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

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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.

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. 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. 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. 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 other 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.6–914 Three studies assessed a higher cut-off of approximately 40 mg/L.6–1016–18 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.71015

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.91016–18 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.7 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 |
|---------------------|---------|--------------------|------------------------|-------------------------|--------------------|-----------------------------------------------------------------------------------------------------|-----------------------------------------------|------------------------|--------------------------------------|
| **Studies in Africa** |         |                    |                        |                         |                    |                                                                                                     |                                               |                        |                                      |
| Carrol et al.       | 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) | 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. | Mozambique | <5 years           | Inpatients            | Clinical severe pneumonia (no malaria) | 586                | Blood culture Immunoturbidimetric assay, ADVIA Chemistry CRP 2 (Siemens)                            | 0.79                                          | 20.9 95 45               | 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.   | 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 (32.2 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. |
| Study            | Country                | Age group           | Inpatients/Outpatients | Disease characteristics | Number of patients | Gold standard for bacterial infection | CRP test     | AUROC (95% CI) | Cut-off* | Sensitivity† | Specificity† | Correlation with bacterial infection |
|------------------|------------------------|---------------------|------------------------|-------------------------|--------------------|--------------------------------------|--------------|---------------|-----------|-------------|-------------|-------------------------------------|
| Huang et al<sup>8</sup> | Gambia and Kenya       | 2 months to 5 years | Inpatients             | Pneumonia               | n=204              | 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<sup>10</sup> | 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<sup>12</sup> | 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) | 47.5      | 46.5        | 80.4        | 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). |
| Mueller et al<sup>11</sup> | 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<sup>13</sup> | Thailand              | ≥15 years           | Inpatients and outpatients | Acute fever             | 231                | Microbiological results including culture, antigen detection, PCR and ELISA for JEV IgM ELISA | NycoCard Reader (Abott, USA) | 0.91 (0.85 to 0.96) | 36        | 88.9        | 86.4        | CRP levels were significantly lower in patients with a viral infection than other infections (p<0.0001 in all comparisons across countries). |
| Lubell et al<sup>14</sup> | 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        | 95 (92 to 97) | 49 (46 to 53) | CRP levels were significantly lower in patients with a viral infection than other infections (p<0.0001 in all comparisons across countries). |

Studies in South-East Asia

| Study            | Country               | Age group | Inpatients/Outpatients | Disease characteristics | Number of patients | Gold standard for bacterial infection | CRP test     | AUROC (95% CI) | Cut-off* | Sensitivity† | Specificity† | Correlation with bacterial infection |
|------------------|-----------------------|-----------|------------------------|-------------------------|--------------------|--------------------------------------|--------------|---------------|-----------|-------------|-------------|-------------------------------------|
| Mueller et al<sup>11</sup> | 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<sup>13</sup> | Thailand              | ≥15 years | Inpatients and outpatients | Acute fever             | 231                | Microbiological results including culture, antigen detection, PCR and ELISA for JEV IgM ELISA | NycoCard Reader (Abott, USA) | 0.91 (0.85 to 0.96) | 36        | 88.9        | 86.4        | CRP levels were significantly lower in patients with a viral infection than other infections (p<0.0001 in all comparisons across countries). |
| Lubell et al<sup>14</sup> | 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        | 95 (92 to 97) | 49 (46 to 53) | CRP levels were significantly lower in patients with a viral infection than other infections (p<0.0001 in all comparisons across countries). |
CRP predicting SBI in children aged 1 month to 16 years, and infants aged 3 months or less, respectively. 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 |
|-------|---------|-----------|-------------------------|--------------------|-----------|--------------------------------------|----------------------|
| 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.
Interestingly, two studies in Tanzania have used CRP testing as part of electronic 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.35–36

### 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 DALYs.9 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).

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 £19705 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

| Study | Country | Assumptions | Results |
|-------|---------|-------------|---------|
| Lubell et al9 | Laos | Patients with CRP >20mg/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 al9 | 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.

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

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, however, the second study demonstrated a significant reduction at a cut-off of 20 mg/L (10 mg/L for the youngest patients). 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. 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.

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