

## C-reactive protein testing in primary care for acute respiratory infections: a cost-effective strategy to mitigate antimicrobial resistance across different income settings



The upcoming 2024 UN General Assembly High-Level Meeting on Antimicrobial Resistance (AMR), the second of its kind, underscores the urgent need to address this escalating global health threat. Antimicrobial use is causally associated with the emergence and spread of antimicrobial resistance. Primary care, in which most human antimicrobial use occurs (particularly for acute respiratory tract infections), should be a key focus for intervention.

C-reactive protein (CRP) testing can quickly determine whether respiratory infections are probably self-limiting, ruling out the need for antibiotics at all. Point-of-care testing in primary care aligns with WHO's people-centred strategy to address AMR and Sustainable Development Goal 3.8—improving access to quality health care, including diagnostic services. Several high-income countries have implemented CRP testing to reduce unnecessary prescriptions for respiratory infections, and efforts are underway in Europe to further expand this approach.<sup>1</sup> We propose that with low-cost devices, the adoption of CRP testing is similarly feasible and justifiable in low-income and middle-income countries (LMICs). The benefits and cost-effectiveness have been shown in trials in public and private health-care settings, often the first point-of-contact for patients in many LMICs.<sup>2-4,9</sup> To support further widescale implementation of CRP testing in LMICs, we address key concerns surrounding its use in this context.

A primary concern is the diagnostic accuracy of CRP tests. Imperfect sensitivity could imply withholding antibiotics from patients who need them. Although most acute respiratory tract infections are of viral origin, health-care workers still require adequate training to identify patients in whom antibiotics or referral might be warranted despite low CRP concentrations. CRP can also be elevated for various reasons, including non-communicable diseases and viral and protozoal infections, limiting its specificity. However, most patients presenting with acute respiratory tract infections, who in many LMIC settings would universally receive antibiotics, have CRP concentrations well below

even the most conservative thresholds of 10–20 mg/L used to rule out their need for antibiotics.<sup>3,4</sup> CRP testing can therefore provide assurance to most patients and health-care workers that antibiotics can be safely withheld, accepting that a small proportion of patients with elevated CRP due to non-bacterial infection would still be prescribed antibiotics unnecessarily.

Policy makers might be disinclined to adopt CRP testing in anticipation of potentially superior tools becoming available, including novel multiplex tests for other host biomarkers or for the detection of specific pathogens. It is notable however that multiplex host biomarker tests commercialised in the past 5 years include CRP with the addition of 1–2 biomarkers that provide modest gains in specificity, which as argued later, are unlikely to justify their much higher costs. Multiplex antigen and molecular tests, although novel and innovative, are affected by both specificity and sensitivity issues that arise when using non-sterile respiratory samples, leading to the detection of colonising organisms often found to be similarly present in healthy controls. Furthermore, in implementation trials, neither multiplex molecular or host biomarker tests have yet been shown to reduce antibiotic use in primary care settings.<sup>5,6</sup>

For all these tests, affordability and cost-effectiveness are a major concern. Pragmatically, with antibiotics widely available in many LMICs for as little as US\$2–3, from patients' and providers' perspectives there is little incentive to purchase more expensive tests, even if their use supports broader efforts to mitigate the effect of AMR. Quantitative CRP tests used in high-income settings are likely to be viewed as prohibitively expensive in LMICs, as are more expensive multiplex host biomarker and pathogen specific tests. However, qualitative and semiquantitative lateral flow CRP tests are widely available, with some priced under \$1.<sup>7</sup> Even at these low costs, it is methodologically challenging to determine whether the use of these tests is justified in terms of downstream costs of AMR averted. Attempts that have been made indicate that CRP testing is

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cost-effective,<sup>8,9</sup> although the outcome was highly dependent on test costs. It is questionable whether modest incremental reductions in prescribing afforded by newer tests justify the tests' higher costs or the time required until these tests have the evidence base to support their widescale use.

Implementation of CRP testing has practical challenges, such as ensuring adherence to test results and guidelines by health-care workers. Past experiences have shown that poor adherence can undermine the effect of CRP testing.<sup>3,4,10</sup> Additionally, there is a risk of over-reliance on testing and therefore reducing sound clinical judgment; indeed, in settings where antibiotic use is already low, the introduction of CRP testing could unduly increase prescribing rates. Comprehensive training and clear guidelines as to the contexts in which CRP testing is beneficial and cost-effective are therefore essential.

These and other challenges and prerequisites for wide-scale deployment of CRP testing in primary care, such as the construction of finance mechanisms and ensuring equitable access, are not insurmountable, but addressing them requires high-level support from policy makers. In anticipation of the UN General Assembly meeting on AMR, we call upon policy makers to take immediate action using available evidence-based tools as a crucial step in preserving antimicrobial efficacy to tackle the most pressing current global health challenge.

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