BMJ Global Health

The good and the bad: using C reactive protein to distinguish bacterial from non-bacterial infection among febrile patients in low-resource settings

Camille Escadafal,[1] Sandra Incardona,[1] B Leticia Fernandez-Carballo,[1] Sabine Dittrich [1,2]

To cite: Escadafal C, Incardona S, Fernandez-Carballo BL, *et al*. The good and the bad: using C reactive protein to distinguish bacterial from non-bacterial infection among febrile patients in low-resource settings. *BMJ Global Health* 2020;**5**:e002396. doi:10.1136/bmjgh-2020-002396

Handling editor Seye Abimbola

Received 11 February 2020
Revised 14 April 2020
Accepted 17 April 2020

[1]Foundation for Innovative New Diagnostics (FIND), Geneva, Switzerland
[2]Nuffield Department of Medicine, University of Oxford, Oxford, UK

Correspondence to
Dr Sabine Dittrich;
sabine.dittrich@finddx.org

ABSTRACT

C reactive protein (CRP), a marker for the presence of an inflammatory process, is the most extensively studied marker for distinguishing bacterial from non-bacterial infections in febrile patients. A point-of-care test for bacterial infections would be of particular use in low-resource settings where other laboratory diagnostics are not always available, antimicrobial resistance rates are high and bacterial infections such as pneumonia are a leading cause of death. This document summarises evidence on CRP testing for bacterial infections in low-income and middle-income countries (LMICs). With a push for universal health coverage and prevention of antimicrobial resistance, it is important to understand if CRP might be able to do the job. The use of CRP polarised the global health community and the aim of this document is to summarise the 'good and the bad' of CRP in multiple settings in LMICs. In brief, the literature that was reviewed suggests that CRP testing may be beneficial in low-resource settings to improve rational antibiotic use for febrile patients, but the positive predictive value is insufficient to allow it to be used alone as a single tool. CRP testing may be best used as part of a panel of diagnostic tests and algorithms. Further studies in low-resource settings, particularly with regard to impact on antibiotic prescribing and cost-effectiveness of CRP testing, are warranted.

Summary box

- C reactive protein (CRP) testing may be beneficial in low-resource settings to improve rational antibiotic use for febrile patients, but the positive predictive value is insufficient to allow it to be used alone as a single tool.
- More extensive cost-effectiveness data across multiple geographies are needed.
- The cut-off used for CRP across studies varies widely and makes it difficult to select a universal cut-off threshold for diagnostic use.

BACKGROUND

The management of febrile patients is a major problem in lower resource areas where access to diagnostics is limited. Fever symptoms can result from a variety of different infections, including parasites like malaria, bacterial or viral pathogens, which are difficult to distinguish from one another based on clinical presentation alone. While the widespread use of rapid diagnostic tests (RDTs) for malaria has transformed the management of fevers in tropical settings, it has been accompanied by an increase in antibiotic prescriptions, since in the absence of further diagnostics, malaria-negative patients are generally treated for bacterial infection.[1 2] Unnecessary use of antibiotics is considered to be a major driver of development of antimicrobial resistance, an increasingly serious threat to global public health.

A rapid point-of-care test (POCT) to detect bacterial infection would be of particular use in resource-constrained settings, where other laboratory diagnostics such as blood culture and radiology are not always available, antimicrobial resistance rates are high, and bacterial infections such as pneumonia are a leading cause of death. Various potential biomarkers have been evaluated, of which C reactive protein (CRP), a marker for the presence of an inflammatory process, is the most extensively studied.[3] A Cochrane review from 2014 focusing on acute non-severe respiratory infections in primary care concluded that CRP was the only sufficiently accurate biomarker for which POCTs are available that could safely and effectively reduce the prescribing of antibiotics.[4] However, the majority of studies evaluating the diagnostic performance of CRP have taken place in high-resource settings. This document summarises existing data in low-income and middle-income countries

(LMICs), and discusses the potential utility of CRP testing in this setting. The practical aim of this work is to help support communication and informed discussions among the global health community by showing the 'good and the bad' in a relatively unbiased manner. This work does not aim to be a systematic review but a pragmatic document that can help a broad community to start off discussions with a similar knowledge base. Data were gathered based on an unstructured search of the PubMed database for studies on CRP in LMICs, published before June 2019.

DIAGNOSTIC PERFORMANCE OF CRP FOR DISTINGUISHING BACTERIAL INFECTIONS

Studies assessing the correlation between elevated CRP levels with presence of bacterial infections and the diagnostic accuracy of CRP for distinguishing between bacterial and non-bacterial infections in LMICs are detailed in table 1. Of seven studies that assessed the correlation between CRP levels and presence of bacterial infection, all seven found that CRP levels were significantly higher in patients with confirmed bacterial infections versus those without.[5–13]

The performance of CRP for distinguishing bacterial from non-bacterial infections varied considerably across studies with areas under the receiver operating curve (AUROC) ranging from 0.62 to 0.91. The high variability in performance across studies may be due to a number of factors, including differences in the clinical presentation of the population studied, the degree of patient severity, the definition used for bacterial infections (the gold standard used; table 1), geographical location of the study, the age of the patients, the specific bacterial pathogens causing infection, concomitant infections and presence of other conditions causing elevated CRP.

Most of the studies identified were performed in African countries (6/8) with children under 5 years of age (6/10), facilitating comparison between studies. Studies carried out with inpatients, independently of the gold standard used for bacterial infection definition, presented high performances (0.72–0.87) except for the study with severe acute malnourished children, which reported an AUROC of 0.66. However, when looking at outpatients, two studies carried out in Tanzania in children and one study in Cambodia in individual 7–49 years reported very different performances. One study which used positive blood culture as gold standard reported a high AUROC of 0.83 and 74.2/77.8 sensitivity/specificity. However, the two other studies, which used a wider definition of bacterial infection (ie, the gold standard for bacterial infection includes microbiological results and/or symptoms in addition to positive cultures), reported lower performances: AUROC of 0.62, 44.6/78.5 sensitivity/specificity and 52.5/84.3 sensitivity/specificity, respectively. In line with this, Lubell *et al* described that the fact of being admitted as an inpatient had an independent effect of elevated levels of CRP (p=0.006).[9]

When looking specifically at HIV-positive and HIV-negative patients, Higdon *et al* found that patients who were HIV positive were more likely to have CRP levels of ≥40 mg/L, and within this group, older children and those with more severe pneumonia were also more likely to have higher CRP levels.[7] Among HIV-negative patients, those from the African study sites were more likely to have CRP levels of ≥40 mg/L than those from the Asian sites.[7]

Three studies evaluated a CRP cut-off level of approximately 20 mg/L.[6 9 14] Three studies assessed a higher cut-off of approximately 40 mg/L.[6 7 10] Five studies calculated the optimal CRP cut-off for distinguishing bacterial from non-bacterial infections. Of these, Hildenwall *et al* and Mueller *et al* proposed a cut-off of 19 and 21.3 mg/L, respectively,[11 14] while Mahende *et al*, Higdon *et al*, and Wangrangsimakul *et al* proposed higher cut-offs of 37.3, 37.1 and 36 mg/L, respectively.[7 10 13]

The method used to detect CRP differed across studies, with the majority of studies using quantitative CRP tests. A study by Phommasone *et al* was the only study to assess commercially available lateral flow CRP tests (DTS233 (Creative Diagnostics, USA), WD-23 (Assure Tech, China) and bioNexia CRPplus (bioMerieux, France)), in comparison to the Nycocard CRP test and reader.[15] At a cut-off of 10 mg/L, all three tests had high sensitivity (ranging from 87% to 98%) and specificity (91% to 98%) in patients with fever in rural Laos, suggesting that lateral flow tests are a viable option in LMIC settings.

CRP levels have been shown to be elevated in patients with malaria, as well as those with bacterial infections (consequently, some studies excluded patients with malaria from their analyses). Studies that assessed the correlation between elevated CRP and malaria infection are detailed in table 2. All five studies found that CRP levels were significantly higher in patients with malaria versus those without.[9 10 16–18] In Tanzania, 80% of children aged 2–59 months presenting with malaria had CRP levels >40 mg/L, the higher of the commonly used CRP cut-offs.[10] Consistent with this, Lubell *et al* found no significant difference in CRP levels between patients with bacterial infections and patients with malaria.[9] The confounding effect of malaria seems to be limited to clinical malaria, as Peto *et al* found that in the general population, only 7.6% of people who tested positive for subclinical malaria had a CRP of >10 mg/L.[17]

Of note, CRP has also been widely evaluated as a predictor for serious infections, and serious bacterial infections (SBI) in particular, however such studies were essentially conducted in high-income countries. For example, CRP in combination with vital signs and objective symptoms measurements achieved a sensitivity of 97.1% (95% CI 94.3% to 98.7%) for identifying children aged 1 month to 16 years with serious infections in clinics and emergency departments in Belgium, classifying them into groups of low, intermediate and high risk with CRP levels of <20, 20–75 and >75 mg/L, respectively.[19] Other studies in the Netherlands and Iran report a receiver operator characteristic curve area of 0.77 and 0.74 for

Table 1 Studies assessing correlation between CRP levels and bacterial infection and diagnostic performance of CRP in LMICs

Study	Country	Age group	Inpatients/ Outpatients	Disease characteristics	Number of patients	Gold standard for bacterial infection	CRP test	Diagnostic performance				Correlation with bacterial infection
								AUROC (95% CI)	Cut-off*	Sensitivity†	Specificity†	
Studies in Africa												
Carrol *et al*[5]	Malawi	2 months to 16 years	Inpatients	Pneumonia or meningitis	377	Culture, microscopy, antigen or PCR from blood, cerebrospinal fluid and/or lung aspirate	Beckman Coulter image immunochemistry system	0.81 (0.73 to 0.89) for serious bacterial	N/A	N/A	N/A	Median CRP values were significantly higher in HIV-negative and HIV-positive patients with serious bacterial infections compared with those without (253 vs 127 mg/L, p=0.0005 and 291 vs 135 mg/L, p=0.0005, respectively).
Díez-Padrisa *et al*[6]	Mozambique	<5 years	Inpatients	Clinical severe pneumonia (no malaria)	586	Blood culture	Immunoturbidimetric assay, ADVIA Chemisty CRP 2 (Siemens)	0.79	20.9 38	95 85	45 57	CRP levels were higher in those with positive bacterial culture vs those with negative bacterial culture (177.65 mg/L vs 26.5 mg/L, p<0.001). Median CRP levels (>18.5 to ≤97.9) were predictive of bacterial culture positivity (OR 15.31, 95% CI 1.91 to 122.45, p=0.01).
Hildenwall *et al*[14]	Tanzania	3 months to 5 years	Outpatients	Fever (malaria negative)	428	Positive urine or blood culture or symptoms suggestive pneumonia as defined in the IMCI	Afinion AS100 Analyzer (Axis-Shield)	0.62	19	44.6 (33.2 to 56.6)	78.5 (73.0 to 83.1)	Of those with CRP <20 mg/L (n=256, 59.8%), 84% had no signs of bacterial infection. Of those with CRP >80 mg/L (n=33, 7.7%), 36.7% were positive for bacterial infection.

Continued

Table 1 Continued

Study	Country	Age group	Inpatients/ Outpatients	Disease characteristics	Number of patients	Gold standard for bacterial infection	CRP test	Diagnostic performance				Correlation with bacterial infection
								AUROC (95% CI)	Cut-off*	Sensitivity†	Specificity†	
Huang *et al*[8]	Gambia and Kenya	2 months to 5 years	Inpatients	Pneumonia	Pneumonia: n=204 Matched controls: n=186	Blood culture or radiograph	ELISA (R&D Systems)	0.72 (0.59 to 0.86)	150, ≥200	70.5	56.1	Median CRP plasma concentration was significantly higher in those with probable bacterial infection (positive blood culture or radiograph) vs those with probable viral infection (negative radiograph and low WBC) (283 vs 175 µg/mL, p<0.001).
Mahende *et al*[10]	Tanzania	2 months to 5 years	Outpatients	Fever	691	Blood culture	Cobas c111 (Roche Diagnostics)	0.83	37.3	74.2	77.8	
Page *et al*[12]	Niger	6 months to 5 years	Inpatients	Severe acute malnutrition	256	Blood, urine, stool culture and radiograph	NycoCard Reader (Abott)	0.66 (0.59 to 0.79) all patients, 0.72 (0.63 to 0.80) malaria-negative patients	47.5 13	46.5 81.1	80.4 58.7	Median CRP levels were significantly higher in those with pneumonia (radiograph positive) vs those with no proved bacterial infection (40.8 vs 12 mg/L, p=0.0014).
Studies in South-East Asia												
Mueller *et al*[11]	Cambodia	7–49 years	Outpatients	Acute fever	Febrile patients: 1193, Matched controls: 282	Microbiological results including culture, PCR, ELISA, RDTs	Latex bead immune-turbidimetric method adapted on Integra 400 (Roche Diagnostics)	NA	21.3	52.5	84.3	
Wangrangsimakul *et al*[13]	Thailand	≥15 years	Inpatients and outpatients	Acute fever	231	Microbiological results including culture, PCR, ELISA, RDTs	NycoCard Reader (Abott, USA)	0.91 (0.85 to 0.96)	36	88.9 (79.3 to 95.1)	86.4 (65.1 to 97.1)	
Lubell *et al*[9]	Cambodia, Laos, Thailand	5–49 years	Inpatients and outpatients	Acute fever	1372	Microbiological results including culture, antigen detection, PCR and ELISA for JEV IgM ELISA	NycoCard Reader (Abott, USA)	0.89 (0.8 to 0.97)	10 20	95 (92 to 97) 86 (82 to 88)	49 (46 to 53) 67 (63 to 71)	CRP levels were significantly lower in patients with a viral infection than other infections (p<0.0001 in all comparisons across countries).
Studies in multiple settings												

Continued

Table 1 Continued

Study	Country	Age group	Inpatients/ Outpatients	Disease characteristics	Number of patients	Gold standard for bacterial infection	CRP test	Diagnostic performance				Correlation with bacterial infection
								AUROC (95% CI)	Cut-off*	Sensitivity†	Specificity†	
Higdon *et al*[7]	Bangladesh, Gambia, Kenya, Mali, South Africa, Thailand and Zambia	<5 years	Inpatients	Pneumonia	Pneumonia: n=3597, controls: n=822	Blood culture or positive lung aspirate or pleural fluid culture or PCR‡	CRP Gen3 or CRP VARIO (Roche Diagnostics)	0.87	37.1	77 (69 to 84)	82 (78 to 85)	77% of HIV-negative cases with confirmed bacterial pneumonia vs 17% (n=556) cases with RSV pneumonia had CRP ≥40 mg/L (p<0.001).

*mg/L.
†%; 95% CI.
‡Compared with 'RSV pneumonia'—nasopharyngeal/oropharyngeal or induced sputum PCR-positive without confirmed/suspected bacterial pneumonia.
AUROC, area under the receiver operator characteristic curve; CRP, C reactive protein; IMCI, integrated management of childhood illness; LMICs, low-income and middle-income countries; N/A, not available; RDT, rapid diagnostic test; RSV, respiratory syncytial virus; WBC, white blood cell count.

CRP predicting SBI in children aged 1 month to 16 years, and infants aged 3 months or less, respectively.[20 21] A cluster randomised controlled trial in Belgium furthermore proposes the use of CRP POCTs as a tool to rule out the need of hospital referral for children aged 1 month to 16 years with CRP levels <5 mg/L at primary healthcare level.[22]

REDUCTION IN ANTIBIOTIC PRESCRIPTION DUE TO CRP TESTING

Only two prospective studies assessed the impact of CRP testing as a standalone tool on antibiotic prescriptions in LMICs (table 3), in combination with clinical judgement; both took place in South-East Asia. Althaus *et al* assessed use of CRP cut-offs of 20 mg/L and CRP of 40 mg/L to guide antibiotic prescription in adults and children aged ≥1 year attending primary care and presenting with fever.[23] While the proportion of patients receiving antibiotics by the fifth day after the initial visit was slightly higher in the group for whom no CRP testing was performed compared with the two CRP groups, only the difference between the 40 mg/L cut-off and the control group was statistically significant. Do *et al* found that a significantly lower percentage of patients with non-severe acute respiratory tract infection who were diagnosed using CRP testing were prescribed antibiotics within 14 days, compared with those in whom no CRP testing was performed.[24] This study used a CRP cut-off of 20 mg/L for patients aged 6–65 years, and a cut-off of 10 mg/L for those aged 1–5 years.

In the study by Althaus *et al*, a higher proportion of patients with elevated CRP concentration were prescribed an antibiotic in the CRP groups versus the control group, suggesting that treatment was targeted.[23] The limited impact of CRP testing on antibiotic prescriptions in this study was therefore unlikely to be due to non-adherence to the test results. However, in the study by Do *et al*, the majority of patients in Vietnam who received immediate antibiotic prescriptions had CRP measurements of <10 mg/L, suggesting that healthcare professionals did not always adhere to test results.[24]

There was a considerable difference between the percentages of patients prescribed antibiotics in the control groups of the studies by Althaus *et al* and Do *et al* (39% vs 78%).[23 24] It is possible that healthcare professionals in the study by Althaus *et al* were more cautious with prescribing of antibiotics due to their participation in the study. However, the Althaus *et al* data are consistent with a retrospective study assessing antibiotic use in 97 230 patients with fever in primary care health centres in Thailand, in which only 46.9% were prescribed antibiotics.[2] Given the differences between Althaus *et al* and Do *et al* in terms of adherence to test results and control groups, further studies are required to better elucidate the impact of CRP testing on reduction in antibiotic prescriptions.

Table 2 Studies assessing correlation between CRP levels and malaria

Study	Country	Age group	Disease characteristics	Number of patients	CRP test	Correlation with malaria infection
Studies in Africa						
Mahende *et al*[10]	Tanzania	2–59 months	Fever	691	Cobas Indianapolis, Indiana, USA	▶ 45 of 56 (80.4%) patients with malaria had elevated CRP levels of >40 mg/L, although they also had low WBC and ANC counts.
Pelkonen *et al*[16]	Angola	≤16 years	Suspected malaria	346	QuikRead 101 (Orion Diagnostica, Finland)	▶ Median CRP was significantly higher in those with malaria vs those without (140 mg/L (IQR 88) vs 69 mg/L (IQR 129), p<0.01).
Sarfo *et al*[18]	Ghana	≤15 years	Fever	541	CRP Test Kit CRP-K10 (Diagnostik Nord, Germany)	▶ 52.2% of those with CRP 10–30 mg/L, and 53.0% of those with CRP >30 mg/L were positive for malaria parasitaemia (ORs 14.2 (95% CI 4.2 to 48.1) and 14.7 (95% CI 4.4 to 48.3) vs those with CRP <10 mg/L). ▶ Increased CRP levels were strongly associated with clinical malaria, defined as parasitaemia >5000 parasites/µL (OR 16.5 (95% CI 2.2 to 121), p<0.001). ▶ In a multivariate analysis, patients whose CRP level increased by >10 mg/L had more than an eightfold likelihood for positive parasitaemia (adjusted OR 8.7 (95% CI 2.5 to 30.5), p<0.001).
Studies in South-East Asia						
Lubell *et al*[9]	Cambodia, Laos, Myanmar	5–49 years	Acute undifferentiated fever	1372	NycoCard Reader (Abott, USA)	▶ CRP levels were significantly higher in malaria infections compared with viral infections (p<0.001). ▶ There was no significant difference in CRP levels between bacterial infections and malaria (p=0.15); the AUROC for discriminating between malaria and bacterial infections was 0.54 (95% CI 0.49 to 0.6).
Peto *et al*[17]	Cambodia	>6 months	General population	Parasitaemia: n=328 Controls: n=328	Solid phase sandwich ELISA	▶ Plasma CRP concentrations were higher in those with malaria compared with matched controls (p=0.025). ▶ 7.6% of malaria-positive cases had CRP of >10 mg/L vs 2.1% of matched controls (p<0.001); 17.3% of malaria-positive cases had CRP of >3 mg/L vs 10.4% of matched controls. ▶ There was a significant association between parasite count and CRP, which remained significant after controlling for fever (p<0.001).

ANC, absolute neutrophil count; AUROC, area under the receiver operator characteristic curve; CRP, C reactive protein; WBC, white blood cell count.

Table 3 Studies assessing reduction in antibiotic prescriptions associated with CRP testing in LMICs

Study	Country	Age group	Disease characteristics	Number of patients	CRP test	Reduction in antibiotic prescriptions	Targeted prescribing
Studies in South-East Asia							
Althaus *et al*[23]	Thailand and Myanmar	≥1 year	Fever	2410	NycoCard Reader (Abott, USA)	► 290 (36%) of 803 patients for whom a CRP cut-off of 20 mg/L was used to guide prescription and 275 (34%) of 800 for whom a CRP cut-off of 40 mg/L was used were prescribed an antibiotic by day 5, compared with 318 (39%) of 807 patients in whom CRP testing was not performed. ► The reduction in antibiotic prescriptions up to day 5 in the CRP 20 mg/mL group was non-significant compared with the control group (risk difference –3.3%, 95% CI –8.0 to 1.4; adjusted OR 0.86, 95% CI 0.70 to 1.06). ► The reduction in antibiotic prescriptions up to day 5 in the CRP 40 mg/mL group was statistically significant (risk difference –5.0%, 95% CI –9.7 to –0.3, adjusted OR 0.80, 95% CI 0.65 to 0.98).	► Compared with control, a higher proportion of patients with elevated CRP were prescribed an antibiotic in the CRP 20 mg/L group (74% (153/206) vs 48% (103/214), p<0.0001) and the CRP 40 mg/L group (78% (92/118) vs 48% (51/107), p<0.0001). ► Conversely, a lower proportion of patients with low CRP concentrations, were prescribed an antibiotic in the CRP 20 mg/L group (20% (119/595) vs 30% (134/445), p<0.0001) and the CRP 40 mg/L group (22% (153/682) vs 34% (186/552), p<0.0001). ► Compared with control more patients in the CRP 20 mg/L (79% vs 63%) and 40 mg/L groups (78% vs 63%) had antibiotics correctly prescribed, assuming those cut-offs were indicative of need for antibiotics.
Do *et al*[24]	Vietnam	1–65 years	Acute respiratory tract infection	2036	NycoCard Reader (Abott, USA)	► The number of patients who used antibiotics within 14 days was 581 (64%) of 902 patients in those in whom CRP testing was performed vs 738 (78%) of 947 patients in the control group, representing a statistically significant reduction (OR 0.49, 95% CI 0.40 to 0.61; p<0.0001).	► Of patients with immediate antibiotic prescriptions, 75% (758/1017) had CRP measurements of <10 mg/L, 133 (13%) of 10–20 mg/L, 101 (10%) of 21–50 mg/L and 25 (2%) of >50 mg/L.

CRP, C reactive protein; LMICs, low-income and middle-income countries.

Table 4 Studies assessing cost-effectiveness of CRP testing in LMICs

Study	Country	Assumptions	Results
Studies in South-East Asia			
Lubell *et al*[27]	Laos	► Patients with CRP >20 mg/L or positive scrub typhus RDT are prescribed an antibiotic; patients with positive dengue RDT do not receive antibiotics. ► If tests are negative, antibiotics are prescribed at a rate of 38% ► Mean cost of CRP test was US$1.5, mean cost of a course of antibiotics was US$0.5. ► Mortality rate for bacterial infections without appropriate treatment was 1% (each death represents a mean loss of 45 life-years). ► Self-limiting/treated infections have a disability weight of 0.053.	► CRP RDT prevented 0.017 DALYs. ► Median ICER for CRP RDT was US$94. ► CRP testing is likely to be cost-effective even at low willingness-to-pay thresholds. ► The CRP tests was approximately 80% likely to be cost-effective at a willingness-to-pay threshold of US$1400 (approximating the Laos GDP/capita).
Lubell *et al*[29]	Vietnam	► Unit cost of US$0.5 to US$3 per CRP test. ► Economic cost of AMR of US$0 to US$14 per full course. ► No difference in clinical outcomes between CRP-tested and non-CRP-tested patients, benefits relate only to the societal costs of AMR averted due to lower prescribing.	► At an AMR cost of US$4.1 and unit costs of US$0.5, CRP testing has a positive net-benefit if adherence to test results is >70%. ► At an AMR cost of US$4.1 and unit costs of US$1, CRP testing has a positive net-benefit if adherence to test results is ≥80%. ► A higher AMR cost of US$14.1 implies a positive net-benefit if adherence is >60%, even at US$3 per unit.

AMR, antimicrobial resistance; CRP, C reactive protein; DALY, disability-adjusted life-years; GDP, gross domestic product; ICER, incremental cost-effectiveness ratio; LMICs, low-income and middle-income countries; RDT, rapid diagnostic test.

Interestingly, two studies in Tanzania have used CRP testing as part of electronical decision algorithms to guide the healthcare staff decisions on the use of antibiotics and hospital referral for management of children aged 2–59 months in a primary healthcare setting. These algorithms combined CRP blood levels at a cut-off of 80 mg/L with other POCTs and/or clinical features, and allowed to reduce antibiotics use by up to 83.4% while at the same time improving clinical outcomes, in comparison with standard recommended clinical algorithms.[25 26]

COST-EFFECTIVENESS OF CRP TESTING

Two studies have evaluated cost-effectiveness of CRP diagnostics in LMICs (table 4). In a model using data from the study of CRP testing in febrile patients in rural Laos,[9] the NycoCard analyser was shown to avert 0.017 disability-adjusted life-years, with a median incremental cost-effectiveness ratio (ICER) of US$94, at a cut-off of 20 mg/L.[27] This model assumed that patients were tested for CRP, dengue fever and scrub typhus, and that in patients who tested negative, antibiotics were prescribed randomly at a rate of 38%. The analysis suggested that CRP testing is likely to be cost-effective even at low willingness-to-pay thresholds.

A model using data from the study in patients with acute respiratory infection in Vietnam[28] showed that CRP testing at a cut-off of 20 mg/L (10 mg/L in those aged 1–5 years) can be cost-beneficial providing that adherence to test results is high (>70% for a unit cost of US$0.5 and >80% for a unit cost of US$1).[29] This assumed an economic cost of antimicrobial resistance of US$4.1, based on published modelling data from Thailand.[30] A higher cost of AMR led to cost-benefits of CRP testing at lower adherence and higher unit cost. Notably, this study assumed no difference in clinical outcomes between CRP-tested and non-tested patients, thus it may represent a conservative estimate.

Findings from the two studies detailed above are generally consistent with studies in higher resource settings, although willingness-to-pay thresholds used in high-income setting models are considerably higher.[31–33] In Norway and Sweden, CRP POCT was associated with a cost per quality-adjusted life-year (QALY) gained of €9391.[31] At a willingness-to-pay threshold of €30 000, there was a 70% probability of CRP being cost-effective. In the UK, CRP POCT in adults with acute respiratory tract infection had ICERs of £19 705 per QALY gained and £16.07 per antibiotic prescription avoided. At a threshold of £20 000 per QALY, the probability of CRP POCT being cost-effective was 0.49 (0.84 in those with lower respiratory tract infection).[32]

More studies would be needed to determine the optimal cost of a CRP rapid test in LMICs, which would obviously vary by country. The two published studies in Laos and Vietnam assume costs ranging from US$0.5 to US$3 per test which seem to be reasonably low and still

Table 5 Overview of the good and the bad

	'The good' (advantages)	'The bad' (disadvantages)
Viability as a marker of bacterial infection	► Correlation between elevated CRP levels and presence of bacterial infection is consistent across studies.	► CRP levels are also elevated in patients with malaria, hence identifying malaria/bacterial co-infections is challenging. ► CRP performance (AUROC, sensitivities and specificities) is variable across studies. ► A universally applicable cut-off point is difficult to determine.
Impact on antibiotic prescribing	► Studies show a reduction in overall number of antibiotic prescriptions with CRP testing.	► Reductions in antibiotic prescriptions were only significant at higher cut-off. ► Number of studies is limited.
Cost-effectiveness	► CRP testing is cost-effective when test results are adhered to.	► Adherence to CRP test results has been variable in studies assessing impact on antibiotic prescription. ► Number of cost-effectiveness studies in low-resource settings is limited.

CRP, C reactive protein.

compatible with the manufacturers' capacities, assuming that current costs of approximately US$3 per test could be driven down if demand increases or if manufacturers accept selling for lower prices in LMICs while making more profit with higher prices in high-income countries.

CONCLUSION

While a significant correlation between elevated CRP levels and the presence of bacterial infections in febrile patients in low-resource settings has been confirmed across several studies, reported sensitivity and specificity values have varied considerably. As such, the optimal cut-off point for diagnostic utility in these settings is difficult to determine. A conservative cut-off of ~20 mg/L would limit the number of false negatives, ensuring that patients with serious bacterial infections are appropriately treated, but the potential impact on antibiotic prescribing would be reduced, since more patients would receive antibiotics unnecessarily. In one of the two studies assessing the impact of CRP testing on antibiotic prescriptions in low-resource settings, only the 40 mg/L cut-off was sufficient to significantly reduce the number of prescriptions[23]; however, the second study demonstrated a significant reduction at a cut-off of 20 mg/L (10 mg/L for the youngest patients).[24] Several studies have demonstrated that CRP levels are also elevated in patients with malaria. In malaria-endemic settings, CRP testing should be performed in conjunction with a malaria RDT, to compensate for the confounding effect of malaria and to limit overtreatment of both conditions. CRP testing has been shown to be cost-effective in high-resource settings, but data in LMICs are limited. Two modelling studies have suggested potential cost benefits, but notably, in one study, the level of adherence to CRP test results had considerable impact on the cost-effectiveness of CRP testing.[29] CRP testing may therefore be most beneficial as part of a diagnostic algorithm that includes test results and clinical symptoms as part of an integrated approach, giving healthcare professionals more confidence in the recommended treatment.

In summary, the use of CRP has advantages and disadvantages that need to be evaluated carefully for each specific use case (table 5). The collation of this evidence, both good and bad, can hopefully facilitate the discussions between researchers and global health decision makers bringing a little objectivity to what can be a much polarised discussion.

Twitter Sabine Dittrich @sabinedittrich

Contributors SD developed the methodology. CE, SI, BLF-C supported data collection and drafted the first draft. SD provided conceptional direction. All authors have read and approved the final draft.

Funding Medical writing assistance to identify and compile the data as well as editorial support, under the direction of the authors, was provided by Rachel Wright, PhD, funded by Foundation for Innovative New Diagnostics (FIND), according to Good Publication Practice guidelines.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data are available via public databases.

ORCID iD
Sabine Dittrich http://orcid.org/0000-0002-4522-2788

REFERENCES

1 Hopkins H, Bruxvoort KJ, Cairns ME, *et al*. Impact of introduction of rapid diagnostic tests for malaria on antibiotic prescribing: analysis of observational and randomised studies in public and private healthcare settings. *BMJ* 2017;356:j1054.
2 Greer RC, Intralawan D, Mukaka M, *et al*. Retrospective review of the management of acute infections and the indications for antibiotic prescription in primary care in northern Thailand. *BMJ Open* 2018;8:e022250.

3 Kapasi AJ, Dittrich S, González IJ, *et al*. Host biomarkers for distinguishing bacterial from non-bacterial causes of acute febrile illness: a comprehensive review. *PLoS One* 2016;11:e0160278.
4 Aabenhus R, Jensen J-US, Jørgensen KJ, *et al*. Biomarkers as point-of-care tests to guide prescription of antibiotics in patients with acute respiratory infections in primary care. *Cochrane Database Syst Rev* 2014;11:CD010130.
5 Carrol ED, Mankhambo LA, Jeffers G, *et al*. The diagnostic and prognostic accuracy of five markers of serious bacterial infection in Malawian children with signs of severe infection. *PLoS One* 2009;4:e6621.
6 Díez-Padrisa N, Bassat Q, Morais L, *et al*. Procalcitonin and C-reactive protein as predictors of blood culture positivity among hospitalised children with severe pneumonia in Mozambique. *Trop Med Int Health* 2012;17:1100–7.
7 Higdon MM, Le T, O'Brien KL, *et al*. Association of C-Reactive Protein With Bacterial and Respiratory Syncytial Virus-Associated Pneumonia Among Children Aged <5 Years in the PERCH Study. *Clin Infect Dis* 2017;64:S378–86.
8 Huang H, Ideh RC, Gitau E, *et al*. Discovery and validation of biomarkers to guide clinical management of pneumonia in African children. *Clin Infect Dis* 2014;58:1707–15.
9 Lubell Y, Blacksell SD, Dunachie S, *et al*. Performance of C-reactive protein and procalcitonin to distinguish viral from bacterial and malarial causes of fever in Southeast Asia. *BMC Infect Dis* 2015;15:511.
10 Mahende C, Ngasala B, Lusingu J, *et al*. Profile of C-reactive protein, white cells and neutrophil populations in febrile children from rural north-eastern Tanzania. *Pan Afr Med J* 2017;26:51.
11 Mueller TC, Siv S, Khim N, *et al*. Acute undifferentiated febrile illness in rural Cambodia: a 3-year prospective observational study. *PLoS One* 2014;9:e95868.
12 Page A-L, de Rekeneire N, Sayadi S, *et al*. Diagnostic and prognostic value of procalcitonin and C-reactive protein in malnourished children. *Pediatrics* 2014;133:e363–70.
13 Wangrangsimakul T, Althaus T, Mukaka M, *et al*. Causes of acute undifferentiated fever and the utility of biomarkers in Chiangrai, Northern Thailand. *PLoS Negl Trop Dis* 2018;12:e0006477.
14 Hildenwall H, Muro F, Jansson J, *et al*. Point-Of-Care assessment of C-reactive protein and white blood cell count to identify bacterial aetiologies in malaria-negative paediatric fevers in Tanzania. *Trop Med Int Health* 2017;22:286–93.
15 Phommasone K, Althaus T, Souvanthong P, *et al*. Accuracy of commercially available C-reactive protein rapid tests in the context of undifferentiated fevers in rural Laos. *BMC Infect Dis* 2016;16:61.
16 Pelkonen T, Albino A, Roine I, *et al*. C-Reactive protein in children with malaria in Luanda, Angola: a prospective study. *Trans R Soc Trop Med Hyg* 2015;109:535–7.
17 Peto TJ, Tripura R, Lee SJ, *et al*. Association between subclinical malaria infection and inflammatory host response in a Pre-Elimination setting. *PLoS One* 2016;11:e0158656.
18 Sarfo BO, Hahn A, Schwarz NG, *et al*. The usefulness of C-reactive protein in predicting malaria parasitemia in a sub-Saharan African region. *PLoS One* 2018;13:e0201693.
19 Verbakel JY, Lemiengre MB, De Burghgraeve T, *et al*. Point-Of-Care C reactive protein to identify serious infection in acutely ill children presenting to hospital: prospective cohort study. *Arch Dis Child* 2018;103:420–6.
20 Bilavsky E, Yarden-Bilavsky H, Ashkenazi S, *et al*. C-Reactive protein as a marker of serious bacterial infections in hospitalized febrile infants. *Acta Paediatr* 2009;98:1776–80.
21 Nijman RG, Moll HA, Smit FJ, *et al*. C-Reactive protein, procalcitonin and the lab-score for detecting serious bacterial infections in febrile children at the emergency department: a prospective observational study. *Pediatr Infect Dis J* 2014;33:e273–9.
22 Verbakel JY, Lemiengre MB, De Burghgraeve T, *et al*. Should all acutely ill children in primary care be tested with point-of-care CRP: a cluster randomised trial. *BMC Med* 2016;14:131.
23 Althaus T, Greer RC, Swe MMM, *et al*. Effect of point-of-care C-reactive protein testing on antibiotic prescription in febrile patients attending primary care in Thailand and Myanmar: an open-label, randomised, controlled trial. *Lancet Glob Health* 2019;7:e119–31.
24 Do NTT, Ta NTD, Tran NTH, *et al*. Point-Of-Care C-reactive protein testing to reduce inappropriate use of antibiotics for non-severe acute respiratory infections in Vietnamese primary health care: a randomised controlled trial. *Lancet Glob Health* 2016;4:e633–41.
25 Keitel K, Kagoro F, Samaka J, *et al*. A novel electronic algorithm using host biomarker point-of-care tests for the management of febrile illnesses in Tanzanian children (e-POCT): a randomized, controlled non-inferiority trial. *PLoS Med* 2017;14:e1002411.
26 Keitel K, Samaka J, Masimba J, *et al*. Safety and efficacy of C-reactive Protein-guided antibiotic use to treat acute respiratory infections in Tanzanian children: a planned subgroup analysis of a randomized controlled Noninferiority trial evaluating a novel electronic clinical decision algorithm (ePOCT). *Clin Infect Dis* 2019;69:1926–34.
27 Lubell Y, Althaus T, Blacksell SD, *et al*. Modelling the impact and cost-effectiveness of biomarker tests as compared with pathogen-specific diagnostics in the management of undifferentiated fever in remote tropical settings. *PLoS One* 2016;11:e0152420.
28 Davido B, Badr C, Lagrange A, *et al*. Serum protein electrophoresis: an interesting diagnosis tool to distinguish viral from bacterial community-acquired pneumonia. *Eur J Clin Microbiol Infect Dis* 2016;35:899–902.
29 Lubell Y, Do NTT, Nguyen KV, *et al*. C-reactive protein point of care testing in the management of acute respiratory infections in the Vietnamese primary healthcare setting - a cost benefit analysis. *Antimicrob Resist Infect Control* 2018;7:119.
30 Shrestha P, Cooper BS, Coast J, *et al*. Enumerating the economic cost of antimicrobial resistance per antibiotic consumed to inform the evaluation of interventions affecting their use. *Antimicrob Resist Infect Control* 2018;7:98.
31 Oppong R, Jit M, Smith RD, *et al*. Cost-effectiveness of point-of-care C-reactive protein testing to inform antibiotic prescribing decisions. *Br J Gen Pract* 2013;63:e465–71.
32 Holmes E, Harris S, Hughes A, *et al*. Cost-Effectiveness analysis of the use of point-of-care C-reactive protein testing to reduce antibiotic prescribing in primary care. *Antibiotics* 2018;7. doi:10.3390/antibiotics7040106. [Epub ahead of print: 07 Dec 2018].
33 Hunter R. Cost-Effectiveness of point-of-care C-reactive protein tests for respiratory tract infection in primary care in England. *Adv Ther* 2015;32:69–85.