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Utility of respiratory viral testing in the risk stratification of young febrile infants presenting to emergency care settings: a protocol for systematic review and meta-analysis

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ABSTRACT

Introduction Febrile infants under 3 months of age are at risk of invasive bacterial infection (IBI). It is currently unclear if testing for respiratory viruses may have a role in IBI risk stratification. If found to be associated with the likelihood of IBI, respiratory viral point-of-care testing may improve patient and caregiver experience, reduce costs and enhance antimicrobial stewardship.

Methods and analysis This is a study protocol for a systematic review and meta-analysis that aims to answer the following question: *In young febrile infants presenting to emergency care settings does a positive respiratory viral test for RSV, Influenza or SARS-CoV2 (relative to a negative test) add value to current risk stratification pathways for the exclusion of invasive bacterial infection, subsequently enabling safe de-escalation of investigation and treatment*?

A search strategy will include MEDLINE, EMBASE, Web of Science, The Cochrane Library and grey literature. Abstracts and then full texts will be independently screened for selection. Data extraction and quality assessment will be completed by two independent authors.

The primary objective is to analyse the ability of a positive respiratory viral test to identify the overall risk of IBI. The secondary objective is to perform a subgroup analysis to investigate how the risk stratification alters based on other variables including virus type, patient characteristics and the presence of an identified source of fever.

Bivariate random-effects meta-analysis will be undertaken. Diagnostic odds ratios (OR), sensitivity, specificity and positive and negative likelihood ratios will be calculated. The degree of heterogeneity and publication bias will be investigated and presented.

Ethics and dissemination Ethical approval is not required. We will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines to disseminate the study results through publication and conference presentations.

PROSPERO registration number This protocol is registered in PROSPERO—ID number: CRD42023433716.

WHAT IS ALREADY KNOWN ON THIS TOPIC?

⇒ Febrile infants under 3 months are at high risk of invasive bacterial infections and are often challenging to diagnose.
⇒ Current clinical practice guidelines support risk stratification to reduce unnecessary procedures and antibiotic use but it is unclear if viral respiratory point-of-care testing is beneficial.

WHAT THIS STUDY ADDS?

⇒ This is the protocol for a systematic review and meta-analysis to evaluate if respiratory viral testing improves risk assessment for febrile infants.
⇒ It will explore if positive viral tests correlate with reduced invasive bacterial infection risk.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY?

⇒ Positive findings could influence guidelines to integrate viral testing into risk assessments in more targeted management, reducing costs and unnecessary interventions while improving antimicrobial stewardship.

INTRODUCTION

This is a study protocol for a systematic review and meta-analysis which aims to answer the following question:

In young febrile infants presenting to emergency care settings (P—Population), does a positive respiratory viral test for respiratory syncytial virus (RSV), influenza or SARS-CoV2 (I—Intervention) relative to a negative test (C—Comparison) add value to current risk stratification pathways for the exclusion of invasive bacterial infection (IBI), subsequently enabling safe de-escalation of investigation and treatment (O—Outcome).

This protocol is registered in PROSPERO with the ID number CRD42023433716.

Rationale

Infants under 3 months of age presenting with fever are at risk of IBIs, namely bacteraemia and meningitis.[1–3] As they often present with non-specific symptoms and signs, risk stratification is challenging for even the most experienced clinicians.[4 5] Historically, an indiscriminate approach has been taken, investigating all with invasive procedures such as lumbar puncture and administering treatment with broad-spectrum parenteral antibiotics.[6]

Multiple clinical decision aids (CDAs) have been developed internationally to tailor this approach, but the ideal management of febrile infants remains a topic of debate without widespread consensus.[2 6–10] All of the CDAs make use of a range of clinical tests, including urinalysis and blood biomarkers such as C reactive protein and more recently procalcitonin.[1 2 11] There is growing interest in the role of respiratory viral testing in risk stratification, with several studies reporting an association between respiratory viral pathogen detection and reduced risk of IBIs.[8 12 13] None of the current CDAs incorporates respiratory viral tests.[2 6–8 14]

The COVID-19 pandemic accelerated the adoption of point-of-care (POC) testing for respiratory viruses, which has now become commonplace in emergency departments.[15 16] These tests enable faster and more affordable results, allowing for timely decisions on patient care. Viruses associated with surges in incidence in febrile infants include RSV and influenza viruses in addition to SARS-CoV-2. POC tests for these three viruses are also commercially available. Implementing POC tests for these may help identify a lower-risk cohort of febrile infants who may safely avoid painful, invasive procedures and parenteral broad-spectrum antibiotics. A positive viral test may therefore not only improve the overall patient experience but also reduce costs and hospital stays and promote better antimicrobial stewardship.

Clinical pathway

Within the UK, the National Institute for Health and Care Excellence sepsis guidance advises that all young febrile infants receive immediate treatment with parenteral antibiotics and hospital admission, regardless of age, clinical findings or investigation results.[6] This initial management should occur within 1 hour of presentation to the acute healthcare setting.[6] A retrospective multicentre cohort study of young infants presenting with fever to emergency departments within the UK between 2018 and 2019 reported that 90% were admitted to hospital, 76% received parenteral antibiotics and 59% underwent lumbar puncture despite only 2% having evidence of IBI.

This contrasts with international approaches adopted in Europe and the USA. CDAs such as the 'Step-by-Step' and the American Academy of Pediatrics CDA support a tailored sequential approach to assessment and treatment.[1 2 8] Well-appearing infants over 28 days old undergo focused investigations and treatment dependent on biomarker testing with a proportion managed in the community without a lumbar puncture or parenteral antibiotics.[1 2 8]

Safely doing less has many benefits including improved antimicrobial stewardship, fewer painful procedures and potential cost savings. Infants aged <3 months have been shown to incur significantly higher resource use than any other age group of children presenting to emergency departments with fever, reported at £1000.28 (95% CI £82.39 to £2993.37) per child.[17]

Figure 1 illustrates the existing clinical pathway within the UK and highlights a potential alternative pathway that could be implemented subject to the safety and efficacy of respiratory viral POC tests.

METHODS AND ANALYSIS

This systematic review and meta-analysis will adhere to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol standards.

Aim

The objective of this systematic review and meta-analysis is to determine if in young febrile infants, up to and including 90 days of age, a positive respiratory viral test alters the likelihood of IBI.

Eligibility criteria

All studies that include respiratory viral testing (for influenza, RSV or SARS-CoV-2) on young febrile infants, up to and including 90 days of age, presenting to the hospital will be considered. There will be no time or language restrictions; papers not in English will be reviewed using the translation services available through Queen's University Belfast.

Inclusion criteria

Participants of eligible studies will be infants aged 90 days or less presenting to a hospital setting (emergency department or assessment unit) with a fever ≥38°C or a history of a fever within 48 hours of presentation (see table 1).

Studies examining respiratory viral tests alongside other biomarkers may be included as long as the data on the diagnostic performance of the respiratory viral test alone can be extracted. Similarly, studies looking at respiratory viral tests for infants beyond the age range specified may be included, and the study authors will be contacted to assist with data extraction.

Exclusion criteria

- Case studies/series (sample size, n<100), editorials or other narrative articles.
- Studies that were exclusively conducted in neonatal units and only included newborns with suspected neonatal sepsis.
- Studies not reporting IBI.
- Studies reporting respiratory viral testing on samples not obtained from the upper respiratory tract (eg, blood or cerebrospinal fluid) will be excluded due to

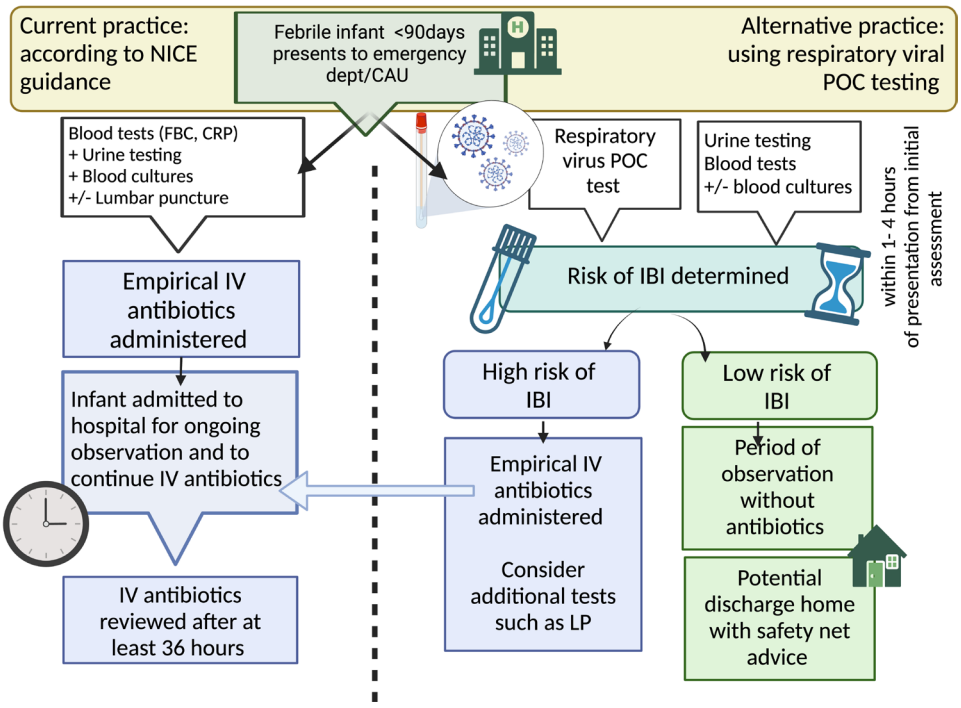

Figure 1 Summary of the current clinical pathway to stratify risk of IBI in the UK in contrast with the prospective integration of POC testing for respiratory viral infections. CAU, clinical assessment unit; CRP, C reactive protein; FBC, full blood count; IBI, invasive bacterial infection; LP, lumbar puncture; NICE, National Institute for Health and Care Excellence; POC, point-of-care.

the invasive procedure required to obtain a sample, limiting the utility for early clinical decisions on risk stratification.

- Studies on the viruses other than RSV, influenza viruses and SARS-CoV-2 will be excluded.
- Studies selecting for samples of positive tests only (ie, no comparator for prevalence of IBI in the two groups; positive viral test, negative viral test).

Information sources and search strategy

A comprehensive electronic search strategy will be performed to identify peer-reviewed articles using MEDLINE, EMBASE, Web of Science and The Cochrane Library. The search strategy will be developed in collaboration with a health librarian. An example of the search strategy is provided in the online supplemental material; however, this may be modified with the final search strategy documented and reported in the published systematic review.

There will be no language restrictions and no time restriction on articles to be included in this review. Unpublished 'grey literature' sources will be identified through clinical trial registries (eg, ClinicalTrials.gov), and during the title and abstract screening, further literature may be identified and considered against eligibility criteria.

Table 1 Inclusion criteria

Inclusion criteria	
Age	≤90 days
Setting	Emergency care (emergency department or assessment unit)
Fever	≥38°C or a history of a fever within 48 hours of presentation
Respiratory viral tests	Commercially available respiratory viral test (for influenza, RSV or SARS-CoV-2) performed on samples obtained from the upper respiratory tract at presentation to the hospital.
IBI	Includes meningitis and bacteraemia defined as positive, non-contaminant, bacterial culture or molecular testing of cerebrospinal fluid (CSF) and blood respectively.

IBI, invasive bacterial infection; RSV, respiratory syncytial virus.

Study records

The results from the systematic search will be independently screened by two of the authors. Screening will initially be limited to titles and abstracts, and subsequently by review of the full text in respect of the inclusion and eligibility criteria as stated. Any disagreement between the two reviewing authors will be resolved independently by a third author. Duplicate studies will be removed. This will be reported and displayed for each stage of study selection.

Data extraction

Data extraction from the selected studies will be undertaken independently by two of the authors. A standardised data extraction tool will be used. Where possible, corresponding authors will be contacted (maximum of three attempts over a 6-week period) and invited to

submit data for studies in which insufficient data is available for inclusion in the meta-analysis.

The following data items will be sought from the included studies:

- Study characteristics: author, publication year, study design, study setting and sample size.
- Reported prevalence of respiratory viral pathogen (SARS-CoV2, RSV and influenza).
- Reported prevalence of IBI by type (meningitis and bacteraemia).
- Participant characteristics: age and clinical features (including well or unwell appearing), and if the child has an apparent source of infection or fever without apparent source (FWAS).
- Inclusion/exclusion of preterm infants (<37 weeks gestational age).
- Index test: type of respiratory viral test, assay used and specimen type.
- Reference standard: definition of IBI, type of culture or PCR used.
- Diagnostic performance metrics: sensitivity, specificity, positive predictive value and negative predictive value.

Data management

A piloting process will be undertaken following screening to tailor the data extraction tool and all amendments will be agreed between the authors. The agreed tool will then be used to assess all of the selected studies. Data management will be performed using *Covidence*. Covidence is a web-based collaboration software platform that streamlines the production of systematic and other literature reviews. All studies will be selected for review and data will be extracted within a timely fashion such that data analysis will be complete within 6 months of the search strategy being performed. A summary of included studies and their quality, according to Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) criteria, will be presented in a table. The data extracted from the selected studies will be reported in a narrative summary together with a table to display key outcomes.

Outcome measures

The primary outcomes of this systematic review and meta-analysis are.

1. To report the number of infants 90 days of age or younger who test positive for a respiratory viral pathogen and have a proven IBI.
2. To report the number of infants 90 days of age or younger who test negative for a respiratory viral pathogen and have a proven IBI.

The secondary outcomes of this systematic review and meta-analysis are.

1. To report the number of infants 90 days of age or younger who test positive for a respiratory viral pathogen and have a proven meningitis.
2. To report the number of infants 90 days of age or younger who test positive for a respiratory viral pathogen and have a proven bacteraemia.
3. To report the number of infants 90 days of age or younger who test negative for a respiratory viral pathogen and have a proven meningitis.
4. To report the number of infants 90 days of age or younger who test negative for a respiratory viral pathogen and have a proven bacteraemia.

Bias assessment

The QUADAS-2 tool will be used independently by the two reviewing authors to assess quality and guide inclusion into the final meta-analyses; any discrepancies will be resolved by the third author.

Data synthesis

The primary objective of this research is to analyse the ability of a positive viral test to identify the overall risk of IBI. The secondary objective is to perform a subgroup analysis to investigate how the risk stratification alters based on other symptoms and factors, including (depending on availability of data):

- Virus type
  - RSV.
  - Influenza viruses.
  - SARS-CoV-2.
- Patient characteristics
  - Well clinical appearance.
  - Biomarkers, including CRP <20 mg/L and procalcitonin (PCT) <0.5 ng/mL.
  - Age grouped by <21 days, 21–28 days and >28 days.
- Identified source of fever (eg, clinical diagnosis of bronchiolitis) or FWAS.

FWAS is defined as axillary or rectal temperature ≥38°C as recorded in the emergency department or reported from a recording at home (within 24 hours), where it is not possible to identify the source of the fever following clinical assessment including medical history and physical examination.

The primary outcome of the meta-analysis will be diagnostic ORs of having IBI when a positive viral test is obtained compared with a negative test. The corresponding 95% CIs will be determined to allow evaluation of the degree of certainty in the estimates obtained. To provide further clinical value, the sensitivity, specificity and positive and negative likelihood ratios will also be calculated.

Forest plots will be used to provide a graphical overview of the results and allow a visual inspection of the degree of heterogeneity in the results of the different studies. The overall effect will be calculated as a weighted average of the individual study ORs. The degree of heterogeneity will be investigated using Cochran's Q and Higgins I^2 statistics and illustrated graphically using funnel plots. Publication bias will be investigated using Egger's test. Bivariate random-effects meta-analysis will be undertaken to account for the anticipated variation in the studies,

with the outcomes summarised both in tables and graphically using summary receiver operating characteristic curves. All analysis will be undertaken within R.

Patient and public involvement

The febrile infants patient and public involvement (PPI) group have helped to inform the research question through a series of virtual meetings. They informed us of the importance of an accurate early diagnosis, the distress of painful investigations such as lumbar puncture, their concerns regarding the overuse of antibiotics and their worries about potentially missed serious infection. The febrile infants PPI group will help to produce a lay summary of the study findings.

Ethics and dissemination

No ethical approval is required for the study since there are no primary data involved. There are no conflicts of interest to declare. This protocol is registered in PROSPERO—ID number: CRD42023433716. Results will be disseminated through presentation at paediatric and emergency medicine conferences and subsequent publication in a peer-reviewed journal.

DISCUSSION

This review and meta-analyses will assess the utility of respiratory viral tests (RSV, SARS-CoV-2 and influenza) in the risk assessment of infants aged 90 days or younger presenting to emergency care settings with possible IBI.

The American Academy of Pediatrics Clinical Practice Guideline *'Evaluation and Management of Well-Appearing Febrile Infants 8 to 60 Days Old'* acknowledges the association between the presence of respiratory viral pathogens and decreased risk of IBIs. However, the challenge lies in determining how a positive viral test result should inform further management, including laboratory evaluation, admission decisions and length of stay. This review and meta-analysis directly respond to the guideline's call for research into how multiplex viral testing may be incorporated into prediction models for IBIs.

If the detection of a respiratory viral pathogen adds value to the performance of current risk stratification practices for febrile young infants, this is likely to hold significant value for patient and family experience, reduction of healthcare costs and improved antimicrobial stewardship.

The benefits of reducing the rate of invasive investigations, such as lumbar punctures, are significant for both infants and their caregivers. Invasive procedures can cause distress and discomfort to infants and anxiety to their caregivers, as confirmed through our Patient and Public Involvement and Engagement (PPIE) group. Implementing less invasive approaches based on viral testing could alleviate these concerns, leading to a more positive experience for families and reduced physical and emotional stress for infants.

The potential to identify a lower-risk cohort through viral testing would enable a more targeted approach, potentially resulting in fewer hospitalisations, less extensive laboratory evaluations and decreased healthcare expenses. Infants aged <3 months incur significantly higher resource use than any other age group of children presenting to emergency departments with fever.[17] This cost-saving potential aligns well with the drive for efficient healthcare resource allocation within not only the UK and Ireland but globally.

If respiratory viral testing is found to be highly sensitive and specific for excluding IBI in this cohort, then this will warrant prospective examination. Policymakers may choose to adopt the use of respiratory viral testing as part of a tailored risk assessment or CDA.

A strength of this review and meta-analysis is its novelty. To the best of the authors' knowledge, this will be the first systematic review and meta-analysis to examine the utility of respiratory viral tests suitable for POC testing (influenza, RSV and SARS-CoV-2) to risk-stratify young febrile infants. It aims to encompass a variety of studies from multiple settings; the heterogeneity is likely to increase the generalisability of the results.

The review and meta-analysis may be limited by the rarity of IBIs and the difficulty in extracting high-quality data in sufficient volumes. This review is primarily focussing on IBI with serious bacterial infection (SBI) examined only as a secondary analysis. It must be noted, however, that caution must be exercised in interpreting results for SBI as it has no universally recognised definition. The results may not be applicable to all settings depending on local practices.

Any important protocol amendments will be documented and clearly stated in the final systematic review.

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Contributors The protocol was initially conceptualised and developed by JE, HN-B and TW. CM and EU further refined the study protocol, contributing to all areas except the search strategy and statistical analysis. JR led the design of the search strategy, while HM and LMcF led the design of the statistical analysis. JE serves as the lead author and guarantor. All authors contributed to revisions of the manuscript and have approved the final version.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, conduct, reporting or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available.

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