National Institute for Health and Care Excellence

Draft for consultation

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

[C2] Evidence review for timing of antibiotics for meningococcal disease

NICE guideline number tbc

Evidence reviews underpinning recommendations 1.2.4, 1.2.5 and 1.5.1 in the NICE guideline

September 2023

Draft for consultation

This evidence review was developed by NICE

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ISBN:

Contents

Timing of antibiotics for meningococcal disease

Review question

What is the optimal timing of antibiotic administration for people with suspected meningococcal disease?

Introduction

Meningococcal disease (meningococcal sepsis with or without an associated meningitis) is a rare but serious infection, which can occur in any age group. Meningococcal disease is a life-threatening infection, which may progress with devastating speed.

Given that meningococcal disease is a medical emergency, it is critical to establish the most appropriate time to initiate antibiotic therapy. The aim of this review is to establish the optimal timing of antibiotic administration for people with suspected meningococcal disease.

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 meningococcal disease (excluding meningococcal meningitis alone, as this is included in the reviews on 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 • Skin, soft tissue or orthopaedic complications requiring surgical intervention (debridement, grafting or amputation) • 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

Twelve studies were included for this review: 1 prospective cohort study (De Greeff 2008), and 11 retrospective cohort studies (Cabellos 2019; Cartwright 1992; Gunnell 1994; Jeffries 1999; Jolly 2001; Norgard 2002; Palmer 1992; Sorensen 1998; Strang 1992; Wood 1996; Woodward 1998).

The included studies are summarised in Table 2.

All studies compared pre-hospital parenteral antibiotic administration to no pre-hospital parenteral antibiotic administration. All studies recruited babies, children and adults and analysed data for all ages combined.

Only 2 studies (Norgard 2002; Sorensen 1998) provided analyses adjusted for confounding factors.

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
Cabellos 2019 Retrospective cohort study Spain	N=446 Invasive meningococcal disease (all ages) Age in years (median, IQR): 19; 14-50 Population treated with pre-admission antibiotics: 14% Case-fatality: 7%	Pre-admission parenteral antibiotics (n=62) Parenteral antibiotics used: IV/IM penicillin/ ampicillin (87%); IV/IM cephalosporin (13%)	No pre-admission parenteral antibiotics (n=384) No further details reported	• Mortality	Analyses unadjusted for confounding factors (rate of meningitis, odynophagia, nuchal stiffness and nausea/ vomiting)
Cartwright 1992 Retrospective cohort study England	N=360 (n=340 referred by GP) Meningococcal disease (all ages) Population <15 years old: 55% Population treated with pre-admission antibiotics administered by GP: 27% Case-fatality: 8%	Pre-admission parenteral antibiotics (n=93) No further details reported	No pre-admission parenteral antibiotic (n=247) No further details reported	• Mortality	Analyses unadjusted for confounding factors (confounding factors unclear due to lack of comparison between baseline characteristics)

Study	Population	Intervention	Comparison	Outcomes	Comments
De Greeff 2008 Prospective cohort study Netherlands	N=752 (n=601 evaluable cases) Meningococcal disease (all ages) Age in years (median, no IQR provided): 5 Population treated with pre-admission antibiotics: 3% Case-fatality: 7%	Pre-admission parenteral antibiotics (n=18) No further details reported	No pre-admission parenteral antibiotics (n=583) No further details reported	• Mortality	Analyses unadjusted for confounding factors (confounding factors unclear due to lack of comparison between baseline characteristics)
Gunnell 1994 Retrospective cohort study England	N=57 (n=46 evaluable cases) Meningococcal disease (all ages) Population <15 years old: 60% Population treated with pre-admission antibiotics: 59% Case-fatality: 11%	Pre-admission parenteral antibiotics (n=27) Parenteral antibiotics used: benzylpenicillin	No pre-admission parenteral antibiotics (n=19) No further details reported	• Mortality	Analyses unadjusted for confounding factors (confounding factors unclear due to lack of comparison between baseline characteristics)
Jeffries 1999 Retrospective cohort study New Zealand	N=106 (n=96 evaluable cases; n=65 referred by GP) Meningococcal disease (all ages) Population <15 years old: 58% Population treated with pre-admission	Pre-admission parenteral antibiotics (n=24) No further details reported	No pre-admission parenteral antibiotics (n=41) No further details reported	• Mortality	Analyses unadjusted for confounding factors (confounding factors unclear due to lack of comparison between baseline characteristics)

Study	Population	Intervention	Comparison	Outcomes	Comments
	antibiotics administered by GP: 37% Case-fatality: 5%				
Jolly 2001 Retrospective cohort study England	N=258 Meningococcal disease (all ages) Population <15 years old: 60% Population treated with pre-admission antibiotics: 28% Case-fatality: 7%	Pre-admission parenteral antibiotics (n=72) Parenteral antibiotics used: penicillin	No pre-admission parenteral antibiotics (n=186) No further details reported	• Mortality	Analyses unadjusted for confounding factors (confounding factors unclear due to lack of comparison between baseline characteristics)
Norgard 2002 Retrospective cohort study Denmark	N=479 Meningococcal disease (all ages) Age in years (median, range): Pre-admission antibiotics: 9; 0-58 No pre-admission antibiotics: 7; 0-82 Population treated with pre-admission antibiotics administered by GP: 16% Case-fatality: 7%	Pre-admission parenteral antibiotics (n=77) No further details reported	No pre-admission parenteral antibiotics (n=402)	• Mortality	Analyses adjusted for confounders: age; sex; and calendar years.
Palmer 1992 Retrospective cohort study	N=119 (n=96 evaluable cases; n=75 referred by	Pre-admission parenteral antibiotics (n=11)	No pre-admission parenteral antibiotics	• Mortality	Analyses unadjusted for confounding

Study	Population	Intervention	Comparison	Outcomes	Comments
Wales	GP) Meningococcal disease (all ages) Population <15 years old: 81% Population treated with pre-admission antibiotics administered by GP: 15% Case-fatality: 9%	Parenteral antibiotics used: penicillin	(n=64) No further details reported		factors (confounding factors unclear due to lack of comparison between baseline characteristics)
Sorensen 1998 Retrospective cohort study Denmark	N=302 Meningococcal disease (all ages) Age in years (median, IQR): Pre-admission antibiotics: 8; 2-17 No pre-admission antibiotics: 7; 2-17 Population treated with pre-admission antibiotics: 15% Case-fatality: 8%	Pre-admission parenteral antibiotics (n=44) No further details reported	No pre-admission parenteral antibiotics (n=258) No further details reported	• Mortality	Analyses adjusted for confounders: age; sex, impaired consciousness, and severity of disease
Strang 1992 Retrospective cohort study England	N=41 Meningococcal disease (all ages) Population <5 years old: 52% Population treated with pre-admission	Pre-admission parenteral antibiotics (n=13) Parenteral antibiotics used: penicillin	No pre-admission parenteral antibiotics (n=28) No further details reported	• Mortality	Analyses unadjusted for confounding factors (confounding factors unclear due to lack of comparison between baseline characteristi

Study	Population	Intervention	Comparison	Outcomes	Comments
	antibiotics: 32% Case-fatality: 15%				cs)
Wood 1996 Retrospective cohort study England	N=40 Meningococcal disease (all ages) Population <5 years old: 55% Population treated with pre-admission antibiotics: 18% Case-fatality: 8%	Pre-admission parenteral antibiotics (n=17) Parenteral antibiotics used: penicillin	No pre-admission parenteral antibiotics (n=33) No further details reported	• Mortality	Analyses unadjusted for confounding factors (confounding factors unclear due to lack of comparison between baseline characteristics)
Woodward 1998 Retrospective cohort study England	N=68 (n=63 referred by GP) Meningococcal disease (all ages) n=31 defined as suspected severe by referring Doctor n=47 defined as severe with haemorrhagic rash on admission Majority of population aged 15-24 years old (based on visual inspection of figure) Population treated with pre-admission antibiotics:	Pre-admission parenteral antibiotics (n=13) No further details reported	No pre-admission parenteral antibiotics (n=55) No further details reported	• Mortality	Analyses unadjusted for confounding factors (confounding factors unclear due to lack of comparison between baseline characteristics)

Study	Population	Intervention	Comparison	Outcomes	Comments
	19% Case-fatality: 4%				

GP: general practitioner; IM: intra-muscular; IQR: interquartile range; IV: intra-venous

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.

Evidence was assessed as being very low quality, with most studies at very high risk of bias due to not adjusting analyses for confounding factors and very seriously imprecise findings (due to the low number of events). See the GRADE tables in appendix F for the certainty of the evidence for each individual outcome.

Overall, there was no significant difference in the unadjusted rate of mortality in the evidence reviewed between those receiving pre-hospital parenteral antibiotics and those not receiving pre-hospital antibiotic treatment.

Only 2 studies adjusted for confounding factors in their analyses and evidence showed an important harm (90% CI 1.44 to 4.82) in terms of adjusted mortality rates associated with receiving pre-hospital antibiotics relative to not receiving antibiotic treatment prior to hospital admission. However, both of these studies were from Denmark, and there was confounding by indication (which was probably not fully accounted for by adjustment) as pre-hospital antibiotics were only indicated in severe presentations of suspected meningococcal disease by Danish health authorities at the time of the studies.

There was not enough evidence to stratify results by age, setting and timing.

All studies reported on mortality, no other outcomes in the protocol were reported.

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

Meningococcal disease is associated with high rates of mortality and morbidity. Antibiotics are the mainstay of treatment for meningococcal disease, 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 meningococcal disease on the ability to carry out certain daily life functions.

In addition to functional impairment in children and babies, skin, soft tissue or orthopaedic complications requiring surgical intervention, hearing impairment and serious intervention-related adverse effects were selected as important outcomes as these are relatively common after meningococcal disease and may be related to 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 using GRADE methodology. Evidence for all-cause mortality was rated as very low quality due to risk of bias (arising from failure to adjust for confounding factors) and imprecision (due to the small number of events). In the 2 studies from Denmark that provided adjusted analyses (Norgard 2002, Sorensen 1998), there was confounding by indication (that was probably not fully accounted for by adjustments) as pre-hospital antibiotics were only recommended in severe presentations of suspected meningococcal disease by Danish health authorities at the time of the studies.

No evidence was found that reported on long-term neurological impairment, functional impairment, severe developmental delay, skin, soft tissue or orthopaedic complications requiring surgical intervention, hearing impairment, serious intervention-related adverse effects, or length of hospitalisation.

Benefits and harms

The committee considered the evidence comparing outcomes between people with meningococcal disease who received pre-hospital antibiotics and those who did not receive antibiotics prior to hospital admission, and noted that overall, there was no evidence for a difference in the unadjusted mortality rate. There was some evidence for an important harm in terms of adjusted mortality rates associated with receiving pre-hospital antibiotics relative to not receiving antibiotic treatment prior to hospital admission. However, the adjusted data came from Danish studies that were conducted at a time when Danish health authorities only recommended pre-hospital antibiotics in severe presentations of suspected meningococcal disease. For this reason, the committee were concerned that there may be confounding by indication that was not fully controlled for by the statistical adjustments to the data. The committee agreed that ideally antibiotics would be administered in hospital rather than in the community for suspected meningococcal disease, because antibiotics can affect the likelihood of obtaining a positive culture result. 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 meningococcal disease is strongly suspected. However, given the rapid progression and seriousness of meningococcal disease, the committee agreed that where meningococcal disease is strongly suspected pre-hospital antibiotics should be given at the earliest opportunity irrespective of transfer time (unlike for bacterial meningitis, see evidence review C1, where pre-hospital antibiotics for

strongly suspected bacterial meningitis are only recommended if transfer to hospital is likely to be significantly delayed). The committee specified ceftriaxone or benzylpenicillin as the antibiotics of choice outside of hospital because these would be available in emergency situations. The committee highlighted that the priority in treating meningococcal disease was to administer antibiotics as early as practicable, however, the priority should be immediate access to hospital care. Therefore, urgent transfer to hospital should not be delayed in order to give antibiotics.

The committee discussed that the optimal route of administration for parenteral antibiotics is intravenous for the treatment of meningococcal disease. 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.

There was no eligible evidence identified comparing early in-hospital antibiotic administration to later antibiotic administration for meningococcal disease. However, based on their clinical knowledge and experience and the potential consequences of delaying treatment of a condition as serious as meningococcal disease, the committee agreed that intravenous antibiotics should be delivered as soon as possible once meningococcal disease 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, blood samples should be taken before starting antibiotic treatment.

The committee discussed the advantages and disadvantages of specifying a time point for in-hospital intravenous antibiotic administration. The committee recognised that suspected meningococcal disease 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. 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).

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 seriousness and rapid progression of meningococcal disease, the committee believed that recommending antibiotic treatment as early as possible would be cost-effective, as it could improve health related quality of life and reduce “downstream” costs associated with adverse outcomes.

However, the committee considered that immediate access to hospital was more important than early antibiotic administration as delays could result in sub-optimal treatment and outcomes. Therefore, they reasoned that it would not be cost-effective to delay urgent transfer to hospital in order to administer parenteral antibiotics and made a recommendation to reflect this.

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 1.2.4, 1.2.5 and 1.5.1 in the NICE guideline. Other evidence supporting recommendations can be found in the evidence review on the optimal timing of antibiotic administration for people with suspected bacterial meningitis (see evidence review C1).

References – included studies

Effectiveness

Cabellos 2019

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

Cartwright 1992

Cartwright, K., Reilly, S., White, D., Stuart, J., Early treatment with parenteral penicillin in meningococcal disease. British medical journal, 305, 143-147, 1992

De Greef 2008

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

Gunnell 1994

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

Jeffries 1999

Jefferies, C., Lennon, D., Stewart, J., Martin, D., Meningococcal disease in Auckland, July 1992 - June 1994. New Zealand Medical Journal, 112, 115-117, 1999

Jolly 2001

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

Norgard 2002

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

Palmer 1992

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

Sorensen 1998

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

Strang 1992

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

Wood 1996

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

Woodward 1995

Woodward,C.M., Jessop,E.G., Wale,M.C., Early management of meningococcal disease. Communicable Disease Report 1995 CDR Review, 5, R135-R137, 1995

Economic

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

Appendices

Appendix A Review protocols

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

Table 3: Review protocol

Field	Content
PROSPERO registration number	CRD42020220281
Review title	Timing of antibiotics for meningococcal disease
Review question	What is the optimal timing of antibiotic administration for people with suspected meningococcal disease?
Objective	This review aims to find out what is the optimal timing for starting antibiotic administration in improving outcomes for people with suspected meningococcal disease 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

Field	Content
	The full search strategies for MEDLINE database will be published in the final review. For each 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 meningococcal disease
Population	Inclusion: All adults, young people, children and babies (excluding neonates defined as aged 28 days old and younger) with suspected meningococcal disease (excluding meningococcal meningitis alone, as this is included in the reviews on 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.
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: • Co-morbidity • Severity of infection at presentation (including sepsis) • Antibiotics administered pre or post lumbar puncture

Field	Content
	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) *For infants and children below school-age, cognitive and behavioural deficits will be assessed at school-age.
Secondary outcomes (important outcomes)	Population: adults • Skin, soft tissue or orthopaedic complications requiring surgical intervention (debridement,

Field	Content
	grafting or amputation) • 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 • Skin, soft tissue or orthopaedic complications requiring surgical intervention (debridement, grafting or amputation) • 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: • 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

Field	Content
	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 • 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

Field	Content	
	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 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

Field	Content		
	☐	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	☑	☑
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		

Field	Content	
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?RecordID=220281	
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.	
Keywords	Meningococcal disease, antibiotic, anti-bacterial, mortality, impairments	
Details of existing review of same topic by same authors	None	
Current review status	☐	Ongoing
	☒	Completed but not published

Field	Content	
	☐	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; NICE: National Institute for Health and Care Excellence; PDI: psychomotor development index; OECD: organisation for economic co-operation and development; PRESS: Peer Review of Electronic Search Strategies; RCT: randomised controlled trial; RoB: risk of bias; ROBINS-I: risk of bias in non-randomised studies – of interventions; ROBIS: Risk of Bias in Systematic Reviews; SD: standard deviation; TBC: to be confirmed

Appendix B Literature search strategies

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

Clinical Search

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

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.

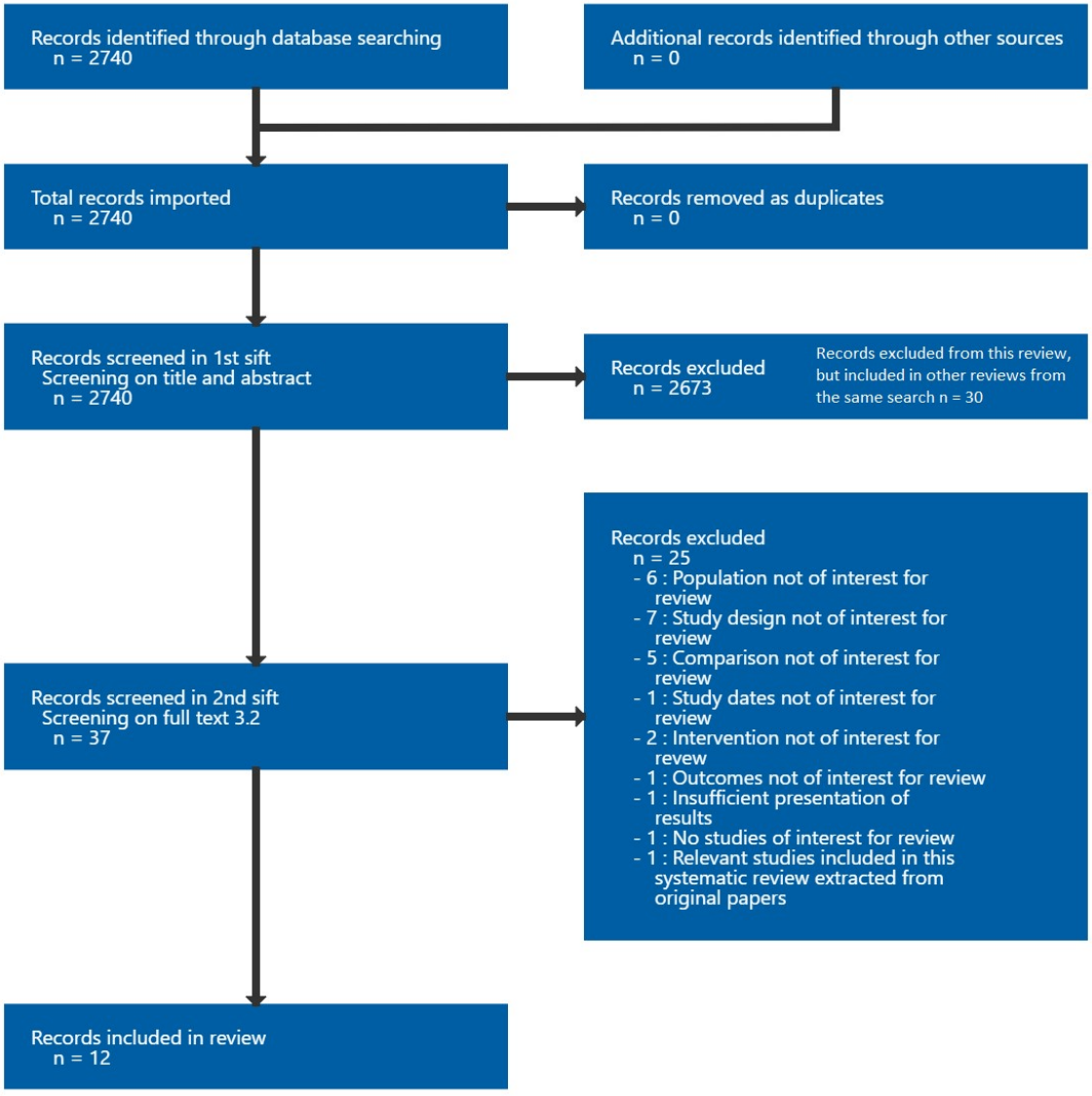
#	Searches
93	86 or 87 or 88 or 89 or 90 or 91 or 92
94	letter.pt. or letter/
95	note.pt.
96	editorial.pt.
97	case report/ or case study/
98	(letter or comment*).ti.
99	94 or 95 or 96 or 97 or 98
100	randomized controlled trial/ or random*.ti,ab.
101	99 not 100
102	animal/ not human/
103	nonhuman/
104	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

1

Appendix C Effectiveness evidence study selection

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

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 meningococcal disease?

Table 4: Evidence tables – effectiveness evidence

Study details	Results and risk of bias assessment using ROBINS-I

Study details	Results and risk of bias assessment using ROBINS-I
Full citation 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 **Ref Id** 1283167 **Country/ies where the study was carried out** Spain **Study type** Retrospective cohort study **Study dates** 1977 – 2019 **Inclusion criteria** People with invasive meningococcal disease, defined as sepsis and/or meningitis and a positive N meningitidis culture, or characteristic skin lesions. **Exclusion criteria** No additional criteria reported **Patient characteristics** N=446 Pre-hospital parenteral antibiotic therapy: n=62 (14%)[2] No pre-hospital antibiotic therapy: n=384 (86%) Age in years (median; IQR): 19; 14-50 Sex: male: 202 (39%); female: 325 (61%) Diagnosis: sepsis: 57 (11%); meningitis with or without sepsis: 470 (89%) Underlying disease: 81 (15%) - including alcoholism, chronic hepatic disease, solid or hematologic neoplasm, immunodeficiency, lupus, splenectomy, myeloma, glomerulonephritis, chemotherapy, corticosteroid	**Results** Outcome: Mortality before discharge[1] Pre-hospital parenteral antibiotic therapy: 0/62 No pre-hospital antibiotic therapy: 32/384 [1]No adjusted data available (rate of meningitis, odynophagia, nuchal stiffness and nausea/ vomiting) **1. Bias due to confounding (Low/Moderate/Serious/Critical/No information)** Critical: data not adjusted for confounding factors **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)** Moderate: Interventions clearly defined but assignment of intervention status was determined retrospectively **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 **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)** Moderate: no indication of selection of the reported analysis from among multiple analyses **Overall risk of bias (Low/Moderate/Serious/Critical/No information)**

Study details	Results and risk of bias assessment using ROBINS-I
Full citation Cartwright, K., Reilly, S., White, D., Stuart, J., Early treatment with parenteral penicillin in meningococcal disease, British medical journal, 305, 143-147, 1992 **Ref Id** 1282853 **Country/ies where the study was carried out** England **Study type** Retrospective cohort study **Study dates** Gloucester: 1 January 1982- 31 December 1991 Plymouth and Bath: 1 January 1988- 31 December 1991 **Inclusion criteria** Meningococcal disease if: a) menigococcus had been isolated from blood or CSF; b) clinical evidence of meningitis had been accompanied by the presence of gram -ve diplococci in CSF c) signs and symptoms of meningitis or septicaemia had been accompanied by a haemorrhagic rash; or d) a haemorrhagic rash or clinical evidence of meningitis; or both, had been accompanied by isolation of a meningococcus from a nasopharyngeal swab, by a rise in meningococcal antibodies, or the presence of IgM specific to meningococcus. **Exclusion criteria** Patients were excluded if, transferred from another hospital, admitted on self-referral, developed meningococcal disease is hospital, or if the final diagnosis was chronic meningococcal sepsis **Patient characteristics** N=360 340/360 referred to hospital via GP	**Results** Outcome: Mortality before discharge[3] Pre-admission parenteral antibiotic: 5/93 No pre-admission parenteral antibiotic: 22/246 [3]no adjusted data available (confounding factors unclear due to lack of comparison between baseline characteristics) **1. Bias due to confounding (Low/Moderate/Serious/Critical/No information)** Critical: data not adjusted for confounding factors **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)** Moderate: Interventions clearly defined but assignment of intervention status was determined retrospectively **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: data available for 360/366 (98%) participants **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)** Moderate: no indication of selection of the reported analysis from among multiple analyses **Overall risk of bias (Low/Moderate/Serious/Critical/No information)**

Study details	Results and risk of bias assessment using ROBINS-I
Full citation 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 **Ref Id** 1283699 **Country/ies where the study was carried out** Netherlands **Study type** Prospective cohort study **Study dates** 1st January 2003 - 1st May 2005 **Inclusion criteria** Patients with meningococcal disease notified to the Netherlands' Health Care Inspectorate. Meningococcal disease defined as clinical presentation consistent with invasive meningococcal disease and Neisseria meningitides in blood or cerebrospinal fluid (CSF), gram-negative diplococci in CSF, blood or skin lesion biopsy, meningococcal antigen in CSF or polymerase chain reaction (PCR) of meningococcal DNA in CSF or blood. **Exclusion criteria** No additional criteria reported **Patient characteristics** N=752 (n=601 included in analysis) Age in years (median): 5 Age in years: <1: 125 (18%); 1-3: 191 (25%); 4-18: 220 (29%); >18: 206 (27%) Sex: male: 358 (48%); female: 394 (52%) In shock at admission: 161/541 (30%) Haemorrhagic skin lesions on admission: 363/601 (60%)	**Results** Outcome: Mortality before discharge[4] Pre-admission antibiotics: 1/18 No pre-admission antibiotics: 35/583 [4]No adjusted data available (confounding factors unclear due to lack of comparison between baseline characteristics) **1. Bias due to confounding (Low/Moderate/Serious/Critical/No information)** Critical: limited comparison between characteristics so cannot determine if there were confounding factors that should have been adjusted for **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 status is not well 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: outcome data was available for 95% of participants **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)** Moderate: no indication of selection of the reported analysis from among multiple analyses **Overall risk of bias (Low/Moderate/Serious/Critical/No information)**

Study details	Results and risk of bias assessment using ROBINS-I
Full citation Gunnell, D. J., Pearson, N., Ley, B., Hill, A., Epidemiology of meningococcal disease and a community outbreak in Somerset, Communicable disease report, CDR review. 4, R101-104, 1994 **Ref Id** 1282973 **Country/ies where the study was carried out** England **Study type** Retrospective cohort study **Study dates** May 1990 - April 1993 **Inclusion criteria** Meningococcal disease if: a) a N. meningitidis had been isolated from blood or CSF; or b) clinical evidence of meningitis had been accompanied by the presence of gram -ve diplococci in CSF; or c) signs and symptoms of meningitis or septicaemia had been accompanied by a haemorrhagic rash **Exclusion criteria** Not reported **Patient characteristics** N=57 (n=46 evaluable cases)Age (in years): <1: 14% 1-4: 28% 5-14: 18% 15-24: 25% ≥25: 16% (% rounded to nearest number, so total is 101%)	**Results** Outcome: mortality prior to discharge[5] Pre-admission benzylpenicillin: 3/27 No-preadmission benzylpenicillin: 2/19 [5]no adjusted data available (confounding factors unclear due to lack of comparison between baseline characteristics) Outcome on long term sequelae not extracted as definition unclear **1. Bias due to confounding (Low/Moderate/Serious/Critical/No information)** Critical: data not adjusted for confounding factors **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)** Moderate: Interventions clearly defined but assignment of intervention status was determined retrospectively **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)** Moderate: data on benzylpenicillin administration was available for 46/57 (80%) of participants **6. Bias in measurement of outcomes (Low/Moderate/Serious/Critical/No information)** Low: objective outcomes of mortality and length of stay **7. Bias in selection of the reported result (Low/Moderate/Serious/Critical/No information)** Low: objective outcome of mortality

Study details	Results and risk of bias assessment using ROBINS-I
Full citation Jefferies, C., Lennon, D., Stewart, J., Martin, D., Meningococcal disease in Auckland, July 1992 - June 1994, New Zealand Medical Journal, 112, 115-117, 1999 **Ref Id** 1283410 **Country/ies where the study was carried out** New Zealand **Study type** Retrospective cohort study **Study dates** July 1992- June 1994 **Inclusion criteria** Meningococcal disease defined as: Probable case: clinical evidence of meningitis or septicaemia in association with petechial/purpuric rash; or when there was isolation of N. meningitides from the throat Confirmed case: one with a clinically compatible illness and either isolation of N. meningitidis from a sterile body site; or gram -ve diplococci in blood, CSF or skin, or the antigen test in CSF Definite case: culture of N. meningitides from CSF, demonstration of gram -ve diplococci, or the antigen in CSF, with a compatible clinical picture. A compatible clinical picture was considered a probable case. **Exclusion criteria** Not reported **Patient characteristics** N=106 confirmed or probable cases: n=61/106 (58%) <15 years old Organism: Meningococcus serogroup B: 57.5%	**Results** Outcome: mortality[6] (time undefined) Pre-admission antibiotics administered by GP: 1/24 No pre-admission antibiotics administered by GP: 2/41 [6]no adjusted data available (confounding factors unclear due to lack of comparison between baseline characteristics) **1. Bias due to confounding (Low/Moderate/Serious/Critical/No information)** Critical: data not adjusted for confounding factors **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)** Moderate: Interventions clearly defined but assignment of intervention status was determined retrospectively **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: 96/106 (90%) of confirmed or probable cases were evaluated **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)** Moderate: no indication of selection of the reported analysis from among multiple analyses **Overall risk of bias (Low/Moderate/Serious/Critical/No information)**

Study details	Results and risk of bias assessment using ROBINS-I
Full citation 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 **Ref Id** 1282957 **Country/ies where the study was carried out** England **Study type** Retrospective cohort study **Study dates** 1 January 1994 - 31 December 1998 **Inclusion criteria** Meningococcal disease was defined as confirmed, probable or possible, in accordance with standard definitions. Confirmed: Patients with N. meningitidis isolated from the CSF, blood or other normally sterile site (excluding throat); or a positive PCR test on blood or CSF for meningococci; or N. meningitidis isolated from a throat swab in a patient with a characteristic rash and clinical symptoms of meningitis or septicaemia Probable: Gram positive diplococci on microscopy, but negative cultures, or a clinical diagnosis of meningitis or septicaemia with a rash Possible: Clinical diagnosis but no rash who were treated with antibiotics **Exclusion criteria** Not reported **Patient characteristics** N=258 meningococcal disease (confirmed, probable, or possible) n=145 meningococcal disease defined as confirmed Of all meningococcal disease:	**Results** Outcome: mortality (time undefined)[7] Pre-admission parenteral benzylpenicillin: 2/72 No pre-admission parenteral benzylpenicillin: 16/186 [7]no adjusted data available (confounding factors unclear due to lack of comparison between baseline characteristics) **1. Bias due to confounding (Low/Moderate/Serious/Critical/No information)** Critical: data not adjusted for confounding factors **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 study **3. Bias in classification of interventions (Low/Moderate/Serious/Critical/No information)** Moderate: Interventions clearly defined but assignment of intervention status was determined retrospectively **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: data available for 326/355 (92%) participants **6. Bias in measurement of outcomes (Low/Moderate/Serious/Critical/No information)** Low: objective outcome of death **7. Bias in selection of the reported result (Low/Moderate/Serious/Critical/No information)** Moderate: no indication of selection of the reported analysis from among multiple analyses **Overall risk of bias (Low/Moderate/Serious/Critical/No information)**

Study details	Results and risk of bias assessment using ROBINS-I
Full citation 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 **Ref Id** 1283715 **Country/ies where the study was carried out** Denmark **Study type** Retrospective cohort study **Study dates** 1 Jan 1980- April 1999 **Inclusion criteria** (a) Certain diagnosis of meningococcal disease: (i) growth of meningococci in blood or spinal fluid specimens; (ii) presence of gram negative diplococci at direct microscopy of the spinal fluid but no growth; (iii) positive meningococcal antigen test or increasing antibody level (MAT), but absence of (i) and (ii). (b) Probable diagnosis of meningococcal disease: (iv) clinical picture typical of MCD (meningitis and/or septicaemia with petechiae) but absence of (i) and (ii). **Exclusion criteria** Not reported **Patient characteristics** N=479 admitted to hospital by GP Age (years in median, range in parentheses): pre-admission parenteral antibiotics 9 (0-58); no pre-admission parenteral antibiotics 7 (0-82)	**Results** Outcome: mortality during hospitalisation[8] Parenteral antibiotics administered by GP: 9/77 No parenteral antibiotics administered by GP: 26/402 Adjusted OR* (95% CI): 2.4 (1.0-5.6) [8]adjusted for age, sex, and calendar years **1. Bias due to confounding (Low/Moderate/Serious/Critical/No information)** Serious: Data adjusted for age, sex, and calendar year. However, covariate of co-morbidity, indicators of severity of illness, and antibiotics administered pre or post lumbar puncture were not accounted for. **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)** Moderate: Interventions clearly defined but assignment of intervention status was determined retrospectively **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: all participants followed up **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)** Serious: significant variables in logistic regression model were not accounted

Study details	Results and risk of bias assessment using ROBINS-I
Full citation 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 **Ref Id** 143245 **Country/ies where the study was carried out** Wales **Study type** Retrospective cohort study **Study dates** 1988 **Inclusion criteria** Patients with reports of laboratory isolations of N. meningitidis from blood and CSF; or in patients with clinical features of meningitis but whose diagnosis was not confirmed by blood or CSF culture, were considered to have meningococcal disease when a purpuric rash and an abnormal CSF were reported also. **Exclusion criteria** Not reported **Patient characteristics** N=119 n=10 without an organism cultured from blood or CSF and without evidence of a purpuric rash. In five of these 10, diplococci were seen in the CSF; in the other five, the CSF was abnormal. Microbiology 105 of 111 strains identified; Group B strain 73% Group C strain 26% Group Y strain 1%	**Results** Outcome: Mortality (time undefined)[9] Pre-admission parenteral penicillin administered by GP: 1/11 No pre-admission parenteral penicillin administered by GP: 6/64 [9]no adjusted data available (confounding factors unclear due to lack of comparison between baseline characteristics) **1. Bias due to confounding (Low/Moderate/Serious/Critical/No information)** Critical: data not adjusted for confounding factors **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 study **3. Bias in classification of interventions (Low/Moderate/Serious/Critical/No information)** Moderate: Interventions clearly defined but assignment of intervention status was determined retrospectively **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)** Moderate: clinical details were available on 96/119 (81%) of patients **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)** Moderate: no indication of selection of the reported analysis from among multiple analyses **Overall risk of bias (Low/Moderate/Serious/Critical/No information)**

Study details	Results and risk of bias assessment using ROBINS-I
Full citation 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 **Ref Id** 115953 **Country/ies where the study was carried out** Denmark **Study type** Retrospective cohort study **Study dates** 1st January 1980 - 31st December 1995 **Inclusion criteria** Patients admitted to hospitals in one Danish county with meningococcal disease, defined as positive blood or cerebral spinal fluid (CSF) culture for meningococci, gram-negative diplococci in the spinal fluid (but no growth), positive meningococcal antigen test/increasing antibody-level or typical clinical presentation for meningococcal disease (including petechiae). **Exclusion criteria** Referred directly to hospital without GP examination (n=18) **Patient characteristics** N=302 Parenteral antibiotics before admission to hospital 44/302 (15%) No parenteral antibiotics before admission to hospital 258/302 (85%) Pre-hospital antibiotic treatment: n=44 Age in years (median; IQR; range): 8; 2-17; 0-51 Fever: 43 (98%) Impaired consciousness: 34 (77%) Petechiae: 39 (89%) Skin bleeding: 7 (16%)	**Results** Outcome: Mortality during hospitalisation Pre-hospital antibiotic treatment: 9/44 No pre-hospital antibiotic treatment: 16/258 Adjusted OR[10] (95%C CI): 3.2 (0.9-10.6) [10]adjusted for age, sex, impaired consciousness and severity of disease **1. Bias due to confounding (Low/Moderate/Serious/Critical/No information)** Serious: unclear if there were differences in rates of comorbidity between groups that could have caused confounding **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 status is not well 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 deviations from intended interventions **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)** Moderate: no indication of selection of the reported analysis from among multiple analyses

Study details	Results and risk of bias assessment using ROBINS-I
Full citation 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 ‘ **Ref Id** 1283422 **Country/ies where the study was carried out** England **Study type** Retrospective cohort study **Study dates** 1 January 1986 - 31 March 1991 **Inclusion criteria** Patients with: a) N. meningitidis isolated from blood or cerebrospinal fluid, or both, or b) Gram -ve diplococci had been seen in the CSF, or c) Clinical signs of meningitis or septicaemia had been accompanied by a haemorrhagic rash **Exclusion criteria** Not reported **Patient characteristics** N=41 Patients seen by GP: n=35; seen by a doctor from the local deputising service: n=6; self-referred to A&E department of the hospital: n=5 Age (in years): <5: 52% 5-24: 37% ≥25: 11% Female: 54%	**Results** Outcome: mortality before discharge[11] Pre-admission parenteral penicillin: 0/13 No pre-admission parenteral penicillin: 6/28 [11]No adjusted data available (confounding factors unclear due to lack of comparison between baseline characteristics) **1. Bias due to confounding (Low/Moderate/Serious/Critical/No information)** Critical: data not adjusted for confounding factors **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)** Moderate: Interventions clearly defined but assignment of intervention status was determined retrospectively **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 **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)** Moderate: no indication of selection of the reported analysis from among multiple analyses **Overall risk of bias (Low/Moderate/Serious/Critical/No information)**

Study details	Results and risk of bias assessment using ROBINS-I
Full citation Wood, A. L., O'Brien, S. J., How long is too long? Determining the early management of meningococcal disease in Birmingham, Public HealthPublic Health, 110, 237-9, 1996 **Ref Id** 1283135 **Country/ies where the study was carried out** England **Study type** Retrospective cohort study **Study dates** 1993 **Inclusion criteria** Discharge diagnosis of meningococcal infection with a microbiological confirmation of the diagnosis was ascertained in one of three ways; a) Bacteriological culture of meningococci; or b) Raised serum antibody levels to N. meningitidis; or c) Presence of meningococcal antigen in CSF **Exclusion criteria** Not reported **Patient characteristics** N=40 Discharge diagnosis: Meningococcal disease: 24 (29%) Meningococcal meningitis: 16 (20%) Pneumococcal meningitis: 10 (12%) H. influenzae type b meningitis: 7 (9%) Other meningitis: 25 (31%) Characteristics of patients with meningococcal infection (n=40): Diagnosis confirmed microbiologically: 24 (60%)	**Results** Outcome: mortality prior to discharge[12] Pre-admission benzylpenicillin administration: 1/7 No pre-admission benzylpenicillin administration: 2/33 [12]No adjusted data available (confounding factors unclear due to lack of comparison between baseline characteristics) **1. Bias due to confounding (Low/Moderate/Serious/Critical/No information)** Critical: data not adjusted for confounding factors **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)** Moderate: Interventions clearly defined but assignment of intervention status was determined retrospectively **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 **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)** Moderate: no indication of selection of the reported analysis from among multiple analyses **Overall risk of bias (Low/Moderate/Serious/Critical/No information)**

Study details	Results and risk of bias assessment using ROBINS-I
Full citation Woodward,C.M., Jessop,E.G., Wale,M.C., Early management of meningococcal disease, Communicable Disease Report, CDR Review. 5, R135-R137, 1995 **Ref Id** 116104 **Country/ies where the study was carried out** England **Study type** Retrospective cohort study **Study dates** 1 January 1990- 31 December 1993 **Inclusion criteria** Review of case notes revealed 1 of the 4 following scenario's: a) N. meningitidis had been isolated from blood or CSF; b) Clinical evidence of meningitis or septicaemia had been accompanied by the presence of gram -ve diplococci in CSF; c) Clinical evidence of meningitis or a haemorrhagic rash[13] had been accompanied by isolation of N. meningitidis from nasopharyngeal swab d) Clinical evidence of meningitis or septicaemia had been accompanied by a haemorrhagic rash [13]Rashes were accepted as haemorrhagic if the GP or hospital clinician defined as haemorrhagic, petechial, purpuric, ecchymotic, or bruising **Exclusion criteria** Not reported **Patient characteristics** Notes available for 114/123 (93%) potential cases. N=68 satisfied the case definition. n=63/68 (93%) referred by GP Age distribution (years) of patients illustrated in figure (without clear n); <1;	**Results** **All cases of meningococcal disease** Outcome: mortality before discharge[14] Pre-admission parenteral antibiotics: 0/13 No pre-admission parenteral antibiotics: 3/55 [14]No adjusted data available (confounding factors unclear due to lack of comparison between baseline characteristics) **1. Bias due to confounding (Low/Moderate/Serious/Critical/No information)** Critical: data not adjusted for confounding factors **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 study **3. Bias in classification of interventions (Low/Moderate/Serious/Critical/No information)** Moderate: Interventions clearly defined but assignment of intervention status was determined retrospectively **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)** Moderate: Notes available for 114/123 (93%) potential cases **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)** Moderate: no indication of selection of the reported analysis from among multiple analyses

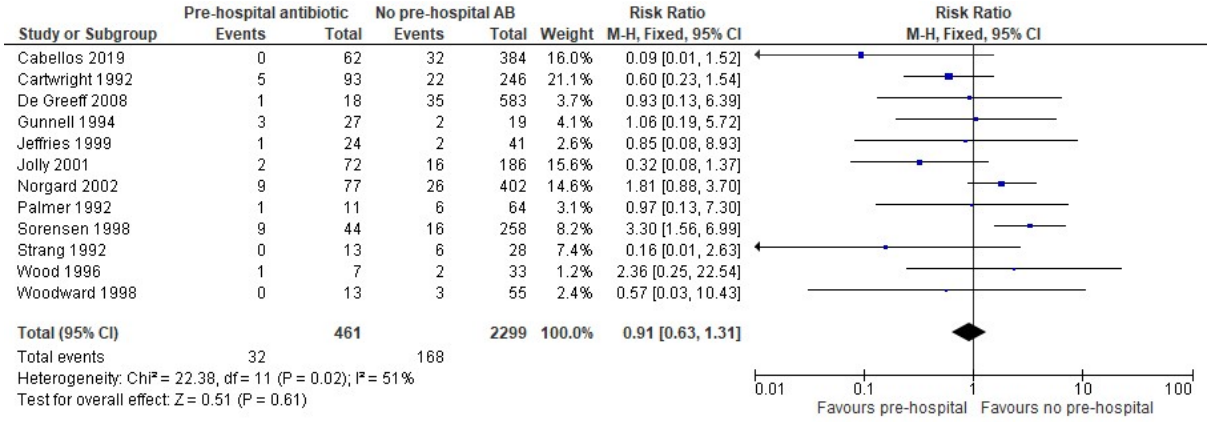
A&E: accident and emergency; CI: confidence interval; CSF: cerebrospinal fluid; DNA: deoxyribonucleic acid; GP: general practitioner; H. influenzae: Haemophilus influenzae, IgM: Immunoglobulin M, IM: intramuscular; IQR: interquartile range; IV: intravenous; MAT: meningococcal antigen typing; MCD: meningococcal disease; N: number of particiants/people; N meningitidis: Neisseria meningitidis; OR: odds ratio; PCR: polymerase Chain Reaction; ROBINS-I: Risk Of Bias In Non-randomised Studies - of Interventions; -ve: negative

Appendix E Forest plots

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

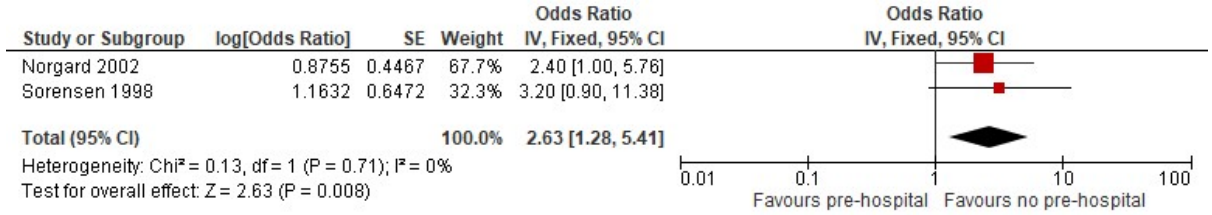
This section includes forest plots only for outcomes that are meta-analysed. Outcomes from single studies are not presented here; the quality assessment for such outcomes is provided in the GRADE profiles in appendix F.

Figure 2: Pre-hospital antibiotics versus no pre-hospital antibiotics for babies, children and adults (combined): All-cause mortality before discharge or when time is undefined (unadjusted analyses)



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

Figure 3: Pre-hospital antibiotics versus no pre-hospital antibiotics for babies, children and adults (combined): All-cause mortality before discharge (adjusted analyses)



CI: confidence interval; IV: inverse variance

Appendix F GRADE tables

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

Table 5: Clinical evidence profile for comparison pre-hospital parenteral antibiotic administration versus no pre-hospital parenteral antibiotic administration– Babies, children and adults combined

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Early	Late	Relative (95% CI)	Absolute	Quality	Importance
Mortality before discharge or when time is undefined (unadjusted analyses) – Adults, children, and babies*												
12**	observational studies	very serious [1]	no serious inconsistencys	no serious indirectness	serious[2]	none	32/461 (6.9%)	168/2299 (7.3%)	RR 0.91 (0.63 to 1.31)	7 fewer per 1000 (from 27 fewer to 23 more)	VERY LOW .	CRITICAL
Mortality before discharge (adjusted analyses) – Adults, children, and babies*												
2**	observational studies	very serious [1]	no serious inconsistency	no serious indirectness	very serious[3]	none	18/121 (14.9%)	42/664 (6.3%)	OR 2.63 (1.28 to 5.41)	88more per 1000 (from 16 more to 204 more)	VERY LOW	CRITICAL

CI: confidence interval; OR: odds ratio; RR: risk ratio
**Mixed population of adults and children or age range of population not reported in the study*
***See corresponding forest plot*
[1] Very serious risk of bias in the evidence contributing to the outcomes as per ROBINS-I
[2] <300 events
[3] <150 events

Appendix G Economic evidence study selection

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

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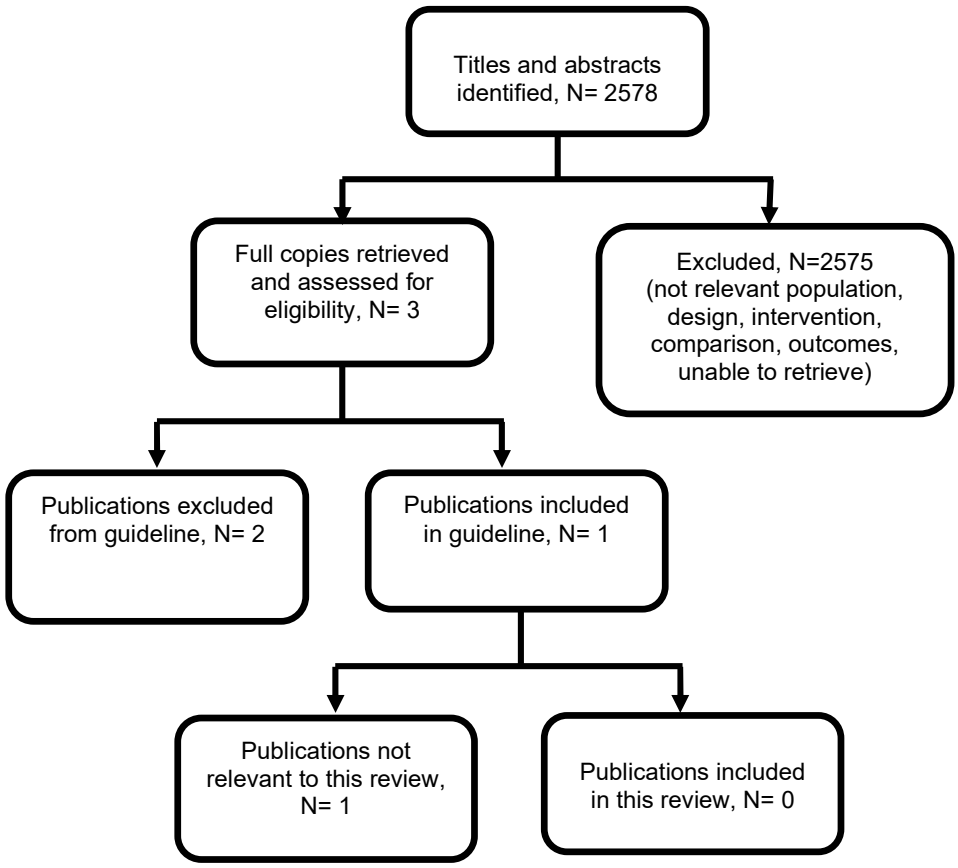
A global economic search was undertaken for the whole guideline, but no economic evidence was identified which was applicable to this review question (see Figure 4).

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 meningococcal disease?

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 meningococcal disease?

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 meningococcal disease?

Excluded effectiveness studies

The excluded studies table only lists the studies that were considered and then excluded at the full-text stage for this review (N=25) and not studies (N=30) that were considered and then excluded from the search at the full-text stage as per the PRISMA diagram in Appendix C for the other review questions in the same search.

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
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	Study included in evidence review in timing of antibiotic in suspected bacterial meningitis
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	Study included in evidence review in timing of antibiotic in suspected bacterial meningitis

Study	Reason for Exclusion
pediatrics, 171, 1365-1371, 2012	
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
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	Study included in evidence review in timing of antibiotic in suspected bacterial meningitis
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	Study included in evidence review in timing of antibiotic in suspected bacterial meningitis
Bonsu, B. K., Harper, M. B., Fever interval before diagnosis, prior antibiotic treatment, and clinical outcome for young children with bacterial meningitis, Clinical infectious diseases, 32, 566-72, 2001	Intervention not of interest for review: combination of oral and parenteral antibiotics, no stratification for parenteral antibiotics
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	Study included in evidence review in timing of antibiotic in suspected bacterial meningitis
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
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

Study	Reason for Exclusion
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)
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
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 Clin Infect Dis, 60, 1162-9, 2015	Study included in evidence review in timing of antibiotic in suspected bacterial meningitis
Grindborg, O., Naucler, P., Sjolin, J., Glimaker, M., Adult bacterial meningitis-a quality registry study: Earlier treatment and favourable outcome if initial management by infectious diseases physicians, Clinical microbiology and infection, 21, 560-566, 2015	Comparison not of interest for review: ID physician vs non ID physician
Hahne, S. J. M, Charlett, A, Purcell, B et al. (2006) Effectiveness of antibiotics given before admission in reducing mortality from meningococcal disease: Systematic review. British medical journal 332(7553): 1299-1301	Relevant studies included in this systematic review extracted from original papers
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.	Comparison not of interest for review: mean

Study	Reason for Exclusion
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	hours 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
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
Kaaresen,P.I., Flaegstad,T., Prognostic factors in childhood bacterial meningitis, Acta Paediatrica, 84, 873-878, 1995	Study included in evidence review in timing of antibiotic in suspected bacterial meningitis
Koster-Rasmussen, R., Korshin, A., Meyer, C. N., Antibiotic treatment delay and outcome in acute bacterial meningitis, Journal of infection, 57, 449-454, 2008	Study included in evidence review in timing of antibiotic in suspected bacterial meningitis
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	Study included in evidence review in timing of antibiotic in suspected bacterial meningitis
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].	Unpublished report
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.,	Population not of interest for review: children

Study	Reason for Exclusion
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	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., 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	Study design not of interest for review: literature review (references checked for additional 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
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
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	Study included in evidence review in timing of antibiotic in suspected bacterial meningitis
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	No full text available (not included in Hahne 2006 SR on pre-hospital antibiotics in meningococcal disease)

Study	Reason for Exclusion
antibiotics before admission in patients with 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)
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)
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; URTI: upper respiratory tract infection

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 meningococcal disease?

No research recommendation was made for this review.