-positive blood cultures is delirium (82% of all adverse events). A typical hospital was projected to experience close to 3 additional

cases of *C. difficile* each year (range: 1 to 8). In the U.S., the number of HACs totalled 117,400, including 10,100 cases of *C. difficile* infection.

At the individual hospital level, the use of a dedicated phlebotomy team or the studied ISDD would reduce HACs by 23 and 34 cases, respectively, and would reduce instances of *C. difficile* infection by 2 and 3 cases, respectively. In the U.S., such calculations translate to approximately 69,300 prevented HACs and 6,000 *C. difficile* events by employing dedicated phlebotomists; or 102,900 prevented HACs and 8,900 *C. difficile* events by using ISDD (Table 2 and Appendix).

Each false-positive blood culture resulted in incremental costs totalling \$6,463, of which \$4,818 was spent during hospitalization. The single largest item was the \$2,955 cost of extended hospitalization itself, making up 61% of the costs from the hospital perspective, and 46% of the costs from a societal perspective. Inpatient blood tests, intravenous access, and imaging charges added \$625 to costs tallied from the hospital perspective (excluding physician fees, and if proceduralists were not employed by the hospital) but added \$829 to costs tallied from the societal perspective (including physician fees). Hospital-associated adverse events were responsible for \$373 during the initial hospitalization, and an overall total of \$592 (12%) of all incremental costs (Appendix). Lesser additional charges accounted for among the incremental costs included \$494 for antibiotics administered on an inpatient basis; \$243 for the primary and infectious diseases teams; and \$127 to draw blood and perform an additional microbiological work-up for each initial false-positive test. Incremental costs incurred on an outpatient basis

added \$1,222 for oral and parenteral antibiotic treatments, including the visits of a home infusion company and weekly safety lab tests.

For a 250–400-bed hospital performing 10,000 blood cultures each year (range: 8,500–13,600) and a false-positive rate of 4.4% (range: 2.0% to 7.2%), we projected the costs resulting from false-positive blood cultures to be \$2.1 million annually (range: \$1.0 million to \$3.5 million). Extrapolating from this projection, we estimated the U.S. burden of false-positive blood cultures to be \$8.5 billion (range: \$2.5 billion to \$14.2 billion).

Dedicated phlebotomists would save \$125 per culture from the hospital perspective, and \$185 per culture drawn from the societal perspective; while ISDD would save \$186 per culture from the hospital perspective, and \$249 from the societal perspective. These projections encompass imminent savings for unused materials, including microbiological reagents and antibiotics: \$14 (hospital) and \$40 (societal) for phlebotomists; and \$21 (hospital) and \$60 (societal) for ISDD.

Before accounting for the costs of implementing either of the two intervention strategies, we projected our calculated savings at the hospital and U.S.-national level on an annual basis. For a small- to medium-sized hospital, phlebotomists would save \$1.3 million, while ISDD would save \$1.9 million annually. In the U.S., dedicated phlebotomists would save \$5.0 billion, while ISDD would save \$7.5 billion each year (Appendix).

The most influential cost factors from a societal perspective include LOS, daily hospital costs, and length of antibiotic treatment. A sensitivity analysis of the proportional effects of reducing false-positive blood cultures on cost savings for a small- to medium-sized hospital and for the U.S. healthcare system revealed that a 50% adoption rate of dedicated phlebotomists would generate U.S.-nationwide savings of \$3.14 billion, while a 50% adoption rate of ISDD use would generate savings of \$4.74 billion. See Figures 2, 3 and Appendix.

Discussion

Patients with false-positive blood cultures generate incremental diagnostic and treatment costs of more than \$6,000, the majority of which result from avoidable incremental prolonged periods of hospitalization. Correspondingly, a typical 250- to 400-bed hospital bears approximately \$2.1 million of additional costs annually, the majority of which are not reimbursed by either public or private payers. The estimated burden in the U.S. for such incremental unnecessary and avoidable healthcare costs related to false-positive blood cultures is a staggering \$8.6 billion.

The use of the studied ISDD is the single most effective intervention so far explored for reducing costs related to false-positive blood cultures. Prior to accounting for the cost of implementing this intervention, ISDD has the potential to reduce typical hospital costs by \$1.9 million annually, and to reduce U.S. healthcare costs by \$7.5 billion each year. At the same time, ISDD use can help to avoid more than 103,000 HACs including more than 9,000 episodes

of *C. difficile* infection. Furthermore, annual ISDD use could reduce antibiotics costs by \$2 billion (26% x 7.5) – an amount that might be lower in settings with lower antibiotic use. Beyond costs, blood culture contamination is both a patient safety and antibiotic stewardship issue as well as contributor to continued antibiotic resistance pressure.

Previous studies in the United States have compared the LOS for patients with false-positive and true-negative blood cultures. A chart review from 1989 found that patients with at least one false-positive blood culture were hospitalized 4.5 days longer than patients with true-negative blood cultures [8]. A case-control study using data from 1991 through 1995 found a LOS difference of 8.4 days [24]. A retrospective analysis of inpatient medical charts from 2002 found an increased median LOS of 3 days (interquartile range: 3; 5) [5]. A prospective study in 2006 followed emergency department patients and found an increased median LOS of 5 days (95% CI: 4; 7) [10]. A retrospective analysis of data from Northern Ireland collected in the period 2007–2008 showed a difference of 5.4 days (95% CI: 2.8; 8.1) [25]. Even though the total LOS for hospitalizations in the U.S. has decreased over time [30], our finding of a mean difference of 2.4 days appears conservative in light of these other studies.

Only a handful of studies have evaluated the economic consequences of blood culture contamination; all except one are older than 6 years [23]. A study from 2006 calculated additional laboratory costs of \$425 (in 2005 U.S. dollars) [5]—a higher value than the \$243 we calculated (in 2017 U.S. dollars) for microbiology laboratory and other blood tests. A 2009

prospective comparison of the costs of dedicated phlebotomist use to the costs of usual emergency department care found a median difference in charges of \$8,720 per false-positive blood culture [10]. The most recent study, from 2015, calculated direct costs of \$2,844 for false-positive cultures [23]. Even after adjusting this study's findings to 2017 U.S. dollars, the amount of \$3,450 is below our calculated value of \$4,362. However, cost estimates of the 2015 study relied on applying a cost-to-charge ratio (CCR), an approach that hinges on the accuracy of the ratio employed. A comparably small increase in the CCR used by the study, from 0.30 to 0.38, yields a result very similar to our own [23].

To our knowledge, the current study is the first to compare the effects of several interventions on the universal costs, clinical burden, and potential savings related to false-positive blood cultures. Based on our results, the greatest cost savings and reduced clinical burden for both individual hospitals and society at large would be achieved by universally deploying ISDD. Some hospitals may have already deployed dedicated phlebotomists; according to our analyses, savings from the use of ISDD can be additional to those already achieved.

The estimates used for our calculations were conservative. In particular, the baseline phlebotomist blood culture contamination rate (and hence the number that could potentially be avoided by ISDD) was greater in the pre- and post- compared to the trial period in the recently published ISDD study (2.6% pre-trial, 2.8% post-trial, compared to 1.8% in-trial) [3]. Likewise, our HAC rates including *C. difficile* were for all hospitalized patients even though

inpatients on antibiotics might have even higher incidences. Nevertheless, even when accounting for uncertainties such as lower hospitalization costs, outpatient antibiotic treatment, or the conservative *C. difficile* rate, the savings for both individual hospitals and society at large are considerable. However, adoption of either intervention would only be justified if implementation costs were lower than the expected cost savings calculated in this study.

A strength of our analysis is that it uses recent primary LOS data. A second advantage is the detailed cost accounting performed for the factors that make up the incremental costs related to false-positive blood cultures. Additionally, while most studies with similar scope have attempted to quantify the burden of contaminated blood cultures for a specific setting, our survey and other input parameters also permit estimates of U.S. utilization levels. Finally, our study explicitly addressed remaining uncertainty in sensitivity analyses.

Our study is subject to several limitations. First, LOS data originated from an annual dataset from a single institution. However, compared to the findings of previous studies, our mean estimated difference between true-negative and false-positive cases is smaller, indicating that our projections are conservative. Second, none of our calculations included the cost of implementing the respective intervention strategies. While costs for ISDD might vary by specific hospital contract and are not fully established yet, it is assumed that ISDD costs will make up no more than 20% of the per-culture cost savings projected in this analysis, suggesting a high

likelihood that ISDD would be cost-saving. Third, some hospitals may have already deployed sterile blood collection kits or taken advantage of dedicated phlebotomy teams. However, we have calculated universal cost savings independent of the intervention in question, so the reduction of false-positive blood cultures can be easily calculated using our estimates. Fourth, phlebotomy services are unlikely to perform all blood draws in a hospital. Therefore, the true reductions in adverse clinical events and expenditures might be smaller depending on the proportion of phlebotomist blood draws. Fifth, while we used actual length-of-stay data, most of our data are based on assumptions that were informed by the existing literature and expert opinion. Nevertheless, we believe these figures represent the best available utilization data, and we were able to show in uncertainty analyses that all the calculated cost savings remained significant. Finally, while reductions of blood culture contamination rates by employing phlebotomists and ISDDs may be seen in other contexts, the absolute risk difference and the clinical and economic consequences – and specifically rate of antibiotic use – may be different in other countries. However, the structure of our model can be used to create country adaptations.

Conclusions

Cost and patient harm from contaminated blood cultures are substantial both for individual hospitals and for society at large. Widespread use of phlebotomists and ISDD are a simple and effective measures to reduce costs and hospital-acquired conditions. Future controlled studies

looking at interventions to reduce false-positive blood cultures should include the endpoints of hospital-acquired adverse events and resource utilization.

ACCEPTED MANUSCRIPT

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Conflict of Interest Statement

R.G.P. is a cofounder and shareholder of Magnolia Medical Technologies, Inc., a manufacturer of initial specimen diversion devices. Wing Tech Inc. (J.B.P., B.P.G.) provided health-economic consulting services to Magnolia Medical Technologies, Inc.

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Table Captions

Table 1. Key input parameters. See Appendix for a complete list of input parameters.

Table 2. Projected annual hospital-associated adverse events in the United States, with potential reductions. All events in thousands, assuming 30 million annual blood cultures and 100% adoption of respective intervention.

Table 1: Key Input Parameters. See Appendix for a complete list of input parameters.

		Units	Unit cost^a	Sources
Additional blood culture sets		1.30	\$9.58	Survey, ^b
Gram stain, identification/speciation, and subculture with susceptibility/resistance		1	\$103	^b
Additional length of stay including primary team coverage and infectious diseases consults	35% infectious disease consultations	2.35 days	\$1,361	Survey; primary analysis[31]; ^b
Antibiotic treatment	Proportion	Days of treatment	Unit cost^a	Sources
Empiric treatment of gram-positive cocci	75%	3 days	\$61	Survey
Empiric treatment of gram-positive rods	59%	3 days	\$73	
Definite composite inpatient treatment	59%	1 days	\$47	

Definite composite outpatient treatment	27%	10 days	\$61	
Outpatient parenteral antibiotic therapy (excluding antibiotics)	13%	10 days	\$385	Survey; [32]
Additional inpatient blood tests and imaging			\$625	^b
Hospitalization-associated adverse events		Incidence^c	Unit cost^a	Sources
CDI – remaining hospitalization		32.6	\$8,560	[26]
CDI – cost for entire episode of care			\$37,077	[33]
Venous thromboembolism ^d		0.4	\$8,138	[27, 34]
Hospital-acquired pneumonia ^e		1.3	\$16,527	[27, 28]
Catheter-related urinary tract infection		18.2	\$1,009	[27, 35]
Fall		14.9	\$332	[27, 28]
Delirium		311.1	\$4,051	[29, 36]

^a in 2017 U.S. dollars; ^b see Appendix ^c in cases per 10,000 hospital days; ^d assuming 90% deep vein thromboses only; ^e assuming 50% penetrance; ^f *Clostridium difficile* infection/colitis;

Table 2: Projected Annual Hospital-associated Adverse Events in the U.S., with Potential Reductions. All events in thousand, assuming 30 million annual blood cultures and 100% adoption of respective intervention.

	Standard of care		Phlebotomists			ISDD ^a		
	estimate	range	estimate	range	reduction	estimate	range	reduction
CDI^b	10.1	3.9; 22.5	4.1	1.6; 9.2	6.1	1.2	0.5; 2.8	8.9
VTE^c	0.1	0.1; 0.3	0.1	0.0; 0.1	0.1	0	0; 0	0.1
HAP^d	0.4	0.2; 0.9	0.2	0.1; 0.4	0.3	0.1	0; 0.1	0.4
CAUTI^e	5.7	2.2; 12.6	2.3	0.9; 5.2	3.4	0.7	0.3; 1.6	5.0
Fall	4.6	1.8; 10.3	1.9	0.7; 4.2	2.8	0.6	0.6; 1.3	4.0
Delirium	96.5	37.3; 214.8	39.6	15.3; 88.1	58.6	11.9	4.6; 26.5	84.6
Total	117.4	45.5; 261.4	48.2	18.6; 107.2	71.3	14.5	5.6; 32.3	102.9

^a ISDD = Initial Specimen Diversion Device; ^b CDI = *Clostridium difficile* infection/colitis; ^c VTE = venous thromboembolism; ^d HAP = hospital-acquired pneumonia; ^e CAUTI = catheter-associated urinary tract infection

Figure Captions

Figure 1. Kaplan-Meier curve of the proportion of discharges over time (in days) for patients with true-negative (blue) versus false-positive (red) blood cultures.

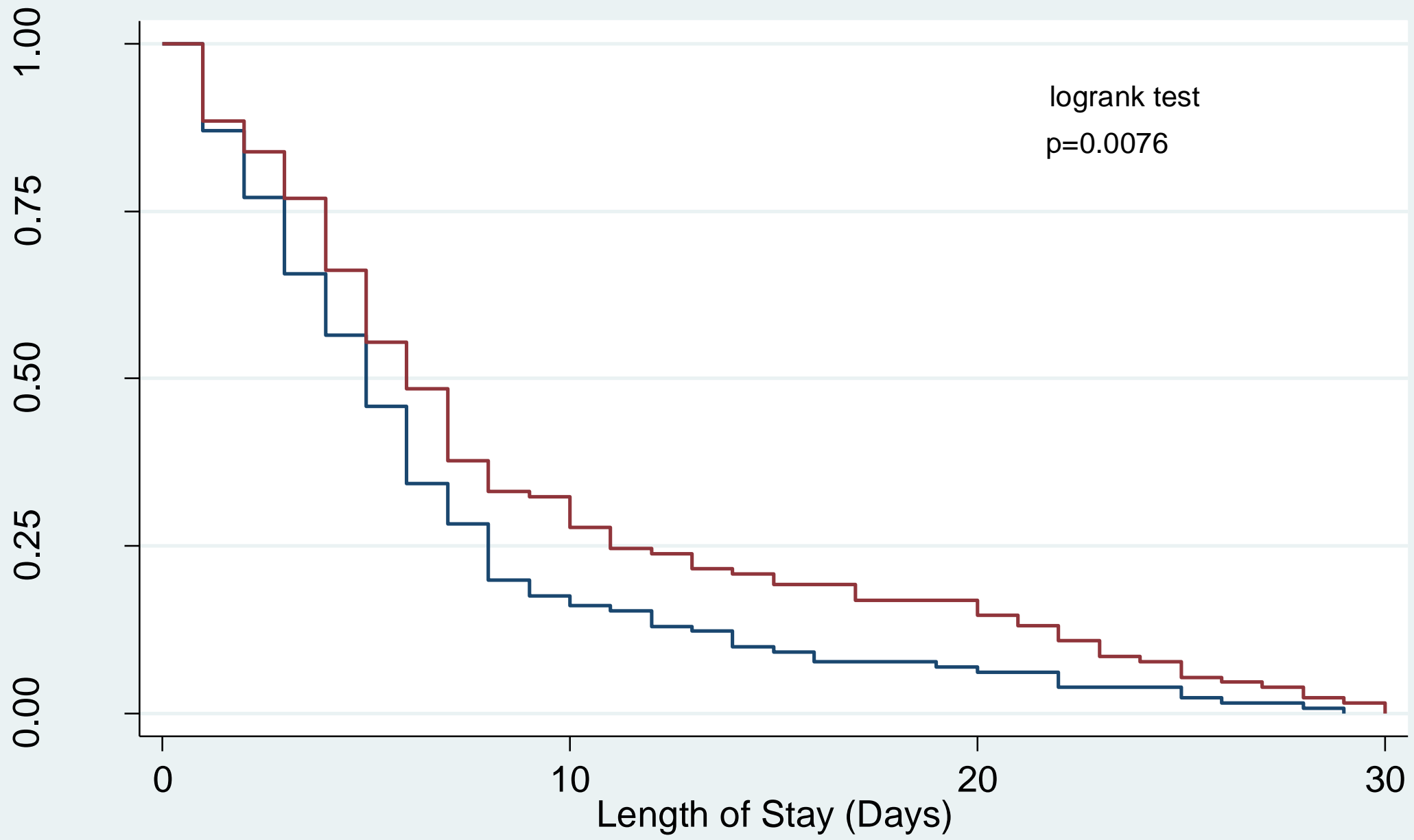
Figure 2. Sensitivity analysis (tornado diagram) of factors influencing societal costs per false-positive blood cultures. Data categories are listed vertically instead of the standard horizontal presentation, and the categories are ordered so that the largest bar (based on the largest spread of societal costs) appears at the top of the chart, the second largest appears second from the top, and so on.

Figure 3. Sensitivity analysis on the influence of relative reduction of false-positive blood cultures on annual costs for a 250- and a 400-bed hospital (blue and red lines, respectively; left axis, in thousand dollars) and annual U.S.-wide savings (red line, right axis, in million dollars). The x-axis is the relative reduction of false-positive blood cultures; for example, phlebotomists have been shown to reduce the incidence by 59% and Initial Specimen Diversion Device by 88%. From this value, the savings for a typical hospital with a volume of 10,000 cultures can be found somewhere in between the blue and the red line, using the left y-axis with the unit thousand dollars. Analogously, the U.S.-national savings can be found using the green line and the right y-axis with the unit million dollars. However, the curves assume a 100% penetrance. Two examples are given: a 50% adoption rate of phlebotomists would generate \$3.14 billion and a 50% adoption of ISDD would generate \$4.74 billion.

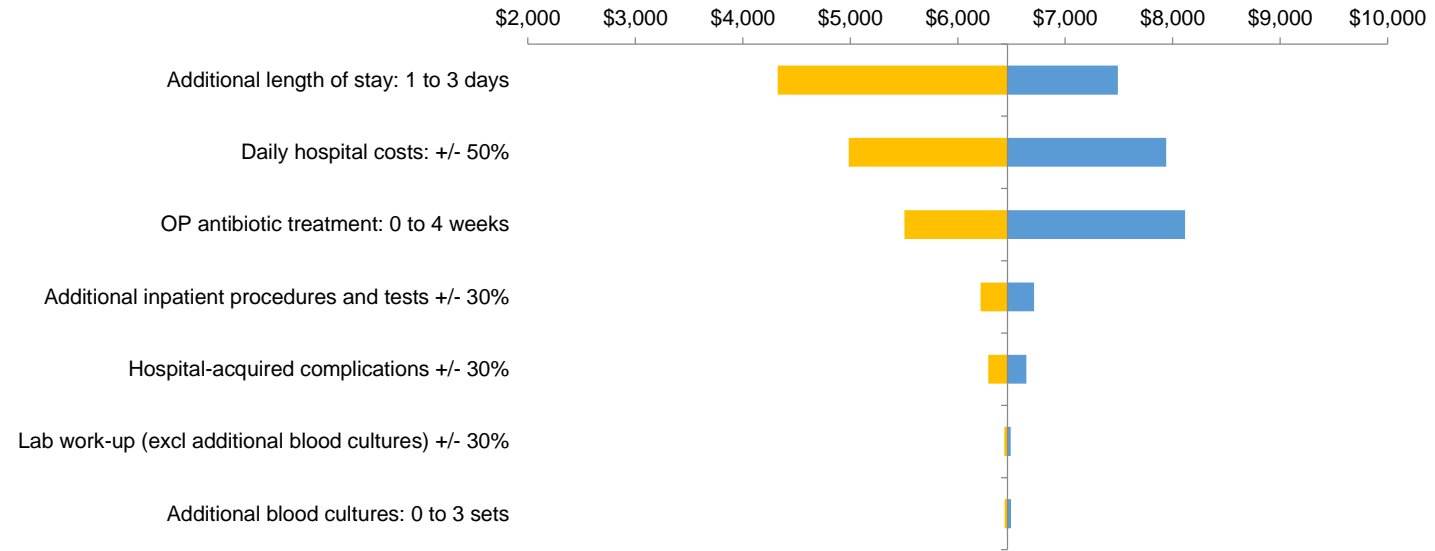
Appendices

Supplementary materials in a technical appendix are provided in a separate file that is published online-only.

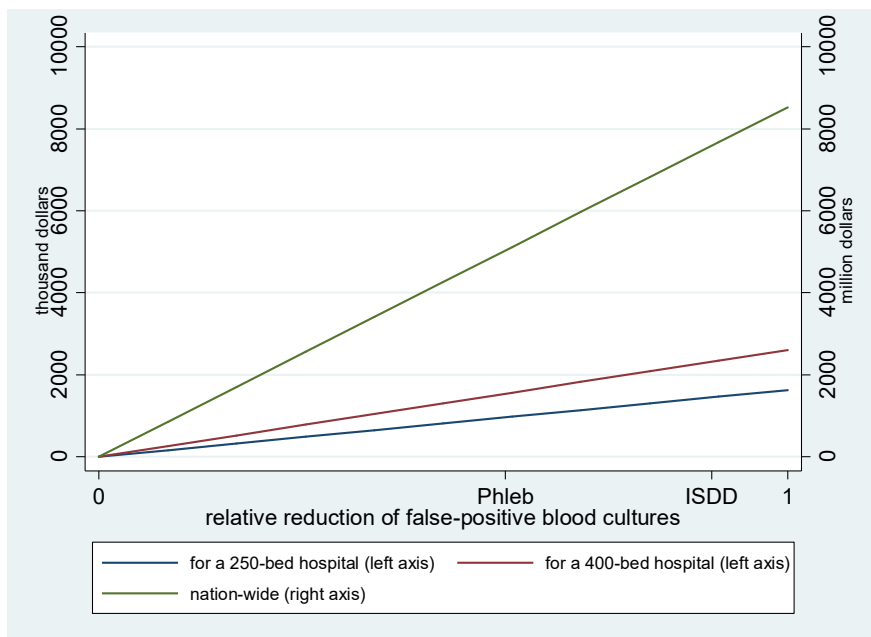
ACCEPTED MANUSCRIPT



— group = true-negative — group = false-positive



a)



b)

