National Institute for Health and Care Excellence

Suspected sepsis: recognition, diagnosis and early management

[D] Evidence reviews for rapid tests for assessing infection in people with suspected sepsis.

NICE guideline NG253

Evidence reviews underpinning research recommendation 4 in the NICE guideline

November 2025

Guideline version (Final)

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

Copyright

ISBN: 978-1-4731-7344-6

Contents

1 Rapid antigen tests (RAT) and polymerase chain reaction (PCR) tests for guiding treatment in people with suspected sepsis

1.1 Review question

In people aged 16 or over with suspected sepsis, what is the diagnostic accuracy of rapid antigen tests (RAT) or rapid polymerase chain reaction (PCR) tests for diagnosing specific infections?

1.1.1 Introduction

In people with suspected sepsis RAT or PCR tests may speed up the process of identifying the source of infection, thus enabling clinicians to prescribe appropriate narrow-spectrum antibiotics sooner which should help improve outcomes for people with suspected sepsis. RAT or PCR testing may also help to rule out infection and empower clinicians not to prescribe antibiotics, which may help to negate antimicrobial resistance.

To determine the usefulness of RAT and PCR tests in suspected sepsis, we evaluated them from two perspectives:

Diagnostic Accuracy: This measures whether the tests can correctly identify those with the condition (sensitivity) and confirm those without it (specificity). Accurate classification is crucial for appropriate risk management.

Clinical Effectiveness: This assesses the impact of introducing the test on patient outcomes, often through "test and treat" studies and RCTs. These studies provide direct evidence of the test's impact on patient care pathways.

Both diagnostic accuracy and patient outcomes are essential and complementary. High sensitivity and specificity are important, but the test's impact on patient outcomes, such as timely treatment decisions, is equally critical. A less accurate test might still be valuable if it improves timely and correct treatment for more patients.

The diagnostic accuracy evidence of RAT and PCR tests are presented in this review (Review D), and the clinical effectiveness (impact on patient outcomes) are presented in Review E.

1.1.2 Summary of the protocol

Table 1: PICOS inclusion criteria

Population	Adults aged 16 or over with suspected sepsis who are symptomatic or asymptomatic Exclusion: • People who are or have recently been pregnant • Populations outside of acute hospital, virtual ward and ambulance settings • People with neutropenic sepsis
Index test	Rapid antigen tests taken when a patient is in hospital and investigations for sepsis are ongoing, limited to the following tests relevant to UK practice: • Pneumococcal and legionella urinary antigens • streptococcus group A throat antigen • influenza • Respiratory syncytial virus (RSV) rapid tests from nasopharyngeal samples Rapid PCRs taken when patient presents at hospital and investigations for sepsis start: • PCR for Streptococcus Group A (throat) (single target) • Multiplex PCR A rapid test is defined as one where test results can be produced within 6 hours. Multiplex PCR must use whole blood sample – not culture
Reference Standard	Microbiological culture
Outcomes	• Sensitivity and specificity • Positive and negative likelihood ratios
Study type	• Cross-sectional and cohort diagnostic test accuracy studies.

	• Systematic reviews and meta-analyses of diagnostic accuracy studies

For the full protocol see appendix A.

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.3.1 Search methods

The searches for the effectiveness evidence were run on 13/02/2024. The following databases were searched: MEDLINE (Ovid), Embase (Ovid), the Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Database of Systematic Reviews (Wiley), and Epistemonikos. Full search strategies for each database are provided in Appendix B.

A NICE senior information specialist conducted the searches. The MEDLINE strategy was quality assured by a trained NICE information specialist and all translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the 2015 PRESS Guideline Statement.

1.1.3.2 Protocol deviations

The population as stated in the review protocol was adults aged 16 and over with suspected sepsis and the search strategy was designed around this. Following the initial title and abstract sift for evidence, no studies looking at the diagnostic accuracy of rapid antigen tests in a suspected sepsis population were found. This is likely because the tests are designed to measure diagnostic accuracy of an underlying infection (e.g. pneumonia) rather than sepsis. Following discussion with the guideline committee, a decision was made to include studies on rapid antigen tests in a non-suspected sepsis population as partially direct evidence. The committee felt that these studies would still be useful as diagnosing underlying infections accurately and rapidly was part of the sepsis pathway and could affect the treatment that someone

with suspected sepsis might receive. Studies that are included as indirect evidence are rated down in the overall GRADE assessment. As studies looking at the diagnostic accuracy of PCR testing in a sepsis population were available, a decision was made not to include indirect evidence in a non-suspected sepsis population for this test.

Following the full text sift, the development team found a number of studies on multiplex PCR tests that were already included in existing NICE diagnostic guidance DG20. Two of the tests covered by this guidance (the LightCycler SeptiFast Test MGRADE and the IRIDICA BAC BSI) are no longer available to the NHS and the third (SepsiTest) was not recommended for routine adoption in the NHS and also falls outside of the review protocol description of rapid (<6hours processing time) for this review. For this reason, these tests were excluded.

1.1.4 Diagnostic evidence

1.1.4.1 Included studies

A systematic search carried out to identify potentially relevant studies found 1642 references (see appendix B for the literature search strategy).

These 1642 references were screened at title and abstract level against the review protocol, with 1585 excluded at this level. 10% of references were screened separately by another reviewer with 100% agreement.

The full texts of 57 diagnostic accuracy studies were ordered for closer inspection. 4 of these studies met the criteria specified in the review protocol (appendix A). For a summary of the 4 included studies see table 2.

The clinical evidence study selection is presented as a PRISMA diagram in appendix C.

See section 1.1.14 References – included studies for the full references of the included studies.

On review of the included studies subgroup analysis was not possible as sufficient data was not available on ICU patients and type of infection to undertake analysis. It

was also noted that none of the studies on rapid antigen tests included 16- or 17-year-olds, with one study specifically in people aged 60 and over.

1.1.4.2 Excluded studies

Details of studies excluded at full text, along with reasons for exclusion are given in appendix J.

1.1.5 Summary of studies included in the diagnostic evidence

Table 2 Summary of studies included in the diagnostic evidence

Study details	Setting/ Funding	Population	Index test	Reference standard	Risk of bias[1]	Directness[2]
RAT: Urinary Antigen Tests						
Huijts, 2013. Cross-sectional study. Holland.	Setting: Dutch hospitals (four academic, 15 teaching and four nonteaching hospitals) Funding: Study sponsored by Wyeth Pharmaceuticals Inc. (acquired by Pfizer in October 2009)	Adult patients aged >18 years with a clinical suspicion of community-acquired pneumonia (CAP) or lower respiratory tract infection (LRTI) presenting at the emergency room of the participating hospitals	Urinary Antigen Test (UAD and Urinary Antigen test immunochromatographic assay BinaxNOW)	Blood culture Sputum culture	High	Partially applicable
Kalina, 2020. Cross-sectional study. USA	Setting: Hospital Funding: Study supported by Pfizer	>18 years Radiographically confirmed CAP	Urinary Antigen Test (UAD-2 assay)	Blood culture	High	Partially applicable
Khaleel, 2023. Cross-sectional study. India.	Setting: University-affiliated teaching hospital. Funding: Indian Council of Medical Research (ICMR) – Short-Term Research Studentship (STS) program.	Patients diagnosed with CAP based on clinical features and chest radiographs without any pre-existing illnesses age >60	Urinary Antigen Test (Rapid urinary antigen test [RUAT])	Blood culture Sputum culture	Moderate	Partially applicable

Study details	Setting/ Funding	Population	Index test	Reference standard	Risk of bias[1]	Directness[2]
PCR tests: Multiplex PCR						
Li, 2023. Cross-sectional study. China.	Setting: Maternal and Child Health Hospital and a People's Hospital Funding: Youth Natural Science Foundation of Shandong Province (ZR2021QH367), the Tai-Shan Scholar Program from Shandong Province (No. tsqn202103116); and the Student Innovation and Entrepreneurship Training Program of Shandong Province (No. x2021003).	Patients who were initially admitted with symptoms of suspected sepsis and not treated with antibacterial drugs before blood collection Age range: 15 – 92 (mean age 48)	Multiplex PCR combined with membrane biochip	Blood culture	Moderate	Partially applicable

1. See appendix D for details of risk of bias.
2. Rating based on population, index test, or reference standard not matching the protocol; 'partially applicable' given if 1 or 2 of these are true. See appendix D for details of applicability ratings.

PCR = Polymerase chain reaction

See appendix D for full evidence tables.

1.1.6 Summary of the diagnostic evidence

Table 3 Summary of the diagnostic evidence

No of studies	Study design	Sample size	Positive likelihood ratio (95%CI)	Negative likelihood ratio (95%CI)	Sensitivity/Specificity (95%CI)	Certainty
3[1, a,b,c]	Cross-sectional	13,540	+LR 6.71 (3.06, 14.71)	-LR 0.40 (0.29, 0.56)	Sens: 0.64 (0.51,0.76)	Very low[2]
					Spec: 0.91 (0.76, 0.97)	Very low[2]
1[d]	Cross-sectional	174	+LR 13.56 (7.39, 24.88)	-LR 0.08 (0.02, 0.29)	Sens: 92.9 (77.4, 98.0)	Very low[3]
					Spec: 93.2 (87.9,96.2)	Very low[3]

1. 3 studies but 4 comparisons
2. Rated down for risk of bias, partial indirectness, imprecision and inconsistency.
3. Rated down for risk of bias and partial indirectness and imprecision

a. Huijts 2013
b. Kalina 2020
c. Khaleel 2023
d. Li 2023

See appendix F for full GRADE tables.

1.1.7 Economic evidence

Economic evidence was not considered for this review question because this question refers to the clinical evidence only. The cost-effectiveness of RAT and PCR tests are considered in the related evidence review E.

1.1.8 The committee's discussion and interpretation of the evidence

1.1.8.1. The outcomes that matter most

The committee agreed that sensitivity and specificity should be the primary outcomes of interest to determine a test's accuracy, a test with high sensitivity would be useful for identifying the largest number of people positive for infection. A low sensitivity would result in a high number of false negatives which could lead to not treating someone with infection quickly enough, discharging them incorrectly or not giving them the right antibiotics. This could have consequences for people with suspected sepsis, potentially leading to a worsening of their condition and/or putting them at higher risk of serious illness or death. The committee also agreed that ruling out infection accurately with a highly sensitive test was important from an antimicrobial stewardship perspective. The committee agreed specificity was also important as a test with low specificity might result in people who did not need them being given antibiotics inappropriately.

In addition to the evidence on diagnostic accuracy, the committee also considered the evidence for review E, which looked for evidence on the clinical effectiveness (patient outcomes) of using these tests.

1.1.8.2 The certainty of the evidence

3 studies assessed as being at high or moderate risk of bias were used in a meta-analysis for the sensitivity and specificity of urinary antigen tests for *streptococcus pneumoniae*. The certainty of this evidence (assessed using GRADE) for sensitivity and specificity was found to be very low. This assessment was based on the high risk of bias assessment, unexplained heterogeneity between the studies and a lack of applicability due to the populations not having suspected sepsis. The committee noted that the evidence for urinary antigen tests excluded those aged 16-17 and one study contained only people over 60, however they felt that based on their expertise and experience, they could extrapolate these results for the whole population. The

committee agreed that while it was useful to review the results from these studies, it was difficult from this limited evidence on one type of test for *streptococcus pneumoniae* to generalise for the diagnostic accuracy or effectiveness of these tests in a suspected sepsis population who might have other types of infection.

1 study on multiplex PCR testing was rated as having a moderate risk of bias, with sensitivity and specificity outcomes given a GRADE assessment of very low. The assessment was based on risk of bias and applicability which was rated down due to the setting of a maternity and children's hospital and the resulting population containing some children and people who are or have recently been pregnant, both of whom were an exclusion from the review protocol. While the committee thought the results from the multiplex PCR test were promising, they felt their ability to make a recommendation for practice was weakened by the low-certainty rating, the fact that this evidence was from a single study with a small partially applicable population and that the availability of multiplex PCR testing varied across the country.

No studies were found on the diagnostic accuracy or effectiveness of rapid tests in ambulance or mental health settings.

Overall, the committee acknowledged there was a gap in high certainty evidence for the diagnostic accuracy and effectiveness of rapid testing to help in the early management of people with suspected sepsis and therefore decided to write a research recommendation to address this gap.

1.1.8.3 Benefits and harms

The committee agreed that while rapid testing in people with suspected sepsis could be useful in understanding if someone has an infection or what that infection is, in practice most clinicians would not withhold giving antibiotics early to people who were seriously ill with a high NEWS2 score regardless of the test results. Committee members discussed the utility of the tests for a suspected sepsis population, commenting that someone could have a positive result for infection but still be very well and conversely someone could have a negative result but be very unwell; the test results alone would not determine how someone is treated.

There was consensus that there could be a role for multiplex PCR tests given the broad range of pathogens these were designed to detect. The committee noted that this type of testing was used in practice variably with critically ill patients who had already been assessed, to provide a more specific diagnosis of the type of infection they have and use this to switch them to pathogen specific antibiotics.

The committee discussed the relative benefits and harms of rapid testing in people at different risk levels according to their NEWS2 score. Some committee members felt high risk patients were most in need of rapid tests to quickly diagnose and accurately treat them given the critical timeframe and risk of complications, however some members felt that people who are high risk should be treated immediately regardless of tests results and that these tests would be more useful for lower risk patients to help stratify their risk further and prevent them becoming more ill.

Overall, the committee felt that the role for rapid testing was in helping to refine the choice of antibiotics in people with suspected sepsis, but that more evidence would be required to make a practice recommendation on this in future. They therefore developed a research recommendation focused on how rapid microbiological testing can guide management in people with suspected sepsis.

1.1.8.4 Cost-effectiveness and resource use

Economic evidence was not considered for this review question. Since no recommendations were made, there are no resource implications or additional costs. The committee discussion of the cost effectiveness of RAT and PCR tests can be found in evidence review E.

1.1.9 Recommendations supported by this evidence review

No recommendations were made from this evidence review but a research recommendation on rapid microbiological testing was developed see Appendix H.

1.1.10 References – included studies

1.1.10.1 Diagnostic

Huijts, Susanne M, Pride, Michael W, Vos, Josephine M I et al. (2013) Diagnostic accuracy of a serotype-specific antigen test in community-acquired pneumonia. The European respiratory journal 42(5): 1283-90

Kalina, Warren V, Souza, Victor, Wu, Kangjian et al. (2020) Qualification and Clinical Validation of an Immunodiagnostic Assay for Detecting 11 Additional Streptococcus pneumoniae Serotype-specific Polysaccharides in Human Urine. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 71(9): e430-e438

Khaleel, Mohammed, Samreen, Sara, Sirangi, Saritha et al. (2023) Evaluation of a Rapid Urine Antigen Detection Assay as a Point-of-Care Test in the Diagnosis of Community-Acquired Pneumonia. Cureus 15(8): e44078

Li, Yun, Zhao, LuJie, Wang, Jingye et al. (2023) A new application of multiplex PCR combined with membrane biochip assay for rapid detection of 9 common pathogens in sepsis. PeerJ 11: e15325

1.1.10.2 Economic

Economic evidence was not considered for this review question.

1.1.11 References – other

No other references were utilised in this review (Review D)

Appendices

Appendix A – Review protocols

Review protocol for rapid antigen testing for diagnosing infection in people with suspected sepsis

ID	Field	Content
0.	PROSPERO registration number	CRD42024521362
1.	Review title	Diagnostic accuracy of rapid antigen tests or rapid PCR tests for infections in people aged 16 or over with suspected sepsis.
2.	Review question	In people aged 16 or over with suspected sepsis, what is the diagnostic accuracy of rapid antigen tests or rapid PCR tests for diagnosing specific infections?
3.	Objective	To determine the diagnostic accuracy of rapid antigen or rapid PCR testing for diagnosing underlying infections in people aged 16 or over with suspected sepsis. A rapid test is defined as one where test results can be produced within 6 hours.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • Epistemonikos • MEDLINE • MEDLINE (Ovid) • Embase (Ovid) • EconLit (Ovid) • INAHTA Searches will be restricted by: • 1980

		• English Language • Human studies • Conference abstracts excluded • OECD countries Other searches: • Reference searching The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Any source infection in people with suspected sepsis
6.	Population	Inclusion: • Adults aged 16 or over with suspected sepsis who are symptomatic or asymptomatic Exclusion: • Children under the age of 16 • People who are or have recently been pregnant • Populations outside of acute hospital, virtual ward and ambulance settings • People with neutropenic sepsis
7.	Test	Rapid antigen tests taken when a patient is in hospital and investigations for sepsis are ongoing, limited to the following tests relevant to UK practice: • Pneumococcal and legionella urinary antigens • streptococcus group A throat antigen • influenza • Respiratory syncytial virus (RSV) rapid tests from nasopharyngeal samples Rapid PCRs taken when patient presents at hospital and investigations for sepsis start: • PCR for Streptococcus Group A (throat) (single target) • Multiplex PCR A rapid test is defined as one where test results can be produced within 6 hours.

		Multiplex PCR must use whole blood sample – not culture.
8.	Reference standard	Microbiological culture
9.	Types of study to be included	• Cross-sectional and cohort diagnostic test accuracy studies. • Systematic reviews and meta-analyses of diagnostic accuracy studies
10.	Other exclusion criteria	• All other study types. • Diagnostic accuracy studies that do not report sufficient information to allow a 2x2 table (TP, FP, TN, FN) to be constructed will be excluded. • Non-English language studies • Studies using different reference standards across participants based on result of index test • Studies on rapid antigen tests or PCR tests that take longer than 6 hours to generate test results • Studies on rapid antigen tests for Malaria and Covid-19
11.	Context	The current guideline recommends that broad-spectrum antibiotics should be given to people with suspected sepsis until the source of infection can be identified, at which point narrow-spectrum antibiotics can be given if appropriate. RAT or PCR tests may speed up the process of identifying the source of infection, thus enabling clinicians to prescribe appropriate narrow-spectrum antibiotics sooner which should help improve outcomes for people with suspected sepsis. RAT or PCR testing may also help to rule out infection and empower clinicians not to prescribe antibiotics, which may help to negate antimicrobial resistance.
12.	Primary outcomes (critical outcomes)	Sensitivity and specificity
13.	Secondary outcomes (important outcomes)	Positive and negative likelihood ratios
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI-reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.2). Study investigators may be contacted for missing data where time and resources allow.

		Where appropriate, this review will make use of the priority screening functionality within the EPPI-reviewer software. At least 50% of the data set will be screened and we will stop screening after that if we screen more than 250 records without an include
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the QUADAS-2 checklist as described in Developing NICE guidelines: the manual.
16.	Strategy for data synthesis	**Approach to meta-analysis** Meta-analysis of diagnostic test accuracy data will be conducted with reference to the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy (Deeks et al. 2010). Where five or more studies are available for all included strata, a bivariate model will be fitted using the mada package in R v3.4.0, which accounts for the correlations between positive and negative likelihood ratios, and between sensitivities and specificities. Where sufficient data is not available (2-4 studies), separate independent pooling will be performed for positive likelihood ratios, negative likelihood ratios, sensitivity and specificity, using Microsoft Excel. This approach is conservative as it is likely to somewhat underestimate test accuracy, due to failing to account for the correlation and trade-off between sensitivity and specificity (see Deeks 2010). Random-effects models (der Simonian and Laird) will be fitted for all syntheses, as recommended in the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy (Deeks et al. 2010). **Approach to GRADE** Evidence from diagnostic accuracy studies will initially be rated as high-quality, and then downgraded according to the standard GRADE criteria (risk of bias, inconsistency, imprecision and indirectness). The choice of primary outcome for decision making will be determined by the committee and GRADE assessments will be undertaken based on these outcomes. This decision will be accounted for and documented as part of the discussion section of the review. In all cases, the downstream effects of diagnostic accuracy on patient- important outcomes will be considered. This will be done explicitly during committee deliberations and reported as part of the discussion section of the review detailing the likely consequences of true positive, true negative, false positive and false negative test results. In reviews where a decision model is being carried (for example, as part of an economic analysis), these consequences will be incorporated here in addition.
17.	Analysis of sub-groups	ICU patients

		Type of infection – bacterial/viral: - Urinary - Respiratory - Influenza		
18.	Type and method of review	☐ Intervention ☒ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)		
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	January 2024		
22.	Anticipated completion date	August 2025		
23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
		Preliminary searches	☑	☑
		Piloting of the study selection process	☑	☑
		Formal screening of search results against eligibility criteria	☑	☑
		Data extraction	☑	☑
		Risk of bias (quality) assessment	☑	☑
		Data analysis	☑	☑
26.	Funding sources/sponsor	This systematic review is being completed by the guideline development team which receives funding from NICE.		
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant		

		interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: tbc
29.	Other registration details	None
30.	Reference/URL for published protocol	tbc
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	Sepsis, Rapid Antigen Testing, PCR, Infection
33.	Details of existing review of same topic by same authors	This is a new review question that will update Sepsis: recognition, diagnosis and early management NG51
34.	Current review status	☐ Ongoing ☐ Completed but not published ☒ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35..	Additional information	N/A
36.	Details of final publication	www.nice.org.uk

Appendix B – Literature search strategies

Background and development

Search design and peer review

A NICE Senior Information Specialist (SIS) conducted the literature searches for the evidence review. The searches were run on 13 02 2024.

This search report is compliant with the requirements of the PRISMA Statement for Reporting Literature Searches in Systematic Reviews (for further details see: Rethlefsen M et al. PRISMA-S. *Systematic Reviews*, 10(1), 39).

The MEDLINE strategies below were quality assured (QA) by a trained NICE SIS. All translated search strategies were peer reviewed by another SIS to ensure their accuracy. Both procedures were adapted from the Peer Review of Electronic Search Strategies Guideline Statement (for further details see: McGowan J et al. PRESS 2015 Guideline Statement. *Journal of Clinical Epidemiology*, 75, 40-46).

The principal search strategies were developed in MEDLINE (Ovid interface) and adapted, as appropriate, for use in the other sources listed in the protocol, taking into account their size, search functionality and subject coverage.

Review management

The search results were managed in EPPI-Reviewer v5. Duplicates were removed in EPPI-R5 using a two-step process. First, automated deduplication is performed using a high-value algorithm. Second, manual deduplication is used to assess "low-probability" matches. All decisions made for the review can be accessed via the deduplication history.

Prior work

The search terms for the sepsis population from '(A) Evidence reviews for stratifying risk of severe illness or death from sepsis' in NG51 (Jan 2024) were used to inform the population terms for the search strategy.

Search limits and other restrictions

Formats

Limits were applied in adherence to standard NICE practice and the review protocol to exclude:

Animal studies

Conference abstracts and posters

Registry entries for ongoing clinical trials or those that contain no results

Papers not published in the English language.

The limit to remove animal studies in the searches was the standard NICE practice, which has been adapted from:

Dickersin K, Scherer R & Lefebvre C. (1994) Systematic Reviews: Identifying relevant studies for systematic reviews. *BMJ*, 309(6964), 1286.

Date limits

A date limit of 1980 to 2024 was applied, as stated in the review protocol.

Search filters and classifiers

Effectiveness searches

Systematic reviews filters:

Lee, E. et al. (2012) An optimal search filter for retrieving systematic reviews and meta-analyses. BMC Medical Research Methodology, 12(1), 51.

In MEDLINE, the standard NICE modifications were used: pubmed.tw added; systematic review.pt added from MeSH update 2019.

In Embase, the standard NICE modifications were used: pubmed.tw added to line medline.tw.

Randomised controlled trials filters:

The MEDLINE RCT filter was McMaster Therapy – Medline - “best balance of sensitivity and specificity” version.

The standard NICE modifications were used: the MeSH heading randomized controlled trial/, which is equivalent to randomized controlled trial.pt was exploded to capture newer, narrower terms equivalence trial/ and pragmatic clinical trial. The free-text term randomized.mp was also changed to the (more inclusive) alternative randomi?ed.mp. to capture both UK and US spellings.

Haynes RB et al. (2005) Optimal search strategies for retrieving scientifically strong studies of treatment from Medline: analytical survey. BMJ, 330, 1179-1183.

The Embase RCT filter was McMaster Therapy – Embase “best balance of sensitivity and specificity” version.

Wong SSL et al. (2006) Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. *Journal of the Medical Library Association*, 94(1), 41-47.

Cohort studies terms:

Terms for cohort studies were used from the observational studies filters. The terms used for observational studies are standard NICE practice that have been developed in house.

OECD countries geographic search filters:

The OECD countries filters were used without modification:

Ayiku, L., Hudson, T., Williams, C., Levay, P., & Jacob, C. (2021). The NICE OECD countries' geographic search filters: Part 2 - Validation of the MEDLINE and Embase (Ovid) filters. Journal of the Medical Library Association, 109(4), 583–589.

Effectiveness care searches

Database results

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Cochrane Central Register of Controlled Trials (CENTRAL)	13th Feb 2024	Wiley	Issue 2 of 12, February 2024	91
Cochrane Database of Systematic Reviews (CDSR)	13th Feb 2024	Wiley	Issue 2 of 12, February 2024	0
Embase	13th Feb 2024	Ovid	Embase <1974 to 2024 February 12>	1131
Epistemonikos	13th Feb 2024	Epistemonikos	Searched 13th February 2024	213
MEDLINE	13th Feb 2024	Ovid	Ovid MEDLINE(R) ALL <1946 to February 12, 2024>	781

Search strategy history

Database name: MEDLINE ALL

Searches	
1	exp sepsis/ (144490)
2	sepsis.ti,ab. (122217)
3	blood-borne pathogens/ (3042)
4	(blood* adj2 (pathogen* or poison*)).ti,ab. (3410)
5	exp systemic inflammatory response syndrome/ (152606)
6	'systemic inflammatory response syndrome*'.ti,ab. (5962)
7	sirs.ti,ab. (6686)
8	(septicaemi* or septicemi*).ti,ab. (22462)
9	((septic or cryptic) adj2 shock).ti,ab. (28001)
10	(pyaemi* or pyemi* or pyohemi*).ti,ab. (266)
11	(bacter?emi* or fung?emi* or parasit?emi* or vir?emi*).ti,ab. (73431)
12	(hypotension adj3 induced adj3 hypoperfusion).ti,ab. (7)
13	or/1-12 (288506)
14	Rapid Diagnostic Tests/ (96)
15	Point-of-Care Systems/ (16985)
16	antigen*.tw. (698255)
17	(RADT* or RDT*).tw. (3719)

Searches
18 ((rapid* or fast* or quick* or time* or short* or (point adj2 care) or poc or bedside or "bed side") adj3 (diagnos* or detect* or assay* or test*)).tw. (328346)
19 or/14-18 (1020571)
20 Streptococcal Infections/ (35270)
21 (pneumococc* or "S pneumoniae*" or legionel* or streptococc*).tw. (143906)
22 Influenza, Human/ (59057)
23 (influenza* or flu).tw. (148438)
24 Respiratory Syncytial Viruses/ (6377)
25 (syncytial* or "rs virus*" or rsv*).tw. (28132)
26 or/20-25 (319887)
27 19 and 26 (36377)
28 exp Polymerase Chain Reaction/ (467490)
29 (Polymerase Chain Reaction* or pcr* or mpcr* or qpcr*).tw. (830261)
30 28 or 29 (1023285)
31 Streptococcal Infections/ (35270)
32 streptococc*.tw. (115281)
33 31 or 32 (125525)
34 30 and 33 (8358)
35 27 or 34 (43510)
36 13 and 35 (1858)
37 (sensitiv: or diagnos:).mp. or di.fs. (7567703)
38 Likelihood Functions/ (23889)
39 likelihood*.tw. (192701)
40 or/37-39 (7705554)
41 36 and 40 (941)
42 exp Case-Control Studies/ (1481195)
43 exp Cohort Studies/ (2572412)
44 Cross-Sectional Studies/ (492558)
45 (cohort adj (study or studies)).tw. (340710)
46 cohort analy$.tw. (12690)
47 (follow up adj (study or studies)).tw. (57625)
48 longitudinal.tw. (338733)
49 prospective.tw. (743668)
50 retrospective.tw. (790773)
51 cross sectional.tw. (547147)
52 case control$.tw. (164117)
53 or/42-52 (4048393)
54 36 and 53 (339)
55 (MEDLINE or pubmed).tw. (348181)
56 systematic review.tw. (291086)
57 systematic review.pt. (252314)
58 meta-analysis.pt. (195012)
59 intervention$.ti. (209932)
60 or/55-59 (726426)
61 36 and 60 (20)
62 41 or 54 or 61 (1030)

Searches
63 afghanistan/ or africa/ or africa, northern/ or africa, central/ or africa, eastern/ or "africa south of the sahara"/ or africa, southern/ or africa, western/ or albania/ or algeria/ or andorra/ or angola/ or "antigua and barbuda"/ or argentina/ or armenia/ or azerbaijan/ or bahamas/ or bahrain/ or bangladesh/ or barbados/ or belize/ or benin/ or bhutan/ or bolivia/ or borneo/ or "bosnia and herzegovina"/ or botswana/ or brazil/ or brunei/ or bulgaria/ or burkina faso/ or burundi/ or cabo verde/ or cambodia/ or cameroon/ or central african republic/ or chad/ or exp china/ or comoros/ or congo/ or cote d'ivoire/ or croatia/ or cuba/ or "democratic republic of the congo"/ or cyprus/ or djibouti/ or dominica/ or dominican republic/ or ecuador/ or egypt/ or el salvador/ or equatorial guinea/ or eritrea/ or eswatini/ or ethiopia/ or fiji/ or gabon/ or gambia/ or "georgia (republic)"/ or ghana/ or grenada/ or guatemala/ or guinea/ or guinea-bissau/ or guyana/ or haiti/ or honduras/ or independent state of samoa/ or exp india/ or indian ocean islands/ or indochina/ or indonesia/ or iran/ or iraq/ or jamaica/ or jordan/ or kazakhstan/ or kenya/ or kosovo/ or kuwait/ or kyrgyzstan/ or laos/ or lebanon/ or liechtenstein/ or lesotho/ or liberia/ or libya/ or madagascar/ or malaysia/ or malawi/ or mali/ or malta/ or mauritania/ or mauritius/ or mekong valley/ or melanesia/ or micronesia/ or monaco/ or mongolia/ or montenegro/ or morocco/ or mozambique/ or myanmar/ or namibia/ or nepal/ or nicaragua/ or niger/ or nigeria/ or oman/ or pakistan/ or palau/ or exp panama/ or papua new guinea/ or paraguay/ or peru/ or philippines/ or qatar/ or "republic of belarus"/ or "republic of north macedonia"/ or romania/ or exp russia/ or rwanda/ or "saint kitts and nevis"/ or saint lucia/ or "saint vincent and the grenadines"/ or "sao tome and principe"/ or saudi arabia/ or serbia/ or sierra leone/ or senegal/ or seychelles/ or singapore/ or somalia/ or south africa/ or south sudan/ or sri lanka/ or sudan/ or suriname/ or syria/ or taiwan/ or tajikistan/ or tanzania/ or thailand/ or timor-leste/ or togo/ or tonga/ or "trinidad and tobago"/ or tunisia/ or turkmenistan/ or uganda/ or ukraine/ or united arab emirates/ or uruguay/ or uzbekistan/ or vanuatu/ or venezuela/ or vietnam/ or west indies/ or yemen/ or zambia/ or zimbabwe/ (1326467)
64 "organisation for economic co-operation and development"/ (588)
65 australasia/ or exp australia/ or austria/ or baltic states/ or belgium/ or exp canada/ or chile/ or colombia/ or costa rica/ or czech republic/ or exp denmark/ or estonia/ or europe/ or finland/ or exp france/ or exp germany/ or greece/ or hungary/ or iceland/ or ireland/ or israel/ or exp italy/ or exp japan/ or korea/ or latvia/ or lithuania/ or luxembourg/ or mexico/ or netherlands/ or new zealand/ or north america/ or exp norway/ or poland/ or portugal/ or exp "republic of korea"/ or "scandinavian and nordic countries"/ or slovakia/ or slovenia/ or spain/ or sweden/ or switzerland/ or turkey/ or exp united kingdom/ or exp united states/ (3531828)
66 european union/ (17900)
67 developed countries/ (21485)
68 or/64-67 (3548041)
69 63 not 68 (1236038)
70 62 not 69 (923)
71 limit 70 to english language (831)
72 limit 71 to yr="1980 -Current" (814)
73 animals/ not humans/ (5162313)
74 72 not 73 (781)

Database name: Embase

Searches
Database: Embase <1974 to 2024 February 12>
Search Strategy:
1 exp sepsis/ (346595)

Searches
2 sepsis.ti,ab. (190893)
3 bloodborne bacterium/ (2169)
4 (blood* adj2 (pathogen* or poison*)).ti,ab. (4445)
5 exp systemic inflammatory response syndrome/ (360202)
6 'systemic inflammatory response syndrome*'.ti,ab. (8816)
7 sirs.ti,ab. (11893)
8 (septicaemi* or septicemi*).ti,ab. (26313)
9 ((septic or cryptic) adj2 shock).ti,ab. (45709)
10 (pyaemi* or pyemi* or pyohemi*).ti,ab. (134)
11 (bacter?emi* or fung?emi* or parasit?emi* or vir?emi*).ti,ab. (101413)
12 (hypotension adj3 induced adj3 hypoperfusion).ti,ab. (8)
13 or/1-12 (480348)
14 rapid test/ (8727)
15 "point of care testing"/ (22395)
16 antigen*.tw. (852873)
17 (RADT* or RDT*).tw. (5752)
18 ((rapid* or fast* or quick* or time* or short* or (point adj2 care) or poc or bedside or "bed side") adj3 (diagnos* or detect* or assay* or test*)).tw. (477128)
19 or/14-18 (1320583)
20 streptococcus infection/ or exp group a streptococcal infection/ (35025)
21 pneumococcal infection/ or pneumococcal bacteremia/ (11462)
22 (pneumococc* or "S pneumoniae*" or legionel* or streptococc*).tw. (167654)
23 exp influenza/ (110511)
24 (influenza* or flu).tw. (174718)
25 pneumovirus/ or exp human respiratory syncytial virus/ (9747)
26 (syncytial* or "rs virus*" or rsv* or pneumovir*).tw. (35839)
27 or/20-26 (397254)
28 19 and 27 (45535)
29 exp polymerase chain reaction/ (1255670)
30 (Polymerase Chain Reaction* or pcr* or mpcr* or qpcr*).tw. (1158690)
31 29 or 30 (1602137)
32 streptococcus infection/ or exp group a streptococcal infection/ (35025)
33 streptococc*.tw. (132023)
34 32 or 33 (149633)
35 31 and 34 (13055)
36 28 or 35 (56695)
37 13 and 36 (3522)
38 (sensitiv: or diagnos:).mp. or di.fs. (9657921)
39 maximum likelihood method/ (17323)
40 likelihood*.tw. (254137)
41 or/38-40 (9828303)
42 37 and 41 (2032)
43 Case control study/ (213314)
44 Cohort analysis/ (1115999)
45 cross-sectional study/ (613811)
46 cohort analy$.tw. (20437)

Searches
47 Longitudinal study/ (206508)
48 Retrospective study/ (1567960)
49 Prospective study/ (905409)
50 (Cohort adj (study or studies)).tw. (490480)
51 (Case control$ adj (study or studies)).tw. (176904)
52 (follow up adj (study or studies)).tw. (75293)
53 longitudinal.tw. (457447)
54 (cross sectional adj (study or studies)).tw. (361795)
55 prospective.tw. (1137388)
56 retrospective.tw. (1311618)
57 or/43-56 (4804063)
58 37 and 57 (664)
59 (MEDLINE or pubmed).tw. (431733)
60 exp systematic review/ or systematic review.tw. (536714)
61 meta-analysis/ (306131)
62 intervention$.ti. (275539)
63 or/59-62 (1012877)
64 37 and 63 (69)
65 42 or 58 or 64 (2233)
66 afghanistan/ or africa/ or "africa south of the sahara"/ or albania/ or algeria/ or andorra/ or angola/ or argentina/ or "antigua and barbuda"/ or armenia/ or exp azerbaijan/ or bahamas/ or bahrain/ or bangladesh/ or barbados/ or belarus/ or belize/ or benin/ or bhutan/ or bolivia/ or borneo/ or exp "bosnia and herzegovina"/ or botswana/ or exp brazil/ or brunei darussalam/ or bulgaria/ or burkina faso/ or burundi/ or cambodia/ or cameroon/ or cape verde/ or central africa/ or central african republic/ or chad/ or exp china/ or comoros/ or congo/ or cook islands/ or cote d'ivoire/ or croatia/ or cuba/ or cyprus/ or democratic republic congo/ or djibouti/ or dominica/ or dominican republic/ or ecuador/ or el salvador/ or egypt/ or equatorial guinea/ or eritrea/ or eswatini/ or ethiopia/ or exp "federated states of micronesia"/ or fiji/ or gabon/ or gambia/ or exp "georgia (republic)"/ or ghana/ or grenada/ or guatemala/ or guinea/ or guinea-bissau/ or guyana/ or haiti/ or honduras/ or exp india/ or exp indonesia/ or iran/ or exp iraq/ or jamaica/ or jordan/ or kazakhstan/ or kenya/ or kiribati/ or kosovo/ or kuwait/ or kyrgyzstan/ or laos/ or lebanon/ or liechtenstein/ or lesotho/ or liberia/ or libyan arab jamahiriya/ or madagascar/ or malawi/ or exp malaysia/ or maldives/ or mali/ or malta/ or mauritania/ or mauritius/ or melanesia/ or moldova/ or monaco/ or mongolia/ or "montenegro (republic)"/ or morocco/ or mozambique/ or myanmar/ or namibia/ or nauru/ or nepal/ or nicaragua/ or niger/ or nigeria/ or niue/ or north africa/ or oman/ or exp pakistan/ or palau/ or palestine/ or panama/ or papua new guinea/ or paraguay/ or peru/ or philippines/ or polynesia/ or qatar/ or "republic of north macedonia"/ or romania/ or exp russian federation/ or rwanda/ or sahel/ or "saint kitts and nevis"/ or "saint lucia"/ or "saint vincent and the grenadines"/ or saudi arabia/ or senegal/ or exp serbia/ or seychelles/ or sierra leone/ or singapore/ or "sao tome and principe"/ or solomon islands/ or exp somalia/ or south africa/ or south asia/ or south sudan/ or exp southeast asia/ or sri lanka/ or sudan/ or suriname/ or syrian arab republic/ or taiwan/ or tajikistan/ or tanzania/ or thailand/ or timor-leste/ or togo/ or tonga/ or "trinidad and tobago"/ or tunisia/ or turkmenistan/ or tuvalu/ or uganda/ or exp ukraine/ or exp united arab emirates/ or uruguay/ or exp uzbekistan/ or vanuatu/ or venezuela/ or viet nam/ or western sahara/ or yemen/ or zambia/ or zimbabwe/ (1743482)
67 exp "organisation for economic co-operation and development"/ (2860)
68 exp australia/ or "australia and new zealand"/ or austria/ or baltic states/ or exp belgium/ or exp canada/ or chile/ or colombia/ or costa rica/ or czech republic/ or denmark/ or estonia/ or europe/ or exp finland/ or exp france/ or exp germany/ or greece/ or hungary/ or iceland/ or ireland/ or israel/ or exp italy/ or japan/ or korea/ or latvia/ or lithuania/ or

Searches
luxembourg/ or exp mexico/ or netherlands/ or new zealand/ or north america/ or exp norway/ or poland/ or exp portugal/ or scandinavia/ or sweden/ or slovakia/ or slovenia/ or south korea/ or exp spain/ or switzerland/ or "Turkey (republic)"/ or exp united kingdom/ or exp united states/ or western europe/ (3838464)
69 european union/ (31844)
70 developed country/ (36036)
71 or/67-70 (3872704)
72 66 not 71 (1587065)
73 65 not 72 (2031)
74 limit 73 to english language (1884)
75 limit 74 to yr="1980 -Current" (1858)
76 nonhuman/ not human/ (5382655)
77 75 not 76 (1721)
78 (conference abstract* or conference review or conference paper or conference proceeding).db,pt,su. (5834696)
79 77 not 78 (1131)

Database name: Cochrane CENTRAL

Searches		
ID	Search	Hits
#1	MeSH descriptor: [Sepsis] explode all trees	6439
#2	sepsis:ti,ab,kw	13857
#3	MeSH descriptor: [Blood-Borne Pathogens] this term only	38
#4	(blood* near/2 (pathogen* or poison*)):ti,ab,kw	369
#5	MeSH descriptor: [Systemic Inflammatory Response Syndrome] explode all trees	6965
#6	'systemic inflammatory response syndrome*':ti,ab,kw	1765
#7	sirs:ti,ab,kw	907
#8	(septicaemi* or septicemi*):ti,ab,kw	1118
#9	((septic or cryptic) near/2 shock):ti,ab,kw	3956
#10	(pyaemi* or pyemi* or pyohemi*):ti,ab,kw	9
#11	(bacter?emi* or fung?emi* or parasit?emi* or vir?emi*):ti,ab,kw	6711
#12	(hypotension near/3 induced near/3 hypoperfusion):ti,ab,kw	2
#13	{or #1-#12}	24365
#14	MeSH descriptor: [Rapid Diagnostic Tests] this term only	1
#15	MeSH descriptor: [Point-of-Care Systems] this term only	687
#16	antigen*:ti,ab,kw	28650
#17	(RADT* or RDT*):ti,ab,kw	557
#18	((rapid* or fast* or quick* or time* or short* or (point adj2 care) or poc or bedside or "bed side") near/3 (diagnos* or detect* or assay* or test*)):ti,ab,kw	37135
#19	{or #14-#18}	65248
#20	MeSH descriptor: [Streptococcal Infections] this term only	769
#21	(pneumococc* or pneumoniae* or legionel* or streptococc*):ti,ab,kw	9783
#22	MeSH descriptor: [Influenza, Human] this term only	3545
#23	(influenza* or flu):ti,ab,kw	13062
#24	MeSH descriptor: [Respiratory Syncytial Viruses] this term only	142

Searches		
#25	(syncytial* or (rs NEXT virus*) or rsv*):ti,ab,kw	1626
#26	{or #20-#25}	22531
#27	#19 and #26	2848
#28	MeSH descriptor: [Polymerase Chain Reaction] explode all trees	2834
#29	(Polymerase Chain Reaction* or pcr* or mpcr* or qpcr*):ti,ab,kw	21918
#30	#28 or #29	21927
#31	MeSH descriptor: [Streptococcal Infections] this term only	769
#32	streptococc*:ti,ab,kw	6813
#33	#31 or #32	6813
#34	#30 and #33	351
#35	#27 or #34	3148
#36	#13 and #35	129
#37	"conference":pt or (clinicaltrials or trialsearch):so	726755
#38	#36 not #37 with Publication Year from 1980 to 2024, with Cochrane Library publication date Between Jan 1980 and Feb 2024, in Trials	91

Database name: Cochrane CDSR

Searches		
ID	Search	Hits
#1	MeSH descriptor: [Sepsis] explode all trees	6439
#2	sepsis:ti,ab,kw	13857
#3	MeSH descriptor: [Blood-Borne Pathogens] this term only	38
#4	(blood* near/2 (pathogen* or poison*)):ti,ab,kw	369
#5	MeSH descriptor: [Systemic Inflammatory Response Syndrome] explode all trees	6965
#6	'systemic inflammatory response syndrome*':ti,ab,kw	1765
#7	sirs:ti,ab,kw	907
#8	(septicaemi* or septicemi*):ti,ab,kw	1118
#9	((septic or cryptic) near/2 shock):ti,ab,kw	3956
#10	(pyaemi* or pyemi* or pyohemi*):ti,ab,kw	9
#11	(bacter?emi* or fung?emi* or parasit?emi* or vir?emi*):ti,ab,kw	6711
#12	(hypotension near/3 induced near/3 hypoperfusion):ti,ab,kw	2
#13	{or #1-#12}	24365
#14	MeSH descriptor: [Rapid Diagnostic Tests] this term only	1
#15	MeSH descriptor: [Point-of-Care Systems] this term only	687
#16	antigen*:ti,ab,kw	28650
#17	(RADT* or RDT*):ti,ab,kw	557
#18	((rapid* or fast* or quick* or time* or short* or (point adj2 care) or poc or bedside or "bed side") near/3 (diagnos* or detect* or assay* or test*)):ti,ab,kw	37135
#19	{or #14-#18}	65248
#20	MeSH descriptor: [Streptococcal Infections] this term only	769
#21	(pneumococc* or pneumoniae* or legionel* or streptococc*):ti,ab,kw	9783
#22	MeSH descriptor: [Influenza, Human] this term only	3545
#23	(influenza* or flu):ti,ab,kw	13062

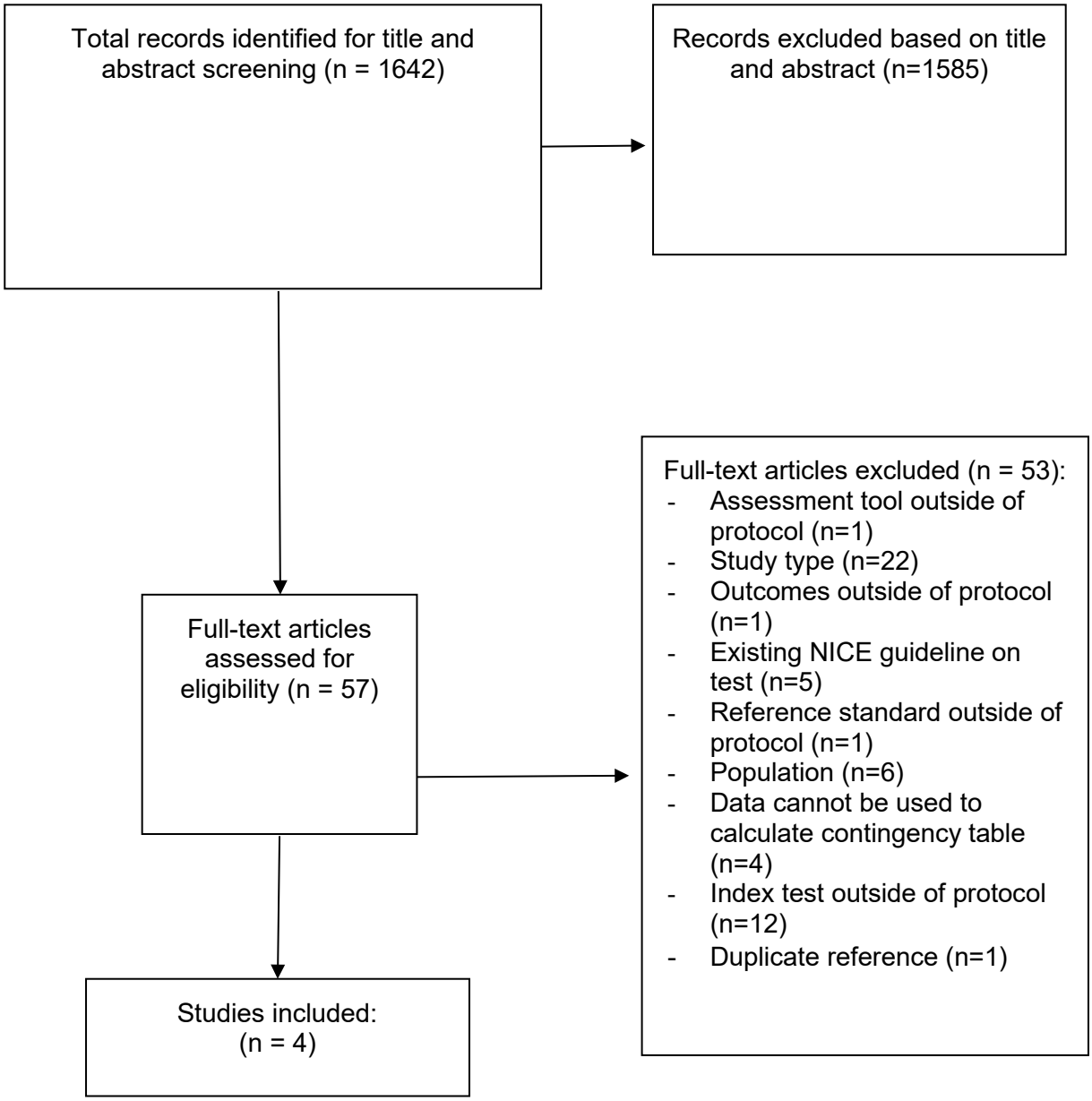
Searches		
#24	MeSH descriptor: [Respiratory Syncytial Viruses] this term only	142
#25	(syncytial* or (rs NEXT virus*) or rsv*):ti,ab,kw	1626
#26	{or #20-#25}	22531
#27	#19 and #26	2848
#28	MeSH descriptor: [Polymerase Chain Reaction] explode all trees	2834
#29	(Polymerase Chain Reaction* or pcr* or mpcr* or qpcr*):ti,ab,kw	21918
#30	#28 or #29	21927
#31	MeSH descriptor: [Streptococcal Infections] this term only	769
#32	streptococc*:ti,ab,kw	6813
#33	#31 or #32	6813
#34	#30 and #33	351
#35	#27 or #34	3148
#36	#13 and #35	129
#37	"conference":pt or (clinicaltrials or trialsearch):so	726755
#38	#36 not #37 with Publication Year from 1980 to 2024, with Cochrane Library publication date Between Jan 1980 and Feb 2024, in Trials	91

Database name: Epistemonikos

Searches
(title:((title:(sepsis OR systemic inflammatory response syndrome* OR sirs OR septi* OR crypti* OR pyaemi* OR pyemi* OR pyohemi* OR bacteremi* OR bacteraemi* OR fungemi* OR fungaemi* OR parasitemi* OR parasiteami* OR viremi* OR vireami* OR hypoperfusion* OR pathogen* OR poison*) OR abstract:(sepsis OR systemic inflammatory response syndrome* OR sirs OR septi* OR crypti* OR pyaemi* OR pyemi* OR pyohemi* OR bacteremi* OR bacteraemi* OR fungemi* OR fungaemi* OR parasitemi* OR parasiteami* OR viremi* OR vireami* OR hypoperfusion* OR pathogen* OR poison*)) AND (title:(antigen* OR RADT* OR RDT* OR diagnos* OR detect* OR assay* OR test* OR pneumococc* OR "S pneumoniae*" OR legionel* OR streptococc* OR influenza* OR flu OR syncytial* OR "rs virus*" OR rsv* OR Polymerase Chain Reaction* OR pcr* OR mpcr* OR qpcr*) OR abstract:(antigen* OR RADT* OR RDT* OR diagnos* OR detect* OR assay* OR test* OR pneumococc* OR "S pneumoniae*" OR legionel* OR streptococc* OR influenza* OR flu OR syncytial* OR "rs virus*" OR rsv* OR Polymerase Chain Reaction* OR pcr* OR mpcr* OR qpcr*))) OR abstract:((title:(sepsis OR systemic inflammatory response syndrome* OR sirs OR septi* OR crypti* OR pyaemi* OR pyemi* OR pyohemi* OR bacteremi* OR bacteraemi* OR fungemi* OR fungaemi* OR parasitemi* OR parasiteami* OR viremi* OR vireami* OR hypoperfusion* OR pathogen* OR poison*) OR abstract:(sepsis OR systemic inflammatory response syndrome* OR sirs OR septi* OR crypti* OR pyaemi* OR pyemi* OR pyohemi* OR bacteremi* OR bacteraemi* OR fungemi* OR fungaemi* OR parasitemi* OR parasiteami* OR viremi* OR vireami* OR hypoperfusion* OR pathogen* OR poison*)) AND (title:(antigen* OR RADT* OR RDT* OR diagnos* OR detect* OR assay* OR test* OR pneumococc* OR "S pneumoniae*" OR legionel* OR streptococc* OR influenza* OR flu OR syncytial* OR "rs virus*" OR rsv* OR Polymerase Chain Reaction* OR pcr* OR mpcr* OR qpcr*) OR abstract:(antigen* OR RADT* OR RDT* OR diagnos* OR detect* OR assay* OR test* OR pneumococc* OR "S pneumoniae*" OR legionel* OR

Searches
streptococc* OR influenza* OR flu OR syncytial* OR "rs virus*" OR rsv* OR Polymerase Chain Reaction* OR pcr* OR mpcr* OR qpcr*))))

Appendix C- Evidence study selection



Appendix D – Diagnostic evidence

Huijts, 2013

Bibliographic Reference	Huijts, Susanne M; Pride, Michael W; Vos, Josephine M I; Jansen, Kathrin U; Webber, Chris; Gruber, William; Boersma, Wim G; Snijders, Dominic; Kluytmans, Jan A J W; van der Lee, Ivo; Kuipers, Bart A F; van der Ende, Arie; Bonten, Marc J M; Diagnostic accuracy of a serotype-specific antigen test in CAP.; The European respiratory journal; 2013; vol. 42 (no. 5); 1283-90

Study Characteristics

Study type	Cross-sectional study
Study details	Study location Holland Setting 23 Dutch hospitals (four academic, 15 teaching and four nonteaching hospitals) Study dates between January 2008 and April 2009 Sources of funding This study was sponsored by Wyeth Pharmaceuticals, Inc., which was acquired by Pfizer in October 2009.
Inclusion criteria	Adult patients aged ≥18 years with a clinical suspicion of CAP or lower respiratory tract infection (LRTI) presenting at the emergency room of the participating hospitals were eligible. A clinical suspicion of CAP or LRTI was defined as the presence of at least two of the following criteria: fever or hypothermia; cough or change in chronic coughing pattern; dyspnoea, tachypnoea, or hypoxia; findings with percussion or auscultation consistent with pneumonia; leukocytosis, leukopenia, left shift or an infiltrate on the chest radiograph.
Exclusion criteria	Episodes of probable pneumococcal CAP that were based on sputum cultures only were excluded from this analysis
Number of participants	n=1095
Length of follow-up	N/A
Loss to follow-up	N/A
Index test(s)	Urinary Antigen Test:

	Urinary antigen detection (UAD) multiplex assay for the identification of 13 serotype-specific polysaccharides of S. pneumoniae (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F) in human urine samples in patients hospitalised with CAP. Urinary Antigen test immunochromatographic assay BinaxNOW
Reference standard (s)	Blood culture Sputum culture
Additional comments	Although authors included the BinaxNOW test as well as the UAD test, data for this was not extracted as insufficient details were provided to calculate metrics.

Study arms
Urinary antigen test vs microbiological culture (N = 1095)

Population characteristics
Arm-level characteristics

Characteristic	Urinary antigen test vs microbiological culture (N = 1095)
median age Median (IQR)	69 (57 to 79)
Male Custom value	62.7%

Critical appraisal - GDT Crit App - QUADAS-2

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	High *(Mismatch in the stated numbers of people who received a blood culture and the data used for analysis. Sputum cultures were excluded from the analysis but no explanation as to why these would not be a valid reference standard or the number excluded. UAD index test only designed to identify 13 specific serotypes. Although blood and urine samples were taken at the same time, it is unclear how much longer afterwards the urine samples were processed off-site)*
Overall risk of bias and directness	Directness	Indirectly applicable *(Not a suspected sepsis population)*

Kalina, 2020

Bibliographic Reference	Kalina, Warren V; Souza, Victor; Wu, Kangjian; Giardina, Peter; McKeen, Andrew; Jiang, Qin; Tan, Charles; French, Roger; Ren, Yanhua; Belanger, Kelly; McElhiney, Susan; Unnithan, Manu; Cheng, Huiming; Mininni, Terri; Giordano-Schmidt, Donna; Gessner, Bradford D; Jansen, Kathrin U; Pride, Michael W; Qualification and Clinical Validation of an Immunodiagnostic Assay for Detecting 11 Additional Streptococcus pneumoniae Serotype-specific Polysaccharides in Human Urine.; Clinical infectious diseases : an official publication of the Infectious Diseases Society of America; 2020; vol. 71 (no. 9); e430-e438

Study Characteristics

Study type	Cross-sectional study
Study details	Study location USA Setting hospital Study dates Unclear Sources of funding This work was supported by Pfizer
Inclusion criteria	Age >18 years Radiographically confirmed CAP
Exclusion criteria	17 non serotyped BCs
Number of participants	11087 with 17 excluded leaving n=11070
Length of follow-up	N/A
Loss to follow-up	N/A
Index test(s)	Urinary Antigen Test UAD-2 assay that identifies 11 additional non-PCV13 pneumococcal serotypes (serotypes 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, and 33F)

Reference standard (s)	Blood culture

Study arms
Urinary Antigen Detection 2 for pneumoniae vs blood culture (N = 11070)

Population characteristics
Study-level characteristics

Characteristic	Study (N = 11070)
% Female Custom value	not provided

Critical appraisal - GDT Crit App - QUADAS-2

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	High *(Including only radiographically confirmed CAP cases and excluding non-serotyped blood cultures may have created selection bias.* Also no patient characteristics reported)
Overall risk of bias and directness	Directness	Indirectly applicable *(Non suspected sepsis population)*

Khaleel, 2023

Bibliographic Reference	Khaleel, Mohammed; Samreen, Sara; Sirangi, Saritha; Dinesh Eshwar, Mummareddi; R M, Padmaja; Dhanekula, Kalyani; Evaluation of a Rapid Urine Antigen Detection Assay as a Point-of-Care Test in the Diagnosis of CAP.; Cureus; 2023; vol. 15 (no. 8); e44078

Study Characteristics

Study type	Cross-sectional study
Study details	Study location India Setting a university-affiliated teaching hospital

	Study dates Between January 2019 and September 2019 (nine months) Sources of funding The Indian Council of Medical Research (ICMR) Short-Term Research Studentship (STS) program was awarded to Sara Samreen (Reference ID: 2019- 02567) (one of the authors) - but unclear if this helped fund the study
Inclusion criteria	All patients diagnosed with CAP based on clinical features and chest radiographs performed at the time of admission consistent with pneumonia and persons without any pre-existing illnesses were included in the study. Patients aged above 60 years and presenting with clinical features compatible with an acute LRTI wherein the patients develop a fever (body temperature >37.8°C), perspiration, body aches, headaches, nasopharyngitis, cough with sputum production, pleuritic chest pain, shortness of breath, and pulmonary consolidation were included in the study.
Exclusion criteria	Patients who were hospitalised within the last 15 days with pneumonia and/or bronchial obstruction, patients with lung cancer, patients suffering from bronchoaspiration, and patients who lost their follow-up were excluded from the study
Number of participants	300
Length of follow-up	N/A
Loss to follow-up	N/A
Index test(s)	Urinary Antigen Test Rapid urinary antigen test (RUAT) that detects S. pneumoniae C-polysaccharide
Reference standard (s)	Blood culture Sputum culture

Study arms

Rapid Urinary Antigen Test vs Microbiological Culture (N = 300)

Rapid urinary antigen test (RUAT) that detects S. pneumoniae C-polysaccharide

Population characteristics

Study-level characteristics

Characteristic	Study (N = 300)
% Female Custom value	30%
Age Custom value	≥60
Diabetes mellitus Nominal	120
Cerebrovascular disease Nominal	20
Prior antibiotic therapy Nominal	80
ICU admission Nominal	40
Current smoker Nominal	80
COPD Nominal	130
Asthma Nominal	110

Critical appraisal - GDT Crit App - QUADAS-2

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	Moderate Unclear if everyone selected due to a positive diagnosis through chest x-ray or if some only had symptoms. Unclear why under 60s were excluded.
Overall risk of bias and directness	Directness	Indirectly applicable *(Not a suspected sepsis population)*

Li, 2023

Bibliographic Reference	Li, Yun; Zhao, LuJie; Wang, Jingye; Qi, Peipei; Yang, Zhongfa; Zou, Xiangyu; Peng, Fujun; Li, Shengguang; A new application of multiplex PCR combined with membrane biochip assay for rapid detection of 9 common pathogens in sepsis.; PeerJ; 2023; vol. 11; e15325

Study Characteristics

Study type	Cross-sectional study
Study details	Study location China Setting Weifang Maternal and Child Health Care Hospital and Weifang People's Hospital. Study dates February 2021 to February 2022 Sources of funding This work was supported by the Youth Natural Science Foundation of Shandong Province (ZR2021QH367), the Tai-Shan Scholar Program from Shandong Province (No. tsqn202103116); and the Student Innovation and Entrepreneurship Training Program of Shandong Province (No. x2021003).
Inclusion criteria	Admitted for suspected sepsis Patients who were initially admitted with symptoms of suspected sepsis, including fever, hypothermia, and abnormal heart and respiratory rates not treated with antibacterial drugs before blood collection
Number of participants	179 (174 in analysis -5 excluded due to 'non-target pathogens')
Length of follow-up	N/A
Loss to follow-up	N/A
Index test(s)	Multiplex PCR combined with membrane biochip A multiplex PCR assay was designed to simultaneously amplify specific conserved regions of nine common pathogenic microorganisms in sepsis, including Acinetobacter baumannii, Escherichia coli, Klebsiella pneumonia, Pseudomonas aeruginosa, Enterococcus faecalis, Staphylococcus aureus, Staphylococcus

	epidermidis, Streptococcus pneumonia, and Candida albicans. The PCR products were analysed by a membrane biochip.
Reference standard (s)	Blood culture
Additional comments	

Study arms

Multiplex PCR combined with membrane biochip vs blood culture (N = 174)

A multiplex PCR assay was designed to simultaneously amplify specific conserved regions of nine common pathogenic microorganisms in sepsis, including Acinetobacter baumannii, Escherichia coli, Klebsiella pneumonia, Pseudomonas aeruginosa, Enterococcus faecalis, Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumonia, and Candida albicans. The PCR products were analysed by a membrane biochip.

Population characteristics

Study-level characteristics

Characteristic	Study (N = 179)
% Female Custom value	40.2%
Mean age Custom value	48 (oldest person was 92, and youngest 15)

Critical appraisal - GDT Crit App - QUADAS-2

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	Moderate *(Unclear how consecutive or random the patient selection was. There were also 5 exclusions based on pathogens that index test was not designed to measure. Reviewed as a generic tests for sepsis this inflates the overall sensitivity.)*
Overall risk of bias and directness	Directness	Partially applicable *(Potentially some pregnant or recently pregnant people included in the sample and authors state the youngest aged participant was 15. Index test included membrane biochip added to standard multiplex PCR methods)*

Appendix E – Forest plots

Table 4: Sensitivity – Rapid Antigen Tests (urinary antigen for community acquired pneumonia)

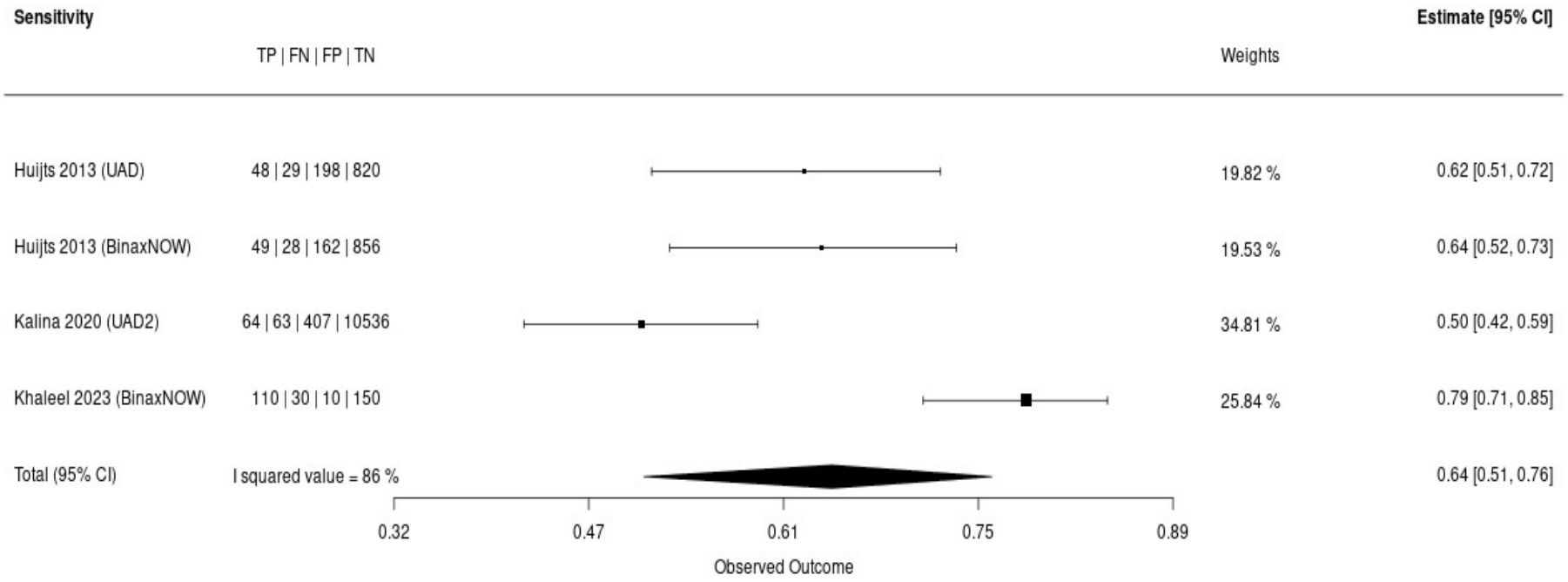


Table 5: Specificity - Rapid Antigen Tests (urinary antigen for community acquired pneumonia)

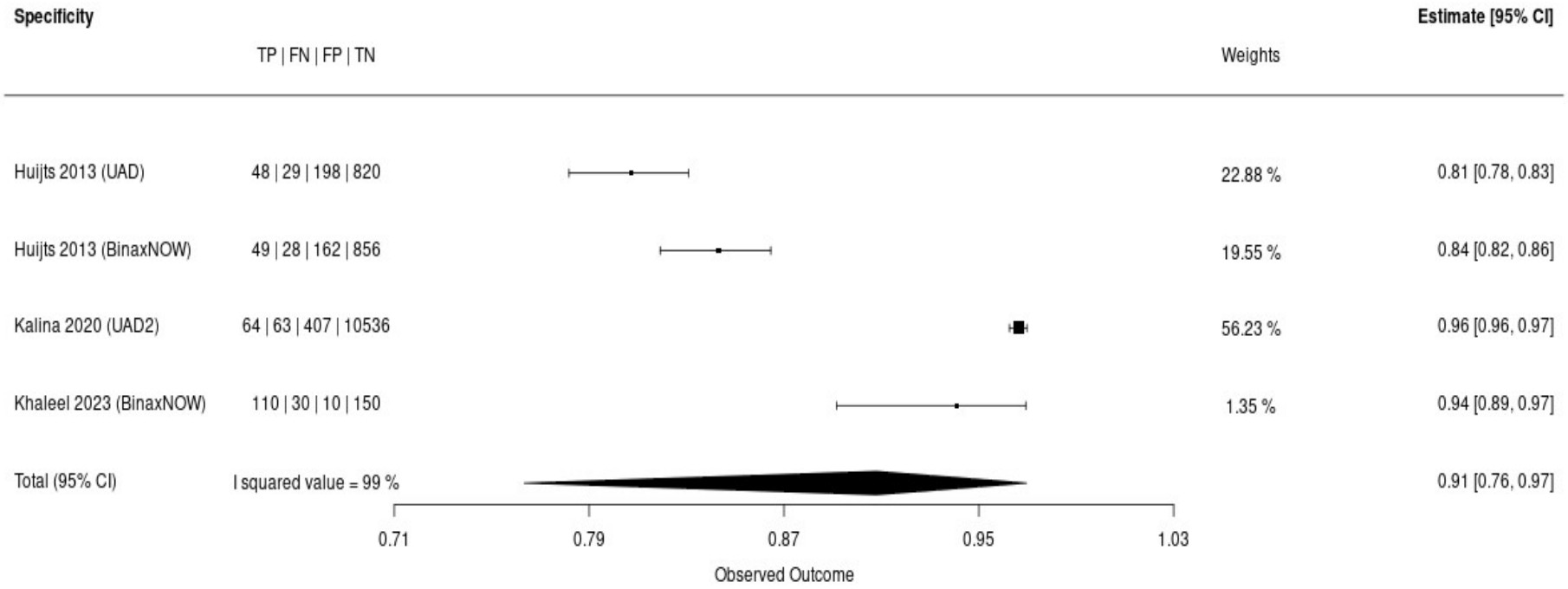


Table 6: Negative likelihood ratio - Rapid Antigen Tests (urinary antigen for community acquired pneumonia)

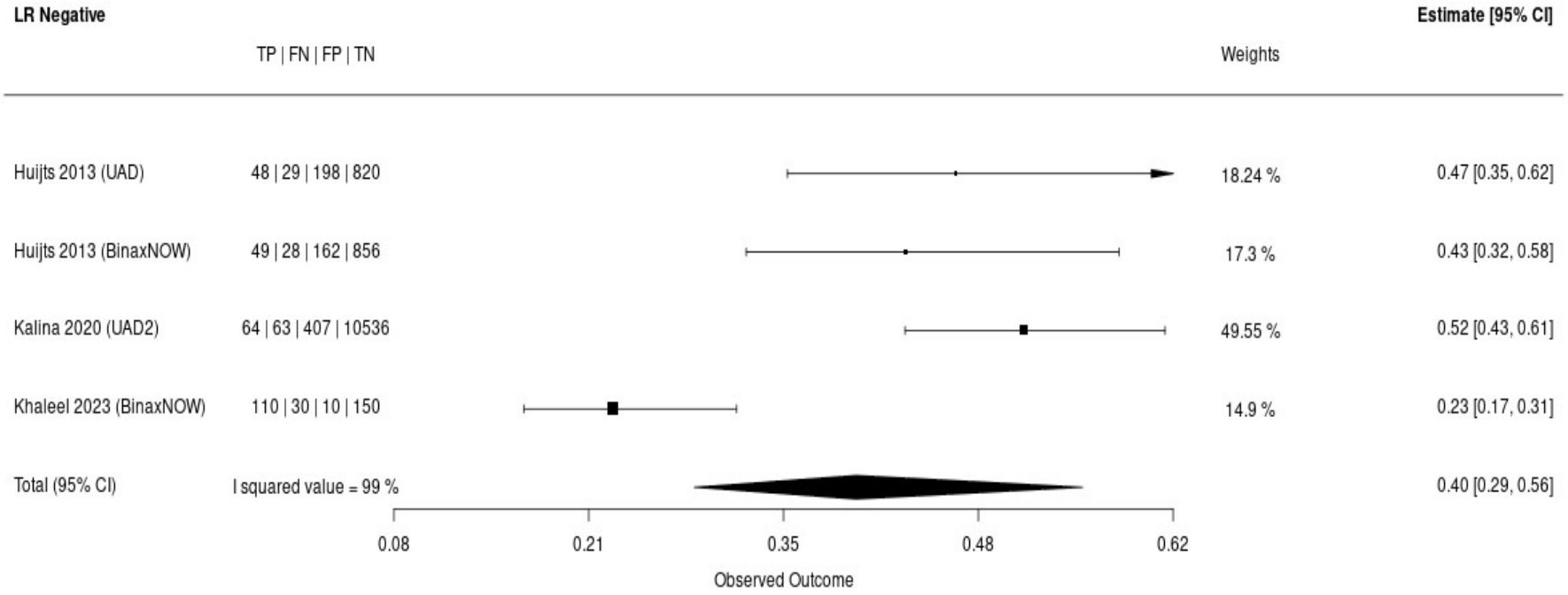
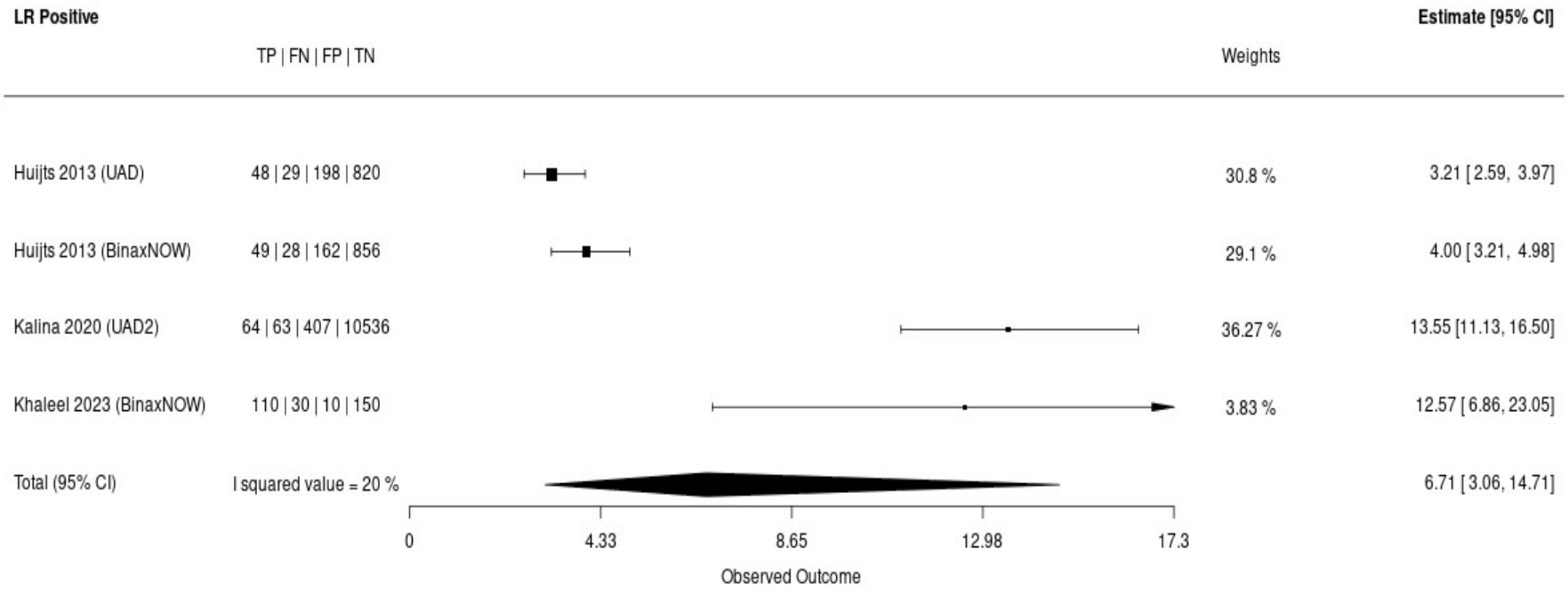


Table 7: Positive likelihood ratio - Rapid Antigen Tests (urinary antigen for community acquired pneumonia)



Appendix F – GRADE Table

No of studies	Study design	Sample size	Positive likelihood ratio	Negative likelihood ratio	Sensitivity /Specificity (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Certainty
RAT: Urinary Antigen Tests										
3[1]	Cross-sectional	13,540	+LR 6.71 (3.06, 14.71)	-LR 0.40 (0.29, 0.56)	Sens: 0.64 (0.51,0.76)	Very serious[2]	Very Serious[3]	Serious[4]	Serious[6]	Very low
					Spec: 0.91 (0.76, 0.97)	Very serious[2]	Very Serious[3]	Serious[4]	Serious[6]	Very low
PCR tests: Multiplex PCR										
1[5]	Cross-sectional	174	+LR 13.56 (7.39, 24.88)	-LR 0.08 (0.02, ,0.29)	Sens: 92.9 (77.4, 98.0)	Serious[2]	N/A	Serious[4]	Serious[6]	Very Low
					Spec: 93.2 (87.9,96.2)	Serious[2]	N/A	Serious[4]	Serious[6]	Very Low

1. 3 studies but 4 comparisons – Huijts 2013, Kalina 2020, Khaleel 2023
2. >50% of studies at high risk of bias
3. Wide variation between point estimates and wide confidence intervals.
4. >50% of studies were partially direct
5. Li 2023
6. Confidence interval crosses one end of the MID (0.6, 0.9)

Appendix G – Excluded studies

Study	Reason for exclusion
Ascher, D P; Wilson, S; Fischer, G W (1991) Comparison of commercially available group B streptococcal latex agglutination assays. Journal of clinical microbiology 29(12): 2895-6	Assessment tool does not match that specified in the protocol [Index test group B strep - not listed in protocol]
Athlin, S, Altun, O, Eriksen, H B et al. (2015) The Uni-Gold TM Streptococcus pneumoniae urinary antigen test: an interassay comparison with the BinaxNOW R Streptococcus pneumoniae test on consecutive urine samples and evaluation on patients with bacteremia. European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology 34(8): 1583-8	Not a relevant study design
Athlin, S; Iversen, A; Ozenci, V (2017) Comparison of the ImmuView and the BinaxNOW antigen tests in detection of Streptococcus pneumoniae and Legionella pneumophila in urine. European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology 36(10): 1933-1938	Not a relevant study design [Participants selected on disease status using ref standard]
Badran, Samir; Chen, Ming; Coia, John E (2021) Multiplex Droplet Digital Polymerase Chain Reaction Assay for Rapid Molecular Detection of Pathogens in Patients With Sepsis: Protocol for an Assay Development Study. JMIR research protocols 10(12): e33746	Study protocol only
Boulware, David R, Daley, Charles L, Merrifield, Cynthia et al. (2007) Rapid diagnosis of pneumococcal pneumonia among HIV-infected adults with urine antigen detection. The Journal of infection 55(4): 300-9	Not a relevant study design
Camou, F, Issa, N, Bessede, E et al. (2015) Usefulness of pneumococcal antigen urinary testing in the intensive care unit?. Medecine et maladies infectieuses 45(8): 318-23	Not a relevant study design [Descriptive study - unable to extract 2x2 contingency data. Unclear if the same patients had the same index test and reference standard]
Casalta, J.P., Gouriet, F., Roux, V. et al. (2009) Evaluation of the LightCycler SeptiFast test in the rapid etiologic diagnostic of infectious endocarditis. European Journal of Clinical Microbiology and Infectious Diseases 28(6): 569-573	Existing NICE guidance on tests
Chang, SS, Hsieh, WH, Liu, TS et al. (2013) Multiplex PCR system for rapid detection of pathogens in patients with presumed sepsis - a systemic review and meta-analysis. PloS one 8(5): e62323	Existing NICE guidance on tests
Chung, Boram, Park, Chulmin, Cho, Sung-Yeon et al. (2016) Multiplex identification of drug-resistant Gram-positive pathogens using stuffer-free MLPA system. Electrophoresis 37(2324): 3079-3083	Not a relevant study design [Laboratory study]

Corless, C E, Guiver, M, Borrow, R et al. (2001) Simultaneous detection of Neisseria meningitidis, Haemophilus influenzae, and Streptococcus pneumoniae in suspected cases of meningitis and septicemia using real-time PCR. Journal of clinical microbiology 39(4): 1553-8	Wrong population [Specimens sampled from 0-90 yrs so including <16 year olds. Not clear the sample were a suspected sepsis population]
Dominguez, J, Gali, N, Blanco, S et al. (2001) Detection of Streptococcus pneumoniae antigen by a rapid immunochromatographic assay in urine samples. Chest 119(1): 243-9	Not a relevant study design [Samples selected on basis of disease status]
Friedman, C A; Wender, D F; Rawson, J E (1984) Rapid diagnosis of group B streptococcal infection utilizing a commercially available latex agglutination assay. Pediatrics 73(1): 27-30	Study does not contain any relevant index tests [Group B Strep RAT - protocol lists Group A]
Fukushima, Kiyoyasu, Kubo, Toru, Ehara, Naomi et al. (2016) A novel method for rapid detection of Streptococcus pneumoniae antigens in blood. Journal of infection and chemotherapy : official journal of the Japan Society of Chemotherapy 22(3): 143-8	Not possible to calculate a contingency table from the data specified in the protocol
Genne, Daniel; Siegrist, Hans H; Lienhard, Reto (2006) Enhancing the etiologic diagnosis of community-acquired pneumonia in adults using the urinary antigen assay (Binax NOW). International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases 10(2): 124-8	Not a relevant study design
Ginn, Andrew N, Hazelton, Briony, Shoma, Shereen et al. (2017) Quantitative multiplexed-tandem PCR for direct detection of bacteraemia in critically ill patients. Pathology 49(3): 304-308	Study does not contain any relevant index tests [Quantitative PCR not multiplex]
Hazelton, Briony J, Thomas, Lee C, Unver, Tuba et al. (2013) Rapid identification of Gram-positive pathogens and their resistance genes from positive blood culture broth using a multiplex tandem RT-PCR assay. Journal of medical microbiology 62(pt2): 223-231	Not a relevant study design [Only positive blood cultures selected for comparison]
Hedlund, J; Ortqvist, A; Kalin, M (1990) Nasopharyngeal culture in the pneumonia diagnosis. Infection 18(5): 283-5	Study does not contain any relevant index tests [Index test is a culture]
Heuser, W., Tirmizi, S., Frieri, M. et al. (2017) Legionella pneumophila: Diagnosis and management for the critically ill and septic patient: A review of the literature. Clinical Pulmonary Medicine 24(1): 6-12	Review article but not a systematic review
Ingram, D L; Pearson, A W; Occhiuti, A R (1983) Detection of bacterial antigens in body fluids with the Wellcogen Haemophilus influenzae b, Streptococcus pneumoniae, and Neisseria meningitidis (ACYW135) latex agglutination tests. Journal of clinical microbiology 18(5): 1119-21	Not a relevant study design [Case-control design]; Wrong population [Wrong setting]
Josefson, P, Stralin, K, Ohlin, A et al. (2011) Evaluation of a commercial multiplex PCR test (SeptiFast) in the etiological diagnosis of community-onset bloodstream infections. European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology 30(9): 1127-34	Existing NICE guidance on tests [DG20]

Kalin, M. and Lindberg, A.A. (1983) Diagnosis of pneumococcal pneumonia: A comparison between microscopic examination of expectorate, antigen detection and cultural procedures. Scandinavian Journal of Infectious Diseases 15(3): 247-255	Not possible to calculate a contingency table from the data specified in the protocol
Kumar, Swati, Wang, Lihua, Fan, Jiang et al. (2008) Detection of 11 common viral and bacterial pathogens causing community-acquired pneumonia or sepsis in asymptomatic patients by using a multiplex reverse transcription-PCR assay with manual (enzyme hybridization) or automated (electronic microarray) detection. Journal of clinical microbiology 46(9): 3063-72	Outcome to be predicted do not match that specified in the protocol [Analytical sensitivity measured not clinical sensitivity]
Li, Y, Ma, M, Xu, X et al. (2022) Value of digital PCR in the early diagnosis of sepsis: A systematic review and meta-analysis. Journal of critical care 72: 154138	Wrong population [Some studies in analysis on child/neonate populations with separate results not reported]
Ljungstrom, L R, Jacobsson, G, Claesson, B E B et al. (2017) Respiratory viral infections are underdiagnosed in patients with suspected sepsis. European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology 36(10): 1767-1776	Study does not contain any relevant index tests [Single target PCR not Strep A as per protocol, multiplex PCR taken from nasopharynx not whole blood as per protocol]
Moore, M S, McCarroll, M G, McCann, C D et al. (2016) Direct Screening of Blood by PCR and Pyrosequencing for a 16S rRNA Gene Target from Emergency Department and Intensive Care Unit Patients Being Evaluated for Bloodstream Infection. Journal of clinical microbiology 54(1): 99-105	Not a relevant study design [Case-control design]
Moy, AC, Kimmoun, A, Merkling, T et al. (2023) Performance evaluation of a PCR panel (FilmArray® Pneumonia Plus) for detection of respiratory bacterial pathogens in respiratory specimens: a systematic review and meta-analysis. Anaesthesia, critical care & pain medicine: 101300	Wrong population [Not a suspected sepsis population]
O'Connor, C., O'Hara, F., McCarthy, C. et al. (2017) Rapid urinary antigen testing for the investigation of bacteraemic respiratory pneumococcal disease; underutilised and undervalued?. Journal of Infection 74(2): 198-200	Not a relevant study design [Letter in a journal]
Oberhettinger, P., Zieger, J., Autenrieth, I. et al. (2020) Evaluation of two rapid molecular test systems to establish an algorithm for fast identification of bacterial pathogens from positive blood cultures. European Journal of Clinical Microbiology and Infectious Diseases 39(6): 1147-1157	Study does not contain any relevant index tests [Taken from culture and not whole blood]
Peri, Anna Maria, Ling, Weiping, Furuya-Kanamori, Luis et al. (2022) Performance of BioFire Blood Culture Identification 2 Panel (BCID2) for the detection of bloodstream pathogens and their associated resistance markers: a systematic review and meta-analysis of diagnostic test accuracy studies. BMC infectious diseases 22(1): 794	Study does not contain any relevant index tests [PCR taken from culture not whole blood]

Pride, Michael W, Huijts, Susanne M, Wu, Kangjian et al. (2012) Validation of an immunodiagnostic assay for detection of 13 Streptococcus pneumoniae serotype-specific polysaccharides in human urine. Clinical and vaccine immunology : CVI 19(8): 1131-41	Duplicate reference [Includes data from the same study as Huijts 2013]
Rajam, Gowrisankar, Zhang, Yuhua, Antonello, Joseph M et al. (2022) Development and Validation of a Sensitive and Robust Multiplex Antigen Capture Assay to Quantify Streptococcus pneumoniae Serotype-Specific Capsular Polysaccharides in Urine. mSphere 7(4): e0011422	Not possible to calculate a contingency table from the data specified in the protocol
Robledo, XG, Arcila, KVO, Riascos, SHM et al. (2022) Accuracy of molecular diagnostic techniques in patients with a confirmed urine culture: A systematic review and meta-analysis. Canadian Urological Association journal = Journal de l'Association des urologues du Canada 16(9): E484-E489	Wrong population [Not a suspected sepsis]
Roson, Beatriz, Fernandez-Sabe, Nuria, Carratala, Jordi et al. (2004) Contribution of a urinary antigen assay (Binax NOW) to the early diagnosis of pneumococcal pneumonia. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 38(2): 222-6	Reference standard in study does not match that specified in protocol
Rutanga, J.P. and Nyirahabimana, T. (2016) Clinical Significance of Molecular Diagnostic Tools for Bacterial Bloodstream Infections: A Systematic Review. Interdisciplinary Perspectives on Infectious Diseases 2016(nopagination): 6412085	Review article but not a systematic review
Sathapatayavongs, B, Kohler, R B, Wheat, L J et al. (1983) Rapid diagnosis of Legionnaires' disease by latex agglutination. The American review of respiratory disease 127(5): 559-62	Not a relevant study design [4 arms - unable to extract 2x2 contingency data for index test and ref standard]
Schreiber, J, Nierhaus, A, Braune, S A et al. (2013) Comparison of three different commercial PCR assays for the detection of pathogens in critically ill sepsis patients. Medizinische Klinik, Intensivmedizin und Notfallmedizin 108(4): 311-8	Existing NICE guidance on tests [SeptiFast and SepsiTest both in NICE DG20 guidance. VYOO - company no longer appears to exist]
Selva, Laura, Esteva, Cristina, Gene, Amadeu et al. (2010) Direct detection of Streptococcus pneumoniae in positive blood cultures by real-time polymerase chain reaction. Diagnostic microbiology and infectious disease 66(2): 204-6	Study does not contain any relevant index tests [Taken from blood culture not whole blood]
Simms, Lisa A, Davies, Corey, Jayasundara, Nadeesha et al. (2023) Performance evaluation of InfectID-BSI: A rapid quantitative PCR assay for detecting sepsis-associated organisms directly from whole blood. Journal of microbiological methods 211: 106783	Study does not contain any relevant index tests [quantitative PCR is an exclude]
Smith, Michael D, Derrington, Petra, Evans, Rachel et al. (2003) Rapid diagnosis of bacteremic pneumococcal infections in adults by using the Binax NOW Streptococcus pneumoniae urinary antigen test: a prospective, controlled clinical evaluation. Journal of clinical microbiology 41(7): 2810-3	Not a relevant study design [case-control design]

Smith, Michael D, Sheppard, Carmen L, Hogan, Angela et al. (2009) Diagnosis of Streptococcus pneumoniae infections in adults with bacteremia and community-acquired pneumonia: clinical comparison of pneumococcal PCR and urinary antigen detection. Journal of clinical microbiology 47(4): 1046-9	Not a relevant study design
Stralin, Kristoffer, Kaltoft, Margit Staum, Konradsen, Helle Bossen et al. (2004) Comparison of two urinary antigen tests for establishment of pneumococcal etiology of adult community-acquired pneumonia. Journal of clinical microbiology 42(8): 3620-5	Not a relevant study design [Case-control]
Suwanagool, S, Eisenach, K D, Smith, S M et al. (1986) Detection of bacterial antigens in body fluids by the Phadebact system. Scandinavian journal of infectious diseases 18(4): 347-52	Not a relevant study design [Case control]
Tansarli, Giannoula S and Chapin, Kimberle C (2022) A Closer Look at the Laboratory Impact of Utilizing ePlex Blood Culture Identification Panels: a Workflow Analysis Using Rapid Molecular Detection for Positive Blood Cultures. Microbiology spectrum 10(5): e0179622	Study does not contain any relevant index tests [Used blood culture not whole blood]
Tat Trung, N., Van Tong, H., Lien, T.T. et al. (2018) Clinical utility of an optimised multiplex real-time PCR assay for the identification of pathogens causing sepsis in Vietnamese patients. International Journal of Infectious Diseases 67: 122-128	Not possible to calculate a contingency table from the data specified in the protocol
Thompson, W E and Wise, R (1983) Comparison of counterimmunoelectrophoresis and latex particle agglutination in the detection of Streptococcus pneumoniae in blood cultures. The Journal of hospital infection 4(2): 165-71	Study does not contain any relevant index tests [Antigen tested directly from blood cultures]
Thu, Ingyin Shun Lae, Tragoolpua, Khajornsak, Intorasoot, Sorasak et al. (2021) Direct Detection of Streptococcus suis from Cerebrospinal Fluid, Positive Hemoculture, and Simultaneous Differentiation of Serotypes 1, 1/2, 2, and 14 within Single Reaction. Pathogens (Basel, Switzerland) 10(8)	Study does not contain any relevant index tests [taken from blood culture not whole blood]
Tootla, Hafsah D, Bamford, Colleen, Centner, Chad M et al. (2021) The BinaxNOW pneumococcal antigen test: An adjunct for diagnosis of pneumococcal bacteraemia. Southern African journal of infectious diseases 36(1): 244	Not a relevant study design [Positive samples from blood culture collected only]
Wang, H.-Y., Kim, J., Kim, S. et al. (2015) Performance of PCR-REBA assay for screening and identifying pathogens directly in whole blood of patients with suspected sepsis. Journal of Applied Microbiology 119(5): 1433-1442	Study does not contain any relevant index tests [PCR-REBA test discontinued]
Warhurst, G, Dunn, G, Chadwick, P et al. (2015) Rapid detection of health-care-associated bloodstream infection in critical care using multipathogen real-time polymerase chain reaction technology: a diagnostic accuracy study and systematic review. Health technology assessment (Winchester, England) 19(35): 1-142	Existing NICE guidance on tests [DG20]
Woodhead, M.A., Macfarlane, J.T., Finch, R.G. et al. (1990) A comparison of countercurrent immunoelectrophoresis and latex agglutination for the detection of pneumococcal antigen in a community based pneumonia study. Serodiagnosis and Immunotherapy in Infectious Disease 4(2): 159-165	Wrong population [Samples taken in community/primary care]
Wu, Simon, Huang, Glen, de St Maurice, Annabelle et al. (2020) The Impact of Rapid Species Identification on Management of Bloodstream Infections: What's in a Name?. Mayo Clinic proceedings 95(11): 2509-2524	Review article but not a systematic review

Zalacain, Rafael, Capelastegui, Alberto, Ruiz, Luis Alberto et al. (2014) Streptococcus pneumoniae antigen in urine: diagnostic usefulness and impact on outcome of bacteraemic pneumococcal pneumonia in a large series of adult patients. Respirology (Carlton, Vic.) 19(6): 936-43	Not possible to calculate a contingency table from the data specified in the protocol;
Zheng, Hao, Chen, Xiaoli, Li, Wenge et al. (2023) Establishment of a Fast Diagnostic Method for Sepsis Pathogens Based on M1 Bead Enrichment. Current microbiology 80(5): 166	Study does not contain any relevant index tests [Does not match protocol and outside of timeframe specified]

Appendix H – Research recommendations – full details

K1.1 Research recommendation

In people aged 16 or over with suspected sepsis what is the clinical and cost effectiveness of rapid microbiological testing in guiding treatment and management? This should take into account:

- consideration of good antimicrobial stewardship
- the time taken to do the test and get a result.

K1.1.1 Why this is important

Diagnosing and treating an underlying infection in someone with or at risk of developing sepsis in a timely manner could prevent serious illness or death. Conversely, treating someone without an infection too early or with the wrong antibiotics could contribute to antimicrobial resistance. Rapid microbiological tests at this point in someone's early management for suspected sepsis could help clinicians diagnose infection more quickly, leading to more timely and targeted treatment and better outcomes for patients. These tests are used variably across the NHS but more research needs to be conducted to measure their effectiveness and cost-effectiveness in a suspected sepsis population.

K1.1.2 Rationale for research recommendation

Importance to 'patients' or the population	There is a lack of evidence on the effectiveness and utility of rapid antigen and PCR testing in people with suspected sepsis in hospital. These tests could be important for treating people quickly, ensuring their illness does not escalate to severe or to help aid decisions on antimicrobial prescribing, ensuring they receive targeted antibiotics where infection is known.
Relevance to NICE guidance	This guideline has considered rapid antigen and PCR testing for the early management of suspected sepsis in hospital, but not enough evidence was found on the effectiveness or cost-effectiveness of these tests to make a recommendation.

Relevance to the NHS	If rapid antigen and PCR testing was shown to be effective in the early management of suspected sepsis, it could reduce the burden of severely ill patients being referred to critical care. Accurate diagnosis of infection would also help aid good antimicrobial stewardship.
National priorities	High
Current evidence base	No evidence of effectiveness or cost-effectiveness in a suspected sepsis population and limited evidence on diagnostic accuracy.
Equality considerations	None known

K1.1.3 Modified PICO table

Population	Adults aged 16 and over with suspected sepsis (including a range of underlying infections)
Intervention	Rapid antigen and PCR tests (including point of care and rapid multiplex tests)
Comparator	Standard of care tests
Outcome	All-cause mortality, length of hospital stay, switch to pathogen specific antimicrobials, critical care unit admission, impact on antimicrobial resistance, quality of life, diagnosis of infection, cost effectiveness outcomes
Study design	RCT's and cohort studies
Timeframe	Short-term
Additional information	Studies should be on tests in hospital, not pre hospital