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Model to evaluate the impact of hospital-based interventions targeting false-positive blood cultures on economic and clinical outcomes

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SUMMARY

Background: Blood culture contamination (BCC) increases length of stay (LOS) and leads to unnecessary antimicrobial therapy and/or hospital-acquired conditions (HACs).
Aim: To quantify the magnitude of additional LOS, costs to hospitals and society, and harm to patients attributable to BCC.
Methods: A retrospective matched survival analysis was performed involving hospitalized patients with septicaemia-compatible symptoms. BCC costs, 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 with interventions for reducing BCC, and estimated annual economic and clinical consequences for a typical hospital and for the USA as a whole.
Findings: Patients with BCC experienced a mean increase in LOS of 2.35 days (P=0.0076). Avoiding BCC would decrease costs by $6463 [$4818 from inpatient care (53% of which was from reduced LOS) and 26% 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 two cases of *Clostridium difficile* infection); based on clinical efficacy evidence, use of the studied initial specimen diversion device (ISDD) would save $1.9 million and prevent 34 HACs (including three cases of *C. difficile* infection). In the USA, the respective strategies would prevent 69,300 and 102,900 HACs (including 6000 and 8900 cases of *C. difficile* infection) and save $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 use of ISDD.

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Introduction

Blood culture is the current gold standard for the diagnosis of bacteraemia, bacterial species identification and antibiotic susceptibility testing [1]. However, contamination of blood cultures with commensal skin flora leads to increased costs, 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 approximately 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—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], use of sterile collection kits [23], 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 USA [25], mostly before 2012 [5,8,10,21,25], and have failed to comprehensively compare the strategies under study [10,23].

The objective of this study was to quantify the potential for cost savings and patient harm reduction for a typical hospital and for the US 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 using a modified Delphi process. Unit costs were obtained from the 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, extrapolations to a small- to medium-sized hospital and to the US-national level were explored. Comprehensive sensitivity analyses were performed 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 A, see online supplementary material). Implementation of dedicated phlebotomists and a more recently evaluated, device-based treatment were chosen as comparators. The relative risk of reducing BCC by using phlebotomists of 0.41 was estimated in a random-effects meta-analysis (Appendix A, see online supplementary material). The device used for the other comparator was Steripath (Magnolia Medical Technologies, Inc., Seattle, WA, USA). This initial specimen diversion device (ISDD) 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 for BCC of 0.12 [3].

Length of stay

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

Each of the 135 patients thus identified as having a false-positive blood culture were then matched with a patient with 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, patients whose LOS exceeded 30 days were excluded. Based on Kaplan—Meier estimates, survival curves were plotted with discharge as the outcome of interest, and a log-rank test using Stata (Stata Corp., College Station, TX, USA) was performed.

Adverse events and resource utilization

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

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. A modified Delphi survey about utilization patterns was conducted among 19 infectious disease physicians (Appendix A, see online supplementary material).

Unit costs, cost analysis and perspectives

Unit costs were derived from the medical literature; if cost estimates were not available, the payment amounts allowed by Medicare as a proxy for true costs were used (Table I and Appendix A, see online supplementary material). Cost analyses were performed 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

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Table I
Key input parameters

		Units	Unit cost[a]	Sources
Additional blood culture sets		1.30	$10	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	$1361	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	$8560	[26]
CDI — cost for entire episode of care			$37,077	[33]
Venous thromboembolism[d]		0.4	$8138	[27,34]
Hospital-acquired pneumonia[e]		1.3	$16,527	[27,28]
Catheter-related urinary tract infection		18.2	$1009	[27,35]
Fall		14.9	$332	[27,28]
Delirium		311.1	$4051	[29,36]

CDI, *Clostridium difficile* infection/colitis.
See Appendix A (online supplementary material) for a complete list of input parameters.
[a] In 2017 US dollars.
[b] See Appendix A (online supplementary material).
[c] In cases per 10,000 hospital-days.
[d] Assuming 90% deep vein thromboses only.
[e] Assuming 50% penetrance.

proceduralists. The hospital perspective was calculated to provide economic insights for members of the hospital team, as they are ultimately responsible for deciding which interventions or programmes 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, a typical, medium-sized hospital with 250—400 beds and an annual volume of 10,000 blood cultures (range 8500—13,600) was assumed. For the societal perspective, it was further assumed that 30 million cultures are drawn annually in the USA (Appendix A, see online supplementary material). 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, sensitivity analyses were performed by varying the input parameters by at least ±30%, the interquartile range for primary data, and a 2—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% confidence interval (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, see online supplementary material).

Annually, a medium-sized hospital would experience approximately 39 HACs attributable to contaminated blood cultures (range 15—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 three additional cases of *C. difficile* infection each year (range 1—8). In the USA, the number of HACs totalled 117,400, including 10,100 cases of *C. difficile* infections.

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

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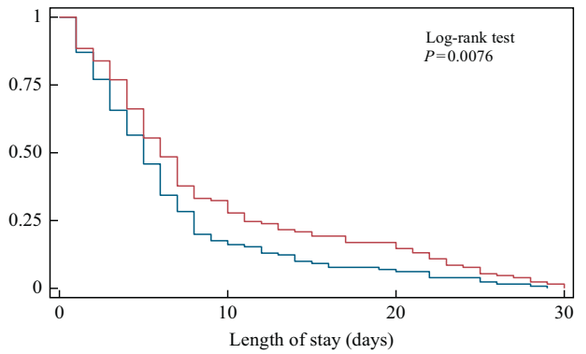

Figure 1. Kaplan–Meier curve of the proportion of discharges over time (in days) for patients with true-negative (blue) vs false-positive (red) blood cultures.

C. difficile infections by two and three cases, respectively. In the USA, such calculations translate to prevention of approximately 69,300 HACs and 6000 *C. difficile* events by employing dedicated phlebotomists, or 102,900 HACs and 8900 *C. difficile* events by using ISDD (Table II and Appendix A, see online supplementary material).

Each false-positive blood culture resulted in incremental costs totalling $6463, of which $4818 was spent during hospitalization. The single largest item was the $2955 cost of extended hospitalization itself, representing 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 A, see online supplementary material). 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 $1222 for oral and parenteral antibiotic treatments, including the visits of a home infusion company and weekly safety laboratory tests.

For a 250- to 400-bed hospital performing 10,000 blood cultures each year (range 8500–13,600) and a false-positive rate of 4.4% (range 2.0–7.2%), the costs resulting from false-positive blood cultures were projected to be $2.1 million annually (range $1.0–3.5 million). Extrapolating from this projection, the US burden of false-positive blood cultures was estimated to be $8.5 billion (range $2.5–14.2 billion).

Dedicated phlebotomists would save $125 per culture from the hospital perspective and $185 per culture from the societal perspective. ISDD would save $186 per culture from the hospital perspective and $249 per culture 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, the calculated savings at the hospital and US-national level were projected on an annual basis. For a small- to medium-sized hospital, phlebotomists would save $1.3 million each year, while ISDD would save $1.9 million. In the USA, dedicated phlebotomists would save $5.0 billion each year, while ISDD would save $7.5 billion (Appendix A, see online supplementary material).

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 US healthcare system revealed that a 50% adoption rate of dedicated phlebotomists would generate US-nationwide savings of $3.14 billion, while a 50% adoption rate of ISDD use would generate savings of $4.74 billion (Figures 2 and 3 and Appendix A, see online supplementary material).

Discussion

Patients with false-positive blood cultures generate incremental diagnostic and treatment costs of more than $6000, 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 USA for such incremental unnecessary and avoidable healthcare costs related to false-positive blood cultures is a staggering $8.6 billion.

Table II
Projected annual hospital-associated adverse events in the USA, with potential reductions

	Standard of care		Phlebotomists			ISDD		
	Estimate	Range	Estimate	Range	Reduction	Estimate	Range	Reduction
CDI	10.1	3.9–22.5	4.1	1.6–9.2	6.1	1.2	0.5–2.8	8.9
VTE	0.1	0.1–0.3	0.1	0.0–0.1	0.1	0	0–0	0.1
HAP	0.4	0.2–0.9	0.2	0.1–0.4	0.3	0.1	0–0.1	0.4
CAUTI	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

ISDD, initial specimen diversion device; CDI, *Clostridium difficile* infection/colitis; VTE, venous thromboembolism; HAP, hospital-acquired pneumonia; CAUTI, catheter-associated urinary tract infection.
All events in thousands, assuming 30 million annual blood cultures and 100% adoption of respective intervention.

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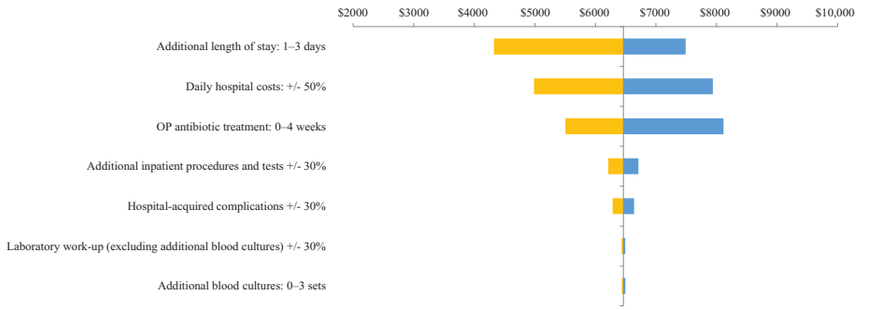

Figure 2. Sensitivity analysis (tornado diagram) of factors influencing societal costs per false-positive blood culture. Data categories are listed vertically instead of the standard horizontal presentation, and the categories are ordered so that the largest bar (based on the largest spread of societal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

The use of the studied ISDD is the single most effective intervention explored to date 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 US 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 9000 episodes of *C. difficile* infection. Furthermore, annual ISDD use could reduce the cost of antibiotics by $2 billion (26% x 7.5); this amount might be lower in settings with lower antibiotic use. Beyond costs, blood culture contamination (BCC) is both a patient safety and antibiotic stewardship issue, as well as a contributor to continued antibiotic resistance pressure.

Previous studies in the USA have compared 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 for 4.5 days longer than patients with true-negative blood cultures [8]. A case—control study using data from 1991 to 1995 found a difference in LOS 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 2007—2008 showed a difference of 5.4 days (95% CI 2.8—8.1) [25]. Although the total LOS for hospitalizations in the USA has decreased over time [30], the present finding of a mean difference of 2.4 days appears to be conservative in light of these other studies.

Only a handful of studies have evaluated the economic consequences of BCC, all of which, except one, were performed more than 6 years ago [23]. A study from 2006 calculated additional laboratory costs of $425 (in 2005 US dollars) [5]; this value is higher than the $243 calculated in the present study (in 2017 US dollars) for microbiology laboratory and other blood tests. A 2009 prospective comparison of the costs of dedicated phlebotomist use with the costs of usual emergency department care found a median difference in charges of $8720 per false-positive blood culture [10]. The most recent study, from 2015, calculated direct costs of $2844 for false-positive cultures [23]. Even after adjusting the findings of this 2015 study to 2017 US dollars, the amount of $3450 is below the

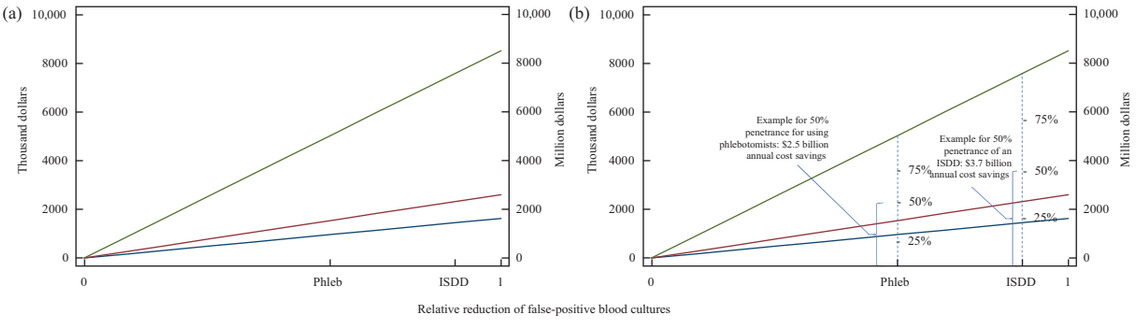

Figure 3. Sensitivity analysis on the influence of relative reduction of false-positive blood cultures on annual costs for a 250- and a 400-bed hospital (blue and red lines, respectively; left axis, in thousand dollars) and annual US-wide savings (red line, right axis, in million dollars). The x-axis is the relative reduction of false-positive blood cultures; for example, phlebotomists (Phleb) have been shown to reduce the incidence by 59% and use of an initial specimen diversion device (ISDD) has been shown to reduce the incidence 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 US-national savings can be found using the green line and the right y-axis with the unit million dollars (a). However, the curves assume 100% penetrance. Two examples are given: a 50% adoption rate of phlebotomists would generate $3.14 billion, and a 50% adoption rate of ISDD would generate $4.74 billion (b).

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value of $4362 calculated in the present study. 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 that of the present study [23].

To the authors' 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 these 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 the present analyses, savings from the use of ISDD can be additional to those already achieved.

The estimates used for the calculations were conservative. In particular, the baseline phlebotomist BCC rate (and hence the number that could potentially be avoided by ISDD) was greater in the pre- and post-trial periods compared with the trial period in the recently published ISDD study (2.6% pre-trial, 2.8% post-trial without ISDD, compared with 1.8% without ISDD and 0.22% with ISDD during the trial) [3]. Likewise, the HAC rates including *C. difficile* were for all hospitalized patients even though inpatients on antibiotics might have even higher incidence rates. 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 this 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, this survey and other input parameters also permit estimates of US utilization levels. Finally, this study explicitly addressed remaining uncertainty in sensitivity analyses.

This study is subject to several limitations. First, LOS data originated from an annual dataset from a single institution. However, compared with the findings of previous studies, the mean estimated difference between true-negative and false-positive cases in this study is smaller, indicating that the projections are conservative. Second, none of the calculations included the cost of implementing the respective intervention strategies. While costs for ISDD might vary by specific hospital contract and are not yet fully established, it is assumed that ISDD costs will account for 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, universal cost savings have been calculated independent of the intervention in question, so the reduction of false-positive blood cultures can be easily calculated using the 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 actual LOS data were used in this study, most of the data are based on assumptions that were informed by the existing literature and expert opinion. Nevertheless, it is believed that these figures represent the best-available utilization data, and uncertainty analyses showed that all the calculated cost savings remained significant. Finally, while reductions of BCC rates by employing phlebotomists and ISDDs may be seen in other contexts, the absolute risk difference and the clinical and economic consequences — specifically, rate of antibiotic use — may be different in other countries. However, the structure of this model can be used to create country adaptations.

In conclusion, 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 simple and effective measures to reduce costs and HACs. Future controlled studies looking at interventions to reduce false-positive blood cultures should include the endpoints of hospital-acquired adverse events and resource utilization.

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Conflict of interest statement
RGP is a cofounder and shareholder of Magnolia Medical Technologies, Inc., a manufacturer of initial specimen diversion devices. Wing Tech Inc. (JBP, BPG) provided health economic consulting services to Magnolia Medical Technologies, Inc.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhin.2019.03.012.

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