National Institute for Health and Care Excellence

Final

Meningitis (bacterial) and meningococcal disease: recognition, diagnosis and management

[C1] Evidence reviews for timing of antibiotics for bacterial meningitis

NICE guideline NG240

Evidence review underpinning recommendations 1.2.3, 1.2.4, 1.2.6, 1.4.1, and 1.6.1 to 1.6.3 in the NICE guideline

March 2024

Final

This evidence review was developed by NICE

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Timing of antibiotics for bacterial meningitis

Review question

What is the optimal timing of antibiotic administration for people with suspected bacterial meningitis?

Introduction

Bacterial meningitis is a rare but serious infection, which can occur in any age group. Early recognition of the condition requires a high index of suspicion.

Once the diagnosis is suspected based on the clinical history and examination findings, urgent investigations are required to confirm the diagnosis and establish the bacterial aetiology. The prescription of antibiotics prior to these urgent investigations may hinder the diagnosis and lead to unnecessary antibiotic use in patients who have non-infective conditions or a viral illness.

The aim of this review is to determine the optimal timing of antibiotic administration for people with suspected bacterial meningitis.

Summary of the protocol

See Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	All adults, young people, children and babies (excluding neonates defined as aged 28 days old and younger) with suspected bacterial meningitis
Intervention	Early administration of parenteral antibiotic therapy (single or in combination), defined as earlier administration than the comparator
Comparison	Late administration of parenteral antibiotic therapy (single or in combination), defined as later administration than the intervention.
Outcome	**Critical** Population: adults, infants and children • All-cause mortality (measured up to 1 year after discharge) • Any long-term neurological impairment (defined as any motor deficits, sensory deficits [excluding hearing impairment], cognitive deficits*, or behavioural deficits*; measured from discharge up to 1 year after discharge) Population: adults • Functional impairment (measured by any validated scale at any time point) Population: infants and children • Severe developmental delay (defined as score of >2 SD below normal on validated assessment scales, or MDI or PDI <70 on Bayleys assessment scale, or inability to assign a score due to cerebral palsy or severity of cognitive delay; measured at the oldest age reported unless there is substantially more data available at a younger age). **Important** Population: adults, infants and children • Diagnosis of epilepsy or occurrence of seizures during hospitalisation • Hearing impairment (defined as any level of hearing impairment; measured from discharge up to 1 year after discharge) • Serious intervention-related adverse effects leading to death, disability or prolonged hospitalisation or that are life threatening or otherwise considered

	medically significant Population: adults • Length of hospitalisation Population: infants and children • Functional impairment (measured by any validated scale at any time point) *For infants and children below school-age, cognitive and behavioural deficits will be assessed at school-age.

MDI: mental development index; PDI: psychomotor development index; SD: standard deviation

For further details see the review protocol in appendix A.

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 document (supplementary document 1).

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

Effectiveness evidence

Included studies

Eight studies were included for this review: 1 prospective cohort study (Auburtin 2006), and 7 retrospective cohort studies (Bargui 2012; Bijlsma 2016; Bodilsen 2016; Bretonniere 2015; Glimaker 2015; Kaaresen 1995; Proulx 2005).

The included studies are summarised in Table 2.

Three studies compared pre-hospital antibiotic administration with no pre-hospital antibiotic administration (Bargui 2012; Bijlsma 2016; Kaaresen 1995), and 5 studies compared antibiotic administration at different time points in hospital (Auburtin 2006; Bodilsen 2016; Bretonniere 2015; Glimaker 2015; Proulx 2005).

Six studies recruited adults only (Auburtin 2006; Bijlsma 2016; Bodilsen 2016; Bretonniere 2015; Glimaker 2015; Proulx 2005). Bargui 2012 and Kaaresen 1995 recruited children only.

All the studies except Kaaresen 1995 performed some adjustment for confounding factors, although even studies that reported adjusted data did not necessarily report adjusted estimates for all outcomes.

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review are listed, and reasons for their exclusion are provided in appendix J.

Summary of included studies

Summaries of the studies that were included in this review are presented in Table 2.

Table 2: Summary of included studies

Study	Population	Intervention	Comparison	Outcomes	Comments
Auburtin 2006	N=156	Antibiotics ≤3 hours after	Antibiotics >3 hours after	• All-cause mortality	Analyses adjusted for

Study	Population	Intervention	Comparison	Outcomes	Comments
Prospective cohort study France	Bacterial meningitis (pneumococcal meningitis) in adults Age (mean, SD): 56 ± 17 years Case-fatality: 32%	hospital admission No further details reported	hospital admission No further details reported		confounding factors except antibiotics administered pre/post lumbar puncture and co-morbidity Initial antibiotics used: third-generation cephalosporin for: 53%; third-generation cephalosporin + vancomycin: 29%; amoxicillin: 18%. Not reported separately based on antibiotic timing Indirect population (26% immunocompromised)
Bargui 2012 Retrospective cohort study France	N=89 Bacterial meningitis in children Age (median, IQR): 8 (4 to 18) months Population treated with pre-admission antibiotics: 28% Case-fatality: 21%	Pre-admission antibiotics No further details reported	No-pre-admission antibiotics No further details reported	• All-cause mortality • Any long-term neurological impairment	Analyses for pre-admission antibiotics versus no pre-admission antibiotics were unadjusted for confounding factors.
Bijlsma 2016 Retrospective	N=1391 (n=1377 evaluable	Pre-admission antibiotics	No pre-admission antibiotic	• Functional impairment (GOS ≤4)	Analyses adjusted for confounding

Study	Population	Intervention	Comparison	Outcomes	Comments
cohort study Netherlands	cases) Bacterial meningitis in adults Age (median, IQR): 61 (47 to 69) years Population treated with pre-admission antibiotics: 11% Case-fatality: 17.5%	No further details reported	No further details reported		factors except co-morbidity; severity of infection, antibiotics administered pre or post lumbar puncture, and infective organisms Initial antibiotics used: amoxicillin + third-generation cephalosporin: 36%; third-generation cephalosporin: 29%; penicillin or amoxicillin: 20%; other regimens: 15%. Not reported separately based on antibiotic timing
Bodilsen 2016 Retrospective cohort study Denmark	N=195 (n=173 evaluable cases) Bacterial meningitis in adults >16 years Age (median, IQR): 58 (45 to 70) years Case-fatality: 23%	Antibiotics 0 to 2h after hospital admission No further details reported	Antibiotics 2 to 4h after hospital admission No further details reported Antibiotics 4 to 6h after hospital admission No further details reported Antibiotics >6h after hospital admission	• All-cause mortality • Functional impairment (GOS ≤4)	n=22 excluded from analysis: n=8 excluded as an accurate time of antibiotic administration could not be obtained; n=1 had not received antibiotics (diagnosis made post-mortem); n=13 had received antibiotic

Study	Population	Intervention	Comparison	Outcomes	Comments
			No further details reported		treatment in the community Mortality and functional impairment analyses adjusted for confounding factors except co-morbidity, antibiotics administered pre/post lumbar puncture and infective organisms and comorbidity and antibiotics administered pre/post lumbar puncture, respectively
Bretonniere 2015 Retrospective cohort study France	N=157 (n=126 evaluable cases) Bacterial meningitis (age group not stated) Age (mean, SD): 45 ± 20 years Case-fatality: 14%	<u>Antibiotics 0 to 2h after hospital admission</u> No further detail reported	<u>Antibiotics ≥2 after hospital admission</u> No further detail reported	• All-cause mortality	Analyses adjusted for confounding factors except antibiotics administered pre/post lumbar puncture and severity Antibiotic status of 31/157 (20%) participants not known Initial antibiotics used: combination 76% (third-generation cephalosporin + vancomycin (68%); third-generation

Study	Population	Intervention	Comparison	Outcomes	Comments
					cephalosporin + rifampin (23%); monotherapy (unclear) 24%. Not reported separately based on antibiotic timing
Glimaker 2015 Retrospective cohort study Sweden	N=712 Bacterial meningitis in adults Age (median, IQR): 61 (17 to 95) years Case-fatality: 10%	<u>Comparison presented per hour of treatment delay following hospital admission</u> Initial antibiotics used: cefotaxime + ampicillin: 41%; cefotaxime: 17%; meropenem: 30%; other antibiotics: 10%. Not reported separately based on antibiotic timing.		• All-cause mortality	Analyses adjusted for confounding factors except antibiotics administered pre/post lumbar puncture and comorbidity
Kaaresen 1995 Retrospective cohort study Norway	N=92 (n=70 evaluable cases) Bacterial meningitis in children Age (median, IQR): 1.9 years (1month to 13.8 years) Population treated with pre-admission parenteral antibiotics: 26.1% Case-fatality: 5.7%	<u>Pre-admission parenteral antibiotics</u> No further details reported	<u>No pre-admission antibiotics</u> No further details reported	• All-cause mortality • Any long-term neurological impairment	Analyses unadjusted for any confounding factors – severity of illness, infective organism, antibiotics pre or post lumbar puncture Initial antibiotics used: benzylpenicillin and chloramphenicol: 79%; ampicillin and chloramphenicol: 10%; cefotaxime and dexamethasone: 4%; other combinations: 5%. Not

Study	Population	Intervention	Comparison	Outcomes	Comments
					reported separately based on antibiotic timing
Proulx 2005 Retrospective case record study Canada	N=123 (n=118 analysed) Bacterial meningitis in adults Age (mean, range): 54 (19-86) years Case-fatality: 13%	Antibiotics ≤6h after hospital admission No further details reported	Antibiotics >6h after hospital admission No further details reported	• All-cause mortality	Analyses adjusted for all confounding factors Initial antibiotics used: third-generation cephalosporin + penicillin or ampicillin 35%; third generation cephalosporin + vancomycin 21%; third-generation cephalosporin alone 16%. Not reported separately based on antibiotic timing

GOS: Glasgow outcome scale; IQR: interquartile range; SD: standard deviation; h: hours

See the full evidence tables in appendix D and the forest plots in appendix E.

Summary of the evidence

This section is a narrative summary of the findings of the review, as presented in the GRADE tables in appendix F. For details of the committee's confidence in the evidence and how this affected recommendations, see The committee's discussion and interpretation of the evidence.

The evidence was assessed as being low to very low quality due to failure to adjust for confounding factors and small number of events. Most of the studies presented adjusted results (for at least some outcomes), however, they rarely reported data at the same time points and only three studies reported data at the same time point (pre-hospital antibiotics). The evidence was stratified by age, setting, and timing of early antibiotic administration. See the GRADE tables in appendix F for the certainty of the evidence for each individual outcome.

The studies assessed the effect of different timings and setting of initial antibiotic administration on mortality, long term neurological impairment and functional impairment.

Evidence comparing outcomes between those who received pre-hospital antibiotics and those who did not receive pre-hospital antibiotics showed no significant difference in mortality and any long-term neurological impairment in children, however, only unadjusted estimates were available. Some evidence also showed no significant difference in (adjusted estimates of) functional impairment between adults who received pre-hospital antibiotics and those who did not.

Overall, early in-hospital antibiotic administration was associated with lower rates of mortality in adults compared to later antibiotic administration. Antibiotics delivered within 2-3 hours and 6 hours of admission showed lower (adjusted) mortality rates compared with antibiotics delivered after 2-3 hours and 6 hours, respectively. Some evidence also showed a relative adjusted increase in mortality rates of 12.6% per hour of antibiotic treatment delay. Although, evidence comparing early in-hospital antibiotic administration (within 2 hours) relative to antibiotics delivered at later timepoints (intervals of 2-4 hours, 4-6 hours and >6 hours after admission) did not show significant differences in (adjusted) mortality rates, there was some evidence for a benefit of earlier administration in terms of lower rates of functional impairment but only when compared against delays greater than 6 hours. There was no evidence assessing the effect of different timings of in-hospital antibiotic administration for babies or children.

There were a number of outcomes in the protocol that were not reported on by any studies, including diagnosis of epilepsy or occurrence of seizures during hospitalisation, hearing impairment, length of hospitalisation, and severe developmental delay.

See appendix F for full GRADE tables.

Economic evidence

Included studies

A single economic search was undertaken for all topics included in the scope of this guideline, but no economic studies were identified which were applicable to this review question.

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

The committee's discussion and interpretation of the evidence

The outcomes that matter most

Bacterial meningitis is associated with high rates of mortality and morbidity. Antibiotics are the mainstay of treatment for bacterial meningitis, therefore all-cause mortality and long-term neurological impairment were prioritised as critical outcomes due to the severity of these outcomes. Severe developmental delay was prioritised over functional impairment in children and babies, as it is a more relevant and important outcome for this population. Functional impairment was prioritised as a critical outcome in adults due to the concern about the potential long-term limitations of bacterial meningitis on the ability to carry out certain daily life functions.

In addition to functional impairment in children and babies, epilepsy or seizures, hearing impairment and serious intervention-related adverse effects were selected as important outcomes as these are relatively common after bacterial meningitis and may be related to the timing of antibiotic therapy. Length of hospitalisation was also included as an important

outcome for adults because this may be considered as an indicator of treatment effectiveness and was expected to be commonly reported in trials.

The quality of the evidence

The quality of the evidence was assessed with GRADE methodology. Evidence for all-cause mortality was rated as very low to low quality due to risk of bias (arising from failure to adjust for confounding factors) and imprecision (due to the small number of events). For the comparison between pre-hospital and no pre-hospital antibiotics for all-cause mortality, no meta-analysis was conducted due to the high level of heterogeneity, which was most likely due to failure to adjust for confounding and a mixed population of intravenous and oral antibiotic use in 1 study (Kaaresen 1995). The evidence for any long-term neurological impairment or functional impairment was assessed as being very low to low quality. As with mortality, the main reasons for downgrading the quality of the evidence were insufficient adjustment for confounding factors and imprecision.

No evidence was identified for severe developmental delay, epilepsy or seizures, hearing impairment, serious intervention-related adverse effects, or length of hospitalisation.

Benefits and harms

The committee considered the evidence comparing outcomes between children who did and did not receive pre-hospital antibiotics and noted no significant difference in all-cause mortality and any long-term neurological impairment. There was also no evidence of a difference in functional impairment between adults who received antibiotics prior to hospital admission and those who did not. These findings were consistent with the clinical expertise of the committee, and as antibiotics can affect the results of blood culture and cerebrospinal fluid (CSF) tests, the committee agreed that antibiotics should not normally be given outside of hospital. Based on the evidence and their clinical knowledge and experience the committee recommended that pre-hospital intravenous or intramuscular antibiotics should only be given where bacterial meningitis is strongly suspected and where a clinically significant delay in transfer to hospital is considered likely. The committee could not give a timeframe for what delay counts as clinically significant, because there was no evidence on this point.

While the committee recommended antibiotics outside of hospital in some circumstances, they highlighted that the priority should be transfer to hospital (so that urgent testing can be done to get a clear diagnosis and start the correct treatment as soon as possible) and recommended that transfer should not be delayed to give antibiotics.

The committee specified ceftriaxone or benzylpenicillin as the antibiotics to use when antibiotics need to be given outside of hospital. Ceftriaxone is the preferred option because it is a more active agent, however it is less commonly available outside of hospital. Benzylpenicillin is commonly available and practical to use in the community. However, given that these are the only antibiotics likely to be available in an emergency situation, the committee recommended that antibiotics should not be given outside of hospital if the person has a severe allergy to benzylpenicillin or ceftriaxone.

The committee discussed that the optimal route of administration for parenteral antibiotics is intravenous for the treatment of bacterial meningitis. However, the committee recognised that this is not always possible in the community as there may be insufficient equipment or training, or issues with intravenous access. Therefore, the option of intramuscular route was included in the recommendation.

Overall, evidence showed that early in-hospital antibiotic administration was associated with lower rates of mortality in adults compared to later antibiotic administration. There was also a benefit of early compared to later in-hospital antibiotic administration in terms of rate of functional impairment, but only when compared against delays greater than 6 hours. Based

on the evidence, and their clinical knowledge and experience, the committee agreed that intravenous antibiotics should be administered as soon as possible once bacterial meningitis is suspected and within 1 hour of arrival in hospital. The committee noted that given the potential for antibiotic treatment to affect the results of blood culture and CSF tests, blood samples should be taken, and lumbar puncture performed prior to starting antibiotic treatment. The committee recognised that lumbar puncture may not always be possible within a very short timeframe as it is a relatively complex technical procedure that needs to be carried out by trained and competent practitioners, however the committee recommended that wherever it is safe to do so lumbar puncture should be performed before starting antibiotics.

The committee discussed the advantages and disadvantages of specifying a time point for in-hospital intravenous antibiotic administration, particularly given that the evidence rarely reported data at the same time points. The committee recognised that suspected bacterial meningitis is a medical emergency, and agreed based on expert clinical consensus that on arrival in hospital a senior clinical decision maker should perform an initial assessment, which is in line with the NICE guideline on sepsis (NICE 2016). Given the potentially serious implications of a delay to treatment (including death), the committee recommended that antibiotics should be started within an hour of arrival at hospital. However, the committee acknowledged that confirming the diagnosis with CSF tests is important in order to guide the correct course of treatment. The committee discussed that 1 hour within arrival in hospital is widely regarded as the golden hour for people with life threatening conditions requiring emergency care. They agreed that 1 hour should be enough time to stabilise the patient and take blood samples (for blood culture) and perform lumbar puncture.

Cost effectiveness and resource use

This review question was not prioritised for economic analysis and therefore the committee made a qualitative assessment of the likely cost-effectiveness of their recommendations. They noted that the economic aspects of this review question did not relate to the cost of the antibiotics themselves as it concerned their timing rather than provision. Given the evidence on the benefits of early in-hospital administration, when compared to later in-hospital administration, they reasoned that early administration would improve health related quality of life and reduce “downstream” costs associated with adverse outcomes.

The committee believed that it would only be cost-effective to administer intravenous or intramuscular antibiotics in people with strongly suspected bacterial meningitis outside of hospital if transfer to hospital was likely to be significantly delayed, reasoning that delays in urgent transfer to hospital could lead to sub-optimal treatment.

The committee did not expect their recommendations to have a significant resource impact as they were in line with current NHS practice.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.2.3, 1.2.4, 1.2.6, 1.4.1, and 1.6.1 to 1.6.3. Other evidence supporting recommendation 1.2.3 can be found in the evidence review on timing of antibiotics for meningococcal disease (see evidence review C2).

References – included studies

Effectiveness

Auburtin 2006

Auburtin, M., Wolff, M., Charpentier, J., Varon, E., Le Tulzo, Y., Girault, C., Mohammedi, I., Renard, B., Mourvillier, B., Bruneel, F., Ricard, J. D., Timsit, J. F., Detrimental role of delayed antibiotic administration and penicillin-nonsusceptible strains in adult intensive care unit patients with pneumococcal meningitis: The PNEUMOREA prospective multicenter study, Critical care medicine, 34, 2758-2765, 2006

Bargui 2012

Bargui, F., D'Agostino, I., Mariani-Kurkdjian, P., Alberti, C., Doit, C., Bellier, N., Morin, L., Gibertini, G. G., Smail, A., Zanin, A., Lorrot, M., Dauger, S., Neve, M., Faye, A., Armoogum, P., Bourrillon, A., Bingen, E., Mercier, J. C., Bonacorsi, S., Nigrovic, L. E., Titomanlio, L., Factors influencing neurological outcome of children with bacterial meningitis at the emergency department, European journal of pediatrics, 171, 1365-1371, 2012

Bijlsma 2016

Bijlsma, M. W., Brouwer, M. C., Kasanmoentalib, E. S., Kloek, A. T., Lucas, M. J., Tanck, M. W., van der Ende, A., van de Beek, D., Community-acquired bacterial meningitis in adults in the Netherlands, 2006-14: a prospective cohort study, The Lancet Infectious Diseases, 16, 339-47, 2016

Bodilsen 2016

Bodilsen, J., Dalager-Pedersen, M., Schonheyder, H. C., Nielsen, H., Time to antibiotic therapy and outcome in bacterial meningitis: A Danish population-based cohort study, BMC Infectious Diseases, 16 (1) (no pagination), 2016

Bretonniere 2015

Bretonniere, C., Jozwiak, M., Girault, C., Beuret, P., Trouillet, J. L., Anguel, N., Caillon, J., Potel, G., Villers, D., Boutoille, D., Guitton, C., Rifampin use in acute community-acquired meningitis in intensive care units: The French retrospective cohort ACAM-ICU study, Critical Care, 19 (1) (no pagination), 2015

Glimaker 2015

Glimaker, M., Johansson, B., Grindborg, O., Bottai, M., Lindquist, L., Sjolin, J., Adult bacterial meningitis: earlier treatment and improved outcome following guideline revision promoting prompt lumbar puncture, Clinical Infectious Diseases, 60, 1162-9, 2015

Kaaresen 1995

Kaaresen, P.I., Flaegstad, T., Prognostic factors in childhood bacterial meningitis, Acta Paediatrica, 84, 873-878, 1995

Proulx 2005

Proulx, N., Frechette, D., Toye, B., Chan, J., Kravcik, S., Delays in the administration of antibiotics are associated with mortality from adult acute bacterial meningitis, QJM - Monthly Journal of the Association of Physicians, 98, 291-298, 2005

Economic

No studies were identified which were applicable to this review question.

Other

NICE 2016

National Institute for Health and Care Excellence (2016). Sepsis: recognition, diagnosis and early management [NICE guideline No. NG51]. Available at: https://www.nice.org.uk/guidance/ng51 [Accessed 21/07/2023]

Appendices

Appendix A Review protocols

Review protocol for review question: What is the optimal timing of antibiotic administration for people with suspected bacterial meningitis?

Table 3: Review protocol

Field	Content
PROSPERO registration number	CRD42020219903
Review title	Timing of antibiotics for bacterial meningitis
Review question	What is the optimal timing of antibiotic administration for people with suspected bacterial meningitis?
Objective	This review aims to find out what is the optimal timing for starting antibiotic administration in improving outcomes for people with suspected bacterial meningitis taking into consideration its effects on, for example, survival, neurological outcomes and treatment related adverse events.
Searches	The following databases will be searched: Cochrane Central Register of Controlled Trials (CENTRAL) Cochrane Database of Systematic Reviews (CDSR) Embase MEDLINE Searches will be restricted by: Date limitations: studies after 1980 English language Human studies The full search strategies for MEDLINE database will be published in the final review. For each

Field	Content
	search, the principal database search strategy is quality assured by a second information scientist using an adaptation of the PRESS 2015 Guideline Evidence-Based Checklist.
Condition or domain being studied	Suspected bacterial meningitis
Population	Inclusion: All adults, young people, children and babies (excluding neonates defined as aged 28 days old and younger) with suspected bacterial meningitis. Exclusion: People: • with known immunodeficiency. • who have brain tumours, pre-existing hydrocephalus, intracranial shunts, previous neurosurgical procedures, or known cranial or spinal anomalies that increase the risk of bacterial meningitis. • with confirmed viral meningitis or viral encephalitis. • with confirmed tuberculous meningitis. • with confirmed fungal meningitis
Intervention/Exposure/Test	Early administration of parenteral antibiotic therapy (single or in combination) Early administration defined as earlier administration than the comparator.
Comparator/Reference standard/Confounding factors	Late administration of parenteral antibiotic therapy (single or in combination) Late administration defined as later administration than the intervention.
Types of study to be included	Include published full-text papers: • Systematic reviews of RCTs • RCTs • If insufficient RCTs: prospective cohort studies • If insufficient prospective cohort studies: retrospective cohort studies Non-randomised studies will be downgraded for risk of bias if they do not adequately adjust for the following covariates, but will not be excluded for this reason:

Field	Content
	• Co-morbidity • Severity of infection at presentation (including sepsis) • Antibiotics administered pre or post lumbar puncture • Infective organism Exclude: • Conference abstracts
Other exclusion criteria	Countries other than OECD high income countries. Studies conducted prior to 1980 as currently used antibiotics were not in common usage prior to this date. Studies published not in English-language.
Context	This guidance will fully update the following: Meningitis (bacterial) and meningococcal septicaemia in under 16s: recognition, diagnosis and management (CG102).
Primary outcomes (critical outcomes)	Population: adults • All-cause mortality (measured up to 1 year after discharge) • Any long-term neurological impairment (defined as any motor deficits, sensory deficits [excluding hearing impairment], cognitive deficits, or behavioural deficits; measured from discharge up to 1 year after discharge) • Functional impairment (measured by any validated scale at any time point) Population: infants and children • All-cause mortality (measured up to 1 year after discharge) • Any long-term neurological impairment (defined as any motor deficits, sensory deficits [excluding hearing impairment], cognitive deficits*, or behavioural deficits*; measured from discharge up to 1 year after discharge) • Severe developmental delay (defined as score of >2 SD below normal on validated assessment scales, or MDI or PDI <70 on Bayleys assessment scale, or inability to assign a score due to cerebral palsy or severity of cognitive delay; measured at the oldest age reported unless there is substantially more data available at a younger age)

Field	Content
	*For infants and children below school-age, cognitive and behavioural deficits will be assessed at school-age.
Secondary outcomes (important outcomes)	Population: adults • Diagnosis of epilepsy or occurrence of seizures during hospitalisation • Hearing impairment (defined as any level of hearing impairment; measured from discharge up to 1 year after discharge) • Serious intervention-related adverse effects leading to death, disability or prolonged hospitalisation or that are life threatening or otherwise considered medically significant • Length of hospitalisation Population: infants and children • Diagnosis of epilepsy or occurrence of seizures during hospitalisation • Hearing impairment (defined as any level of hearing impairment; measured from discharge up to 1 year after discharge) • Functional impairment (measured by any validated scale at any time point) • Serious intervention-related adverse effects leading to death, disability or prolonged hospitalisation or that are life threatening or otherwise considered medically significant
Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into STAR and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Dual sifting will not be undertaken for this question. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion A standardised form will be used to extract data from studies. The following data will be extracted: study details (reference, country where study was carried out, type and dates), participant characteristics, inclusion and exclusion criteria, details of the interventions if relevant, setting and follow-up, relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.
Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklists:

Field	Content
	• ROBIS tool for systematic reviews • Cochrane RoB tool v.2 for RCTs and quasi-RCTs • Cochrane ROBINS-I tool for non-randomised (clinical) controlled trials and cohort studies The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.
Strategy for data synthesis	Quantitative findings will be formally summarised in the review. Where multiple studies report on the same outcome for the same comparison, meta-analyses will be conducted using Cochrane Review Manager software. A fixed effect meta-analysis will be conducted and data will be presented as risk ratios if possible or odds ratios when required (for example if only available in this form in included studies) for dichotomous outcomes, and mean differences or standardised mean differences for continuous outcomes. Heterogeneity in the effect estimates of the individual studies will be assessed by visual inspection of the forest plots and consideration of the I2 statistic. Heterogeneity will be explored as appropriate using sensitivity analyses and pre-specified subgroup analyses. If heterogeneity cannot be explained through subgroup analysis then a random effects model will be used for meta-analysis, or the data will not be pooled if the random effects model does not adequately address heterogeneity. The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/ **Minimally important differences:** • All-cause mortality: statistical significance • Serious intervention-related adverse effects: statistical significance • Length of hospitalisation: 1 day • Validated scales: Published MIDs where available; if not GRADE default MIDs • All other outcomes: GRADE default MIDs
Analysis of sub-groups	Evidence will be stratified by: Age: • Younger Infants: >28 days to ≤3 months of age

Field	Content
	• Older infants and children: >3 months to 18* years of age • Adults: ≥18* years of age *There is variation in clinical practice regarding the treatment of 16 to 18 year olds. Therefore, we will be guided by cut-offs used in the evidence when determining if 16 to 18 year olds should be treated as adults or children Setting: • Early and late both delivered pre-hospital • Early delivered pre-hospital and late delivered in hospital • Early and late both delivered in hospital Timing of early antibiotic administration: • <1 hour • 1-4 hours • 4 hours Stratifications will be dealt with in a hierarchy (that is, where possible stratify first by age, then within that by setting, and within that by timing) Evidence will be subgrouped by the following only in the event that there is significant heterogeneity in outcomes: • Young and middle aged adults • Older adults* *There is variation regarding the age at which adults should be considered older adults. Therefore, we will be guided by cut-offs used in the evidence when determining this threshold. Where evidence is stratified or subgrouped the committee will consider on a case by case basis if separate recommendations should be made for distinct groups. Separate recommendations may be

Field	Content			
	made where there is evidence of a differential effect of interventions in distinct groups. If there is a lack of evidence in one group, the committee will consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others.			
Type and method of review	☒	Intervention		
	☐	Diagnostic		
	☐	Prognostic		
	☐	Qualitative		
	☐	Epidemiologic		
	☐	Service Delivery		
	☐	Other (please specify)		
Language	English			
Country	England			
Anticipated or actual start date	28/10/2020			
Anticipated completion date	07/12/2023			
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		☑	☑

Field	Content
Named contact	Named contact: National Guideline Alliance Named contact e-mail: meningitis&meningococcal@nice.org.uk Organisational affiliation of the review: National Institute for Health and Care Excellence (NICE) and National Guideline Alliance
Review team members	National Guideline Alliance
Funding sources/sponsor	This systematic review is being completed by the National Guideline Alliance which receives funding from NICE.
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.
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: https://www.nice.org.uk/guidance/indevelopment/gid-ng10149.
Other registration details	None
Reference/URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020219903
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.

Field	Content	
Keywords	Bacterial meningitis, antibiotic, anti-bacterial, mortality, impairments	
Details of existing review of same topic by same authors	None	
Current review status	☐	Ongoing
	☒	Completed but not published
	☐	Completed and published
	☐	Completed, published and being updated
	☐	Discontinued
Additional information	None	
Details of final publication	www.nice.org.uk	

CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; GRADE: Grading of Recommendations Assessment, Development and Evaluation; MDI: mental development index; MID: minimally important difference; NGA: National Guideline Alliance;; NICE: National Institute for Health and Care Excellence; PDI: psychomotor development index; OECD: organisation for economic co-operation and development; RCT: randomised controlled trial; RoB: risk of bias; ROBIS: risk of bias in systematic reviews; ROBINS-I: risk of bias in non-randomised studies – of interventions; SD: standard deviation

Appendix B Literature search strategies

Literature search strategies for review question: What is the optimal timing of antibiotic administration for people with suspected bacterial meningitis?

Clinical Search

This was a combined search to cover both this review (evidence review C1) and also evidence review C2.

Database(s): Medline & Embase (Multifile) – OVID interface
Embase Classic+Embase 1947 to 2020 October 15, **Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily** 1946 to October 16, 2020
Date of last search: 19 October 2020
Multifile database codes: emczd = Embase Classic+Embase; ppez= MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily

#	Searches
1	Meningitis/ or Meningitis, Bacterial/ or Meningitis, Escherichia Coli/ or Meningitis, Haemophilus/ or Meningitis, Listeria/ or Meningitis, Meningococcal/ or Meningitis, Pneumococcal/ or Meningoencephalitis/
2	1 use ppez
3	meningitis/ or bacterial meningitis/ or haemophilus meningitis/ or listeria meningitis/ or pneumococcal meningitis/ or meningoencephalitis/
4	3 use emczd
5	((bacter* or infect*) adj3 (meningit* or meninges* or leptomeninges* or subarachnoid space?)).ti,ab.
6	(meningit* adj3 (e coli or escherichia coli or h?emophilus or hib or h?emophilus influenz* or h influenz* or listeria* or meningococc* or pneumococc* or gram-negativ* bacill* or gram negativ* bacill* or streptococc* or group B streptococc* or GBS or streptococcus pneumon* or s pneumon* or septic* or sepsis* or bacter?emi?)).ti,ab.
7	((e coli or escherichia coli or h?emophilus or hib or h?emophilus influenz* or h influenz* or listeria* or meningococc* or pneumococc* or gram-negativ* bacill* or gram negativ* bacill* or streptococc* or group B streptococc* or GBS or streptococcus pneumon* or s pneumon*) adj3 (septic* or sepsis* or bacter?emi?)).ti,ab.
8	mening?encephalitis*.ti,ab.
9	or/2,4-8
10	Meningococcal Infections/ or exp Neisseria meningitidis/
11	10 use ppez
12	Meningococcosis/ or Meningococcemia/ or Neisseria Meningitidis/
13	12 use emczd
14	(meningococc* adj3 (sepsis* or septic* or toxic* or endotoxic* or disease? or infection?)).ti,ab.
15	(meningococcus* or meningococci* or meningococc?emi?).ti,ab.
16	(Neisseria* mening* or n mening*).ti,ab.
17	or/11,13-16
18	exp Anti-Bacterial Agents/ or exp Penicillins/ or exp Cephalosporins/ or exp Cefotaxime/ or exp Amoxicillin/ or exp Ampicillin/
19	18 use ppez
20	exp antibiotic agent/ or exp penicillin derivative/ or exp cephalosporin derivative/
21	20 use emczd
22	(anti?biotic* or anti?bacterial* or anti?biotherap*).ti,ab.
23	(empiric* adj2 (therap* or treatment*)).ti,ab.
24	(abbocillin or adimicin or alcomicin or alpen or amblosin or amcill or amfipen or aminobenzylpenicillin or amox?cillin or amoxil* or ampicillin or ancef or anticepim or apogen or axepim* or ayercillin or benzo?penicillin* or benzyl?penicillin* or bicillin or binotal or biomox or bmy 28142 or bmy?28142 or bristagen or bristamox or cedax or cefatriaxon* or cefepim* or cefixim* or cefizox or cefobid* or cefotan or cefotaxim* or ceftin or ceftriaxon* or ceftriazon* or cefuroxim* or cefzil or cepazin* or cephotaxim* or cephuroxim* or cepim?x or chloramphenicol or claforan or clamoxyl or compocillin or cosmopen or cotrimoxazol* or co trimoxazol* or crysticillin or deripen or dexamethasone or diatracin or doktacillin or duricef or elobact or gelacillin or gentam?cin* or gent?mycin* or gentamyl* or gentamytrex or gentaplus or gentarad or gentaso* or gentasporin or gentatrim or gent?cin* or gent?cyn* or geocillin* or geomycin* or guicitrin* or hexam?cin* or hiconcil or histocillin or ibiamox or imacillin or jenamicin or kefurox or kefzol or klaforan or lendacin or longacef or longaceph or lyphocin or mandol or maxcef or maxipim* or mefoxin or megacillin or meropen* or miram?cin* or monocid or moxacin or oftagen* or omnipen or optigen* or penbritin* or penbrock or penicillin? or penicline or pentids or pentrex or pentrexl or pentrexyl or permapen or pfizerpen or polycillin or polymox or primafen or principen or refobacin* or ribom?cin* or rifampicin or rocefalin or rocefin or rocephin* or roscillin or sagestam* or spectrobid or sulm?cin* or supen or terram?cin* or totacillin or totapen or trimox or u?gencin* or ukapen or ultrabion or vamysin or vancam* or vanccostacin or vancin or vancom* or vancomycin or vankom* or velosef or vetramox* or viccillin or voncon* or wycillin or zimox or zinacef or zin?at).mp.
25	or/19,21-24
26	Time Factors/ or Time-to-Treatment/
27	26 use ppez
28	time factor/ or time to treatment/
29	28 use emczd

#	Searches
30	(initiat* or start* or introduc* or begin* or commenc* or inaugurat* or launch* or instigat* or establish* or set* up or timing or early or earlier or prompt* or quick* or speed* or rapid* or fast or delay* or late? or wait* or slow* or postpon* or put* off or defer* or push* back or belated*).ti.
31	((prompt* or rapid* or early or earlier or late or later or delay*) adj administ*).ti,ab.
32	or/27,29-31
33	(9 or 17) and 25 and 32
34	((initiat* or start* or introduc* or begin* or commenc* or inaugurat* or launch* or instigat* or establish* or set* up or timing or early or earlier or prompt* or quick* or speed* or rapid* or fast or delay* or late? or wait* or slow* or postpon* or put* off or defer* or push* back or belated* or preadmi* or pre-admi* or pre admi* or postadmi* or post-admi* or post admi* or prehospital* or pre-hospital* or pre hospital* or posthospital* or post-hospital* or post hospital* or before admi* or after admi* or before hospital* admi* or after hospital admi*) adj5 (anti?biotic* or anti?bacterial* or anti?biotherap* or anti?microbial* or abbocillin or adimicin or alcomicin or alpen or amblosin or amcill or amfipen or aminobenzylpenicillin or amox?cillin or amoxil* or ampicillin or ancef or anticepim or apogen or axepim* or ayercillin or benzo?penicillin* or benzyl?penicillin* or bicillin or binotal or biomox or bmy 28142 or bmy28142 or bristagen or bristamox or cedax or cefatriaxon* or cefepim* or cefixim* or cefizox or cefobid* or cefotan or cefotaxim* or ceftin or ceftriaxon* or ceftriazon* or cefuroxim* or cefzil or cepazin* or cephotaxim* or cephuroxim* or cepim?x or chloramphenicol or claforan or clamoxyl or compocillin or cosmopen or cotrimoxazol* or co trimoxazol* or crysticillin or deripen or dexamethasone or diatracin or doktacillin or duricef or elobact or gelacillin or gentam?cin* or gent?mycin* or gentamyl* or gentamytrex or gentaplus or gentarad or gentaso* or gentasporin or gentatrim or gent?cin* or gent?cyn* or geocillin* or geomycin* or guicitrin* or hexam?cin* or hiconcil or histocillin or ibiamox or imacillin or jenamicin or kefurox or kefzol or klaforan or lendacin or longacef or longaceph or lyphocin or mandol or maxcef or maxipim* or mefoxin or megacillin or meropen* or miram?cin* or monocid or moxacin or oftagen* or omnipen or optigen* or penbritin* or penbrock or penicillin? or penicline or pentids or pentrex or pentrexl or pentrexyl or permapen or pfizerpen or polycillin or polymox or primafen or principen or refobacin* or ribom?cin* or rifampicin or rocefalin or rocefin or rocephin* or roscillin or sagestam* or spectrobid or sulm?cin* or supen or terram?cin* or totacillin or totapen or trimox or u?gencin* or ukapen or ultrabion or vamysin or vancam* or vanccostacin or vancin or vancom* or vancomycin or vankom* or velosef or vetramox* or viccillin or voncon* or wycillin or zimox or zinacef or zin?at)).ti,ab.
35	(9 or 17) and 34
36	33 or 35
37	limit 36 to English language
38	limit 37 to yr="1980 -Current"
39	(controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or drug therapy.fs. or (groups or placebo or randomi#ed or randomly or trial).ab.
40	crossover procedure/ or double blind procedure/ or randomized controlled trial/ or single blind procedure/ or (assign* or allocat* or crossover* or cross over* or ((doubl* or singl*) adj blind*) or factorial* or placebo* or random* or volunteer*).ti,ab.
41	meta-analysis/
42	meta-analysis as topic/
43	systematic review/
44	meta-analysis/
45	(meta analy* or metanaly* or metaanaly*).ti,ab.
46	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
47	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
48	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
49	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
50	(search* adj4 literature).ab.
51	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
52	cochrane.jw.
53	((pool* or combined) adj2 (data or trials or studies or results)).ab.
54	letter/
55	editorial/
56	news/
57	exp historical article/
58	Anecdotes as Topic/
59	comment/
60	case report/
61	(letter or comment*).ti.
62	54 or 55 or 56 or 57 or 58 or 59 or 60 or 61
63	randomized controlled trial/ or random*.ti,ab.
64	62 not 63
65	animals/ not humans/
66	exp Animals, Laboratory/
67	exp Animal Experimentation/
68	exp Models, Animal/
69	exp Rodentia/
70	(rat or rats or mouse or mice).ti.
71	64 or 65 or 66 or 67 or 68 or 69 or 70
72	letter.pt. or letter/
73	note.pt.
74	editorial.pt.
75	case report/ or case study/

#	Searches
76	(letter or comment*).ti.
77	72 or 73 or 74 or 75 or 76
78	randomized controlled trial/ or random*.ti,ab.
79	77 not 78
80	animal/ not human/
81	nonhuman/
82	exp Animal Experiment/
83	exp Experimental Animal/
84	animal model/
85	exp Rodent/
86	(rat or rats or mouse or mice).ti.
87	79 or 80 or 81 or 82 or 83 or 84 or 85 or 86
88	71 use ppez
89	87 use emczd
90	88 or 89
91	39 use ppez
92	40 use emczd
93	91 or 92
94	(or/41-42,45,47-52) use ppez
95	(or/43-46,48-53) use emczd
96	94 or 95
97	38 not 90
98	97 and (93 or 96)

Database(s): Cochrane Library – Wiley interface
Cochrane Database of Systematic Reviews, Issue 10 of 12, October 2020, **Cochrane Central Register of Controlled Trials**, Issue 10 of 12, October 2020
Date of last search: 19 October 2020

#	Searches
#1	MeSH descriptor: [Meningitis] this term only
#2	MeSH descriptor: [Meningitis, Bacterial] this term only
#3	MeSH descriptor: [Meningitis, Escherichia coli] this term only
#4	MeSH descriptor: [Meningitis, Haemophilus] this term only
#5	MeSH descriptor: [Meningitis, Listeria] this term only
#6	MeSH descriptor: [Meningitis, Meningococcal] this term only
#7	MeSH descriptor: [Meningitis, Pneumococcal] this term only
#8	MeSH descriptor: [Meningoencephalitis] this term only
#9	((((bacter* or infect*) NEAR/3 (meningit* or meninges* or leptomeninges* or "subarachnoid space*")))):ti,ab,kw
#10	(((meningit* NEAR/3 (“e coli” or “escherichia coli” or haemophilus or hemophilus or hib or “haemophilus influenz*” or “hemophilus influenz*” or “h influenz*” or listeria* or meningococc* or pneumococc* or “gram-negativ* bacill*” or “gram negativ* bacill*” or streptococc* or “group B streptococc*” or GBS or “streptococcus pneumon*” or “s pneumon*” or septic* or sepsis* or bacteraemia* or bacteremia*))):ti,ab,kw
#11	((((“e coli” or “escherichia coli” or haemophilus or hemophilus or hib or “haemophilus influenz*” or “hemophilus influenz*” or “h influenz*” or listeria* or meningococc* or pneumococc* or “gram-negativ* bacill*” or “gram negativ* bacill*” or streptococc* or “group B streptococc*” or GBS or “streptococcus pneumon*” or “s pneumon*”) NEAR/3 (septic* or sepsis* or bacteraemia* or bacteremia*))):ti,ab,kw
#12	(((meningencephalitis* or meningoencephalitis*))):ti,ab,kw
#13	MeSH descriptor: [Meningococcal Infections] this term only
#14	MeSH descriptor: [Neisseria meningitidis] explode all trees
#15	(((meningococc* NEAR/3 (sepsis* or septic* or toxic* or endotoxic* or disease or diseases or infection or infections)))):ti,ab,kw
#16	(((meningococcus* or meningococci* or meningococcaemia* or meningococcemia*))):ti,ab,kw
#17	(Neisseria* NEXT mening*):ti,ab,kw
#18	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17
#19	MeSH descriptor: [Anti-Bacterial Agents] explode all trees
#20	MeSH descriptor: [Penicillins] explode all trees
#21	MeSH descriptor: [Cephalosporins] explode all trees
#22	MeSH descriptor: [Cefotaxime] explode all trees
#23	MeSH descriptor: [Amoxicillin] explode all trees
#24	MeSH descriptor: [Ampicillin] explode all trees
#25	((antibiotic* or antibacterial* or antibiotherap* or anti-biotic* or anti-bacterial* or anti-biotherap* or "anti biotic*" or "anti bacterial*" or "anti biotherap*")):ti,ab,kw
#26	((empiric* NEAR/2 (therap* or treatment*))):ti,ab,kw
#27	((abbbocillin or adimicin or alcomicin or alpen or amblosin or amcill or amfipen or aminobenzylpenicillin or amox?cillin or amoxil* or ampicillin or ancef or anticepim or apogen or axepim* or ayercillin or benzo?penicillin* or benzyl?penicillin* or bicillin or binotal or biomox or “bmy 28142” or bmy-28142 or bmy28142 or bristagen or bristamox or cedax or cefatriaxon* or cefepim* or cefixim* or cefizox or cefobid* or cefotan or cefotaxim* or ceftin or ceftriaxon* or ceftriazon* or cefuroxim* or cefzil or cepazin* or cephotaxim* or cephuroxim* or cepim?x or chloramphenicol or claforan or clamoxyl or compocillin or cosmopen or cotrimoxazol* or “co trimoxazol*” or co-

#	Searches
	trimoxazol or crysticillin or deripen or dexamethasone or diatracin or doktacillin or duricef or elobact or gelacillin or gentam?cin* or gent?mycin* or gentamyl* or gentamytrex or gentaplus or gentarad or gentaso* or gentasporin or gentatrim or gent?cin* or gent?cyn* or geocillin* or geomycin* or guicitrin* or hexam?cin* or hiconcil or histocillin or ibiamox or imacillin or jenamicin or kefurox or kefzol or klaforan or lendacin or longacef or longaceph or lyphocin or mandol or maxcef or maxipim* or mefoxin or megacillin or meropen* or miram?cin* or monocid or moxacin or oftagen* or omnipen or optigen* or penbritin* or penbrock or penicillin? or penicline or pentids or pentrex or pentrexl or pentrexyl or permapen or pfizerpen or polycillin or polymox or primafen or principen or refobacin* or ribom?cin* or rifampicin or rocefalin or rocefin or rocephin* or roscillin or sagestam* or spectrobid or sulm?cin* or supen or terram?cin* or totacillin or totapen or trimox or u?gencin* or ukapen or ultrabion or vamysin or vancam* or vanccostacin or vancin or vancom* or vancomycin or vankom* or velosef or vetramox* or viccillin or voncon* or wycillin or zimox or zinacef or zin?at)):ti,ab,kw
#28	#19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27
#29	#18 AND #28

Database(s): Database of Abstracts of Reviews of Effects (DARE); HTA Database – CRD interface

Date of last search: 19 October 2020

#	Searches
1	MeSH DESCRIPTOR Meningitis IN DARE,HTA
2	MeSH DESCRIPTOR Meningitis, Bacterial IN DARE,HTA
3	MeSH DESCRIPTOR Meningitis, Escherichia coli IN DARE,HTA
4	MeSH DESCRIPTOR Meningitis, Haemophilus IN DARE,HTA
5	MeSH DESCRIPTOR Meningitis, Listeria IN DARE,HTA
6	MeSH DESCRIPTOR Meningitis, Meningococcal IN DARE,HTA
7	MeSH DESCRIPTOR Meningitis, Pneumococcal IN DARE,HTA
8	MeSH DESCRIPTOR Meningoencephalitis IN DARE,HTA
9	MeSH DESCRIPTOR Meningococcal infections IN DARE,HTA
10	(((((bacter* or infect*) NEAR3 (meningit* or meninges* or leptomeninges* or "subarachnoid space*"))))) IN DARE, HTA
11	(meningit*) IN DARE, HTA
12	((((meningencephalitis* or meningoencephalitis*)))) IN DARE, HTA
13	((((meningococc* NEAR3 (sepsis* or septic* or toxic* or endotoxic* or disease or diseases or infection or infections))))) IN DARE, HTA
14	((((meningococcus* or meningococci* or meningococcaemia* or meningococcemia*)))) IN DARE, HTA
15	((Neisseria* NEAR1 mening*)) IN DARE, HTA
16	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15
17	MeSH DESCRIPTOR Anti-Bacterial Agents EXPLODE ALL TREES IN DARE,HTA
18	MeSH DESCRIPTOR Penicillins EXPLODE ALL TREES IN DARE,HTA
19	MeSH DESCRIPTOR Cephalosporins EXPLODE ALL TREES IN DARE,HTA
20	MeSH DESCRIPTOR Cefotaxime EXPLODE ALL TREES IN DARE,HTA
21	MeSH DESCRIPTOR Amoxicillin EXPLODE ALL TREES IN DARE,HTA
22	MeSH DESCRIPTOR Ampicillin EXPLODE ALL TREES IN DARE,HTA
23	(((antibiotic* or antibacterial* or antibiotherap* or anti-biotic* or anti-bacterial* or anti-biotherap* or "anti biotic*" or "anti bacterial*" or "anti biotherap*"))) IN DARE, HTA
24	(((empiric* NEAR2 (therap* or treatment*)))) IN DARE, HTA
25	(((abbbocillin or adimicin or alcomicin or alpen or amblosin or amcill or amfipen or aminobenzylpenicillin or amox?cillin or amoxil* or ampicillin or ancef or anticepim or apogen or axepim* or ayercillin or benzo?penicillin* or benzyl?penicillin* or bicillin or binotal or biomox or bmy 28142 or bmy-28142 or bmy28142 or bristagen or bristamox or cedax or cefatriaxon* or cefepim* or cefixim* or cefizox or cefobid* or cefotan or cefotaxim* or ceftin or ceftriaxon* or ceftriazon* or cefuroxim* or cefzil or cepazin* or cephotaxim* or cephuroxim* or cepim?x or chloramphenicol or claforan or clamoxyl or compocillin or cosmopen or cotrimoxazol* or co trimoxazol* or co-trimoxazol or crysticillin or deripen or dexamethasone or diatracin or doktacillin or duricef or elobact or gelacillin or gentam?cin* or gent?mycin* or gentamyl* or gentamytrex or gentaplus or gentarad or gentaso* or gentasporin or gentatrim or gent?cin* or gent?cyn* or geocillin* or geomycin* or guicitrin* or hexam?cin* or hiconcil or histocillin or ibiamox or imacillin or jenamicin or kefurox or kefzol or klaforan or lendacin or longacef or longaceph or lyphocin or mandol or maxcef or maxipim* or mefoxin or megacillin or meropen* or miram?cin* or monocid or moxacin or oftagen* or omnipen or optigen* or penbritin* or penbrock or penicillin? or penicline or pentids or pentrex or pentrexl or pentrexyl or permapen or pfizerpen or polycillin or polymox or primafen or principen or refobacin* or ribom?cin* or rifampicin or rocefalin or rocefin or rocephin* or roscillin or sagestam* or spectrobid or sulm?cin* or supen or terram?cin* or totacillin or totapen or trimox or u?gencin* or ukapen or ultrabion or vamysin or vancam* or vanccostacin or vancin or vancom* or vancomycin or vankom* or velosef or vetramox* or viccillin or voncon* or wycillin or zimox or zinacef or zin?at))) IN DARE, HTA
26	#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25
27	#16 AND #26

Economic Search

One global search was conducted for economic evidence across the guideline.

Database(s): NHS Economic Evaluation Database (NHS EED), HTA Database – CRD interface

Date of last search: 11 March 2021

#	Searches
1	MeSH DESCRIPTOR meningitis IN NHSEED,HTA
2	MeSH DESCRIPTOR Meningitis, Bacterial IN NHSEED,HTA
3	MeSH DESCRIPTOR Meningitis, Escherichia coli IN NHSEED,HTA
4	MeSH DESCRIPTOR Meningitis, Haemophilus EXPLODE ALL TREES IN NHSEED,HTA
5	MeSH DESCRIPTOR Meningitis, Listeria IN NHSEED,HTA
6	MeSH DESCRIPTOR Meningitis, Meningococcal IN NHSEED,HTA
7	MeSH DESCRIPTOR Meningitis, Pneumococcal IN NHSEED,HTA
8	MeSH DESCRIPTOR Meningoencephalitis IN NHSEED,HTA
9	(((bacter* or infect*) NEAR3 (meningit* or meninges* or leptomeninges* or subarachnoid space*))) IN NHSEED, HTA
10	((meningit* NEAR3 (e coli or escherichia coli or h?emophilus or hib or h?emophilus influenz* or h influenz* or listeria* or meningococc* or pneumococc* or gram-negativ* bacill* or gram negativ* bacill* or streptococc* or group B streptococc* or GBS or streptococcus pneumon* or s pneumon* or septic* or sepsis* or bacter?emi?))) IN NHSEED, HTA
11	(((e coli or escherichia coli or h?emophilus or hib or h?emophilus influenz* or h influenz* or listeria* or meningococc* or pneumococc* or gram-negativ* bacill* or gram negativ* bacill* or streptococc* or group B streptococc* or GBS or streptococcus pneumon* or s pneumon*) NEAR3 (septic* or sepsis* or bacter?emi?))) IN NHSEED, HTA
12	((meningencephalitis* or meningoencephalitis* or meningit*)) IN NHSEED, HTA
13	MeSH DESCRIPTOR Meningococcal Infections IN NHSEED,HTA
14	MeSH DESCRIPTOR Neisseria meningitidis EXPLODE ALL TREES IN NHSEED,HTA
15	((meningococc* NEAR3 (sepsis* or septic* or toxic* or endotoxic* or disease* or infection*))) IN NHSEED, HTA
16	((meningococcus* or meningococci* or meningococcaemia* or meningococcemia*)) IN NHSEED, HTA
17	((Neisseria* NEXT mening*)) IN NHSEED, HTA
18	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17

Database(s): Medline & Embase (Multifile) – OVID interface

Embase Classic+Embase 1947 to 2021 March 10, **Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily** 1946 to March 09, 2021

Date of last search: 11 March 2021

Multifile database codes: emczd = Embase Classic+Embase; ppez= MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily

#	Searches
1	Meningitis/ or Meningitis, Bacterial/ or Meningitis, Escherichia Coli/ or Meningitis, Haemophilus/ or Meningitis, Listeria/ or Meningitis, Meningococcal/ or Meningitis, Pneumococcal/ or Meningoencephalitis/
2	1 use ppez
3	meningitis/ or bacterial meningitis/ or haemophilus meningitis/ or listeria meningitis/ or pneumococcal meningitis/ or meningoencephalitis/
4	3 use emczd
5	((bacter* or infect*) adj3 (meningit* or meninges* or leptomeninges* or subarachnoid space?)).ti,ab.
6	(meningit* adj3 (e coli or escherichia coli or h?emophilus or hib or h?emophilus influenz* or h influenz* or listeria* or meningococc* or pneumococc* or gram-negativ* bacill* or gram negativ* bacill* or streptococc* or group B streptococc* or GBS or streptococcus pneumon* or s pneumon* or septic* or sepsis* or bacter?emi?)).ti,ab.
7	((e coli or escherichia coli or h?emophilus or hib or h?emophilus influenz* or h influenz* or listeria* or meningococc* or pneumococc* or gram-negativ* bacill* or gram negativ* bacill* or streptococc* or group B streptococc* or GBS or streptococcus pneumon* or s pneumon*) adj3 (septic* or sepsis* or bacter?emi?)).ti,ab.
8	(mening?encephalitis* or meningit*).ti,ab.
9	or/2,4-8
10	Meningococcal Infections/ or exp Neisseria meningitidis/
11	10 use ppez
12	Meningococcosis/ or Meningococcemia/ or Neisseria Meningitidis/
13	12 use emczd
14	(meningococc* adj3 (sepsis* or septic* or toxic* or endotoxic* or disease? or infection?)).ti,ab.
15	(meningococcus* or meningococci* or meningococc?emi?).ti,ab.
16	(Neisseria* mening* or n mening*).ti,ab.
17	or/11,13-16
18	Economics/ use ppez
19	Value of life/ use ppez
20	exp "Costs and Cost Analysis"/ use ppez
21	exp Economics, Hospital/ use ppez
22	exp Economics, Medical/ use ppez
23	Economics, Nursing/ use ppez
24	Economics, Pharmaceutical/ use ppez
25	exp "Fees and Charges"/ use ppez
26	exp Budgets/ use ppez
27	health economics/ use emczd

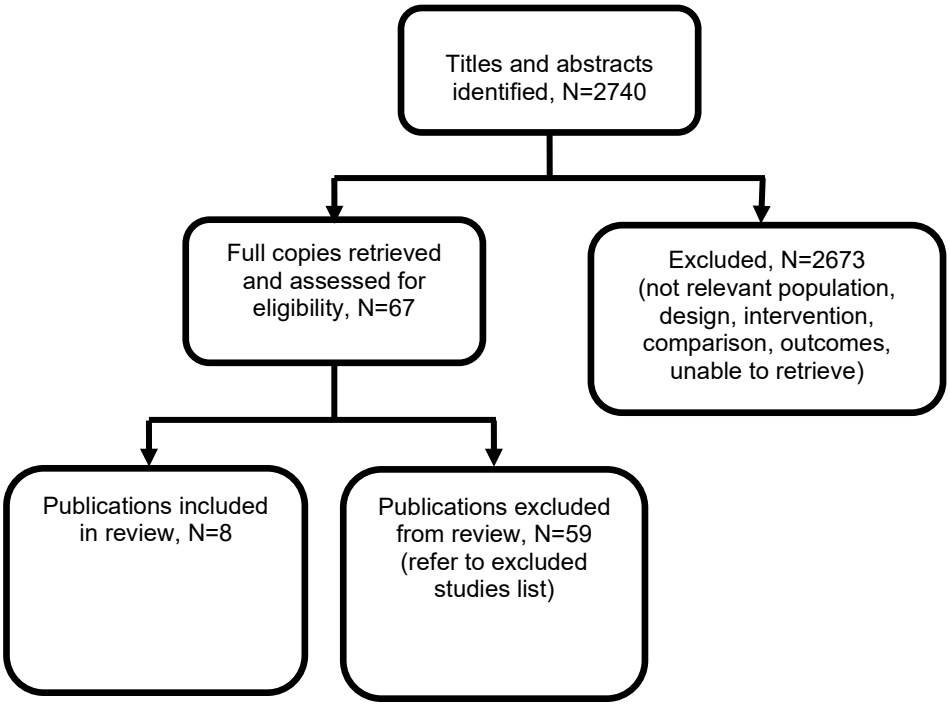
#	Searches
28	exp economic evaluation/ use emczd
29	exp health care cost/ use emczd
30	exp fee/ use emczd
31	budget/ use emczd
32	funding/ use emczd
33	budget*.ti,ab.
34	cost*.ti.
35	(economic* or pharmaco?economic*).ti.
36	(price* or pricing*).ti,ab.
37	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
38	(financ* or fee or fees).ti,ab.
39	(value adj2 (money or monetary)).ti,ab.
40	or/18-39
41	Quality-Adjusted Life Years/ use ppez
42	Sickness Impact Profile/
43	quality adjusted life year/ use emczd
44	"quality of life index"/ use emczd
45	(quality adjusted or quality adjusted life year*).tw.
46	(qaly* or qal or qald* or qale* or qtime* or qwb* or daly).tw.
47	(illness state* or health state*).tw.
48	(hui or hui2 or hui3).tw.
49	(multiattibute* or multi attribute*).tw.
50	(utilit* adj3 (score*1 or valu* or health* or cost* or measur* or disease* or mean or gain or gains or index*)).tw.
51	utilities.tw.
52	(eq-5d* or eq5d* or eq-5* or eq5* or euroqual* or euro qual* or euroqual 5d* or euro qual 5d* or euro qol* or euroqol*or euro quol* or euroquol* or euro quol5d* or euroquol5d* or eur qol* or eurqol* or eur qol5d* or eurqol5d* or eur?qul* or eur?qul5d* or euro* quality of life or european qol).tw.
53	(euro* adj3 (5 d* or 5d* or 5 dimension* or 5dimension* or 5 domain* or 5domain*)).tw.
54	(sf36 or sf 36 or sf thirty six or sf thirtysix).tw.
55	(time trade off*1 or time tradeoff*1 or tto or timetradeoff*1).tw.
56	Quality of Life/ and ((quality of life or qol) adj (score*1 or measure*1)).tw.
57	Quality of Life/ and ec.fs.
58	Quality of Life/ and (health adj3 status).tw.
59	(quality of life or qol).tw. and Cost-Benefit Analysis/ use ppez
60	(quality of life or qol).tw. and cost benefit analysis/ use emczd
61	((qol or hrqol or quality of life).tw. or *quality of life/) and ((qol or hrqol* or quality of life) adj2 (increas* or decreas* or improv* or declin* or reduc* or high* or low* or effect or effects or worse or score or scores or change*1 or impact*1 or impacted or deteriorat*)).ab.
62	Cost-Benefit Analysis/ use ppez and cost-effectiveness ratio*.tw. and (cost-effectiveness ratio* and (perspective* or life expectanc*)).tw.
63	cost benefit analysis/ use emczd and cost-effectiveness ratio*.tw. and (cost-effectiveness ratio* and (perspective* or life expectanc*)).tw.
64	*quality of life/ and (quality of life or qol).ti.
65	quality of life/ and ((quality of life or qol) adj3 (improv* or chang*)).tw.
66	quality of life/ and health-related quality of life.tw.
67	Models, Economic/ use ppez
68	economic model/ use emczd
69	care-related quality of life.tw,kw.
70	((capability$ or capability-based$) adj (measure$ or index or instrument$)).tw,kw.
71	social care outcome$.tw,kw.
72	(social care and (utility or utilities)).tw,kw.
73	or/41-72
74	(9 or 17) and 40
75	(9 or 17) and 73
76	letter/
77	editorial/
78	news/
79	exp historical article/
80	Anecdotes as Topic/
81	comment/
82	case report/
83	(letter or comment*).ti.
84	76 or 77 or 78 or 79 or 80 or 81 or 82 or 83
85	randomized controlled trial/ or random*.ti,ab.
86	84 not 85
87	animals/ not humans/
88	exp Animals, Laboratory/
89	exp Animal Experimentation/
90	exp Models, Animal/
91	exp Rodentia/
92	(rat or rats or mouse or mice).ti.

#	Searches
93	86 or 87 or 88 or 89 or 90 or 91 or 92
94	letter.pt. or letter/
95	note.pt.
96	editorial.pt.
97	case report/ or case study/
98	(letter or comment*).ti.
99	94 or 95 or 96 or 97 or 98
100	randomized controlled trial/ or random*.ti,ab.
101	99 not 100
102	animal/ not human/
103	nonhuman/
104	exp Animal Experiment/
105	exp Experimental Animal/
106	animal model/
107	exp Rodent/
108	(rat or rats or mouse or mice).ti.
109	101 or 102 or 103 or 104 or 105 or 106 or 107 or 108
110	93 use ppez
111	109 use emczd
112	110 or 111
113	74 not 112
114	limit 113 to English language
115	75 not 112
116	limit 115 to English language
117	114 or 116

Appendix C Effectiveness evidence study selection

Study selection for: What is the optimal timing of antibiotic administration for people with suspected bacterial meningitis?

Figure 1: Study selection flow chart



Appendix D Evidence tables

Evidence tables for review question: What is the optimal timing of antibiotic administration for people with suspected bacterial meningitis?

Table 4: Evidence tables – effectiveness evidence

Study details	Results and risk of bias assessment using ROBINS-I
Full citation Auburtin, M., Wolff, M., Charpentier, J., Varon, E., Le Tulzo, Y., Girault, C., Mohammedi, I., Renard, B., Mourvillier, B., Bruneel, F., Ricard, J. D., Timsit, J. F., Detrimental role of delayed antibiotic administration and penicillin-nonsusceptible strains in adult intensive care unit patients with pneumococcal meningitis: The PNEUMOREA prospective multicenter study, Critical care medicine, 34, 2758-2765, 2006 **Ref Id** 1282753 **Country/ies where the study was carried out** France **Study type** Prospective cohort study **Study dates** October 2001 to April 2003 **Inclusion criteria** All consecutive patients older than 18 yrs Suspected meningitis, CSF pleocytosis (10 cells/L), and one or more of the following criteria: - a positive CSF or blood culture; - Gram-positive diplococci in the CSF; - and pneumococcal antigens in the CSF, detected by a latex agglutination method	**Results** All-cause mortality in adults (3 months) ≤3h = 14/82 (17.1%) >3h = 37/74 (50%) Adjusted OR* (95% CI) = 0.07 (0.02 to 0.25) [1]OR and 95% CI were reported on the effect of >3h antibiotic administration compared with ≤3h. This estimate has been recalculated to show the effectiveness of ≤3h antibiotic administration compared with >3h. **1. Bias due to confounding (Low/Moderate/Serious/Critical/No information)** Serious: multivariate analyses failed to adjust for antibiotics administered pre/post lumbar puncture and co-morbidity **2. Bias in selection of participants into the study (Low/Moderate/Serious/Critical/No information)** Low: there is no indication that selection was based on the intervention and/or outcome **3. Bias in classification of interventions (Low/Moderate/Serious/Critical/No information)** Moderate: Initial antibiotic therapy was defined, albeit retrospectively, raising concerns around whether this was influenced by the outcome **4. Bias due to deviations from intended interventions (Low/Moderate/Serious/Critical/No information)** Low: There was no evidence of deviation from intended intervention

Study details	Results and risk of bias assessment using ROBINS-I
Exclusion criteria Not reported **Patient characteristics** N=156 Mean age ± SD = 56 ± 17 yrs (range, 18–90 yrs) Sex: male: 92 (59%); female: 64 (41%) Mean GCS scores ± SD = 10 ± 3 Predisposing factors for pneumococcal infection or pneumococcal meningitis = 82 (53%) - an immunocompromised state = 41 (HIV infection, 9; asplenia, 5; malignancy or immunosuppressive therapy, 8; and diabetes mellitus, 19); - documented or suspected dural fistula = 43; - coexisting otitis or sinusitis = 61 (39%) **Interventions** Antibiotics ≤3 hours after hospital admission = 82 (52.6%) Antibiotics >3 hours after hospital admission = 74 (47.4%) Initial antibiotic treatment consisted of a third-generation cephalosporin for 53% of the episodes, a combination of third-generation cephalosporin and vancomycin for 29%, and amoxicillin for 18%. **Follow-up** During hospitalisation: survival and neurologic impairment were assessed at hospital discharge and at 3 months after ICU admission	**5. Bias due to missing data (Low/Moderate/Serious/Critical/No information)** Low: Data were available for all participants **6. Bias in measurement of outcomes (Low/Moderate/Serious/Critical/No information)** Low: The outcomes are objective outcomes, therefore, no apparent biases in the measurement **7. Bias in selection of the reported result (Low/Moderate/Serious/Critical/No information)** Low: The data time point reported was based on the results of a univariate analysis **Overall risk of bias (Low/Moderate/Serious/Critical/No information)** Serious **Source of funding** Not reported **Other information** 26% of the participants included in the study were immunocompromised
Full citation Bargui, F., D'Agostino, I., Mariani-Kurkdjian, P., Alberti, C., Doit, C., Bellier, N., Morin, L., Gibertini, G. G., Smail, A., Zanin, A., Lorrot, M., Dauger, S., Neve, M., Faye, A., Armoogum, P., Bourrillon, A., Bingen, E., Mercier, J. C., Bonacorsi, S., Nigrovic, L. E., Titomanlio, L., Factors influencing neurological outcome of children with bacterial meningitis at the emergency department, European journal of pediatrics, 171, 1365-1371, 2012	**Results** All-cause mortality during hospitalisation in children[1] Pre-admission antibiotics = 4/25 (16%) No pre-admission antibiotics = 15/64 (23.4%) [1]no adjusted data available Any long-term neurological impairment (Neurological deficit) in children[2]

Study details	Results and risk of bias assessment using ROBINS-I
Ref Id 1283039 **Country/ies where the study was carried out** France **Study type** Retrospective cohort study **Study dates** January 1995 to December 2004 **Inclusion criteria** Not explicitly stated, however, the study indicates the following were used in identifying participants: 1.) Disease codes for bacterial meningitis, viral meningitis or unspecified meningitis. 2.) Cultures positive for bacterial pathogens *Bacterial meningitis case was defined as a patient who presented a positive CSF culture, CSF pleocytosis (defined by CSF WBC >10,000 cells/mm3) in association with a positive blood culture for a bacterial pathogen **Exclusion criteria** Missing contact information; refused consent **Patient characteristics** N=89 Median age at time of diagnosis (IQR) = 8 (4 to 18) months Sex: male 21 (24%); female: 68 (76%) Glasgow Coma Scale score <12 = 15 **Interventions** Pre-admission antibiotics: 25/89	Pre-admission antibiotics = 14/25 (56%) No pre-admission antibiotics = 14/64 (21.9%) [2]no adjusted data available **1. Bias due to confounding (Low/Moderate/Serious/Critical/No information)** Serious for adverse long-term neurologic outcome: multivariate analyses did not control for antibiotic administration pre/post lumbar puncture, co-morbidity and infective organisms; Critical for mortality: results were not adjusted at all. **2. Bias in selection of participants into the study (Low/Moderate/Serious/Critical/No information)** Low: all eligible participants were included and exclusion of participants was not related to the intervention/outcome **3. Bias in classification of interventions (Low/Moderate/Serious/Critical/No information)** Low: intervention was well defined **4. Bias due to deviations from intended interventions (Low/Moderate/Serious/Critical/No information)** Low: There was no evidence of deviation from intended intervention **5. Bias due to missing data (Low/Moderate/Serious/Critical/No information)** Low: Although 11% of participants were excluded, the authors report that baseline clinical characteristics of the excluded patients did not differ from included patients **6. Bias in measurement of outcomes (Low/Moderate/Serious/Critical/No information)** Low: Data were pre-recorded and used retrospectively **7. Bias in selection of the reported result (Low/Moderate/Serious/Critical/No information)** Moderate: There is no indication of selection of the reported analysis from

Study details	Results and risk of bias assessment using ROBINS-I
No-pre admission antibiotics: 64/89 Antibiotics ≤24 hours after start of symptoms Antibiotics >24 hours after start of symptoms No information about the antibiotics used. **Follow-up** Median period of 10.2 years (IQR, 7.6–12.3 years) from the time of bacterial meningitis diagnosis.	among multiple analyses; **Overall risk of bias (Low/Moderate/Serious/Critical/No information)** Serious for adverse neurologic outcome; Critical for mortality **Source of funding** Not stated
Full citation Bijlsma, M. W., Brouwer, M. C., Kasanmoentalib, E. S., Kloek, A. T., Lucas, M. J., Tanck, M. W., van der Ende, A., van de Beek, D., Community-acquired bacterial meningitis in adults in the Netherlands, 2006-14: a prospective cohort study, The Lancet Infectious DiseasesLancet Infect Dis, 16, 339-47, 2016 **Ref Id** 560091 **Country/ies where the study was carried out** Netherlands **Study type** Retrospective cohort study **Study dates** Jan 1 2006 to July 1 2014 **Inclusion criteria** Adults (older than age 16 years) listed in the database of the Netherlands Reference Laboratory for Bacterial Meningitis. *Bacterial meningitis defined as a bacterial pathogen cultured in CSF, or the	**Results** Functional impairment (Unfavourable outcome: GOS 1 - 4) in adults Pre-admission antibiotics: 55/152 (36.2%) No pre-admission antibiotics: 464/1225 (37.9%) Adjusted OR (95% CI)[1] = 1. 10 (0.72 to 1.68) [1]OR and 95% CI were reported on the effect of no pre-hospital antibiotics compared with pre-hospital antibiotics. These estimates have been recalculated to show the effectiveness of pre-hospital compared with no pre-hospital antibiotic administration **1. Bias due to confounding (Low/Moderate/Serious/Critical/No information)** Critical: The data were not adjusted for important covariates such as co-morbidity; severity of infection at presentation (including sepsis); antibiotics administered pre or post lumbar puncture; infective organisms. **2. Bias in selection of participants into the study (Low/Moderate/Serious/Critical/No information)** Low: All eligible participants were included and followed up in the trial **3. Bias in classification of interventions (Low/Moderate/Serious/Critical/No information)** Serious: intervention was well defined

Study details	Results and risk of bias assessment using ROBINS-I
combination of a positive PCR or antigen test in CSF for Streptococcus pneumoniae or Neisseria meningitidis with at least one specific CSF finding predictive of bacterial meningitis (that is, glucose concentration <340 mg/L, CSF glucose:blood glucose ratio <0·23, protein concentration >2200 mg/L, white cell count >2000 cells/microlitre, or >1180 poly morphonuclear leucocytes/microlitre **Exclusion criteria** Hospital acquired meningitis; head trauma or neurosurgery in the previous month; or those with a neurosurgical device or missing outcome. **Patient characteristics** N=1391 (n=1377 evaluable cases) Median age (interquartile range): 61 (47 to 69) years Sex: male 707 (50%); female 705 (50%) History of meningitis: 93/1396 (7%) Median score on Glasgow Coma Scale (interquartile range): 11 (9–14) Mortality: 244/1391 (17.5%) (Data was not reported separately for each group) Infective organism: Streptococcus pneumoniae 1017/1412 (72%) Neisseria meningitidis 150/1412 (11%) Listeria monocytogenes 74/1412 (5%) Haemophilus influenzae 47/1412 (3%) Streptococcus pyogenes 24/1412 (2%) Streptococcus agalactiae 21/1412 (1%) Other streptococcal species 35/1412 (2%) Staphylococcus aureus 21/1412 (1%) Other 23/1412 (2%) **Interventions** Pre-admission antibiotics = 152 No pre-admission antibiotics = 1225 Initial antibiotic treatment included: amoxicillin and a third-generation cephalosporin (36%), a third-generation cephalosporin alone (29%),	**4. Bias due to deviations from intended interventions (Low/Moderate/Serious/Critical/No information)** Low: There was no evidence of deviation from intended intervention **5. Bias due to missing data (Low/Moderate/Serious/Critical/No information)** Serious: Around 15% of participant data were missing and not accounted for in the analysis **6. Bias in measurement of outcomes (Low/Moderate/Serious/Critical/No information)** Low: The data were pre-recorded and used retrospectively **7. Bias in selection of the reported result (Low/Moderate/Serious/Critical/No information)** Moderate: There is no indication that the reported analysis was selected from among multiple analyses **Overall risk of bias (Low/Moderate/Serious/Critical/No information)** Serious **Source of funding** Not industry funded **Other information** 1% of participants were HIV positive and 8% were on immunosuppressive drugs.

Study details	Results and risk of bias assessment using ROBINS-I
penicillin or amoxicillin (20%), and other regimens (15%) **Follow-up** During hospitalisation	
Full citation Bodilsen, J., Dalager-Pedersen, M., Schonheyder, H. C., Nielsen, H., Time to antibiotic therapy and outcome in bacterial meningitis: A Danish population-based cohort study, BMC Infectious Diseases, 16 (1) (no pagination), 2016 **Ref Id** 1284098 **Country/ies where the study was carried out** Denmark **Study type** Retrospective cohort study **Study dates** 1 January 1998 to 31 December 2014 **Inclusion criteria** Patients aged over 16 years with a clinical presentation strongly suggestive of CABM, and at least one of the following: 1. Positive CSF culture 2. Positive blood culture and >10 leukocytes × 10^6/L in CSF 3. Presence of bacteria in Gram stain of CSF 4. Non-culture detection of bacteria in CSF by either bacterial antigen test or 16S rRNA gene amplification. **Exclusion criteria** Cerebral abscess, hospital-acquired bacterial meningitis, implanted neurosurgical device, or where exact time of antibiotic treatment or clinical	**Results** All-cause mortality in adults Antibiotics 0-2 h after hospital admission = 12/83 (14%) Antibiotics 2-4 h after hospital admission = 6/37 (16%) Antibiotics 4-6 h after hospital admission = 2/10 (20%) Antibiotics >6h after hospital admission = 13/43 (30%) *[1]Adjusted RR (95% CI) for in-hospital mortality Antibiotics 2-4 h after hospital admission versus 0-2h = RR 0.83 (0.37 to 2) Antibiotics 4-6 h after hospital admission versus 0-2h = RR 0.71 (0.28 to 2) Antibiotics >6h after hospital admission versus 0-2h = RR 0.63 (0.31 to 1.25) *[1]Adjusted for age >65 years, Glasgow Coma Score <13 and arterial systolic hypotension (<90 mmHg) at admission Functional impairment (Unfavourable outcome at discharge: GOS1-4) in adults Antibiotics 0-2 h after hospital admission = 29/83 (35%) Antibiotics 2-4 h after hospital admission = 18/37 (49%) Antibiotics 4-6 h after hospital admission = 4/10 (40%) Antibiotics >6h after hospital admission = 26/43 (60%) [2]Adjusted RR (95% CI) for functional impairment at discharge Antibiotics 2-4 h after hospital admission versus 0-2h = RR 0.67 (0.45 to 1.11) Antibiotics 4-6 h after hospital admission versus 0-2h = RR 0.91 (0.45 to 1.67) Antibiotics >6h after hospital admission versus 0-2h = RR 0.67 (0.45 to 1) [2]Adjusted for age >65 years, Glasgow Coma Score <13, arterial systolic hypotension (<90 mmHg), bacterial aetiology (S. pneumoniae yes/no) and adjunctive dexamethasone treatment (yes/no). **1. Bias due to confounding (Low/Moderate/Serious/Critical/No information)**

Study details	Results and risk of bias assessment using ROBINS-I
records could not be retrieved **Patient characteristics** N=173 included in analyses Median age (IQR) = 58 (45 to 70) years Sex: male 84 (49%); female 89 (51%) Glasgow Coma Score: 12 to 15 = 82 (47%); 9 to 12 = 61 (35%); <9 = 30 (17%) Aetiology: Streptococcus pneumoniae = 96/173 (55%); Neisseria meningitidis = 36/173 (21%); Other = 41/173 (24%) **Interventions** N=195 participants (173 evaluable) Group 1: Antibiotics 0-2 h after hospital admission = 83 (48%) Group 2: Antibiotics 2-4 h after hospital admission = 37 (21%) Group 3: Antibiotics 4-6 h after hospital admission = 10 (6%) Group 4: Antibiotics >6h after hospital admission = 43 (25%) No further details reported. **Follow-up** Up to discharge	Serious for in-hospital mortality: multivariate analysis failed to adjust for co-morbidity, antibiotics administered pre/post lumbar puncture and infective organisms; Serious for functional impairment: multivariate analysis failed to adjust for comorbidity and antibiotics administered pre/post lumbar puncture **2. Bias in selection of participants into the study (Low/Moderate/Serious/Critical/No information)** Low: all eligible participants were included and exclusion of participants was not related to the intervention/outcome **3. Bias in classification of interventions (Low/Moderate/Serious/Critical/No information)** Low: intervention was well defined **4. Bias due to deviations from intended interventions (Low/Moderate/Serious/Critical/No information)** Low: The study used retrospective data and there was no evidence of deviation from intended intervention **5. Bias due to missing data (Low/Moderate/Serious/Critical/No information)** Low: data were available for 95% of participants meeting the inclusion criteria **6. Bias in measurement of outcomes (Low/Moderate/Serious/Critical/No information)** Low: Mortality was objectively assessed, therefore, no apparent biases in measurement **7. Bias in selection of the reported result (Low/Moderate/Serious/Critical/No information)** Low: There is clear evidence that all reported results correspond to all intended outcomes, analyses and sub-cohorts. All data time points are represented in the reported results **Overall risk of bias (Low/Moderate/Serious/Critical/No information)**

Study details	Results and risk of bias assessment using ROBINS-I
	Serious **Source of funding** No funding was received
Full citation Bretonniere, C., Jozwiak, M., Girault, C., Beuret, P., Trouillet, J. L., Anguel, N., Caillon, J., Potel, G., Villers, D., Boutoille, D., Guitton, C., Rifampin use in acute community-acquired meningitis in intensive care units: The French retrospective cohort ACAM-ICU study, Critical Care, 19 (1) (no pagination), 2015 **Ref Id** 1283908 **Country/ies where the study was carried out** France **Study type** Retrospective cohort study **Study dates** Not reported (participants admitted 1 January 2004 to 31 December 2008) **Inclusion criteria** - Admission to one of the five participating ICUs from 1 January 2004 to 31 December 2008 for community-acquired bacterial meningitis -CSF samples had to show white cell count >5/mm^3, unless there was contraindication to lumbar puncture, in which case clinical/biological diagnosis was accepted. **Exclusion criteria** Nosocomial meningitis, tuberculosis, viral or parasitic aetiology, cerebral abscess, or secondary endocarditis	**Results** All-cause mortality in adults Antibiotics 0-2h after hospital admission = 5/62 (8%) Antibiotics ≥2h after hospital admission = 13/64 (20%) Adjusted OR (95% CI) for antibiotics 0-2h after hospital admission compared with ≥2h = 0.30 (0.0 to 1.6) **1. Bias due to confounding (Low/Moderate/Serious/Critical/No information)** Serious: multivariate analysis failed to adjust for antibiotics administered pre/post lumbar puncture and severity **2. Bias in selection of participants into the study (Low/Moderate/Serious/Critical/No information)** Low: all eligible participants were included and exclusion of participants was not related to the intervention/outcome **3. Bias in classification of interventions (Low/Moderate/Serious/Critical/No information)** Low: intervention was well defined **4. Bias due to deviations from intended interventions (Low/Moderate/Serious/Critical/No information)** Low: Study was carried out retrospectively and there was no evidence of deviation from intended intervention **5. Bias due to missing data (Low/Moderate/Serious/Critical/No information)** Critical: Around 15% of data were missing and not accounted for in the analysis

Study details	Results and risk of bias assessment using ROBINS-I
Patient characteristics N=157 Mean age ± SD = 45 ± 20 years Sex: male 97 (62%); female 60 (38%) Mean Glasgow Coma Scale (GCS) score ± SD = 11 ± 4 Mean SAPS II = 33±21 Previous episode of meningitis (n=8; 5 %), HIV infection (n=8; 5 %), and asplenia (n=6; 4 %). **Interventions** Group 1: Antibiotics 0-2h after hospital admission (0<2h) = 62/157 Group 2: Antibiotics ≥2 hours after hospital admission (2-4, 4-6 and 6-12h groups combined) = 64/157 Group 5: 31/157 (not accounted for in the study) An antibiotic combination was the initial prescription for 119 patients (76 %). A third-generation cephalosporin (89 %) was generally used with vancomycin (68 %) or rifampin (23 %). During the study period, vancomycin use decreased and rifampin use became more frequent **Follow-up** During hospitalisation	**6. Bias in measurement of outcomes (Low/Moderate/Serious/Critical/No information)** Low: The data were pre-recorded and used retrospectively **7. Bias in selection of the reported result (Low/Moderate/Serious/Critical/No information)** Moderate: There is no indication of selection of the reported analysis from among multiple analyses **Overall risk of bias (Low/Moderate/Serious/Critical/No information)** Critical **Source of funding** Not industry funded **Other information** Data for 31 participants were not accounted for in the study. Of these 31 participants 6 appear to have died, however, mortality data for these participants were not accounted for in the analysis Data were also reported specifically for rifampin and vancomycin but this was not of interest for current review
Full citation Glimaker, M., Johansson, B., Grindborg, O., Bottai, M., Lindquist, L., Sjolin, J., Adult bacterial meningitis: earlier treatment and improved outcome following guideline revision promoting prompt lumbar puncture, Clinical Infectious DiseasesClin Infect Dis, 60, 1162-9, 2015 **Ref Id** 1134726 **Country/ies where the study was carried out** Sweden	**Results** [1]Treatment delay was significantly associated with an increased risk for fatal outcome in adults, with a relative increase in all-cause mortality of 12.6% per hour treatment delay (95% CI, 3.1%–23.1%); p < .01. This was interpreted as RR 0.89 (0.81 to 0.97) [1]Per hour treatment delay and 95% CI were reported on the effect of delayed antibiotic administration. These estimates have been recalculated to show the effectiveness of early antibiotic administration **1. Bias due to confounding (Low/Moderate/Serious/Critical/No information)**

Study details	Results and risk of bias assessment using ROBINS-I
Study type Retrospective cohort **Study dates** 2005 to 2012 **Inclusion criteria** Adults with acute community acquired bacterial meningitis. Diagnoses were based on clinical criteria with or without cerebrospinal fluid (CSF) analyses **Exclusion criteria** Not reported **Patient characteristics** N=712 Sex: male 341 (48%) = 341/371 Median age (IQR) = 61 (17–95) Mental status on admission: RLS >2/GCS <12 = 215 (37.7); RLS ≤2/GCS ≥12 = 356 (62.3) Aetiology: Streptococcus pneumoniae = 361 (50.7%); Neisseria meningitides = 86 (12.1%); Haemophilus influenza = 47 (6.6%); Listeria monocytogenes = 28 (3.9%); Streptococcus spp. = 41 (5.8%); Other bacteria = 64 (9.0%); [1]Unknown = 85 (11.9%) [1]Culture-negative diagnoses. **Interventions** Initial antibiotic used involved Cefotaxime + Ampicillin (41%); Cefotaxime	Serious: multivariate analysis failed to adjust for antibiotics administered pre/post lumbar puncture and comorbidity **2. Bias in selection of participants into the study (Low/Moderate/Serious/Critical/No information)** Low: all eligible participants were included and exclusion of participants was not related to the intervention/outcome **3. Bias in classification of interventions (Low/Moderate/Serious/Critical/No information)** Low: intervention was well defined **4. Bias due to deviations from intended interventions (Low/Moderate/Serious/Critical/No information)** Low: No evidence of deviation from intended interventions **5. Bias due to missing data (Low/Moderate/Serious/Critical/No information)** No information **6. Bias in measurement of outcomes (Low/Moderate/Serious/Critical/No information)** Low: Data were already pre-recorded and collected retrospectively **7. Bias in selection of the reported result (Low/Moderate/Serious/Critical/No information)** Low: All data time points were taken into account. **Overall risk of bias (Low/Moderate/Serious/Critical/No information)** Serious **Source of funding** Not industry funded

Study details	Results and risk of bias assessment using ROBINS-I
(17%); Meropenem (30%); and other antibiotics (10%). **Follow-up** During hospitalisation and at 2-6 months after discharge	
Full citation Kaaresen, P.I., Flaegstad, T., Prognostic factors in childhood bacterial meningitis, Acta Paediatrica, 84, 873-878, 1995 **Ref Id** 141201 **Country/ies where the study was carried out** Norway **Study type** Retrospective cohort study **Study dates** 1980-1993 **Inclusion criteria** Children between 1 month and 15 years admitted to the paediatric department with bacterial meningitis. Bacterial meningitis was defined as the presence of >100 x 10^6/l cells in the CSF and bacterial growth in CSF and/or blood. Patients with negative cultures were included if they presented with a typical clinical picture of meningococcal meningitis. **Exclusion criteria** Patients with a prosthetic device (for example, ventriculoperitoneal shunt) and immunosuppressed patients were excluded **Patient characteristics** Median age (range): 1.9 years (1 month to 13.8 years)	**Results** All-cause mortality during hospital stay in children[1] Pre-admission parenteral antibiotics = 3/24 (12.5%) No pre-admission antibiotics = 1/46 (2.2%) Any long-term neurological impairment (motor deficits, hydrocephalus, cerebral palsy, ataxia, mental retardation, hearing impairment, seizure, or focal neurological findings; >1 year)[1] Pre-admission parenteral antibiotics = 3/24 (12.5%) No pre-admission antibiotics = 8/46 (17.4%) [1]No adjusted data available **1. Bias due to confounding (Low/Moderate/Serious/Critical/No information)** Critical: Not adjusted for any covariates. **2. Bias in selection of participants into the study (Low/Moderate/Serious/Critical/No information)** Low: All eligible participants were included and followed up in the trial **3. Bias in classification of interventions (Low/Moderate/Serious/Critical/No information)** Low: Interventions clearly defined. **4. Bias due to deviations from intended interventions (Low/Moderate/Serious/Critical/No information)** Low: No deviations from intended interventions **5. Bias due to missing data (Low/Moderate/Serious/Critical/No information)** Low: No missing data

Study details	Results and risk of bias assessment using ROBINS-I
Aetiology: Haemophilus influenzae (n=45); Neisseria meningitidis (n=38); Streptococcus pneumoniae (n=7) Other (n=2) **Interventions** N=92 Group 1: Pre-admission parenteral antibiotics (usually benzlypenicillin) = 24 (26.1%) Group 2: No pre-admission antibiotics = 46 (50%) Patients were initially treated with benzylpenicillin and chloramphenicol (79%), nine with ampicillin and chloramphenicol (10%), four with cefotaxime and dexamethasone (4%) and five with other combinations (5%). The treatment was usually changed to benzylpenicillin alone for meningococcal and pneumococcal meningitis, and ampicillin for Haemophilus meningitis, once aetiology was known, except in patients treated with cefotaxime and dexamethasone. **Follow-up** Before discharge and approximately 6 weeks after discharge. Further follow-up was given for those with suspected neurological sequelae; only sequelae still present at 1 year were reported.	**6. Bias in measurement of outcomes (Low/Moderate/Serious/Critical/No information)** Moderate: Objective outcome of death and subjective outcome (neurological impairment) clearly defined apriori. However, outcomes were drawn retrospectively from medical records and were reliant on accurate documentation. **7. Bias in selection of the reported result (Low/Moderate/Serious/Critical/No information)** Serious: Pre-admission parenteral antibiotic therapy not reported in the univariate table with other risk factors for sequelae or death to populate the multivariate analysis. The data on pre-admission parenteral antibiotic is reported in the text which is difficult for the reader to find. **Overall risk of bias (Low/Moderate/Serious/Critical/No information)** Critical **Source of funding** Not reported **Other information** Another group of participants (22/92) received pre-admission oral antibiotics, however, this group is not of interest for this review
Full citation Proulx, N., Frechette, D., Toye, B., Chan, J., Kravcik, S., Delays in the administration of antibiotics are associated with mortality from adult acute bacterial meningitis, QJM - Monthly Journal of the Association of Physicians, 98, 291-298, 2005 **Ref Id** 1282739	**Results** All-cause mortality before discharge in adults[1] Antibiotics ≤6h after hospital admission: 6/80 (7.5%) Antibiotics >6h after hospital admission (n=38): 10/38 (26.3%) Adjusted OR[2] (95% CI) RR 0.12 (0.02 to 0.59) [1]adjusted for afebrility at presentation, severely impaired mental status at presentation (defined as responsive to pain only or coma), age >60 years old,

Study details	Results and risk of bias assessment using ROBINS-I
Country/ies where the study was carried out Canada **Study type** Retrospective case record study **Study dates** January 1990 - March 2002 **Inclusion criteria** Aged ≥16 years with one of the following: (i) positive CSF culture; (ii) negative CSF culture with neutrophilic pleocytosis and at least one of: positive blood cultures, positive CSF gram stain, CSF high protein (40.60 g/l) and low glucose (52.7 mmol/l), positive CSF bacterial antigen test; (iii) a negative CSF culture without neutrophilic pleocytosis but with positive blood culture and at least one of: CSF high protein (40.60 g/l) and low glucose (52.7 mmol/l), positive CSF gram stain, positive bacterial antigen test; (iv) autopsy confirmation. **Exclusion criteria** Bacterial meningitis occurring in the presence of an intraventricular neurosurgical prosthesis; patients with proven viral, fungal or mycobacterial meningitis. **Patient characteristics** N= 119 adults (123 cases (118 evaluable cases) Mean age in years (range): 54 (19-86) Sex: male: 77 (63%); female: 46 (37%) Aetiology: Streptococcus pneumonia (56%); Staphylococcus aureus (9%); Neisseria meningitidis (7%); Haemophilus influenzae (7%);	staphylococcus aureus in multivariate analysis. [2]OR and 95% CI were reported on the effect of antibiotics >6h after hospital admission compared with ≤6h after hospital admission. These estimates have been recalculated to show the effectiveness of ≤6h compared with >6h **1. Bias due to confounding (Low/Moderate/Serious/Critical/No information)** Low: data was adjusted for afebrility at presentation, severely impaired mental status at presentation (defined as responsive to pain only or coma), age >60 years old, staphylococcus aureus in multivariate analysis. **2. Bias in selection of participants into the study (Low/Moderate/Serious/Critical/No information)** Low: All eligible participants were included and followed up in the trial **3. Bias in classification of interventions (Low/Moderate/Serious/Critical/No information)** Low: Interventions clearly defined **4. Bias due to deviations from intended interventions (Low/Moderate/Serious/Critical/No information)** Low: No deviations from intended interventions **5. Bias due to missing data (Low/Moderate/Serious/Critical/No information)** Low: The door-to-antibiotic time was available for 118/123 cases (96%). **6. Bias in measurement of outcomes (Low/Moderate/Serious/Critical/No information)** Low: objective outcome of mortality. **7. Bias in selection of the reported result (Low/Moderate/Serious/Critical/No information)** Low: Only statistically significant predictors in the multivariate analysis were reported.

Study details	Results and risk of bias assessment using ROBINS-I
Listeria monocytogenes (7%). Predisposing factor n (%): [1]Neurosurgery: 9 (7); Cerebrospinal fluid leak: 17 (14); Immunosuppressant drug: 16 (13); [1]Head injury: 3 (2); [1]These occurred within 1 month of meningitis onset. **Interventions** Group 1: Antibiotics ≤6h after hospital admission = 80 (67.8%) Group 2: Antibiotics >6h after hospital admission = 38 (32.2%) Common antibiotic regimens used were a third-generation cephalosporin plus penicillin or ampicillin (35%), one or more of a third generation cephalosporin plus vancomycin (21%), and a third-generation cephalosporin alone (16%). Antibiotic treatment was considered appropriate by type in 86% of cases and by dose in 83% of cases. **Follow-up** During hospitalisation	**Overall risk of bias (Low/Moderate/Serious/Critical/No information)** Low **Source of funding** Not reported **Other information** Door-to-antibiotic time >3.8 hours (study median) was also reported, however, only crude results were available. Therefore, it was not extracted as there was other adjusted data available for the effect of in-hospital antibiotic timing on mortality. Around 36% of the participants included in the study do not meet the inclusion criteria of the review leading to indirectness of population. Predisposing factors which occurred earlier than 1 month of meningitis onset were disregarded.

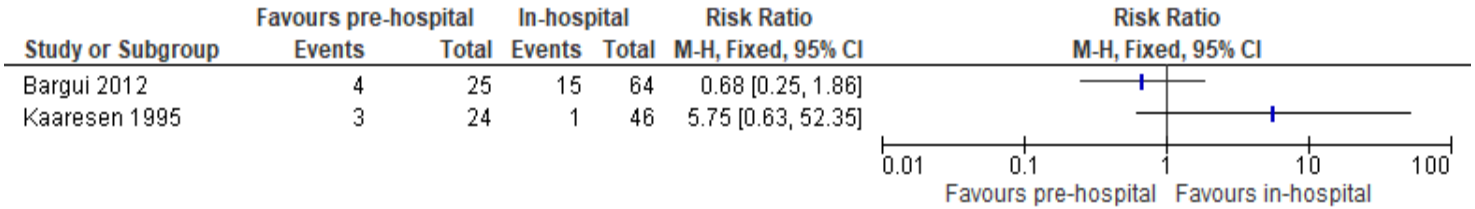
ABM: Acquired bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; E. Coli: Escherichia coli; GOS: Glasgow Outcome Scale; GP: general practitioner; HR: hazard ratio; IM: intramuscular; IQR: interquartile range; IV: intravenous; MIC: minimal inhibitory concentration; N: number of participants/people; RR: risk ratio; OR: odds ratio; RR: ROBINS-I: Risk Of Bias In Non-randomised Studies - of Interventions

Appendix E Forest plots

Forest plots for review question: What is the optimal timing of antibiotic administration for people with suspected bacterial meningitis?

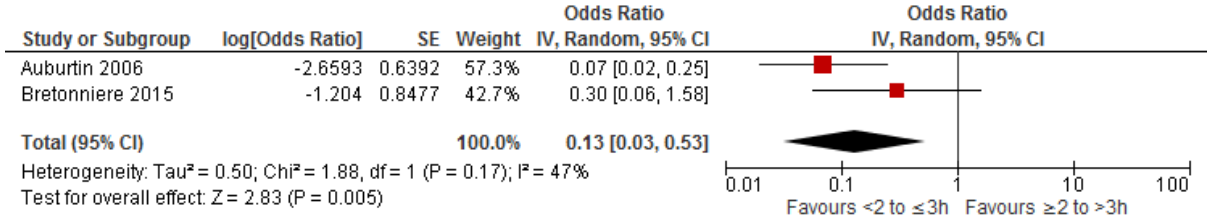
This section includes forest plots only for outcomes that are meta-analysed. Outcomes from single studies are not presented here; the quality assessment for such outcomes is provided in the GRADE profiles in appendix F.

Figure 2: Pre-hospital versus no pre-hospital antibiotics: All-cause mortality in children (unadjusted analysis)



CI: confidence interval; M-H: Mantel-Haenszel

Figure 3: <2 to ≤3h versus ≥2 to >3h in-hospital antibiotics: All-cause mortality in adults (adjusted analysis)



CI: confidence interval; IV: inverse variance; SE: standard error
CI boundaries do not match the reporting in Bretonniere 2015 (95% CI; 0.0 to 1.6) due to adjustments made in Review Manager

Appendix F GRADE tables

GRADE tables for review question: What is the optimal timing of antibiotic administration for people with suspected bacterial meningitis?

Table 5: Clinical evidence profile for comparison early versus late parenteral antibiotic administration

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Early	Late	Relative (95% CI)	Absolute		
Pre-hospital versus no pre-hospital antibiotics: All-cause mortality (unadjusted) - Children												
2*	observational studies	very serious [3]	very serious[4]	serious[5]	very serious[6]	none	7/49 (14.3%)	16/110 (14.5%)	Not pooled[2]: Bargui 2012: RR 0.68 (0.25 to 1.86) Kaaresen 1995: RR 5.75 (0.63 to 52.35)	Not pooled[2]: Bargui 2012: 74 fewer per 1000 (from 173 fewer to 157 more) Kaaresen 1995: 103 more per 1000 (from 8 fewer to 1000 more)	VERY LOW	CRITICAL
Pre-hospital versus no pre-hospital antibiotics: Any long-term neurological impairment (motor deficits, hydrocephalus, cerebral palsy, ataxia, mental retardation, hearing impairment, seizure, or focal neurological findings; >1 year) (unadjusted) – Children												
1 (Kaaresen 1995)	observational studies	very serious [3]	no serious inconsistency	serious[5]	very serious[6]	none	3/24 (12.5%)	8/46 (17.4%)	RR 0.72 (0.21 to 2.46)	49 fewer per 1000 (from 137 fewer to 254 more)	VERY LOW	CRITICAL
Prehospital vs. no pre-hospital antibiotics: Functional impairment (GOS ≤4) (adjusted) - Adults												
1 (Bijlsma 2016)	observational studies	serious [1]	no serious inconsistency	serious[5]	no serious imprecision	none	55/152 (36.2%)	464/1225 (37.9%)	OR 1.10 (0.72 to 1.68)	23 more per 1000 (from 74 fewer to 127 more)	LOW	IMPORTANT
<2 to ≤3h versus ≥2 to >3h in-hospital antibiotics: All-cause mortality (adjusted) - Adults												
2*	observational studies	very serious [3]	serious[7]	no serious indirectness	serious[2]	none	19/144 (13.2%)	50/138 (36.2%)	OR 0.13 (0.03 to 0.53)	294 fewer per 1000 (from 131 to 346 fewer)	VERY LOW	CRITICAL
0 to 2h versus 2 to 4h in-hospital antibiotics: All-cause mortality (adjusted) - Adults												
1 (Bodilsen 2016)	observational studies	serious [1]	no serious inconsistency	no serious indirectness	very serious[6]	none	12/83 (14.4%)	6/37 (16.2%)	RR 0.83 (0.37 to 2)	28 fewer per 1000 (from 102 fewer to 162	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Early	Late	Relative (95% CI)	Absolute		
										more)		
0 to 2h versus 2 to 4h in-hospital antibiotics: Functional impairment (GOS≤4) (adjusted) - Adults												
1 (Bodilsen 2016)	observational studies	serious [1]	no serious inconsistency	no serious indirectness	very serious[6]	none	29/83 (34.9%)	18/37 (48.6%)	RR 0.67 (0.45 to 1.11)	160 fewer per 1000 (from 267 fewer to 53 more)	VERY LOW	IMPORTANT
0 to 2h versus 4 to 6h in-hospital antibiotics: All-cause mortality (adjusted) - Adults												
1 (Bodilsen 2016)	observational studies	serious [1]	no serious inconsistency	no serious indirectness	very serious[6]	none	12/83 (14.4%)	2/10 (20%)	RR 0.71 (0.28 to 2)	58 fewer per 1000 (from 114 fewer to 200 more)	VERY LOW	CRITICAL
0 to 2h versus 4 to 6h in-hospital antibiotics: Functional impairment (GOS≤4) (adjusted) - Adults												
1 (Bodilsen 2016)	observational studies	serious [1]	no serious inconsistency	no serious indirectness	very serious[6]	none	29/83 (34.9%)	4/10 (40%)	RR 0.91 (0.45 to 1.67)	36 fewer per 1000 (from 220 fewer to 268 more)	VERY LOW	IMPORTANT
0 to 2h versus >6h in-hospital antibiotics: All-cause mortality (adjusted) - Adults												
1 (Bodilsen 2016)	observational studies	serious [1]	no serious inconsistency	no serious indirectness	very serious[6]	none	12/83 (14.4%)	13/43 (30.2%)	RR 0.63 (0.31 to 1.25)	112 fewer per 1000 (from 208 fewer to 76 more)	VERY LOW	CRITICAL
0 to 2h versus >6h in-hospital antibiotics: Functional impairment (GOS≤4) (adjusted) - Adults												
1 (Bodilsen 2016)	observational studies	serious [1]	no serious inconsistency	no serious indirectness	serious[2]	none	29/83 (34.9%)	26/43 (60.5%)	RR 0.67 (0.45 to 1)	200 fewer per 1000 from 333 fewer to 0 more)	LOW	IMPORTANT
≤6h versus >6h in-hospital antibiotics: All-cause mortality (adjusted) - Adults												
1 (Proulx 2005)	observational studies	no serious risk of bias	no serious inconsistency	serious[8]	serious[2]	none	6/80 (7.5%)	10/38 (26.3%)	OR 0.12 (0.02 to 0.59)	222 fewer per 1000 (from 256 to 89 fewer)	LOW	CRITICAL
All-cause mortality per hour increase in treatment delay (adjusted) – Adults												
1 (Glimaker 2015)	observational studies	serious [1]	no serious inconsistency	no serious indirectness	**serious[2]	none	0h = 7.5%; 1 h = 8%;	10h = 15%; 14h = 20%	RR 0.89 (0.81 to 0.97)	NC***	LOW	CRITICAL

CI: confidence interval; HR: hazard ratio; RR: risk ratio; OR: odds ratio; NC: not calculable; NR: not reported
**See corresponding forest plot*
***Imprecision was judged based on number of events estimated from the overall mortality rates reported*
****Absolute effect not calculated from reported event rates as these correspond to discrete time points and the relative effect corresponds to per hour of treatment delay*
[1] Serious risk of bias in the evidence contributing to the outcomes as per ROBINS-I
[2]<150 events
[3] Very serious risk of bias in the evidence contributing to the outcomes as per ROBINS-I

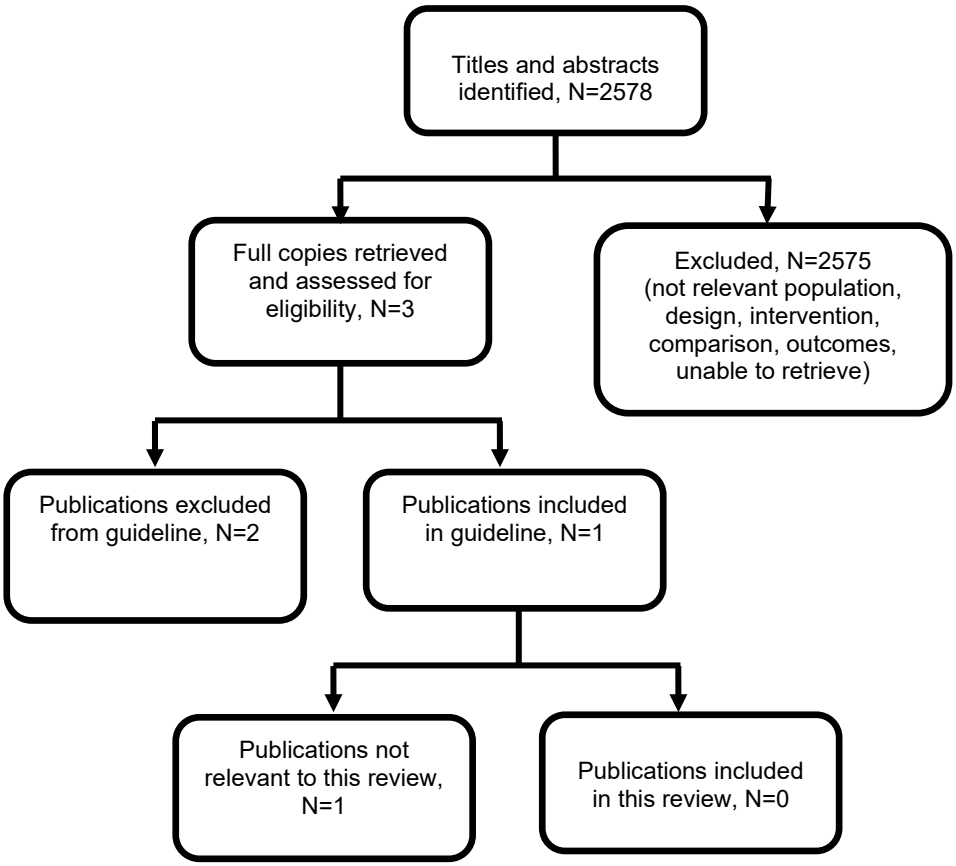
[4] *Very serious heterogeneity unexplained by subgroup analysis*
[5] *Intervention is indirect due to uncertainty around the route of administration (oral and IM)*
[6] *95% CI crosses 1 MID and <150 events*
[7] *Serious heterogeneity unexplained by subgroup analysis*
[8] *Population is indirect due to over 25% of the participants being immunocompromised*

Appendix G Economic evidence study selection

Study selection for: What is the optimal timing of antibiotic administration for people with suspected bacterial meningitis?

A global economic search was undertaken for the whole guideline, but no economic evidence was identified which was applicable to this review question (see Figure 2).

Figure 4: Study selection flow chart



Appendix H Economic evidence tables

Economic evidence tables for review question: What is the optimal timing of antibiotic administration for people with suspected bacterial meningitis?

No evidence was identified which was applicable to this review question.

Appendix I Economic model

Economic model for review question: What is the optimal timing of antibiotic administration for people with suspected bacterial meningitis?

No economic analysis was conducted for this review question.

Appendix J Excluded studies

Excluded studies for review question: What is the optimal timing of antibiotic administration for people with suspected bacterial meningitis?

Although there was a combined search to cover both this review (evidence review C1) and evidence review C2, the excluded studies list only reflects those excluded from the current review (C1).

Excluded effectiveness studies

Table 6: Excluded studies and reasons for their exclusion

Study	Reason for Exclusion
Anonymous,, Bacterial meningitis: causes for concern. The Research Committee of the BSSI, Journal of infection, 30, 89-94, 1995	Intervention not of interest for review: no details on pre-admission antibiotic administered (unclear if oral or parenteral)
Anttila, M., Anttolainen, I., Ellmén, J., Eskola, J., Joki, T., Kaartinen, L., Kaski, U., Kataja, M., Kojo, N., Korppi, M., Antibiotic treatment of bacterial meningitis in children--results from a Finnish multicenter study, Duodecim; laaketieteellinen aikakauskirja, 107, 149â□□157, 1991	Article published in Finnish
Aronin, S. I., Peduzzi, P., Quagliarello, V. J., Community-acquired bacterial meningitis: risk stratification for adverse clinical outcome and effect of antibiotic timing, Annals of Internal Medicine, 129, 862-9, 1998	Comparison not of interest for review: adverse effect vs no adverse effect in bacterial meningitis and effect on antibiotic timing
Askim, A., Mehl, A., Paulsen, J., DeWan, A. T., Vestrheim, D. F., Asvold, B. O., Damas, J. K., Solligard, E., Epidemiology and outcome of sepsis in adult patients with Streptococcus pneumoniae infection in a Norwegian county 1993-2011: An observational study, BMC Infectious Diseases, 16 (1) (no pagination), 2016	Population not of interest for review: Only 6.3% of study population diagnosed with meningitis
Barquet, N., Domingo, P., Cayla, J. A., Gonzalez, J., Rodrigo, C., Fernandez-Viladrich, P., Moraga-Llop, F. A., Marco, F., Vazquez, J., Saez-Nieto, J. A., Casal, J., Canela, J., Foz, M., Meningococcal disease in a large urban population (Barcelona, 1987-1992): predictors of dismal prognosis. Barcelona Meningococcal Disease Surveillance Group, Archives of internal medicine, 159, 2329-40, 1999	Population not of interest for review: the preadmission antibiotics were given solely for an upper respiratory tract infection (URTI) and without any suspicion of meningococcal disease
Barquet, N., Domingo, P., Cayla, J. A., Gonzalez, J., Rodrigo, C., Fernandez-Viladrich, P., Moraga-Llop, F. A., Marco, F., Vazquez, J., Saez-Nieto, J. A., Casal, J., Canela, J., Foz, M., Prognostic factors in meningococcal disease. Development of a bedside predictive model and scoring system. Barcelona Meningococcal Disease Surveillance Group, JAMA, 278, 491-6, 1997	Data included in Barquet 1999
Bonsu, B. K., Harper, M. B., Fever interval before diagnosis, prior antibiotic treatment, and clinical outcome for young children with bacterial	Intervention not of interest for review: combination of oral and parenteral antibiotics, no

Study	Reason for Exclusion
meningitis, Clinical infectious diseases, 32, 566-72, 2001	stratification for parenteral antibiotics
Bryan, C. S., Reynolds, K. L., Crout, L., Promptness of antibiotic therapy in acute bacterial meningitis, Annals of Emergency Medicine, 15, 544-547, 1986	Comparison not of interest for review: children vs adults antibiotic timing
Cabellos, C., Pelegrin, I., Benavent, E., Gudiol, F., Tubau, F., Garcia-Somoza, D., Verdaguer, R., Ariza, J., Viladrich, P. F., Impact of pre-hospital antibiotic therapy on mortality in invasive meningococcal disease: a propensity score study. European Journal of Clinical Microbiology and Infectious Diseases, 38, 1671-1676, 2019	Study included in evidence review in timing of antibiotic in suspected meningococcal disease
Cartwright, K., Reilly, S., White, D., Stuart, J., Early treatment with parenteral penicillin in meningococcal disease. British medical journal, 305, 143-147, 1992	Study included in evidence review in timing of antibiotic in suspected meningococcal disease
Cooke, M. E., Prehospital administration of benzyl penicillin by paramedics in the UK, Journal of Emergency Primary Health Care, 3 (1-2) (no pagination), 2005	Study design not of interest for review: audit
Costerus, J. M., Brouwer, M. C., Bijlsma, M. W., van de Beek, D., Community-acquired bacterial meningitis, Current Opinion in Infectious DiseasesCurr Opin Infect Dis, 30, 135-141, 2017	Study design not of interest for review: literature review
D. E. Gaudio M, Chiappini, E., Galli, L., D. E. Martino M, Therapeutic management of bacterial meningitis in children: a systematic review and comparison of published guidelines from a European perspective, Journal of ChemotherapyJ Chemother, 22, 226-37, 2010	Studies included in systematic review not of interest for review: guidelines (references checked for additional studies to search)
De Greeff, S. C., De Melker, H. E., Schouls, L. M., Spanjaard, L., Van Deuren, M., Pre-admission clinical course of meningococcal disease and opportunities for the earlier start of appropriate intervention: A prospective epidemiological study on 752 patients in the Netherlands, 2003-2005. European Journal of Clinical Microbiology and Infectious Diseases, 27, 985-992, 2008	Study included in evidence review in timing of antibiotic in suspected meningococcal disease
Fang, C. T., Chen, Y. C., Chang, S. C., Sau, W. Y., Luh, K. T., Klebsiella pneumoniae meningitis: Timing of antimicrobial therapy and prognosis, QJM - Monthly Journal of the Association of Physicians, 93, 45-53, 2000	Comparison not of interest: no data on antibiotic administration timing
Giner, A. M., Kuster, S. P., Zbinden, R., Ruef, C., Ledergerber, B., Weber, R., Initial management of and outcome in patients with pneumococcal bacteremia: A retrospective study at a Swiss university hospital, 2003-2009, Infection, 39, 519-526, 2011	Population not of interest for review: Only 9.8% of study population diagnosed with meningitis
Grindborg, O., Naucler, P., Sjolin, J., Glimaker, M., Adult bacterial meningitis-a quality registry study: Earlier treatment and favourable outcome	Comparison not of interest for review: ID physician vs non ID physician

Study	Reason for Exclusion
if initial management by infectious diseases physicians, Clinical microbiology and infection, 21, 560-566, 2015	
Gunnell, D. J., Pearson, N., Ley, B., Hill, A., Epidemiology of meningococcal disease and a community outbreak in Somerset. Communicable disease report 1994 CDR review, 4, R101-104, 1994	Study included in evidence review in timing of antibiotic in suspected meningococcal disease
Hahne, S. J. M., Charlett, A., Purcell, B., Samuelsson, S., Camaroni, I., Ehrhard, I., Heuberger, S., Santamaria, M., Stuart, J. M., Effectiveness of antibiotics given before admission in reducing mortality from meningococcal disease: Systematic review. British medical journal, 332, 1299-1301, 2006	Study included in evidence review in timing of antibiotic in suspected meningococcal disease
Halstensen, A., Pedersen, S. H., Haneberg, B., Bjorvatn, B., Solberg, C. O., Case fatality of meningococcal disease in western Norway, 19, 35-42, 1987	Study dates not of interest for review: study data collection in 1970's
Harnden,A., Ninis,N., Thompson,M., Perera,R., Levin,M., Mant,D., Mayon-White,R., Parenteral penicillin for children with meningococcal disease before hospital admission: Case-control study, British Medical Journal, 332, 1295-1297, 2006	Study design not of interest for review: case-control
Heckenberg, S. G. B., De Gans, J., Brouwer, M. C., Weisfelt, M., Piet, J. R., Spanjaard, L., Van Der Ende, A., Van De Beek, D., Clinical features, outcome, and meningococcal genotype in 258 adults with meningococcal meningitis: A prospective cohort study, Medicine, 87, 185-192, 2008	Intervention not of interest for review: no data on timing of antibiotic administration
Hounsom,L., Grayson,K., Melzer,M., Mortality and associated risk factors in consecutive patients admitted to a UK NHS trust with community acquired bacteraemia, Postgraduate Medical Journal, 87, 757-762, 2011	Population not of interest for review: community acquired bacteraemia with no stratification for bacterial meningitis
Hsu, C. L., Chang, C. H., Wong, K. N., Chen, K. Y., Yu, C. J., Yang, P. C., Management of severe community-acquired septic meningitis in adults: From emergency department to intensive care unit, Journal of the Formosan Medical Association, 108, 112-118, 2009	Comparison not of interest for review: mean hrs to antibiotic treatment between survivors and non-survivors
Irwin, A. D., Drew, R. J., Marshall, P., Nguyen, K., Hoyle, E., Macfarlane, K. A., Wong, H. F., Mekonnen, E., Hicks, M., Steele, T., Gerrard, C., Hardiman, F., McNamara, P. S., Diggle, P. J., Carrol, E. D., Etiology of childhood bacteremia and timely antibiotics administration in the emergency department, Pediatrics, 135, 635-42, 2015	Population not of interest for review: community acquired bacteraemia with no stratification for bacterial meningitis
Jefferies, C., Lennon, D., Stewart, J., Martin, D., Meningococcal disease in Auckland, July 1992 - June 1994. New Zealand Medical Journal, 112, 115-117, 1999	Study included in evidence review in timing of antibiotic in suspected meningococcal disease

Study	Reason for Exclusion
Johansen, Michael, In suspected cases of meningococcal disease, do preâ□□admission antibiotics improve outcomes?, Cochrane Clinical Answers, 2017	Study design not of interest for review: clinical editorial
Jolly, K., Stewart, G., Epidemiology and diagnosis of meningitis: results of a five-year prospective, population-based study. Communicable disease and public health / PHLS, 4, 124-129, 2001	Study included in evidence review in timing of antibiotic in suspected meningococcal disease
Koster-Rasmussen, R., Korshin, A., Meyer, C. N., Antibiotic treatment delay and outcome in acute bacterial meningitis, Journal of infection, 57, 449-454, 2008	No outcomes of interest for review (only combined mortality and functional impairment outcome)
Lala, H. M., Mills, G. D., Barratt, K., Bonning, J., Manikkam, N. E., Martin, D., Meningococcal disease deaths and the frequency of antibiotic administration delays, Journal of infection, 54, 551-7, 2007	Study design not of interest for review: case-control
Lepur, D., Barsic, B., Community-acquired bacterial meningitis in adults: Antibiotic timing in disease course and outcome, Infection, 35, 225-231, 2007	Country not of interest for review: not an OECD high income country (Croatia)
Lu, C. H., Huang, C. R., Chang, W. N., Chang, C. J., Cheng, B. C., Lee, P. Y., Lin, M. W., Chang, H. W., Community-acquired bacterial meningitis in adults: the epidemiology, timing of appropriate antimicrobial therapy, and prognostic factors, Clinical Neurology & NeurosurgeryClin Neurol Neurosurg, 104, 352-8, 2002	Comparison not of interest of review: appropriate antimicrobial therapy includes no details on timing
Martin D, Kieft C, Miller J. The epidemiology of meningococcal disease in New Zealand in 1998. A report to the Ministry of Health. [Unpublished Report 1999].	Study included in evidence review in timing of antibiotic in suspected meningococcal disease
Meadow, W. L., Lantos, J., Tanz, R. R., Mendez, D., Unger, R., Wallskog, P., Ought 'standard care' be the 'standard of care'? A study of the time to administration of antibiotics in children with meningitis, American Journal of Diseases of Children, 147, 40-4, 1993	No outcomes of interest for review
Miner,J.R., Heegaard,W., Mapes,A., Biros,M., Presentation, time to antibiotics, and mortality of patients with bacterial meningitis at an urban county medical center, Journal of Emergency Medicine, 21, 387-392, 2001	Comparison not of interest for review: ED antibiotics vs no ED antibiotics (administration as inpatients or in clinics)
Mittal, Y., Sankar, J., Dhochak, N., Gupta, S., Lodha, R., Kabra, S. K., Decreasing the Time to Administration of First Dose of Antibiotics in Children with Severe Sepsis, Journal for Healthcare Quality, 41, 32-38, 2019	Population not of interest for review: children with severe sepsis with no stratification for bacterial meningitis
Mundy, L., Merlin, T., Pre-hospital administration of antibiotics by paramedics for suspected cases of meningococcal disease, 2006	Study design not of interest for review: literature review (references checked for additional studies to search)
Naucler, P., Huttner, A., van Werkhoven, C. H., Singer, M., Tattevin, P., Einav, S., Tangden, T.,	Study design not of interest for review: literature review (references checked for additional

Study	Reason for Exclusion
Impact of time to antibiotic therapy on clinical outcome in patients with bacterial infections in the emergency department: implications for antimicrobial stewardship, Clinical microbiology and infection., 2020	studies to search)
Nemescu, R. E., Iancu, L. S., Dorneanu, O. S., Ursu, R. G., Dorobat, C. M., Influence of antibiotic therapy prior to admission on the efficacy of classical methods for the diagnosis of meningococcal disease, Revista medico-chirurgicala a Societatii de Medici si Naturalisti din Iasi, 118, 497-502, 2014	Outcomes not of interest for review: CSF and blood culture
Norgard, B., Sorensen, H. T., Jensen, E. S., Faber, T., Schonheyder, H. C., Nielsen, G. L., Pre-hospital parenteral antibiotic treatment of meningococcal disease and case fatality: a Danish population-based cohort study. Journal of infection, 45, 144-51, 2002	Study included in evidence review in timing of antibiotic in suspected meningococcal disease
Palmer,S.R., Corson,J., Hall,R., Payne,S., Ludlow,J., Deere,B., Jones,H., Kaul,S., Stubbins,J., Williams,R., Walapu,M., Spence,A., Jenkins,P., Donald,D., Meningococcal disease in Wales: Clinical features, outcome and public health management. Journal of Infection, 25, 321-328, 1992	Study included in evidence review in timing of antibiotic in suspected meningococcal disease
Perea-Milla,E., Olalla,J., Sanchez-Cantalejo,E., Martos,F., Matute-Cruz,P., Carmona-Lopez,G., Fornieles,Y., Cayuela,A., Garcia-Alegria,J., Pre-hospital antibiotic treatment and mortality caused by invasive meningococcal disease, adjusting for indication bias, BMC Public Health, 9 , 2009. Article Number, -, 2009	Intervention not of interest for review: oral antibiotics
Ramasamy, R., Willis, L., Kadambari, S., Kelly, D. F., Heath, P. T., Nadel, S., Pollard, A. J., Sadarangani, M., Management of suspected paediatric meningitis: a multicentre prospective cohort study, Archives of Disease in ChildhoodArch Dis Child, 103, 1114-1118, 2018	Comparison not of interest for review: no comparison of antibiotic timing
Riordan, F. A., Improving promptness of antibiotic treatment in meningococcal disease, Emergency medicine journal, 18, 162-3, 2001	Comparison not of interest for review: pre- vs post-teaching programme on meningococcal disease implementation
Riordan, F. A. I., Thomson, A. P. J., Sills, J. A., Hart, C. A., Prospective study of 'door to needle time' in meningococcal disease, Journal of Accident and Emergency Medicine, 15, 249-251, 1998	Comparison not of interest for review: no comparison on timing of antibiotics
Rothrock, S. G., Green, S. M., Wren, J., Letai, D., Daniel-Underwood, L., Pillar, E., Pediatric bacterial meningitis: is prior antibiotic therapy associated with an altered clinical presentation?, Annals of Emergency Medicine, 21, 146-52, 1992	Intervention not of interest for review: combination of oral and parenteral antibiotics, no stratification for parenteral antibiotics
Roznovsky, L., Krizova, P., Struncova, V., Dostal, V., Plisek, S., Kasal, E., Burget, I., Chalupa, P., Dlouhy, P., Administration of antibiotics before admission in patients with	No full text available (not included in Hahne 2006 SR on pre-hospital antibiotics in meningococcal disease)

Study	Reason for Exclusion
meningococcal disease, Central European Journal of Public Health, 11, 14-18, 2003	
Schuh, S., Lindner, G., Exadaktylos, A. K., Muhlemann, K., Tauber, M. G., Determinants of timely management of acute bacterial meningitis in the ED, American journal of emergency medicine, 31, 1056-1061, 2013	Comparison not of interest for review: no comparison of antibiotic timing
Sheley, J., Willman, D., Downen, J., Bergman, S., Investigation of the Selection and Timing of Pharmacological Therapy in Community-Acquired Bacterial Meningitis, P & TP T, 41, 437-41, 2016	Intervention not of interest: "appropriate antimicrobial therapy" defined as agent according to age and administration within 8 hours
Short, W. R., Tunkel, A. R., Timing of Administration of Antimicrobial Therapy in Bacterial Meningitis, Current Infectious Disease Reports, 3, 360-364, 2001	Study design not of interest: literature review (references checked for additional studies to search)
Sorensen,H.T., Nielsen,G.L., Schonheyder,H.C., Steffensen,F.H., Hansen,I., Sabroe,S., Dahlerup,J.F., Hamburger,H., Olsen,J., Outcome of pre-hospital antibiotic treatment of meningococcal disease. Journal of Clinical Epidemiology, 51, 717-721, 1998	Study included in evidence review in timing of antibiotic in suspected meningococcal disease
Strang, J. R., Pugh, E. J., Meningococcal infections: Reducing the case fatality rate by giving penicillin before admission to hospital. British medical journal, 305, 141-143, 1992	Study included in evidence review in timing of antibiotic in suspected meningococcal disease
Sudarsanam, T. D., Rupali, P., Tharyan, P., Abraham, O. C., Thomas, K., Preâ□□admission antibiotics for suspected cases of meningococcal disease, Cochrane Database of Systematic Reviews, 2017	No studies of interest for review: only 1 study included from Niger (country not of interest for review)
Talan, D. A., Guterman, J. J., Overturf, G. D., Singer, C., Hoffman, J. R., Lambert, B., Analysis of emergency department management of suspected bacterial meningitis, Annals of Emergency Medicine, 18, 856-862, 1989	Comparison not of interest for review: no comparison of timing of antibiotics
Talan,D.A., Zibulewsky,J., Relationship of clinical presentation to time to antibiotics for the emergency department management of suspected bacterial meningitis, Annals of Emergency Medicine, 22, 1733-1738, 1993	Comparison not of interest for review: no comparison of timing of antibiotics
Tippett, V., Bonham, R., Review of the evidence for prehospital administration of benzyl penicillin in meningococcal septicaemia - Experience in Queensland, Journal of Emergency Primary Health Care, 3 (1-2) (no pagination), 2005	Study design not of interest for review: literature review (references checked for additional studies to search)
Walker, T., Pre-hospital paramedic administration of Ceftriaxone for suspected meningococcal septicaemia in Victoria, Australia, Journal of Emergency Primary Health Care, 3 (1-2) (no pagination), 2005	Study design not of interest for review: literature review (references checked for additional studies to search)
Wood, A. L., O'Brien, S. J., How long is too long? Determining the early management of meningococcal disease in Birmingham. Public Health, 110, 237-9, 1996	Study included in evidence review in timing of antibiotic in suspected meningococcal disease

Study	Reason for Exclusion
Woodward,C.M., Jessop,E.G., Wale,M.C., Early management of meningococcal disease. Communicable Disease Report 1995 CDR Review, 5, R135-R137, 1995	Study included in evidence review in timing of antibiotic in suspected meningococcal disease
Zhao, Z., Hua, X., Yu, J., Zhang, H., Li, J., Li, Z., Duration of empirical therapy in neonatal bacterial meningitis with third generation cephalosporin: A multicenter retrospective study, Archives of Medical Science, 15, 1482-1489, 2019	Country not of interest for review: not an OECD high income country (China)

CSF: cerebrospinal fluid; ED: emergency department; ID: infectious disease; OECD: organisation for economic co-operation and development

Excluded economic studies

No studies were identified which were applicable to this review question.

Appendix K Research recommendations – full details

Research recommendations for review question: What is the optimal timing of antibiotic administration for people with suspected bacterial meningitis?

No research recommendation was made for this review.