National Institute for Health and Care Excellence

Draft for consultation

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

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

*NICE guideline number tbc*

*Evidence review underpinning recommendations 1.2.3, 1.2.5, 1.4.1, 1.4.9, and 1.6.1 to 1.6.3 in the NICE guideline*

*September 2023*

*Draft for consultation*

*This evidence review was developed by NICE*

NICE accredited
www.nice.org.uk/accreditation

**Disclaimer**

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

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

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 All NICE guidance is subject to regular review and may be updated or withdrawn.

**Copyright**

© NICE 2023. All rights reserved. Subject to Notice of rights.

ISBN:

## Contents

**Timing of antibiotics for bacterial meningitis ..... 6**
Review question ..... 6
Introduction ..... 6
Summary of the protocol ..... 6
Methods and process ..... 7
Effectiveness evidence ..... 7
Summary of included studies ..... 7
Summary of the evidence ..... 12
Economic evidence ..... 13
Economic model ..... 13
The committee's discussion and interpretation of the evidence ..... 13
Recommendations supported by this evidence review ..... 15
References – included studies ..... 16
**Appendices ..... 18**
**Appendix A Review protocols ..... 18**
Review protocol for review question: What is the optimal timing of antibiotic administration for people with suspected bacterial meningitis? ..... 18
**Appendix B Literature search strategies ..... 27**
Literature search strategies for review question: What is the optimal timing of antibiotic administration for people with suspected bacterial meningitis? .. 27
**Appendix C Effectiveness evidence study selection ..... 34**
Study selection for: What is the optimal timing of antibiotic administration for people with suspected bacterial meningitis? ..... 34
**Appendix D Evidence tables ..... 35**
Evidence tables for review question: What is the optimal timing of antibiotic administration for people with suspected bacterial meningitis? ..... 35
**Appendix E Forest plots ..... 49**
Forest plots for review question: What is the optimal timing of antibiotic administration for people with suspected bacterial meningitis? ..... 49
**Appendix F GRADE tables ..... 50**
GRADE tables for review question: What is the optimal timing of antibiotic administration for people with suspected bacterial meningitis? ..... 50
**Appendix G Economic evidence study selection ..... 53**
Study selection for: What is the optimal timing of antibiotic administration for people with suspected bacterial meningitis? ..... 53
**Appendix H Economic evidence tables ..... 54**
Economic evidence tables for review question: What is the optimal timing of antibiotic administration for people with suspected bacterial meningitis? .. 54
**Appendix I Economic model ..... 55**
Economic model for review question: What is the optimal timing of antibiotic

administration for people with suspected bacterial meningitis? ..... 55

**Appendix J Excluded studies ..... 56**

Excluded studies for review question: What is the optimal timing of antibiotic administration for people with suspected bacterial meningitis? ..... 56

**Appendix K Research recommendations – full details ..... 63**

Research recommendations for review question: What is the optimal timing of antibiotic administration for people with suspected bacterial meningitis?.. 63

# Timing of antibiotics for bacterial meningitis

## Review question

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

### Introduction

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

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

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

### Summary of the protocol

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

**Table 1: Summary of the protocol (PICO table)**

| | |
|---|---|
| **Population** | All adults, young people, children and babies (excluding neonates defined as aged 28 days old and younger) with suspected bacterial meningitis |
| **Intervention** | Early administration of parenteral antibiotic therapy (single or in combination), defined as earlier administration than the comparator |
| **Comparison** | Late administration of parenteral antibiotic therapy (single or in combination), defined as later administration than the intervention. |
| **Outcome** | **Critical**<br>Population: adults, infants and children<br>• All-cause mortality (measured up to 1 year after discharge)<br>• 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)<br>Population: adults<br>• Functional impairment (measured by any validated scale at any time point)<br>Population: infants and children<br>• 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).<br><br>**Important**<br>Population: adults, infants and children<br>• Diagnosis of epilepsy or occurrence of seizures during hospitalisation<br>• Hearing impairment (defined as any level of hearing impairment; measured from discharge up to 1 year after discharge)<br>• Serious intervention-related adverse effects leading to death, disability or prolonged hospitalisation or that are life threatening or otherwise considered |

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

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

For further details see the review protocol in appendix A.

## Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document (supplementary document 1).

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

## Effectiveness evidence

### Included studies

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

The included studies are summarised in Table 2.

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

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

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

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

### Excluded studies

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

## Summary of included studies

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

**Table 2: Summary of included studies**

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

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

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

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

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

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

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

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

## Summary of the evidence

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

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

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

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

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

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

See appendix F for full GRADE tables.

## Economic evidence

### Included studies

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

## Economic model

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

## The committee's discussion and interpretation of the evidence

### The outcomes that matter most

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

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

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

**The quality of the evidence**

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

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

**Benefits and harms**

The committee considered the evidence comparing outcomes between children who did and did not receive pre-hospital antibiotics and noted no significant difference in all-cause mortality and any long-term neurological impairment. There was also no evidence of a difference in functional impairment between adults who received antibiotics prior to hospital admission and those who did not. These findings were consistent with the clinical expertise of the committee, and they agreed that ideally antibiotics would be administered in hospital rather than in the community for suspected bacterial meningitis, because antibiotics can affect the results of blood culture and cerebrospinal fluid (CSF) tests. The committee also discussed the difficulty in distinguishing bacterial meningitis from other illnesses that do not require antibiotics. Based on the evidence and their clinical knowledge and experience the committee recommended that pre-hospital intravenous or intramuscular antibiotics should only be given where bacterial meningitis is strongly suspected and where a clinically significant delay in transfer to hospital is considered likely. The committee also recommended that transfer to hospital should not be delayed to give antibiotics to people with suspected or strongly suspected bacterial meningitis. The committee specified ceftriaxone or benzylpenicillin as the antibiotics of choice for use outside of hospital because these would be available in emergency situations.

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

Overall, evidence showed that early in-hospital antibiotic administration was associated with lower rates of mortality in adults compared to later antibiotic administration. There was also a benefit of early compared to later in-hospital antibiotic administration in terms of rate of functional impairment, but only when compared against delays greater than 6 hours. Based on the evidence, and their clinical knowledge and experience, the committee agreed that intravenous antibiotics should be administered as soon as possible once bacterial meningitis is suspected and within 1 hour of arrival in hospital. The committee noted that given the potential for antibiotic treatment to affect the results of blood culture and CSF tests, blood samples should be taken, and lumbar puncture performed prior to starting antibiotic treatment. The committee recognised that lumbar puncture may not always be possible within a very short timeframe as it is a relatively complex technical procedure that needs to be carried out by trained and competent practitioners, however the committee recommended

that wherever it is safe to do so lumbar puncture should be performed before starting antibiotics.

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

### Cost effectiveness and resource use

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

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

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

## Recommendations supported by this evidence review

This evidence review supports recommendations 1.2.3, 1.2.5, 1.4.1, 1.4.9, and 1.6.1 to 1.6.3. Other evidence supporting the recommendation 1.2.5 can be found in the evidence review on timing of antibiotics for meningococcal disease (see evidence review C2).

# References – included studies

## Effectiveness

**Auburtin 2006**

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

**Bargui 2012**

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

**Bijlsma 2016**

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

**Bodilsen 2016**

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

**Bretonniere 2015**

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

**Glimaker 2015**

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

**Kaaresen 1995**

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

**Proulx 2005**

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

**Economic**

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

**Other**

**NICE 2016**

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

# Appendices

## Appendix A Review protocols

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

**Table 3: Review protocol**

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

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

| Field | Content |
|---|---|
| | • Co-morbidity<br>• Severity of infection at presentation (including sepsis)<br>• Antibiotics administered pre or post lumbar puncture<br>• Infective organism<br><br>Exclude:<br>• Conference abstracts |
| Other exclusion criteria | Countries other than OECD high income countries.<br>Studies conducted prior to 1980 as currently used antibiotics were not in common usage prior to this date.<br>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<br>• All-cause mortality (measured up to 1 year after discharge)<br>• 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)<br>• Functional impairment (measured by any validated scale at any time point)<br><br>Population: infants and children<br>• All-cause mortality (measured up to 1 year after discharge)<br>• 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)<br>• Severe developmental delay (defined as score of >2 SD below normal on validated assessment scales, or MDI or PDI <70 on Bayleys assessment scale, or inability to assign a score due to cerebral palsy or severity of cognitive delay; measured at the oldest age reported unless there is substantially more data available at a younger age) |

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

| Field | Content |
|---|---|
| | • ROBIS tool for systematic reviews<br>• Cochrane RoB tool v.2 for RCTs and quasi-RCTs<br>• Cochrane ROBINS-I tool for non-randomised (clinical) controlled trials and cohort studies<br>The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer. |
| Strategy for data synthesis | Quantitative findings will be formally summarised in the review. Where multiple studies report on the same outcome for the same comparison, meta-analyses will be conducted using Cochrane Review Manager software. A fixed effect meta-analysis will be conducted and data will be presented as risk ratios if possible or odds ratios when required (for example if only available in this form in included studies) for dichotomous outcomes, and mean differences or standardised mean differences for continuous outcomes. Heterogeneity in the effect estimates of the individual studies will be assessed by visual inspection of the forest plots and consideration of the I2 statistic.<br>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.<br>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/<br><br>**Minimally important differences:**<br>• All-cause mortality: statistical significance<br>• Serious intervention-related adverse effects: statistical significance<br>• Length of hospitalisation: 1 day<br>• Validated scales: Published MIDs where available; if not GRADE default MIDs<br>• All other outcomes: GRADE default MIDs |
| Analysis of sub-groups | Evidence will be stratified by:<br>Age:<br>• Younger Infants: >28 days to ≤3 months of age |

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

| Field | Content | | | |
|---|---|---|---|---|
| | made where there is evidence of a differential effect of interventions in distinct groups. If there is a lack of evidence in one group, the committee will consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others. | | | |
| Type and method of review | ☒ | Intervention | | |
| | ☐ | Diagnostic | | |
| | ☐ | Prognostic | | |
| | ☐ | Qualitative | | |
| | ☐ | Epidemiologic | | |
| | ☐ | Service Delivery | | |
| | ☐ | Other (please specify) | | |
| Language | English | | | |
| Country | England | | | |
| Anticipated or actual start date | 28/10/2020 | | | |
| Anticipated completion date | 07/12/2023 | | | |
| Stage of review at time of this submission | Review stage | | Started | Completed |
| | Preliminary searches | | ☑ | ☑ |
| | Piloting of the study selection process | | ☑ | ☑ |
| | Formal screening of search results against eligibility criteria | | ☑ | ☑ |
| | Data extraction | | ☑ | ☑ |
| | Risk of bias (quality) assessment | | ☑ | ☑ |

| Field | Content |
|---|---|
| | Data analysis ☑ ☑ |
| Named contact | Named contact: National Guideline Alliance<br><br>Named contact e-mail: meningitis&meningococcal@nice.org.uk<br><br>Organisational affiliation of the review: National Institute for Health and Care Excellence (NICE) and National Guideline Alliance |
| Review team members | National Guideline Alliance |
| Funding sources/sponsor | This systematic review is being completed by the National Guideline Alliance which receives funding from NICE. |
| Conflicts of interest | All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline. |
| Collaborators | Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10149. |
| Other registration details | None |
| Reference/URL for published protocol | https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020219903 |
| Dissemination plans | NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as:<br>notifying registered stakeholders of publication<br>publicising the guideline through NICE's newsletter and alerts |

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

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

# Appendix B Literature search strategies

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

### Clinical Search

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

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

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

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

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

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

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

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

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

Date of last search: 19 October 2020

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

## Economic Search

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

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

Date of last search: 11 March 2021

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

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

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

Date of last search: 11 March 2021

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

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

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

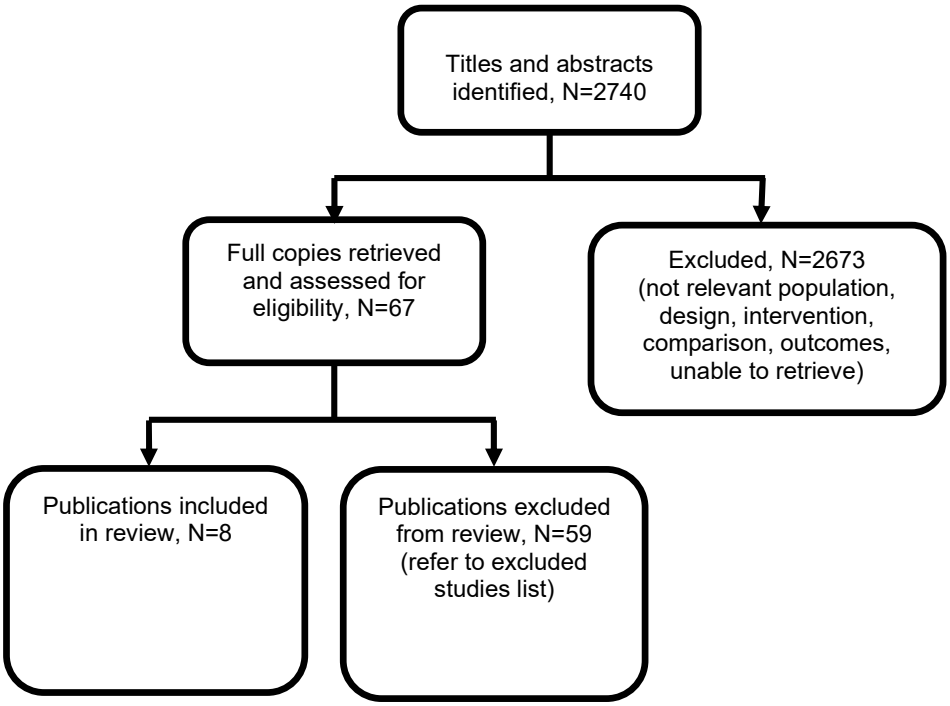
| # | Searches |
|---|---|
| 93 | 86 or 87 or 88 or 89 or 90 or 91 or 92 |
| 94 | letter.pt. or letter/ |
| 95 | note.pt. |
| 96 | editorial.pt. |
| 97 | case report/ or case study/ |
| 98 | (letter or comment*).ti. |
| 99 | 94 or 95 or 96 or 97 or 98 |
| 100 | randomized controlled trial/ or random*.ti,ab.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

1

# Appendix C Effectiveness evidence study selection

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

**Figure 1: Study selection flow chart**



# Appendix D Evidence tables

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

**Table 4: Evidence tables – effectiveness evidence**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

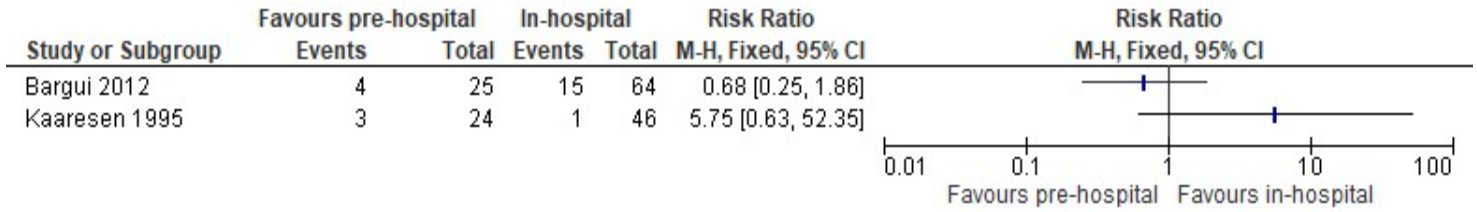
*ABM: Acquired bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; E. Coli: Escherichia coli; GOS: Glasgow Outcome Scale; GP: general practitioner; HR: hazard ratio; IM: intramuscular; IQR: interquartile range; IV: intravenous; MIC: minimal inhibitory concentration; N: number of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

# Appendix E Forest plots

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

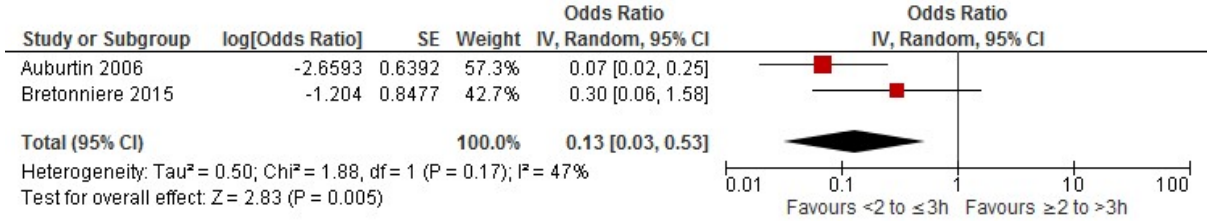
This section includes forest plots only for outcomes that are meta-analysed. Outcomes from single studies are not presented here; the quality assessment for such outcomes is provided in the GRADE profiles in appendix F.

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




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

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




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

# Appendix F GRADE tables

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

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

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Early | Late | Relative (95% CI) | Absolute | | |
| **Pre-hospital versus no pre-hospital antibiotics: All-cause mortality (unadjusted) - Children** | | | | | | | | | | | | |
| 2* | observational studies | very serious [3] | very serious[4] | serious[5] | very serious[6] | none | 7/49 (14.3%) | 16/110 (14.5%) | Not pooled[2]:<br><br>Bargui 2012: RR 0.68 (0.25 to 1.86)<br><br>Kaaresen 1995: RR 5.75 (0.63 to 52.35) | Not pooled[2]:<br><br>Bargui 2012: 74 fewer per 1000 (from 173 fewer to 157 more)<br><br>Kaaresen 1995: 103 more per 1000 (from 8 fewer to 1000 more) | VERY LOW | CRITICAL |
| **Pre-hospital versus no pre-hospital antibiotics: Any long-term neurological impairment (motor deficits, hydrocephalus, cerebral palsy, ataxia, mental retardation, hearing impairment, seizure, or focal neurological findings; >1 year) (unadjusted) – Children** | | | | | | | | | | | | |
| 1 (Kaaresen 1995) | observational studies | very serious [3] | no serious inconsistency | serious[5] | very serious[6] | none | 3/24 (12.5%) | 8/46 (17.4%) | RR 0.72 (0.21 to 2.46) | 49 fewer per 1000 (from 137 fewer to 254 more) | VERY LOW | CRITICAL |
| **Prehospital vs. no pre-hospital antibiotics: Functional impairment (GOS ≤4) (adjusted) - Adults** | | | | | | | | | | | | |
| 1 (Bijlsma 2016) | observational studies | serious [1] | no serious inconsistency | serious[5] | no serious imprecision | none | 55/152 (36.2%) | 464/1225 (37.9%) | OR 1.10 (0.72 to 1.68) | 23 more per 1000 (from 74 fewer to 127 more) | LOW | IMPORTANT |
| **<2 to ≤3h versus ≥2 to >3h in-hospital antibiotics: All-cause mortality (adjusted) - Adults** | | | | | | | | | | | | |
| 2* | observational studies | very serious [3] | serious[7] | no serious indirectness | serious[2] | none | 19/144 (13.2%) | 50/138 (36.2%) | OR 0.13 (0.03 to 0.53) | 294 fewer per 1000 (from 131 to 346 fewer) | VERY LOW | CRITICAL |
| **0 to 2h versus 2 to 4h in-hospital antibiotics: All-cause mortality (adjusted) - Adults** | | | | | | | | | | | | |
| 1 (Bodilsen 2016) | observational studies | serious [1] | no serious inconsistency | no serious indirectness | very serious[6] | none | 12/83 (14.4%) | 6/37 (16.2%) | RR 0.83 (0.37 to 2) | 28 fewer per 1000 (from 102 fewer to 162 more) | VERY LOW | CRITICAL |
| **0 to 2h versus 2 to 4h in-hospital antibiotics: Functional impairment (GOS≤4) (adjusted) - Adults** | | | | | | | | | | | | |
| 1 (Bodilsen 2016) | observational studies | serious [1] | no serious inconsistency | no serious indirectness | very serious[6] | none | 29/83 (34.9%) | 18/37 (48.6%) | RR 0.67 (0.45 to 1.11) | 160 fewer per 1000 (from 267 fewer to 53 more) | VERY LOW | IMPORTANT |
| **0 to 2h versus 4 to 6h in-hospital antibiotics: All-cause mortality (adjusted) - Adults** | | | | | | | | | | | | |
| 1 (Bodilsen 2016) | observational studies | serious [1] | no serious inconsistency | no serious indirectness | very serious[6] | none | 12/83 (14.4%) | 2/10 (20%) | RR 0.71 (0.28 to 2) | 58 fewer per 1000 (from 114 | VERY LOW | CRITICAL |

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

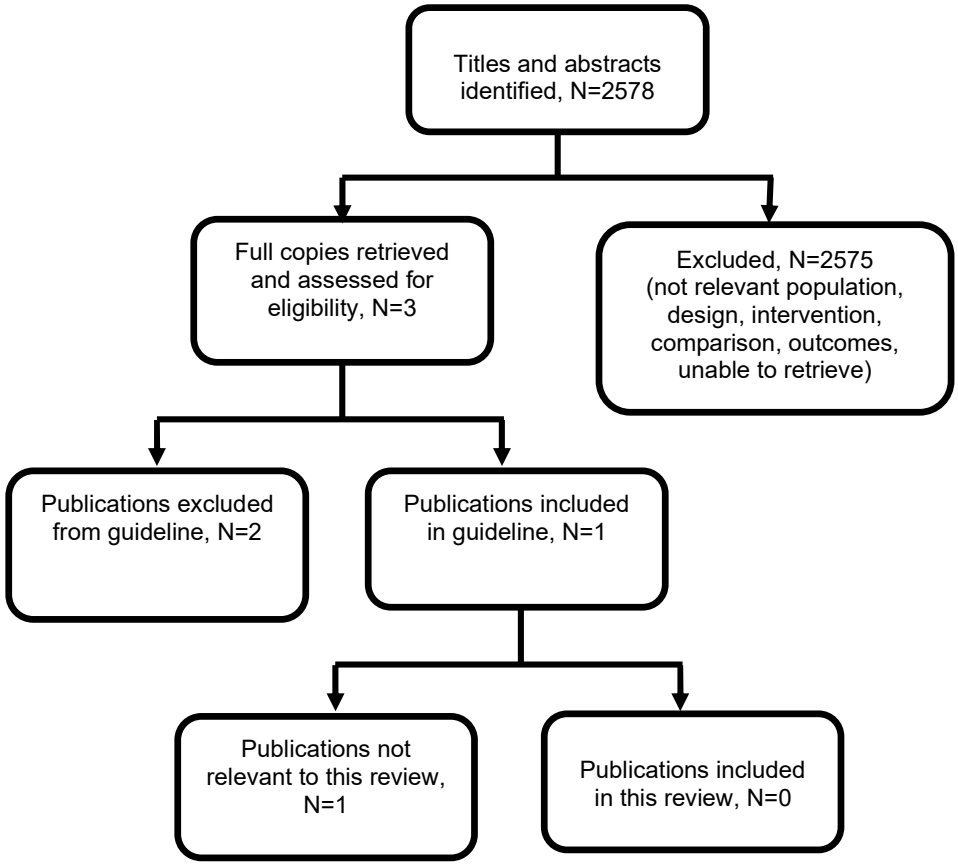
*CI: confidence interval; HR: hazard ratio; RR: risk ratio; OR: odds ratio; NC: not calculable; NR: not reported*
**See corresponding forest plot*
***Imprecision was judged based on number of events estimated from the overall mortality rates reported*
****Absolute effect not calculated from reported event rates as these correspond to discrete time points and the relative effect corresponds to per hour of treatment delay*
*[1] Serious risk of bias in the evidence contributing to the outcomes as per ROBINS-I*
*[2]<150 events*
*[3] Very serious risk of bias in the evidence contributing to the outcomes as per ROBINS-I*
*[4] Very serious heterogeneity unexplained by subgroup analysis*
*[5] Intervention is indirect due to uncertainty around the route of administration (oral and IM)*
*[6] 95% CI crosses 1 MID and <150 events*
*[7] Serious heterogeneity unexplained by subgroup analysis*
*[8] Population is indirect due to over 25% of the participants being immunocompromised*

# Appendix G Economic evidence study selection

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

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

**Figure 4: Study selection flow chart**



# Appendix H Economic evidence tables

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

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

# Appendix I Economic model

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

No economic analysis was conducted for this review question.

# Appendix J Excluded studies

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

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

### Excluded effectiveness studies

**Table 6: Excluded studies and reasons for their exclusion**

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

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

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

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

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

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

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

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

### Excluded economic studies

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

# Appendix K Research recommendations – full details

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

No research recommendation was made for this review.