Novel biomarkers to distinguish bacterial from non-bacterial infection: a systematic review

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Background

- Distinguishing between serious and invasive bacterial infections and non-bacterial aetiologies is challenging, particularly in high-risk groups such as febrile infants under 90 days old.
- Clinicians tend to adopt a cautious approach, potentially leading to the overuse of antibiotics.
- Existing biomarkers to identify bacterial infection such as C-reactive protein and procalcitonin have limitations.
- Several novel biomarkers are emerging to improve diagnosis.

Objectives

- Provide an updated literature search for novel biomarkers of bacterial infection
- Assess the diagnostic performance of the biomarkers for distinguishing bacterial from non-bacterial infection
- Assess the extent of biomarker research for bacterial infections in febrile infants

Methods

Inclusions:	Exclusions:
• participants of any age	• reviews
• presenting with signs and symptoms of infection	• laboratory models/ animal studies
• proteins/ biomarkers in blood plasma or serum	• non-novel biomarkers e.g. CRP and PCT only
• diagnostic performance (bacterial vs non-bacterial infection)	• haematological markers
• English language	• immunocompromised patients
• published January 2019- January 2024	• flow cytometry only

Literature search (Medline Ovid, January 11, 2024)

List of studies included in previous systematic reviews compiled

Screening by title and abstract (Rayyan online management programme)

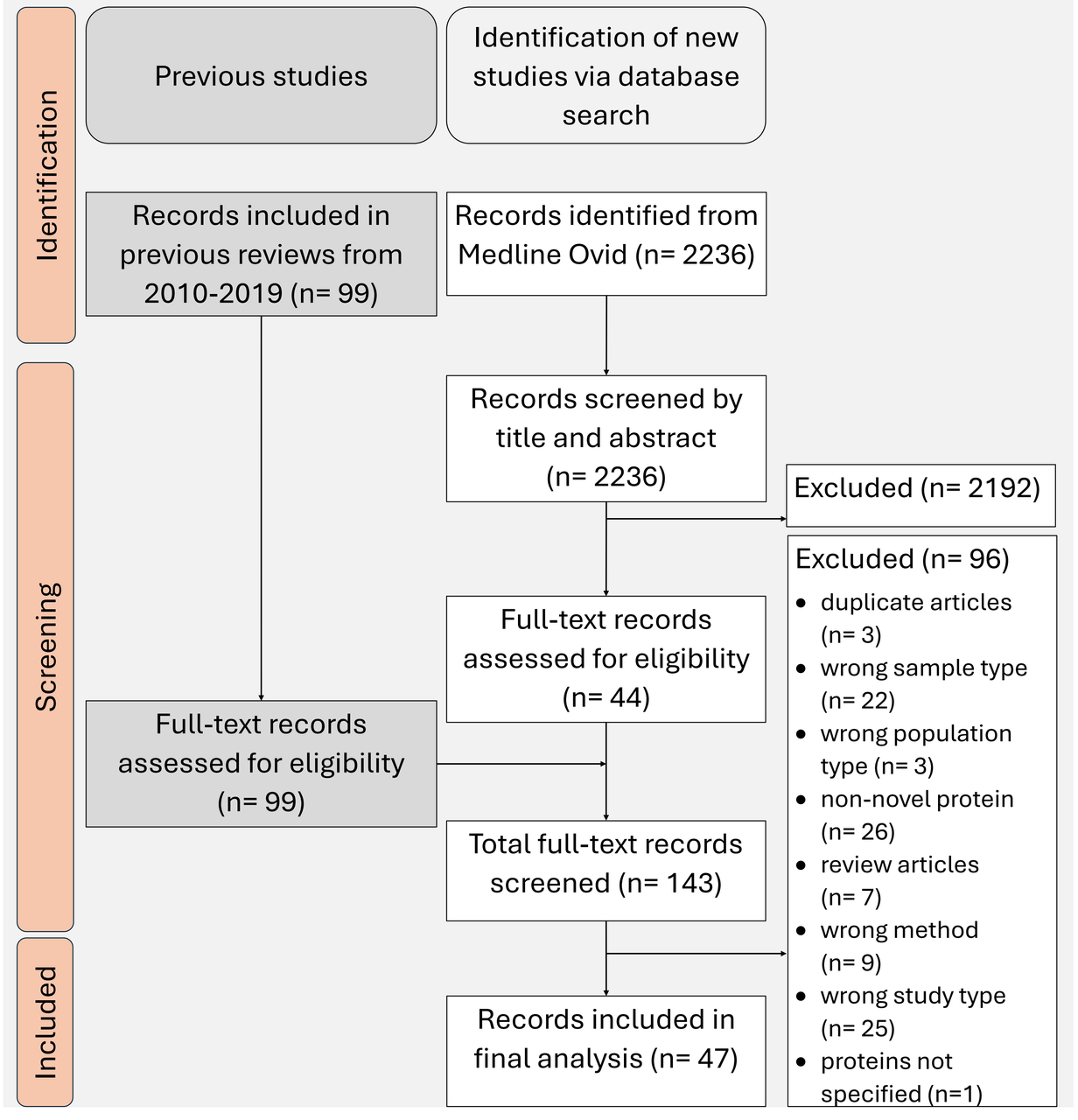
Full-text review (excel spreadsheet)

Data extraction (standardised data extraction tool)

Applicability and risk of bias (QUADAS-2 assessment tool)

Selection of biomarkers-
- low risk of bias
- sensitivity ≥90% & specificity ≥80%
or
AUC ≥0.9

Results



Biomarker/ Signature	Number of Publications	Number of Participants	Sensitivity / %	Specificity / %	AUC
IFN-γ [1]	6	962	100.0	88.2	0.94
IFN-a [2]	1	101			0.93
LCN2 [3,4]	9	2,220	98.5	94.3	0.97
			91.8	81.2	0.91
TRAIL+IP-10+CRP [5,6,7,8,9,10]	8	2,638	93.5	94.3	
			87.0	90.0	0.94
			93.8	89.8	
			86.7	91.1	0.90
			94.0	88.0	
			98.1	88.4	
SELE+IL18+NCAM1+ LG3BP+LCN2+IFN-γ [11]	1	306	90.4	89.6	0.89

- 26 studies included a paediatric population, with 42% (11/26) excluding infants.
- Of the 11 studies in which the biomarkers or signatures met the pre-specified thresholds, 27% (3/11) excluded infants and 9% (1/11) excluded neonates <seven days old.

Conclusions & Next Steps

- IFN-γ, LCN2, TRAIL and IP-10 identified, consistent with findings from previous reviews [12,13].
- Infants excluded from several studies and remain under-represented.
- The diagnostic performance of the biomarkers appeared to vary across different clinical settings.
- TRAIL, IP-10, and CRP have shown to change expression depending on infection severity, may hold important prognostic roles.
- Incorporating patient-centred outcomes into clinical trials is important to assess if biomarkers with high diagnostic performance translate into practical benefits for the patients.
- **Next step: validation.**

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