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Performance Requirements to Achieve Cost-Effectiveness of Point-of-Care Tests for Sepsis among Patients with Febrile Illness in Low-Resource Settings

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Abstract. Bacterial sepsis is an important cause of mortality in low- and middle-income countries, yet distinguishing patients with sepsis from those with other illnesses remains a challenge. Currently, management decisions are based on clinical assessment using algorithms such as Integrated Management of Adolescent and Adult Illness. Efforts to develop and evaluate point-of-care tests (POCTs) for sepsis to guide decisions on the use of antimicrobials are underway. To establish the minimum performance characteristics of such a test, we varied the characteristics of a hypothetical POCT for sepsis required for it to be cost-effective and applied a decision tree model to a population of febrile patients presenting at the district hospital level in a low-resource setting. We used a case fatality probability of 20% for appropriately treated sepsis and of 50% for inappropriately treated sepsis. On the basis of clinical assessment for sepsis with established sensitivity of 0.83 and specificity of 0.62, we found that a POCT for sepsis with a sensitivity of 0.83 and a specificity of 0.94 was cost-effective, resulting in parity in survival but costing $1.14 less per live saved. A POCT with accuracy equivalent to the best malaria rapid diagnostic test was cheaper and more effective than clinical assessment.

INTRODUCTION

Malaria point-of-care tests (POCTs) have become an integral part of the management of febrile patients in low-resource areas in the tropics.[1] The excellent sensitivity, specificity, and cost-effectiveness of many malaria POCTs[2] mean that results when followed[3] can safely form the basis of decisions to prescribe or withhold malaria treatment, resulting in better targeting of costly artemisinin-based combination therapy. One consequence of more widespread use of malaria POCTs has been the unmasking of the problem of malaria overdiagnosis among febrile patients in many areas.[4] With apparent declines in malaria,[5] health-care workers are faced with a growing proportion of febrile patients confirmed not to have malaria but little evidence upon which to base decisions about their further management.[6]

Beyond malaria, bacterial or fungal sepsis represents a serious cause of febrile illness for which prompt and appropriate therapy may be lifesaving.[7,8] However, the detection of bloodstream infections presents a number of challenges. Clinical assessment using algorithms such as the World Health Organization (WHO) Integrated Management of Childhood Illness (IMCI) and WHO Integrated Management of Adolescent and Adult Illness (IMAI) can be rapid but lack sensitivity and specificity,[9] which risks overtreatment of patients without sepsis and failure to treat others. Blood cultures are considered the reference standard laboratory tests for the detection of bloodstream infections, but these lack sensitivity and do not produce results in a timeframe that can inform initial patient management. In light of these challenges, there is considerable interest in the development of assays amenable to a POCT format for sepsis that could be used in low-resource areas to guide the use of broad-spectrum antimicrobials and other measures designed to improve sepsis outcomes.[10,11] Although showing some promise, many such POCTs have not approached the performance characteristics achieved by malaria POCTs.[2,12,13]

To establish performance targets for potential sepsis POCTs, we sought to identify the levels of accuracy at which a hypothetical POCT for sepsis would out-perform clinical assessment. We were interested in the cost of such a test relative to clinical assessment and also its impacts on treatment costs and patient survival.

MATERIALS AND METHOD

Overview. To establish the minimum performance characteristics of a POCT required for it to be cost-effective, we compared existing data on clinical assessment for sepsis to hypothetical data for a POCT for sepsis. We modeled costs and outcomes occurring during hospital admission for a hypothetical cohort of febrile patients presenting at the district hospital level in a low-resource setting. We first assessed a base-case scenario and then investigated varying the test performance characteristics of sensitivity and specificity. We sought to identify the sensitivity and specificity required to reach parity with clinical assessment in terms of cost and to assess the effect of altering cost, mortality, and prevalence assumptions. For each scenario we calculated survival per 100,000 patients and expected cost per patient for both clinical assessment and POCT. Where relevant, we also calculated the incremental cost-effectiveness ratio (ICER), or the marginal cost per additional life saved, using a POCT. The ICER is commonly used to provide a practical approach to decision making regarding health interventions.[14]

Base case. Table 1, Column 2, describes all the input parameters used in the base-case scenario. 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.[15]

Test performance. For the clinical assessment of sepsis we used data from a 2003 study of neonates presenting with illness to health facilities in four countries (Ethiopia,

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TABLE 1
Input parameters for the point-of-care test compared with clinical assessment for sepsis model

Input variable	Base–case assumption	Worst case	Best case	References
Prevalence of sepsis (%)	13.4	34.5	8.5	15
Probability of survival (%)*				16–20
Test true positive	80	32	90	
Test false positive	100	92	–	21, Assumed
Test true negative	100	–	–	Assumed
Test false negative	50	25	65	16–20
Clinical assessment of sepsis diagnostic performance				
Sensitivity	0.83	–	–	9
Specificity	0.62	–	–	
Point-of-care test for sepsis performance†				
Sensitivity	0.83	0.32	1.00	2
Specificity	0.94	0.09	1.00	
Cost of clinical assessment for sepsis, $ per case‡				
Labor	1.02	–	–	JA Crump, pers.
Total	1.02	–	–	comm., 2014, 22
Cost of point-of-care test for sepsis, $ per test§				
Labor	3.05	–	–	16, JA Crump, pers.
Rapid diagnostic test	0.53	1	0.3	comm., 2014, 23,24
Total	3.58	4.05	3.35	
Cost of antimicrobial treatment, $ per case‖				
Emergency dose	0.59	–	–	25,26
Standard treatment	12.63	–	–	
Total	13.22	–	–	

HIV = human immunodeficiency virus; RDT = rapid diagnostic test; WHO = World Health Organization.
*It is assumed that true positive test cases are treated with appropriate antimicrobials and false-negative test cases are inappropriately treated. The probability of mortality values used in the model reflects the likelihood of mortality among septic patients receiving appropriate or inappropriate antimicrobial treatment respectively. Assumed a negligible death rate in non-cases (false positives and true positives).
†Rapid diagnostic test for sepsis performance characteristics are derived from the WHO Product testing of Malaria RDTs (2012). Sensitivity values are based on the average (base case), highest (best case) and lowest (worst case) panel detection scores from the 200 parasites/μL for pf only tests. Specificity values are based on average (most likely), highest (worst case), and lowest (best case) total false-positive rates from clean negative samples.
‡Based on cost of labor for a laboratory technician performing an HIV RDT of $6.10 per hour. It is assumed that a clinical assessment for sepsis takes 10 minutes. Costs adjusted to 2011 U.S. dollar ($) values using gross domestic product (GDP) deflator.
§It is assumed that positive and negative RDT tests incur the same costs. Costs adjusted to 2011 U.S. dollar ($) values using gross domestic product (GDP) deflator.
‖Cost of antimicrobial treatment is based on costs of treating with ampicillin and gentamicin. Costs adjusted to 2011 U.S. dollar ($) values using gross domestic product (GDP) deflator.

The Gambia, Papua New Guinea, and the Philippines).[9] Using a rule requiring observation of at least 1 of 9 clinical signs of sepsis and other severe illness, the authors found a diagnostic performance of clinical assessment of 0.83 sensitivity and 0.62 specificity. For the hypothetical POCT for sepsis we assumed the same sensitivity as clinical assessment to ensure parity in survival. To determine the specificity of the POCT, we used WHO product testing of existing malaria POCTs as a proxy, taking as our base case the mean specificity values across malaria POCTs, at 0.94.[2]

Costs. Our cost estimates relied largely on data from a clinical laboratory operating to good clinical laboratory practice standards in northern Tanzania (J. A. Crump, personal communication, 2014). It was assumed that appropriate diagnostic facilities would be present at the district hospital level and that facility costs would not differ between the clinical assessment or POCT scenarios. Accordingly, no fixed costs were included in the model. All costs are expressed in 2011 U.S. dollars ($). For clinical assessment, we assumed that labor was the only cost and based our value on the cost per hour for a laboratory technician performing a human immunodeficiency virus (HIV) POCT ($6.10/hour). Assuming that clinical assessment takes 10 minutes, labor costs for the clinical assessment were set at $1.02 per patient, consistent with costs reported in earlier studies.[22] For the POCT for sepsis, we estimated the labor cost at $3.05 based on the cost of a laboratory technician performing a 30-minute HIV POCT. The cost of the assay itself was valued at $0.53 in the base case.[16,23,24] This gave a total cost of $3.58 per case for the sepsis POCT. The cost of antimicrobial treatment was set at $13.22 based on the cost for an antimicrobial emergency dose and standard treatment using ampicillin and gentamicin for 5 days.[25,26]

Patient survival. Our primary outcome of interest was patient survival. A base-case survival for sepsis of 80% for individuals who tested true positive was calculated based on published data.[16–20] We used the same sources to determine the survival for individuals who tested false negative and calculated a base-case survival of 50%. These numbers assume that true positive test cases were treated with appropriate antimicrobials and treatment was inappropriately withheld among those with false-negative tests. For individuals who do not have sepsis, regardless of whether they tested false positive or true negative, we assumed a case fatality ratio of zero. Figure 1 illustrates the decision tree used, prefilled with data from the base-case scenario.

Sensitivity analysis. *Test performance.* First, we assessed a worst- and best-case scenario based on the performance and costs of existing malaria POCTs.[2] We then explored the impact of altering just the sensitivity and specificity of the hypothetical sepsis POCT. We investigated the effect of POCT test performance characteristics on patient survival relative to clinical assessment and the level of specificity needed for the POCT to reach cost parity with clinical assessment. Holding POCT sensitivity or specificity at the base-case values, we varied the sensitivity and specificity of the POCT test from 0.00 through 1.00, comparing the difference in mortality and costs to the base-case clinical assessment scenario. We also considered the effect on cost parity of using ceftriaxone as an alternative antimicrobial treatment. On the

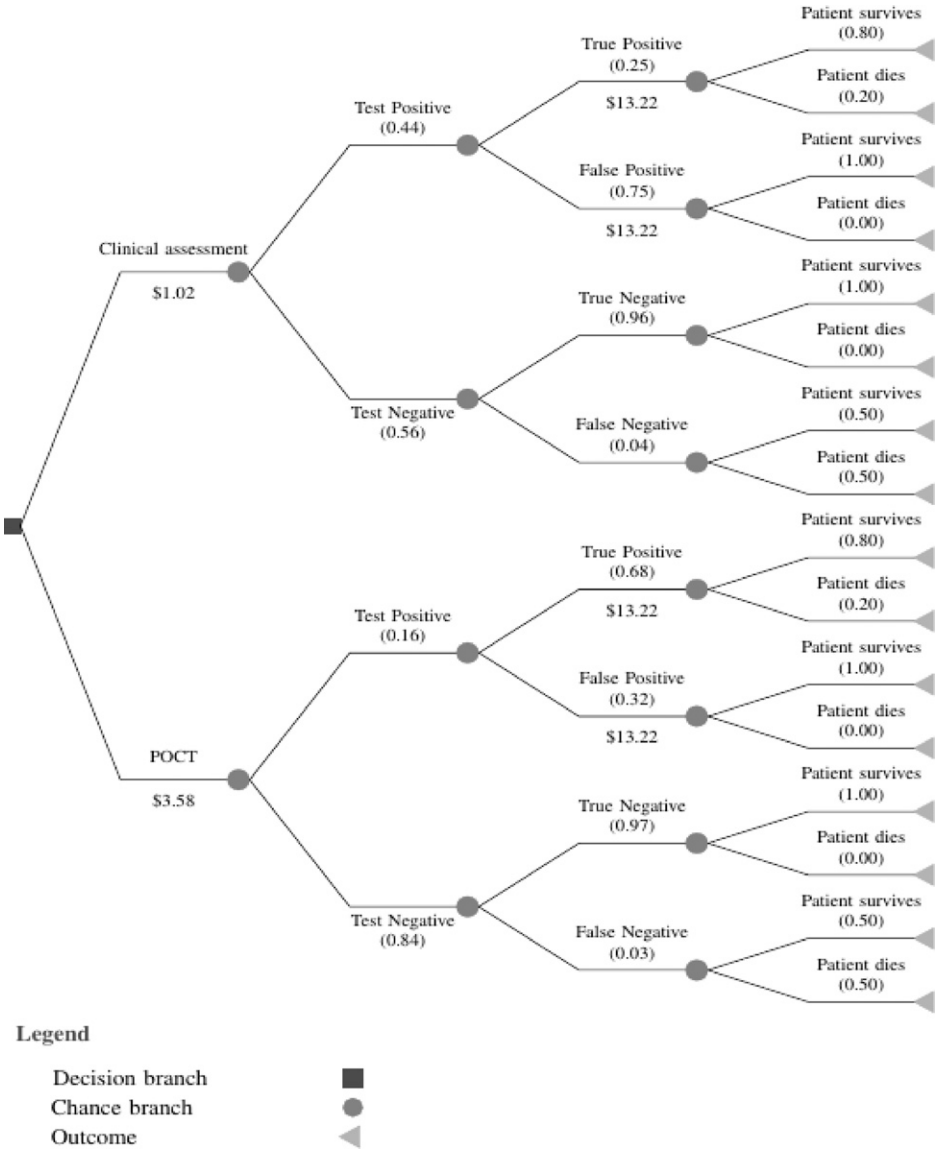

FIGURE 1. Decision tree representing base-case probabilities and costs and outcomes for a febrile patient presenting at a district hospital in a low-resource setting with sepsis diagnosis by either clinical assessment protocols or a point-of-care test. Cost figures represent the total costs of tests and antimicrobial treatment. Probabilities of an event occurring are shown in in brackets. The prevalence of sepsis is 0.134 throughout the tree, although the implied prevalence suggested by the values presented in the tree differs slightly from this due to all presented values being rounded to two decimal places. The full precision available in Excel (15 significant figures) was used in all calculations.

basis of the cost of one emergency dose and 5 days of standard treatment, we estimated treatment with ceftriaxone would cost $26.46.[25,26] In addition, we set the sensitivity of the POCT at a level where the POCT was marginally more effective than clinical assessment and explored the effect of POCT specificity on cost-effectiveness.

Costs. Second, we allowed for variation in the cost of the hypothetical POCTs, using the range of costs reported in a price analysis of malaria POCTs tests from Africa.[23]

Prevalence. Third, we considered the effect of prevalence of sepsis on cost-effectiveness of a POCT. We varied the prevalence of sepsis between 8.5% and 34.5% based on the reported prevalence of community-acquired bloodstream infections among different subgroups of febrile patients presenting to district hospitals in Africa.[15]

Patient survival. Fourth, we allowed for variation in survival when testing true positive or false negative from 32% and 25% in the worst case[19] to 90% and 65% in the best case,[16,17] respectively. In addition, to investigate the potential effect of false-positive results masking non-sepsis febrile disease states such as malaria, we allowed for a probability of survival for patients with a false positive of either 99% or 92% based on the estimates of the probability that untreated malaria in high transmission area becomes severe and then progresses to death.[21]

Antimicrobial courses avoided. Finally, as a secondary outcome of interest, we explored the number of antimicrobial courses avoided using a POCT at different levels of specificity compared with using clinical assessment. Holding POCT sensitivity at the base-case value, we varied the specificity of the POCT test from 0.00 through 1.00, comparing the difference

TABLE 2
The base-case with worst- and best-case scenarios for a POCT test compared with clinical assessment for sepsis

Measure	Base case		Worst case		Best case	
	Clinical assessment	POCT	Clinical assessment	POCT	Clinical assessment	POCT
(Column number)	(1)	(2)	(3)	(4)	(5)	(6)
Sensitivity	0.83	0.83	0.83	0.32	0.83	1
Specificity	0.62	0.94	0.62	0.009	0.62	1
Cost of test	1.02	3.58	1.02	4.05	1.02	3.35
Expected cost per patient, $	6.84	5.74	6.84	15.96	6.84	5.12
Deaths per 100,000 patients	3,363	3,363	3,363	5,414	3,363	2,680
Difference in cost per patient, $		−1.10		9.12		−1.72
Difference in survival per 100,000 patients		0		−2,050		683

POCT = point-of-care test.
Numbers in parentheses refer to columns as cited in text.

in the number of patients who tested positive using a POCT with the number who tested positive in the base-case clinical assessment scenario.

RESULTS

Base case. The total cost per patient under clinical assessment with sensitivity of 0.83 and specificity of 0.62 was $6.84 with 3,363 anticipated deaths per 100,000 patients. The hypothetical sepsis POCT with sensitivity of 0.83 and specificity of 0.94 yielded a total cost per patient of $5.74 with 3,363 deaths per 100,000 patients. Thus, there was no difference in survival between the base-case POCT and clinical assessment but the POCT was less expensive (Table 2, Columns 1 and 2).

Sensitivity analysis. *Test performance.* We first evaluated a worst- and best-case scenario, altering the sensitivity and specificity and the costs of the POCT but keeping the clinical assessment parameters the same as in the base case. Table 2, Columns 3 and 4, present results from the "worst-case" scenario, where the hypothetical POCT was set at its highest possible cost, and its lowest possible sensitivity and specificity based on values from the literature. Under this scenario the POCT was dominated by clinical assessment that both saved 2,050 more lives and cost less per patient ($6.84 versus $15.96). Table 2, Columns 5 and 6, show the "best-case" scenario where the hypothetical POCT was set at its lowest possible cost and its highest possible sensitivity and specificity. In this case, the POCT dominated, saving 683 more lives and costing $1.72 less per patient than clinical assessment.

Table 3, Columns 1 through 4, show the effect of changing only the sensitivity and specificity of the hypothetical POCT. Altering sensitivity and specificity of the sepsis POCT to match the sensitivity and specificity of the best available malaria POCT showed that the POCT dominated clinical assessment, saving 683 more lives and costing $1.49 less per patient.

Table 4 focuses on the effect on survival of altering the sensitivity and the specificity of the POCT. The mortality parity observed in the base case, where the sensitivity of a POCT was equivalent to clinical assessment at 0.83 but specificity was higher than clinical assessment at 0.94, remained if the specificity of the POCT was lowered to equal that of clinical assessment at 0.62 or if specificity of the POCT was lowered to 0.00. In both of these cases, the costs per patient were lower in the clinical assessment case. However, if the specificity was set at the base-case value of 0.94 but the sensitivity decreased 1% to 0.82, the POCT cost $1.12 less per patient but was associated with 40 more deaths per 100,000 patients than clinical assessment. Figure 2 further illustrates these results, showing that for every 1% gain in sensitivity relative to clinical assessment a POCT saved an additional 40 lives per 100,000 patients.

Table 5, Columns 1 and 2, examine the sensitivity and specificity needed for a POCT to reach parity with clinical assessment for both mortality and cost. At a sensitivity of 0.83 and a specificity of approximately 0.84, the POCT and

TABLE 3
Worst-case and best-case sensitivity and specificity values for a POCT test compared with clinical assessment for sepsis

Measure	POCT low sensitivity/specificity		POCT high sensitivity/specificity	
	Clinical assessment	POCT	Clinical assessment	POCT
(Column number)	(1)	(2)	(3)	(4)
Sensitivity	0.83	0.32	0.83	1
Specificity	0.62	0.009	0.62	1
Expected cost per patient, $	6.84	15.49	6.84	5.35
Deaths per 100,000 patients	3,363	5,414	3,363	2,680
Difference in cost per patient, $		9.05		−1.49
Difference in survival per 100,000 patients		−2,050		683

POCT = point-of-care test.
Numbers in parentheses refer to columns as cited in text.

TABLE 4
Effect of sepsis POCT performance characteristics on survival

Measure	Effect of specificity on survival				Effect of sensitivity on survival	
	Clinical assessment	POCT	Clinical assessment	POCT	Clinical assessment	POCT
(Column number)	(1)	(2)	(3)	(4)	(5)	(6)
Sensitivity	0.83	0.83	0.83	0.83	0.83	0.82
Specificity	0.62	0.62	0.62	0.00	0.62	0.94
Expected cost per patient, $	6.84	9.40	6.84	16.50	6.84	5.72
Deaths per 100,000 patients	3,363	3,363	3,363	3,363	3,363	3,404
Difference in cost per patient, $		2.56		9.66		−1.12
Difference in survival per 100,000 patients		0		0		−40

POCT = point-of-care test.
Numbers in parentheses refer to columns as cited in text.

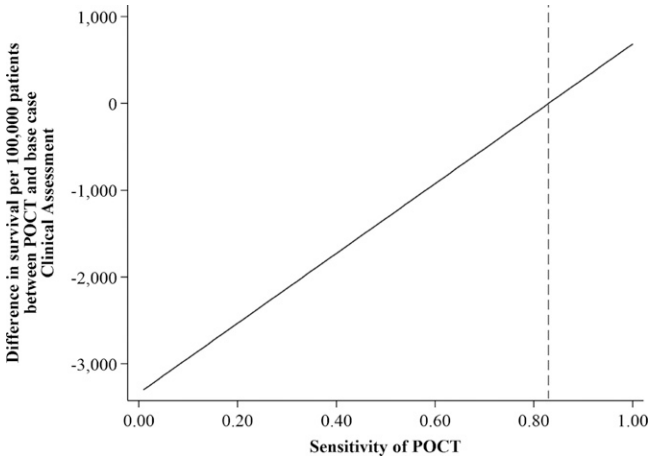

FIGURE 2. Difference in survival per 100,000 patients at varying levels of sepsis point-of-care test sensitivity compared with base case clinical assessment scenario. Based on point-of-care test specificity of 0.94 and varying sensitivity compared with base case clinical assessment with sensitivity 0.83 and specificity 0.62. A negative value on the y axis indicates a reduction in survival. The vertical dotted line indicates the sensitivity at which parity in survival per 100,000 patients between clinical assessment and a point-of-care test for sepsis is achieved.

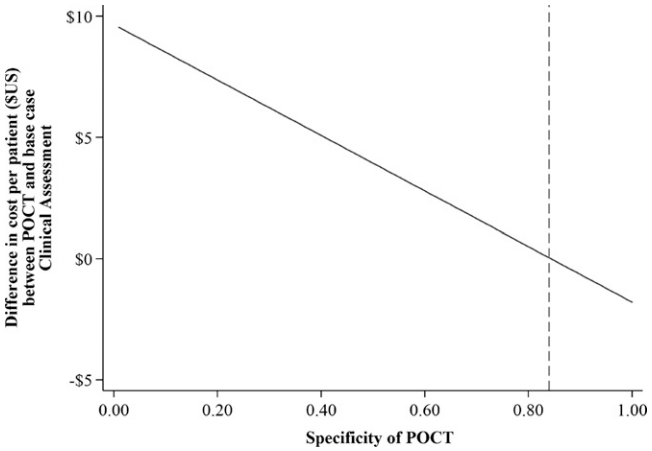

FIGURE 3. Difference in cost per patient ($) at varying levels of sepsis point-of-care test specificity compared with base-case clinical assessment scenario. Based on point-of-care test sensitivity of 0.83 and varying specificity compared with base case clinical assessment with sensitivity 0.83 and specificity 0.62. $ = U.S. Dollar. The vertical dotted line indicates the specificity at which parity in cost per patient between clinical assessment and a point-of-care test for sepsis is achieved.

clinical assessment had identical survival and cost structures (3,363 deaths per 100,000 patients at a cost of $6.84 per patient). Figure 3 illustrates this, showing the changing cost structure of the POCT as its specificity was varied. Finally, Table 5, Columns 3 and 4, explores ceftriaxone as an alternative antimicrobial treatment. Under this scenario, our results show that at a specificity of 0.73 clinical assessment and the POCT reached cost parity.

Table 6 explores the impact of specificity on cost-effectiveness in scenarios where a hypothetical POCT had a higher sensitivity, and was therefore more effective in terms of survival, than clinical assessment. Holding the specificity at the base case but setting the POCT sensitivity at 0.84, the minimum required for it to be more effective than clinical assessment, the POCT saved an additional 40 lives per 100,000 patients and cost $1.09 less per patient compared with clinical assessment (Table 6, Columns 1 and 2). Table 6, Columns 3 through 6, show that the gain in mortality associated with greater sensitivity was maintained as the specificity dropped. However, below a specificity of 0.85 the POCT was relatively more expensive than clinical assessment, yielding an ICER of between $5,000 and $0 within the specificity range 0.67–0.84. Table 6, Columns 7 through 10, show that as the POCT sensitivity increased the case fatality ratio dropped and the specificity required for the ICER to remain below $5,000 reduced, falling to 0.50 and 0.35 for a POCT with a sensitivity of 0.85 and 0.86, respectively.

Costs. In Table 7, Columns 1 through 4, only the costs of the hypothetical POCT are changed, keeping the sensitivity and specificity at the base-case level. Under both a high- and low-cost scenario, the POCT was less expensive than clinical assessment, costing $0.63 and $1.33 less per patient, respectively.

TABLE 5

Sepsis POCT performance characteristics required to achieve cost and mortality parity with clinical assessment

	Mortality and cost parity			
Measure	Clinical assessment	POCT	Clinical assessment	POCT
(Column number)	(1)	(2)	(3)	(4)
Sensitivity	0.83	0.83	0.83	0.83
Specificity	0.62	0.84	0.62	0.73
Expected cost per patient, $	6.84	6.84	12.67	12.67
Deaths per 100,000 patients	3,363	3,363	3,363	3,363
Difference in cost per patient, $		0		0
Difference in survival per 100,000 patients		0		0

POCT = point-of-care test.

Columns 1 through 4 explore mortality and cost parity, first keeping the cost structure as in the base case (columns 1 and 2), and then using ceftriaxone instead of ampicillin and gentamicin for the costs.

Numbers in parentheses refer to columns as cited in text.

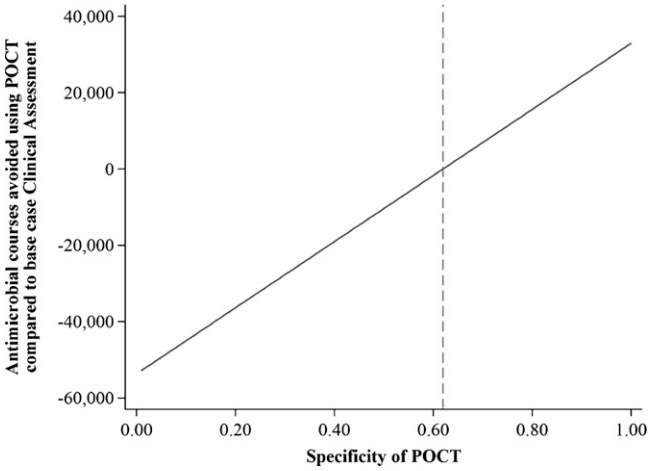

FIGURE 4. Number of antimicrobial courses avoided at varying levels of sepsis point-of-care test specificity compared with base-case clinical assessment scenario. Notes: Based on point-of-care test sensitivity of 0.83 and varying specificity compared with base-case clinical assessment with sensitivity 0.83 and specificity 0.62. A positive value on the y axis indicates a fewer antimicrobial courses. The vertical dotted line indicates the specificity at which parity in number of courses of antimicrobials per 100,000 patients between clinical assessment and a point-of-care test for sepsis is achieved.

TABLE 6
Effect of sepsis POCT performance characteristics on cost-effectiveness

Measure	Effect of altering sensitivity and specificity on the cost-effectiveness of a POCT									
	Clinical assessment	POCT	Clinical assessment	POCT	Clinical assessment	POCT	Clinical assessment	POCT	Clinical assessment	POCT
(Column number)	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)
Sensitivity	0.83	0.84	0.83	0.84	0.83	0.84	0.83	0.85	0.83	0.86
Specificity	0.62	0.94	0.62	0.84	0.62	0.67	0.62	0.50	0.62	0.35
Expected cost per patient, $	6.84	5.75	6.84	6.90	6.84	8.85	6.84	10.81	6.84	12.55
Deaths per 100,000 patients	3363	3323	3,363	3,323	3,363	3,323	3,363	3,283	3,363	3,242
Difference in cost per patient, $	–	−1.09	–	0.06	–	2.01	–	3.97	–	5.70
Difference in survival per 100,000 patients	–	40	–	40	–	40	–	80	–	121
ICER, $	–	–	–	147	–	4,988	–	4,937	–	4,730

ICER = incremental cost-effectiveness ratio; POCT = point-of-care test.
Numbers in parentheses refer to columns as cited in text.

Prevalence of sepsis. Setting the performance and mortality values at base-case levels for both clinical assessment and POCT, Table 8, Columns 1 through 6, shows that as the prevalence of sepsis increased from 8.5% to 34.5%, the expected cost per patient and mortality per 100,000 patients associated with both clinical assessment and the POCT increased. However, the difference in cost per patient between the two tests became smaller. In a setting where the prevalence of sepsis was 34.5% a POCT with a sensitivity of 0.84 (Table 8, Columns 7 and 8), 1% higher than clinical assessment, cost $0.17 less per patient and led to 104 fewer deaths per 100,000 patients.

Patient survival. Table 9 investigates the role of altering the probability of survival for both the POCT and clinical assessment. In a high case fatality scenario, there were 9,272 deaths per 100,000 patients under clinical assessment and POCT; whereas in the low case fatality scenario, deaths were 1,910 per 100,000 patients under clinical assessment and POCT (Table 9, Columns 1 through 4). Costs per patient were lower for the POCT in both scenarios. Table 9, Columns 5 through 8, show the effect of mortality among patients with false-positive results (ranging from 1% to 8%) for both clinical assessment and the hypothetical POCT, keeping the probability of survival for true positives, true negatives, and false negatives at base-case values. In these scenarios, the POCT dominated clinical assessment, being both less expensive and resulting in between 277 and 2,217 fewer deaths.

TABLE 7
The effect of altering the cost of a sepsis POCT

Measure	POCT high cost		POCT low cost	
	Clinical assessment	POCT	Clinical assessment	POCT
(Column number)	(1)	(2)	(3)	(4)
Sensitivity	0.83	0.83	0.83	0.83
Specificity	0.62	0.94	0.62	0.94
Cost of test	1.02	4.05	1.02	3.35
Expected cost per patient, $	6.84	6.21	6.84	5.51
Deaths per 100,000 patients	3,363	3,363	3,363	3,363
Difference in cost per patient, $		−0.63		−1.33
Difference in survival per 100,000 patients		0		0

POCT = point-of-care test.
Numbers in parentheses refer to columns as cited in text.

Antimicrobial courses avoided. As a secondary outcome, we investigated the number of antimicrobial courses avoided using a POCT test compared with clinical assessment. Varying the specificity of the POCT but keeping the sensitivity set at 0.83, Table 10 shows the effect of POCT specificity on the number of antimicrobial courses avoided compared with base-case clinical assessment. Using base-case test performance values, the hypothetical POCT resulted in 27,712 fewer courses of antimicrobials per 100,000 patients than clinical assessment. A POCT with the same sensitivity as clinical assessment but set at 1.00 specificity avoided 32,908 courses of antimicrobials per 100,000 patients. Figure 4 illustrates this, demonstrating that for every 1% gain in specificity relative to clinical assessment, a POCT would result in 856 fewer antimicrobial courses per 100,000 patients.

DISCUSSION

Using a decision tree model, we varied the characteristics of a hypothetical POCT for sepsis required for it to be cost-effective and applied it to a population of febrile patients presenting at the district hospital level in a low-resource setting. Using parameters informed by the literature, our base-case scenario showed that compared with clinical assessment the hypothetical POCT achieved mortality parity, but was more cost-effective at $1.10 less per patient. The lower cost per patient of the POCT was due to the higher specificity relative to clinical assessment, with clinical assessment set at 0.67 and the POCT set at 0.94. Using base-case survival assumptions, we found varying the specificity of the POCT drove differences in the cost per patient between the two tests but did not impact survival. Conversely, varying the sensitivity of a POCT relative to clinical assessment had a small effect on costs but primarily drove differential survival outcomes, with the more sensitive test associated with lower case fatality ratios. Accordingly, if the POCTs test characteristics were set so they were equivalent to the best malaria POCT with a sensitivity and specificity of 1.00, the POCT would be associated with 683 fewer deaths per 100,000 patients at a cost of $1.49 less per patient, thus clearly dominating clinical assessment under these conditions.

Given that 100% sensitivity and specificity are unlikely to be achieved by a laboratory assay for sepsis, our results also showed that a hypothetical POCT reaches cost parity with clinical assessment at a specificity of approximately 0.84, well within the range of performance characteristics of tests for other common conditions such as malaria and HIV.

TABLE 8
Effect of varying the prevalence of sepsis on cost and survival outcomes of a sepsis POCT

	Prevalence of sepsis							
	8.5%		15.0%		34.5%		34.5%	
Measure	Clinical assessment	POCT	Clinical assessment	POCT	Clinical assessment	POCT	Clinical assessment	POCT
(Column number)	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Sensitivity	0.83	0.83	0.83	0.83	0.83	0.83	0.83	0.84
Specificity	0.62	0.94	0.62	0.94	0.62	0.94	0.62	0.94
Expected cost per patient, $	6.55	5.24	6.94	5.90	8.10	7.89	8.10	7.93
Deaths per 100,000 patients	2,134	2,134	3,765	3,765	8,660	8,660	8,660	8,556
Difference in cost per patient, $	–	−1.31	–	−1.04	–	−0.21	–	−0.17
Difference in survival per 100,000 patients	–	0	–	0	–	0	–	104

POCT = point-of-care test.
Columns 1 through 6 look at the effect of varying the prevalence of sepsis on costs and outcomes using base-case test performance values for clinical assessment and the POCT. Columns 7 and 8 look at the effect of varying the prevalence of sepsis and the sensitivity of a POCT compared with base-case clinical assessment. Numbers in parentheses refer to columns as cited in text.
Numbers in parentheses refer to columns as cited in text.

Moreover, if one considers ceftriaxone as the appropriate antimicrobial, the two tests reached cost parity at a specificity of 0.73. At a sensitivity of 0.84, the POCT would cost less than clinical assessment at specificities above 0.84 and cost below an additional $5,000 per additional life saved at a specificity as low as 0.67.

The prevalence of both sepsis and other febrile diseases also impact on the cost-effectiveness of a POCT and illustrate the relationship between test performance and the characteristics of the target population. In settings where other febrile diseases such as malaria and Q fever are also highly prevalent, false-positive results may mask other febrile conditions and result in poorer survival outcomes. Under these conditions a POCT would dominate clinical assessment as the greater specificity drives both lower costs per patient and greater survival outcomes than clinical assessment. Among populations where the prevalence of sepsis is high, for example populations where the prevalence of underlying conditions such as HIV infection is high,[15] the cost savings associated with the higher specificity of the POCT are diminished but the impact of sensitivity on survival is heightened.

This study has a number of limitations. Few studies describe the performance of the current method for diagnosis of sepsis in low-resource areas using clinical algorithms such as the WHO IMCI or IMAI. Consequently, we used data from studies that may not accurately reflect the performance of clinical evaluation across all age groups. Our assumptions about sepsis prevalence were based on studies using a single blood culture, which lacks sensitivity. Therefore, it is likely that we underestimated sepsis prevalence in our base case. Our sensitivity analyses suggest that in populations where the prevalence of sepsis is high the test performance characteristics of a POCT are particularly important as differences in survival are amplified. We did not include costs associated with additional care for patients who received inadequate or inappropriate treatment. As a result, our model likely underestimated costs for patients with false-negative results. Incorporating these costs in the model would increase the cost-effectiveness of tests with superior performance. In addition, we chose ampicillin plus gentamicin as our base-case antimicrobial regimen. Because ceftriaxone is replacing ampicillin and gentamicin for sepsis management and is more effective,[28] we studied it as an alternative agent in our model. We assumed that clinicians would base their management decisions on the result of the sepsis POCT, which is often not the case for malaria POCTs.[3]

Our findings set targets for the performance characteristics of POCTs for sepsis to reach and exceed parity with clinical assessment in low-resource areas. The levels of accuracy required for a sepsis POCT to reach parity are well below those of many existing malaria RDTs. However, development of an assay for the detection of a single genus parasitic bloodstream infection is likely to be less technically demanding than developing a POCT for sepsis, where the broad range of potential pathogens and the diversity of the host response pose substantial challenges. Whether such an assay could be developed at levels of complexity and cost appropriate for use in low-resource areas remains unclear. Nonetheless, an accurate POCT for sepsis would

TABLE 9
Effect of altering mortality in both sepsis clinical assessment and POCTs and effect of mortality among patients with false-positive results

	High case fatality both POCT and CA		Low case fatality both POCT and CA		1% False-positive mortality		8% False-positive mortality	
Measure	CA	POCT	CA	POCT	CAt	POCT	CA	POCT
(Column number)	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Sensitivity	0.83	0.83	0.83	0.83	0.83	0.83	0.83	0.83
Specificity	0.62	0.94	0.62	0.94	0.62	0.94	0.62	0.94
Expected cost per patient, $	6.84	5.74	6.84	5.74	6.84	5.74	6.84	5.74
Deaths per 100,000 patients	9,272	9,272	1,910	1,910	3,693	3,415	5,996	3,779
Difference in cost per patient, $	–	−1.12	–	−1.12	–	−1.12	–	−1.12
Difference in survival per 100,000 patients	–	0	–	0	–	−277	–	−2,217

CA = clinical assessment; POCT = point-of-care test.
Numbers in parentheses refer to columns as cited in text.

TABLE 10
Effect of sepsis POCT performance on antimicrobial courses avoided

Measure	Parity in number of antimicrobial courses		Base-case specificity: number of antimicrobial courses		Best-case specificity: number of antimicrobial courses	
	Clinical assessment	POCT	Clinical assessment	POCT	Clinical assessment	POCT
(Column number)	(1)	(2)	(3)	(4)	(5)	(6)
Sensitivity	0.83	0.83	0.83	0.83	0.83	0.83
Specificity	0.62	0.62	0.62	0.94	0.62	1.00
Expected cost per patient, $	6.84	9.40	6.84	5.74	6.84	5.05
Expected courses of antimicrobials per 100,000 patients	44,030	44,030	44,030	16,318	44,030	11,122
Difference in cost per patient, $	–	2.56	–	−1.12	–	−1.79
Antimicrobial courses avoided per 100,000 patients	–	0	–	27,712	–	32,908

POCT = point-of-care test.
Numbers in parentheses refer to columns as cited in text.

be an invaluable tool for targeting potentially lifesaving treatment to a seriously ill population while supporting the judicious use of antimicrobial agents.

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