Cost-Effectiveness of Surveillance for Bloodstream Infections for Sepsis Management in Low-Resource Settings

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Abstract. Bacterial sepsis is a leading cause of mortality among febrile patients in low- and middle-income countries, but blood culture services are not widely available. Consequently, empiric antimicrobial management of suspected bloodstream infection is based on generic guidelines that are rarely informed by local data on etiology and patterns of antimicrobial resistance. To evaluate the cost-effectiveness of surveillance for bloodstream infections to inform empiric management of suspected sepsis in low-resource areas, we compared costs and outcomes of generic antimicrobial management with management informed by local data on etiology and patterns of antimicrobial resistance. We applied a decision tree model to a hypothetical population of febrile patients presenting at the district hospital level in Africa. We found that the evidence-based regimen saved 534 more lives per 100,000 patients at an additional cost of \$25.35 per patient, resulting in an incremental cost-effectiveness ratio of \$4,739. This ratio compares favorably to standard cost-effectiveness thresholds, but should ultimately be compared with other policy-relevant alternatives to determine whether routine surveillance for bloodstream infections is a cost-effective strategy in the African context.

INTRODUCTION

Sepsis due to bacterial bloodstream infection is a serious and life threatening condition that is common among hospitalized patients in the tropics.^{1,2} Timely and appropriate antimicrobial therapy can be lifesaving.³ There is considerable geographic and temporal variation in causes of bloodstream infection and in antimicrobial susceptibility patterns of isolated organisms.^{1,2} Consequently, a robust understanding of locally important causes of bloodstream infection and patterns of antimicrobial resistance among bacteria isolated from the bloodstream is essential to form empiric treatment strategies for patients with suspected sepsis.

Blood cultures lack in sensitivity, and the time from collecting the sample to detection means that the results cannot inform the initial management of seriously ill patients. However, aggregate blood culture data from a health-care facility provides invaluable information on the local epidemiology of bloodstream infections for the selection of empiric antimicrobial therapy for sepsis. Yet clinical microbiology services are limited in many low-resource areas and blood culture services are often absent.^{4,5} Consequently, antimicrobial therapy for sepsis in much of the developing world is based on international guidelines, such as the Integrated Management of Adolescent and Adult Illness (IMAI),^{6,7} without adaptation to locally important infections, risking mismatching of pathogens and treatment.

We sought to understand the costs and benefits of routine surveillance for bloodstream infections among hospitalized patients in low-resource settings. We were interested in the cost, as well as the impacts on treatment costs and patient survival, of having data to adapt empiric antimicrobial therapy to the local epidemiology of bloodstream infections.

MATERIALS AND METHODS

Overview. To evaluate the cost-effectiveness of surveillance for bloodstream infections to inform empiric management of suspected sepsis in low-resource settings, we compared costs and outcomes of generic antimicrobial management with management informed by local data on etiology and patterns of antimicrobial resistance. Using susceptibility patterns from bloodstream infections in Africa, we assessed a number of scenarios, varying the mix of pathogens and antimicrobial susceptibility patterns across different regions. We then investigated the effect on mortality for appropriately and inappropriately treated sepsis on cost-effectiveness. For each scenario, we calculated survival per 100,000 patients and the cost per patient for both the generic and evidence-based antimicrobial regimens, as well as the incremental cost-effectiveness ratio (ICER), or the marginal cost per additional life saved, of surveillance for sepsis. The ICER is commonly used to provide a practical approach to decision making regarding health interventions. Although ultimately it is preferable to compare ICERs to the policy relevant alternatives,⁸ we measured cost-effectiveness against an ICER threshold of \$5,000 per additional life saved based on World Health Organization (WHO) threshold values developed for the “choosing interventions that are cost effective” (CHOICE) project for intervention cost-effectiveness in the Afro D region.⁹ The WHO threshold values are based on a maximum cost per disability-adjusted life year averted, not lives saved, using a threshold of between one to three times the Gross Domestic Product per capita by region. Thus this threshold is extremely conservative.

Base case. Table 1 describes the probability input parameters used in our model. Our population of interest was febrile patients presenting at the district hospital level in a low-resource setting. The prevalence of sepsis among patients admitted to district hospitals was assumed to be 13.4%, based on a systematic review of community-acquired bloodstream infections in Africa.² For the performance of clinical assessment of sepsis, we used data from a 2003 study on

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TABLE 1
Model variables: base-case and best- and worst-case probabilities

Input variable	Base case, %	Worst case, %	Best case, %	References
Prevalence of sepsis	13.4	—	—	2
Clinical assessment of sepsis test performance				
Sensitivity	83	—	—	10
Specificity	62	—	—	
Probability organisms are susceptible to antimicrobials				2
Generic antimicrobials				
North Africa	45	8	52	
West and central Africa	22	13	45	
Southern Africa	24	16	56	
East Africa	29	14	48	
All of Africa	27	12	36	
Hypothetical 1*	7	0	10	
Hypothetical 2†	25	5	30	
Evidence-based antimicrobials				
North Africa	56	56	58	
West and central Africa	56	45	57	
Southern Africa	62	44	62	
East Africa	47	38	49	
All of Africa	43	42	44	
Hypothetical 1*	35	35	35	
Hypothetical 2†	34	34	35	
Probability of survival				11–15
Appropriate antimicrobials	80	32	90	
Inappropriate antimicrobials	50	25	85	
Difference in survival (base-case and extremes)‡	30	65	53	
Test false positive	100	—	—	Estimate
Test true negative	100	—	—	Estimate
Test false negative	50	—	—	Estimate

*Hypothetical scenario 1: based on all of Africa prevalence values. Reconfigured such that all *Salmonella enterica* and *Streptococcus pneumoniae* isolates are resistant to ampicillin.

†Hypothetical scenario 2: based on north Africa prevalence values. Reconfigured such that *Salmonella enterica* and *Brucella* spp. prevalence values are exchanged (note that it is assumed that *Salmonella* serotype Typhi remains predominant *Salmonella enterica* serovar).

‡Differences in survival estimated based on differences in ranges reported in the literature. Worst-case difference in survival shows the difference between best-case probability of survival using appropriate antimicrobials and worst-case probability of survival using inappropriate antimicrobials. Best-case difference in survival shows the difference between best-case probability of survival using inappropriate antimicrobials and worst-case probability of survival using appropriate antimicrobials.

neonates presenting with illness to health facilities in four countries (Ethiopia, The Gambia, Papua New Guinea, and The Philippines).¹⁰ Using a rule requiring observation of at least one of nine clinical signs of severe illness including sepsis, the authors found a diagnostic performance of clinical assessment of 83% sensitivity and 62% specificity.

Patient survival. Our outcome of interest was patient survival. A base-case survival of 80% for individuals who test true positive was calculated based on published data.^{11–15} We used the same sources to determine the survival for individuals who test false negative and estimated a base-case survival of 50% based on the range of values reported in the literature. We assumed that true positive test cases were treated with appropriate antimicrobials and that treatment was inappropriately withheld among those with false-negative tests. For individuals who were negative, regardless of whether they test false positive or true negative, we assumed a case fatality ratio of zero. The studies that informed our survival estimates reported survival data for appropriately and inappropriately treated patients infected with a range of pathogens. Because robust case fatality ratio data were not available by pathogen, we adopted a single case fatality ratio across all pathogens.

Antimicrobial therapy. Antimicrobial treatment recommendations in the IMAI district clinician manual (2011) were used to inform the generic and evidence-based antimicrobial therapy scenarios.⁷ It was assumed generic antimicrobial therapy would consist of ampicillin and gentamicin, whereas ceftriaxone was selected as an example of an evidence-based antimicrobial therapy.

Antimicrobial susceptibility patterns. To reflect the different etiology and susceptibility patterns present in different regions of Africa, the probability that a febrile patient presenting with sepsis would be infected with an organism susceptible to either the generic (ampicillin and gentamicin) or the evidence-based (ceftriaxone) antimicrobial regimens was derived from susceptibility and prevalence data reported in the systematic review of community-acquired bloodstream infections in Africa.² Estimates of the proportion of isolates susceptible to the antimicrobial regimen were calculated based on the three most common isolates identified in blood cultures in the north, west and central, southern and eastern regions of Africa over the period 1984–2006.² In addition, the four most prevalent pathogens from across Africa were used to estimate susceptibility patterns for the entire African region.

The proportion of organisms susceptible to a given antimicrobial was based on reported antimicrobial susceptibilities of bloodstream isolates in Africa, by region. Because the generic antimicrobial regimen used both ampicillin and gentamicin, susceptibility probabilities were estimated based on the component antimicrobial that was more effective against a given organism. The base-case scenarios were calculated by multiplying the proportion of positive blood cultures attributable to each of the top three (or, in the case of Africa as a whole, four) organisms in each region by the proportion of those organisms found to be susceptible to either the generic or evidence-based antimicrobial treatment regimens (Table 2). Thus, the probability that an antimicrobial was appropriate captured both the prevalence of the

TABLE 2
Base-case probability that a patient presenting with sepsis is infected with an organism susceptible to the antimicrobial regimen

	Proportion of total isolates	Predominant serotype	Proportion of predominant subtype	Probability of susceptibility			
				Ampicillin	Gentamicin	"Generic" regimen	Evidence-based (ceftriaxone)
North Africa							
<i>Salmonella enterica</i>	0.499	Serotype Typhi	0.99	0.440	0.000	0.440	0.484
<i>Brucella</i> spp.	0.269	—	—	0.000	0.000	0.000	0.000
<i>Staphylococcus aureus</i>	0.077	—	—	0.007	0.000	0.007	0.077
Other	0.155	—	—	0.000	0.000	0.000	0.000
Total	1.000	—	—	0.447	0.000	0.447	0.561
West and central Africa							
<i>Salmonella enterica</i>	0.208	Non-typhoidal	0.87	0.030	0.000	0.030	0.203
<i>Streptococcus pneumoniae</i>	0.189	—	—	0.171	0.000	0.171	0.189
<i>Staphylococcus aureus</i>	0.172	—	—	0.016	0.000	0.016	0.172
Other	0.431	—	—	0.000	0.000	0.000	0.000
Total	1.000	—	—	0.216	0.000	0.216	0.564
Southern Africa							
<i>Salmonella enterica</i>	0.290	Non-typhoidal	0.97	0.016	0.000	0.016	0.283
<i>Streptococcus pneumoniae</i>	0.240	—	—	0.217	0.000	0.217	0.240
<i>Staphylococcus aureus</i>	0.094	—	—	0.009	0.000	0.009	0.094
Other	0.376	—	—	0.000	0.000	0.000	0.000
Total	1.000	—	—	0.241	0.000	0.241	0.617
East Africa							
<i>Streptococcus pneumoniae</i>	0.212	—	—	0.191	0.000	0.191	0.205
<i>Salmonella enterica</i>	0.178	Non-typhoidal	0.88	0.024	0.000	0.024	0.174
<i>Escherichia coli</i>	0.095	—	—	0.008	0.076	0.076	0.095
Other	0.515	—	—	0.000	0.000	0.000	0.000
Total	1.000	—	—	0.224	0.076	0.291	0.474
All of Africa							
<i>Salmonella enterica</i>	0.291	Serotype Typhimurium	0.081	0.001	0.000	0.001	0.023
	—	Serotype Enteritidis	0.041	0.004	0.000	0.004	0.012
	—	Serotype Typhi	0.099	0.026	0.000	0.026	0.028
	—	All other	0.069	0.007	0.000	0.007	0.020
	—	Total	—	—	—	0.037	0.083
<i>Streptococcus pneumoniae</i>	0.183	—	—	0.165	0.000	0.165	0.183
<i>Staphylococcus aureus</i>	0.095	—	—	0.009	0.000	0.009	0.095
<i>Escherichia coli</i>	0.073	—	—	0.006	0.059	0.059	0.073
Other	0.358	—	—	0.000	0.000	0.000	0.000
Total	1.000	—	—	—	—	0.270	0.434

Based on data sourced from Reddy and others (2010).²

most common bacterial isolates in a given region and the susceptibility patterns of those organisms based on data from across Africa. Worst- and best-case scenarios were calculated based on the reported lower and upper ranges of the proportion of isolates susceptible for each organism.² All isolates not accounted for in the top three most common isolates were assumed to be resistant to treatment with either generic or evidence-based antimicrobials. In addition, it was assumed that all *Salmonella enterica* and *Staphylococcus aureus* isolates were resistant to gentamicin and that all *Brucella* spp. isolates were resistant to both the generic and evidence-based antimicrobial regimens. In the west and central, southern and eastern African regions *Salmonella enterica* serotype Enteritidis susceptibilities were used as a proxy for non-typhoidal *Salmonella*.

Two additional hypothetical scenarios were developed to test the effect of potential changes in resistance and prevalence. *Salmonella enterica* and *Streptococcus pneumoniae* are a leading cause of community-acquired bloodstream infection in Africa.² Since antimicrobial resistance, including to ampicillin, is increasing among both pathogens and ampicillin has been a widely recommended component of antimicrobial management of severe febrile illness, the first hypothetical scenario examined the cost-effectiveness of blood culture surveillance using prevalence values for the entire

African continent but reconfigured such that all *Salmonella enterica* and *Streptococcus pneumoniae* were resistant to ampicillin. In areas where brucellosis is endemic, such as parts of north Africa, *Brucella* spp. is often a leading cause of community-acquired bloodstream infection.² However, the antimicrobial management of brucellosis differs substantially from regimens widely recommended for the antimicrobial management of severe febrile illness. Therefore, the second hypothetical scenario examined the cost-effectiveness of blood culture surveillance in a setting where brucellosis was common and where empiric antimicrobial management regimens might otherwise be poorly matched with infecting organisms.

Costs. Table 3 describes the cost inputs in the model. Our cost data relied largely on data from a clinical laboratory operating to Good Clinical Laboratory Practices standards in northern Tanzania. All costs are expressed in 2011 U.S. dollars (\$). For the clinical assessment, we assumed that labor is the only cost, and base our value on the cost per hour for a laboratory technician performing an human immunodeficiency virus (HIV) point of care test (\$6.10/hour) (JA Crump, personal communication, 2014). Assuming that clinical assessment takes 10 minutes, labor costs for the clinical assessment were set at \$1.02 per case, consistent with costs reported in earlier studies.¹⁶

TABLE 3
Costs used in the model*

Cost variable		References
IMAI Assessment, \$ per test		
Labor	1.02	J. A. Crump, pers. comm., 2014, ¹⁶
Total	1.02	
Laboratory assessment for sepsis		
Negative blood culture, \$ per test		J. A. Crump, pers. comm., 2014
Reagents and Supplies	6.20	
Labor	2.27	
Indirect costs	1.79	
Equipment	1.15	
Total cost negative blood culture	11.41	
Positive blood culture, \$ per test		J. A. Crump, pers. comm., 2014
Reagents and supplies	10.26	
Labor	6.85	
Indirect costs	1.79	
Equipment	1.15	
Subtotal	20.05	
ID and susceptibilities, \$ per test		J. A. Crump, pers. comm., 2014
Reagents and supplies	44.02	
Labor	6.10	
Indirect costs	1.79	
Subtotal	51.91	
Total cost positive blood culture	71.96	
Cost of antimicrobial treatment, \$ per case		7,17
Generic antimicrobials		
Emergency dose	0.59	
Standard treatment	12.63	
Total cost generic antimicrobials	13.22	
Evidence-based antimicrobials, \$ per case		
Emergency dose	4.41	
Standard treatment	22.05	
Total cost evidence-based antimicrobials	26.46	

IMAI = Integrated Management of Adolescent and Adult Illness.

*Costs adjusted to 2011 U.S. dollars (\$) values using gross domestic product (GDP) deflator.

The costs of laboratory assessment for sepsis were based on the costs associated with a single blood culture. To assess the value of bloodstream infection surveillance for patients with fever, it was assumed all patients would have a blood culture taken, irrespective of whether they were diagnosed as having sepsis using clinical assessment protocols. Where patients were incorrectly diagnosed as having sepsis (a false positive), it was assumed blood cultures would remain negative, giving a cost of \$11.41. Where patients were correctly diagnosed (a true positive), it was assumed additional costs associated with processing a positive blood culture would be incurred, for a cost of \$20.05. The costs of carrying out identification and susceptibility testing were valued at \$51.91. In total, the cost associated with a positive blood culture was \$71.96. Patients incorrectly diagnosed as not having sepsis (a false negative) also incurred the costs of a positive blood culture, whereas those correctly diagnosed as not having sepsis (a true negative) incurred the costs of a negative blood culture.

Based on IMAI guidelines that patients diagnosed with sepsis receive 6 days of antimicrobial therapy, consisting of an emergency dose (one day) and 5 days of standard treatment, the cost of treatment with generic antimicrobials was valued at \$13.22 compared with \$26.46 for evidence-based therapy.^{7,17} Figure 1 illustrates the decision tree used, pre-filled with data from the base-case scenario for the all Africa case.

Sensitivity analysis. We conducted sensitivity analysis across three dimensions. First, we assessed the effect of varying susceptibility patterns using the best- and worst-case susceptibility patterns in different regions of Africa, based on the

upper and lower ranges of susceptibility reported by Reddy and others (2010).² Second, we allowed for variation in survival for testing true positive or false negative from 32% and 25% (worst case)¹² to 90% and 65% (best case),^{13,15} respectively. Third, we explored the impact of investment in laboratory infrastructure and instruments on the cost-effectiveness of surveillance, using base-case values of prevalence and cost for all of Africa. We assumed that district hospitals would have existing space allocated for clinical laboratory services, but allowed for variation in initial capital costs from \$25,000 to \$100,000. We assumed that facilities and instruments would have a useful life of 10 years and calculated annualized costs per person using interest rates set at 0%, 3%, 5%, and 10%. In addition, we allowed for variation in test volumes of between 1,000 and 10,000 blood cultures per annum. Costs of labor, reagents, consumables, and indirect costs were accounted for in cost per test estimates from Tanzania.

RESULTS

Base case. Compared with generic antimicrobials, the additional cost of laboratory monitoring for sepsis and evidence-based antimicrobial treatment was \$25.35 per patient. Using clinical assessment with fixed sensitivity and specificity values as the entry point for the model, the additional cost per patient was identical across all subregions. Using all of Africa data, compared with generic antimicrobials, blood cultures and evidence-based antimicrobials saved 534 more lives per 100,000 patients (Table 4, Column 2). This corresponded

FIGURE 1. Decision tree representing probabilities, costs, and outcomes for a febrile patient presenting at a district hospital in a low-resource setting and receiving either generic or evidence-based antimicrobial treatment using base case all of Africa data. Cost figures represent the total costs of tests and antimicrobial treatment. Probabilities of an event occurring are shown in brackets. Probabilities are rounded to two decimal places.

to an ICER of \$4,749 per life saved. The corresponding numbers for east Africa were 601 more lives saved per 100,000 patients (Table 4, Column 4), for north Africa were 367 (Table 4, Column 6), for southern Africa were 1,268 (Table 5, Column 2), and for west and central Africa were 1,134

(Table 5, Column 4). ICERs ranged from \$2,000 (southern Africa) to \$6,908 (north Africa) per life saved.

Figure 2 illustrates the ICER of evidence-based antimicrobial therapy, varying the susceptibility probabilities for evidence-based drugs between 0.00 and 1.00, compared with base-case

TABLE 4

The base-case scenario for generic antimicrobials compared with the combination of blood culture monitoring and evidence-based antimicrobials (all of Africa, east Africa, and north Africa)

Measure	All of Africa		East Africa		North Africa	
	Generic antimicrobials	Blood culture monitoring + evidence-based antimicrobials	Generic antimicrobials	Blood culture monitoring + evidence-based antimicrobials	Generic antimicrobials	Blood culture monitoring + evidence-based antimicrobials
(Column number)	(1)	(2)	(3)	(4)	(5)	(6)
Probability antimicrobials appropriate	0.27	0.43	0.29	0.47	0.45	0.56
Probability mortality if antimicrobials appropriate	0.20	0.20	0.20	0.20	0.20	0.20
Probability mortality if antimicrobials inappropriate	0.50	0.50	0.50	0.50	0.50	0.50
Probability patient lives	0.94	0.95	0.94	0.95	0.95	0.95
Expected cost per patient, \$	6.84	32.19	6.84	32.19	6.84	32.19
Deaths per 100,000 patients	5,799	5,265	5,732	5,132	5,199	4,832
Difference in survival	–	534	–	601	–	367
Difference in expected cost per patient, \$	–	25.35	–	25.35	–	25.35
ICER, \$	–	4,749	–	4,221	–	6,908

ICER = incremental cost-effectiveness ratio.

Values in parentheses refer to columns as cited in text. For all scenarios, the prevalence of sepsis is 0.134. Sensitivity is set at 0.83 and specificity at 0.62. The cost of antimicrobials is \$13.22 in the generic case and \$26.46 in the evidence-based case. In the evidence-based case, there is an additional cost of \$11.41 for a negative blood culture test and \$71.96 for a positive blood culture test. Numbers in parentheses refer to columns as cited in text.

generic therapy using all of Africa prevalence and susceptibility data. Above a probability of approximately 0.40 that an organism will be susceptible to evidence-based treatment, the ICER fell below \$5,000 per life saved.

Table 6 includes the two hypothetical scenarios. In Table 6, Columns 1 and 2 show the relative cost-effectiveness of generic antimicrobials versus blood cultures and evidence-based antimicrobials using the prevalence values for the entire African continent but assuming that all *Salmonella enterica* and *Streptococcus pneumoniae* isolates were resistant to ampicillin. Under this scenario, blood cultures and evidence-based antimicrobials saved 934 more lives per 100,000 patients, corresponding to an ICER of \$2,714 per life saved. Columns 3 and 4 show the relative cost-effectiveness of generic antimicrobials versus blood cultures and evidence-based antimicrobials using prevalence figures for north Africa assuming that the prevalence of *Salmonella enterica* and *Brucella* spp. is exchanged. Under this scenario, blood cultures and evidence-based antimicrobials saved 300 more lives per 100,000 patients, corresponding to an ICER of \$8,443 per life saved.

Sensitivity analysis. When considering extreme susceptibility patterns of generic and evidence-based antimicrobial treat-

ment, using the best-case susceptibility patterns for evidence-based antimicrobials and the worst-case susceptibility patterns for generic antimicrobials across all of Africa, evidence-based treatment saved 1,068 more lives per 100,000 patients (Table 7, Column 2). This corresponded to an ICER of \$2,375 per life saved. Across the four regions, additional lives saved varied from 1,168 to 1,668 per 100,000 patients. ICERs ranged from \$1,520 to \$2,171 per life saved (Tables 7 and 8).

Table 9 shows the impact of different levels of capital investment on cost-effectiveness, at different volumes of blood cultures and interest rates. Allowing for capital investment of between \$25,000 and \$50,000 with interest rates of up to 10% per annum in facilities processing 1,000 blood cultures per annum, evidence-based treatment cost an expected \$34.19–\$39.59 per patient and yielded ICERs of between \$5,124 and \$6,134. For facilities processing 5,000 blood cultures per annum, the expected cost per patient of evidence-based treatment was \$25.75–\$26.83 with ICERs of \$4,824–\$5,026. Allowing for capital investment of \$100,000 in facilities processing 5,000–10,000 blood cultures per annum and interest rates between 0% and 10%, the expected costs per patient of evidence-based treatment

TABLE 5

The base-case scenario for generic antimicrobials compared with the combination of blood culture monitoring and evidence-based antimicrobials (southern Africa and west and central Africa)

Measure	Southern Africa		West and central Africa	
	Generic antimicrobials	Blood culture monitoring + evidence-based antimicrobials	Generic antimicrobials	Blood culture monitoring + evidence-based antimicrobials
(Column number)	(1)	(2)	(3)	(4)
Probability antimicrobials appropriate	0.24	0.62	0.22	0.56
Probability mortality if antimicrobials appropriate	0.20	0.20	0.20	0.20
Probability mortality if antimicrobials inappropriate	0.50	0.50	0.50	0.50
Probability patient lives	0.94	0.95	0.94	0.95
Expected cost per patient, \$	6.84	32.19	6.84	32.19
Deaths per 100,000 patients	5,899	4,631	5,966	4,832
Difference in survival	–	1,268	–	1,134
Difference in expected cost per patient, \$	–	25.35	–	25.35
ICER, \$	–	2,000	–	2,235

ICER = incremental cost-effectiveness ratio.

Values in parentheses refer to columns as cited in text. For all scenarios, the prevalence of sepsis is 0.134. Sensitivity of clinical assessment is set at 0.83 and specificity at 0.62. The cost of antimicrobials is \$13.22 in the generic case and \$26.46 in the evidence-based case. In the evidence-based case, there is an additional cost of \$11.41 for a negative blood culture test and \$71.96 for a positive blood culture test.

Numbers in parentheses refer to columns as cited in text.

FIGURE 2. Incremental cost-effectiveness ratio of evidence-based antimicrobial treatment at differing levels of susceptibility compared with base-case generic antimicrobial treatment using all of Africa prevalence and susceptibility data. The vertical dotted line indicates the probability of susceptibility to evidence-based antimicrobials at which the incremental cost-effectiveness ratio falls below \$5,000 per life saved.

ranged from \$26.35 to \$28.31 and ICERs fell between \$4,936 and \$5,303.

DISCUSSION

Using a decision tree model applied to a hypothetical population of febrile patients presenting at the district hospital level in Africa, we compared costs and survival of generic antimicrobial management with management informed by local data on etiology and patterns of antimicrobial resistance. Our results showed that compared with generic antimicrobial management, blood culture surveillance-directed evidence-based antimicrobials saved 367–534 more lives per 100,000 patients at an additional cost of \$25.35 per patient. Using all of Africa data, we found that evidence-based antimicrobial management could be considered cost-effective when the probability of susceptibility rose above approximately 0.40, costing no more than an additional \$5,000 more per life

saved (Figure 2). Furthermore, our results indicate that for facilities processing at least 5,000 blood cultures per year, evidence-based antimicrobial management would cost less than an additional \$5,026 per patient given an initial investment of \$25,000–\$100,000.

Besides the development of laboratory services to support large vertical programs for HIV, tuberculosis, and malaria, clinical microbiology services have been neglected in many low-resource areas.^{4,5} Because of the structure of burden of disease estimates, bacterial sepsis after the neonatal period does not feature as a category in global burden of disease estimates.^{18,19} Nonetheless, bacteremia is commonly associated with severe febrile illness in inpatient studies in both Africa and Asia.^{1,2} Furthermore, the high case fatality ratio associated with sepsis, combined with the potential impact of timely and appropriate antimicrobial therapy,³ means that considerable survival gains can be achieved by carefully selecting empiric antimicrobial therapy. However, selection of locally appropriate antimicrobial regimens for suspected sepsis depends on local information about the epidemiology of bloodstream infections and patterns of antimicrobial resistance. Although conventional clinical microbiology services are not widely available in low-resource areas, we demonstrate that their use for surveillance for bloodstream infections is cost effective.

We focused on bloodstream infections because of their high case fatality ratio and the potential for better matching of antimicrobial therapy to patterns of antimicrobial resistance to improve patient survival.³ We studied only two antimicrobial regimens, ampicillin with gentamicin and ceftriaxone alone, because these are widely used and recommended for empiric sepsis management in low-resource areas.^{6,7} However, it is likely that closer tailoring of antimicrobial regimens to the local epidemiology of bloodstream infections would be possible if a wider range of antimicrobial agents and combinations was considered. This could be examined in future refinements of the model. In addition, pathogens that are either not detected or not readily detected by blood culture may be responsible for a large proportion of severe febrile illness in some settings.^{20,21} For example, rickettsial infections are very common in some areas of the tropics²² and would not be treated by either antimicrobial

TABLE 6

The base-case scenario for generic antimicrobials compared with the combination of blood culture monitoring and evidence-based antimicrobials for two hypothetical scenarios

Measure	Hypothetical 1		Hypothetical 2	
	Generic antimicrobials	Blood culture monitoring + evidence-based antimicrobials	Generic antimicrobials	Blood culture monitoring + evidence-based antimicrobials
(Column number)	(1)	(2)	(3)	(4)
Probability antimicrobials appropriate	0.07	0.35	0.25	0.34
Probability mortality if antimicrobials appropriate	0.20	0.20	0.20	0.20
Probability mortality if antimicrobials inappropriate	0.50	0.50	0.50	0.50
Probability patient lives	0.94	0.94	0.94	0.94
Expected cost per patient, \$	6.84	32.19	6.84	32.19
Deaths per 100,000 patients	6,466	5,532	5,866	5,566
Difference in survival	—	934	—	300
Difference in expected cost per patient, \$	—	25.35	—	25.35
ICER, \$	—	2,714	—	8,443

ICER = incremental cost-effectiveness ratio.

Hypothetical 1 used the prevalence values for the entire African continent but was reconfigured such that all *Salmonella enterica* and *Streptococcus pneumoniae* isolates were resistant to ampicillin. Hypothetical 2 was based on prevalence figures for north Africa and was reconfigured such that the prevalence of *Salmonella enterica* and *Brucella* spp. is exchanged. Values in parentheses refer to columns as cited in text. For all scenarios, the prevalence of sepsis is 0.134. Sensitivity of clinical assessment is set at 0.83 and specificity at 0.62. The cost of antimicrobials is \$13.22 in the generic case and \$26.46 in the evidence-based case. In the evidence-based case, there is an additional cost of \$11.41 for a negative blood culture test and \$71.96 for a positive blood culture test.

Numbers in parentheses refer to columns as cited in text.

TABLE 7

Susceptibility extremes for generic antimicrobials (worst case) compared with the combination of blood culture monitoring and evidence-based antimicrobials (best case) in all of Africa, east Africa, and north Africa

Measure	All of Africa		East Africa		North Africa	
	Generic antimicrobials	Blood culture monitoring + evidence-based antimicrobials	Generic antimicrobials	Blood culture monitoring + evidence-based antimicrobials	Generic antimicrobials	Blood culture monitoring + evidence-based antimicrobials
(Column number)	(1)	(2)	(3)	(4)	(5)	(6)
Probability antimicrobials appropriate	0.12	0.44	0.14	0.49	0.08	0.58
Probability mortality if antimicrobials appropriate	0.20	0.20	0.20	0.20	0.20	0.20
Probability mortality if antimicrobials inappropriate	0.50	0.50	0.50	0.50	0.50	0.50
Probability patient lives	0.94	0.95	0.94	0.95	0.94	0.95
Expected cost per patient, \$	6.84	32.19	6.84	32.19	6.84	32.19
Deaths per 100,000 patients	6,300	5,232	6,233	5,065	6,433	4,765
Difference in survival	–	1,068	–	1,168	–	1,668
Difference in expected cost per patient, \$	–	25.35	–	25.35	–	25.35
ICER, \$	–	2,375	–	2,171	–	1,520

ICER = incremental cost-effectiveness ratio.

Values in parentheses refer to columns as cited in text. For all scenarios, the prevalence of sepsis is 0.134. Sensitivity of clinical assessment is set at 0.83 and specificity at 0.62. The cost of antimicrobials is \$13.22 in the generic case and \$26.46 in the evidence-based case. In the evidence-based case, there is an additional cost of \$US11.41 for a negative blood culture test and \$71.96 for a positive blood culture test.

Numbers in parentheses refer to columns as cited in text.

regimen evaluated in our study. Extending our model to include microbiologic evaluations beyond blood culture would allow for assessment of the cost-effectiveness of a wider group of diagnostic evaluations for pathogens causing severe disease in the tropics.

This study has a number of limitations. Our assumptions about sepsis prevalence were based on studies using a single blood culture, which lacks sensitivity. Therefore, it is likely that we underestimated the prevalence of bacteremia. We chose ampicillin plus gentamicin as our base-case antimicrobial regimen. Since ceftriaxone is replacing ampicillin and gentamicin for sepsis management and is more effective,²³ we studied it as an alternative agent in our model. However, it is likely that empiric antimicrobial regimens other than those that we studied may be appropriate in other epidemiologic settings. For example, ceftriaxone may be a poor choice in areas where Enterobacteriaceae are often resistant to extended-spectrum cephalosporins. We did not account for externalities of antibacterial use, such as impacts of antimicrobial selection and use on the promotion of antimicrobial resistance.²⁴ We also did not account for costs for patients who receive inadequate or

inappropriate initial treatment and who subsequently seek additional care. As a result, our model likely underestimated costs for patients who receive inappropriate antimicrobial therapy. Incorporating these costs in the model would likely increase the cost-effectiveness of implementing blood culture surveillance and evidence-based antimicrobial treatment. In addition, we focus on the district hospital level since bloodstream infection surveillance may be feasible at this level of the health system in low-resource areas. We used data from Tanzania as an estimate of the average costs of operating a surveillance program. However, based on limited data available, there is likely to be heterogeneity in the costs of operating surveillance programs.

Our findings suggest that by informing empiric antimicrobial management of severe febrile illness, routine surveillance for bloodstream infections among patients admitted to district hospitals with febrile illness saves lives and is likely cost effective in low-resource settings. Although we ultimately need to compare surveillance to other relevant policy interventions, these results suggest that additional investment in clinical microbiology services in low-resource areas should be considered.

TABLE 8

Susceptibility extremes for generic antimicrobials (worst case) compared with the combination of blood culture monitoring and evidence-based antimicrobials (best case) (southern Africa and west and central Africa)

Measure	Southern Africa		West and central Africa	
	Generic antimicrobials	Blood culture monitoring + evidence-based antimicrobials	Generic antimicrobials	Blood culture monitoring + evidence-based antimicrobials
(Column number)	(1)	(2)	(3)	(4)
Probability antimicrobials appropriate	0.16	0.62	0.13	0.57
Probability mortality if antimicrobials appropriate	0.20	0.20	0.20	0.20
Probability mortality if antimicrobials inappropriate	0.50	0.50	0.50	0.50
Probability patient lives	0.94	0.95	0.94	0.95
Expected cost per patient, \$	6.84	32.19	6.84	32.19
Deaths per 100,000 patients	6,166	4,631	6,266	4,798
Difference in survival	–	1,535	–	1,468
Difference in expected cost per patient, \$	–	25.35	–	25.35
ICER, \$	–	1,652	–	1,727

ICER = incremental cost-effectiveness ratio.

Values in parentheses refer to columns as cited in text. For all scenarios, the prevalence of sepsis is 0.134. Sensitivity of clinical assessment is set at 0.83 and specificity at 0.62. The cost of antimicrobials is \$13.22 in the generic case and \$26.46 in the evidence-based case. In the evidence-based case, there is an additional cost of \$11.41 for a negative blood culture test and \$71.96 for a positive blood culture test.

Numbers in parentheses refer to columns as cited in text.

TABLE 9
Effect of different levels of capital investment on cost-effectiveness of blood culture monitoring and evidence-based antimicrobials

All of Africa									
Initial capital investment, \$	Number of blood cultures per annum	Interest rate, %	Generic antimicrobials	Blood culture monitoring + evidence-based antimicrobials			Difference in expected cost per patient, \$	ICER, \$	
			Expect cost per patient generic antimicrobials, \$	Cost of negative blood culture, \$	Cost of positive blood culture, \$	Expected cost per patient evidence based, \$			
25,000	1,000	0	7.26	13.41	73.96	34.19	27.35	5,124	
		3	7.26	13.69	74.24	34.47	27.63	5,175	
		5	7.26	13.88	74.43	34.66	27.82	5,175	
		10	7.26	14.37	74.92	35.15	28.31	5,303	
	5,000	0	7.26	11.81	72.36	32.59	25.75	4,824	
		3	7.26	11.87	72.42	32.65	25.81	4,834	
		5	7.26	11.90	72.45	32.69	25.85	4,842	
		10	7.26	12.00	72.55	32.79	25.95	4,860	
	50,000	1,000	0	7.26	16.41	76.96	37.19	30.35	5,686
			3	7.26	17.10	77.65	37.88	31.04	5,815
5			7.26	17.58	78.13	38.36	31.52	5,904	
10			7.26	18.81	79.36	39.59	32.75	6,135	
100,000	5,000	0	7.26	12.41	72.96	33.19	26.35	4,936	
		3	7.26	12.55	73.10	33.33	26.49	4,962	
		5	7.26	12.64	73.19	33.43	26.59	4,980	
		10	7.26	12.89	73.44	33.67	26.83	5,026	
	10,000	5,000	0	7.26	13.41	73.96	34.19	27.35	5,124
			3	7.26	13.69	74.24	34.47	27.63	5,175
			5	7.26	13.88	74.43	34.66	27.82	5,211
			10	7.26	14.37	74.92	35.15	28.31	5,303
			0	7.26	12.41	72.96	33.19	26.35	4,936
			3	7.26	12.55	73.10	33.33	26.49	4,962
	10,000	5	7.26	12.64	73.19	33.43	26.59	4,980	
		10	7.26	12.89	73.44	33.67	26.83	5,026	

ICER = incremental cost-effectiveness ratio.

All scenarios use all of Africa base-case values for both generic and evidence-based cases. Capital investment costs are added as annualized per patient costs to the base-case cost of blood culture monitoring and evidence-based antimicrobials, set at \$71.96 per patient.

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