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Review Article

Complete Blood Count with C-Reactive Protein for Rapid Differentiation of Bacterial from Viral Infections: Clinical Evidence, Machine Learning Validation, FDA-Approved Diagnostics, and Implications for Point-of-Care Testing in India

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Abstract

The accurate differentiation of bacterial from viral infections at the point of care remains one of the most clinically consequential and diagnostically challenging problems in medicine. Inappropriate antibiotic prescribing, overwhelmingly driven by diagnostic uncertainty, fuels antimicrobial resistance, increases treatment costs, and exposes patients to avoidable harm. The complete blood count (CBC) and C-reactive protein (CRP), obtained routinely in almost every clinical setting worldwide, encode a rich pattern of host-response signals that differ fundamentally between bacterial and viral infections. This review synthesises the biological basis of these differences, evaluates the discriminatory performance of individual CBC parameters and CRP, and examines landmark machine learning (ML) evidence including a 44,120-case XGBoost model achieving an AUC of 0.905 [1] that confirms the superior power of integrating CBC with CRP over CRP alone, particularly in the diagnostically ambiguous 10-40 mg/L CRP grey zone. We further review recently FDA-cleared point-of-care tests, including the FebriDx MxA/CRP lateral flow assay and the MeMed BV TRAIL/IP-10/CRP host-response platform, appraising their performance and their practical and economic feasibility in the Indian context. We conclude that an intelligently implemented CBC+CRP approach, supported by an offline computational app running on a smartphone or computer, offers India a scientifically validated, diagnostically powerful, and economically accessible solution, one that is highly synergistic with existing laboratory infrastructure across public and private healthcare settings.

Keywords: Complete Blood Count; C-Reactive Protein; Neutrophil-to-Lymphocyte Ratio; Bacterial Infection; Viral Infection; Machine Learning; FebriDx; MxA; Antimicrobial Stewardship; Point-of-Care Testing; India

Introduction

The differentiation of bacterial from viral infection is among the most consequential clinical decisions made in daily practice. Over 13 million emergency department visits annually in the United States alone are attributable to acute respiratory infections, and similar burdens are seen in Europe and Asia. The price of diagnostic failure is steep in both directions: untreated bacterial infection may progress to sepsis and death, while unnecessary antibiotic prescribing drives the selection of resistant organisms, a process that already causes an estimated 1.27 million deaths per year globally and threatens to become the leading cause of mortality by 2050 (WHO, 2023; Laxminarayan., *et al*. Lancet 2016 [10]).

In high-income countries, 23% of antibiotic prescriptions for acute respiratory illness have been judged inappropriate (Chua., *et al*. BMJ 2019). Among children hospitalised with bronchiolitis, 25% received antibiotics despite 70% of them having no documented bacterial focus (Papenburg., *et al*. J Pediatr Infect Dis 2019). The situation in lower- and middle-income countries (LMICs), including India, is likely worse, where empirical antibiotic use is the norm and diagnostic resources are constrained.

The search for a practical, rapid, and affordable tool to distinguish bacterial from viral illness has spanned several decades. C-reactive protein (CRP), introduced into clinical practice in the 1930s, remains the most widely used biochemical marker. Procalcitonin (PCT), introduced in the 1990s, offers superior specificity for bacteraemia but has remained expensive and less accessible in many settings. More recently, a new generation of host-response biomarkers, including Myxovirus resistance protein A (MxA), TRAIL, and IP-10 and ML-based multiparameter models have entered the arena, offering qualitative and quantitative improvements over single biomarker thresholds.

The complete blood count (CBC), performed as a routine investigation in virtually every hospital and most primary care laboratories worldwide, provides 16 or more discrete parameters reflecting the host's haematological and immune response to infection. When combined with CRP, these parameters collectively constitute a "multi-dimensional" host-response signature. This review evaluates the scientific basis and clinical utility of that signature, examines the contribution of machine learning models trained on large real-world datasets, and assesses the practical implications of newer FDA-cleared tests within the context of the Indian healthcare system where CBC with CRP, running on a simple computational platform, may represent the most democratically accessible diagnostic advance available today.

Pathophysiological basis of differential CBC and CRP responses

The innate immune response to bacterial infection

Bacterial pathogens are recognised primarily by pattern-recognition receptors (PRRs) such as Toll-like receptors (TLRs) and NOD-like receptors (NLRs) via pathogen-associated molecular patterns (PAMPs), including lipopolysaccharide (LPS), peptidoglycan, and flagellin. This recognition triggers rapid release of pro-inflammatory cytokines, principally interleukin (IL)-1β, IL-6, IL-8, and tumour necrosis factor-α (TNF-α). IL-6 drives hepatic synthesis of acute-phase reactants, most importantly CRP, which rises within 4-6 hours and peaks at 36-48 hours. IL-8 acts as a potent neutrophil chemoattractant, driving the characteristic neutrophilia that defines the haematological response to bacterial infection. Granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage CSF (GM-CSF) stimulate bone marrow production of mature neutrophils, raising the absolute neutrophil count and the neutrophil percentage of the white cell differential.

The innate immune response to viral infection

Viral pathogens are primarily detected by intracellular sensors including RIG-I and MDA5 (for RNA viruses) and cGAS-STING (for DNA viruses), triggering a type I interferon (IFN-α/β) response. Type I interferons activate the JAK-STAT signalling pathway and induce the expression of interferon-stimulated genes (ISGs) including Myxovirus resistance protein A (MxA), TRAIL, IP-10 (CXCL10), and IFIT proteins. Critically, type I interferons do not arise in response to even severe bacterial infections, providing the mechanistic basis for MxA as a viral-specific biomarker. Viral infections characteristically favour lymphocyte expansion and activation rather than neutrophil recruitment, and CRP elevation is generally modest (typically below 40 mg/L), though exceptions exist with severe viral pneumonia (e.g., influenza, COVID-19). Viral infections are also associated with suppression of platelet production and increased platelet destruction, leading to thrombocytopenia, a finding that contrasts with the reactive thrombocytosis commonly seen in bacterial infection.

Implications for diagnostic biomarkers

These mechanistic differences directly predict the distinctive patterns seen across CBC parameters and CRP in bacterial versus viral illness. No single parameter is pathognomonic, but the combination of parameters, assessed jointly through clinical algorithms or machine learning models, captures a powerful and reproducible diagnostic signal. This is the conceptual foundation on which the CBC+CRP approach rests.

CBC Parameters and CRP as discriminators: Parameter-by-parameter analysis

Table 1 summarises the directional changes in key CBC parameters and their clinical significance in bacterial versus viral infections, integrating evidence from clinical studies and the Shapley value analysis of the Guncar., *et al*. machine learning model (Heliyon 2024) [1].

Parameter	Bacterial infection	Viral infection	Clinical significance
WBC (x10^9/L)	Elevated (>11.0)	Normal or mildly elevated/low	Raised by cytokine-driven bone marrow release
Neutrophil count/%	Increased (>75%)	Normal or decreased	Neutrophilia = hallmark of acute bacterial response
Lymphocyte count/%	Decreased (<20%)	Normal, elevated, or atypical lymphocytes	Lymphopenia in bacterial sepsis; lymphocytosis in viral
NLR	>6.77 (bacterial)	<2.07 (viral)	Most discriminating single ratio; AUC ~0.82-0.86
Monocyte %	Variable	Often elevated	Virus-driven monocyte activation
CRP (mg/L)	Usually >40, often >80	Usually <20; rarely >40	Excellent separator at extremes; grey zone 10-40 mg/L
Platelet count	Often elevated (reactive thrombocytosis)	Often decreased (viral thrombocytopenia)	Key SHAP contributor in ML model
Hb/Hct	May decrease in severe/chronic infection	Usually normal acutely	Secondary effect, not primary discriminator
RDW	May increase in sepsis	Less affected acutely	Anisocytosis marker; elevated SHAP contribution
MCV, MCH, MCHC	Usually normal acutely	Usually normal	Lower SHAP impact; useful for concomitant anaemia context

Table 1: CBC and CRP Parameters in Bacterial versus Viral Infections.

NLR = Neutrophil-to-Lymphocyte Ratio; RDW = Red Cell Distribution Width; SHAP = Shapley Additive Explanations; POC = Point of Care.

White blood cell count and differential

The total white blood cell (WBC) count, while widely used, has a sensitivity of only 50-70% for bacterial infection and is confounded by stress, steroid use, haematological malignancy, and immune suppression. Its value lies primarily in combination with the differential. Neutrophilia (absolute neutrophil count >7.5 × 10^9/L or neutrophil percentage >75%) with left shift (band forms, metamyelocytes) is the classical hallmark of acute bacterial infection. Lymphocytosis or relative lymphocytosis (lymphocyte% >40%) suggests viral aetiology. Atypical lymphocytes on the automated differential, flagged by modern analysers, are a specific sign of viral illness (most classically infectious mononucleosis, CMV, dengue).

The Neutrophil-to-Lymphocyte ratio (NLR)

The NLR integrates the two most discriminating single parameters into a ratio that amplifies their combined signal. In the landmark 44,120-case machine learning study (Guncar., *et al*. Heliyon 2024) [1], the median NLR was 6.77 in confirmed bacterial infections versus 2.07 in viral infections, a more than three-fold difference. Published literature has validated the following reference thresholds: NLR >6.77 strongly favours bacterial infection; NLR <2.07 strongly favours viral infection; NLR 2.07-6.77 is indeterminate and warrants integration of other parameters.

The NLR has been independently validated as a discriminator in multiple clinical settings. De Jager., *et al*. (PLoS ONE 2012) [7] demonstrated an AUC of 0.74 for NLR in community-acquired pneumonia severity prediction. Cataudella., *et al*. (Am Geriatr Soc 2017) [8] confirmed the NLR's predictive value for bacterial aetiology in elderly patients. Regolo., *et al*. (J Clin Med 2022) demonstrated NLR's utility in COVID-19 severity and admission prediction. Its computation requires no additional test beyond the CBC differential, making it universally available and cost-free.

C-Reactive protein

CRP is the most widely studied single biomarker for bacterial-viral differentiation. C-reactive protein rises within 4-6 hours of

bacterial infection onset, peaks at 36-48 hours and has a half-life of approximately 19 hours. Classical thresholds suggest that CRP >80 mg/L is highly indicative of bacterial infection (specificity >80%), while CRP <20 mg/L makes serious bacterial infection unlikely (sensitivity ~85%). However, the clinically critical and diagnostically frustrating "grey zone" of CRP 10-40 mg/L, where neither bacterial nor viral aetiology can be reliably distinguished, encompasses approximately 14% of all febrile patients and represents the principal limitation of CRP as a standalone diagnostic. It is precisely in this grey zone that the ML-based CBC+CRP model demonstrates its greatest added value.

Limitations of CRP include: (1) non-specificity : CRP rises in any inflammatory state including autoimmune disease, trauma, and malignancy; (2) temporal lag: false-negative results within the first 6 hours of illness onset; (3) overlap at intermediate values; (4) variability with age, sex, obesity, and medication (notably statins and NSAIDs that suppress CRP). Despite these limitations, CRP remains the most economically accessible acute-phase reactant globally, making it an indispensable component of any combined diagnostic strategy.

Platelet count and red cell parameters

Platelet count emerges as the second most discriminating CBC parameter in the Shapley value analysis of the Guncar., *et al*. model [1]. Bacterial infections are associated with reactive thrombocytosis driven by IL-6-mediated hepatic thrombopoietin production, whereas viral infections, particularly dengue, influenza, COVID-19, and infectious mononucleosis cause thrombocytopenia through immune-mediated platelet destruction and suppression of megakaryopoiesis. Red cell distribution width (RDW) is elevated in sepsis and severe infections due to dyserythropoiesis, and contributes meaningfully to the ML model's decision-making. Haemoglobin, haematocrit, MCV, MCH, and MCHC contribute less as acute discriminators but provide important context regarding baseline health and comorbidity.

Machine learning evidence: From single biomarkers to integrative models

The XGBoost CBC+CRP model (Guncar., et al. Heliyon 2024) [1]

Guncar and colleagues at the University Medical Centre Ljubljana published a landmark study applying XGBoost, a gradient-boosted decision tree algorithm, to 44,120 adult cases with confirmed ICD-10-encoded bacterial or viral diagnoses (Heliyon 10, 2024, e29372) [1]. This represents, to our knowledge, the largest validated ML dataset applied to the bacterial-viral diagnostic problem using only routine CBC and CRP parameters.

The model incorporated 16 routine blood parameters (WBC, neutrophil count, neutrophil%, lymphocyte count, lymphocyte%, monocyte count, monocyte%, platelet count, RBC, Hb, Hct, MCV, MCH, MCHC, RDW, MPV) plus CRP, NLR, biological sex, and age. Semi-supervised bootstrap labelling (SBAS) was used to handle cases with both bacterial and viral diagnoses, ensuring appropriate classification of ambiguous cases. Key performance metrics across the full evaluation dataset are summarised below:

- AUC (area under the ROC curve): 0.905
- Accuracy: 82.2%
- Sensitivity (bacterial): 79.7%
- Specificity (bacterial): 84.5%
- Brier score (calibration): 0.129

The model significantly outperformed the simple CRP decision rule (CRP threshold of 24 mg/L) across all metrics, particularly in the 10-40 mg/L CRP grey zone. In this zone, encompassing 14.3% of all evaluation cases (884 patients), the XGBoost model achieved 73.2% (± 2.9%) accuracy compared to only 55.3% (± 3.3%) for CRP alone: a 17.9 percentage-point improvement. This is the diagnostic scenario where the model delivers its greatest incremental clinical value, and where clinical decision is most uncertain and antibiotic prescribing most likely to be inappropriate.

Shapley value analysis: Understanding feature contributions

To ensure interpretability, a prerequisite for clinical trust in ML models, the authors applied Shapley Additive exPlanations (SHAP) to quantify each parameter's contribution to the model's decision-making [1]. The rank order of parameter importance, from highest to lowest, was: CRP, Age, Platelet count, Lymphocyte%, WBC, Neutrophil count, Monocyte %, RDW, Hct, Hb, MCV, Neutrophil%, NLR, RBC, MCH, Lymphocyte count, Biological sex, Monocyte count, MCHC, MPV.

This SHAP analysis has directly practical implications: It confirms that while CRP contributes the most to model accuracy, it is insufficient alone. Platelet count and lymphocyte percentage

are the next strongest contributors, both readily available from the CBC differential. NLR, while clinically the most discussed derived parameter, ranks 13th in SHAP importance, suggesting that the raw neutrophil and lymphocyte counts contain additional independent information beyond their ratio. The importance of age as the second-ranked parameter underscores the biological reality that older patients mount attenuated lymphocyte responses to viral infection while having higher baseline CRP and greater bacterial infection rates.

Performance without age as a feature

To assess real-world applicability (e.g., paediatric settings or where age data may be unavailable), the authors built an age-excluded model. Performance fell by only 2 percentage points, suggesting the model remains clinically useful even when age is unknown, a critical finding for triage and emergency settings.

Corroborating machine learning studies

The Guncar., *et al*. [1] study is part of a growing body of ML-based infection discrimination research. Notably:

- Oved., *et al*. (J Infect 2015) [6] demonstrated that a combined TRAIL + IP-10 + CRP algorithm achieved an AUC of 0.94 in febrile children, superior to CRP alone (AUC 0.84) and procalcitonin (AUC 0.84).
- Lien., *et al*. (BMC Infect Dis 2022) [14] showed that an ML model using complete blood count with differential leukocyte count achieved performance comparable to procalcitonin in bacteraemia prediction.
- Ramgopal., *et al*. (Paediatrics 2020) [15] developed an ML model predicting serious bacterial infections in young febrile infants using clinical and laboratory parameters, highlighting the value of integrative approaches.
- Li., *et al*. (PLoS ONE 2022) identified CRP as the single most predictive variable in 293 patients with suspected lower respiratory tract infections and/or sepsis, but with substantially superior discrimination when combined with CBC parameters.

Collectively, these studies converge on a consistent finding: no single biomarker provides clinically adequate discrimination between bacterial and viral infection; integrative approaches, whether statistical scores, derived ratios, or trained ML models consistently outperform any individual parameter.

The FebriDx MxA/CRP point-of-care test

Biological basis: Myxovirus resistance protein A

Myxovirus resistance protein A (MxA) is an interferon-stimulated gene product with properties that make it uniquely attractive as a viral biomarker. MxA is induced exclusively by type I interferons, the innate immune system's antiviral mediators and does not rise in response to bacterial pathogens, TNF-α, IL-1β, or other pro-inflammatory mediators of bacterial infection (Haller & Kochs, J Interferon Cytokine Res 2011). MxA levels rise within 1-2 hours of interferon induction and remain elevated for approximately 2 days, providing a practical detection window. MxA inhibits transcription and replication of a broad range of RNA and DNA viruses, including influenza A/B, RSV, parainfluenza, SARS-CoV-2, EBV, CMV, HSV-1/2, adenovirus, and many others — giving the test broad viral coverage.

When combined with CRP in a single assay, the two markers provide complementary signals: MxA-positive/CRP-negative strongly suggests viral infection; MxA-negative/CRP-positive in the appropriate clinical context suggests bacterial infection; dual-positive results may indicate co-infection or a bacterial infection with an early viral phase. The FebriDx lateral flow assay (Lumos Diagnostics) incorporates qualitative detection of MxA (≥40 ng/mL) and CRP (≥20 mg/L) in a single disposable device, with results available in 10 minutes from a fingerstick or venous blood sample.

Clinical performance evidence

FebriDx has been evaluated in five major prospective clinical studies (Table 2). Allan-Blitz and Klausner (Clinical Infectious Diseases, 2025) [2] provide the most comprehensive synthesis of this evidence to date.

The consistently high negative predictive values (89-99%) across all five studies are the most clinically actionable finding: a negative FebriDx result: MxA negative, CRP negative, effectively excludes serious bacterial infection in the appropriate clinical context, with sufficient confidence to withhold empirical antibiotics. The 2022 multicenter study of 520 outpatients (Shapiro., *et al*. JAMA Network Open) [3] is particularly noteworthy, using

Year/Author	Country	N	Age (mean)	Clinical setting	NPV (95% CI)	PPV (95% CI)
Sambursky 2015	USA	54	37 yrs	Febrile pharyngitis/ LRTI	80% (56-94%)	88% (73-97%)
Self 2017	USA	205	29 yrs	Febrile URTI	97% (94-99%)	63% (45-79%)
Shapiro 2018	USA	220	37 yrs	Febrile URTI (confirmed/no fever)	99% (93-100%)	76% (59-87%)
Shapiro 2022	USA	520	35 yrs	Febrile ARTI (outpatient)	93% (97-99%)	58% (49-67%)
Tong-Minh 2023	Netherlands	224	58 yrs	ED (respiratory symptoms)	89% (82-94%)	60% (51-68%)

Table 2: Clinical Performance of the FebriDx (MxA/CRP) Assay Across Major Prospective Studies.

NPV = Negative Predictive Value; PPV = Positive Predictive Value; URTI = Upper Respiratory Tract Infection; ARTI = Acute Respiratory Tract Infection; ED = Emergency Department. Sensitivity for bacterial infections ranged 80-93%; specificity 67-93%.

reference testing that included PCR for 28 distinct pathogens plus procalcitonin, and achieving 93% sensitivity and 88% specificity for bacterial infection.

Impact on antibiotic prescribing

Antibiotic stewardship is the primary justification for investing in infection discrimination tests. FebriDx has demonstrated meaningful antibiotic-sparing effects across multiple practice settings:

- Davidson (2017, UK primary care): Antibiotic deferral in 67% (8/12) of patients initially suspected of bacterial RTI.
- De la Matta Farrando., *et al*. (2024, Spain, paediatric): 10% change in therapeutic plan, with antibiotic deferral as the dominant action.
- Wilcox., *et al*. (2024, UK primary care) [4]: 41% reduction in antibiotic prescriptions for lower RTI, with no increase in clinical representation at 28 days, a critical patient-safety validation.
- Economic modelling (Dick & Schneider, J Health Econ Outcomes Res 2021) [11]: An MxA/CRP assay with 95% sensitivity for bacterial infection would save >$2.5 billion/ year in the United States alone, with savings sustained even at 75% sensitivity.

Limitations of the FebriDx assay

Several important limitations must be acknowledged when considering FebriDx for clinical deployment:

- The assay was predominantly studied in emergency department and primary care settings, performance in ICU, inpatient wards, or immunocompromised patients is not well characterised.
- Novel viral variants may attenuate MxA induction: one study during a novel SARS-CoV-2 variant wave observed sensitivity for viral infection falling to 56% (Buntine., *et al*. BMJ Open 2022).
- Bacterial-viral co-infection occurs in 3-15% of pneumonia cases and may produce MxA-positive/CRP-positive results, potentially leading to inappropriate antibiotic deferral if the bacterial component is not recognised.
- CRP peaks after 36 hours; thus, tests performed very early in illness (within 6 hours of symptom onset) may show false-negative CRP.
- No gold standard diagnostic can definitively classify all infections as bacterial or viral — all comparative performance data are therefore subject to reference standard limitations.
- The qualitative (positive/negative) output provides less actionable information than quantitative results for intermediate cases.

Other recently FDA-cleared diagnostic tests for bacterial-viral differentiation

Beyond FebriDx, several additional diagnostic platforms have received FDA clearance or Breakthrough Device designation in

the past five years targeting the bacterial-viral differentiation challenge. Table 3 provides a comparative overview.

Test/Platform	Biomarker(s)	FDA Status	TAT	Sensitivity/Specificity	Cost tier
FebriDx (Lumos Dx)	MxA + CRP (POC lateral flow)	FDA cleared (510k)	10 min	Sens 80-93% / Spec 67-93% (bacterial)	Moderate (~USD 25-40/ test)
MeMed BV (MeMed Key)	TRAIL + IP-10 + CRP (host response)	FDA cleared 2022	15 min	AUC 0.94; NPV ~95% (viral)	High (~USD 50-80/test)
Procalcitonin (multiple, e.g. Abbott, bioMérieux)	PCT	FDA cleared (several)	20-60 min (lab)/POC 20 min	Sens ~77%/Spec ~79% (bacterial sepsis)	Moderate-High
BioFire FilmArray (Resp Panel 2.1)	Multiplex PCR - 22 pathogens	FDA cleared/ EUA	~45 min	Pathogen-specific (not host-response)	High (~USD 150-250/ panel)
Inflammatix TriVerity	3 class gene mRNA of seven host genes	Breakthrough Device designation; EUA studies	~60-90 min (lab)	AUC 0.88-0.93 in published studies	Research/emerging
CBC + CRP (Horiba Microsemi + CRP)	16 CBC parameters + CRP (host response)	Routine diagnostic (components cleared)	15-30 min (POC lab)	NLR AUC ~0.82; XGB model AUC 0.905	Very low (~USD 2-5 in India)

Table 3: Comparison of FDA-Cleared/Authorised Tests for Bacterial-Viral Differentiation vs CBC+CRP.

TAT = Turnaround Time; NPV = Negative Predictive Value; POC = Point of Care; ED = Emergency Department; EUA = Emergency Use Authorisation. Cost tiers are approximate; actual costs depend on setting, contract, and country.

MeMed BV (MeMed Key Platform)

- MeMed's bacterial-viral (BV) score integrates three host-response biomarkers: TRAIL (a pro-apoptotic cytokine elevated in viral infection), IP-10/CXCL10 (an interferon-gamma-inducible chemokine elevated virally), and CRP (elevated bacterially) into a validated algorithmic score ranging 0 to 100, where scores <35 indicate viral aetiology and >65 indicate bacterial aetiology. The MeMed Key system received FDA clearance in 2022 and produces results in approximately 15 minutes. Published studies across paediatric and adult cohorts demonstrate AUC values of 0.90-0.95 and NPV for bacterial infection approaching 95%.
- The biological logic is elegant and well-validated: TRAIL and IP-10 rise specifically in response to type I interferon signalling (as does MxA), while CRP reflects the acute-phase bacterial response. The system provides a superior combination of viral- and bacterial-specific signals compared to CRP or procalcitonin alone.
- Limitations: The MeMed Key platform requires dedicated hardware and reagent cartridges, with unit costs in the USD 50-80 range per test. It has not yet been evaluated extensively in LMIC settings, and the hardware investment (approximately USD 10,000-15,000 per analyser) places it beyond the reach of the majority of Indian primary and secondary care facilities.

Procalcitonin

Procalcitonin (PCT) a propeptide of calcitonin induced by bacterial infection via IL-6, IL-1β, and TNF-α, but suppressed by viral type I interferons, remains the most extensively studied bacterial biomarker beyond CRP. Multiple FDA-cleared PCT assays exist from Roche, bioMérieux, Abbott, Siemens, and others, including point-of-care formats. PCT demonstrates superior performance to CRP for diagnosing bacteraemia and bacterial pneumonia (sensitivity ~77%, specificity ~79%) [9] and is guideline-endorsed for antibiotic stewardship in lower respiratory

tract infections and sepsis (IDSA/SCCM guidelines). However, PCT can be falsely elevated in severe non-infectious states (major trauma, post-surgery, cardiogenic shock, pancreatitis), and is less sensitive for focal bacterial infections (e.g., urinary tract infections) where bacteraemia is absent. Cost in India ranges from INR 500-1,500 (≈ USD 6-18), making it less accessible than CRP for routine outpatient use.

Multiplex molecular platforms (BioFire FilmArray)

The BioFire FilmArray Respiratory Panel 2.1 (bioMérieux) and similar multiplex PCR platforms (e.g., Luminex NxTAG, Hologic Panther Fusion) detect up to 22-40 respiratory pathogens simultaneously in approximately 45-90 minutes. These platforms identify specific viral and bacterial pathogens rather than providing a host-response classification. Their primary utility is in pathogen identification, essential for appropriate antiviral therapy (e.g., oseltamivir for influenza) and outbreak surveillance rather than the binary bacterial-versus-viral triage decision. Unit costs of USD 150-250 per panel (INR 12,000-20,000) make these platforms entirely impractical for routine outpatient use in India and most LMICs. Their role is appropriately confined to secondary and tertiary care where pathogen identification directly impacts management (e.g., immunocompromised patients, ICU, transplant units).

Inflammatix TriVerity

Inflammatix has developed TriVerity, a three-class host-response classifier using mRNA expression of seven host genes measured from whole blood, distinguishing bacterial infection, viral infection, and non-infectious illness simultaneously. The test has received FDA Breakthrough Device designation and generated promising data in multicentre prospective studies (AUC 0.88-0.93). However, it requires a dedicated laboratory workflow and has not yet achieved routine commercial clearance or widespread availability. Its potential for the most accurate three-way classification (bacterial/viral/non-infectious) makes it scientifically attractive, but it remains an emerging platform with limited accessibility at present.

The Indian context: CBC+CRP versus advanced diagnostics

The healthcare landscape

India presents a distinctive and challenging context for infection diagnostics. With 1.4 billion people, India's healthcare system is characterised by massive heterogeneity: world-class tertiary centres coexist with primary care facilities that lack even basic laboratory infrastructure. The per capita healthcare expenditure is approximately USD 85 (2023), compared to USD 12,500 in the United States. Outpatient consultations are often brief (fewer than 3 minutes on average in the public system), and empirical antibiotic prescribing — driven by diagnostic uncertainty — is the norm. India is classified as the world's largest consumer of antibiotics by volume. Antimicrobial resistance rates for critical pathogens (*E. coli*, Klebsiella, Acinetobacter) are among the highest globally, with carbapenem resistance approaching 50-70% in ICU isolates in some centres (ICMR AMR Surveillance Network, 2023) [12]. The need for accessible, accurate diagnostic tools to rationalise antibiotic use is therefore not merely clinically desirable, it is a public health emergency.

Availability and cost: A Decisive advantage for CBC+CRP

The CBC is performed in virtually every Indian diagnostic laboratory, from government primary health centres to corporate tertiary hospitals. The Horiba Microsemi CBC analyser, used in many such settings, provides a 16-parameter CBC (including 3-part white cell differential) as a routine output. CRP is equally accessible as a semi-quantitative turbidimetric test or a quantitative immunoturbidimetric assay, available in most laboratories at a cost of INR 50-150 (≈ USD 0.60-1.80). The combined cost of CBC + CRP in India is typically INR 150-300 (≈ USD 2-4), an order of magnitude lower than FebriDx (≈ USD 25-40) and two orders of magnitude lower than multiplex PCR panels (≈ USD 150-250).

The critical transformation enabled by the CBC+CRP app, built on the Guncar., *et al*. XGBoost evidence [1] and clinical literature, is the intelligent, algorithmic integration of all 16 CBC parameters with CRP, NLR, age, and sex into a probability score and clinical recommendation. This converts a set of numbers that clinicians already have and may read in isolation or with only partial pattern recognition, into a structured, evidence-based diagnostic output available within seconds, without internet connectivity, without additional hardware, and at zero marginal cost per test.

The inirial app was created by Smart Blood Analytics Swiss SA.

Subsequently using Claude Cowork, a similar but stand alone file has been created to be used along with Horiba's Microsemi CRP to generate, print or transmit report. Using this format.

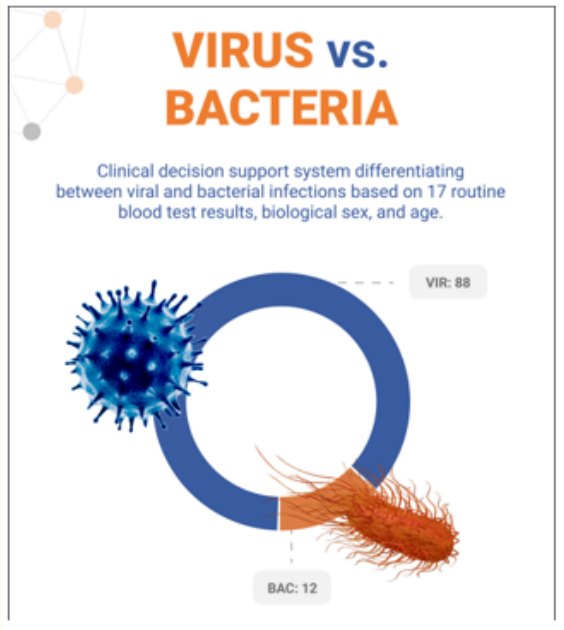

Figure 1

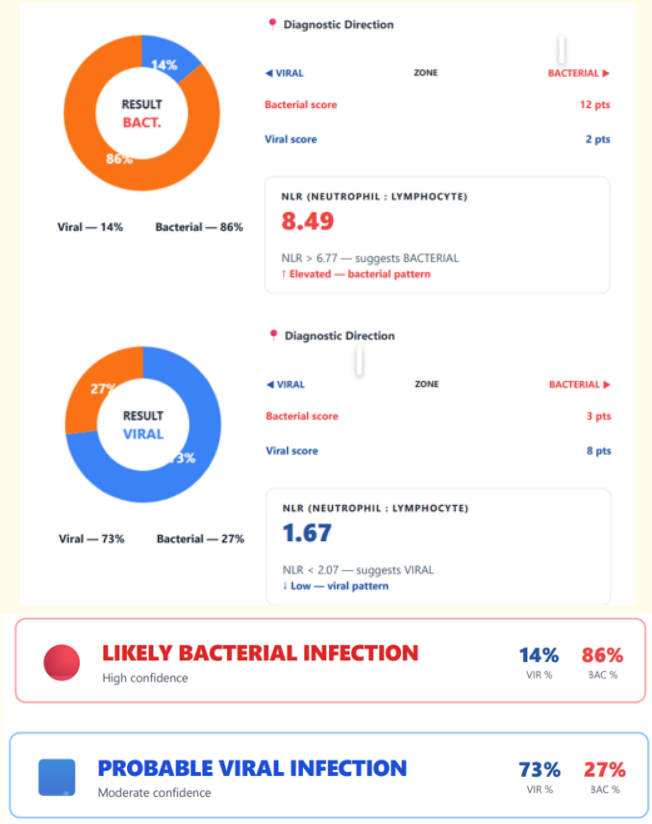

Figure 2

Comparison with Advanced FDA-Cleared Tests: Pros and Cons for India

The following assessment contextualises each platform for Indian clinical practice:

FebriDx (MxA/CRP)

- **Pros:** Rapid (10 min), POC-compatible, no laboratory infrastructure needed, excellent NPV, validated in multiple real-world settings, antibiotic-sparing effect demonstrated.
- **Cons:** USD 25-40 per test (INR 2,000-3,300), prohibitively expensive for routine outpatient use in India; qualitative output only; dedicated device required; limited validation in Indian or tropical-infection contexts; dengue, malaria, and typhoid endemic in India may confound CRP interpretation. MxA may be less sensitive for atypical viral strains circulating in India.

MeMed BV

- **Pros:** Highest diagnostic accuracy among POC platforms (AUC ~0.94), three-component design provides redundancy, quantitative score enables calibrated clinical decision-making.
- **Cons**: USD 50-80 per test (INR 4,000-6,600), plus analyser hardware cost (USD 10,000-15,000); designed for US/EU hospital markets; no published validation in India or LMIC settings; not commercially available in India as of 2026.

Procalcitonin

- **Pros:** Well-established, guideline-endorsed, available in many tertiary Indian centres, FDA-cleared, superior to CRP for bacteraemia detection.
- **Cons**: INR 500-1,500 per test; false positives in non-infectious inflammatory states; POC versions less widely available; adds cost without the comprehensiveness of the full CBC+CRP multi-parameter approach; not informative about viral aetiology specifically.

Multiplex PCR (BioFire, Luminex)

- **Pros:** Identifies specific pathogens, enables targeted antiviral therapy, superior for ICU/immunocompromised patients, outbreak surveillance.

- **Cons:** INR 12,000-20,000 per test; dedicated instrument required; 45-90 minute TAT; no role in primary care or routine outpatient triage; host-response classification not provided, a positive influenza result does not exclude secondary bacterial infection.

CBC+CRP with Computational App

- **Pros:** INR 150-300 per test; universally available; no additional hardware; offline functionality (works without internet); integrates 16 CBC parameters + CRP + NLR + age in evidence-based algorithm; quantitative probability output; generates shareable patient-specific reports; validated in 44,120-case ML study; provides directional guidance in the 10-40 mg/L CRP grey zone where standalone CRP fails; immediate result.
- **Cons:** Does not identify the specific pathogen; not FDA-cleared as a medical device (though its component tests are); clinical integration requires user training; performance in specific Indian disease contexts (tropical infections, co-morbidities, malnutrition) not yet formally validated in a prospective Indian cohort.

Tropical infections and confounders specific to India

Any diagnostic tool deployed in India must account for the endemic burden of tropical infections that can confound standard CBC and CRP interpretation. Dengue fever causes characteristic thrombocytopenia, leukopenia, and haemoconcentration, producing a CBC pattern that the app's algorithm correctly interprets as viral. Malaria can cause thrombocytopenia and anaemia but may elevate CRP substantially during haemolytic crises, potentially generating intermediate scores. Typhoid (enteric fever) produces characteristic relative bradycardia and progressive leukopenia with elevated CRP, a pattern that may generate intermediate bacterial probability scores. COVID-19 produces variable CBC patterns (lymphopenia with high CRP in severe disease, or near-normal CBC with low CRP in mild illness). These disease-specific considerations reinforce the importance of clinical context, the app is explicitly designed as a decision-support tool, not a standalone diagnostic, and its output should always be interpreted alongside history, examination, and clinical probability.

Implementation pathway for the CBC+CRP app in India

An evidence-based, technology-enabled implementation pathway for the CBC+CRP app in the Indian context would include the following steps:

- **Prospective validation study:** A multi-centre prospective cohort study across tertiary, secondary, and primary care facilities in India, enrolling 5,000 febrile patients, with microbiologically confirmed endpoints, to validate and calibrate the algorithm in the Indian disease spectrum.
- **Regulatory pathway:** Registration as Class B (low-moderate risk) software as a medical device (SaMD) under the Central Drugs Standard Control Organisation (CDSCO) regulatory framework, following the Medical Device Rules 2017 (amended 2020).
- **Integration with existing infrastructure:** Pilot deployment in facilities already using the Horiba Microsemi CBC analyser, enabling direct paste-in of machine-generated results into the app for automated parsing.
- **Training and rollout**: Brief (2-hour) training modules for medical officers and laboratory staff; integration into clinical decision-making protocols for febrile illness management.
- **Antibiotic stewardship monitoring**: Prospective tracking of antibiotic prescription rates, clinical outcomes, and cost savings in intervention versus control facilities.

Future Directions

The convergence of routine haematology, machine learning, and mobile computing creates an unprecedented opportunity to transform infection diagnosis globally. Several research directions deserve priority:

- **Large-scale Indian validation:** A dedicated prospective study calibrating the ML model to the Indian disease spectrum, including tropical infections, is essential before widespread deployment.
- **Temporal dynamics:** CBC and CRP change over the disease course; incorporating serial measurements into the model could substantially improve accuracy in early-presentation cases.
- **Paediatric adaptation**: The current Guncar., *et al.* [1] model was trained exclusively on adults. Dedicated paediatric validation, particularly important given higher rates of febrile illness in children, is a priority.

- **Integration with specific pathogen testing:** The greatest diagnostic accuracy will likely be achieved by combining host-response classification (CBC+CRP or MxA/CRP) with targeted pathogen identification (e.g., rapid influenza/COVID/malaria antigen tests). These approaches are complementary, not competitive.
- **AI-driven threshold personalisation**: Future algorithms may incorporate patient-specific baseline parameters e.g., baseline WBC in patients with known chronic infections to generate personalised, rather than population-based, probability thresholds.
- **Federated learning for continuous model improvement:** As the app generates anonymised usage data across multiple centres, federated ML approaches could enable continuous model refinement without compromising patient privacy.

Conclusions

The complete blood count, taken together with C-reactive protein, constitutes a scientifically robust, biologically grounded, and clinically validated multi-parameter host-response signature that discriminates bacterial from viral infection with clinically meaningful accuracy. Machine learning analysis of 44,120 adult cases confirms that the integration of all CBC parameters with CRP, through an XGBoost model, achieves an AUC of 0.905 [1], outperforming CRP alone by 17.9 percentage points in the critical diagnostic grey zone (CRP 10-40 mg/L). The neutrophil-to-lymphocyte ratio (NLR >6.77 bacterial; <2.07 viral) provides a computationally trivial but clinically powerful single derived metric accessible from any CBC differential.

Newer FDA-cleared diagnostic platforms, including the FebriDx MxA/CRP lateral flow assay and the MeMed BV TRAIL/IP-10/CRP host-response score, represent genuine scientific advances and are appropriate additions to the diagnostic armamentarium in well-resourced settings. Their consistently high negative predictive values provide actionable clinical confidence for antibiotic deferral. However, their current costs (USD 25-80 per test), hardware requirements, and limited validation in LMIC and tropical-infection contexts render them impractical for routine deployment across the vast majority of Indian clinical settings.

In the Indian context, the CBC+CRP computational approach, implemented as an offline, device-agnostic app that intelligently integrates the Horiba Microsemi's 16-parameter output with CRP and clinical variables, offers a democratically accessible, scientifically grounded, and immediately deployable solution. It leverages infrastructure that already exists in Indian laboratories, generates results within seconds, produces shareable patient reports, and costs effectively nothing beyond the marginal cost of the routine CBC and CRP tests that would have been ordered regardless. Formal prospective validation in Indian cohorts and regulatory registration under CDSCO guidelines are the priority next steps to transform this approach from a clinically promising tool into a standard-of-care diagnostic resource.

The "holy grail" of infection discrimination may not require expensive innovation, it may be hiding in plain sight in the data that Indian laboratories generate every day, waiting to be unlocked by algorithmic intelligence.

Clinical Disclaimer

This review article is intended for educational and scientific purposes for qualified healthcare professionals. The CBC+CRP computational app described herein is a clinical decision-support tool, not a standalone diagnostic device, and its outputs must always be interpreted in conjunction with clinical history, physical examination, and professional clinical judgement. All diagnostic thresholds cited in this article are derived from published literature and may require calibration for specific patient populations, disease settings, and geographies. The authors assume no liability for clinical decisions made on the basis of this review.

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