National Institute for Health and Care Excellence

Final

Suspected sepsis: recognition, diagnosis and early management

(B) Evidence review for managing and treating suspected sepsis in acute hospital settings; antibiotic treatment in people with suspected sepsis

NICE guidelines NG253, NG254 and NG255

Evidence reviews underpinning recommendations and recommendations for research in the NICE guidelines

January 2024

Final

These evidence reviews were developed by NICE

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1.1 Review question

In adults and young people (16 and over) with suspected sepsis and at different NEWS2 risk brackets (0, 1 to 4, 5 to 6, greater than 7), what are the most clinically and cost-effective timings of antibiotic administration?

1.1.1 Introduction

Sepsis is defined as a life-threatening organ dysfunction due to a dysregulated host response to infection. It requires early recognition and immediate management to prevent the progression of the condition towards a septic shock (a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities and substantially increased mortality). With an estimated 918,000 adult sepsis admissions per year, and 66,096 deaths in the UK, sepsis constitutes a major public health concern. Early recognition and management of sepsis can avert its progression and decrease the associated mortality, morbidity and financial burden.

The recommendations on managing people with sepsis in acute hospital settings are organised around stratification of risk. Currently, it is recommended that broad spectrum antibiotics be administered within one hour of presentation in higher risk categories. But beyond the apparent benefits, broad-spectrum antibiotics can cause considerable harm, including antibiotic-associated adverse effects and antibiotic resistance. And while the apparent side-effects are usually tolerated because the benefits of treatment outweigh the toxic effects, the less apparent and often less immediate adverse effects, such as the overgrowth of resistant microorganisms which can itself precipitate a secondary infection that can be more difficult to treat is less understood. Furthermore, evidence also shows that inappropriate initial antibiotic treatment is independently associated with heightened mortality. Overprescribing of antibiotics, especially overuse of broad-spectrum antibiotics is a major public health concern. Therefore, optimising antibiotic use and prescribing source specific antibiotics are essential to ensure successful outcomes and to promote antibiotic stewardship.

The review focused on the most clinically and cost-effective timings on antibiotic administration triggered by the Academy of Medical Royal Colleges (AoMRC) report. This report proposes that urgency of treatment of people aged 16 and over with suspected sepsis is based on National Early Warning Score 2 (NEWS2) risk stratification, combined with clinical and laboratory assessments of severity, urgency and probability of infection. For patients with possible, probable or definite infection, infection-specific diagnostic tests and administration of antibiotics should be completed within 6, 3, or 1 hour of recording a NEWS2 of 1-4, 5-6, or ≥7, respectively.

This review is part of an update of the NICE guideline on Sepsis: recognition, diagnosis and early management (NG51).

The aim of this review is to identify the most appropriate and cost-effective timing for initiating antibiotic treatment in people with suspected sepsis and at different NEWS2 risk brackets (0, 1 to 4, 5 to 6, greater than 7) in people aged 16 and over.

1.1.2 Summary of the protocol

The review aimed to identify studies assessing the association between timing of antibiotic delivery at different NEWS2 risk brackets in people with suspected sepsis aged 16 and over and primary and secondary outcomes, as listed in Table 1. The criteria were specified during protocol developed in agreement with the committee members. For full details of the review protocol see Appendix A.

Table 1: PICO table summary

Population	**Inclusion criteria:** • Adults and young people (16 and over) with suspected sepsis and at different NEWS/NEWS2 risk brackets (0, 1 to 4, 5 to 6, 7 or above) • Acute hospital setting, mental health facilities, ambulance services **Exclusion criteria:** • Children (15 and under) • Pregnant and recently pregnant women • People undergoing anticancer treatment with suspected or confirmed neutropenic sepsis
Intervention	Deferred antibiotic administration based on NEWS2 risk bracket recommendation: • within 3 hours for scores 5-6 • within 6 hours for score 0 and 1-4.
Comparator	• Immediate antibiotic administration (within 1 hour) • Note: within 1 hrs corresponds to NEWS>7
Outcomes	**Primary outcomes:** • All-cause mortality at 28 days (or nearest time point) • Health related quality of life (measured by EQ5D or SF-36) **Secondary outcomes:** • Duration of hospital stay • Duration of critical care stay • Hospital readmission rates • Organ failure and need for organ support e.g., additional medication, mechanical organ support, increase in SOFA score or as reported in included studies • Adverse events: diarrhoea, inability to tolerate drug • Antibiotic resistance (defined in a clinical context as an indicator of the likely outcome of therapy, including • Longer- and shorter-term mortality related to sepsis • Long-term adverse outcomes due to severe sepsis such as those affecting physical, psychological or emotional functions
Outcome measures	• Adjusted relative risk (RR) or odds ratio (OR) measured at a specific time point • Adjusted hazard ratios (HRs) if outcomes are measured over time
Study type	• Randomised controlled trials • Prospective cohort studies • Systematic reviews of these studies • Retrospective cohort studies (added post-hoc as a protocol deviation)

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 and the methods section in Appendix B.

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

As the NEWS 2 tool was introduced in 2017, the evidence-base was expected to be small. Therefore, the committee members agreed to also include studies that assess the NEWS tool (the first version of the tool introduced in 2012) and the associated risk of severe illness or death from sepsis in adults and young people (16+). In this case, the studies assessing the NEWS tool were downgraded for indirectness in the GRADE analysis.

Randomised controlled trials (RCTs) and prospective cohort studies were considered in addition to systematic reviews of these study types. However, due to the small number of retrieved studies, inclusion criteria were expanded to also consider retrospective cohort studies, as noted in section 1.1.3.3 Protocol deviations.

The review protocol specified that where possible, a meta-analytic approach will be used to give an overall summary effect. However, this was not statistically possible due to insufficient number of studies that met eligibility criteria (n=1). Forest plots were used to visualise the effect of immediate and deferred antibiotic administration in people aged 16 and over with suspected sepsis at different NEWS risk categories.

The review protocol also specified that, where possible, subgroup analyses would be conducted for age (young people, adults, and older adults), people at high risk of infection, countries outside the UK which might have a different resistance profile, different settings (emergency department, hospital ward, intensive care units, mental health trusts etc.) and the type of tool used (NEWS and NEWS2). However, these subgroups could not be analysed due to insufficient data.

1.1.3.1 Search methods – clinical evidence

A NICE information specialist conducted the searches on 30th July 2022. 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 2016 PRESS Checklist.

The following databases were searched: Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley); Cochrane Database of Systematic Reviews (CDSR) (Wiley); Embase (OVID); Medline (OVID) and MEDLINE Epub Ahead-of-Print (OVID).

Detailed search strategies for each database and method are provided in Appendix C.

1.1.3.2 Search methods – cost-effectiveness evidence

A NICE information specialist conducted the searches on 30th June 2022. 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 2016 PRESS Checklist.

The following databases were searched: Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley); Cochrane Database of Systematic Reviews (CDSR) (Wiley); Embase (OVID); Medline (OVID) and MEDLINE Epub Ahead-of-Print (OVID).

Detailed search strategies for each database and method are provided in Appendix C.

1.1.3.3 Protocol deviations

Several sources were added during the search as the numbers of articles being obtained were relatively low and it was feasible within the time and resources available to expand the list of sources beyond those specified in the protocol. Websites covering government, charities and sepsis related organisations such as the NHS England, the Department of Health and Social Care, the Royal College of Physicians, the Royal College of Emergency Medicine, Sepsis Trust, Surviving Sepsis Campaign, the Sepsis Alliance, the Sepsis Research, First Response, TRIP (Turning Research into Practice), FERN (Find Evidence, Retrieve Now) were searched on 4th and 5th July 2022. This was to ensure comprehensive coverage of the potential literature.

As the evidence base was very small and RCTs or prospective cohort studies that met eligibility criteria were not identified, retrospective cohort studies were also considered for inclusion. For this, no additional searches were necessary, as the search strategy was not limited by study type (see Appendix C for details).

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

A systematic search, limited to 2012 onwards (since the endorsement of the first version of the NEWS tool) which was carried out to identify studies specified for this evidence review identified 509 records initially identified in the protocol through database searching and 17 records identified through other searches. After deduplication, 377 records were screened at title and abstract stage. 369 records were discarded as they did not fulfil the review inclusion criteria. 8 records were sourced for full text screening. Of these, 7 full-text articles were further excluded with reasons. After the full text screening, one retrospective cohort study fulfilled the eligibility criteria and was included for narrative synthesis.

The full search strategy is presented in Appendix C. The PRISMA diagram for the study selection process is included in Appendix D.

1.1.4.2 Excluded studies

All excluded references with reasons for exclusion are given in Appendix J.

1.1.5 Summary of studies included in the effectiveness evidence

Studies that used the NEWS2 risk brackets (0, 1 to 4, 5 to 6, greater than 7) to identify the most appropriate timing for initiating antibiotic treatment in patients with suspected sepsis in people aged 16 and over were not found.

The indirect evidence using the NEWS as a risk stratification tool, comes from 1 retrospective cohort study (Althunayyan et al, 2021) conducted in an emergency department (ED) of a hospital in Saudi Arabia. The study aimed to assess the mortality benefits of timely antibiotic treatment of adults presenting to the ED with sepsis and compare 1 hour administration and 3 hour administration of antibiotics starting from the time of triage (time 0).

Suspected sepsis was defined as NEWS score greater than 4, sepsis was defined as a life-threatening organ dysfunction due to a dysregulated host response to infection (Sepsis 3 definition) and severe sepsis was defined as sepsis combined with systolic blood pressure (SBP <90 mmHg or mean arterial pressure MAP < 65 mmHg).

The total number of participants was 292 with a mean age of 56.3. The participants with suspected sepsis and risk score NEWS>4 were divided into two groups: 1) the immediate

group, which received the first IV antibiotics within an hour of triage (from 0 to 60 min) with a sample size of 250, and 2) the early group, which received the first antibiotics between one and 3 hours (61 to 180 min) after sepsis diagnosis with a sample size of 42.

The summary of the study is presented in Table 2 below:

Table 2: Summary of included study

Study, type, location and setting	Population and subgroups characteristics, definitions	Intervention and comparator	Outcomes, measures, subgroups and follow up	Risk of bias, applicability
Althunayyan et al, 2021 Retrospective cohort study (retrospective analyses of data July 2018-June 2019) - Saudi Arabia - ED of King Saud Medical City	People (≥18) with suspected sepsis and NEWS>4 Cohort: N=292 Mean age: 56.3 years SD 23.6 Subgroup: people with severe sepsis n=65 **Definitions used:** Suspected sepsis: NEWS>4 Sepsis: Sepsis 3 Severe sepsis: Sepsis and SBP <90 mmHg or MAP < 65 mmHg	**Intervention:** Early (1-3 hrs) antibiotic administration N=42 **Comparator:** Immediate (≤1 hrs) antibiotic administration N=250	Mortality (in hospital) of the cohort: Number of deaths in the Early (1-3 hours) vs Immediate (≤1 hour) antibiotic administration Subgroup analyses: mortality in people with severe sepsis (n=65; 7 vs 58) Follow up not specified	- Low - Indirectly applicable
ED-Emergency Department; SBP-systolic blood pressure; MAP-mean arterial pressure; SD-standard deviation *NEWS-National Early Warning Score*				

Participants selection and baseline characteristics were reported in detail with no significant baseline differences between the participants in the intervention and comparator group. The most common comorbidities reported in the cohort were hypertension (n=101) and diabetes mellitus (n=87). A subgroup analyses of people with severe sepsis (n=65) was also performed.

The study assessed mortality (in hospital) between the early and immediate antibiotic administration groups, however the length of follow up was not specified. To visualise the associated risk for the immediate vs early antibiotic administration and mortality in people with suspected sepsis and severe sepsis, forest plots were generated (Appendix F).

Other outcomes of interest e.g., health related quality of life, hospital readmission rates, unplanned critical care admission, organ failure, adverse events, antibiotic resistance were not reported.

The study was judged to be of a low risk of bias.

The detailed evidence tables, risk of bias and assessment of study applicability are presented in Appendix E. The study is referenced in full in section 1.1.14.

1.1.6 Summary of the effectiveness evidence

1.1.6.1 NEWS and NEWS2 model summary

NEWS2 is the latest version of the National Early Warning Score (NEWS), first produced in 2012 and updated in December 2017, which improves the detection and response to clinical deterioration in adult and young people (16 and over), including those with sepsis, and is a key element of patient safety and improving patient outcomes.

1.1.6.1.1. The NEWS and NEWS2 scoring system

The National Early Warning Score (NEWS and NEWS2) is a system for scoring the physiological measurements that are routinely recorded at the patient's bedside. It should be used as an aid to clinical assessment and not as a substitute for competent clinical judgement. The Royal College of Physicians recommends the use of the national early warning score to standardise the assessment of acute-illness severity when patients present in acute hospitals and also in the prehospital assessment for example by ambulance services. However, the use of national early warning score should not be used in children and young people under 16 years or people who are pregnant because the physiological response to acute illness can be modified in these groups.

1.1.6.1.2 Differences between NEWS and NEWS2 tools

In NEWS, oxygen saturations (SpO2) receive increasing weights for values of 95% or less, and oxygen therapy receives a flat weight. However, guidance for the management of patients with type II respiratory failure (T2RF) and those deemed at risk of T2RF before blood gas analysis, suggests lower SpO2 values (88–92%) should be targeted. Consequently, it is suggested that the NEWS SpO2 weighting system is inappropriate for patients with/at risk of T2RF.

NEWS2 includes several modifications to the NEWS vital sign weightings. To account for concerns about NEWS and T2RF, NEWS2 includes a new SpO2 scoring scale for patients with/at risk of T2RF. This scale, termed *SpO_2 scale 2* assigns weights at lower SpO_2 thresholds than NEWS and combines these lower thresholds with weights for the use of supplemental oxygen at higher SpO_2 levels, reflecting the concern of hyperoxia-induced hypercapnic respiratory failure.

The NEWS2 updates are outlined below:

1	The recording of physiological parameters has been reordered to align with the Resuscitation Council (UK) ABCDE sequence
2	The ranges for the boundaries of each parameter score are now shown on the chart
3	The chart has a dedicated section (spo2 Scale 2) for use in patients with hypercapnic respiratory failure (usually due to COPD) who have clinically recommended oxygen saturation of 88–92%
4	The section of the chart for recording the rate of (L/min) and method/device for supplemental oxygen delivery has been improved
5	The importance of considering serious sepsis in patients with known or suspected infection, or at risk of infection, is emphasised. A new score of 5 or more is the key trigger threshold for urgent clinical review and action

6	The addition of 'new confusion' (which includes disorientation, delirium or any new alteration to mentation) to the AVPU score, which becomes ACVPU (where C represents confusion)
7	The chart has a new colour scheme, reflecting the fact that the original red amber–green colours were not ideal for staff with red/green colour blindness

To account for these differences, the evidence from studies that used the NEWS rather than NEWS2 tool was downgraded for indirectness (see protocol, Appendix A).

1.1.6.2 Summary of primary outcomes included in the effectiveness evidence

The study reported number of events for each group (immediate vs early antibiotic administration) in people with NEWS>4. A subgroup analyses and number of events was also reported for people with severe sepsis. Based on the number of events that have occurred in a specific time point, the RRs and corresponding confidence intervals (CI) were calculated. RRs greater than 1 indicate an increased risk of a particular outcome (e.g., mortality) in the intervention group (early antibiotic administration within 1-3 hours) relative to the low-risk group (immediate antibiotic administration within 1 hour).

Forest plots were used for the visualisation of the calculated RRs between the intervention and comparator in people with suspected sepsis and people with severe sepsis which are reported in the GRADE tables. The MID default threshold of 0.8 to 1.25 was used to rate imprecision in GRADE. The forest plots are presented in Appendix F, with the detailed GRADE tables in Appendix G.

The summary of GRADE tables for the outcome in-hospital mortality in people with suspected sepsis and people with severe sepsis is presented in Table 3 and Table 4 respectively.

Table 3: Mortality in people with suspected sepsis and NEWS>4 who received antibiotics within 1 hour versus those who received antibiotics between 1-3 hours

Outcome: In hospital mortality	Sample size	MID	Number of events	Effect size RR [95% CI]	Quality	Interpretation of effect*
Early antibiotic (1-3h) vs Immediate antibiotic (≤1 h)	292 (early 42 vs immediate 250)	0.8 to 1.25	14 vs 79	1.05 [0.66, 1.68]	Very Low**	Could not differentiate
*RR greater than 1 favours early administration (≤1 h) ** Downgraded for indirectness and downgraded by 2 increments for imprecision *RR=risk ratio. CI=confidence interval.*						

Table 4: Mortality in people with severe sepsis who received antibiotics within 1 hour versus those who received antibiotics between 1-3 hours

Outcome: In hospital mortality	Sample size	MID	Number of events	Effect size RR [95% CI]	Quality	Interpretation of effect*
Early antibiotic (1-3h) vs Immediate antibiotic (≤1 h)	65 (early 7 vs immediate 58)	0.8 to 1.25	3 vs 22	1.13 [0.45, 2.83]	Very Low**	Could not differentiate

*RR greater than 1 favours early administration (≤1 h)
** Downgraded for indirectness and downgraded by 2 increments for imprecision
RR=risk ratio. CI=confidence interval.

Other primary outcomes were not reported in the study.

1.1.6.3 Summary of secondary outcomes included in the effectiveness evidence

Data for the secondary outcomes prespecified in the protocol were not reported.

1.1.7 Economic evidence

1.1.7.1 Included studies

A single search was performed to identify published economic evaluations of relevance to any of the questions in this guideline update (see Appendix C). Only a small number of studies (n=359) were returned using the clinical effectiveness search strategy, and a further economic filter was not applied given the low number. An additional 2 studies were identified from other sources, giving a total of 361 studies retrieved from the search. Based on title and abstract screening, 359 studies were of the studies could confidently be excluded for this review question. Neither of the two studies reviewed at the full-text stage were considered applicable because they did not include both costs and outcomes and therefore no health economic studies were included. In the absence of cost effectiveness evidence regarding the timings of antibiotic administration for people with suspected sepsis with different NEWS2 risk brackets, the committee considered the effectiveness of the tool alongside the costs of treatment to qualitatively evaluate the cost effectiveness of different timing strategies based on NEWS2 score. An additional study estimating the costs associated with the treatment of sepsis by Whitewater charitable trust (2017) was identified as a citation within the excluded study by NHS England and NHS Rightcare (2018). Whitewater charitable trust (2017) neither refers to NEWS2 nor includes both costs and outcomes this study could not be included as health economic evidence because the inclusion criteria was not met. This study has been used to inform the costs associated with the treatment of sepsis.

1.1.7.2 Excluded studies

Two economic studies relating to this review question were identified but were excluded due to limited applicability. These are listed in Appendix J, with reasons for exclusion given.

See also the health economic study selection flow chart in Appendix D.

1.1.8 Summary of included economic evidence

No relevant health economic studies were identified for this review question.

1.1.9 Economic model

This area was not prioritised for new cost-effectiveness analysis.

1.1.10 Unit costs

Relevant unit costs for antibiotics for the treatment of adults are provided below to aid consideration of cost effectiveness.

Where use of specific antibiotics have been stated, these are costed up below. Due to differences in the source of infection and different infection patterns in different areas, not all recommendations from this guideline state a specific type of antibiotic, as local guidance should be followed.

Many doses depend on person bodyweight (assumed to be 75kg) and duration of treatment.

Table 5: Antibiotic costs

Resource	Assumed daily dose [BNF]	Cost per unit (£)	Total daily cost (£)	Source
Piperacillin with tazobactam	4.5 g by IV infusion every 8 hours	£7.65 per 2g (powder for infusion)	£68.85	NHS Drug Tariff September 2022
Ceftriaxone	2g once daily by IV [complicated skin and soft tissue infections]	£9.58 per 1g (powder for injection vials)	£19.16	NHS Drug Tariff September 2022
Vancomycin	15–20 mg/kg by IV every 8–12 hours [complicated skin and soft tissue infections]	£5.49 per 500mg (powder for infusion)	£32.94	NHS Drug Tariff September 2022 assuming patient weight of 75kg every 12 hours
Amoxicillin (oral administration)	500 mg by mouth every 8 hours, increased if necessary to 1 g every 8 hours, increased dose used in severe infections. [Susceptible infections]	£0.07 per 500mg capsule (£1.39 per pack of 21 capsules)	£0.20	NHS Drug Tariff September 2022
Amoxicillin (IV administration)	2g every 4 hours [Endocarditis]	£1.92 per 1g powder for injection vials	£23.04	NHS Drug Tariff September 2022
Gentamicin	Initially 5–7 mg/kg once daily [Adult Septicaemia and leg ulcer infection]	£1.38 per 80mg (ampoule for injection)	£9.63	NHS Drug Tariff September 2022 assuming patient weight of 75kg
Benzylpenicillin	1.2 g every 4 hours, dose may be increased if necessary to 2.4g every	£4.38 per 1200mg (solution for injection vial)	£17.52	NHS Drug Tariff September

Resource	Assumed daily dose [BNF]	Cost per unit (£)	Total daily cost (£)	Source
	4 hours by intravenous route [Endocarditis]			2022 based on 1.2g dose
Meropenem	2g every 8 hours [Meningitis]	£20.38 per 1g (powder for injection vials)	£122.28	NHS Drug Tariff September 2022
Co-amoxiclav oral tablets	500/125mg every 8 hours for 7 days [Adult leg ulcer infection]	£0.10 per 500mg/125mg tablet (£2.10 per pack of 21 tablets)	£0.30	NHS Drug Tariff September 2022
Co-amoxiclav powder for infusion	1.2g every 8 hours [Adult leg ulcer infection]	£1.49 per 500mg/100mg (powder for injection vials)	£13.41	BNF September 2022
Co-amoxiclav oral suspension	10 mL twice daily; increased if necessary to 10 mL 3 times a day for severe infection. [Infections due to beta-lactamase-producing strains]	£2.16 per 100ml oral suspension	£0.65	NHS Drug Tariff September 2022
Clarithromycin oral	500mg twice daily [Community-acquired pneumonia]	£0.13 per 500mg tablet (1.87 per pack of 14 tablets)	£0.27	NHS Drug Tariff September 2022
Clarithromycin IV	500 mg every 12 hours [Community-acquired pneumonia]	£9.45 per 500mg (powder for infusion vials)	£18.90	NHS Drug Tariff September 2022

IV: Intravenous,
Note: the number of vials required have been rounded up because vials would not be shared,

Whitewater charitable trust (2017) estimated the costs associated with hospital treatment for patients with sepsis. The authors highlighted the challenges associated with estimating the costs of treatment for sepsis due to limited data available, particularly for those patients who do not require ICU. This is partly due to sepsis having a complicated definition making it difficult to define prevalence and incidence and to collect data on treatment. The authors assumed that approximately only one third of patients with sepsis require ICU. The cost of inpatient care was estimated to be £15,908 for the most severe illness (Table 6) and £1,943 (Table 7) for the remaining two thirds of patients with sepsis.

Table 6: Cost of adult patients with severe sepsis requiring intensive care unit

Description	Cost (per day) (£)	Duration (days)	Total cost (£)	Source
Intensive care unit	£1,456	7.8	£11,354	Whitewater charitable trust (2017) Weighted average NHS reference costs 2015/2016

Description	Cost (per day) (£)	Duration (days)	Total cost (£)	Source
Additional hospital inpatient days	£304	15	£4,553	Whitewater charitable trust (2017) Weighted average of excess bed days
Total cost for patients with severe sepsis and sepsis shock			£15,908	

All costs based on 2015/2016 costs have been inflated using the latest indices available within PSSRU

Table 7: Cost of adult patients with sepsis not requiring intensive care unit

Description	Cost (per day) (£)	Duration (days)	Total cost (£)	Source
Hospital inpatient	£304	6.4	£1,943	Whitewater charitable trust (2017) Weighted average of excess bed days, inflated

All costs based on 2015/2016 costs have been inflated using the latest indices available within PSSRU

Whitewater charitable trust (2017) discussed after the acute treatment of sepsis there are likely to be ongoing routine follow up care costs and the costs for treating complications. However, because no routine follow up care costs were identified within the literature these were unable to be included. 21.5% of patients requiring ICU were estimated to experience an adverse event. Only the costs associated with the treatment of some of the complications were able to be included. This is because some of the complications relate to conditions which are either too complex or are too vague making it not possible to identify unit costs. A conservative assumption was made by the authors to only include the adverse events of the most specific complications for which it is possible to obtain a unit cost, these are presented in Table 8.

Table 8: Adverse event costs (Whitewater charitable trust (2017))

Post-sepsis complication	Annual cost per patient (£)	Rate (%)	Source
Kidney function	£892	14.1	Kerr (2017), assumed to be treatment for CKD
Amputation	£854	8.5	NICE type 2 diabetes guideline health economic appendix
PTSD	£1,132	9.9	NICE guideline on PTSD
Depression	£536	2.8	NICE guideline on depression anti-depressant treatment

All costs based on 2015/2016 costs have been inflated using the latest indices available within PSSRU

1.1.11 Evidence statements

Health economics

No health economic evidence was identified for this review question. A study estimating the costs associated with sepsis by Whitewater charitable trust (2017) was identified from one of the excluded studies within the searches. Whitewater charitable trust estimated the individual and population level costs associated with sepsis and

identifies the key challenges associated with estimating the true costs. This study has been used as a reference to identify the costs associated with sepsis, including intensive care unit costs and some of the costs of complications.

1.1.12 The committee's discussion and interpretation of the evidence

1.1.12.1. The outcomes that matter most

The committee members agreed that mortality is a critical outcome to assess the most clinically effective timings of antibiotic administration in adults and young people (16 and over) with suspected sepsis and at different NEWS2 risk brackets (0, 1 to 4, 5 to 6, greater than 7). Health-related quality of life was considered to be a critical outcome however, no evidence for this outcome was found.

No evidence was found for the following outcomes - duration of hospital stay, duration of critical care stay, hospital readmission rates, organ failure and need for organ support, adverse events (diarrhoea and inability to tolerate medication), antibiotic resistance, longer- and shorter-term mortality related to sepsis and long-term adverse outcomes due to severe sepsis. These were considered important outcomes by the committee.

1.1.12.2 The quality of the evidence

The committee acknowledged that studies that used the NEWS2 tool to compare different timings of antibiotic administration in adults and young people (16 and over) with suspected sepsis and at different NEWS2 risk brackets were not identified. There also needs to be consideration of bias caused by changes to the review protocols. A deviation to the review protocol was made for the inclusion of a retrospective cohort study as no prospective cohort studies that met the eligibility criteria were identified.

The committee agreed that although the NEWS2 update refines and improves the NEWS tool, it does not change its core principles and does not affect the stratification of people with suspected sepsis, thus prompting similar timing for antibiotic administration. They concluded that the indirect evidence could be used to inform the current review but accepted to downgrade the evidence for indirectness. The default threshold cut-off points (0.8 to 1.25) used to assess imprecision in GRADE were also accepted, as no thresholds for MIDs were defined at review protocol stage.

The indirect evidence presented based on the NEWS tool was limited and comes from one retrospective cohort study conducted in Saudi Arabia (N=292). The study used NEWS cut-off point of 5 and above when assessing the effect of immediate (within 1 hour) versus deferred (1-3 hours) antibiotic administration on mortality in adults with suspected sepsis. The study also provided data for a subset of people with severe sepsis, defined as sepsis combined with systolic blood pressure SBP <90 mmHg or mean arterial pressure MAP < 65 mmHg. A meta-analysis could not be conducted. The certainty of the body of evidence was judged to be very low due to indirectness and very serious imprecision. The committee therefore made consensus recommendations based on their clinical experience and expertise due to the intervention reducing mortality and the high value placed on life preserving benefit. The committee considered several other factors when linking the evidence to recommendations.

Given the lack of direct evidence, the committee also discussed recommendations for future research. RCTs, retrospective and prospective cohort studies that assess the effects of deferred antibiotic administration in people with low, moderate and high risk of severe illness or death from sepsis stratified using the NEWS2 tool were needed.

The committee agreed that routine real-world healthcare data such as local audit data could also complement clinical trial evidence. Studies should include assessment of all critical outcomes such as mortality, unscheduled ICU admission, health related quality of life, hospital readmission rates, unplanned critical care admission, mortality time points other than 30 days, antibiotic resistance, adverse events and long-term disability in people who have suffered severe sepsis or septic shock. Qualitative studies with an emphasis on patient-oriented outcomes such health-related quality of life of people with long term disabilities due to sepsis and the impact on carers and families were also suggested.

In addition, initiation of antibiotic treatment in people with suspected sepsis and a NEWS2 score of 3 in a single parameter was a matter of concern due to lack of evidence which was also highlighted by the AoMRC report. The committee decided that more evidence for a NEWS2 score of 3 in a single physiological parameter would help to identify the particular risk of organ dysfunction and clarify the management and treatment approach of this specific category of people with confirmed or suspected sepsis. Research recommendations are outlined in Appendix K.

1.1.12.3 Benefits and harms

Failure to recognise or act on signs that a patient is deteriorating is a key patient safety issue. In the current context, the aim of the NEWS2 as a track-and-trigger early warning score system is early recognition of people who have or who are at risk of developing a systemic response to infection that may be life-threatening. The NEWS2 score should then be interpreted in the light of clinical assessment which includes rapidity of deterioration and trajectory, possible diagnosis (such as infection and sepsis), immune status, and evidence of organ dysfunction. In parallel with risk stratification into NEWS2 categories (very low, low, moderate or high), the clinician should also consider the likelihood of infection.

The evidence in this review regarding survival of people with sepsis and a NEWS score of 5 and above by administering antibiotics within one hour from triage, compared with three hours was inconclusive. However, the committee considered that antibiotic delivery is most beneficial when treatment priorities are matched to severity of illness as it allows clinicians sufficient time to make a more accurate diagnosis and to collect data to determine the source of infection. This was thought to be beneficial for several reasons. The NICE sepsis guideline (2016) recommended that broad spectrum antibiotics be administered within one hour in people where any high-risk criteria are met. The committee highlighted the potential harms that could be caused by early administration of antibiotics in people at the lower NEWS2 risk categories which could be avoided. Such harms might arise from a greater proportion of patients receiving antibiotics unnecessarily because less time is available for clinicians to evaluate alternate aetiologies for the patient's presentation. Furthermore, the committee agreed that adverse outcomes are even greater for patients receiving inappropriate e.g. broad-spectrum antibiotics, indicating the importance of matching treatment to pathogen, a diagnostic process which takes time. Therefore, the committee concluded that the use of source-specific antibiotics once the likely source of infection becomes clear or is confirmed should be recommended.

In light of the lack of evidence, the committee agreed by consensus to recommend the clinical decision support framework for initial evaluation of sepsis as outlined in the AoMRC report. Namely, for patients with low, moderate and high risk of severe illness or death from sepsis, infection-specific diagnostic tests (for example taking two sets of blood cultures) and administration of antibiotics should be completed within 6, 3, 1 hour or routine NEWS2 monitoring based on local practice respectively following assessment by clinician with core competencies in care of acutely ill patients. In this

way, by recommending the framework on antibiotic delivery time of 6, 3, 1 hour or routine NEWS2 monitoring of recording a NEWS2 score of 0, 1 to 4, 5 to 6, or 7 and above respectively and the use of source specific antibiotics in line with existing local antimicrobial guidance, have the potential to reduce the risk of possible antibiotic related harm of people with suspected sepsis and to promote antimicrobial stewardship.

However, the committee agreed for people with suspected sepsis where the source of infection was unknown, broad-spectrum antibiotics should be considered within the recommended timeframe for each NEWS2 risk category to prevent a delay in treatment. Once the organism source and antibiotic sensitivity is identified, the broad-spectrum antibiotics should be replaced with a source specific antibiotic. Both approaches were thought to be giving due consideration to the risk of severe illness and death from sepsis, while decreasing the risk of adverse effects associated with inappropriate antibiotic delivery at the same time.

To optimise the use of antibiotics, the committee agreed that to find the source of infection, best efforts need to be taken to enable microbial samples to be taken promptly and prior to the administration of antibiotics. For the adequate time to take microbial samples for people with suspected infection, the committee referred to the recommendation 1.1.27 of the Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use guideline. On how to find the source of infection in people with suspected sepsis, reference to the relevant section in the existing NG51 guideline was made. The committee concluded that a more accurate diagnosis may enable the use of source specific antibiotics which supports good antimicrobial stewardship and has the potential to reduce immediate adverse effects of broad-spectrum antibiotics.

Special consideration was given for the category of NEWS2 score of 3 in 1 parameter. The committee agreed that a NEWS2 score of 3 in a single parameter may be suggestive of organ dysfunction as it measures a parameter as being an extreme deranged value. Therefore, despite the lack of evidence, and based on their clinical expertise, the committee members concluded that for this specific risk group, clinical judgement is needed to determine whether antibiotic administration can be deferred and by how much. For example, for someone with a NEWS2 score of 4 towards which a single parameter contributes 3 of these 4 points, the clinician should judge whether antimicrobial administration can be deferred up to 3 or up to 6 hours.

The committee agreed that the purpose of postponing the time of antibiotic delivery is not to delay treatment, but to gain extra time to gather information for a more specific diagnosis. However, the committee also discussed that once a decision is made to give antimicrobials, do not delay administration any further. In conclusion, it was agreed that risk stratification framework and antibiotic delivery time framework based on the NEWS2 tool gives due consideration to both patient safety and antimicrobial stewardship. This allows clinicians to gather information for a more specific diagnosis and exercise accountable judgement in the care of individual patients, where lower risk of death from sepsis seems apparent.

Within a broader context, recording physiological parameters is now part of the NHS routine acute care. Converting these separate measurements into a single aggregate score would enable prompt and early recognition and subsequently timely and standardised management and treatment of people with suspected sepsis.

1.1.12.4 Cost effectiveness and resource use

No relevant economic evaluations were identified for this question.

The committee considered the costs for treating sepsis with antibiotic treatment. Antibiotics are a vital part of the treatment for a patient with sepsis. Although there are many antibiotics used in practice, some of the key antibiotics used in practice were presented within the evidence review. In general, the cost of antibiotics is considered to be low, however in some cases patients may be required to be on them for longer or may be given a more expensive option. The committee discussed that intravenous administration was the most used, however sometimes oral antibiotics may be given. The cost per day was estimated due to large variations in the length of time patients may need to take antibiotics for.

The committee highlighted the importance of sampling, including blood cultures, before administering antibiotics to increase the yield to identify the causative organism thus to reduce the duration of broad-spectrum antibiotics required and to ensure reliable test results. The committee did raise concerns that care needed to be taken to ensure culture tests are carried out correctly to avoid the costs and consequences associated with contamination. However, it was discussed that owing to the time delay between sampling and results becoming available, it would not always be possible to wait until the results had been obtained before starting treatment as this could delay treatment.

The committee considered the costs presented within Whitewater charitable trust (2017) analysis on the costs of hospitalisation and consequences of sepsis. The authors assumed that only around a third of patients with sepsis require ICU admission, these patients were assumed to be those with severe sepsis and septic shock. It was estimated that the total cost of treatment for a patient with severe sepsis would be £15,908 based on 7.8 days stay in ICU, followed by additional 15 days in hospital stay. The cost for adult patients not requiring ICU is substantially lower based on 6.4 days average duration, estimated to be £1,943. Whitewater charitable trust (2017) assumed a third of patients would require ICU, however the reporting of patients with sepsis who do not require ICU is poor and the committee discussed the proportion is only between 5-10% patients. However, the authors noted there is substantial uncertainty around the exact incidence and prevalence of sepsis and the resources used for treatment, particularly for those patients not requiring ICU.

The committee weighed up the increased costs associated with treating a larger population with antibiotics, including the risk of future antibiotic resistance against the consequences of delayed treatment, such as increased mortality, greater length of hospital stays, including intensive care units. The Whitewater charitable trust analysis highlighted the large differences in costs associated with the more severe cases of sepsis. The committee considered the resource implications associated with frequent monitoring of patients who may not be at the high risk of developing sepsis based on NEWS2 score given the current capacity constraints faced within emergency departments. No resource impact is anticipated because of this guideline update, it is anticipated these recommendations will be cost neutral. The risk stratification and antibiotic delivery time framework based on the NEWS2 tool gives due consideration to both patient safety and antimicrobial stewardship.

1.1.12.5 Other factors the committee took into account

The recommendations made by the committee were informed by the evidence review on the effects of immediate and deferred antibiotic delivery in adults (16 and above) with sepsis and severe sepsis on mortality based on the NEWS cut-off score of 5 and above and the clinical experience of the committee. The committee made reference to the AoMRC report and that it was consistent with the recommendations they have made.

The committee discussed the use of the terms '*antibiotic*' and '*antimicrobial*' and acknowledged that the latter includes antibacterial, antifungal and antiviral agents. However, the committee acknowledged that time intervals specified above refer to antibacterial agents in line with the evidence presented in this review. After a long discussion, the committee agreed to use the term '*antibiotics*' in the recommendations they proposed. Elsewhere in the guideline, where the aetiology of sepsis does not affect management plans, the committee proposed to use the term '*antimicrobial*' in line with the antimicrobial stewardship guideline.

The committee gave special consideration for people with neutropenic sepsis such as those on anti-cancer treatment and immunosuppressive therapies as sepsis shares many of the same immunosuppressive mechanisms (increased production of the immunosuppressive inflammatory factors such as cytokine interleukin 10, T regulatory cells, myeloid derived suppressor cells, and PD-1 and PD-L1 with T-cell exhaustion). These processes were thought to be similar among all people with neutropenic sepsis, regardless of its aetiology e.g., due to anti-cancer treatment, transplants or congenital causes and require urgent management and treatment. Hence, in order to prompt an urgent treatment without any delay for all people with neutropenic sepsis regardless of its cause, referral to the guideline Neutropenic sepsis: prevention and management in people with cancer was made.

The committee discussed what constitutes time zero which would guide the appropriate timing of antibiotic delivery. After a long discussion, the committee agreed to define time zero as a first NEWS2 score aggregated on presentation to emergency department or ward deterioration when accompanied by suspicion of infection and acknowledged that this was in line with the AoMRC report. However, concern was raised regarding possible delays of clinical assessment and subsequent review of people with suspected or confirmed sepsis presenting to NHS ambulance services, mental health facilities, emergency departments and acute hospitals due to the higher influx of patients and the already strained NHS system. This issue was particularly pertinent to the lay members of the committee. Within that context, in prehospital settings where transfer time is long or in emergency departments where admission may be delayed, the timely administration of antibiotics may be limited. Thus, the committee wished to emphasise the need for assessment by a clinician with core competencies in care of acutely ill patients and their clinical judgement to give due consideration of the potential lag-time in monitoring and diagnosis when prioritising care for an individual patient to ensure that outer time limits are not exceeded. To reinforce the need to address this issue, the committee also amended an existing recommendation in the NICE Sepsis guideline (2015). This was based on committee consensus advising where transfer time or admission to the emergency department is more than 1 hour ensure GPs and ambulance services have mechanisms in place to give antibiotics to people with high risk of severe illness or death from sepsis.

This was considered to be of a great importance, as acute illness is a dynamic state and changes in the patient's condition might indicate the need to upgrade actions and timelines. The delay of results from diagnostic testing was also considered and the committee wished to highlight that recommended antibiotic administration timeframe should be respected even in cases of lack or incomplete diagnostic test results.

The impact of the stratified risk approach and antibiotic delivery timeframe based on the NEWS2 risk categories on NHS practice was also discussed. The committee agreed that for ambulance services, mental health facilities, emergency departments and acute hospitals that already have incorporated the NEWS2 tool in their practices and management plans, these recommendations would not have a major impact on practice.

1.1.13 Recommendations supported by this evidence review

This evidence review supports recommendations on risk stratification and antibiotic administration including 1.1.8, 1.11.4, 1.11.6, 1.11.7, 1.11.8, 1.12.4, 1.12.5, 1.13.3, 1.13.9, 1.13.10, 1.13.14, 1.14.1 and the research recommendation 2 of the update to the NG51 guideline. Research recommendations are detailed in Appendix K of this evidence review.

1.1.14 References

Althunayyan, Saqer M; Aljanoubi, Mohammed A; Alghadeer, Sultan M; Alharthi, Musab Z; Alotaibi, Raied N; Mubarak, Abdullah M; Almutary, Abdulaziz M; The impact of emergency antibiotic administration time on patients with sepsis.; *Saudi medical journal*; 2021; vol. 42 (no. 9); 1002-1008

Whitewater charitable trust (2017) The Cost of Sepsis Care in the UK. Available at: https://sepsistrust.org/whitewater-charitable-trust-the-cost-of-sepsis-care-in-the-uk/

Appendices

Appendix A Review protocols

Review protocol for managing and treating suspected sepsis in acute hospital settings; Antibiotic treatment in people with suspected sepsis.

ID	Field	Content
0.	PROSPERO registration number	CRD42022345271
1.	Review title	Managing and treating suspected sepsis in acute hospital settings; Antibiotic treatment in people with suspected sepsis
2.	Review question	In adults and young people (16 and over) with suspected sepsis and at different NEWS2 risk brackets (0, 1 to 4, 5 to 6, greater than 7), what are the most clinically and cost-effective timings of antibiotic administration?
3.	Objective	To identify the most appropriate timing for antimicrobial treatment in patients with suspected sepsis.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE ((including Medline Epub ahead of print) Searches will be restricted by: • 2012 onwards • English language

		• Human studies The full search strategies will be published in the final review. Note: As the evidence base for NEWS2 tool is expected to be small, studies on NEWS tool will also be included as indirect evidence (these studies will be downgraded for indirectness in the GRADE analysis).
5.	Condition or domain being studied	Sepsis: recognition, diagnosis and early management Domain: timing for antibiotic delivery for different risk categories
6.	Population	Inclusion: People aged 16 and over with suspected sepsis and at different NEWS/NEWS2 risk brackets (0, 1 to 4, 5 to 6, 7 or above) Exclusion: • Children (15 and under) • Pregnant and recently pregnant women (women who have given birth or had a termination of pregnancy or miscarriage in the past 4 weeks) • People undergoing anticancer treatment with suspected or confirmed neutropenic sepsis Note: In the current NG51 guideline, recommendations are made for young people and adults (12 and over), therefore this must be accounted for when making new recommendations for young people and adults of 16 and over. Note: In pregnant and recently pregnant women (<4 weeks since birth or termination of pregnancy) with suspected sepsis the MEWS tool is used.

		Note: For people undergoing anticancer treatment with suspected or confirmed neutropenic sepsis a cross reference to the NICE CG151 Neutropenic sepsis: prevention and management of neutropenic sepsis in cancer patients will be made.
7.	Intervention/Exposure/Test	Deferred antibiotic administration based on NEWS2 risk bracket recommendation (0, 1 to 4, 5 to 6, 7 and above): within 3 hours for scores 5-6, within 6 hours for score 0 and 1 to 4. Note: The review will consider any type of antibiotics at the timing recommended in the NEWS2 tool (within 1, 3 or 6 hours). Different types of antibiotics, different modes of administration (e.g. intravenous, oral, intramuscular) and different doses of antibiotics will not be compared.
8.	Comparator/Reference standard/Confounding factors	Immediate antibiotic administration (within 1 hour) Note: the immediate antibiotic administration corresponds to NEWS2 risk bracket of 7 and above
9.	Types of study to be included	• Randomised controlled trials • Prospective cohort studies • Systematic reviews of these studies
10.	Other exclusion criteria	• All other study types • Non-English language
11.	Context	This review is part of an update of the NICE guideline on Sepsis: recognition, diagnosis and early management (NG51). This guideline update will cover young people and adults of age 16 and over presenting in acute hospital settings in which NHS care is received. This review will focus on the appropriate timing for antibiotic delivery for different risk categories triggered by the report from the Academy of Medical Royal Colleges (AoMRC) on the risk

		stratification and initial antimicrobial management of patients with suspected sepsis. The AoMRC report proposes that urgency of treatment of adults and young people (16+) with suspected sepsis is based on National Early Warning Scores (NEWS2) combined with clinical and laboratory assessments of severity, urgency and probability of infection. A structured approach is presented in the form of clinical decision support frameworks linking time frames for initial assessment and treatment to severity bands.
12.	Primary outcomes (critical outcomes)	• All-cause mortality at 28 days (or nearest time point) • Health related quality of life (measured by EQ5D or SF-36)

13.	Secondary outcomes (important outcomes)	• Duration of hospital stay
		• Duration of critical care stay
		• Hospital readmission rates
		• Organ failure and need for organ support e.g., additional medication, mechanical organ support, increase in SOFA score or as reported in included studies
		• Adverse events:
		  • diarrhoea
		  • inability to tolerate drug
		• Antibiotic resistance (defined in a clinical context as an indicator of the likely outcome of therapy, including the ability of an antibiotic to eliminate an infection) using detection methods such as:
		  ✓ Minimum inhibitory concentration (MIC) and concentrations that inhibit 50% (MIC50) or 90% (MIC90) of bacterial isolates
		  ✓ Drug resistance index (DRI) as a probability of inadequate treatment given observed drug use
		  ✓ Failure of empiric therapy by assessing Empiric Coverage Index (ECI) which measures available empiric coverage of common infections and/or

		Empiric Options Index (EOI) which measures the empiric value of the current stock of antibiotics ✓ Molecular techniques to determine the presence of genetic determinants of bacteria ✓ Other methods as reported in included studies • Longer- and shorter-term mortality related to sepsis (e.g., 2, 14 days or over 30 days e.g. 3 months, 6 months, 9 months, 12 months) or as reported in included studies • Long-term adverse outcomes due to severe sepsis such as those affecting physical, psychological or emotional functions (e.g., amputation, pain, fatigue, sleeping problems, cognitive impairment or as reported in studies. Outcome measures: • Adjusted relative risk (RR) or odds ratio (OR) (and ultimately risk difference) for patient outcomes between those receiving immediate antibiotic administration and those with deferred antibiotic administration. • Adjusted hazard ratios (HRs) if outcomes are measured over time.
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 6.4).
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual: RCTs and cohort studies will be appraised using the Cochrane RoB (2.0) and the Cochrane ROBINS-I tool respectively. For quality assessment of systematic reviews, the ROBIS appraisal checklist will be used.
16.	Strategy for data synthesis	Data on all included studies will be extracted into evidence tables. Where statistically possible, a pairwise meta-analytic approach will be used to give an overall summary effect. Meta-analyses of outcome data will be conducted for all comparators that are reported by more than one study, with reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011). Fixed- and random-effects models (der Simonian and Laird) will be fitted for all comparators, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models will be the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model is clearly not met, even after appropriate pre-specified subgroup analyses is conducted, random-effects results are presented. Fixed-effects models are deemed to be inappropriate if one or both of the following conditions was met: • Significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. • The presence of significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$. Meta-analyses will be performed in Cochrane Review Manager V5.3. In the pairwise analysis, subgroup analysis will also be conducted by age, setting, country which might have a different antibiotic resistance profile (UK vs other countries). All key outcomes from evidence will be presented in GRADE profiles and further summarised in evidence

		statements. Evidence from NEWS tool will be downgraded for indirectness. Network meta-analysis is not planned for this review.
17.	Analysis of sub-groups	• Age (young people, adults, older adults) • People at high risk of infection (e.g. people with indwelling catheters, or who have had recent surgery) • Countries outside the UK which might have a different resistance profile • Different settings (emergency department, hospital ward, intensive care units, mental health trusts etc.) If there are sufficient studies, sensitivity analyses will be used to explore, quantify, and control for sources of heterogeneity between studies by excluding studies at high and unclear risk of bias to ensure our conclusions are robust.
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	

22.	Anticipated completion date	March 2023		
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	☐	☐
24.	Named contact	**5a. Named contact** Guideline Development Team **5b Named contact e-mail**		

		Sepsis@nice.org.uk **5c Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE) and Guideline Development Team
25.	Review team members	From the Guideline Development Team: • Caroline Mulvihill • Teuta Gjuladin-Hellon • Kirsty Hounsell • Daniel Tuvey • Jonathan Littler
26.	Funding sources/sponsor	This systematic review is being completed by the Guideline Development Team, Centre for Guidelines 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: [NICE guideline webpage].

29.	Other registration details	
30.	Reference/URL for published protocol	Guidelines Update Team, Caroline Mulvihill, Teuta Gjuladin-Hellon, Daniel Tuvey, Lindsay Claxton, Kirsty Luckham. Managing and treating suspected sepsis in acute hospital settings; Antibiotic treatment in people with suspected sepsis. PROSPERO 2022 CRD42022345271 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022345271
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	NEWS, antibiotic treatment, suspected sepsis
33.	Details of existing review of same topic by same authors	
34.	Current review status	☐ Ongoing ☐ Completed but not published ☐ Completed and published ☐ Completed, published and being updated

		☐ Discontinued
35.	Additional information	
36.	Details of final publication	www.nice.org.uk

Health economic review protocol

No health economic review protocol is included for this review question.

Appendix B Methods

Literature search, screening, and study selection

Search methods

The searches for the prognostic evidence were run on 30th July 2022. The following databases were searched: Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley); Cochrane Database of Systematic Reviews (CDSR) (Wiley); Embase (OVID); Medline (OVID). MEDLINE Epub Ahead-of-Print (OVID).

The database searches were supplemented with additional search methods. Searches for grey literature were also undertaken on websites covering government, charities and related organisations.

The searches for the cost effectiveness evidence were run on 30th July. The following databases were searched: Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley); Cochrane Database of Systematic Reviews (CDSR) (Wiley); EconLit (OVID); Embase (OVID); International HTA database (INAHTA); Medline (OVID). MEDLINE Epub Ahead-of-Print (OVID).

Detailed search strategies for each database and method are provided in Appendix C.

Priority screening

The reviews undertaken for this guideline all made use of the priority screening functionality with the EPPI-reviewer systematic reviewing software. This uses a machine learning algorithm (specifically, an SGD classifier) to take information on features (1, 2 and 3 word blocks) in the titles and abstracts of papers marked as being 'includes' or 'excludes' during the title and abstract screening process, and re-orders the remaining records from most likely to least likely to be an include, based on that algorithm. This re-ordering of the remaining records occurs every time 25 additional records have been screened.

Research is currently ongoing as to what are the appropriate thresholds where reviewing of abstracts can be stopped, assuming a defined threshold for the proportion of relevant papers which it is acceptable to miss on primary screening. As a conservative approach until that research has been completed, the following rules were adopted during the production of this guideline:

- In every review, at least 50% of the identified abstracts (or 1,000 records, if that is a greater number) were always screened.

- After this point, the number of included studies was recorded after every 1,000 records were screened. If, assuming studies were to be found in the remainder of the dataset at the same rate as in that 1,000 records (for example, if 5 includes were found, every subsequent 1,000 records would contain 5 includes), it was estimated that at least 95% of the includable studies in the database had been identified, then the screening was stopped.

As an additional check to ensure this approach did not miss relevant studies, the included studies lists of potentially relevant systematic reviews were searched to identify any papers not identified through the primary search. Evidence from the previous version of the guideline was also reviewed.

The full text of potentially eligible studies was retrieved and assessed according to the criteria specified in the review protocol. A standardised form was used to extract data from included studies. Study investigators were not contacted for missing data.

Incorporating published systematic reviews

For all review questions where a literature search was undertaken looking for a particular study design, systematic reviews containing studies of that design were also included. All potentially eligible studies from those systematic reviews were screened to identify any additional relevant primary studies not found as part of the initial search. However, during this process, systematic reviews or included primary studies that met the eligibility criteria were not identified during the full-text screening.

Evidence of interventional studies

In this guideline, RCTs that met inclusion criteria specified in the protocol were not identified. One cohort study was included in the review. Data is presented as RRs calculated from the number of events at a specific time-point as reported in the study.

Quality assessment

The cohort study was quality assessed using the ROBINS-I tool. Evidence on each outcome for each individual study was classified into one of the following groups:

- Low risk of bias – The true effect size for the study is likely to be close to the estimated effect size.
- Moderate risk of bias – There is a possibility the true effect size for the study is substantially different to the estimated effect size.
- High risk of bias – It is likely the true effect size for the study is substantially different to the estimated effect size.
- Critical risk of bias (ROBINS-I only) - It is very likely the true effect size for the study is substantially different to the estimated effect size.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, predictors and/or outcomes in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, predictors and/or outcomes.
- Partially indirect – Important deviations from the protocol in one of the population, predictors and/or outcomes.
- Indirect – Important deviations f Each domain was assessed as being at low, high or unclear risk of bias.

Quality assessment and directness are presented in Appendix E.

Methods of combining intervention evidence

Combining the evidence from intervention studies using meta-analysis was not performed due to the insufficient number of included studies (n=1). Forest plots were generated in RevMan5 to visualise the risk ratios (RRs) in the different intervention groups and are presented in Appendix F.

Minimal clinically important differences (MIDs)

The Guideline Committee did not prospectively define clinical decision thresholds for association outcomes based on the degree of association that would be considered clinically important for decision making. Therefore, the Core Outcome Measures in Effectiveness Trials (COMET) database was searched to identify published minimal clinically important difference thresholds relevant to this guideline, however none were identified.

In cases where the minimal clinically important difference thresholds could not be identified in the COMET data base and committee were unable to define a clinical decision threshold by consensus, for RRs a default clinical decision threshold for dichotomous outcomes of 0.8 to 1.25 was used for the purpose of rating imprecision in GRADE.

GRADE for intervention studies

GRADE was used to assess the quality of evidence for the outcomes specified in the review protocol. Data from the cohort study (which was quality assessed using the ROBINS-I) was initially rated as high quality with the quality of the evidence for each outcome then downgraded or not from this initial point.

Rationale for downgrading quality of evidence

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels. Extremely serious: If greater than 33.3% of the weight in a meta-analysis came from studies at critical risk of bias, the outcome was downgraded three levels Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies at high and low risk of bias.
Indirectness	Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between direct and indirect studies.

GRADE criteria	Reasons for downgrading quality
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the I^2 statistic. N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study. Not serious: If the I^2 was less than 33.3%, the outcome was not downgraded. Serious: If the I^2 was between 33.3% and 66.7%, the outcome was downgraded one level. Very serious: If the I^2 was greater than 66.7%, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies with the smallest and largest effect sizes.
Imprecision	If an MID other than the line of no effect was defined for the outcome, the outcome was downgraded once if the 95% confidence interval for the effect size crossed one line of the MID, and twice if it crosses both lines of the MID. If the line of no effect was defined as an MID for the outcome, it was downgraded once if the 95% confidence interval for the effect size crossed the line of no effect (i.e., the outcome was not statistically significant). If relative risk could not be estimated (due to zero events in both arms), outcome was downgraded for very serious imprecision as effect size could not be calculated. Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios.

The quality of evidence for each outcome was upgraded if either of the following conditions were met:

- Data showing an effect size sufficiently large that it cannot be explained by confounding alone.
- Data where all plausible residual confounding is likely to increase our confidence in the effect estimate.

Summary of evidence is presented in section 1.1.5. and 1.1.6. These sections summarise the characteristics of the studies, effect size, quality of evidence and interpretation of the evidence in relation to the significance of the data. The full GRADE tables can be found in Appendix G.

Publication bias

Publication bias was not assessed due to the small number of included studies (n=1).

Appendix C Literature search strategies

Evidence review for stratifying risk of severe illness or death from sepsis.

Background and development

Search design and peer review

A NICE information specialist conducted the literature searches for the evidence review. The searches were run on 30 June 2022. This search report is compliant with the requirements of PRISMA-S.

The MEDLINE strategy below was quality assured (QA) by a trained NICE information specialist. All translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the 2016 PRESS Checklist.

The principal search strategy was 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 sepsis terms were based on the strategy used for Sepsis: recognition, diagnosis and early management (2017) NICE guideline 51.

Limits and restrictions

English language limits were applied in adherence to standard NICE practice and the review protocol.

The search was limited from 2012 to 2022 as defined in the review protocol.

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.

Key decisions

The review protocols were only interested in evidence related to one assessment tool (NEWS and NEWS 2) as opposed to the multiple tools that were included in the original guideline (Sepsis: recognition, diagnosis and early management (2017) NICE guideline 51). The scoping search (March 2022) identified less than 500 records in Medline and just over 100 in Medline in Process, which was a very small evidence base. The original guideline search included a set of umbrella terms for assessment tools and a set of named tools. As the review protocols only wanted evidence on NEWS and NEWS2 the broader set of umbrella terms nor the set of name tools were not included in the search strategy. To maximise the number of NEWS and NEWS2 results, the strategy was kept short and focused with 2 sets (sepsis AND news/news2).

Due to the small number of results from the effectiveness search it was decided not to apply a cost-effectiveness filter to the cost-effectiveness searches.

Clinical/public health searches

Main search – Databases

Database	Date searched	Database Platform	Database segment or version	No. of results downloaded
Cochrane Central Register of Controlled Trials (CENTRAL)	30/06/22	Wiley	Issue 6 of 12, June 2022	10
Cochrane Database of Systematic Reviews (CDSR)	30/06/22	Wiley	Issue 6 of 12, June 2022	1
Embase	30/06/22	Ovid	Embase 1996 to 2022 June 29	353
MEDLINE	30/06/22	Ovid	Ovid MEDLINE(R) 1996 to June 29, 2022	138
MEDLINE Epub Ahead-of-Print	30/06/22	Ovid	Ovid MEDLINE(R) Epub Ahead of Print June 29, 2022	7

Main search – Additional methods

Additional method	Date searched	No. of results downloaded
Web searching	4-5 July 2022	19

Search strategy history

Database name: Cochrane Central Register of Controlled Trials (CENTRAL)

#1 MeSH descriptor: [Sepsis] explode all trees 4918
#2 sepsis:ti,ab,kw 12176
#3 MeSH descriptor: [Blood-Borne Pathogens] this term only 30
#4 (blood* near/2 (pathogen* or poison*)):ti,ab,kw 329
#5 MeSH descriptor: [Systemic Inflammatory Response Syndrome] explode all trees 5312
#6 "systemic inflammatory response syndrome*":ti,ab,kw 1167
#7 sirs:ti,ab,kw 794
#8 (septicaemi* or septicemi*):ti,ab,kw 1075
#9 ((septic or cryptic) near/2 shock):ti,ab,kw 3417
#10 (pyaemi* or pyemi* or pyohemi*):ti,ab,kw 8
#11 (bacter?emi* or fung?emi* or parasit?emi* or vir?emi*):ti,ab,kw 6146
#12 (hypotension near/3 induced near/3 hypoperfusion) 1
#13 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 21320
#15 ("National Early Warning Score*"):ti,ab,kw (Word variations have been searched) 121
#16 ("National Early Warning Score* 2"):ti,ab,kw (Word variations have been searched) 34
#17 (NEWS2):ti,ab,kw (Word variations have been searched) 51
#18 (NEWS):ti,ab,kw (Word variations have been searched) 2813
#19 #15 or #16 or #17 or #18 2877
#20 #13 and #19 with Cochrane Library publication date Between Jan 2012 and Jun 2022 25

#21 #13 and #19 with Publication Year from 2012 to 2022, in Trials 20
#22 "conference":pt or (clinicaltrials or trialsearch):so 599319
#23 #20 not #22 1
#24 #21 not #22 10
#25 ("systemic inflammatory response syndrome*"):ti,ab,kw (Word variations have been searched) 1170

Database name: Cochrane Database of Systematic Reviews (CDSR)

#1 MeSH descriptor: [Sepsis] explode all trees 4918
#2 sepsis:ti,ab,kw 12176
#3 MeSH descriptor: [Blood-Borne Pathogens] this term only 30
#4 (blood* near/2 (pathogen* or poison*)):ti,ab,kw 329
#5 MeSH descriptor: [Systemic Inflammatory Response Syndrome] explode all trees 5312
#6 "systemic inflammatory response syndrome*":ti,ab,kw 1167
#7 sirs:ti,ab,kw 794
#8 (septicaemi* or septicemi*):ti,ab,kw 1075
#9 ((septic or cryptic) near/2 shock):ti,ab,kw 3417
#10 (pyaemi* or pyemi* or pyohemi*):ti,ab,kw 8
#11 (bacter?emi* or fung?emi* or parasit?emi* or vir?emi*):ti,ab,kw 6146
#12 (hypotension near/3 induced near/3 hypoperfusion) 1
#13 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 21320
#15 ("National Early Warning Score*"):ti,ab,kw (Word variations have been searched) 121
#16 ("National Early Warning Score* 2"):ti,ab,kw (Word variations have been searched) 34
#17 (NEWS2):ti,ab,kw (Word variations have been searched) 51
#18 (NEWS):ti,ab,kw (Word variations have been searched) 2813
#19 #15 or #16 or #17 or #18 2877
#20 #13 and #19 with Cochrane Library publication date Between Jan 2012 and Jun 2022 25
#21 #13 and #19 with Publication Year from 2012 to 2022, in Trials 20
#22 "conference":pt or (clinicaltrials or trialsearch):so 599319
#23 #20 not #22 1
#24 #21 not #22 10
#25 ("systemic inflammatory response syndrome*"):ti,ab,kw (Word variations have been searched) 1170

Database name: Embase

1	exp sepsis/	272511
2	sepsis.ti,ab.	152596
3	bloodborne bacterium/	1921
4	(blood* adj2 (pathogen* or poison*)).ti,ab.	3583
5	exp systemic inflammatory response syndrome/	283102
6	'systemic inflammatory response syndrome*'.ti,ab.	7991
7	sirs.ti,ab.	10649

8	(septicaemi* or septicemi*).ti,ab.	16169
9	((septic or cryptic) adj2 shock).ti,ab.	37554
10	(pyaemi* or pyemi* or pyohemi*).ti,ab.	80
11	(bacter?emi* or fung?emi* or parasit?emi* or vir?emi*).ti,ab.	79492
12	(hypotension adj3 induced adj3 hypoperfusion).ti,ab.	6
13	or/1-12	373042
14	"National Early Warning Score*".ti,ab,kw.	787
15	"National Early Warning Score* 2".ti,ab,kw.	119
16	NEWS2.ti,ab,kw.	204
17	NEWS.ti,ab,kw.	25102
18	National Early Warning Score/	308
19	or/14-18	25512
20	13 and 19	422
21	limit 20 to yr="2012 -Current"	358
22	limit 21 to english language	353
23	Animals/ not (Humans/ and Animals/)	576993
24	22 not 23	353

Database name: MEDLINE

1	exp sepsis/	101110
2	sepsis.ti,ab.	78657
3	blood-borne pathogens/	2719
4	(blood* adj2 (pathogen* or poison*)).ti,ab.	2302
5	exp systemic inflammatory response syndrome/	108074
6	'systemic inflammatory response syndrome*'.ti,ab.	4745
7	sirs.ti,ab.	5229
8	(septicaemi* or septicemi*).ti,ab.	10082
9	((septic or cryptic) adj2 shock).ti,ab.	18638
10	(pyaemi* or pyemi* or pyohemi*).ti,ab.	47
11	(bacter?emi* or fung?emi* or parasit?emi* or vir?emi*).ti,ab.	47902
12	(hypotension adj3 induced adj3 hypoperfusion).ti,ab.	3
13	or/1-12	184174
14	"National Early Warning Score*".ti,ab,kw.	431
15	"National Early Warning Score* 2".ti,ab,kw.	74
16	NEWS2.ti,ab,kw.	116
17	NEWS.ti,ab,kw.	13435
18	or/14-17	13643

19	13 and 18	164
20	limit 19 to yr="2012 -Current"	145
21	limit 20 to english language	138
22	Animals/ not (Humans/ and Animals/)	2802987
23	21 not 22	138

Database name: MEDLINE Epub Ahead-of-Print

1	sepsis.ti,ab.	1264
2	(blood* adj2 (pathogen* or poison*)).ti,ab.	32
3	'systemic inflammatory response syndrome*'.ti,ab.	58
4	sirs.ti,ab.	74
5	(septicaemi* or septicemi*).ti,ab.	101
6	((septic or cryptic) adj2 shock).ti,ab.	267
7	(pyaemi* or pyemi* or pyohemi*).ti,ab.	0
8	(bacter?emi* or fung?emi* or parasit?emi* or vir?emi*).ti,ab.	515
9	(hypotension adj3 induced adj3 hypoperfusion).ti,ab.	0
10	or/1-9	2068
11	"National Early Warning Score*".ti,ab,kw.	17
12	"National Early Warning Score* 2".ti,ab,kw.	7
13	NEWS2.ti,ab,kw.	12
14	NEWS.ti,ab,kw.	820
15	or/11-14	834
16	10 and 15	7
17	limit 16 to yr="2012 -Current"	7
18	limit 17 to english language	7

Additional search methods

Source name: NHS England

Name	NHS England
URL	https://www.england.nhs.uk/
Date searched	04/07/22
Segment or dates covered by search, including any specific sections browsed	2017 onwards
Search terms	Sepsis AND (NEWS or NEWS2) + date range (from 01/01/17)
How the results were selected	Browsed for relevance

[state how many results you reviewed if you did not check them all e.g. the first 100 results or the first 10 pages]	
No. of results	6

Source name: Department of Health and Social Care

Name	Department of Health and Social Care
URL	https://www.gov.uk/
Date searched	05/07/22
Segment or dates covered by search, including any specific sections browsed	Search function: Health and social care as topic
Search terms	Sepsis AND (news or news2)
How the results were selected [state how many results you reviewed if you did not check them all e.g. the first 100 results or the first 10 pages]	Any result referring to NEWS or NEWS2
No. of results	0

Source name: Royal College of Physicians

Name	Royal College of Physicians
URL	https://www.rcplondon.ac.uk/
Date searched	04/07/22
Segment or dates covered by search, including any specific sections browsed	2017 onwards
Search terms	Sepsis
How the results were selected [state how many results you reviewed if you did not check them all e.g. the first 100 results or the first 10 pages]	Reviewed 34 results
No. of results	8

Source name: Royal College of Emergency Medicine

Name	Royal College of Emergency Medicine
URL	https://rcem.ac.uk/
Date searched	04/07/22
Segment or dates covered by search, including any specific sections browsed	2017 onwards
Search terms	Sepsis
How the results were selected [state how many results you reviewed if you did not check them all e.g. the first 100 results or the first 10 pages]	Any result referring to NEWS or NEWS2
No. of results	1

Source name: Sepsis Trust

Name	Sepsis Trust
URL	Home - Sepsis Trust
Date searched	05/07/22
Segment or dates covered by search, including any specific sections browsed	2017 onwards
Search terms	Browsed "Professional resources"
How the results were selected [state how many results you reviewed if you did not check them all e.g. the first 100 results or the first 10 pages]	Any result referring to NEWS or NEWS2
No. of results	3

Source name: Surviving Sepsis Campaign

Name	Surviving Sepsis Campaign
URL	Surviving Sepsis Campaign (SSC) | SCCM

Date searched	05/07/22
Segment or dates covered by search, including any specific sections browsed	2017 onwards
Search terms	Browsed: Guidelines and bundles; Tools and education
How the results were selected [state how many results you reviewed if you did not check them all e.g. the first 100 results or the first 10 pages]	Any result referring to NEWS or NEWS2
No. of results	1

Source name: Sepsis Alliance

Name	Sepsis Alliance
URL	Sepsis Alliance
Date searched	05/07/22
Segment or dates covered by search, including any specific sections browsed	2017 onwards. Browsed: Sepsis information guides;
Search terms	-
How the results were selected [state how many results you reviewed if you did not check them all e.g. the first 100 results or the first 10 pages]	Any result referring to NEWS or NEWS2
No. of results	0

Source name: Sepsis Research

Name	Sepsis Research
URL	https://sepsisresearch.org.uk/
Date searched	05/07/22
Segment or dates covered by search, including any specific sections browsed	2017 onwards
Search terms	NEWS or NEWS2
How the results were selected	No relevant results

[state how many results you reviewed if you did not check them all e.g. the first 100 results or the first 10 pages]	
No. of results	0

Source name: First Response

Name	First Response
URL	https://www.firstresponse.org.uk/medical-training/news2
Date searched	05/07/22
Segment or dates covered by search, including any specific sections browsed	2017 onwards
Search terms	Browsed: Medical training: NEWS2
How the results were selected [state how many results you reviewed if you did not check them all e.g. the first 100 results or the first 10 pages]	No relevant results
No. of results	0

Source name: TRIP (Turning Research into Practice) database

Name	TRIP (Turning Research into Practice) database
URL	https://www.tripdatabase.com/
Date searched	05/07/22
Segment or dates covered by search, including any specific sections browsed	2017 onwards
Search terms	Sepsis AND (news OR news2)
How the results were selected [state how many results you reviewed if you did not check them all e.g. the first 100 results or the first 10 pages]	Browsed first 50 results
No. of results	0

Source name: FERN (Find Evidence, Retrieve Now)

Name	FERN (Find Evidence, Retrieve Now)
URL	Internal NICE database
Date searched	05/07/22
Segment or dates covered by search, including any specific sections browsed	2017 onwards
Search terms	Sepsis AND (news or news2)
How the results were selected [state how many results you reviewed if you did not check them all e.g. the first 100 results or the first 10 pages]	Browsed first 100 results for references to NEWS or NEWS2
No. of results	1

Source name: Google

Name	Google
URL	https://www.google.co.uk/
Date searched	05/07/22
Segment or dates covered by search, including any specific sections browsed	2017 onwards
Search terms	Sepsis AND (news or news2)
How the results were selected [state how many results you reviewed if you did not check them all e.g. the first 100 results or the first 10 pages]	Browsed first 100 results for references to NEWS or NEWS2
No. of results	5

Cost-effectiveness searches

Main search – Databases

EconLit	30/06/22	OVID	Econlit 1886 to June 23, 2022	0
Embase	30/06/22	Ovid	Embase 1996 to 2022 June 29	353
INAHTA	30/06/22	INAHTA	-	5
MEDLINE	30/06/22	Ovid	Ovid MEDLINE(R) 1996 to June 29, 2022	138
MEDLINE Epub Ahead-of-Print	30/06/22	Ovid	Ovid MEDLINE(R) Epub Ahead of Print June 29, 2022	7
Cochrane Central Register of Controlled Trials (CENTRAL)	30/06/22	Wiley	Issue 6 of 12, June 2022	10
Cochrane Database of Systematic Reviews (CDSR)	30/06/22	Wiley	Issue 6 of 12, June 2022	1

Search strategy history

Database name: EconLit

1	sepsis.ti,ab.	18
2	(blood* adj2 (pathogen* or poison*)).ti,ab.	0
3	'systemic inflammatory response syndrome*'.ti,ab.	0
4	sirs.ti,ab.	13
5	(septicaemi* or septicemi*).ti,ab.	2
6	((septic or cryptic) adj2 shock).ti,ab.	1
7	(pyaemi* or pyemi* or pyohemi*).ti,ab.	0
8	(bacter?emi* or fung?emi* or parasit?emi* or vir?emi*).ti,ab.	7
9	(hypotension adj3 induced adj3 hypoperfusion).ti,ab.	0
10	or/1-9	40
11	"National Early Warning Score*".ti,ab,kw.	1
12	"National Early Warning Score* 2".ti,ab,kw.	0
13	NEWS2.ti,ab,kw.	0
14	NEWS.ti,ab,kw.	9211
15	or/11-14	9211
16	10 and 15	0
17	limit 16 to yr="2012 -Current"	0

Database name: Embase

1	exp sepsis/	272511
2	sepsis.ti,ab.	152596
3	bloodborne bacterium/	1921
4	(blood* adj2 (pathogen* or poison*)).ti,ab.	3583
5	exp systemic inflammatory response syndrome/	283102
6	'systemic inflammatory response syndrome*'.ti,ab.	7991
7	sirs.ti,ab.	10649
8	(septicaemi* or septicemi*).ti,ab.	16169
9	((septic or cryptic) adj2 shock).ti,ab.	37554
10	(pyaemi* or pyemi* or pyohemi*).ti,ab.	80
11	(bacter?emi* or fung?emi* or parasit?emi* or vir?emi*).ti,ab.	79492
12	(hypotension adj3 induced adj3 hypoperfusion).ti,ab.	6
13	or/1-12	373042
14	"National Early Warning Score*".ti,ab,kw.	787
15	"National Early Warning Score* 2".ti,ab,kw.	119
16	NEWS2.ti,ab,kw.	204
17	NEWS.ti,ab,kw.	25102
18	National Early Warning Score/	308
19	or/14-18	25512
20	13 and 19	422
21	limit 20 to yr="2012 -Current"	358
22	limit 21 to english language	353
23	Animals/ not (Humans/ and Animals/)	576993
24	22 not 23	353

Database name: INAHTA

((NEWS)[abs]) OR ((NEWS)[title]) OR ((NEWS)[abs]) OR ((NEWS2)[abs]) OR ((NEWS2)[title]) OR (("National Early Warning Score 2")[title]) OR (("National Early Warning Score 2")[abs]) OR (("National Early Warning Score")[abs]) OR (("National Early Warning Score")[title])

Database name: MEDLINE

1	exp sepsis/	101110
2	sepsis.ti,ab.	78657
3	blood-borne pathogens/	2719

4	(blood* adj2 (pathogen* or poison*)).ti,ab.	2302
5	exp systemic inflammatory response syndrome/	108074
6	'systemic inflammatory response syndrome*'.ti,ab.	4745
7	sirs.ti,ab.	5229
8	(septicaemi* or septicemi*).ti,ab.	10082
9	((septic or cryptic) adj2 shock).ti,ab.	18638
10	(pyaemi* or pyemi* or pyohemi*).ti,ab.	47
11	(bacter?emi* or fung?emi* or parasit?emi* or vir?emi*).ti,ab.	47902
12	(hypotension adj3 induced adj3 hypoperfusion).ti,ab.	3
13	or/1-12	184174
14	"National Early Warning Score*".ti,ab,kw.	431
15	"National Early Warning Score* 2".ti,ab,kw.	74
16	NEWS2.ti,ab,kw.	116
17	NEWS.ti,ab,kw.	13435
18	or/14-17	13643
19	13 and 18	164
20	limit 19 to yr="2012 -Current"	145
21	limit 20 to english language	138
22	Animals/ not (Humans/ and Animals/)	2802987
23	21 not 22	138

Database name: MEDLINE Epub Ahead-of-Print

1	sepsis.ti,ab.	1264
2	(blood* adj2 (pathogen* or poison*)).ti,ab.	32
3	'systemic inflammatory response syndrome*'.ti,ab.	58
4	sirs.ti,ab.	74
5	(septicaemi* or septicemi*).ti,ab.	101
6	((septic or cryptic) adj2 shock).ti,ab.	267
7	(pyaemi* or pyemi* or pyohemi*).ti,ab.	0
8	(bacter?emi* or fung?emi* or parasit?emi* or vir?emi*).ti,ab.	515
9	(hypotension adj3 induced adj3 hypoperfusion).ti,ab.	0
10	or/1-9	2068
11	"National Early Warning Score*".ti,ab,kw.	17
12	"National Early Warning Score* 2".ti,ab,kw.	7
13	NEWS2.ti,ab,kw.	12

14	NEWS.ti,ab,kw.	820
15	or/11-14	834
16	10 and 15	7
17	limit 16 to yr="2012 -Current"	7
18	limit 17 to english language	7

Database name: Cochrane Central Register of Controlled Trials (CENTRAL)

#1 MeSH descriptor: [Sepsis] explode all trees 4918
#2 sepsis:ti,ab,kw 12176
#3 MeSH descriptor: [Blood-Borne Pathogens] this term only 30
#4 (blood* near/2 (pathogen* or poison*)):ti,ab,kw 329
#5 MeSH descriptor: [Systemic Inflammatory Response Syndrome] explode all trees 5312
#6 "systemic inflammatory response syndrome*":ti,ab,kw 1167
#7 sirs:ti,ab,kw 794
#8 (septicaemi* or septicemi*):ti,ab,kw 1075
#9 ((septic or cryptic) near/2 shock):ti,ab,kw 3417
#10 (pyaemi* or pyemi* or pyohemi*):ti,ab,kw 8
#11 (bacter?emi* or fung?emi* or parasit?emi* or vir?emi*):ti,ab,kw 6146
#12 (hypotension near/3 induced near/3 hypoperfusion) 1
#13 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 21320
#15 ("National Early Warning Score*"):ti,ab,kw (Word variations have been searched) 121
#16 ("National Early Warning Score* 2"):ti,ab,kw (Word variations have been searched) 34
#17 (NEWS2):ti,ab,kw (Word variations have been searched) 51
#18 (NEWS):ti,ab,kw (Word variations have been searched) 2813
#19 #15 or #16 or #17 or #18 2877
#20 #13 and #19 with Cochrane Library publication date Between Jan 2012 and Jun 2022 25
#21 #13 and #19 with Publication Year from 2012 to 2022, in Trials 20
#22 "conference":pt or (clinicaltrials or trialsearch):so 599319
#23 #20 not #22 1
#24 #21 not #22 10
#25 ("systemic inflammatory response syndrome*"):ti,ab,kw (Word variations have been searched) 1170

Database name: Cochrane Database of Systematic Reviews (CDSR)

#1 MeSH descriptor: [Sepsis] explode all trees 4918
#2 sepsis:ti,ab,kw 12176
#3 MeSH descriptor: [Blood-Borne Pathogens] this term only 30
#4 (blood* near/2 (pathogen* or poison*)):ti,ab,kw 329
#5 MeSH descriptor: [Systemic Inflammatory Response Syndrome] explode all trees 5312
#6 "systemic inflammatory response syndrome*":ti,ab,kw 1167
#7 sirs:ti,ab,kw 794
#8 (septicaemi* or septicemi*):ti,ab,kw 1075

#9 ((septic or cryptic) near/2 shock):ti,ab,kw 3417
#10 (pyaemi* or pyemi* or pyohemi*):ti,ab,kw 8
#11 (bacter?emi* or fung?emi* or parasit?emi* or vir?emi*):ti,ab,kw 6146
#12 (hypotension near/3 induced near/3 hypoperfusion) 1
#13 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 21320
#15 ("National Early Warning Score*"):ti,ab,kw (Word variations have been searched) 121
#16 ("National Early Warning Score* 2"):ti,ab,kw (Word variations have been searched) 34
#17 (NEWS2):ti,ab,kw (Word variations have been searched) 51
#18 (NEWS):ti,ab,kw (Word variations have been searched) 2813
#19 #15 or #16 or #17 or #18 2877
#20 #13 and #19 with Cochrane Library publication date Between Jan 2012 and Jun 2022 25
#21 #13 and #19 with Publication Year from 2012 to 2022, in Trials 20
#22 "conference":pt or (clinicaltrials or trialsearch):so 599319
#23 #20 not #22 1
#24 #21 not #22 10
#25 ("systemic inflammatory response syndrome*"):ti,ab,kw (Word variations have been searched) 1170

Appendix D Intervention evidence study selection

Figure 1: Flow chart of clinical study selection for the review of managing and treating suspected sepsis in acute hospital settings; Antibiotic treatment in people with suspected sepsis

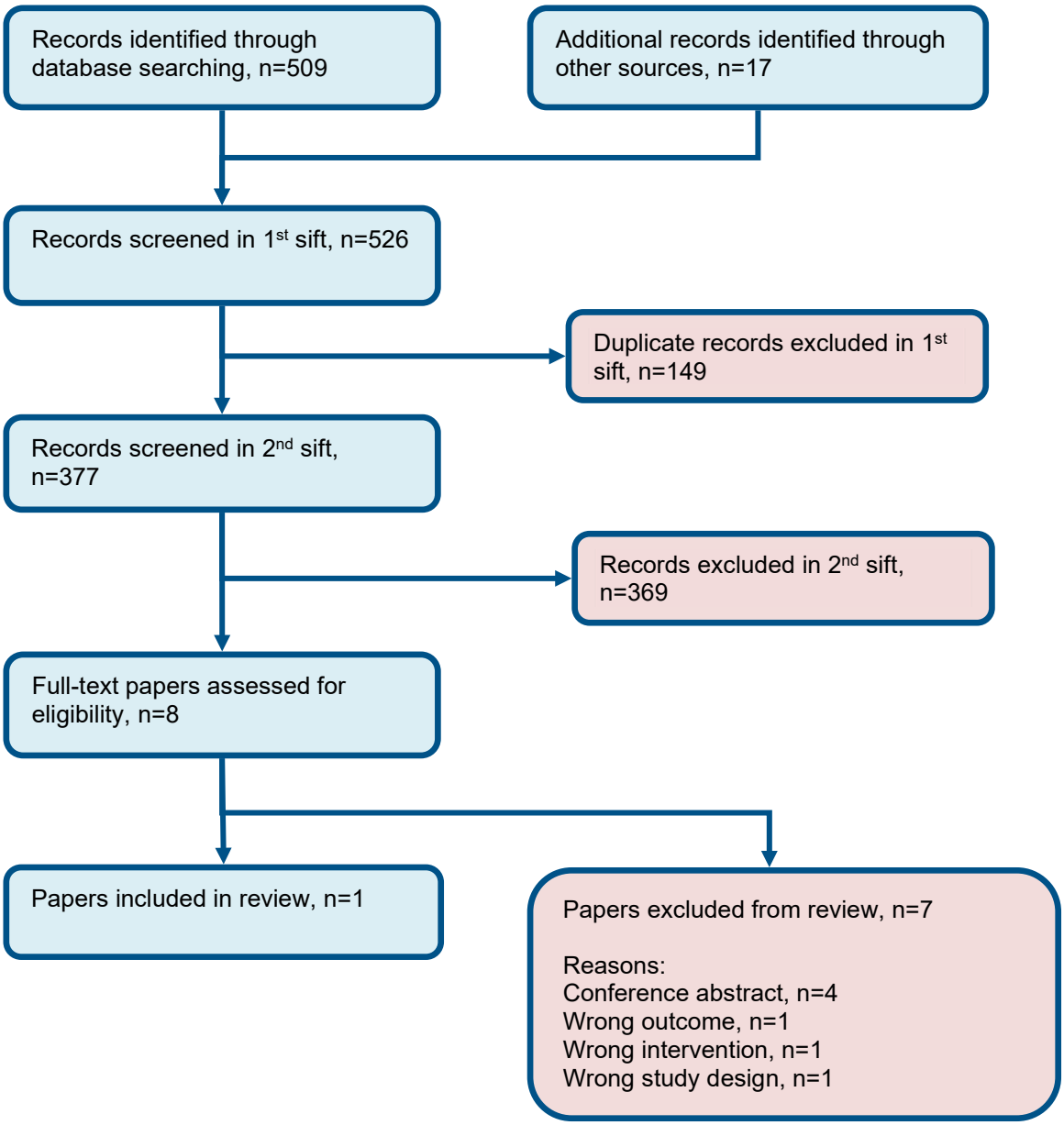
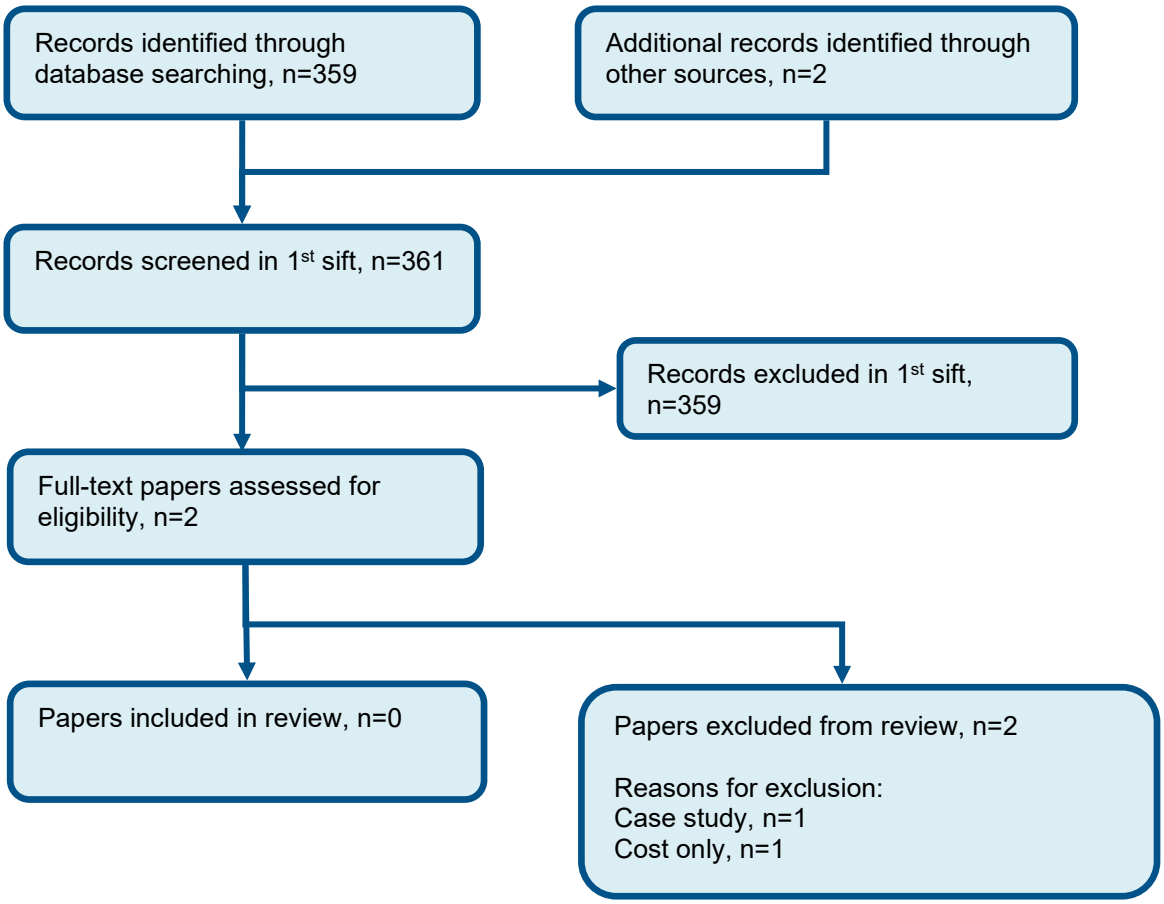


Figure 2: Flow chart of economic study selection for the review of managing and treating suspected sepsis in acute hospital settings; Antibiotic treatment in people with suspected sepsis


Records identified through database searching, n=359
Additional records identified through other sources, n=2
Records screened in 1st sift, n=361
Records excluded in 1st sift, n=359
Full-text papers assessed for eligibility, n=2
Papers included in review, n=0
Papers excluded from review, n=2
Reasons for exclusion:
Case study, n=1
Cost only, n=1

Appendix E Evidence table

Althunayyan et al, 2021

Bibliographic Reference	Althunayyan, Saqer M; Aljanoubi, Mohammed A; Alghadeer, Sultan M; Alharthi, Musab Z; Alotaibi, Raied N; Mubarak, Abdullah M; Almutary, Abdulaziz M; The impact of emergency antibiotic administration time on patients with sepsis.; Saudi medical journal; 2021; vol. 42 (no. 9); 1002-1008

Study details

Secondary publication of another study- see primary study for details	Almutary A, Althunayyan S, Alenazi K, Alqahtani A, Alotaibi B, Ahmed M, Osman IS, Kakpuri A, Alanazi A, Arafat M, Al-Mutairi A, Bashraheel F, Almazroua F. National Early Warning Score (NEWS) as Prognostic Triage Tool for Septic Patients. Infect Drug Resist. 2020 Oct 27;13:3843-3851. doi: 10.2147/IDR.S275390. PMID: 33149629; PMCID: PMC7602891.
Study type	Retrospective cohort study
Study location	Saudi Arabia
Study setting	Emergency Department, King Saud Medical City, Riyadh, Saudi Arabia.
Study dates	Data were collected retrospectively between July 2018 and June 2019
Sources of funding	Not reported
Inclusion criteria	People with suspected sepsis Patients were enrolled in the sepsis management protocol according to a NEWS value >4 or a clinical sepsis suspect was enrolled by the ED physician who triaged him/her to the high acuity area to start standardized ED sepsis management protocol according to King Saud Medical City's guidelines
Exclusion criteria	Pregnancy, less than 18 years old, discharged against medical advice, had a comorbid diagnosis (asthma exacerbation, paroxysmal supraventricular tachycardia, hepatic encephalopathy, and diabetic ketoacidosis), and did not take antibiotics within 1 hours of enrolment or missed the time
Outcome measures	In-hospital mortality for each group
Number of participants	292

Duration of follow-up	Not reported
Study arm 1	**≤1 hours antibiotic administration (N = 250)** The immediate group, which received the first IV antibiotics within an hour of triage (from 0 to 60 min)
Study arm 2	**1-3 hours antibiotic administration (N = 42)** The early group, which received the first antibiotics between one and 3 hours (61 to 180 min) after sepsis diagnosis.
Loss to follow-up	All participants accounted for
Methods of analysis	The difference between groups was analysed using a 2-tailed student's t-test for continuous variables in variables normally distributed and a Chi-square test for categorical variables. For variables that not normally distributed, the median and interquartile ranges are presented, and the Mann–Whitney U-test was used to analyse intergroup differences. Complete case analysis was performed, and statistical significance was determined at $p<0.05$ in all analysis sections.
Additional comments	Sepsis 3 definition used. Severe sepsis defined as systolic blood pressure SBP <90 mmHg or mean arterial pressure MAP < 65 mmHg. The most common comorbidities reported in the final cohort were hypertension (n=101) and diabetes mellitus (n=87). Most of those patients received immediate antibiotics. Patients who received antibiotics later were older than those who received immediate antibiotics (with a mean age of 61.2 ± 22.2 years versus 55.3 ± 23.8 years) but was not statistically significant (p=0.1754). Non-statistically significant variation between the 2 groups in the number of patients with SBP<90 mmHg.

Characteristics

Study-level characteristics

Characteristic	Study (N = 292)
Mean age (SD) Mean (SD)	56.3 (23.6)
Age within 1 hour Mean (SD)	55.3 (23.8)
Age within 1-3 hours Mean (SD)	61.2 (22.2)

Characteristic	Study (N = 292)
Any comorbidities Sample size	n = 145 ; % = 49.6
Diabetes mellitus Sample size	n = 87 ; % = 29.8
Hypertension Sample size	n = 101 ; % = 34.6
Congestive heart failure Sample size	n = 12 ; % = 4.1
Kidney failure Sample size	n = 21 ; % = 7.2
Oncology Sample size	n = 19 ; % = 6.5
Pneumonia empyema Sample size	n = 108 ; % = 37
Urinary tract infection Sample size	n = 29 ; % = 9.9
Acute abdominal infection Sample size	n = 8 ; % = 2.7
Meningitis Sample size	n = 14 ; % = 4.8
Skin/soft tissue infection Sample size	n = 32 ; % = 11
Bone/joint infection Sample size	n = 7 ; % = 2.4
Wound infection	n = 7 ; % = 2.4

Characteristic	Study (N = 292)
Sample size	
Blood stream catheter infection Sample size	n = 7 ; % = 2.4
Mortality Sample size	N=93; 31.8% Within 1 hrs: 14; 33.3% 1-3 hrs: 79; 31.6% (p=n.s.)

Subgroup characteristics

Severe septic patients

Patients with systolic blood pressure <90 mmHg or mean arterial pressure <65 mmHg	≤1 hours antibiotic administration (N = 250)	1-3 hours antibiotic administration (N = 42)
Sample size	n=58	n=7
Age Mean (SD)	59.86 (21.65)	67.8 (21.58)
Mortality Sample size	n = 22 ; % = 43.1	n = 3 ; % = 42.8

Critical appraisal - GDT Crit App - ROBINS-I: a tool for non-randomised studies of interventions

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Probably no
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	Yes
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Not applicable
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes

Section	Question	Answer
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Yes
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Not applicable
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	No information
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	Risk of bias judgement for confounding	Low
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Not applicable
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	No

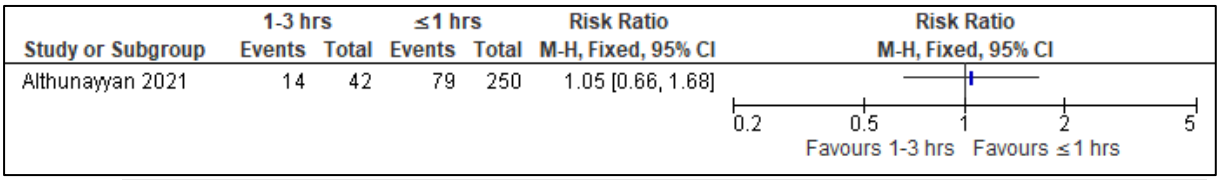
Section	Question	Answer
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	No
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	Not applicable
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	Yes
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	Probably yes
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	Not applicable
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	No
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	Not applicable
5. Bias due to missing data	Risk of bias judgement for missing data	Low
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Probably no

Section	Question	Answer
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	No information
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	Yes
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	Probably no
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	No
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	No
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	No
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Low
Overall bias	Directness	Indirectly Applicable

SBP = systolic blood pressure; MAP = mean arterial pressure; NEWS = National Early Warning Score

Appendix F Forest plots

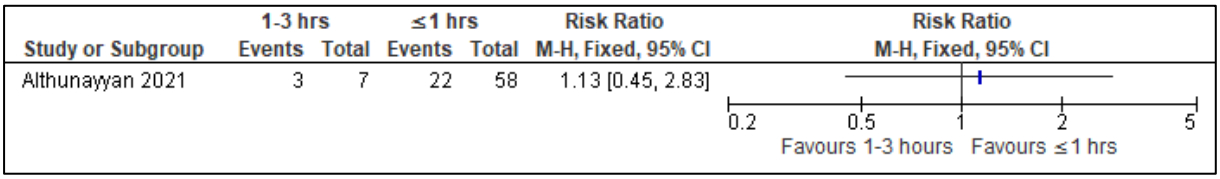
Forest plot for mortality in people with sepsis who received antibiotics within 1 hour versus those who received antibiotics between 1-3 hours



Notes: *RR greater than 1 favours immediate antibiotic administration within 1 hours

Forest plot for mortality in people with severe sepsis who received antibiotics within 1 hour versus those who received antibiotics between 1-3 hours

Notes: *RR greater than 1 favours immediate antibiotic administration within 1 hours



Appendix G GRADE tables for intervention studies

Mortality in people with sepsis who received antibiotics within 1 hour versus those who received antibiotics between 1-3 hours

Sample size, study	Study event rates (%)		MID	Effect size RR (95% CI)	Anticipated absolute effects		Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
	≤1 hour administration	1-3 hrs administration			Risk with ≤1 hour administration	Risk difference with 1-3 hrs administration					
Mortality in septic patients between Early (within 1-3 hours) vs Immediate (≤1 hrs) antibiotic administration [RR>1 favours immediate (≤1 hrs) antibiotic administration]											
292 (cohort study)	14/42 (33.3%)	79/250 (31.6%)	[0.8-1.25]	**RR 1.05** [0.66-1.68]	333 per 1,000	**17 more per 1,000** (from 113 fewer to 227 more)	Not serious	NA[1]	Serious[2]	Very serious[3]	⨁◯◯◯ Very low

RR= risk ratio. CI=confidence interval. NA = not applicable.

1. Only one study, inconsistency not applicable
2. Downgraded for indirectness as data assessed using the NEWS tool (as per protocol, Appendix A)
4. Downgraded by 2 increments as 95% CI cross both ends of the defined MID

Mortality in people with severe sepsis who received antibiotics within 1 hour versus those who received antibiotics between 1-3 hours

Sample size, study	Study event rates (%)		MID	Effect size RR [95% CI]	Anticipated absolute effects		Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
	≤1 hour administration	1-3 hrs administration			Risk with ≤1 hour administration	Risk difference with 1-3 hrs administration					
Mortality in severe septic patients between Early (within 1-3 hours) vs Immediate (≤1 hrs) antibiotic administration [RR>1 favours immediate (≤1 hrs) antibiotic administration]											
65 (cohort study)	3/7 (42.9%)	22/58 (37.9%)	[0.8-1.25]	**RR 1.13** [0.45-2.83]	429 per 1,000	**56 more per 1,000** (from 236 fewer to 784 more)	Not serious	NA[1]	Serious[2]	Very serious[3]	⨁◯◯◯ Very low

RR= risk ratio. CI=confidence interval. NA = not applicable.

1. Only one study, inconsistency not applicable
2. Downgraded for indirectness as data assessed using the NEWS tool (as per protocol, Appendix A)
3. Downgraded by 2 increments as 95% CI cross both ends of the defined MID

Appendix H Economic evidence tables

No relevant health economic studies were identified for this review question.

Appendix I – Health economic model

Original health economic modelling was not prioritised for this question.

Appendix J Excluded studies

Clinical studies

A list of studies excluded from this review at full-text stage and reasons for exclusion:

Study	Code [Reason]
Academy of Medical Royal Colleges (2022) Statement on the initial antimicrobial treatment of sepsis .: 1-97	- Review article but not a systematic review
Churpek, Matthew M, Snyder, Ashley, Sokol, Sarah et al. (2017) Investigating the Impact of Different Suspicion of Infection Criteria on the Accuracy of Quick Sepsis-Related Organ Failure Assessment, Systemic Inflammatory Response Syndrome, and Early Warning Scores. Critical care medicine 45(11): 1805-1812	- Study does not contain outcomes of interest *Does not look at timing of delivery of antibiotic*
Gonzalez Del Castillo, Juan, Wilson, Darius Cameron, Clemente-Callejo, Carlota et al. (2019) Biomarkers and clinical scores to identify patient populations at risk of delayed antibiotic administration or intensive care admission. Critical care (London, England) 23(1): 335	- Study does not contain a relevant intervention *Study compares blood biomarkers and clinical scores (Sequential Organ Failure Assessment (SOFA), National Early Warning Score (NEWS), and quick SOFA) to identify patient populations at risk of delayed treatment initiation*
Khandhia, A.; Hardwick, J.; Wilkinson, J. (2019) National Early Warning Score and time to antibiotics-an audit of emergency department practice at Northampton General Hospital NHS Trust. Journal of the Intensive Care Society 20(2supplement): 140-141	- Conference abstract
Kopczynska, M., Sharif, B., Unwin, H. et al. (2019) Antibiotics use in patients at risk of sepsis on general wards. Intensive Care Medicine Experimental 7(supplement3)	- Conference abstract
Mothukuri, R., John, H., Kakollu, M. et al. (2018) The implementation of antibiotic therapy as part of sepsis six bundle: A twelve month single centre study of compliance with antibiotic therapy and outcomes. Intensive Care Medicine Experimental 6(supplement2)	- Conference abstract
Pugh, E. (2016) Timings of antibiotic administration for patients with sepsis in the emergency department. Anaesthesia 71(suppl2): 37	- Conference abstract

Health Economic studies

Published health economic studies excluded from this review at full-text stage and reasons for exclusion:

Table 3: Studies excluded from the health economic review

Reference	Reason for exclusion
Bray, Alison, Kampouraki, Emmanouela, Winter, Amanda et al. (2020) High Variability in Sepsis Guidelines in UK: Why Does It Matter? International journal of environmental research and public health 17(6)	Excluded as this is not a cost effectiveness study
NHS England and NHS Rightcare (2018) NHS RightCare scenario: The variation between sub-optimal and optimal pathways. 1-33	Excluded as not a cost effectiveness study, only costs are considered for two hypothetical scenarios.

Appendix K Research recommendations – full details

[NICE's process and methods guide for research recommendations sets out how research recommendations are developed in response to gaps in the evidence.

K.1 Research recommendation

In adults and young people (16 and over) with suspected sepsis and at different NEWS2 risk brackets (0, 1 to 4, 5 to 6, greater than 7), what are the most clinically effective timings of antibiotic administration?

As a separate subgroup, the following research recommendation was made:

In adults and young people (16 and over) with suspected sepsis and NEWS2 score of 3 in a single parameter, what are the most clinically effective timings of antibiotic administration?

K.1.1 Why this is important

NEWS2 has been introduced in 2017 and is widely used across the NHS prehospital and acute care settings. However, evidence on NEWS2 tool was not found. There is only indirect and very scarce data base (one study) on the earlier version of the tool (NEWS, published in 2012) on the mortality benefits of timely antibiotic treatment of adults presenting with sepsis, comparing 1 hour administration and 3 hour administration of antibiotics starting from the time of triage. It is important to investigate the success, safety and possible implications on patients and staff of using the NEWS2 tool categories and likelihood of infection which prompts antibiotic delivery within different timeframes. Trials also need to consider the longer-term risk of severe illness or death over a 5- to 10-year period. As a specific subgroup within this population, the category of a NEWS2 score of 3 in a single category was also of concern as there is a lack of data around its stratification and the possible risk of deterioration remains uncertain. Data regarding the timing of antibiotic administration in people with suspected sepsis and a NEWS2 score of 3 in one parameter was not found.

K.1.2 Rationale for research recommendation

Importance to 'patients' or the population	Little is known about the most clinically effective timings of antimicrobial administration in people with suspected sepsis and in different NEWS2 categories (0, 1 to 4, 5 to 6, 7 or above). Furthermore, there is little evidence on the different time frames and the risk of severe illness or death from sepsis in adults and young people (16 and over) with suspected sepsis presenting to acute hospital settings, ambulance trusts and acute mental health facilities. This would clarify existing uncertainties regarding outcomes such as health-related quality of life, ICU and critical care admission, long or short-term mortality, long-term adverse events due to severe sepsis and impact on patients and carers for which no direct or indirect evidence was found. Of a particular interest is to investigate the impact on antimicrobial resistance in line with good antimicrobial stewardship.

Relevance to NICE guidance	The NEWS2 tool has been considered in this guideline but no data was found on different NEWS2 risk categories and corresponding antibiotic delivery timings in people with high, moderate to high and low risk of severe illness or death from sepsis. More robust clinical trial evidence is therefore needed. NICE is using more routine real-world healthcare data to assess the effectiveness of interventions, resolve gaps in knowledge and drive forward access to innovation for patients. Using clinical trial evidence in combination with real-world data will help further understand the issue of antibiotic delivery timing for different NEWS2 risk categories. Findings would generate data which could feed into future guideline updates and more specific evidence-based recommendations.
Relevance to the NHS	The findings would ensure a more structured approach to the management and treatment of people with suspected sepsis and their risk of acute illness and death. Early recognition and timely management has the potential to decrease morbidity and mortality and reduce NHS cost incurred due to delayed or inappropriate management. This in turn may involve ICU or critical care admission and length of hospital stay.
National priorities	High
Current evidence base	As highlighted, data on the effect of antibiotic delivery based on the NEWS2 risk categories on critical and important outcomes were not found.
Equality considerations	Further evidence on antibiotic timing for different NEWS2 risk categories may help to address the known inequalities. Using routine healthcare data will ensure a broader population is captured, rather than just those eligible for clinical trials.

K.1.3 Modified PICO table

Population	Patients with low, moderate or high risk of severe illness or death from sepsis
Intervention	Antimicrobial administration in people with suspected sepsis within the NEWS2 risk categories (0, 1 to 4, 5 to 6, 7 or above).
Comparator	Antimicrobial administration within 1 hour
Outcome	Health-related quality of life, ICU and critical care admission, long or short-term mortality, long-term adverse events due to severe sepsis and impact on patients and carers.
Study design	RCT

	Prospective cohort studies Routine healthcare data Registries / audits
Timeframe	Long term
Additional information	None

K.1.4 Rationale for research recommendation

Importance to 'patients' or the population	Little evidence exists about the association between a NEWS2 score of 3 in a single parameter, prompt antibiotic delivery and risk of severe illness or death in adults and young people (16 and over) with suspected sepsis presenting to acute hospital settings, ambulance trusts and acute mental health facilities as a separate subgroup of people with suspected sepsis. This would clarify existing uncertainties regarding outcomes such as health-related quality of life, ICU and critical care admission, long or short-term mortality, long-term adverse events due to severe sepsis and impact on patients and carers for which no direct or indirect evidence was found. Of a particular interest is to investigate the impact on antimicrobial resistance in line with good antimicrobial stewardship.
Relevance to NICE guidance	The NEWS2 tool has been considered in this guideline but no data was found on people with a NEWS2 score of 3 in a single parameter and corresponding antibiotic delivery timings. More robust clinical trial evidence is therefore needed. NICE is using more routine real-world healthcare data to assess the effectiveness of interventions, resolve gaps in knowledge and drive forward access to innovation for patients. Using clinical trial evidence in combination with real-world data will help further understand the issue of antibiotic delivery timing for different NEWS2 risk categories. Findings would generate data which could feed into future guideline updates and more specific evidence-based recommendations.
Relevance to the NHS	The findings would ensure a more structured approach to the management and treatment of people with suspected sepsis and their risk of acute illness and death. Early recognition and timely management has the potential to decrease morbidity and mortality and reduce NHS cost incurred due to delayed or inappropriate management. This in turn may involve ICU or critical care admission and length of hospital stay.
National priorities	High

Current evidence base	As highlighted, data on the effect of antibiotic delivery based on the NEWS2 risk categories on critical and important outcomes were not found.
Equality considerations	Further evidence on antibiotic timing for different NEWS2 risk categories may help to address the known inequalities Using routine healthcare data will ensure a broader population is captured, rather than just those eligible for clinical trials.

K.1.5 Modified PICO table

Population	Patients with low, medium or high risk of severe illness or death from sepsis
Intervention	Antimicrobial administration in people with suspected sepsis and NEWS2 score of 3 in a single parameter.
Comparator	Antimicrobial administration within 1 hour
Outcome	Health-related quality of life, ICU and critical care admission, long or short-term mortality, long-term adverse events due to severe sepsis and impact on patients and carers.
Study design	RCT Prospective cohort studies Routine healthcare data Registries / audits
Timeframe	Long term
Additional information	None