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REVIEW ARTICLE

Point-of-Care Biomarkers to Guide Antibiotic Prescription for Acute Febrile Illness in Sub-Saharan Africa: Promises and Caveats

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Empiric malaria treatment in Sub-Saharan Africa has significantly decreased with the scaling-up of malaria rapid diagnostic tests; this coincided with a pronounced increase in empiric antibiotic prescriptions. In high-income countries, guidance for antibiotic prescriptions using biomarkers such as C-reactive protein (CRP) and procalcitonin (PCT) has reduced antibiotic use while safeguarding patient safety. Importantly, several low-cost point-of-care CRP/PCT tests are currently available. However, only a few studies on the role of CRP/PCT in differentiating bacterial vs viral infections in acute febrile illness have been conducted in Sub-Saharan Africa. Studies from Central and West Africa (most of which is malaria-endemic) are particularly scarce, and only 1 has included adults. The evidence base for point-of-care use of CRP/PCT biomarkers in acute fever in Sub-Saharan Africa should be urgently built. Before engaging in clinical trials to assess clinical impact, pilot studies should be conducted to address key knowledge gaps including recommended CRP/PCT cutoff values and the effect of malaria coinfection.

Keywords. antibiotic; CRP; procalcitonin: point of care; Sub-Saharan Africa.

Febrile syndromes are particularly challenging in low-resource settings [1]. Etiologies are countless, and some of the causative infections may be rapidly associated with adverse outcomes [2]. In the absence of adequate diagnostic workup, antibiotics are often used empirically. This approach may be justified for fever associated with septic signs, skin infection, or genitourinary symptoms, because bacterial pathogens are largely predominant in these syndromes [3]. In case of fever with intestinal symptoms (ie, diarrhea), while bacteria are often incriminated in tropical settings [3], administration of antibiotics can be restricted to a subgroup of patients with well-defined clinical criteria of invasive dysentery [4]. Two fever syndromes, namely respiratory tract infection and undifferentiated fever (absence of focus of infection), are, however, much more difficult to adequately manage. The clinical presentation, at least at an early stage, usually does not allow to distinguish viral etiologies, which are far more frequent, from bacterial pathogens, which may be much more dangerous [5]. Consequently, administering antibiotics is often the default option of care providers facing these 2 syndromes, while it is most of the time unnecessary [6].

Antimicrobial resistance has become one of the biggest global health challenges [7–9]. There is a well-established correlation between resistance and excessive prescription of antibiotics, as observed in recent surveys and clinical experience, including in low-resource settings [10]. To contribute to rational use of antibiotics, many experts recommend deploying rapid point-of-care (POC) low-cost diagnostics to guide antibiotic prescription at the primary and secondary levels of care [9]. Although still imperfect, several markers are of diagnostic value to rule in or rule out serious infections [11]. In high-income countries, the use of (bacterial) biomarkers such as C-reactive protein (CRP) and procalcitonin (PCT) has been demonstrated to have the potential to reduce antibiotic consumption while safeguarding patient safety [12]. This has been observed across different settings, ranging from the use of POC CRP lateral-flow assays at the primary health care level to the determination of PCT concentration with automated analyzers in intensive care settings [12–14]. Other prototype markers have been clinically investigated, but none as extensively as CRP and PCT, which are, in addition, the only 2 bacterial biomarkers that are commercially available [11].

With the development of biomarker POC assays that can be reliably used in field settings [15], biomarkers should also be explored to guide patient management in low-resource settings. POC biomarker tests would be valuable to rapidly stratify, depending on different cutoff values, those patients presenting with serious infections requiring antibiotic treatment and/or

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referral to a higher health care level vs those with less severe febrile illness (particularly viral infections) where antibiotics can be safely withheld.

EVIDENCE BASE IN SOUTHEAST ASIA

Encouraging work has been done in Southeast Asia. Some studies have assessed the diagnostic accuracy of biomarkers including CRP and PCT to differentiate bacterial and viral infections in febrile patients with respiratory or nonfocal symptoms [16, 17]. A post hoc analysis observed areas under the receiver operating characteristics (AUROC) curves of 0.83 and 0.74 for CRP and PCT, respectively, for diagnosing bacterial diseases vs identified viral infections [16], while a prospective study demonstrated AUROC curves of 0.91 and 0.80, respectively, for the same end point [17]. More importantly, 2 clinical trials have been conducted to evaluate the impact of CRP test results on antibiotic use [18, 19].

In an individually randomized clinical trial at the primary health care level in Vietnam, antibiotic use guided by a quantitative CRP result at the POC was compared with routine care for nonsevere acute respiratory infection in children or adults [19]. The proportion of patients to whom antibiotics were administered significantly decreased from 78% to 64% without compromising outcomes. Adverse events were rare, with no deaths. The cutoffs used to recommend against antibiotic use were CRP levels ≤20 mg/L (≤10 mg/L if aged 1–5 years) and in favor of antibiotics if CRP levels were ≥100 mg/L (≥50 mg/L if aged 1–5 years). Of interest, these cutoffs were essentially derived from studies conducted in high-income countries.

In a more recent clinical trial from Myanmar and Thailand, the effect of the introduction of 2 CRP thresholds (>20 mg/L and >40 mg/L) at the POC to guide antibiotic prescription was studied in children and adults presenting with nonsevere (undifferentiated) febrile illness at the primary health care level [18]. Cutoffs used in the trial were reportedly based on previous literature, including studies from Southeast Asia. While antibiotic prescription up to day 5 decreased from 39% to 36% (using CRP threshold >20 mg/L) and to 34% (using CRP threshold >40 mg/L) with no difference in clinical outcomes, only the latter decrease was statistically significant. Both trials applied individual rather than cluster randomization, potentially reducing the effect size by contamination.

Importantly, CRP was done systematically for all patients in both trials. Some have argued that—at least at the primary health care level—CRP testing should be done only for individuals who are clinically assessed to be at higher risk of serious bacterial infection [20, 21].

EVIDENCE BASE IN SUB-SAHARAN AFRICA

In Sub-Saharan Africa, relatively few studies on the role of CRP and PCT to differentiate bacterial vs nonbacterial infections in acute febrile illness have been conducted. Relevant studies are summarized in Table 1. With the vast majority of the studies originating from a few East African countries (Malawi, Mozambique, Tanzania), the evidence base on the potential value of CRP and PCT POC tests in Central and West Africa, where malaria is still much more predominant, is extremely limited. Moreover, only 1 of these studies included adults. Of note, in contrast to Asia, none of the biomarker studies conducted in Africa that investigated viral pathogens included an asymptomatic control group, potentially leading to misinterpretation about the actual etiologies of fever.

Several of the studies in Table 1 looked at optimal cutoff values to differentiate bacterial and viral infections, with the aim to maximize sensitivity and specificity. Overall, the performance of CRP and PCT was fairly similar. However, in real life, biomarker results should not be used in isolation, but rather combined with clinical information and also taking pretest probability of bacterial/severe infections into account (which differs regionally and between health care levels).

In this regard, pivotal work has been done by Keitel and colleagues in febrile children in Tanzania (the vast majority with respiratory symptoms) [6]. After having developed and evaluated the utility of a smartphone-based tool (ALMANACH) improving the Integrated Management of Childhood Illness (IMCI) guidelines [22], they designed a novel electronic algorithm (called e-POCT) that combines clinical information with POC determination of hemoglobin, CRP, PCT, and oxygen saturation levels. The proposed cutoff values recommending antibiotic use were relatively high (CRP >80 mg/dL or PCT >4 μg/L) based on data from an acute fever study from the same setting [22]. Under the assumption that only a minority of patients at the primary health care level require antibiotics, CRP/PCT testing was restricted to children with severity indicators and was used to rule in the need for antibiotics. An impressive reduction of antibiotic use was demonstrated in the interventional arm (11.5% compared with 94.9% in routine care) in this study setting, with a trend to lower mortality [6,23].

Effect of Malaria Infection on CRP Levels in Sub-Saharan Africa

Few studies have systematically assessed the impact of malaria infection on CRP profiles in endemic settings in Sub-Saharan Africa. The findings of a selection of them, with an adequate methodology and sample size, are summarized in Table 2 and compared with a few studies assessing CRP values in healthy African participants (with no malaria infection). Malaria-infected individuals had consistently higher mean or median CRP values than healthy controls. However, differences were small between noninfected volunteers and participants with asymptomatic parasitemia, who displayed either normal (<10 mg/L) or slightly elevated (10–50 mg/L) CRP values. Elevation of mean or median CRP values was usually more pronounced (often >50 mg/L) in patients with clinical malaria and

Table 1. Overview of Publications From Sub-Saharan Africa Assessing the Diagnostic and Prognostic Value of CRP and PCT Biomarkers to Differentiate Bacterial vs Nonbacterial Infections in Acute Infectious Episodes

Ref	Study Population/Period	Outcome of Interest	Cutoff, mg/L[a]	Sensitivity, %	Specificity, %	Diagnostic ROC AUC	Comments
[24]	Rural Mozambique hospitalized children aged <5 y with severe clinical pneumonia (total n meeting inclusion criteria = 835; 9/2006–9/2007), malaria excluded from analysis	Malaria (-) bacterial (BC+; n = 82) vs viral pneumonia (n = 64)	Malaria (-)			Malaria (-)	AUC for mortality (11%) in malaria (-)
			CRP: 20.9	95	54.2	CRP: 0.87	CRP: 0.64
			PCT: 0.72	94.6	74.2	PCT: 0.90	PCT: 0.64
							Test: automated analyzer (for both CRP and PCT)
[37]	Rural Mozambique hospitalized children aged <5 y with severe clinical pneumonia but no malaria (total n meeting inclusion criteria = 653, n all samples available = 586; 9/2006–9/2007)	BC+ (n = 84) vs BC- (n = 246)	PCT			0.80	Test: automated analyzer (for both CRP and PCT)
			0.64	95	56		
			0.83	90	60		
			1.02	85	62		
			1.15	80	63		
			1.4	75	64		
			CRP			0.79	Mortality of 13%; 30% HIV coinfection (but missing for 120/330)
			20.9	95	45		
			27.9	90	50		
			38	85	57		
			59.8	80	66		
			73	75	68		
[38]	Rural Tanzania; OPD; febrile children aged <5 y (total n meeting inclusion criteria = 867, n all samples available = 660; 1–10/2013)	BC+ (n = 17) vs BC- (n = 643)	CRP: 37.3	74.2	77.8	0.83	45/56 malaria cases had CRP >40 mg/dL; test: automated analyzer
[39]	Rural Tanzania; OPD; children aged <5 y with nonsevere febrile illness & malaria (-) (n included = 428; 7/2011–11/2012)	All bacterial infections (n = 90)	CRP: 19	44.6	78.5	0.62	Test: POC No. 34, CRP (Supplementary Table 1)
		UTI (n = 24)		57.1	78.4	0.62	
		Bacteremia (n = 6)		50.0	78.5	0.60	
		IMCI pneumonia (n = 60) vs nonbacterial (n = 341)		37.5	78.5	0.60	
[35]	Urban Malawi, referral hospital; children aged <16 y with suspected meningitis (n included = 282) or pneumonia (n = 95; 4/2004–10/2006)	Serious bacterial infection (n = 280), vs no detectable bacterial infection (n = 97)	CRP	-	-	0.81	HIV 50%; malaria 4%
			PCT	-	-	0.86	AUC for mortality (22%): CRP: 0.43; PCT 0.61
							Test: PCT: sandwich immuno-assay; CRP: automated analyzer
[40]	Tanzania (1 rural, 1 urban center); OPD; children aged <10 y with clinical pneumonia (n included = 155), malaria excluded from analysis (4–12/2008)	End point pneumonia (n = 30) vs normal x-ray (n = 94)	CRP: 44.1	80.0	78.7	0.85	Cutoff with highest combined sensitivity/specificity; test: CRP and PCT: ELISA
			PCT: 0.51	70.0	69.2	0.70	
[41]	Multicountry (South Africa, Zambia, Kenia, Gambia, Mali, Bangladesh, Thailand), 9 sites in urban and rural settings	Confirmed bacterial pneumonia (n = 145; 119 HIV-; 26 HIV+) vs RSV pneumonia (n = 567; 556 HIV-; 11 HIV+)	CRP: 37.1	77	82	0.87	Proportion among different sites, study period not mentioned in the study
	Hospitalized children aged <5 y, with WHO criteria for severe or very severe pneumonia (n included with CRP results = 3357 HIV-, 240 HIV+)						Test: CRP: automated analyzer
[42]	South Africa, referral hospital; hospitalized children aged <5 y with severe pneumonia (n meeting inclusion criteria = 570; 3/97–8/98)	Bacteremic pneumonia (n = 50) and pneumonia of mixed etiology (n = 10) vs viral pneumonia (n = 146) and pneumonia of undefined pneumonia (n = 364)	CRP: 10	92.4	28.2	0.8 (0.83 in HIV+, 0.72 in HIV-)	42.8% HIV+ (recorded in 514/570 children)
			CRP: 40	75.8	59.9		Test: CRP automated analyzer
[43]	Tanzania, 2 hospitals; in- and outpatients with history of/documented fever, all ages (n with available CRP results = 804; 9/2011–5/2014)	Bacterial bloodstream infection (n = 31)	CRP: 10	97	N/A	N/A	Self-reported HIV infection (18.4%); 2 patients with bacterial infection co-infected with *Plasmodium falciparum*; test: CRP automated analyzer
			CRP: 20	94			
			CRP: 40	90			
		Bacterial zoonosis (n = 61)	CRP: 10	87			
			CRP: 20	82			
			CRP: 40	72			

Abbreviations: BC, blood culture; CRP, C-reactive protein; IMCI, integrated management of childhood illness; OPD, outpatient department; POC, point of care; PCT, procalcitonin; ROC AUC, receiver operating characteristics area under the curve.

[a]Units: CRP: mg/L; PCT: µg/L.

Table 2. CRP Values in Different Patient Groups in a Selection of Studies in Malaria-Endemic Settings in Sub-Saharan Africa

Study Group	Study	Country	Study Period	Study Population	No.	Representation	CRP Level[b]	CRP Analysis
Healthy (malaria negative)	[44][a]	Burkina Faso	9–12/2009	Healthy children, 6–23 mo, with Hb >6 g/dL	212	Mean ± SD	1.2 ± 0.1	/
	[45]	The Gambia	10/1993–10/1994	Healthy children with T <37.5°C (mean age, 2.5 y)	40	Median (25th–75th percentiles)	1 (0–2)	ELISA
	[46]	Nigeria	/	Adults, 30–65 y	40	Mean ± SD	3.2 ± 1.2	Agglutination assay
Asymptomatic parasitemia	[44][a]	Burkina Faso	9–12/2009	Healthy children, 6–23 mo, with Hb >6 g/dL	225	Mean ± SD	4.6 ± 0.3	/
	[45]	The Gambia	10/1993–10/1994	Healthy children with T <37.5°C (mean age, 2.7 y)	32	Median (25th–75th percentiles)	11 (3–48)	ELISA
Uncomplicated malaria	[47]	Angola	10/2013–7/2014	Children, ≤16 y	127	Median (IQR)	140 (93)	POC No. 37
	[48]	Sudan	8–12/2010	Pregnant women	32	Median (25th–75th percentiles)	63.0 (22.5–81.7)	POC No. 32
	[49]	Cameroun	7–10/2009	Children, <15 y	31	25th–75th percentiles	0–24	Agglutination assay
	[50]	Gabon	/	Children, 4–15 y	41	Mean ± SD	46 ± 43	Immuno-diffusion assay
	[50]	Gabon	/	Adults, 16–64 y	23	Mean ± SD	49 ± 40	Immuno-diffusion assay
Severe malaria	[48]	Sudan	8–12/2010	Pregnant women	32	Median (25th–75th percentiles)	79.0 (36.2–110.5)	POC No. 32
	[50]	Gabon	/	Children, 0.5–10 y	29	Mean ± SD	137 ± 71	Immuno-diffusion assay
Cerebral malaria	[47]	Angola	10/2013–7/2014	Children, ≤16 y	28	Median (IQR)	116 (101)	POC No. 37
	[6]	Cameroun	7–10/2009	Patients, <15 y	23	25th–75th percentiles	15.0–70	Agglutination assay
	[51]	Uganda	6/2010–12/2013	Children, 18 mo–5 y	79	Median (25th–75th percentiles)	581.3 (334.6–842.7)	Line immune-assay
Malaria with severe anemia	[47]	Angola	10/2013–7/2014	Children, ≤16 y	29	Median (IQR)	153 (56)	POC No. 37
	[51]	Uganda	6/2010–12/2013	Children, 18 mo–5 y	77	Median (25th–75th percentiles)	822.5 (555.4–1103.9)	Line immune-assay

We found 19 studies reporting CRP levels in different types of malaria patients (clinic- or laboratory-based) that either (1) had as main purpose to assess the affect of malaria on CRP levels or (2) reported on such associations for another study purpose but with at least 100 malaria patients included. The table contains the 8 studies that (1) had a clearly defined study population; (2) reported medians, means, or another measure of spread of the CRP values; (3) reported clearly defined CRP units.

Abbreviations: /, not mentioned; CRP, C-reactive protein; ELISA, enzyme-linked immune-sorbent assay; Hb, hemoglobin; IQR, interquartile range; POC, point of care.

[a]All malaria diagnoses through microscopy, except malaria diagnosis through HRP2 concentrations.

[b]Units CRP: mg/L.

reached and exceeded 100 mg/L most of the time in severe/complicated cases. The discriminatory value of CRP for bacterial and viral infections in the presence of malaria co-infection remains little studied. In a small study in febrile children presenting with suspected pneumonia in Mozambique, CRP levels between viral and invasive bacteria groups were significantly different in the absence of *P. falciparum* infection, while this was not the case when *P. falciparum* infection was diagnosed (overlapping CRP distribution) [24]. No study has assessed the PCT profile in malaria-infected individuals in Sub-Saharan Africa.

AVAILABILITY AND COST OF POC CRP & PCT DEVICES

While a range of biomarkers have been evaluated to discriminate bacterial and viral infections, the evidence base and the product development process are clearly most advanced for CRP and PCT [11]. Table 3 gives an overview of POC tests for CRP (n = 44) and PCT (n = 21) that are, to the best of our knowledge, currently on the market and immediately available for clinical research (Supplementary Table 1). Only a few POC tests have been evaluated for user-friendliness and practical performance (interobserver agreement, importance of reading time, optimal threshold) [25,26], and insufficiently so in low-resource settings [15]. Different cassette or strip formats are available for qualitative, semiquantitative, or quantitative detection with Web-based prices that vary between $0.5 and $17 USD depending on the number of tests per batch order (average $3.5 USD for CRP and $6 USD for PCT).

All CRP RDTs can be applied on whole blood, even on small volumes collected by finger prick, and provide results within 5 to 15 minutes. In contrast, PCT RDTs mostly require serum or plasma as the sample type, need higher volumes, and have a longer time to result reading.

Not all so-called "POC" tests can easily be implemented and used in resource-constrained settings, especially when more

expensive and larger analyzers are needed to quantify the biomarker levels. The World Health Organization ASSURED (affordable, sensitive, specific, user-friendly, rapid and robust, equipment-free, and deliverable to end users) criteria provide a good framework to select the POC devices for these settings. According to the target product profile convened by an expert panel, a test that differentiates bacterial from nonbacterial infections in nonsevere patients in low-resource settings should be simple to use, battery-powered or disposable, available for a price below $5 USD, and have >90% sensitivity and >80% specificity [27]. A high sensitivity is important for screening tools to improve early detection of patients who would need antibiotic treatment, while a satisfactory specificity would limit false positivity and lead to a strong reduction of the current "default" antibiotic use.

Tests with different complexities are currently available, ranging from qualitative lateral flow assays to tests providing quantitative results using a small machine. Future studies should evaluate how these perform in terms of reliability, user-friendliness, and feasibility across different health care levels of various settings in Sub-Saharan Africa. CRP is currently in the WHO Essential diagnostic list, but only for use in clinical laboratories, not at the primary care level [28].

The combination of the greater availability of several semiquantitative POC tests and lower cost suggests that for the time being, CRP RDTs without the need for an analyzer or with only a small handheld reader should be given priority in further trials and/or field implementation studies. A new RDT (STANDARD Q Malaria/CRP Duo Test) that simultaneously detects malaria and CRP is currently under field evaluation and is promising for use in malaria-endemic regions (https://www.finddx.org/newsroom/pr-24apr19/).

POTENTIAL STRATEGIES OF USING CRP/PCT POC TESTS IN SUB-SAHARAN AFRICA

At the primary health care level, the proportion of patients with severe disease/requiring antibiotics is presumably small, and most antibiotic prescriptions are probably unnecessary; routine testing of CRP or PCT in febrile patients could be a way forward to reduce the overconsumption of antibiotics. The chosen cutoff should aim first at high sensitivity. A low CRP value—or PCT value—in a non–severely sick patient with no underlying immunosuppression could reassure the health care provider that antibiotics can be safely withheld, with no risk to miss an invasive bacterial infection. Over time, the routine use might convince providers that biomarker levels are low in most febrile patients, justifying restricted use of antibiotics.

At a later stage, an alternative strategy could be explored, entailing targeted testing of only patients with risk factors for severity (ie, breathlessness, high fever, clinical concerns). In a study in Belgium using this type of clinical prediction rule, this reduced the proportion being tested by 80%, without increasing unfavorable outcomes [20]. Similarly, with ePOCT in the Tanzanian study, the CRP/PCT result at a high cutoff value was used to rule in bacterial disease, as this test was targeted toward those with a higher pretest probability based on clinical severity signs. This would, however, require a sound evidence base on which severity indicators to use. Another recommended strategy, as also employed in the trial in Vietnam and in several studies from high-income countries, is to use 2 thresholds, a lower cutoff value to rule out the need of antibiotics and a higher threshold to rule in the need and leave the management to clinician discretion for intermediate values [18].

Table 3. Point-of-Care Tests for CRP and PCT on the Market

Biomarker	Format	On Market	Qualitative	Semiquantitative	Price/Test, $USD	Reading Time, min
CRP	**RDT**	**25**			**0.5–17**	**5–15**
	CRP only		6	17	0.5–6	
	With MxA (viral marker)		1		ND	
	With malaria		1		17	
	Q-rapid test	**17**			**2–6.5**	**2–22**
	RDT with reader	7			2–5	3–22
	RDT with lateral-flow device	10			4–6.5	2–10
PCT	**RDT**	**10**			**0.5–16**	**10–30**
	PCT only		7	3		
	Q-rapid test	**11**			**15**	**13–20**
	RDT with reader	4			Not available	13–15
	RDT with device	7			15	13–20

Rapid diagnostic test format refers to lateral flow rapid tests (strips or cassettes), while the Q-rapid test format refers to rapid point-of-care tests (strip, tube, cassette) that require a reader (handheld, <0.800 kg) or a device (bench model, >0.800 kg) for quantitative (Q) detection (for CRP: 1–200 mg/L; for PCT: 0.1–100 ng/mL). Semiquantitative detection for CRP mostly <10, 10–40, 40–80, and >80 mg/L; and for PCT: <0.5, 0.5–2, 2–10, and >10 ng/mL (depending on 2- or 3-band format). All CRP tests can be used on whole blood (5–25 µL), serum, and plasma, except 5 tests for whole blood only and 2 tests for serum only. All PCT tests can be used on serum and plasma (25–200 µL), and 14 PCT tests can also be used on whole-blood samples (10–20 µL). Data as of July 2019.

Abbreviations: CRP, C-reactive protein; PCT, procalcitonin; RDT, rapid diagnostic test.

The use of biomarkers would probably be different in (referral) hospital settings where the proportion presenting with serious bacterial infection is likely to be high and empiric antibiotic treatment is probably justified for the majority of patients. In this setting, POC testing could predominantly be used to monitor the response to antibiotics, to tailor the duration of antibiotic treatment, or to identify those with an unfavorable evolution (a clinical scenario for which PCT has been better studied in high-income hospitals). Additionally, POC testing could assist in identifying the subgroup of patients for whom antibiotics could be safely withheld or delayed, but in such cases biomarkers and cutoff values with strong excluding power if normal should be required.

BUILDING THE EVIDENCE BASE FOR USE OF CRP/PCT POC TESTS IN SUB-SAHARAN AFRICA

Given the availability of several CRP POC tests, the current priority should be to conduct cluster-randomized clinical trials evaluating CRP-targeted antibiotic prescription in both adults and children in Sub-Saharan Africa, based on the Southeast Asian and East African experience. As several interesting tests for PCT are available as well, it might be relevant to compare the performance of PCT RDTs in parallel. While the use of electronic algorithms is appealing, a simpler approach such as that used in the Southeast Asian trials would be more feasible in many remote, under-resourced settings, at least in the short term. Moreover, there is currently no validated ePOCT software for adults or for febrile children presenting without respiratory symptoms. Before engaging in clinical trials, we recommend that pilot studies be conducted at different health care levels and across Sub-Saharan Africa to address a number of outstanding research gaps and operational issues, including the reference normal values of biomarkers in these populations.

Preliminary work should entail the operational challenges of introducing CRP/PCT testing, as immunochromatography-based lateral flow POC tests have been found to be slightly less accurate when applied in field settings/at the point of care compared with a controlled laboratory environment [29]. As CRP testing mediates its effect on antibiotic consumption via behavioral/prescription changes, its use should be integrated into meaningful clinical guidelines and algorithms. To ensure a good uptake by health care providers, their perceptions on the current practices (guidelines used, antibiotic prescription patterns, indications for hospitalization and referral, patient expectations) and the acceptability and potential use of a POC CRP testing to guide antibiotic prescription would be critical pre-trial information [30]. The low adherence to CRP-guided antibiotic prescription in the trials in Southeast Asia, with a relatively high number of patients receiving antibiotics despite low CRP values, underscores this point [31]. When malaria RDTs were introduced, it similarly took a long time before these were fully adopted by health care providers [32]. Such studies should also integrate the patient perspective, expectations, and practices in terms of antibiotic use. Additionally, economic studies should also explore the potential health system implications of such tests and how they translate in terms of cost-effectiveness. Such studies should integrate the fact that, compared with diagnostic tests, antibiotics are cheap. This provides a disincentive for testing and an incentive for empiric treatment.

Second, more data on the effect of malaria infection on CRP and PCT levels across different levels of malaria endemicity are needed. In settings with very high malaria endemicity (mainly in West and Central Africa), it might be impossible for a substantial number of patients with high malaria-related CRP/PCT levels to rule out a bacterial infection. In such settings, the value of CRP/PCT testing would be limited, making CRP/PCT biomarker clinical trials futile, and other biomarkers, including some targeting viral biomarkers, might have to be explored. In terms of CRP/PCT thresholds, it would be prudent not to extrapolate findings from other continents and East Africa to the rest of Africa, where the normal CRP/PCT values in the healthy population might be different. At least some pilot data should be collected to confirm thresholds used in other settings to discriminate bacterial from nonbacterial infections in West/Central Africa as well, and how malaria endemicity interplays with this. For countries with seasonal malaria transmission, studies should also explore the impact of malaria infection in different seasons and whether algorithms should tailored to the season. Also, the discriminative value of biomarkers has to be carefully explored in groups of patients presenting with underlying conditions that notoriously impact CRP levels, such as HIV infection, malnutrition, pregnancy, or extreme ages (neonates, elderly).

In particular, studies should also be conducted in areas with a high burden of HIV infection. In some studies in Eastern and Southern Africa, disseminated tuberculosis and fungal infections have been found to be common in adults presenting with fever at the hospital level [33, 34]. In such settings, the effect of tuberculosis and/or HIV on CRP/PCT levels should be assessed, and diagnostic algorithms should also evaluate and integrate a diagnostic workup for HIV & HIV-associated opportunistic infections.

More data on the prognostic performance of CRP/PCT levels should be collected as well. High biomarker concentrations at baseline might indicate which patients are at higher risk of nonresponse or death. Based on this information, closer patient follow-up or referral to a higher health care level could be better indicated than immediate blind administration of antibiotics in primary care. While the value of CRP/PCT to predict mortality in Sub-Saharan febrile patients has generally been limited [24, 35], other markers such as sTREM-1 have performed better [36]. Also, the prognostic value of CRP/PCT levels to predict clinical failure remains largely unexplored.

Finally, as the clinical outcome in bacterial infections ultimately depends on appropriate antibiotic prescription covering the causative pathogen, more (context-specific) information on the etiology of bacterial infections in different clinical syndromes and antibiotic susceptibility patterns is also highly needed for Sub-Saharan Africa. Also, the development of novel pathogen-specific POC assays is high on the research agenda for tropical settings, and substantial progress has been made for the diagnosis of dengue, sleeping sickness, and visceral leishmaniasis, to name a few. Integrating these assays, wherever geographically relevant, in sound clinical algorithms could be another way to contribute to reducing indiscriminate antibiotic use, in addition to accelerating adequate diagnosis.

In conclusion, the evidence base for POC use of bacterial biomarkers to guide antibiotic prescription in Sub-Saharan Africa should be urgently built in a concerted effort, after preliminary promising experiences in some other tropical settings. Pending the development and evaluation of other POC tests, CRP-based tests should be evaluated first because these are immediately available at a reasonable price. Before engaging in clinical trials to assess clinical impact, pilot exploratory studies should be conducted to address key knowledge gaps in standard reference values at the population level and the possible influence of malaria coinfection or other underlying conditions. Given the paucity of data in these regions compared with other areas, such studies should be conducted, with priority in West and Central Africa. As the vast majority of antibiotics are prescribed in the outpatient department, such services should be prioritized in future research.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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