WHO guidelines on meningitis diagnosis, treatment and care

Web Annex C. Evidence-to-Decision frameworks

World Health Organization

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Contents

Abbreviations

CSF	cerebrospinal fluid
DIC	disseminated intravascular coagulation
HIC	high-income country
LP	lumbar puncture
LMIC	low- and middle-income country
WBC	white blood cells
WHO	World Health Organization

Evidence-to-Decision framework

Priority of the problem
Criteria and definition Is the problem a priority? The more serious a problem is, the more likely it is that an option that addresses the problem should be a priority (e.g. diseases that are fatal or disabling are likely to be a higher priority than diseases that only cause minor distress). The more people who are affected, the more likely it is that an option that addresses the problem should be a priority.
Example questions Are the consequences of the problem serious (i.e. severe or important in terms of the potential benefits or savings)? Is the problem urgent? Is it a recognized priority (such as based on a political or policy decision)? [Not relevant when an individual patient perspective is taken]
Judgement options ☐ No ☐ Probably no ☐ Probably yes ☐ Yes ☐ Varies ☐ Don't know
Desirable effects
Criteria and definition How substantial are the desirable anticipated effects? The larger the benefit, the more likely it is that an option should be recommended.
Example questions How substantial (large) are the desirable anticipated effects (including health and other benefits) of the option, taking into account the severity or importance of the desirable consequences and the number of people affected?
Judgement options ☐ Trivial ☐ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don’t know
Undesirable effects

Criteria and definition How substantial are the undesirable anticipated effects? The greater the harm, the less likely it is that an option should be recommended.
Example questions How substantial (large) are the undesirable anticipated effects (including harms to health and other harms) of the option, taking into account the severity or importance of the adverse effects and the number of people affected?
Judgment options ☐ Large ☐ Moderate ☐ Small ☐ Trivial ☐ Varies ☐ Don't know
Certainty of the evidence
Criteria and definition What is the overall certainty of the evidence of effects? The less certain the evidence is for critical outcomes (those that are driving a recommendation), the less likely that an option should be recommended (or the more important it is likely to be to conduct a pilot study or impact evaluation, if it is recommended).
Example questions What is the overall certainty of this evidence of effects, across all of the outcomes that are critical to making a decision?
Judgement options ☐ Very low ☐ Low ☐ Moderate ☐ High ☐ No included studies
Values
Criteria and definition Is there important uncertainty about or variability in how much people value the main outcomes? The more likely it is that differences in values would lead to different decisions, the less likely it is that there will be a consensus that an option is a priority (or the more important it is likely to be to obtain evidence of the values of those affected by the option). Values in this context refer to the relative importance of the outcomes of interest (how much people value each of those outcomes). These values are sometimes called “utility values”.

Example questions

Is there important uncertainty about how much people value each of the main outcomes?

Is there important variability in how much people value each of the main outcomes?

Judgement options

☐ Important uncertainty or variability ☐ Possibly important uncertainty or variability ☐ Probably no important uncertainty or variability ☐ No important uncertainty or variability

Balance of effects

Criteria and definition

Does the balance between desirable and undesirable effects favour the intervention or the comparison?

The larger the desirable effects in relation to the undesirable effects, taking into account the values of those affected (i.e. the relative value they attach to the desirable and undesirable outcomes), the more likely it is that an option should be recommended.

Example questions

Judgements regarding each of the 4 preceding criteria.

To what extent do the following considerations influence the balance between the desirable and undesirable effects?

How much people value outcomes that are in the future compared to outcomes that occur now (their discount rates)

People’s attitudes towards undesirable

Judgement options

☐ Favours the comparison ☐ Probably favours the comparison ☐ Does not favour either the intervention or the comparison ☐ Probably favours the intervention ☐ Favours the intervention ☐ Varies ☐ Don't know

Resources required

Criteria and definition

How large are the resource requirements (costs)?

The greater the cost, the less likely it is that an option should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.

Example questions How large is the difference in each item of resource use for which fewer resources are required? How large is the difference in each item of resource use for which more resources are required? How large an investment of resources would the option require or save?
Judgement options ☐ Large costs ☐ Moderate costs ☐ Negligible costs and savings ☐ Moderate savings ☐ Large savings ☐ Varies ☐ Don't know
Certainty of the evidence on resources required
Criteria and definition What is the certainty of the evidence of resource requirements (costs)?
Example questions Have all important items of resource use that may differ between the options being considered been identified? How certain is the evidence of differences in resource use between the options being considered?
Judgement options ☐ Very low ☐ Low ☐ Moderate ☐ High ☐ No included studies
Cost-effectiveness
Criteria and definition Does the cost-effectiveness of the intervention favour the intervention or the comparison? The greater the cost per unit of benefit, the less likely it is that an option should be a priority.
Example questions Is the cost-effectiveness ratio sensitive to 1-way sensitivity analyses? Is the cost-effectiveness ratio sensitive to multivariable sensitivity analysis? Is the economic evaluation on which the cost-effectiveness estimate is based reliable? Is the economic evaluation on which the cost-effectiveness estimate is based applicable to the setting(s) of interest?

Judgement options

☐ Favours the comparison ☐ Probably favours the comparison ☐ Does not favour either the intervention or the comparison ☐ Probably favours the intervention ☐ Favours the intervention ☐ Varies ☐ No included studies

Health equity, equality and non-discrimination

Criteria and definition

What would be the impact on health equity, equality and non-discrimination?

Health equity and equality reflect a concerted and sustained effort to improve health for individuals across all population, and to reduce avoidable systematic differences in how health and its determinants are distributed. Equality is linked to the legal principle of non-discrimination, which is designed to ensure that individuals or population groups do not experience discrimination on the basis of their sex, age, ethnicity, culture or language, sexual orientation or gender identity, disability status, education, socioeconomic status, place of residence or any other characteristics. All recommendations should be in accordance with universal human rights standards and principles. The greater the likelihood that the intervention increases health equity and/or equality and that it reduces discrimination against any particular group, the greater the likelihood of a general recommendation in favour of this intervention.

Example questions

How are the condition and its determinants distributed across different population groups? Is the intervention likely to reduce or increase existing health inequalities and/or health inequities? Does the intervention prioritize and/or aid those furthest behind?

How are the benefits and harms of the intervention distributed across the population? Who carries the burden (e.g. all)? Who benefits (e.g. a very small subgroup)?

How affordable is the intervention for individuals, workplaces or communities?

How accessible – in terms of physical as well as informational access – is the intervention across different population groups?

Is there any suitable alternative to addressing the condition? Does the intervention represent the only available option? Is this option proportionate to the need and will it be subject to periodic review?

Judgement options

☐ Reduced ☐ Probably reduced ☐ Probably no impact ☐ Probably increased ☐ Increased ☐ Varies ☐ Don't know

Feasibility
Criteria and definition Is the intervention feasible to implement? The less feasible (capable of being accomplished or brought about) an option is, the less likely it is that it should be recommended (i.e. the more barriers there are that would be difficult to overcome).
Example questions Can the option be accomplished or brought about? Is the intervention or option sustainable? Are there important barriers that are likely to limit the feasibility of implementing the intervention (option) or require consideration when implementing it?
Judgement options ☐ No ☐ Probably no ☐ Probably yes ☐ Yes ☐ Varies ☐ Don't know
Human rights and sociocultural acceptability
Criteria and definition Is the intervention aligned with human rights principles and socioculturally acceptable? This criterion encompasses two distinct constructs. The first refers to an intervention's compliance with universal human rights standards and other considerations laid out in international human rights law beyond the right to health (as the right to health provides the basis of other criteria and sub-criteria in this framework). The second, sociocultural acceptability, is highly time-specific and context-specific and reflects the extent to which those implementing or benefiting from an intervention as well as other relevant stakeholder groups consider it to be appropriate, based on anticipated or experienced cognitive and emotional responses to the intervention. The greater the sociocultural acceptability of an intervention to all or most relevant stakeholders, the greater the likelihood of a general recommendation in favour of this intervention.
Example questions Is the intervention in accordance with universal human rights standards and principles? Is the intervention socioculturally acceptable to patients/beneficiaries as well as to those implementing it? To what extent do patients/beneficiaries value different non-health outcomes? Is the intervention socioculturally acceptable to the public and other relevant stakeholder groups? Is the intervention sensitive to sex, age, ethnicity, culture or language, sexual orientation or

gender identity, disability status, education, socioeconomic status, place of residence or any other relevant characteristics? How does the intervention affect an individual's, population group's or organization's autonomy (i.e. their ability to make a competent, informed and voluntary decision)? How intrusive is the intervention, ranging from low intrusiveness (e.g. providing information) to intermediate intrusiveness (e.g. guiding choices) to high intrusiveness (e.g. restricting or eliminating choices)? Where applicable, are high intrusiveness and/or impacts on the privacy and dignity of concerned stakeholders justified?
Judgement options ☐ No ☐ Probably no ☐ Probably yes ☐ Yes ☐ Varies ☐ Don't know

1. Initial cerebrospinal fluid investigations

1.1 Guideline question

In individuals with suspected acute meningitis, should cerebrospinal fluid (CSF) tests (i.e. Gram stain, white blood cell [WBC] count and differential, glucose, total protein, lactate) be performed?

Population: Suspected cases of acute meningitis

Index test: CSF tests (Gram stain, leukocyte count and differential, glucose, total protein, lactate)

Reference standard: Consensus diagnosis excluding index test[1]

Outcome: *Critical*: Sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of index test

Full details of the evidence, including references, are provided in Web Annex A (1. Initial cerebrospinal fluid investigations) and Web Annex B (Qualitative and economic evidence reports).

[1] Consensus diagnosis excluding index test is defined as clinical characteristics (including peripheral WBC count, C-reactive protein, procalcitonin), blood culture, CSF culture and/or CSF polymerase chain reaction (PCR).

1.2 Evidence-to-Decision framework

Priority of the problem
Judgement: Yes Acute meningitis is a life-threatening condition that requires timely and accurate diagnosis to ensure appropriate patient management. Culture and molecular tests are generally regarded as the reference standard for pathogen identification. However, to inform timely clinical decisions and guide antimicrobial treatment, additional investigations with faster turnaround times and rapidly available results are normally conducted on cerebrospinal fluid (CSF) samples, including Gram stain, cellularity (total and differential cell count), glucose, protein, and lactate levels. These investigations play a crucial role in differentiating acute bacterial meningitis from other forms of acute meningitis, including viral meningitis. Moreover, culture and/or molecular tests may not be routinely or readily available, accessible or affordable, especially in resource-limited settings, further emphasizing the importance of additional CSF investigations in the diagnostic and treatment approach to individuals with suspected meningitis.
Desirable effects
Judgement: Large The judgement was based on the available evidence as well as additional inputs from the Guideline Development Group (GDG): • Sensitivity varied based on CSF investigation (from low to moderate to high), indicating differences in the ability to accurately identify individuals with bacterial meningitis when used alone. • CSF investigations demonstrated moderate to very high specificity, indicating varied ability to accurately identify individuals who do not have bacterial meningitis when used alone. • While the systematic review focused on the diagnostic performance of individual CSF investigations, the GDG highlighted the benefits of a combined, integrated approach to the interpretation of CSF findings, which can assist the differential diagnosis by providing results in a relatively short turnaround time.
Source of evidence
A systematic review was conducted to assess the diagnostic performance of CSF investigations.

Direct evidence

The following estimates refer to the performance of each individual test in diagnosing acute bacterial meningitis.

CSF Gram stain

- High-certainty evidence showed that CSF Gram stain had moderate to high sensitivity (6 studies/1962 patients, pooled effect: 85%, 95% CI 55–96%); moderate-certainty evidence suggested that it likely had very high specificity (1 study/131 patients, 99%, 95% CI not reported).
- Moderate-certainty evidence suggested that CSF Gram stain likely had high positive likelihood ratio (LR+) (1 study/131 patients, 88.4, 95% CI not reported) and low negative likelihood ratio (LR-) (1 study/131 patients, 0.09, 95% CI not reported).

CSF white blood cells (WBCs)

- High-certainty evidence showed that CSF WBC count had moderate sensitivity (12 studies/1634 patients, pooled effect: 77%, 95% CI 74–81%) and moderate to high specificity (12 studies/1643 patients, pooled effect: 83%, 95% CI 75–92%).
- High-certainty evidence showed that CSF WBC count had moderate LR+ (12 studies/1634 patients, median: 6.39, range: 1.45–64), and moderate LR- (12 studies/1634 patients, median: 0.28, range: 0.21–0.73).

CSF neutrophils

- Moderate-certainty evidence suggested that CSF neutrophil count likely had moderate to high sensitivity (10 studies/6013 patients, pooled effect: 82%, 95% CI 70–94%); high-certainty evidence showed that it had moderate to high specificity (10 studies/6013 patients, pooled effect: 84%, 95% CI 77–90%).
- Moderate-certainty evidence suggested that CSF neutrophil count likely had moderate to high positive predictive value (PPV) and low to very high negative predictive value (NPV): PPV was reported in 2 studies (1341 patients) ranging from 72% (95% CI 66–78%) to 89% (95% CI not reported); NPV was also reported in 2 studies (1341 patients) ranging from 48% (95% CI not reported) to 97% (95% CI 96–99%).
- High-certainty evidence showed that CSF neutrophil count had low LR+ (10 studies/6013 patients, median: 3.58, range: 2.28–9.1), and moderate LR- (10 studies/6013 patients, median: 0.17, range: 0–0.83).

CSF mononuclear cells

- Moderate-certainty evidence suggested that CSF mononuclear cell count likely had moderate to low sensitivity (2 studies/265 patients, pooled effect: 64%, 95% CI 19.7–100%), and moderate to high specificity (2 studies/265 patients, pooled effect: 88.4%, 95% CI 80–97%).

- Moderate-certainty evidence from 1 study (131 patients) showed that CSF mononuclear cell count likely had moderate LR+ (5.1, 95% CI not reported) and moderate LR- (0.18, 95% CI not reported).

CSF neutrophil-to-lymphocyte ratio

- High-certainty evidence showed that CSF neutrophil-to-lymphocyte ratio had moderate to high sensitivity (2 studies/4687 patients, pooled effect: 87%, 95% CI 82–92%), and moderate specificity (2 studies/4687 patients, pooled effect: 78%, 95% CI 74–82%).
- High-certainty evidence showed that CSF neutrophil-to-lymphocyte ratio had low LR+ (2 studies/4687 patients, range: 3.60–4.16), and moderate LR- (2 studies/4687 patients, range: 0.13–0.19).

CSF glucose

- Low-certainty evidence suggested that CSF glucose concentration may have had moderate to low sensitivity (8 studies/3336 patients, pooled effect: 66%, 95% CI 52–79%); high-certainty evidence showed that it had moderate to high specificity (8 studies/3336 patients, pooled effect: 85%, 95% CI 72–98%).
- Moderate-certainty evidence suggested that CSF glucose concentration likely had moderate to high PPV (1 study/623 patients, 89%, 95% CI not reported), and low NPV (1 study/623 patients, 37%, 95% CI not reported).
- High-certainty evidence showed that CSF glucose concentration had high LR+ (8 studies/3336 patients, median: 10.49, range: 1.13–16.63), and moderate LR- (8 studies/3336 patients, median: 0.38, range: 0.16–0.83).

CSF-to-blood glucose ratio

- High-certainty evidence showed that CSF-to-blood glucose ratio had moderate to high sensitivity (6 studies/488 patients, pooled effect: 88%, 95% CI 83–93%); moderate-certainty evidence showed that it likely had moderate specificity (6 studies/488 patients, pooled effect: 78%, 95% CI 52–100%).
- High-certainty evidence showed that CSF-to-blood glucose ratio had moderate LR+ (6 studies/488 patients, median: 5, range: 1.07–60), and moderate LR- (6 studies/488 patients, median: 0.21, range: 0.08–0.60).

CSF protein

- High-certainty evidence showed that CSF protein concentration had moderate to high sensitivity (12 studies/1974 patients, pooled effect: 86%, 95% CI 80–92%), and moderate specificity (12 studies/1974 patients, pooled effect: 79%, 95% CI 70–88%).

- Moderate-certainty evidence suggested that CSF protein concentration likely had moderate to high PPV (1 study/623 patients, 84%, 95% CI not reported), and low NPV (1 study/623 patients, 60%, 95% CI not reported).
- High-certainty evidence showed that CSF protein concentration had low LR+ (12 studies/1974 patients, median: 3.75, range: 1.65–16.95), and moderate LR- (12 studies/1974 patients, median: 0.18, range: 0–0.54).

CSF lactate

- High-certainty evidence showed that CSF lactate concentration had high sensitivity (6 studies/1166 patients, pooled effect: 94%, 95% CI 91–98%), and moderate to high specificity (6 studies/1166 patients, pooled effect: 86%, 95% CI 74–98%).
- Moderate-certainty evidence suggested that CSF lactate concentration likely had high PPV (1 study/154 patients, 94%, 95% CI 79–98%), and moderate to high NPV (1 study/154 patients, 86%, 95% CI 72–97%).
- High-certainty evidence showed that CSF lactate concentration had moderate LR+ (6 studies/1166 patients, median: 5.53, range: 2.54–10.1), and low LR- (6 studies/1166 patients, median: 0.05, range: 0–0.13).

Additional evidence

CSF Gram stain

Evidence from the guidelines by the European Society of Microbiology and Infectious Diseases (ESCMID) on acute bacterial meningitis (van de Beek et al. 2016) showed that CSF Gram stain had very high specificity (approaching 100%) if the hospital's infrastructure and the experience of the assessor were optimal and varying sensitivity (93% for *Streptococcus pneumoniae,* 30–89% for *Neisseria meningitidis*, 25–65% for *Haemophilus influenzae* type b, 10–25% for *Listeria monocytogenes,* 80–90% for *Streptococcus agalactiae,* 20–44% for *Staphylococcus aureus,* 66–73% for *Streptococcus pyogenes,* 50% for *Streptococcus suis*).

CSF lactate

Additional evidence from a meta-analysis performed on the diagnostic use of CSF lactate concentration in the differentiation of bacterial meningitis from other types of meningitis showed high diagnostic accuracy (Sakushima et al. 2011). The meta-analysis included 33 studies with 1885 patients (adults and children) and demonstrated a pooled sensitivity of 93% (95% CI 89–96%), pooled specificity of 96% (95% CI 93–98%), pooled LR+ of 22.9 (95% CI 12.6–41.9), and a pooled LR- of 0.07 (95% CI 0.05–0.12). In patients receiving antimicrobial treatment prior to lumbar puncture (LP), CSF lactate concentration had a lower sensitivity (49%) compared to those not receiving antimicrobial treatment before lumbar puncture (98%). The conclusions were therefore consistent across the two presented bodies of evidence and showed excellent sensitivity and

good specificity of CSF lactate for diagnosing acute bacterial meningitis in a selected subset of individuals with suspected acute meningitis.

Undesirable effects

Judgement: Trivial

The judgement was based on the available evidence as well as additional inputs from GDG:

- Sensitivity varied based on CSF investigation (from low to moderate to high), indicating differences in the ability to accurately identify individuals with bacterial meningitis when used alone.
- CSF investigations demonstrated moderate to very high specificity, indicating varied ability to accurately identify individuals who do not have bacterial meningitis when used alone.
- CSF tests are seldom performed in isolation for diagnostic purposes. Instead, the combined use and interpretation of these tests, along with clinical judgement and possibly other diagnostic tools, contributes to mitigating and/or minimizing the risks associated with the diagnostic performance of individual investigations (i.e. risk of false negatives and/or false positives).

Source of evidence

A systematic review was conducted to assess the diagnostic performance of CSF investigations.

Direct evidence

Outcome-specific data are presented above. No additional undesirable effects were investigated.

Certainty of the evidence

Judgement: Moderate

The certainty of evidence was moderate for the outcomes of most test parameters.

Values

Judgement: Probably no important uncertainty or variability

Based on the available evidence and their knowledge and experience, the GDG agreed that there probably was no important uncertainty or variability regarding the value of each of the main outcomes.

Source of evidence

A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.

Direct evidence

No direct evidence was identified regarding the uncertainty about or variability in how much people value the main outcomes. However, the synthesis of community perceptions and attitudes towards meningitis diagnostic tests in low- and middle-income countries (LMICs), as reflected in the literature, is provided as part of the indirect evidence.

Indirect evidence

LMICs

Meningitis is universally recognized as a potentially fatal condition that can result in severe sequelae, disability and death, particularly when care is not timely (3 studies, moderate confidence).

Some studies highlighted a recognition among patients and caregivers of the importance of health services. Health-care facilities were acknowledged as a place to seek help and conventional medicine was valued as the most effective in diagnosis and treatment. Despite this recognition, the uptake of health services, including potentially life-saving procedures such as LP, was hindered by several barriers strongly linked with community values and beliefs. Evidence from 4 studies in which participants from different LMICs were interviewed (including adult patients, carers of adult and paediatric patients, and community members) suggested that a major barrier was related to traditional beliefs and scepticism in the communities about orthodox medicine. The perception of meningitis by most patients and caregivers as having spiritual causes, which should be treated with "traditional" rather than "orthodox" medicine, highlighted a conflict between cultural values and the acceptance of conventional medical practices (4 studies, moderate confidence).

Additionally, a single study reflected patients' experience of suboptimal health services, including long waiting times, insufficient examination and verbal mistreatment (2 studies, very low confidence). Fear of paralysis or death were cited by most patients/caregivers as reasons to refuse LP. Specifically, death was attributed to late procedure uptake or poor overall condition, while the position during and/or after the procedure was associated with paralysis as an outcome (1 study, moderate confidence).

Balance of effects

Judgement: Favours the intervention

The judgement was based on the evidence and judgements presented above.

Resources required
Judgement: Moderate costs
Source of evidence A scoping review was undertaken to compile information regarding costs, resource utilization and cost-effectiveness associated with meningitis diagnosis, treatment and management of sequelae.
Direct evidence The included studies found some limited but not very recent evidence of CSF testing costs in LMICs and high-income countries (HICs). *LMICs* The scoping review identified 2 studies providing information on the cost of CSF testing. In children under 5 years of age with meningitis in 7 Kenyan hospitals, the unit cost for basic CSF analysis and lumbar puncture laboratory supplies was US$ 14.69 and US$ 1.4 (2005 US$), respectively. In 1 hospital in Gambia, the unit cost of CSF examination was US$ 45.88 (2010 US$). One retrospective analysis examined the cost of case-based surveillance in Niger. The system was based on the performance of LP and the collection and analysis of CSF specimens for each suspected meningitis case. Laboratory resources accounted for 19% (US$ 374 816 at 2012 US$) of the aggregated national cost of meningitis surveillance. *HICs* The scoping review identified 2 retrospective cohort studies from the United States of America providing information on the unit cost of CSF testing in hospitalized infants and children with suspected meningitis who received an LP. The first study, conducted from 1990 to 1993, reported a cost of US$ 61 for Gram stain, culture and antimicrobial susceptibility testing, US$ 32 for cell count and differential, and US$ 54 for protein and glucose analysis. The second study reported a mean (±standard deviation [SD]) unit cost in 2015 US$ of Gram stain, leukocyte count and differential, glucose and protein of 36 (±26), 28 (±22), 13 (±12) and 16 (±15), respectively, in infants. In children, the mean (± SD) unit cost in 2015 US$ of Gram stain, leukocyte count and differential, glucose and protein was 33 (±25), 41 (±49), 13 (±11) and 14 (±12), respectively.
Certainty of the evidence on resources required
Judgement: Very low The judgement reflected several limitations in the available evidence, including the lack of a comprehensive evaluation of all resource use items, the absence of comparison between different tests and resource use and the variability in costs across settings.

Cost-effectiveness
Judgement: No included studies A scoping review was undertaken to compile information regarding costs, resource utilization and cost-effectiveness associated with meningitis diagnosis, treatment and management of sequelae. However, no cost-effectiveness studies were found that would be applicable to this guideline question.
Health equity, equality and non-discrimination
Judgement: Probably increased Based on the available indirect evidence and their knowledge and experience, the GDG agreed that increased high-quality, effective, safe and affordable diagnostics is likely to contribute to reducing equity gaps and discrimination in health-care access, especially in resource-limited settings.
Source of evidence A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.
Direct evidence None of the included qualitative studies directly focused on health equity, equality or non-discrimination in relation to CSF investigations. However, the main relevant findings on health services for meningitis diagnosis are summarized as part of the indirect evidence.
Indirect evidence *LMICs* None of the studies directly assessed the impact of diagnosis services for meningitis on health equity, equality or non-discrimination in LMICs. However, accessibility of LP could be limited due to informational barriers. Some patients and caregivers cited a lack of information from health-care workers about the procedure as a reason to refuse LP. All stakeholders, including patients, caregivers and health-care workers, highlighted a need for further education about LP (1 study, low confidence). Some qualitative studies reported the lack of affordability of health services for patients and carers. Financial constraints acted as a barrier to initiating help-seeking, including transportation to health-care facilities, and often prompted patients and caregivers to seek alternative treatments (3 studies, moderate confidence).

HICs

None of the studies conducted in HICs directly assessed the impact of diagnostic procedures for meningitis on health equity, equality or non-discrimination. A single study identified several barriers that hindered access to health services. Among these, some caregivers expressed reluctance to seek help, fearing the potential misuse or overuse of health-care resources, which in turn delayed the decision to seek medical attention (1 study, low confidence). Furthermore, parents often hesitated to access timely care due to uncertainty about the severity of the illness (1 study, moderate confidence).

Information access emerged as a significant limitation in several studies. Caregivers frequently reported not knowing enough about the symptoms and consequences of meningitis, underscoring a pressing need for readily accessible information about their children's health conditions. Often, parents were more likely to notice their child's overall poor health rather than specific warning signs of meningitis. In addition, carers described a lack of communication and support and expressed dissatisfaction with the health-care workers' complex use of medical jargon, which often complicated understanding (5 studies, low confidence).

Feasibility

Judgement: Probably yes

Based on the available evidence and their knowledge and experience, the GDG agreed that CSF laboratory tests should be routinely feasible across the continuum of care, including in peripheral health-care facilities and district hospitals. Where not available, CSF samples should be collected and appropriately transported to higher-level laboratories.

The feasibility of these tests can be limited in settings where lumbar puncture is not widely or immediately accessible. However, the GDG emphasized that the implementation of capacity-building initiatives and training activities for the health-care workforce and laboratory personnel could contribute to addressing some of the well known barriers to performing LP in low-resource settings, including the lack of a trained health-care workforce and inadequate infection prevention and control practices in health-care facilities.

Source of evidence

A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.

Direct evidence

None of the included qualitative studies directly focused on the feasibility of CSF investigations. However, the main relevant findings on health services for meningitis diagnosis are summarized as part of the indirect evidence.

Indirect evidence

LMICs

Several barriers limiting LP's feasibility were identified in studies conducted in LMICs. Health-care workers reported poor organization of health care, including poor hospital logistics, lack of sterility, lack of time and need for a computed tomography (CT) scan prior to LP (1 study, moderate confidence).

Lack of knowledge about contraindications was considered a barrier to performing a LP by some doctors. Additionally, some health-care workers questioned doctors' expertise and cited this as a reason they would refuse LP themselves (1 study, low confidence).

However, several factors improved LP feasibility. Doctors reported that modifying the consent process was considered a facilitator for LP uptake. Minimizing or omitting risks during the consent process allowed doctors to increase the likelihood of obtaining consent. Other practices included omitting written consent, obtaining only verbal consent and shortening or skipping the process to save patient care time. Health-care workers believed that effective communication through simple explanations and multiple conversations about LP increased the probability of obtaining consent. Also, during communication with patients/caregivers, they emphasized that LP was necessary to make accurate diagnoses (1 study, moderate confidence).

Human rights and sociocultural acceptability

Judgement: Varies

Based on the available evidence and their knowledge and experience, the GDG agreed that sociocultural acceptability of LP and CSF diagnostic tests may vary across different settings.

Source of evidence

A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services

Direct evidence

None of the included qualitative studies directly focused on the compliance of CSF investigations with universal human rights standards or its sociocultural acceptability. However, some aspects which influenced the ability of patients/caregivers to make a competent, informed and voluntary decision regarding LP are summarized as part of the indirect evidence.

Indirect evidence

LMICs

Health-care workers reported the practices they used to obtain consent for LP from patients/caregivers. First, consent was provided only verbally, as it was the norm for LP in this area. By omitting written consent, health-care workers believed they could prevent patients from having misconceptions. While consent was obtained only verbally, refusal of LP was formally documented in medical records. Second, health-care workers prioritized patient care over the consent process to save time. While some entirely skipped the consent process, others modified it to obtain consent more rapidly. Finally, they recalled manipulating (i.e. minimizing or omitting) discussion of the risks of LP during the consent process to reduce the probability of LP refusal (1 study, moderate confidence).

Further to this, it was found that patients and carers of adult and paediatric patients perceived LP as a potentially fatal procedure associated with adverse outcomes. Most notably, the fear of paralysis or death emerged as dominant concerns, acting as a primary deterrent against the uptake of the procedure. These fears were not unfounded in the minds of the patients and carers, many of whom reported being personally acquainted with individuals who had suffered poor outcomes following an LP. The attribution of death to delayed procedure uptake or a patient's poor overall condition, along with concerns that the patient's position during or after the procedure could lead to paralysis, highlighted a significant barrier to LP acceptance (1 study, moderate confidence).

Furthermore, the study revealed an apprehension by health-care workers about iatrogenic infections resulting from the LP procedure. This fear of infection served as a testament to the broader apprehensions surrounding the safety and potential complications of LP, particularly in settings where health-care resources and procedural standards may have varied (1 study, very low confidence).

While LP was generally more acceptable to caregivers when the patient's overall health condition was deteriorating, health-care workers were hesitant to perform LP in terminal cases. This reluctance stemmed from concerns that other patients or caregivers might perceive a patient's death following the procedure as proof of LP's inherent risks or fatality (1 study, low confidence).

The accumulation of these fears and perceived risks significantly impacted the decision-making process for patients and caregivers, leading to a reluctance or outright refusal to undergo LP. This resistance was further fuelled by second-hand experiences with adverse outcomes, which deeply influenced perceptions of the procedure's safety and efficacy (1 study, moderate confidence).

CT: computed tomography; CSF: cerebrospinal fluid; GDG: Guideline Development Group; HICs: high-income countries; LMICs: low- and middle-income countries; LP: lumbar puncture; LR+/-: positive/negative likelihood ratio; NPV: negative predictive value; PCR: polymerase chain reaction; PPV: positive predictive value; SD: standard deviation.

2. Cerebrospinal fluid molecular testing

2.1 Guideline question

In individuals with suspected acute meningitis, should CSF polymerase chain reaction (PCR) be performed?

Population: Suspected cases of acute meningitis

Index test: CSF PCR

Reference standard: Consensus diagnosis excluding index test[2]

Outcome: *Critical*: Sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of index test

Full details of the evidence, including references, are provided in Web Annex A (2a and 2b. Cerebrospinal fluid molecular testing) and Web Annex B (Qualitative and economic evidence reports).

[2] Consensus diagnosis excluding index test is defined as clinical characteristics (including peripheral WBC count, C-reactive protein, procalcitonin), CSF characteristics (Gram stain, leukocyte count and differential, glucose, total protein, lactate), blood culture and CSF culture.

2.2 Evidence-to-Decision framework

Priority of the problem
Judgement: Yes Acute meningitis is a life-threatening condition that requires timely and accurate diagnosis to ensure appropriate patient management. The increasing availability and use of nucleic acid amplification tests, including individual and panel-based (multiplex) tests, have revolutionized the diagnostic approach to meningitis. Where available, polymerase chain reaction (PCR)-based tests on cerebrospinal fluid (CSF) samples allow for pathogen identification (both bacteria and viruses) and are often used to confirm the diagnosis of bacterial meningitis (alongside culture and antimicrobial susceptibility testing). Nevertheless, in spite of significant advancements in test design, some limitations in diagnostic accuracy remain, highlighting the importance of having evidence-based recommendations on the use of molecular tests in clinical settings.
Desirable effects
Judgement: Large Based on the available evidence and their clinical knowledge and experience, the Guideline Development Group (GDG) highlighted the benefits of PCR-based tests for pathogen identification. Individual PCR testing is highly sensitive and specific across the most common bacterial pathogens, while the diagnostic performance is lower for enteroviruses. Multiplex PCR testing demonstrates an overall high diagnostic yield, but sensitivity and specificity may vary substantially based on the causative pathogen and setting. Most studies identified in the systematic reviews used CSF culture as the reference standard. The GDG highlighted the inherent challenge of estimating the diagnostic performance of CSF PCR when sample transportation and preservation practices may be suboptimal and/or prior antimicrobial treatment may have sterilized the specimen. Under such circumstances, the sensitivity of CSF culture may be affected, leading to negative results despite CSF characteristics and clinical signs suggestive of bacterial meningitis.
Source of evidence
A systematic review was conducted to assess the diagnostic performance of individual PCR tests by integrating empirical evidence from both low- and middle-income countries (LMICs) and high-income countries (HICs). In addition, an evidence synthesis on the diagnostic performance of

multiplex PCR in HICs was performed by extracting relevant studies from a separate systematic review (NICE, 2024).

Direct evidence on individual PCR

Streptococcus pneumoniae

- High-certainty evidence showed that CSF PCR (individual) had high sensitivity (90%, 95% CI 70–100%; 2 studies/2440 patients) and very high specificity (97%, 95% CI 93–100%, 2 studies/2440 patients).
- Low-certainty evidence suggested that CSF PCR (individual) may have had moderate to low positive predictive value (PPV) (36%, 95% CI 22–52%; 1 study/2006 patients); moderate-certainty evidence suggested that it likely had very high negative predictive value (NPV) (100%, 95% CI 99–100%; 1 study/2006 patients).
- High-certainty evidence showed that CSF PCR (individual) had high positive likelihood ratio (LR+) (15.8–71.1; 2 studies/2440 patients) and moderate to low negative likelihood ratio (LR-) (0.0–0.22; studies/2440 patients).

Neisseria meningitidis

- Moderate-certainty evidence showed that CSF PCR (individual) likely had high sensitivity (95%, 95% CI 91–99%; 2 studies/484 patients) and high specificity (94%, 95% CI 92–97%; 2 studies/484 patients).
- Moderate-certainty evidence showed that CSF PCR (individual) likely had moderate to high PPV (81%, 95% CI 74–88%; 2 studies/484 patients) and very high NPV (99%, 95% CI 98–100%; 2 studies/484 patients).
- Moderate-certainty evidence suggested that CSF PCR (individual) likely had high LR+ (9.1–19; 2 studies/484 patients) and moderate to low LR- (0.05–0.1; 2 studies/484 patients).

Haemophilus influenzae (type b)

- Moderate-certainty evidence showed that CSF PCR (individual) likely had moderate to high sensitivity (81%, 1 study/434 patients) and very high specificity (97%,1 study/44 patients).
- Moderate-certainty evidence suggested that CSF PCR (individual) likely had low PPV (54%, 1 study/434 patients) and very high NPV (99%, 1 study/434 patients).
- Moderate-certainty evidence suggested that CSF PCR (individual) likely had high LR+ (27, 1 study/434 patients) and moderate LR- (0.2, 1 study/434 patients).

Listeria monocytogenes

- Moderate-certainty evidence showed that CSF PCR (individual) likely had very high sensitivity (100%, 1 study/24 patients) and moderate to low specificity (67%, 1 study/24 patients).

- Low-certainty evidence suggested that CSF PCR (individual) may have had moderate to low PPV (64%, 1 study/24 patients); moderate-certainty evidence suggested that it likely had very high NPV (100%, 1 study/24 patients).
- Moderate-certainty evidence suggested that CSF PCR (individual) likely had low LR+ (3.03, 1 study/24 patients) and low LR- (0, 1 study/24 patients).

Enteroviruses

- High certainty evidence showed that CSF PCR (individual) had moderate to high sensitivity (12 studies/1256 patients; pooled effect: 89%, 95% CI 81–96%) and moderate specificity (12 studies/1256 patients; pooled effect: 79%, 95% CI 68–91%).
- Low-certainty evidence suggested that CSF PCR (individual) may have had moderate PPV (5 studies/771 patients; pooled effect: 72%, 95% CI 46–97%); moderate-certainty evidence showed that it likely had high NPV (5 studies/771 patients; pooled effect: 94%, 95% CI 87–100%).
- High-certainty evidence showed that CSF PCR (individual) had low LR+ (12 studies/1256 patients; median: 2.90, range: 1.29–164.3) and moderate LR- (12 studies/1256 patients; median: 0.19, range: 0–0.69).

Borrelia burgdorferi

- Moderate-certainty evidence suggested that CSF PCR (individual) likely had low sensitivity (5%, 95% CI 0–25%; 1 study/108 patients) and very high specificity (99%, 95% CI 93–99%; 1 study/108 patients).
- Moderate-certainty evidence suggested that CSF PCR (individual) likely had low PPV (50%, 1 study/108 patients) and moderate to high NPV (82%, 1 study/108 patients).
- Moderate-certainty evidence suggested that CSF PCR (individual) likely had low LR+ (4.7, 1 study/108 patients) and high LR- (0−96, 1 study/108 patients).

Direct evidence on multiplex PCR

Streptococcus pneumoniae

- Low-certainty evidence suggested that CSF PCR (multiplex) may have had very high sensitivity (9 studies/6137 patients; pooled effect: 98%, 95% CI 93–100%).
- Moderate-certainty evidence suggested that CSF PCR (multiplex) likely had very high specificity (9 studies/6137 patients; pooled effect: 99%, 95% CI 99–100%).

Neisseria meningitidis

- Low-certainty evidence suggested that CSF PCR (multiplex) may have had very high sensitivity (7 studies/4483 patients; pooled effect: 99%, 95% CI 91–100%).

- Moderate-certainty evidence suggested that CSF PCR (multiplex) likely had very high specificity (7 studies/4483 patients; pooled effect: 100%, 95% CI 100–100%).

Haemophilus influenzae (type b)

- Low-certainty evidence suggested that CSF PCR (multiplex) may have had very high sensitivity (5 studies/3822 patients; pooled effect: 100%, 95% CI 97–100%).
- Moderate-certainty evidence suggested that CSF PCR (multiplex) likely had very high specificity (5 studies/3822 patients; pooled effect: 96%, 95% CI 87–100%).

Listeria monocytogenes

- Low-certainty evidence suggested that CSF PCR (multiplex) may have had very high sensitivity (4 studies/1510 patients; pooled effect: 100%, 95% CI 70–100%).
- Moderate-certainty evidence suggested that CSF PCR (multiplex) likely had very high specificity (4 studies/1510 patients; pooled effect: 100%, 95% CI 100–100%).

Streptococcus agalactiae

- Low-certainty evidence suggested that CSF PCR (multiplex) may have had very high sensitivity (4 studies/2109 patients; pooled effect: 96%, 95% CI 76–100%).
- Moderate-certainty evidence suggested that CSF PCR (multiplex) likely had very high specificity (4 studies/2109 patients; pooled effect: 100% (95% CI 100–100%).

Escherichia coli

- Low-certainty evidence suggested that CSF PCR (multiplex) may have had very high sensitivity (4 studies/3623 patients; pooled effect: 100%, 95% CI 78–100%).
- Moderate-certainty evidence suggested that CSF PCR (multiplex) likely had very high specificity (4 studies/3623 patients; pooled effect: 100% (95% CI 100–100%).

Additional evidence

The findings from another recent systematic review on multiplex PCR (Filmarray Meningitis/Encephalitis panel) including 19 studies with over 11 000 patients from both LMICs and HICs were considered relevant and are summarized below (Trujillo-Gomez et al. 2022). Notably, the systematic review did not provide sufficient detail to enable data extraction and integration with the evidence report on multiplex PCR, and the certainty of evidence was assessed as low for all outcomes.

All bacteria

- The sensitivity pooled across 16 studies (6183 patients) was 89.5% (95% CI 81.1–94.4%) or 92.1% (95% CI 86.8–95.3%) using culture or adjudicated diagnosis as 2 reference standards, respectively.

- The specificity pooled across 16 studies (6183 patients) was 97.4% (95% CI 94–98.9%) and 99.2% (95% CI 98.3–99.6%), using culture or adjudicated diagnosis as 2 reference standards, respectively.

Streptococcus pneumoniae

- The sensitivity pooled across 16 studies (7090 patients) was 87.5% (95% CI 77%–94%) or 93% (95% CI 83.3%–97.2%) using culture or adjudicated diagnosis as 2 reference standards, respectively.
- The specificity pooled across 16 studies (7090 patients) was 98.5% (95% CI 97%–99.3%) or 99.4% (95% CI 98.2%–99.8%), using culture or adjudicated diagnosis as 2 reference standards, respectively.

Neisseria meningitidis

- The sensitivity pooled across 10 studies (3501 patients) was 74.5% (95% CI 52.9–88.4%) or 84.4% (95% CI 53.9–96.2%) using culture or adjudicated diagnosis as 2 reference standards, respectively.
- The specificity pooled across 10 studies (3501 patients) was 99.1% (95% CI 98.6–99.5%) or 99.1% (95 % CI 98.8–99.9%) using culture or adjudicated diagnosis as 2 reference standards, respectively.

Haemophilus influenzae (type b)

- The sensitivity pooled across 10 studies (4959 patients) was 64.9% (95% CI 39.5–84%) or 81.1% (95% CI 55.6–93.6%) using culture or adjudicated diagnosis as 2 reference standards, respectively.
- The specificity pooled across 10 studies (4959 patients) was 99.4% (95% CI 98.9–99.6%) or 99.8% (95% CI 99.5–99.9%) using culture or adjudicated diagnosis as 2 reference standards, respectively.

Listeria monocytogenes

- The sensitivity pooled across 7 studies (1332 patients) was 70.4% (95% CI 40%–89.5%) or 80.4% (95% CI 40.4%–96.1%) using culture or adjudicated diagnosis as 2 reference standards, respectively.
- The specificity pooled across 7 studies (1332 patients) was 98.9% (95% CI 96.9–99.6%) or 99.5% (95% CI 97.8–99.9%) using culture or adjudicated diagnosis as 2 reference standards, respectively.

Streptococcus agalactiae

- The sensitivity pooled across 10 studies (5266 patients) was 71.5% (95% CI 49.6–86.5%) or 81.4% (95% CI 52.3–94.6%) using culture or adjudicated diagnosis as 2 reference standards, respectively.

- The specificity pooled across 10 studies (5266 patients) was 99.5% (95% CI 98.5–99.9%) or 99.4% (95% CI 97.7–99.9%) using culture or adjudicated diagnosis as 2 reference standards, respectively.

Escherichia coli

- The sensitivity pooled across 11 studies (4743 patients) was 70.9 % (95% CI 50.2–85.5%) or 76.3% (95% CI 47.6–91%) using culture or adjudicated diagnosis as 2 reference standards, respectively.
- The specificity pooled across 11 studies (4743 patients) was 99.6% (95% CI 99.1–99.8%) or 99.6% (95% CI 98.7–99.9%) using culture or adjudicated diagnosis as 2 reference standards, respectively.

Enteroviruses

- The sensitivity pooled across 3 studies (6883 patients) was 93.8% (95% CI 87–97.2%) or 99.8% (95% CI 86.1–97.4%) using viral PCR or adjudicated diagnosis as 2 reference standards, respectively.
- The specificity pooled across 3 studies (6883 patients) was 99.3% (95% CI 98.7–99.7%) or 99.9% (99.7–100%) using viral PCR or adjudicated diagnosis as 2 reference standards, respectively.

Herpes simplex virus 1 (HSV-1)

- The sensitivity pooled across 3 studies (6883 patients) was 75.5% (51.2–90.1%) or 78.2% (95% CI 58.1–90.3%) using viral PCR or adjudicated diagnosis as 2 reference standards, respectively.
- The specificity pooled across 3 studies (6883 patients) was 99.9% (95% CI 94.7–100%) or 99.9% (95% CI 99.8–100%) using viral PCR or adjudicated diagnosis as 2 reference standards, respectively.

Herpes simplex virus 2 (HSV-2)

- The sensitivity pooled across 3 studies (6883 patients) was 94.4% (95% CI 83.9–98.2%) or 94.5% (95% CI 84.2–98.2%) using viral PCR or adjudicated diagnosis as 2 reference standards, respectively.
- The specificity pooled across 3 studies (6883 patients) was 99.9% (95% CI 99.7–100%) or 99.9% (95% CI 99.8–100%) using viral PCR or adjudicated diagnosis as 2 reference standards, respectively.

Varicella-Zoster virus (VZV)

- The sensitivity pooled across 4 studies (6897 patients) was 91.4% (95% CI 78.9–96.9%) or 93.3% (95% CI 83.6–97.4%) using viral PCR or adjudicated diagnosis as 2 reference standards, respectively.
- The specificity pooled across 4 studies (6897 patients) was 99.8% (95% CI 98.7–100%) or 99.9%

(95% CI 99.6–100%) using viral PCR or adjudicated diagnosis as 2 reference standards, respectively.

Undesirable effects

Judgement: Varies

Based on the available evidence and their clinical knowledge and experience, the GDG emphasized that the undesirable effects of PCR-based investigations may vary substantially based on the causative pathogen, setting, and type of test. The potential for false positives and negatives remains – especially for certain pathogens – underscoring the importance of interpreting the results in combination with the pre-test probability of infection.

Source of evidence

A systematic review was conducted to assess the diagnostic performance of individual PCR tests by integrating empirical evidence from both LMICs and HICs. In addition, an evidence synthesis on the diagnostic performance of multiplex PCR in HICs was performed by extracting relevant studies from a separate systematic review (NICE, 2024).

Direct evidence

Outcome-specific data are presented above. No additional undesirable effects were investigated.

Certainty of the evidence

Judgement: Low

The certainty of evidence was low for the outcomes of most test parameters.

Values

Judgement: Probably no important uncertainty or variability

Based on the available evidence and their knowledge and experience, the GDG agreed that there probably is no important uncertainty or variability regarding the value of each of the main outcomes.

Source of evidence

A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.

Direct evidence

No direct evidence was identified regarding the uncertainty about or variability in how much people value the main outcomes. However, the synthesis of community perceptions and attitudes towards meningitis diagnostic tests in LMICs, as reflected in the literature, is provided as part of the indirect evidence.

Indirect evidence

LMICs

Meningitis is universally recognized as a potentially fatal condition that can result in severe sequelae, disability and death, particularly when care is not timely (3 studies, moderate confidence).

Some studies highlighted a recognition among patients and caregivers of the importance of health services. Health-care facilities were acknowledged as places to seek help and conventional medicine was valued as the most effective option for diagnosis and treatment. Despite this recognition, the uptake of health services, including potentially life-saving procedures such as LP, was hindered by several barriers strongly linked with community values and beliefs. Evidence from 4 studies in which participants in different LMICs were interviewed (including adult patients, carers of adult and paediatric patients and community members) suggested that a major barrier was related to traditional beliefs and scepticism in the communities about orthodox medicine. The perception of meningitis by most patients and caregivers as having spiritual causes, which should be treated with "traditional" rather than "orthodox" medicine, highlighted a conflict between cultural values and the acceptance of conventional medical practices (4 studies, moderate confidence).

Additionally, a single study reflected patients' experiences of suboptimal health services, including long waiting times, insufficient examination and verbal mistreatment (2 studies, very low confidence). Fear of paralysis or death was cited by most patients/caregivers as a reason to refuse LP. Specifically, death was attributed to late procedure uptake or poor overall condition, while the position during/after the procedure was associated with paralysis as an outcome (1 study, moderate confidence).

Balance of effects

Judgement: Probably favours the intervention

This judgement was based on the evidence and judgements presented above.

Resources required

Judgement: Large costs

Source of evidence

A scoping review was undertaken to compile information regarding costs, resource utilization and cost-effectiveness associated with meningitis diagnosis, treatment and management of sequelae.

Direct evidence

HICs

Overall, 4 studies included information on the cost of CSF PCR in HICs. Three studies reported information on the cost of a real-time multiplex PCR meningitis/encephalitis panel (Filmarray Meningitis/Encephalitis panel, BioFire). The unit cost of the test varied from € 180 in 2018 in France to US$ 191 (2021 US$) in Chile in 2021 and US$ 214.44 in the United States of America in 2015. An additional one-time cost of US$ 35 550 (2015 US$) for the acquisition of the PCR platform was reported in the study conducted in the United States of America. One observational study conducted in Switzerland between 2002 and 2009 utilized a home-made PCR and a GeneXpert Enterovirus Assay for rapid detection of enterovirus in CSF in patients with aseptic meningitis reporting a cost of US$ 114 and 121 (2009 US$), respectively.

Certainty of the evidence on resources required

Judgement: Very low

The judgement reflected the limitations in directly applying cost data from HICs to LMICs, the partial identification of cost components relevant to LMICs, and the variability in costs across settings. It also acknowledges the lack of a comprehensive evaluation of the evidence quality, making it difficult to fully assess the financial implications of using CSF PCR for meningitis diagnosis in LMICs.

Cost-effectiveness

Judgement: Probably favours the intervention

Source of evidence

A scoping review was undertaken to compile information regarding costs, resource utilization and cost-effectiveness associated with meningitis diagnosis, treatment and management of sequelae.

Direct evidence

HICs

The scoping review identified 5 studies providing information on the cost-effectiveness of CSF PCR in HICs. Three studies evaluated cost savings associated with the use of multiplex real-time PCR meningoencephalitis panel and the overall cost savings varied across different regions. In Chile, the implementation of CSF PCR saved between US$ 2916 and US$ 12 240 (2021 US$) in the cost of intensive care unit (ICU) bed-days over 14 months. Additionally, the study showed an

improvement in quality of care with respect to an increase in positive identification of the etiology in central nervous system infections, ranging from 2.6% to 28.1% in infants under 6 months of age, and from 5.9% to 20.8% in infants and children older than 6 months. In France, the use of this diagnostic technology saved € 26 242 over 1 year (2016–2017), taking into account the multiplex PCR tests acquisition cost. In Greece, the total benefit in hospitalization cost for the group of children who had their CSF tested with multiplex PCR was calculated at € 22 834 over 1 year (2018–2019). Two studies evaluated cost-savings associated with rapid detection of enterovirus in CSF. In Switzerland, the use of a PCR-based assay for enterovirus meningitis (GeneXpert Enterovirus Assay) was associated with a median cost reduction of hospitalization costs of US$ 4537 (2009 US$) compared to patients with no PCR or negative PCR. In the Kingdom of the Netherlands, the use of a rapid enterovirus molecular test showed an average cost reduction per patient of more than US$ 1450 (2007–2009).

Health equity, equality and non-discrimination

Judgement: Probably increased

Based on the available evidence and their knowledge and experience, the GDG agreed that increased high-quality, effective, safe and affordable diagnostics, including molecular tests, is likely to contribute to reducing equity gaps and discrimination in health-care access, especially in resource-limited settings.

Source of evidence

A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.

Direct evidence

None of the included qualitative studies directly focused on health equity, equality or non-discrimination in relation to CSF investigations. However, the main relevant findings on health services for meningitis diagnosis are summarized as part of the indirect evidence.

Indirect evidence

LMICs

Accessibility of LP may be limited due to informational barriers. Some patients and caregivers cited a lack of information from healthcare workers about the procedure as a reason to refuse LP. All stakeholders, including patients, caregivers and health-care workers, highlighted a need for further education about LP (1 study, low confidence).

Some qualitative studies reported the lack of affordability of health services for patients and carers. Financial constraints acted as a barrier to initiating help-seeking, including transportation

to health-care facilities, and often prompted patients and caregivers to seek alternative treatments (3 studies, moderate confidence).

HICs

A single study identified several barriers that hindered access to health services. Among these, some caregivers expressed reluctance to seek help, fearing the potential misuse or overuse of health-care resources, which in turn delayed the decision to seek medical attention (1 study, low confidence). Furthermore, parents often hesitated to access timely care due to uncertainty about the severity of the illness (1 study, moderate confidence).

Information access emerged as a significant limitation in several studies. Caregivers frequently reported not knowing enough about the symptoms and consequences of meningitis, underscoring a pressing need for readily accessible information about their children's health conditions. Often, parents were more likely to notice their child's overall poor health rather than specific warning signs of meningitis. In addition, carers described a lack of communication and support and expressed dissatisfaction with health-care workers' complex use of medical jargon, which often complicated understanding (5 studies, low confidence).

Feasibility

Judgement: Varies

Further to the themes identified in the qualitative evidence review, several barriers may contribute to limiting the feasibility of PCR testing on CSF samples, with significant variations across different settings, countries and regions based on available technical, infrastructural and financial resources.

Adequate laboratory infrastructure across the health-care system and a context-appropriate, national testing strategy with clearly defined sample pathways are required to facilitate access to meningitis diagnosis, including molecular testing. However, these might not be systematically available or well-established, especially in resource-limited settings and LMICs. In addition, the well known barriers hindering LP performance in low-resource settings can negatively impact molecular testing of CSF samples. These include the lack of trained health-care workforce, inadequate infection prevention and control practices in health-care facilities, lack of specimen transportation materials, low acceptability of LP within communities and financial constraints.

Source of evidence

A qualitative evidence review focused on end users’ values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.

Direct evidence

None of the included qualitative studies directly focused on the feasibility of CSF investigations. However, the main relevant findings on health services for meningitis diagnosis are summarized as part of the indirect evidence.

Indirect evidence

LMICs

Several barriers limiting LP's feasibility were identified in studies conducted in LMICs. Health-care workers reported poor organization of health care, including poor hospital logistics, lack of sterility, lack of time and need for a computed tomography (CT) scan prior to LP (1 study, moderate confidence).
Lack of knowledge about contraindications was considered a barrier to performing LP by some doctors. Additionally, some health-care workers questioned doctors' expertise and cited this as a reason they would refuse LP themselves (1 study, low confidence).
However, several factors improved LP feasibility. Doctors reported that modifying the consent process was considered a facilitator for LP uptake. Minimizing or omitting risks during the consent process allowed doctors to increase the likelihood of obtaining consent. Other practices included omitting written consent, obtaining only verbal consent and shortening or skipping the process to save patient care time. Health-care workers believed that effective communication through simple explanations and multiple conversations about LP increased the probability of obtaining consent. Also, during communication with patients/caregivers, they emphasized that LP was necessary to make accurate diagnoses (1 study, moderate confidence).

Human rights and sociocultural acceptability

Judgement: Varies

Based on the available evidence and their knowledge and experience, the GDG agreed that sociocultural acceptability of LP and CSF diagnostic tests may vary across different settings.

Source of evidence

A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.

Direct evidence

None of the included qualitative studies directly focused on the compliance of CSF investigations with universal human rights standards or its sociocultural acceptability. However, some aspects which influenced the ability of patients/caregivers to make a competent, informed and voluntary decision regarding LP are summarized as part of the indirect evidence.

Indirect evidence

LMICs

Health-care workers reported the practices they used to obtain consent for LP from patients/caregivers. First, consent was provided only verbally, as it was the norm for LP in this area. By omitting written consent, health-care workers believed they could prevent patients from having misconceptions. While consent was obtained only verbally, LP refusal was formally documented in medical records. Second, health-care workers prioritized patient care over the consent process to save time. While some entirely skipped the consent process, others modified it to obtain consent more rapidly. Finally, they recalled manipulating (i.e. minimizing or omitting) discussion of the risks of LP during the consent process to reduce the probability of LP refusal (1 study, moderate confidence).

Further to this, it was found that patients and carers of adult and paediatric patients perceived LP as a potentially fatal procedure associated with adverse outcomes. Most notably, the fear of paralysis or death emerged as a dominant concern, acting as a primary deterrent against the uptake of the procedure. These fears were not unfounded in the minds of the patients and carers, many of whom reported being personally acquainted with individuals who had suffered poor outcomes following an LP. The attribution of death to delayed procedure uptake or a patient's poor overall condition, along with concerns that the patient's position during or after the procedure could lead to paralysis, highlighted a significant barrier to LP acceptance (1 study, moderate confidence).

Furthermore, the study revealed an apprehension by health-care workers about iatrogenic infections resulting from the LP procedure. This fear of infection served as a testament to the broader apprehensions surrounding the safety and potential complications of LP, particularly in settings where health-care resources and procedural standards may have varied (1 study, very low confidence).

While LP was generally more acceptable to caregivers when the patient's overall health condition was deteriorating, health-care workers were hesitant to perform LP in terminal cases. This reluctance stemmed from concerns that other patients or caregivers might perceive a patient's death following the procedure as proof of LP's inherent risks or fatality (1 study, low confidence).

The accumulation of these fears and perceived risks significantly impacted the decision-making process for patients and caregivers, leading to a reluctance or outright refusal to undergo LP. This resistance was further fuelled by second-hand experiences with adverse outcomes, which deeply influenced perceptions of the procedure's safety and efficacy (1 study, moderate confidence).

CSF: cerebrospinal fluid; HICs: high-income countries; ICU: intensive care unit; LMICs: low- and middle-income countries; LP: lumbar puncture; LR+/-: positive/negative likelihood ratio; NPV: negative predictive value; PCR: polymerase chain reaction; PPV: positive predictive value.

3. Serum markers of bacterial infection

3.1 Guideline question

In individuals with suspected acute meningitis, should WBC count and differential, C-reactive protein and/or procalcitonin be performed on peripheral blood samples?

Population: Suspected cases of acute meningitis

Index test: Peripheral blood testing (all of the following tests alone or in combination: WBC count and differential, C-reactive protein, procalcitonin)

Reference standard: Consensus diagnosis excluding index test[3]

Outcome: *Critical*: Sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of index test

Full details of the evidence, including references, are provided in Web Annex A (3. Serum markers of bacterial infection) and Web Annex B (Qualitative and economic evidence reports).

[3] Consensus diagnosis excluding index test is defined as clinical characteristics, CSF characteristics (Gram stain, leukocyte count and differential, glucose, total protein, lactate), blood culture, CSF culture and/or CSF PCR.

3.2 Evidence-to-Decision framework

Priority of the problem
Judgement: Yes Meningitis is a life-threatening condition that requires timely and accurate diagnosis to ensure appropriate patient management. Culture and molecular tests are generally regarded as the reference standard for pathogen identification. However, to inform timely clinical decisions and guide antimicrobial treatment, additional investigations with faster turnaround times and rapidly available results are normally conducted on cerebrospinal fluid (CSF) and blood samples. Specifically, peripheral white blood cell (WBC) count, C-reactive protein (CRP) and procalcitonin (PCT) are often used as auxiliary tests that may contribute to meningitis diagnosis, including for differentiating bacterial from non-bacterial disease.
Desirable effects
Judgement: Moderate The judgement was based on the available evidence as well as additional inputs from the Guideline Development Group (GDG): • None of the peripheral blood tests considered in the systematic review were characterized by high or very high diagnostic performance. However, WBC count, CRP and/or PCT are likely to be useful when results are interpreted in the context of clinical presentation (i.e. medical history, symptoms and signs) and CSF characteristics. • Leukocytosis, an increased relative neutrophil count, elevated PCT levels and very high CRP levels are consistent with the presence of a bacterial infection. While they contribute to discriminating between acute bacterial meningitis and viral meningitis, their added value may be more limited in the differential diagnosis when other bacterial infections were suspected (e.g. sepsis, pneumonia). • Most studies included in the systematic review used non-bacterial meningitis as a comparator, whereas other bacterial systemic infections without central nervous system involvement were not considered.
Source of evidence
A systematic review was conducted to assess the diagnostic performance of peripheral WBC count, CRP and PCT.

Direct evidence

The following estimates refer to the performance of each individual test in diagnosing acute bacterial meningitis.

Peripheral white blood cells (WBCs)

- Low-certainty evidence suggested that peripheral WBC count may have had moderate to low sensitivity (12 studies/2057 patients, pooled effect: 68%, 95% CI 59–78%) and moderate specificity (12 studies/2057 patients, pooled effect: 74%, 95% CI 69–79%).
- Moderate-certainty evidence showed that peripheral WBC count likely had moderate to high positive predictive value (PPV) (3 studies/828 patients, median: 84%, range: 7–85%); high-certainty evidence showed that it had moderate to low negative predictive value (NPV) (3 studies/828 patients, median: 60%, range: 35–84%).
- Moderate-certainty evidence suggested that peripheral WBC count likely had low positive likelihood ration (LR+) (12 studies/2057 patients, median: 2.71, range: 1.11–4.16) and moderate negative likelihood ratio (LR-) (12 studies/2057 patients, median: 0.40, range: 0.12–0.94).

Peripheral neutrophils

- Moderate-certainty evidence suggested that peripheral neutrophil count likely had moderate to high sensitivity (2 studies/350 patients, pooled effect: 89%, 95% CI 84–92%); low-certainty evidence suggested that it may have had low specificity (2 studies/350 patients, pooled effect: 58%, 95% CI 33–84%).
- Moderate-certainty evidence suggested that peripheral neutrophil count likely had low LR+ (2 studies/350 patients, range: 1.6–3.2) and low to moderate LR- (2 studies/350 patients, range: 0.13–0.27).

C-reactive protein (CRP)

- High-certainty evidence showed that CRP had moderate to high sensitivity (15 studies/2345 patients, pooled effect: 82%, 95% CI 74–89%) and moderate to high specificity (15 studies/2345 patients, pooled effect: 84%, 95% CI 77–92%).
- Moderate-certainty evidence suggested that CRP likely had moderate to high PPV (3 studies/350 patients, median: 85%, range: 11–93%) and moderate to low NPV (3 studies/350 patients, median: 63%, range: 54–98%).
- High-certainty evidence showed that CRP had low LR+ (15 studies/2354 patients, median: 3.33 range: 1.78–36.12) and moderate LR- (15 studies/2354 patients, median: 0.27 range: 0–0.68).

Procalcitonin (PCT)

- High-certainty evidence showed that PCT had moderate to high sensitivity (13 studies/1336 patients, pooled effect: 87%, 95% CI 75–98%) and moderate to high specificity (13 studies/1336 patients, pooled effect: 86%, 95% CI 79–93%).
- Moderate-certainty evidence suggested that PCT likely had moderate to very high PPV (2 studies/199 patients, range: 88–99%) and moderate to high specificity (2 studies/199 patients, range: 72–91%).
- High-certainty evidence showed that PCT had moderate LR+ (13 studies/1336 patients, median: 5.21, range: 1.64–58.24) and low LR- (13 studies/1336 patients, median: 0.05, range: 0–0.80).

Undesirable effects

Judgement: Small

The judgement was based on the available evidence as well as additional inputs from the GDG:

- None of the peripheral blood tests considered in the systematic review were characterized by high or very high diagnostic performance. Thus, the risk of false-positive or false-negative results may not be trivial, especially when these tests were interpreted alone and/or in the absence of CSF laboratory investigations.
- Most studies included in the systematic review used non-bacterial meningitis as a comparator, whereas other bacterial systemic infections without central nervous system involvement were not considered.

Source of evidence

A systematic review was conducted to assess the diagnostic performance of peripheral WBC count, CRP and PCT.

Direct evidence

Outcome-specific data are presented above. No additional undesirable effects were investigated.

Certainty of the evidence

Judgement: Low (WBCs); Moderate (neutrophils, CRP, PCT)

The certainty of evidence was low for peripheral WBCs and moderate for the other index tests.

Values

Judgement Probably no important uncertainty or variability

Based on the available evidence and their knowledge and experience, the GDG agreed that there probably was no important uncertainty or variability regarding the value of each of the main outcomes.

Source of evidence

A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.

Direct evidence

No direct evidence was identified regarding the uncertainty about or variability in how much people value the main outcomes. However, the synthesis of community perceptions and attitudes towards meningitis diagnostic tests in low- and middle-income countries (LMICs), as reflected in the literature, is provided as part of the indirect evidence.

Indirect evidence

LMICs

Meningitis is universally recognized as a potentially fatal condition that can result in severe sequelae, disability, and death, particularly when care is not timely (3 studies, moderate confidence).

Some studies highlighted a recognition among patients and caregivers of the importance of health services. Health-care facilities were acknowledged as a place to seek help and conventional medicine was valued as the most effective in diagnosis and treatment. Despite this recognition, the uptake of health services is hindered by several barriers strongly linked with the community values and beliefs. Evidence from 4 studies in which participants in different LMICs were interviewed (including adults, carers of adult and paediatric patients with meningitis, and community members) suggested that a major barrier was related to traditional beliefs and scepticism in the communities about orthodox medicine. The perception of meningitis as having spiritual causes, which should be treated with "traditional" rather than "orthodox" medicine, highlighted a conflict between cultural values and the acceptance of conventional medical practices (4 studies, moderate confidence).

Balance of effects

Judgement: Probably favours the intervention

The judgement was based on the evidence and judgements presented above.

Resources required

Judgement: Moderate savings

Source of evidence

A scoping review was undertaken to compile information regarding costs, resource utilization and cost-effectiveness associated with meningitis diagnosis, treatment and management of sequelae.

Direct evidence

The included studies conducted in LMICs did not directly address the cost of peripheral blood testing but found evidence on laboratory investigation costs as an aggregated cost item. None of the studies conducted in HICs were considered applicable to this guideline question.

Indirect evidence

LMICs

The scoping review identified 1 study conducted in Gambia that directly addressed the cost of peripheral blood testing. Four laboratories performed full blood count with a median (range) cost of US$ 6.62 (1.84–6.84) (2010 US$). Several studies reported the cost of laboratory investigations as a single aggregated cost item. When not stated otherwise, it was assumed that laboratory investigations included peripheral blood testing. However, laboratory investigations are likely to include multiple diagnostic tests, such as CSF testing in people with suspected acute meningitis, and how reliably it approximates the cost of peripheral blood testing in LMICs is debatable.

One cross-sectional study on children and neonates with pneumococcal meningitis hospitalized in 2 Nigerian hospitals reported mean investigation costs of US$ 17 (standard deviation [SD] ±7) and US$ 8.6 (SD ±1.4), respectively (2020 US$). An incidence-based cost-of-illness analysis of hospitalized children with suspected/probable/definite pneumococcal meningitis in one Vietnamese hospital showed a laboratory cost of US$ 8.82 (SD ±16.72), US$ 19.62 (SD ±5.44) and US$ 30.10 (SD ±43.84), respectively (2006 US$).

Certainty of the evidence on resources required

Judgement: Very low

The judgement reflected several limitations in the available evidence, including the lack of a comprehensive evaluation of all resource use items, the absence of comparison between different tests and resource use and the variability in costs across settings.

Cost-effectiveness

Judgement: No included studies

A scoping review was undertaken to compile information regarding costs, resource utilization and cost-effectiveness associated with meningitis diagnosis, treatment and management of sequelae.

However, no cost-effectiveness studies were found that would be applicable to this guideline question.

Health equity, equality and non-discrimination

Judgement: Probably increased

Based on the available indirect evidence and their knowledge and experience, the GDG agreed that increased high-quality, effective, safe and affordable diagnostics is likely to contribute to reducing equity gaps and discrimination in health-care access, especially in resource-limited settings.

Source of evidence

A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.

Direct evidence

None of the included qualitative studies directly focused on health equity, equality or non-discrimination in relation to blood tests. However, the main relevant findings on health services for meningitis diagnosis are summarized as part of the indirect evidence.

Indirect evidence

LMICs

Some qualitative studies reported the lack of affordability of health services for patients and carers. Financial constraints acted as a barrier to initiating help-seeking, including transportation to health-care facilities, and often prompted patients and caregivers to seek alternative treatments (3 studies, moderate confidence).

HICs

A single study identified several barriers that hindered access to health services. Among these, some caregivers expressed reluctance to seek help, fearing the potential misuse or overuse of health-care resources, which in turn delayed the decision to seek medical attention (1 study, low confidence). Furthermore, parents often hesitated to access timely care due to uncertainty about the severity of the illness (1 study, moderate confidence).

Information access emerged as a significant limitation in several studies. Caregivers frequently reported not knowing enough about the symptoms and consequences of meningitis, underscoring a pressing need for readily accessible information about their children's health conditions. Often, parents were more likely to notice their child's overall poor health rather than specific warning signs of meningitis. In addition, carers described a lack of communication and

support and expressed dissatisfaction with the health-care workers' complex use of medical jargon, which often complicated understanding (5 studies, low confidence).
Feasibility
Judgement: Varies Based on their knowledge and experience, the GDG agreed that complete blood count should be routinely available and feasible across the continuum of care, including in peripheral health-care facilities and district hospitals. On the other hand, routine use of CRP and PCT may be subject to variations across settings, depending on available financial and infrastructural resources.
Source of evidence A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.
Direct evidence None of the included qualitative studies directly focused on the feasibility of peripheral blood tests.
Human rights and sociocultural acceptability
Judgement: Probably yes Based on their knowledge and experience, the GDG agreed that the interventions are aligned with human rights principles and are likely to be socioculturally acceptable in most settings.
Source of evidence A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.
Direct evidence None of the included qualitative studies directly focused on sociocultural acceptability of peripheral blood tests.

CRP: C-reactive protein; CSF: cerebrospinal fluid; GDG: Guideline Development Group; HICs: high-income countries; LMICs: low- and middle-income countries; LR+/-: positive/negative likelihood ratio; NPV: negative predictive value; PCT: procalcitonin; PPV: positive predictive value; SD: standard deviation; WBC: white blood cells.

4. Cranial imaging

4.1 Guideline question

In individuals with suspected acute meningitis, should clinical characteristics be used to predict the presence on cranial imaging of intracranial abnormalities associated with increased risk of adverse events secondary to lumbar puncture (LP)?[4]

Population: Suspected cases of acute meningitis

Intervention: Presence of any of the following clinical characteristics: Focal neurological deficits, altered consciousness, new-onset seizures, severe immunocompromised status, signs of increased intracranial pressure (including but not limited to papilledema)

Comparator: Absence of any of the above-mentioned clinical characteristics

Outcome: *Critical:* Intracranial abnormalities on cranial imaging associated with increased risk of adverse events secondary to lumbar puncture (LP).

Full details of the evidence, including references, are provided in Web Annex A (4. Cranial imaging) and Web Annex B (Qualitative and economic evidence reports).

[4] Intracranial abnormalities associated with increased risk of adverse events secondary to LP are defined as cerebral space-occupying lesions with midline shift detected on cranial imaging.

4.2 Evidence-to-Decision framework

Priority of the problem
Judgement: Yes Lumbar puncture (LP) is a critical tool for meningitis diagnosis. However, in the presence of cerebral space-occupying lesions with midline shift detected on cranial imaging, it may contribute to brain herniation and poor outcome. Nonetheless, cranial imaging (e.g. computed tomography [CT] scan) may not be widely available or accessible, especially in resource-limited settings, which could lead to delays in treatment initiation. Globally, variations exist in clinical practice regarding the use of cranial imaging prior to LP. It is therefore important to identify which clinical characteristics could be used to select individuals at risk for cerebral herniation where cranial imaging should be performed or, in the absence of cranial imaging, LP would be contraindicated and should be deferred.
Desirable effects
Judgement: Small Based on the available evidence and their knowledge and experience, the Guideline Development Group (GDG) highlighted the potential benefits of using clinical characteristics to identify individuals at higher risk for cerebral herniation and determine whether LP should be deferred and performed after cranial imaging (where possible).
Source of evidence A systematic review was conducted to investigate the role of clinical characteristics to predict the presence of abnormal findings on cranial imaging associated with adverse events following LP.
Direct evidence No study directly addressed the guideline question by focusing on intracranial abnormalities that are specifically associated with an increased risk of adverse events following LP.
Indirect evidence A prospective cohort study included 235 patients aged > 16 years with clinically suspected meningitis, who were investigated for baseline clinical characteristics associated with increased risk of *any* abnormal findings on cranial imaging (CT scan) (Hasbun et al. 2001). Low-certainty-evidence showed that among patients who underwent brain CT scan, a number of factors may have been associated with *any* abnormal findings on cranial imaging. These included 60 or more years of age (RR 4.3, 95% CI 2.9–6.4), immunocompromised state (RR 1.8, 95% CI 1.1–2.8), history

of central nervous system disease (RR 4.8, 95% CI 3.3–6.9), seizure within 1 week of presentation (RR 3.2, 95% CI 2.1–5.0), abnormal level of consciousness (RR 3.3, 95% CI 2.2–4.4), inability to answer 2 consecutive questions correctly (RR 3.8, 95% CI 2.5–5.8), gaze palsy (RR 3.2, 95% CI 1.9–5.4), abnormal visual fields (RR 4.0, 95% CI 2.7–5.9), facial palsy (RR 4.9, 95% CI 3.8–6.3), arm drift (RR 4.0, 95% CI 2.7–5.8), leg drift (RR 4.4, 95% CI 3.0–6.5) or abnormal language (i.e. aphasia, dysarthria or extinction; RR 4.3, 95% CI 2.9–6.5).

A retrospective cohort study was conducted on 712 adults with acute community-acquired bacterial meningitis to assess the effect on time-to-antibiotic and clinical outcomes of a 2009 Swedish guideline revision in which impaired mental status and new-onset seizures were removed as contraindications to initial LP (Glimaker et al. 2015). Compared to patients who received a CT scan prior to LP, patients without prior CT had a shorter time between hospital admission and initiation of antibiotics (24.9% vs 39.0%, $P < 0.01$), lower all-cause mortality rate (3.4% vs 11.4%, $P < 0.01$) and lower rate of any long-term neurological impairment (21.2% vs 35.5%, $P < 0.01$). Adjusted estimates for relevant outcomes were not reported.

A prospective cohort study was conducted on 815 adults with acute bacterial meningitis to assess the effect of adherence to the Swedish, European Society of Microbiology and Infectious Diseases (ESCMID), and Infectious Diseases Society of America (IDSA) guidelines on mortality and favourable outcomes at 2–6 months of follow-up (Glimaker et al. 2018). Immunocompromised patients accounted for 38% of the total population. Indications for LP were observed in 7%, 32% and 65% according to the Swedish, ESCMID and IDSA guidelines, respectively. Compared to neuroimaging prior to LP, receiving LP without neuroimaging was associated with an adjusted OR of 0.38 (95% CI, 0.18–0.77) for mortality and 2.11 (95% CI, 1.47–3.00) for favourable outcome. Prompt LP performance was associated with favourable outcomes regardless of mental status and immunocompromised state.

Undesirable effects

Judgement: Trivial

Based on the available evidence and their knowledge and experience, the GDG emphasized that the undesirable effects of using clinical characteristics to identify individuals at higher risk for cerebral herniation are trivial.

Source of evidence

A systematic review was conducted to investigate the role of clinical characteristics to predict the presence of abnormal findings on cranial imaging associated with adverse events following LP.

Direct evidence

No study directly addressed the guideline question by focusing on intracranial abnormalities that are specifically associated with an increased risk of adverse events following LP.

Indirect evidence

The challenges of reliably assessing the risks associated with LP through cranial imaging were investigated in a Dutch case–control study nested in a nationwide cohort (Costerus et al. 2018). Patients with community-acquired laboratory-confirmed bacterial meningitis and clinical deterioration possibly caused by LP were individually matched to controls with similar age and presenting Glasgow Coma Score (GCS) but a good clinical outcome. Four experts, including 2 neurologists and 2 neuroradiologists, assessed cranial CT results to identify contraindications for LP. Out of 1533 episodes, 47 (3.1%) with clinical deterioration possibly due to LP were identified, with 43 undertaking cranial CT prior to LP. Presenting clinical characteristics and treatment of the 43 patients with deterioration and cranial CT prior to LP and their 43 matched controls were similar. The interrater reliability of contraindications for LP on cranial CT was moderate (Fleiss' generalized kappa 0.47; 95% CI 0.38–0.55, $p < 0.0001$), indicating the interpretation of cranial imaging in acute settings can be difficult. Clinical deterioration occurred within 1 hour after LP in 2 out of 47 patients (0.1% of the total episodes).

In a prospective single-centre cohort study in a tertiary care facility in the Kingdom of the Netherlands, adherence to criteria for cranial imaging provided by various clinical guidelines was investigated (Costerus et al. 2020). A total of 203 patients (median age 44, IQR 29–59) who presented to the emergency department with the suspicion of a central nervous system infection underwent a cerebrospinal fluid (CSF) examination, Final diagnoses of infections were made in 56 patients (27.6%) and 16 were diagnosed with bacterial meningitis (8%). A brain CT scan was performed prior to LP in 130 of 203 (64.0%) of patients. Criteria by the IDSA, ESCMID, Swedish and Dutch guidelines showed indications for imaging in 64%, 39%, 39% and 40% of patients, respectively. CT abnormalities were observed in 70 patients (53.8%) and were considered related to the current illness only in 19 patients (14.6%). The performance of a cranial CT before an LP was not associated with the delayed initiation of empirical antimicrobial treatment (median time with and without CT was 134 minutes [IQR 58–292] vs. 141 minutes [IQR 52–227], P = 0.74). Similar results were observed when limiting the analysis to the 49 patients (68.1%) treated for suspected bacterial meningitis (P = 0.34). As a primary limitation, the study did not include patients where LP was not performed due to cranial imaging abnormalities.

Certainty of the evidence

Judgement: Very low

The certainty of evidence was considered very low due to the lack of direct evidence addressing the guideline question.

Values

Judgement: Possibly important uncertainty or variability

Based on the available evidence and their knowledge and experience, the GDG agreed that there might be important uncertainty or variability regarding the value of the main outcome.

Source of evidence

A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.

Direct evidence

No direct evidence was identified regarding the uncertainty about or variability in how much people value the main outcomes. However, the synthesis of community perceptions and attitudes towards meningitis diagnostic tests in low- and middle-income countries (LMICs), as reflected in the literature, is provided as part of the indirect evidence.

Indirect evidence

LMICs

Meningitis is universally recognized as a potentially fatal condition that can result in severe sequelae, disability and death, particularly when care is not timely (3 studies, moderate confidence).

Some studies highlighted a recognition among patients and caregivers of the importance of health services. Health-care facilities were acknowledged as a place to seek help and conventional medicine was valued as the most effective for diagnosis and treatment. Despite this recognition, the uptake of health services, including potentially life-saving procedures such as LP, was hindered by several barriers strongly linked with community values and beliefs. Evidence from 4 studies in which participants from different LMICs were interviewed, including adult patients, carers of adult and paediatric patients, and community members, suggested that a major barrier was related to traditional beliefs and scepticism in the communities about orthodox medicine. The perception of meningitis by most patients and caregivers as having spiritual causes, which should be treated with "traditional" rather than "orthodox" medicine, highlighted a conflict between cultural values and the acceptance of conventional medical practices (4 studies, moderate confidence).

Additionally, a single study reflected patients' experiences of suboptimal health services, including long waiting times, insufficient examination and verbal mistreatment (2 studies, very low confidence). Fear of paralysis or death was cited by most patients/caregivers as a reason to refuse LP. Specifically, death was attributed to late procedure uptake or poor overall condition, while the position during/after the procedure was associated with paralysis as an outcome (1 study, moderate confidence).

Balance of effects
Judgement: Favours the intervention The judgement was based on the evidence and judgements of the criteria above. Specifically, the GDG highlighted that the benefits of using clinical characteristics to defer LP and perform cranial imaging outweigh the risks among selected individuals (i.e. those presenting with clinical characteristics that are associated with increased risk of cerebral space-occupying lesions with midline shift).
Resources required
Judgement: Don't know A scoping review was undertaken to compile information regarding costs, resource utilization and cost-effectiveness associated with meningitis diagnosis, treatment and management of sequelae. However, none of the identified cost and resource utilization studies were considered applicable to this guideline question.
Certainty of the evidence on resources required
Judgement: No included studies
Cost-effectiveness
Judgement: No included studies A scoping review was undertaken to compile information regarding costs, resource utilization and cost-effectiveness associated with meningitis diagnosis, treatment and management of sequelae. However, no cost-effectiveness studies were found that would be applicable to this guideline question.
Health equity, equality and non-discrimination
Judgement: Probably increased Based on the available evidence and their knowledge and experience, the GDG agreed that increased access to high-quality diagnostic investigations, including cranial imaging in selected individuals, is likely to contribute to reducing equity gaps and discrimination in health-care access, especially in resource-limited settings.
Source of evidence

A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.

Direct evidence

None of the included qualitative studies directly focused on health equity, equality or non-discrimination in relation to this guideline question. However, the main relevant findings on health services for meningitis diagnosis in LMICs and high-income countries (HICs) are summarized as part of the indirect evidence.

Indirect evidence

LMICs

Some qualitative studies reported the lack of affordability of health services for patients and carers. Financial constraints acted as a barrier to initiating help-seeking, including transportation to health-care facilities, and often prompted patients and caregivers to seek alternative treatments (3 studies, moderate confidence).

HICs

A single study identified several barriers that hindered access to health services. Among these, some caregivers expressed reluctance to seek help, fearing the potential misuse or overuse of health-care resources, which in turn delayed the decision to seek medical attention (1 study, low confidence). Furthermore, parents often hesitated to access timely care due to uncertainty about the severity of the illness (1 study, moderate confidence).

Information access emerged as a significant limitation in several studies. Caregivers frequently reported not knowing enough about the symptoms and consequences of meningitis, underscoring a pressing need for readily accessible information about their children's health conditions. Often, parents were more likely to notice their child's overall poor health rather than specific warning signs of meningitis. In addition, carers described a lack of communication and support and expressed dissatisfaction with the health-care workers' complex use of medical jargon, which often complicated understanding (5 studies, low confidence).

Feasibility

Judgement: Varies

Based on the available evidence and their knowledge and experience, the GDG agreed that the feasibility of cranial imaging prior to LP may vary across settings. Specifically, the use of clinical characteristics to determine whether LP should be deferred primarily depends on the patient's medical history and physical examination. As a result, this approach can be implemented in both

high-resource and low-resource settings and for most clinical characteristics, as it might not necessarily require specialized clinical skills or capacities. On the other hand, cranial imaging is not widely available in low-resource settings and may be difficult to implement in the absence of infrastructural, financial and/or human resources. In this context, multisectoral interventions, including building specialized clinical capacity, would be crucial for ensuring access to cranial imaging while strengthening the health system across all levels of care.
Source of evidence A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.
Direct evidence None of the included qualitative studies directly focused on the role of clinical characteristics to predict the presence of abnormal findings on cranial imaging associated with adverse events following LP.
Human rights and sociocultural acceptability
Judgement: Varies Based on the available evidence and their knowledge and experience, the GDG agreed that the sociocultural acceptability of LP deferral and cranial imaging may vary across settings.
Source of evidence A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.
Direct evidence None of the included qualitative studies directly focused on the role of clinical characteristics to predict the presence of abnormal findings on cranial imaging associated with adverse events following LP.

CSF: cerebrospinal fluid; CT: computed tomography; ESCMID: European Society of Clinical Microbiology and Infectious Diseases; GDG: Guideline Development Group; GSC: Glasgow Coma Scale/Score; HICs: high-income countries; IDSA: Infectious Diseases Society of America; LMICs: low- and middle-income countries; LP: lumbar puncture.

5. Timing of empiric antimicrobial treatment

5.1 Guideline question

In individuals with suspected acute meningitis, should empiric antimicrobial treatment be provided as soon as possible?[5]

Population: Suspected cases of acute meningitis

Intervention: Empiric antimicrobial treatment administered as soon as possible[6]

Comparator: Delayed empiric antimicrobial treatment[7]

Outcome:

Critical: Mortality, time to resolution of symptoms, disease complications (sepsis, disseminated intravascular coagulation [DIC], neurological complications, including neurological sequelae)

Important: Adverse effects, CSF culture positivity rate, blood culture positivity rate

Full details of the evidence, including references, are provided in Web Annex A (5. Timing of empiric antimicrobial treatment) and Web Annex B (Qualitative and economic evidence reports).

[5] Empiric antimicrobial treatment administered before admission into an inpatient setting (health centre, hospital), before referral, during transport (ambulance) and/or before LP and/or cranial imaging.

[6] Ibid.

[7] Empiric antimicrobial treatment administered contingent upon admission, referral and/or lumbar puncture and/or cranial imaging results.

5.2 Evidence-to-Decision framework

Priority of the problem
Judgement: Yes Acute bacterial meningitis is a medical emergency that requires prompt diagnosis and urgent care in appropriate, adequately equipped health-care facilities. Antibiotics remain the mainstay of treatment and often serve as a critical disease control strategy by reducing the duration of the infectious period and mitigating the risk of transmission to close contacts. Therefore, the Guideline Development Group (GDG) agreed on the critical importance of formulating recommendations on the timing of empiric therapy, including before and after admission or transfer to an appropriate health-care facility. Furthermore, in resource-limited environments, the time required for a patient to arrive at a health-care facility may be long and result in suboptimal treatment and poorer outcomes, further highlighting the need for evidence-based recommendations on early antimicrobial treatment.
Desirable effects
Judgement: Large As a preliminary remark to the discussion, the GDG emphasized that timely admission or urgent transfer or referral to an appropriate health-care facility should be ensured and prioritized for all individuals with suspected acute meningitis in order to conduct diagnostic tests and start the appropriate treatment as soon as possible. Based on the body of direct and indirect evidence as well as their clinical knowledge and experience, the GDG highlighted the large desirable effects resulting from early initiation of empiric antimicrobial treatment upon admission, transfer or referral to an appropriate health-care facility. In addition, as acute bacterial meningitis is a medical emergency requiring urgent care, they agreed that empiric antimicrobial treatment may also be warranted prior to admission, transfer or referral, especially when a clinically significant delay is expected and a bacterial infection is strongly suspected. Throughout the discussion, despite the use of the term “hospital” in the included studies, “health-care facility” was preferred so as to adequately account for the differences in service provision and levels of care across countries and regions.
Source of evidence
A systematic review was conducted to compare early vs delayed empiric antimicrobial treatment and included 3 prospective cohort studies.

Direct evidence

Two studies assessed pre-hospital antimicrobial treatment and 1 study investigated early vs delayed in-hospital antimicrobial treatment (≤ 3 hours vs > 3 hours).

Mortality

- Pre-hospital therapy: Very-low-certainty evidence from 2 prospective cohort studies involving 445 patients showed that the effect of pre-hospital antimicrobial treatment was uncertain (RR 0.68, 95% CI 0.29–1.63).
- Early in-hospital therapy: Low-certainty evidence from 1 prospective cohort study involving 156 adults showed that early in-hospital antimicrobial treatment may have reduced mortality (RR 0.34, 95% CI 0.20–0.58).
- Early therapy (pre-hospital and early in-hospital therapy): Very-low-certainty evidence from 3 prospective cohort studies involving 601 patients (children and adults) showed that the effect of early initiation of antimicrobial treatment (including pre-hospital and early in-hospital therapy) was uncertain (RR 0.41, 95% CI 0.26–0.65).

Hearing loss

Very-low-certainty evidence from 1 prospective cohort study involving 281 children showed that the effect of pre-hospital therapy on hearing loss was uncertain (RR 2.98, 95% CI 1.09–8.13). The probable reason for the point estimate favouring the delayed empiric antimicrobial treatment was the delay in admission in the pre-hospital antimicrobial treatment group (median of 3 days in the intervention arm vs median of 1 day in the comparator).

Motor neurological deficits (paresis)

Very-low-certainty evidence from 1 prospective cohort study involving 281 children showed that the effect of pre-hospital therapy on paresis was uncertain (RR 2.21, 95% CI 0.93–5.25). The probable reason for the point estimate favouring the delayed empiric antimicrobial treatment was the delay in admission in the pre-hospital antimicrobial treatment group (median of 3 days in the intervention arm vs median of 1 day in the comparator).

Additional evidence

Retrospective studies were not included in the systematic review. However, the main findings of 10 retrospective studies addressing the guideline question are described in Web Annex A and summarized below.

Mortality

- Pre-hospital therapy: Four retrospective studies (2 conducted on children and 2 on children and adults) reported no significant differences in mortality risk between antimicrobial treatment prior to admission and antimicrobial treatment after admission.

- Early in-hospital therapy: Five retrospective studies conducted on adults reported a possible beneficial effect of early in-hospital therapy on mortality risk when compared to delayed in-hospital therapy (especially after 6 hours).

Functional impairment

- Pre-hospital therapy: Two retrospective studies (1 conducted on children and 1 on adults) reported no significant differences in functional impairment between antimicrobial treatment prior to admission and antimicrobial treatment after admission.
- Early in-hospital therapy: One retrospective study conducted on adults reported a possible harmful effect on functional impairment, defined as Glasgow Outcome Scale ≤ 4 at discharge, when antimicrobial treatment delays exceeded 6 hours as compared to antimicrobial treatment within 2 hours of admission (RR 1.5, 95% CI 1.0–2.2).

Undesirable effects

Judgement: Moderate

In addition to considering the available evidence, the GDG highlighted several undesirable effects potentially resulting from antibiotic administration outside an appropriate health-care facility. These included the inappropriate use of broad-spectrum antibiotics and the associated risk of antimicrobial resistance, the challenges in managing severe adverse reactions and the reduced diagnostic yield of laboratory investigations on blood and cerebrospinal fluid (CSF) samples, including Gram stain, culture and molecular tests.

Source of evidence

A systematic review was conducted to compare early vs delayed empiric antimicrobial treatment and included 3 prospective cohort studies.

Direct evidence

Two studies assessed pre-hospital antimicrobial treatment, while 1 study investigated early vs delayed in-hospital antimicrobial treatment (≤ 3 hours vs > 3 hours).

Adverse events

Very-low-certainty evidence from 1 prospective cohort study involving 148 adults showed that the effect of early in-hospital therapy on adverse events was uncertain (RR 0.70, 95% CI 0.53–0.92).

CSF culture positivity rate

Very-low-certainty evidence from 1 prospective cohort study involving 281 children showed that the effect of pre-hospital therapy on CSF culture positivity rate was uncertain (RR 0.95, 95% CI 0.90–1.01).

Blood culture positivity rate

Very-low-certainty evidence from 1 prospective cohort study involving 281 children showed that the effect on pre-hospital therapy on blood culture positivity rate was uncertain (RR 0.90, 95% CI 0.80–1.01).

Additional evidence

Among the retrospective studies included as additional evidence, none investigated outcomes related to adverse events.

Certainty of the evidence

Judgement: Very low (pre-hospital therapy); Low (early in-hospital therapy)

The certainty of evidence on pre-hospital therapy was very low. The certainty of evidence on early in-hospital therapy was low.

Values

Judgement: Possibly important uncertainty or variability

Based on the available evidence and their knowledge and experience, the GDG agreed that there might be important uncertainty or variability across settings in how much people value the main outcomes.

Source of evidence

A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.

Direct evidence

No direct evidence was identified regarding the uncertainty about or variability in how much people value the main outcomes. However, the included studies highlighted a complex landscape of values and beliefs surrounding the treatment of meningitis, underscoring the diversity in health-care decision-making processes across different communities in both low- and middle-income countries (LMICs) and high-income countries (HICs). Particularly, some insights into patient and caregiver values provided a nuanced understanding of treatment preferences and healthcare-seeking behaviours and are summarized as indirect evidence.

Indirect evidence

LMICs

Studies focused on the values of patients/caregivers related to meningitis treatment reported that biomedical treatments are most effective in diagnosing, treating and managing the disease. This

acknowledgement reflected the value placed on conventional medical approaches for addressing the physical aspects of the disease (2 studies, low confidence).

However, the choice of treatment was profoundly influenced by the perceived cause of the illness. A significant portion of patients and caregivers, especially those attributing the disease to supernatural forces, declared a preference for traditional and Islamic treatment methods (4 studies, moderate confidence).

The initial response to meningitis symptoms in caregivers and adult patients often involved a combination of self-medication and seeking advice or treatment from traditional healers and soothsayers, particularly to discern if the disease had supernatural origins (4 studies, moderate confidence). Patronage of government hospitals was considered the last resort when the illness became severe and not amenable to alternative care. This pattern of health-care utilization underscored the significant influence of cultural practices on health-care decisions, indicating a complex interplay between traditional beliefs, perceived efficacy of treatments and the severity of the disease in guiding treatment choices (1 study, low confidence).

Collective decision-making was also a barrier to timely help-seeking. As patients and caregivers were dependent on the community or senior household members to fund the emergency care expenses, social validation of the illness severity was essential to warrant funding (2 studies, very low confidence).

Studies indicated that the increase in disease severity initiated help-seeking behaviour. The key factor at the household level was the ability to recognize when the illness had become severe enough to necessitate seeking treatment, rather than recognizing specific signs and symptoms of acute bacterial meningitis. Factors such as disruption of social life, weakness, loss of appetite and the inability to work were among the most commonly cited reasons that individuals sought help (2 studies, moderate confidence).

HICs

One study pointed out that health-care workers in primary care settings may have lacked experience with treating meningitis. As a result, they were more focused on getting a child hospitalized as early as possible rather than starting treatment on their own (1 study, moderate confidence).

The literature consistently indicated that caregivers' primary concern revolved around the survival of their child, with many expressing profound worry about this outcome (5 studies, low confidence).

Finally, one study highlighted that the complexity of treatment trajectories could be a source of dissatisfaction with health services (1 study, very low confidence).

Balance of effects

Judgement: Probably favours the intervention

Pre-hospital therapy

Based on the body of direct and indirect evidence and their clinical knowledge and experience, the GDG agreed that the benefits of parenteral antibiotics as soon as possible may outweigh the undesirable consequences in selected settings, especially where bacterial meningitis is strongly suspected and a clinically significant delay in admission, transfer or referral to an appropriate health-care facility is considered likely. On the other hand, the GDG clearly indicated that antimicrobial treatment should never delay or hinder hospital admission or transfer and referral efforts.

Early in-hospital therapy

Based on the body of direct and indirect evidence and their clinical knowledge and experience, the GDG indicated the benefits of initiating intravenous antimicrobial treatment as early as possible upon admission, transfer or referral to an appropriate health-care facility. They also highlighted that empiric antimicrobial treatment should ideally be initiated after lumbar puncture (LP) and blood sampling but any delay in or deferral of diagnostic investigations should not delay therapy administration.

Resources required

Judgement: Varies

Based on the available evidence indicating the benefits of early in-hospital antimicrobial treatment, health-care costs and resources associated with functional impairment and disability for individuals receiving early therapy administration might be reduced. On the other hand, pre-hospital treatment is likely to necessitate additional resources, including in primary health-care facilities (e.g. staff training, procurement of medicines and medical devices).

Source of evidence

A scoping review was undertaken to compile information regarding costs, resource utilization and cost-effectiveness associated with meningitis diagnosis, treatment and management of sequelae.

Direct evidence

The included studies did not directly address the cost of empirical antimicrobial treatment associated with the timing of administration but found indirect evidence of the unit cost of different antibiotics in LMICs. None of the studies conducted in HICs were considered applicable to this guideline question.

Indirect evidence

LMICs

One study conducted in Gambia reported the unit cost of each vial of ceftriaxone (2 ml/250 mg), penicillin (2 ml/1 000 000 IU), ampicillin (2 ml/500 mg), amoxicillin (100 ml bottle, 125 mg/5 ml), chloramphenicol (2 ml/1 g) was US$ 2.5, 0.26, 0.3, 0.64, 0.5, respectively (2010 US$). In another study conducted in Viet Nam, the unit cost of each vial of ceftriaxone (250 mg/vial) and cefotaxime (1g/vial) was US$ 4.24 and 1.35 (2006 US$), respectively.

Certainty of the evidence on resources required

Judgement: Very low

The judgement reflected the limited scope of the available evidence and the absence of a comprehensive cost analysis.

Cost-effectiveness

Judgement: No included studies

A scoping review was undertaken to compile information regarding costs, resource utilization and cost-effectiveness associated with meningitis diagnosis, treatment and management of sequelae. However, no cost-effectiveness studies were found that would be applicable to this guideline question.

Health equity, equality and non-discrimination

Judgement: Probably increased

Based on the available evidence and their knowledge and experience, the GDG agreed that timely initiation of antimicrobial treatment is likely to contribute to reducing equity gaps and discrimination in health-care access, especially in resource-limited settings, and may improve health-related quality of life. In addition, the antibiotics commonly used for meningitis are widely available and accessible, including in primary health-care settings as well as hospital emergency departments. Finally, affordability considerations possibly play a marginal role when addressing the optimal timing of antimicrobial treatment compared to the type of antibiotic or duration of therapy.

Source of evidence

A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.

Direct evidence

None of the included qualitative studies directly focused on health equity, equality or non-discrimination in relation to the timing of antibiotic therapy.

Feasibility

Judgement: Probably yes

Pre-hospital therapy

Administration of antibiotics prior to admission or transfer to an appropriate health-care facility might be particularly challenging in fragile, vulnerable and conflict-affected settings, where access to health care is disrupted or severely limited. However, the GDG emphasized the need to draw on proven strategies and practices and leverage successful experiences in the management of other infectious diseases, including severe malaria, when operationalizing similar interventions for meningitis in resource-limited settings. While highlighting that antimicrobial treatment should be administered intravenously, the GDG also acknowledged that intramuscular administration should be considered in settings where intravenous administration is not possible and/or an intravenous line cannot be secured.

Early in-hospital therapy

The GDG agreed that early intravenous administration of antibiotics is likely to be feasible when conducted in an appropriate health-care facility. In addition, while emphasizing that blood sampling and, in the absence of contraindications or reasons for deferral, LP should be performed prior to antimicrobial treatment, they highlighted that any delay in diagnostic investigations should not serve as a barrier to therapy administration.

Source of evidence

A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.

Direct evidence

HICs

Challenges related to early therapy initiation faced by health-care workers in primary care settings were notably significant. These included the belief that antibiotics should be administered via injections in hospital settings, a hesitation to administer injections in primary care due to a lack of experience and anxiety caused by limited familiarity with the process. Difficulties with gaining intravenous access as a barrier to initiating antimicrobial treatment was also highlighted (2 studies, low confidence).

Organizational barriers also played a role in delaying antimicrobial treatment initiation among health-care workers. These included specific advice from emergency departments, perceived

disapproval from the national prescribing service regarding the general use of antibiotics and the unavailability of antibiotics (1 study, very low confidence).

Evidence also highlighted that general practitioners were inclined to start antimicrobial treatment when they were certain of the diagnosis. Failure to start treatment seemed to be related to uncertainty about the diagnosis, partly because of the tendency to focus on extreme signs (2 studies, moderate confidence). Early empirical treatment initiated by paediatricians could save time regardless of diagnostic certainty (1 study, very low confidence).

Human rights and sociocultural acceptability

Judgement: Probably yes

Based on the available evidence and their knowledge and experience, the GDG agreed that early antimicrobial treatment is fully aligned with human rights principles and probably considered an acceptable intervention by both patients and health-care professionals.

Source of evidence

A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.

Direct evidence

None of the included qualitative studies directly focused on the compliance of the timing of antimicrobial treatment with universal human rights standards or its sociocultural acceptability. However, the main relevant findings on meningitis treatment in LMICs are summarized as part of the indirect evidence. None of the studies conducted in HICs were considered applicable to this guideline question.

Indirect evidence

LMICs

Some studies indicated a preference for conventional medicine as a treatment choice. Participants, including older patients and their caregivers, favoured medical interventions over traditional treatment practices. However, some patients and caregivers highlighted that "Western" practitioners typically focused on diagnosing peripheral causes and managing symptoms, whereas traditional healers addressed the root cause of the illness (4 studies, moderate confidence).

Narratives from caregivers of children who had encountered meningitis, as well as those whose neighbours' or relatives' children had previous meningitis episodes, underscored that health-care

facilities were the primary point of care for meningitis, suggesting trust in the ability of formal health-care settings to provide necessary and effective treatment (2 studies, low confidence).

Two studies highlighted the ways that gender dynamics influenced decision-making processes in health care. Specifically, women often sought validation from their husbands, adult relatives or neighbours regarding the severity of health conditions before seeking care. This trend was exacerbated by the fact that many women had limited or no formal education and were unemployed, factors that constrained their capacity to make informed health decisions for their families. In contrast, men were more likely to make health-care decisions independently, underscoring a gender disparity in autonomy and access to health-care decision-making (2 studies, moderate confidence).

Another study reported that cultural beliefs and care-seeking behaviour related to meningitis in LMICs were still influenced by traditional thinking. However, despite the dominance of traditional views, there was a gradual shift towards embracing modern understandings of disease and, consequently, more contemporary approaches to care-seeking (2 studies, low confidence).

CSF: cerebrospinal fluid; GDG: Guideline Development Group; HICs: high-income countries; LMICs: low- and middle-income countries; LP: lumbar puncture.

6. Empiric antimicrobial treatment regimen (Part 1)

6.1 Guideline question

In individuals with suspected or probable acute bacterial meningitis, should empiric treatment with parenteral ceftriaxone or cefotaxime combined with additional antimicrobials be used rather than monotherapy with ceftriaxone or cefotaxime?

Population: Suspected or probable cases of acute bacterial meningitis

Subgroups: Age groups (children, adults, people aged > 60 years), pregnancy, immunocompromised status, prevalence of pneumococcal resistance to beta-lactams

Intervention: Parenteral ceftriaxone or cefotaxime combined with additional antimicrobials[8]

Comparator: Monotherapy with ceftriaxone or cefotaxime

Outcome:

Critical: Mortality, time to resolution of symptoms, disease complications (sepsis, DIC, neurological complications including neurological sequelae)

Important: Adverse effects

Full details of the evidence, including references, are provided in Web Annex A (6. Empiric antimicrobial treatment regimen, Part 1) and Web Annex B (Qualitative and economic evidence reports).

[8] Additional antimicrobials include ampicillin, amoxicillin, vancomycin and rifampicin.

6.2 Evidence-to-Decision framework

Priority of the problem
Judgement: Yes Acute meningitis is a life-threatening condition that requires prompt initiation of empiric antimicrobial treatment. In some forms of acute bacterial meningitis, including meningococcal and pneumococcal meningitis, antimicrobial treatment is also instrumental in reducing the duration of the infectious period and mitigating the risk of transmission to close contacts. Empiric antibiotic selection is directed at the most likely bacteria and primarily determined by the age of the patient, the presence of specific risk factors and the local prevalence of drug-resistant pathogens (e.g. susceptibility to penicillin and third-generation cephalosporins of *Streptococcus pneumoniae*). However, there are some variations in treatment approaches across different settings, potentially affecting patient outcomes and resource utilization. As antimicrobial treatment remains the mainstay of treatment for acute bacterial meningitis, the Guideline Development Group (GDG) emphasized the critical importance of formulating recommendations on empiric antibiotic therapy, even in the absence of comparative studies addressing the guideline question.
Desirable effects
Judgement: Varies The GDG discussed the most common causative agents in various age groups, including *S. pneumoniae*, *Neisseria meningitidis, Haemophilus influenzae* and, among children aged 1–3 months, *Escherichia coli* and *Streptococcus agalactiae.* They therefore emphasized the benefits of intravenous ceftriaxone or cefotaxime when used as the initial empiric treatment regimen for children aged > 1 month and adults with suspected or probable acute bacterial meningitis. In addition, they highlighted available evidence showing that ceftriaxone is effective in eradicating nasopharyngeal carriage of *N. meningitidis* (Zalmanovici et al. 2013) and contributes to reducing infection transmission during meningococcal and pneumococcal meningitis epidemics. Based on the available evidence and their clinical knowledge and experience, the GDG agreed that patients at risk for *Listeria* infection comprise individuals aged > 60 years, pregnant women and immunocompromised hosts and highlighted the benefits of intravenous ampicillin or amoxicillin when given in addition to the initial antimicrobial regimen in the presence of any of the above-mentioned risk factors. The GDG also discussed the clinical and public health importance of penicillin-resistant or third-generation cephalosporin-resistant strains of *S. pneumoniae* and emphasized the need for intravenous vancomycin, rifampicin or linezolid in addition to the initial antimicrobial regimen in

settings with demonstrated high prevalence of penicillin or cephalosporin resistance among pneumococcal isolates.

Source of evidence

A systematic review was conducted to compare combined empiric antimicrobial treatment (ceftriaxone or cefotaxime with additional antimicrobials) with monotherapy (ceftriaxone or cefotaxime).

Direct evidence

No relevant comparative studies were found. However, additional evidence that was considered relevant to the guideline question is summarized below.

Additional evidence

Risk factors for Listeria *infection*

Invasive infections due to *Listeria monocytogenes*, including meningitis and meningoencephalitis, are often associated with one or more risk factors, including advanced age, pregnancy and immunocompromised status (Koopmans et al. 2023).

Ageing entails both functional and structural changes in the immune system leading to reduced capability to fight infections. According to a report from the United States Centers for Disease Control and Prevention (CDC), individuals aged ≥ 65 years have 4 times higher incidence of *Listeria* infection compared to the general population (CDC, 2013). The increasing incidence of *Listeria* infections with age was also observed in a prospective observational study conducted in France (Charlier et al. 2017). The reported incidence rate spanned from 0.05 per 100 000 individuals aged < 65 years to 0.38 and 0.98 cases per 100 000 individuals aged 65–74 years and > 75 years, respectively.

Pregnant women have an increased risk of *Listeria* infection, probably as a consequence of immunological changes during pregnancy. According to a CDC report, pregnant women have 10 times higher incidence of *Listeria* infection than the general population (CDC, 2013). In addition, when compared to non-pregnant women of reproductive age, pregnant women have > 100 times higher risk of *Listeria* infection (Pouillot et al. 2012).

One prospective observational study conducted in France with 818 patients reported that 93% of all patients with listeriosis had a least one immunocompromising comorbidity (Charlier et al. 2017). Several studies investigated immunocompromising conditions that are associated with a higher risk of *Listeria* infection, identifying the following: immunosuppressive therapy, including systemic corticosteroids, cytotoxic agents, TNF-alpha antagonists (Charlier et al. 2017; Annaissie E et al. 1992; Sheybani et al. 2022); solid organ transplantation (Goulet et al. 2012); haematopoietic stem cell transplantation (Chang et al. 1995); acquired immunodeficiency syndrome (Goulet V et al. 2012; Schuchat et al. 1992); solid tumours and haematologic malignancies (Costerus et al.

2016; Pomar et al. 2017); diabetes mellitus (Charlier et al. 2017); alcohol use disease (van Veen et al. 2017); end-stage kidney disease, including in patients requiring dialysis (Goulet et al. 2012); chronic liver disease (Lim et al. 2017).

Pneumococcal penicillin resistance

A growing body of evidence indicates the presence of high penicillin resistance rates among *Streptococcus pneumoniae* isolates in several regions, including several countries in Europe, Africa, Asia and the Americas (McGill et al. 2016, van de Beek et al. 2012). Penicillin resistance rates may range from 1% up to 50% in some countries and are usually markers of resistance or decreased susceptibility to other antibiotics, including third-generation cephalosporins.

Undesirable effects

Judgement: Moderate

The GDG highlighted the risks associated with the inappropriate use of broad-spectrum antibiotics, including antimicrobial resistance, drug toxicity and drug interactions (including in settings where traditional medicine is widely used). They also raised some concerns about the use of rifampicin in settings with a high tuberculosis burden and discussed its potential role in promoting drug resistance among individuals with tuberculosis infection or disease.

Source of evidence

A systematic review was conducted to compare combined empiric antimicrobial treatment (ceftriaxone or cefotaxime with additional antimicrobials) with monotherapy (ceftriaxone or cefotaxime).

Direct evidence

No relevant comparative studies were found.

Certainty of the evidence

Judgement: Very low

The certainty of evidence was considered very low due to the lack of direct evidence addressing the guideline question.

Values

Judgement: Possibly important uncertainty or variability

Based on the available evidence and their knowledge and experience, the GDG agreed that there might be important uncertainty or variability across settings in how much people value the main outcomes.

Source of evidence

A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.

Direct evidence

No direct evidence was identified regarding the uncertainty about or variability in how much people value the main outcomes. However, the included studies highlighted a complex landscape of values and beliefs surrounding the treatment of meningitis, underscoring the diversity in health-care decision-making processes across different communities in both low- and middle-income countries (LMICs) and high-income countries (HICs). Particularly, some insights into patient and caregiver values provided a nuanced understanding of treatment preferences and healthcare-seeking behaviours and are summarized as indirect evidence.

Indirect evidence

LMICs

Studies focused on patients'/caregivers' values related to meningitis treatment reported that biomedical treatments were most effective in diagnosing, treating and managing the disease. This acknowledgement reflected a value placed on conventional medical approaches when it came to addressing the physical aspects of the disease (2 studies, low confidence).

However, the choice of treatment was profoundly influenced by the perceived cause of the illness. A significant portion of patients and caregivers, especially those attributing the disease to supernatural forces, declared a preference for traditional and Islamic treatment methods (4 studies, moderate confidence).

The initial response to meningitis symptoms in caregivers and adult patients often involved a combination of self-medication and seeking advice or treatment from traditional healers and soothsayers, particularly to discern if the disease had supernatural origins (4 studies, moderate confidence). Patronage of government hospitals was considered the last resort when the illness became severe and not amenable to alternative care. This pattern of health-care utilization underscored the significant influence of cultural practices on health-care decisions, indicating a complex interplay between traditional beliefs, perceived efficacy of treatments and the severity of the disease in guiding treatment choices (1 study, low confidence).

Collective decision-making was also a barrier to timely help-seeking. As patients and caregivers were dependent on the community or senior household members to fund emergency care expenses, social validation of the illness severity was essential to warrant funding (2 studies, very low confidence).

Studies indicated that an increase in disease severity initiated help-seeking behaviour. The key factor at the household level was the ability to recognize when the illness had become severe enough to necessitate seeking treatment, rather than recognizing specific signs and symptoms of acute bacterial meningitis. Factors such as disruption of social life, weakness, loss of appetite and the inability to work were among the most cited reasons prompting individuals to seek help (2 studies, moderate confidence).

HICs

One study pointed out that health-care workers in primary care settings may have lacked experience with treating meningitis. As a result, they were more focused on getting a child hospitalized as early as possible rather than starting treatment on their own (1 study, moderate confidence).

The literature consistently indicated that caregivers' primary concern revolved around the survival of their child, with many expressing profound worry about this outcome (5 studies, low confidence).

Finally, one study highlighted that the complexity of treatment trajectories could be a source of dissatisfaction with health services (1 study, very low confidence).

Balance of effects

Judgement: Probably favours the comparison

The judgement was based on the evidence and judgements presented above.

Resources required

Judgement: Moderate costs

Combination therapy with ceftriaxone or cefotaxime and at least another antimicrobial inherently increases the treatment costs compared to monotherapy. In LMICs, where health-care resources are often limited, even small increases in drug costs can significantly impact budget allocations and treatment accessibility. On the other hand, increased direct costs related to antimicrobial treatment must be balanced against the potential savings related to the prevention of long-term complications and disability and/or reduced hospitalization, especially among selected individuals (e.g. those with risk factors for *L. monocytogenes*) and/or in certain geographical settings (e.g. those with prevalent reduced susceptibility to penicillin of *S. pneumoniae*) where combination therapy is often warranted.

Source of evidence

A scoping review was undertaken to compile information regarding costs, resource utilization and cost-effectiveness associated with meningitis diagnosis, treatment and management of sequelae.

Direct evidence

The included studies did not directly address the cost of combined antimicrobial regimens or monotherapy but found evidence of the unit cost of different antibiotics in LMICs. None of the studies conducted in HICs were considered applicable to this guideline question.

LMICs

One study conducted in Gambia reported the unit cost of each vial of ceftriaxone (2 ml/250mg), ampicillin (2 ml/500mg) and amoxicillin (100 ml bottle, 125 mg/5 ml) was US$ 2.5, 0.3 and 0.64, respectively (2010 US$). In another study conducted in Viet Nam, the unit cost of each vial of ceftriaxone (250 mg/vial) and cefotaxime (1 g/vial) was US$ 4.24 and 1.35 (2006 US$), respectively.

Certainty of the evidence on resources required

Judgement: Very low

The judgement reflected the limited scope of the evidence, the absence of comprehensive cost comparisons between treatment options and the potential variability in cost data across different LMICs.

Cost-effectiveness

Judgement: No included studies

A scoping review was undertaken to compile information regarding costs, resource utilization and cost-effectiveness associated with meningitis diagnosis, treatment and management of sequelae. However, no cost-effectiveness studies were found that would be applicable to this guideline question.

Health equity, equality and non-discrimination

Judgement: Varies

Empiric therapy consisting of a third-generation cephalosporin combined with another antimicrobial may significantly increase the financial burden on patients or their families, particularly in resource-limited settings where treatment is not provided free of charge. Moreover, while amoxicillin or ampicillin are widely accessible, other antibiotics, such as vancomycin, are often not readily available and/or affordable in resource-constrained environments, posing additional challenges in treatment access. On the other hand, the GDG highlighted that combined antimicrobial treatment in selected settings (e.g. presence of risk factors for *Listeria* infection) is likely to reduce health inequalities.

Source of evidence

A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.

Direct evidence

None of the included qualitative studies directly focused on health equity, equality or non-discrimination in relation to different empiric treatment regimens. However, the main relevant findings on meningitis treatment in LMICs are summarized as part of the indirect evidence. None of the studies conducted in HICs were considered applicable to this guideline question.

Indirect evidence

LMICs

Reviewed evidence highlighted a lack of knowledge about meningitis symptoms in all stakeholder groups (caregivers, patients and communities), which was associated with a delay in timely help-seeking (2 studies, moderate confidence). Misdiagnosing meningitis with malaria also contributed to difficulties in the provision of prompt and appropriate care (2 studies, very low confidence).

As reported in most studies, orthodox treatment carried a great financial burden for both caregivers and adult patients. The lack of funds was the primary reason for seeking alternative types of treatment before going to the hospital. Interviews revealed that prescriptions were costly, resulting in increased financial dependency and substantial debts incurred by patients and caregivers to afford treatment expenses (2 studies, low confidence).

These factors collectively contributed to the majority of respondents favouring alternative medicine as a more affordable approach to seeking care (2 studies, low confidence). Additionally, gender disparities played a significant role in accessing care and its timeliness. Women often required the approval of family and community before deciding to seek help, in contrast to men, who generally made such decisions independently (2 studies, moderate confidence).

Feasibility

Judgement: Varies

Based on their technical knowledge and experience, the GDG agreed that feasibility of combined antimicrobial treatment varies across different settings, depending on available human, financial and infrastructural resources. They also emphasized some practical benefits of using ceftriaxone over cefotaxime, including its wider availability in resource-limited settings and longer half-life, which allowed twice daily administration and resource optimization. On the other hand, cefotaxime was considered equally appropriate as ceftriaxone for empiric treatment in non-epidemic settings and may offer advantages when used alongside calcium-containing solutions, which are incompatible with ceftriaxone administration. Finally, they highlighted that intravenous

administration, dosing and monitoring of vancomycin might be impractical in some resource-limited settings.

Source of evidence

A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.

Direct evidence

None of the included qualitative studies directly focused on the feasibility of different empiric antimicrobial regimens. However, the main relevant findings on meningitis treatment in LMICs and HICs are summarized as part of the indirect evidence.

Indirect evidence

LMICs

The qualitative evidence review identified barriers potentially limiting the feasibility of timely care. Lack of knowledge about meningitis causes and symptoms among health-care workers was highlighted. Misdiagnosing meningitis with malaria also contributed to difficulties in the provision of prompt and appropriate care (2 studies, very low confidence).

Evidence showed elevated expenses incurred by households for medicines, despite the official government policy and the regular scarcity of complementary medicines supplied by ministries of health. If this happened, patients paid for their own medicines, including procuring them from costlier private pharmacies when they arrived outside the operating hours of the health centre's pharmacy (2 studies, very low confidence).

Reports among primary health-care workers and patients highlighted a lack of quality care, with long waiting times, presumptive diagnosis without examination, verbal mistreatment and underestimation of caregivers' concerns (2 studies, very low confidence).

Further to this, a significant barrier to effective management and treatment of meningitis in LMICs was the prevailing belief in supernatural explanations for the illness. This belief system was associated with a preference for alternative diagnostic and treatment approaches, often at the expense of seeking timely and appropriate medical care. The inclination towards alternative health-care providers, driven by cultural norms and low socioeconomic status, delayed the use of effective treatments that were crucial for mitigating the disease's impact (5 studies, moderate confidence).

HICs

Challenges faced by health-care workers in primary care settings were significant. These included the belief that antibiotics should be administered via injections in hospital settings, a hesitation to

administer injections in primary care due to a lack of experience and anxiety caused by a limited familiarity with the process. Difficulties with gaining intravenous access as a barrier to initiating antimicrobial treatment was also highlighted (2 studies, low confidence).

Organizational barriers also played a role in delaying antimicrobial treatment initiation among health-care workers. These included specific advice from emergency departments, perceived disapproval from national prescribing services regarding the general use of antibiotics and the unavailability of antibiotics (1 study, very low confidence).

One study pointed out that complex treatment paths could lead to discontent with health services and complicate prompt access to health care (1 study, very low confidence).

Two studies also found that general practitioners were inclined to start antimicrobial treatment when they were certain of the diagnosis. Failure to start treatment seemed to be related to uncertainty about the diagnosis, partly because of the tendency to focus on extreme signs (2 studies, moderate confidence). Early empirical treatment initiated by paediatricians could have saved time regardless of diagnostic certainty (1 study, very low confidence).

Human rights and sociocultural acceptability

Judgement: Varies

Based on the available evidence and their knowledge and experience, the GDG agreed that the acceptability of the intervention is likely to vary across settings depending on cultural beliefs regarding conventional medicine and trust in the health-care system.

Source of evidence

A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.

Direct evidence

None of the included qualitative studies directly focused on the compliance of different empiric antimicrobial regimens with universal human rights standards or their sociocultural acceptability. However, the main relevant findings on meningitis treatment in LMICs are summarized as part of the indirect evidence. None of the studies conducted in HICs were considered applicable to this guideline question.

Indirect evidence

LMICs

Some studies indicated a preference for conventional medicine as a treatment choice. Participants, including older patients and their caregivers, favoured medical interventions over

traditional treatment practices. However, some patients and caregivers highlighted that "Western" practitioners typically focused on diagnosing peripheral causes and managing symptoms, whereas traditional healers addressed the root cause of the illness (4 studies, moderate confidence).

Narratives from caregivers of children who had encountered meningitis, as well as those whose neighbours' or relatives' children had previous meningitis episodes, underscored that health-care facilities were the primary point of care for meningitis, suggesting trust in the ability of formal health-care settings to provide necessary and effective treatment (2 studies, low confidence).

Two studies highlighted the ways that gender dynamics influenced decision-making processes in health care. Specifically, women often sought validation from their husbands, adult relatives or neighbours regarding the severity of health conditions before seeking care. This trend was exacerbated by the fact that many women had limited or no formal education and were unemployed, factors that constrained their capacity to make informed health decisions for their families. In contrast, men were more likely to make health-care decisions independently, underscoring a gender disparity in autonomy and access to health-care decision-making (2 studies, moderate confidence).

Another study reported that cultural beliefs and care-seeking behaviour related to meningitis in LMICs were still influenced by traditional thinking. However, despite the dominance of traditional views, there was a gradual shift towards embracing modern understandings of disease and, consequently, more contemporary approaches to care-seeking (2 studies, low confidence).

CDC: Centers for Disease Control and Prevention. GDG: Guideline Development Group; HICs: high-income countries; LMICs: low- and middle-income countries.

7. Empiric antimicrobial treatment regimen (Part 2)

7.1 Guideline question

In individuals with suspected or probable acute bacterial meningitis, should alternative parenteral antimicrobial regimens (penicillin [i.e. benzylpenicillin, ampicillin, amoxicillin] or chloramphenicol alone or in combination) be used rather than monotherapy with ceftriaxone or cefotaxime?

Population: Suspected or probable cases of acute bacterial meningitis

Subgroups: Age groups (children, adults, people aged > 60 years), pregnancy, immunocompromised status, prevalence of pneumococcal resistance to beta-lactams

Intervention: Alternative parenteral antimicrobial regimens (penicillin [i.e. benzylpenicillin, ampicillin, amoxicillin] or chloramphenicol alone or in combination)

Comparator: Monotherapy with ceftriaxone or cefotaxime

Outcome:

Critical: Mortality, time to resolution of symptoms, disease complications (sepsis, DIC, neurological complications, including neurological sequelae)

Important: Adverse effects

Full details of the evidence, including references, are provided in Web Annex A (7. Empiric antimicrobial treatment regimen, Part 2) and Web Annex B (Qualitative and economic evidence reports).

7.2 Evidence-to-Decision framework

Priority of the problem
Judgement: Yes Acute meningitis is a life-threatening condition that requires prompt initiation of empiric antimicrobial treatment. In some forms of acute bacterial meningitis, including meningococcal and pneumococcal meningitis, prompt initiation of antimicrobial treatment is also instrumental in reducing the duration of the infectious period and mitigating the risk of transmission to close contacts. While third-generation cephalosporins, including ceftriaxone and cefotaxime, are widely used as the backbone of empiric treatment regimen in most settings, they may not always be available or accessible where resources are limited, leading to significant variations in clinical practice.
Desirable effects
Judgement: Trivial The Guideline Development Group (GDG) emphasized that the available evidence was of very low certainty and did not show a clear direction of effect in favour or against alternative parenteral antimicrobial regimens. They also highlighted that the included studies were conducted up to 4 decades prior to the current publication and may thus not adequately represent the current epidemiological landscape of antimicrobial resistance. Most studies compared ceftriaxone or cefotaxime to combinations of alternative antibiotics (i.e. chloramphenicol *and* any of the following: benzylpenicillin, ampicillin or amoxicillin). Moreover, the GDG expressed concerns about the use of benzylpenicillin or ampicillin monotherapy in settings with high prevalence of reduced susceptibility to penicillin among *Neisseria meningitidis* isolates, penicillin-resistant *Streptococcus pneumoniae*, or beta-lactamase producing *Haemophilus influenzae*. Similarly, the GDG was concerned regarding the use of chloramphenicol alone where resistance among *S. pneumoniae* or *N. meningitis* isolates is common.
Source of evidence
A systematic review was conducted to compare alternative parenteral antimicrobial regimens with monotherapy with ceftriaxone or cefotaxime.
Direct evidence
Overall, 20 randomized controlled trials (RCTs) conducted in children and adults were included. No data were available for the subgroups of interest, including elderly patients, pregnant women or immunocompromised individuals.

All-cause mortality

Very-low-certainty evidence from 13 RCTs in 1203 patients showed that the effect of alternative parenteral antibiotics on mortality compared to ceftriaxone or cefotaxime was uncertain (RR 1.02, 95% CI 0.68–1.53). All studies were small trials with a low number of events and high risk of bias. The confidence interval was wide, ranging from moderate benefit to significant harm.

Time to resolution of fever

Very-low-certainty evidence from 12 RCTs with 509 patients showed that the effect of alternative parenteral antibiotics on time to fever resolution compared to ceftriaxone or cefotaxime was uncertain (MD 0.75 days, 95% CI 0.26–1.24).

Neurological sequelae

Very-low-certainty evidence from 14 RCTs with 1141 patients showed that the effect of alternative parenteral antibiotics on neurological sequelae compared to ceftriaxone or cefotaxime was uncertain (RR 1.11, 95% CI 0.88–1.41). The confidence interval was very wide, ranging from moderate benefit to significant harm.

Undesirable effects

Judgement: Varies

Side effects and drug toxicity varies based on the antibiotic type and class. Use of beta-lactams, including penicillin, ampicillin, amoxicillin, and third-generation cephalosporins, may be associated with several adverse effects. These included IgE-mediated allergic reactions (e.g. anaphylaxis), skin rash, diarrhoea and gastrointestinal complaints, renal toxicity and other hypersensitivity and immune-mediated manifestations. Moreover, penicillins are most commonly linked encephalopathy and high doses may increase the risk of seizures.

Chloramphenicol is associated with both irreversible idiosyncratic and dose-related reversible bone marrow toxicity, resulting in aplastic anaemia, leukopenia and/or thrombocytopenia. In addition, when administered during the third trimester of pregnancy, chloramphenicol may be responsible for "gray baby syndrome", especially among premature neonates.

Prolonged use of beta-lactams and/or chloramphenicol may lead to fungal or bacterial superinfection, including *Clostridioides difficile*-associated diarrhoea and colitis.

Source of evidence

A systematic review was conducted to compare alternative parenteral antimicrobial regimens with monotherapy with ceftriaxone or cefotaxime.

Direct evidence

Overall, 20 RCTs conducted in children and adults were included. Very-low-certainty evidence from 10 RCTs with 630 patients showed that the effect of alternative parenteral antibiotics on adverse events compared to ceftriaxone or cefotaxime was uncertain (RR 0.70, 95% CI 0.46–1.04). No data were available for the subgroups of interest, including elderly patients, pregnant women or immunocompromised individuals.

Certainty of the evidence

Judgement: Very low

The certainty of evidence was very low for all critical outcomes.

Values

Judgement: Possibly important uncertainty or variability

Based on the available evidence and their knowledge and experience, the GDG agreed that there might be important uncertainty or variability across settings in how much people value the main outcomes.

Source of evidence

A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.

Direct evidence

No direct evidence was identified regarding the uncertainty about or variability in how much people value the main outcomes. However, the included studies highlighted a complex landscape of values and beliefs surrounding the treatment of meningitis, underscoring the diversity in health-care decision-making processes across different communities in both low- and middle-income countries (LMICs) and high-income countries (HICs). Particularly, some insights into patient and caregiver values provided a nuanced understanding of treatment preferences and healthcare-seeking behaviours and are summarized as indirect evidence.

Indirect evidence

LMICs

Studies focused on patients'/caregivers' values related to meningitis treatment reported that biomedical treatments were most effective in diagnosing, treating and managing the disease. This acknowledgement reflected a value placed on conventional medical approaches when it came to addressing the physical aspects of the disease (2 studies, low confidence).

However, the choice of treatment was profoundly influenced by the perceived cause of the illness. A significant portion of patients and caregivers, especially those attributing the disease to supernatural forces, declared a preference for traditional and Islamic treatment methods (4 studies, moderate confidence).

The initial response to meningitis symptoms in caregivers and adult patients often involved a combination of self-medication and seeking advice or treatment from traditional healers and soothsayers, particularly to discern if the disease had supernatural origins (4 studies, moderate confidence). Patronage of government hospitals was considered the last resort when the illness became severe and not amenable to alternative care. This pattern of health-care utilization underscored the significant influence of cultural practices on health-care decisions, indicating a complex interplay between traditional beliefs, perceived efficacy of treatments and the severity of the disease in guiding treatment choices (1 study, low confidence).

Collective decision-making was also a barrier to timely help-seeking. As patients and caregivers were dependent on the community or senior household members to fund emergency care expenses, social validation of the illness severity was essential to warrant funding (2 studies, very low confidence).

Studies indicated that an increase in disease severity initiated help-seeking behaviour. The key factor at the household level was the ability to recognize when the illness had become severe enough to necessitate seeking treatment, rather than recognizing specific signs and symptoms of acute bacterial meningitis. Factors such as disruption of social life, weakness, loss of appetite and the inability to work were among the most cited reasons prompting individuals to seek help (2 studies, moderate confidence).

HICs

One study pointed out that health-care workers in primary care settings may have lacked experience with treating meningitis. As a result, they were more focused on getting a child hospitalized as early as possible rather than starting treatment on their own (1 study, moderate confidence).

The literature consistently indicated that caregivers' primary concern revolved around the survival of their child, with many expressing profound worry about this outcome (5 studies, low confidence).

Finally, one study highlighted that the complexity of treatment trajectories could be a source of dissatisfaction with health services (1 study, very low confidence).

Balance of effects

Judgement: Probably favours the comparison

The judgement was based on the evidence and judgements presented above.

Resources required
Judgement: Moderate savings The GDG highlighted that the included studies were context-specific, partially outdated, and lacked comprehensive estimates capturing the costs associated with staff and consumables. Based on their clinical knowledge and experience, however, the GDG indicated that penicillins (including benzylpenicillin, amoxicillin, and ampicillin) and chloramphenicol generally incur lower costs than third-generation cephalosporins. On the other hand, they acknowledged the difficulty of providing reliable estimates of medicine costs, as various factors, including inflation and limited supply, may significantly impact prices across different countries.
Source of evidence A scoping review was undertaken to compile information regarding costs, resource utilization and cost-effectiveness associated with meningitis diagnosis, treatment and management of sequelae.
Direct evidence The included studies did not directly address the cost of combined antimicrobial regimens or monotherapy but found evidence of the unit cost of different antibiotics in LMICs. None of the studies conducted in HICs were considered applicable to this guideline question. *LMICs* One study conducted in Gambia reported the unit cost of each vial of ceftriaxone (2 ml/250 mg), penicillin (2 ml/1 000 000 IU), ampicillin (2 ml/500 mg), amoxicillin (100 ml bottle, 125 mg/5 ml), chloramphenicol (2 ml/1 g) was US$ 2.5, 0.26, 0.3, 0.64, 0.5, respectively (2010 US$). In another study conducted in Viet Nam, the unit cost of each vial of ceftriaxone (250 mg/vial) and cefotaxime (1g/vial) was US$ 4.24 and 1.35 (2006 US$), respectively.
Certainty of the evidence on resources required
Judgement: Very low The judgement reflected the limited scope of the evidence, the absence of comprehensive cost comparisons between treatment options and the potential variability in cost data across different LMICs.
Cost-effectiveness
Judgement: No included studies A scoping review was undertaken to compile information regarding costs, resource utilization and cost-effectiveness associated with meningitis diagnosis, treatment and management of sequelae.

However, no cost-effectiveness studies were found that would be applicable to this guideline question.

Health equity, equality and non-discrimination

Judgement: Varies

Penicillins and chloramphenicol are readily available and/or accessible in most settings. In addition, empiric therapy with these antibiotics may be more affordable for patients or their families than third-generation cephalosporins, particularly in resource-limited settings where treatment is not provided free of charge. On the other hand, third-generation cephalosporins are likely to be more beneficial and reduce health inequalities where resistance to penicillins is on the rise.

Source of evidence

A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.

Direct evidence

None of the included qualitative studies directly focused on health equity, equality or non-discrimination in relation to different empiric treatment regimens. However, the main relevant findings on meningitis treatment in LMICs are summarized as part of the indirect evidence. None of the studies conducted in HICs were considered applicable to this guideline question.

Indirect evidence

LMICs

Reviewed evidence highlighted a lack of knowledge about meningitis symptoms in all stakeholder groups (caregivers, patients and communities), which was associated with a delay in timely help-seeking (2 studies, moderate confidence). Misdiagnosing meningitis with malaria also contributed to difficulties in the provision of prompt and appropriate care (2 studies, very low confidence).

As reported in most studies, orthodox treatment carried a great financial burden for both caregivers and adult patients. The lack of funds was the primary reason for seeking alternative types of treatment before going to the hospital. Interviews revealed that prescriptions were costly, resulting in increased financial dependency and substantial debts incurred by patients and caregivers to afford treatment expenses (2 studies, low confidence).

These factors collectively contributed to the majority of respondents favouring alternative medicine as a more affordable approach to seeking care (2 studies, low confidence). Additionally, gender disparities played a significant role in accessing care and its timeliness. Women often

required the approval of family and community before deciding to seek help, in contrast to men, who generally made such decisions independently (2 studies, moderate confidence).

Feasibility

Judgement: Varies

While ceftriaxone is often available, access to third-generation cephalosporins may be limited in some resource-limited environments and/or during bacterial meningitis epidemics, resulting in significant implementation challenges. Conversely, the alternative use of penicillins and/or chloramphenicol as empiric therapy may be more easily operationalized in these settings, although it typically requires multiple daily intravenous administrations. Regardless of the antibiotic regimen, however, multi-day treatment courses remain challenging to implement when health services are stretched to capacity.

Source of evidence

A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.

Direct evidence

None of the included qualitative studies directly focused on the feasibility of different empiric antimicrobial regimens. However, the main relevant findings on meningitis treatment in LMICs and HICs are summarized as part of the indirect evidence.

Indirect evidence

LMICs

The qualitative evidence review identified barriers potentially limiting the feasibility of timely care. Lack of knowledge about meningitis causes and symptoms among health-care workers was highlighted. Misdiagnosing meningitis with malaria also contributed to difficulties in the provision of prompt and appropriate care (2 studies, very low confidence).

Evidence showed elevated expenses incurred by households for medicines, despite the official government policy and the regular scarcity of complementary medicines supplied by ministries of health. If this happened, patients paid for their own medicines, including procuring them from costlier private pharmacies when they arrived outside the operating hours of the health centre's pharmacy (2 studies, very low confidence).

Reports among primary health-care workers and patients highlighted a lack of quality care, with long waiting times, presumptive diagnosis without examination, verbal mistreatment and underestimation of caregivers' concerns (2 studies, very low confidence).

Further to this, a significant barrier to effective management and treatment of meningitis in LMICs was the prevailing belief in supernatural explanations for the illness. This belief system was associated with a preference for alternative diagnostic and treatment approaches, often at the expense of seeking timely and appropriate medical care. The inclination towards alternative health-care providers, driven by cultural norms and low socioeconomic status, delayed the use of effective treatments that were crucial for mitigating the disease's impact (5 studies, moderate confidence).

HICs

Challenges faced by health-care workers in primary care settings were significant. These included the belief that antibiotics should be administered via injections in hospital settings, a hesitation to administer injections in primary care due to a lack of experience and anxiety caused by a limited familiarity with the process. Difficulties with gaining intravenous access as a barrier to initiating antimicrobial treatment was also highlighted (2 studies, low confidence).

Organizational barriers also played a role in delaying antimicrobial treatment initiation among health-care workers. These included specific advice from emergency departments, perceived disapproval from national prescribing services regarding the general use of antibiotics and the unavailability of antibiotics (1 study, very low confidence).

One study pointed out that complex treatment paths could lead to discontent with health services and complicate prompt access to health care (1 study, very low confidence).

Two studies also found that general practitioners were inclined to start antimicrobial treatment when they were certain of the diagnosis. Failure to start treatment seemed to be related to uncertainty about the diagnosis, partly because of the tendency to focus on extreme signs (2 studies, moderate confidence). Early empirical treatment initiated by paediatricians could have saved time regardless of diagnostic certainty (1 study, very low confidence).

Human rights and sociocultural acceptability

Judgement: Varies

Based on the available evidence and their knowledge and experience, the GDG agreed that the acceptability of the intervention is likely to vary across settings depending on cultural beliefs regarding conventional medicine and trust in the health-care system.

Source of evidence

A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.

Direct evidence

None of the included qualitative studies directly focused on the compliance of different empiric antimicrobial regimens with universal human rights standards or their sociocultural acceptability. However, the main relevant findings on meningitis treatment in LMICs are summarized as part of the indirect evidence. None of the studies conducted in HICs were considered applicable to this guideline question.

Indirect evidence

LMICs

Some studies indicated a preference for conventional medicine as a treatment choice. Participants, including older patients and their caregivers, favoured medical interventions over traditional treatment practices. However, some patients and caregivers highlighted that "Western" practitioners typically focused on diagnosing peripheral causes and managing symptoms, whereas traditional healers addressed the root cause of the illness (4 studies, moderate confidence).

Narratives from caregivers of children who had encountered meningitis, as well as those whose neighbours' or relatives' children had previous meningitis episodes, underscored that health-care facilities were the primary point of care for meningitis, suggesting trust in the ability of formal health-care settings to provide necessary and effective treatment (2 studies, low confidence).

Two studies highlighted the ways that gender dynamics influenced decision-making processes in health care. Specifically, women often sought validation from their husbands, adult relatives or neighbours regarding the severity of health conditions before seeking care. This trend was exacerbated by the fact that many women had limited or no formal education and were unemployed, factors that constrained their capacity to make informed health decisions for their families. In contrast, men were more likely to make health-care decisions independently, underscoring a gender disparity in autonomy and access to health-care decision-making (2 studies, moderate confidence).

Another study reported that cultural beliefs and care-seeking behaviour related to meningitis in LMICs were still influenced by traditional thinking. However, despite the dominance of traditional views, there was a gradual shift towards embracing modern understandings of disease and, consequently, more contemporary approaches to care-seeking (2 studies, low confidence).

GDG: Guideline Development Group; HICs: high-income countries; LMICs: low- and middle-income countries; RCT: randomized controlled trial.

8. Duration of empiric antimicrobial treatment in non-epidemic settings

8.1 Guideline question

In non-epidemic settings, in individuals with suspected or probable acute bacterial meningitis, in the absence of pathogen identification, should empiric antimicrobial empiric treatment be administered for 10 days compared to a shorter or longer treatment course?

Population: Suspected or probable cases of acute bacterial meningitis in non-epidemic settings

Subgroups: Age groups (children, adults, people aged > 60 years), pregnancy, immunocompromised status, prevalence of pneumococcal resistance to beta-lactams

Intervention: Empiric antimicrobial treatment for a total duration of 10 days

Comparator: Empiric antimicrobial treatment for a total duration of less than 10 days (5–7 days) or more than 10 days (14–21 days)

Outcome:

Critical: Mortality, disease relapse, disease complications (sepsis, DIC, neurological complications, including neurological sequelae)

Important: Adverse effects

Full details of the evidence, including references, are provided in Web Annex A (8. Duration of empiric antimicrobial treatment in non-epidemic settings) and Web Annex B (Qualitative and economic evidence reports).

8.2 Evidence-to-Decision framework

Priority of the problem
Judgement: Yes Acute meningitis is a life-threatening condition that requires prompt initiation of empiric antimicrobial treatment. In non-epidemic settings, there is a notable lack of consensus on the optimal duration of antimicrobial treatment, especially in the absence of pathogen identification. This uncertainty can lead to variations in treatment approaches, potentially affecting patient outcomes and resource utilization. Particularly when the causative pathogen remains unidentified, determining the optimal treatment duration may be challenging and often relies on clinical and laboratory findings, including cerebrospinal fluid (CSF) results. In resource-limited settings, culture and molecular tests (e.g. polymerase chain reaction [PCR]) may not be readily available, accessible or affordable or may be conducted after initiation of antimicrobial treatment, potentially yielding negative results. As a result, the Guideline Development Group (GDG) agreed on the importance of making recommendations on treatment duration when the causative pathogen remains unknown.
Desirable effects
Judgement: Trivial Based on the body of direct and indirect evidence as well as their clinical knowledge and experience, the GDG indicated that empiric antimicrobial treatment for 10 days compared to empiric treatment for fewer or more than 10 days may have resulted in little to no difference on all-cause mortality, disease relapse and disease complications.
Source of evidence A systematic review was conducted to compare empiric antimicrobial treatment of 10 days with shorter or longer treatment regimens.
Direct evidence Overall, 2 randomized controlled trials (RCTs) were included. Both RCTs were carried out among children and compared a 10-day antimicrobial treatment regimen with shorter therapy regimens. No data were available for adults or other subgroups of interest or comparisons between 10 days of treatment and longer regimens. *All-cause mortality* Low-certainty evidence from 1 RCT with 330 children (aged 2 months to 12 years) revealed that empiric antimicrobial treatment for 10 days may have resulted in little to no difference in all-cause

mortality compared to empiric treatment for less than 10 days. The events were very rare and the confidence interval was wide, ranging from important benefit to significant harm (RR 0.96, 95% CI 0.28–3.27).

Disease relapse

Low-certainty evidence from 1 RCT with 104 children (aged 3 months to 14 years) revealed that empiric antimicrobial treatment for 10 days may have resulted in little to no difference in disease relapse compared to empiric antimicrobial treatment for less than 10 days. The events were very rare and the confidence interval was wide, ranging from important benefit to appreciable harm (RR 0.86, 95% CI 0.31–2.38).

Disease complications

Low-certainty evidence from 2 RCTs with 434 children revealed that the empiric antimicrobial treatment for 10 days may have resulted in little to no difference in disease complications (i.e. neurological sequelae, hearing loss and hydrocephalus) compared to empiric antimicrobial treatment for less than 10 days. The confidence interval was wide, ranging from moderate benefit to harm (RR 0.85, 95% CI 0.58–1.23).

Indirect evidence

Several studies did not meet the criteria for inclusion in the systematic review (e.g. treatment duration established after pathogen identification; no study arm with a 10-day regimen) but were considered as indirect evidence.

All-cause mortality

Two RCTs and 1 prospective multicentre study conducted in 240 children (age 3 weeks to 15 years) reported no significant differences in mortality between short (up to 7 days) and long (8–14 days) course therapies, with 2 of the studies reporting no deaths in any treatment groups.

Clinical recovery (disease relapse)

One prospective multicentre study conducted in 119 children (aged 3 weeks to 15 years) reported similar complete recovery rates in the short course (4–7 days) and long course therapy (8–14 days) arms (91% vs 89%, respectively).

Disease complications

Two RCTs and 1 quasi-randomized trial conducted in 239 children (age 1 month to 12 years) reported no significant differences in the frequency and types of neurological complications (i.e. long-term neurological impairment, hearing impairment, occurrence of seizures) between the short (4–7 days) and long (7–10 days) course therapy arms. Follow-up periods in these studies varied from 1 to 3 months after hospital discharge.

One RCT with 52 children beyond the neonatal period reported 1 ataxia and 3 hearing loss cases in the long course therapy arm (8–14 days) and no disease complications in the short therapy arm (4–7 days).
Undesirable effects
Judgement: Varies The GDG agreed that adverse events associated with antibiotics were more likely with regimens longer than 10 days and less likely with regimens shorter than 10 days. Similarly, adverse events related to hospitalization (e.g. hospital-acquired infections) are usually more common with longer duration regimens while they are likely to occur less often with shorter courses of treatment.
Source of evidence A systematic review was conducted to compare empiric antimicrobial treatment of 10 days with shorter or longer treatment regimens.
Direct evidence Overall, 2 RCTs were included. Both RCTs were conducted among children and compared a 10-day antimicrobial treatment regimen with shorter therapy regimens. No data were available on specific adverse effects directly related to the duration of antimicrobial treatment (e.g. increased risk of antibiotic resistance, adverse drug reactions).
Indirect evidence One prospective multicentre study did not meet the criteria for inclusion in the systematic review (treatment duration established after pathogen identification and no study arm with a 10-day regimen) but was considered as indirect evidence. Conducted in 119 children (aged between 3 weeks and 15 years), the study reported more frequent antibiotic adverse events in the long course therapy (8–14 days) compared with the short course therapy (4–7 days) arm (P = 0.065).
Certainty of the evidence
Judgement: Low The certainty of evidence was very low for all critical outcomes.
Values
Judgement: Possibly important uncertainty or variability

Based on the available evidence and their knowledge and experience, the GDG agreed that there might be important uncertainty or variability across settings in how much people value the main outcomes.

Source of evidence

A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.

Direct evidence

No direct evidence was identified regarding the uncertainty about or variability in how much people value the main outcomes. However, the included studies highlighted a complex landscape of values and beliefs surrounding the treatment of meningitis, underscoring the diversity in health-care decision-making processes across different communities in both low- and middle-income countries (LMICs) and high-income countries (HICs). Particularly, some insights into patient and caregiver values provided a nuanced understanding of treatment preferences and healthcare-seeking behaviours and are summarized as indirect evidence.

Indirect evidence

LMICs

Studies focused on patients'/caregivers' values related to meningitis treatment reported that biomedical treatments were most effective in diagnosing, treating and managing the disease. This acknowledgement reflected a value placed on conventional medical approaches when it came to addressing the physical aspects of the disease (2 studies, low confidence).

However, the choice of treatment was profoundly influenced by the perceived cause of the illness. A significant portion of patients and caregivers, especially those attributing the disease to supernatural forces, declared a preference for traditional and Islamic treatment methods (4 studies, moderate confidence).

The initial response to meningitis symptoms in caregivers and adult patients often involved a combination of self-medication and seeking advice or treatment from traditional healers and soothsayers, particularly to discern if the disease had supernatural origins (4 studies, moderate confidence). Patronage of government hospitals was considered the last resort when the illness became severe and not amenable to alternative care. This pattern of health-care utilization underscored the significant influence of cultural practices on health-care decisions, indicating a complex interplay between traditional beliefs, perceived efficacy of treatments and the severity of the disease in guiding treatment choices (1 study, low confidence).

Collective decision-making was also a barrier to timely help-seeking. As patients and caregivers were dependent on the community or senior household members to fund emergency care

expenses, social validation of the illness severity was essential to warrant funding (2 studies, very low confidence).

Studies indicated that an increase in disease severity initiated help-seeking behaviour. The key factor at the household level was the ability to recognize when the illness had become severe enough to necessitate seeking treatment, rather than recognizing specific signs and symptoms of acute bacterial meningitis. Factors such as disruption of social life, weakness, loss of appetite and the inability to work were among the most cited reasons prompting individuals to seek help (2 studies, moderate confidence).

HICs

One study pointed out that health-care workers in primary care settings may have lacked experience with treating meningitis. As a result, they were more focused on getting a child hospitalized as early as possible rather than starting treatment on their own (1 study, moderate confidence).

The literature consistently indicated that caregivers' primary concern revolved around the survival of their child, with many expressing profound worry about this outcome (5 studies, low confidence).

Finally, one study highlighted that the complexity of treatment trajectories could be a source of dissatisfaction with health services (1 study, very low confidence).

Balance of effects

Judgement: Probably favours the comparison

The GDG highlighted the potential benefits of shorter duration antibiotic regimens (< 10 days) based on the limited available evidence and emphasized the risk of adverse events associated with longer duration treatment (> 10 days). Therefore, the GDG agreed to indicate antimicrobial treatment of less than 10 days as a favourable comparison.

Resources required

Judgement: Varies

The GDG agreed that treatment costs are more likely to increase with regimens longer than 10 days and decrease with those shorter than 10 days.

Source of evidence

A scoping review was undertaken to compile information regarding costs, resource utilization and cost-effectiveness associated with meningitis diagnosis, treatment and management of sequelae.

Direct evidence

The included studies did not directly address the cost of empirical antimicrobial regimens associated with treatment duration but found evidence of the unit cost of different antibiotics in LMICs. None of the studies conducted in HICs were considered applicable to this guideline question.

LMICs

One study conducted in Gambia reported the unit cost of each vial of ceftriaxone (2 ml/250mg), ampicillin (2 ml/500mg) and amoxicillin (100 ml bottle, 125 mg/5 ml) was US$ 2.5, 0.3 and 0.64, respectively (2010 US$). In another study conducted in Viet Nam, the unit cost of each vial of ceftriaxone (250 mg/vial) and cefotaxime (1 g/vial) was US$ 4.24 and 1.35 (2006 US$), respectively.

Certainty of the evidence on resources required

Judgement: Very low

The judgement reflected the limited scope of the evidence, the absence of comprehensive cost comparisons between treatment durations and the potential variability in cost data across different LMICs.

Cost-effectiveness

Judgement: No included studies

A scoping review was undertaken to compile information regarding costs, resource utilization and cost-effectiveness associated with meningitis diagnosis, treatment and management of sequelae. However, no cost-effectiveness studies were found that would be applicable to this guideline question.

Health equity, equality and non-discrimination

Judgement: Varies

The GDG agreed that empiric antimicrobial treatment administered for 10 days, compared to a shorter duration, causes additional financial burden for patients and their families, potentially leading to increased inequalities among communities. In contrast, empiric treatment for 10 days may be more affordable and accessible when compared to longer duration regimens.

Source of evidence

A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.

Direct evidence

None of the included qualitative studies directly focused on health equity, equality or non-discrimination in relation to empiric treatment duration. However, the main relevant findings on meningitis treatment in LMICs are summarized as part of the indirect evidence. None of the studies conducted in HICs were considered applicable to this guideline question.

Indirect evidence

LMICs

Reviewed evidence highlighted a lack of knowledge about meningitis symptoms in all stakeholder groups (caregivers, patients and communities), which was associated with a delay in timely help-seeking (2 studies, moderate confidence). Misdiagnosing meningitis with malaria also contributed to difficulties in the provision of prompt and appropriate care (2 studies, very low confidence).

As reported in most studies, orthodox treatment carried a great financial burden for both caregivers and adult patients. The lack of funds was the primary reason for seeking alternative types of treatment before going to the hospital. Interviews revealed that prescriptions were costly, resulting in increased financial dependency and substantial debts incurred by patients and caregivers to afford treatment expenses (2 studies, low confidence).

These factors collectively contributed to the majority of respondents favouring alternative medicine as a more affordable approach to seeking care (2 studies, low confidence). Additionally, gender disparities played a significant role in accessing care and its timeliness. Women often required the approval of family and community before deciding to seek help, in contrast to men, who generally made such decisions independently (2 studies, moderate confidence).

Feasibility

Judgement: Varies

The GDG indicated that shorter antibiotic regimens may be easier to implement in resource-limited settings, whereas longer treatment regimens might be more challenging to operationalize, depending on available resources.

Source of evidence

A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.

Direct evidence

None of the included qualitative studies directly focused on the feasibility of empiric antimicrobial regimens based on duration. However, the main relevant findings on meningitis treatment in LMICs and HICs are summarized as part of the indirect evidence.

Indirect evidence

LMICs

The qualitative evidence review identified barriers potentially limiting the feasibility of timely care. Lack of knowledge about meningitis causes and symptoms among health-care workers was highlighted. Misdiagnosing meningitis with malaria also contributed to difficulties in the provision of prompt and appropriate care (2 studies, very low confidence).

Evidence showed elevated expenses incurred by households for medicines, despite the official government policy and the regular scarcity of complementary medicines supplied by ministries of health. If this happened, patients paid for their own medicines, including procuring them from costlier private pharmacies when they arrived outside the operating hours of the health centre's pharmacy (2 studies, very low confidence).

Reports among primary health-care workers and patients highlighted a lack of quality care, with long waiting times, presumptive diagnosis without examination, verbal mistreatment and underestimation of caregivers' concerns (2 studies, very low confidence).

Further to this, a significant barrier to effective management and treatment of meningitis in LMICs was the prevailing belief in supernatural explanations for the illness. This belief system was associated with a preference for alternative diagnostic and treatment approaches, often at the expense of seeking timely and appropriate medical care. The inclination towards alternative health-care providers, driven by cultural norms and low socioeconomic status, delayed the use of effective treatments that were crucial for mitigating the disease's impact (5 studies, moderate confidence).

HICs

Challenges faced by health-care workers in primary care settings were significant. These included the belief that antibiotics should be administered via injections in hospital settings, a hesitation to administer injections in primary care due to a lack of experience and anxiety caused by a limited familiarity with the process. Difficulties with gaining intravenous access as a barrier to initiating antimicrobial treatment was also highlighted (2 studies, low confidence).

Organizational barriers also played a role in delaying antimicrobial treatment initiation among health-care workers. These included specific advice from emergency departments, perceived disapproval from national prescribing services regarding the general use of antibiotics and the unavailability of antibiotics (1 study, very low confidence).

One study pointed out that complex treatment paths could lead to discontent with health services and complicate prompt access to health care (1 study, very low confidence).

Two studies also found that general practitioners were inclined to start antimicrobial treatment when they were certain of the diagnosis. Failure to start treatment seemed to be related to uncertainty about the diagnosis, partly because of the tendency to focus on extreme signs (2

studies, moderate confidence). Early empirical treatment initiated by paediatricians could have saved time regardless of diagnostic certainty (1 study, very low confidence).

Human rights and sociocultural acceptability

Judgement: Varies

Based on the available evidence and their knowledge and experience, the GDG agreed that the acceptability of the intervention (10-day treatment) compared to shorter or longer treatment regimens is likely to vary across settings, depending on cultural beliefs regarding conventional medicine and trust in the health-care system.

Source of evidence

A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.

Direct evidence

None of the included qualitative studies directly focused on the compliance of empiric antimicrobial regimens of different durations with universal human rights standards or their sociocultural acceptability. However, the main relevant findings on meningitis treatment in LMICs are summarized as part of the indirect evidence. None of the studies conducted in HICs were considered applicable to this guideline question.

Indirect evidence

LMICs

Some studies indicated a preference for conventional medicine as a treatment choice. Participants, including older patients and their caregivers, favoured medical interventions over traditional treatment practices. However, some patients and caregivers highlighted that "Western" practitioners typically focused on diagnosing peripheral causes and managing symptoms, whereas traditional healers addressed the root cause of the illness (4 studies, moderate confidence).

Narratives from caregivers of children who had encountered meningitis, as well as those whose neighbours' or relatives' children had previous meningitis episodes, underscored that health-care facilities were the primary point of care for meningitis, suggesting trust in the ability of formal health-care settings to provide necessary and effective treatment (2 studies, low confidence).

Two studies highlighted the ways that gender dynamics influenced decision-making processes in health care. Specifically, women often sought validation from their husbands, adult relatives or neighbours regarding the severity of health conditions before seeking care. This trend was exacerbated by the fact that many women had limited or no formal education and were

unemployed, factors that constrained their capacity to make informed health decisions for their families. In contrast, men were more likely to make health-care decisions independently, underscoring a gender disparity in autonomy and access to health-care decision-making (2 studies, moderate confidence).

Another study reported that cultural beliefs and care-seeking behaviour related to meningitis in LMICs were still influenced by traditional thinking. However, despite the dominance of traditional views, there was a gradual shift towards embracing modern understandings of disease and, consequently, more contemporary approaches to care-seeking (2 studies, low confidence).

CSF: cerebrospinal fluid; GDG: Guideline Development Group; HICs: high-income countries; LMICs: low- and middle-income countries; PCR: polymerase chain reaction; RCT: randomized controlled trial.

9. Duration of empiric antimicrobial treatment in epidemic settings

9.1 Guideline question

In epidemic settings, in cases with suspected or probable acute bacterial meningitis, should empiric treatment with parenteral ceftriaxone be administered for 5 days compared to an alternative treatment course duration?

Population: Suspected or probable cases of acute bacterial meningitis in epidemic settings

Subgroups: Age groups (children, adults), causative pathogen (meningococcal disease outbreak, pneumococcal disease outbreak, mixed outbreak)

Intervention: Parenteral ceftriaxone for a total duration of 5 days

Comparator: Parenteral ceftriaxone for a total duration shorter than 5 days (1–4 days) or longer than 5 days (7–14 days)

Outcome:

Critical: Case fatality rate, disease relapse, time to resolution of symptoms, disease complications (sepsis, DIC, neurological complications, including neurological sequelae)

Important: Adverse effects

Full details of the evidence, including references, are provided in Web Annex A (9. Duration of empiric antimicrobial treatment in epidemic settings) and Web Annex B (Qualitative and economic evidence reports).

9.2 Evidence-to-Decision framework

Priority of the problem
Judgement: Yes Acute meningitis is a life-threatening condition that requires prompt initiation of empiric antimicrobial treatment. The epidemiological landscape of epidemic-prone meningitis has changed over the past decade, with non-serogroup A *Neisseria meningitidis* and, less often, *Streptococcus pneumoniae,* responsible for the majority of epidemics within and outside the African meningitis belt region. During large-scale outbreaks, especially in resource-limited settings, laboratory confirmation and pathogen isolation may be difficult to perform for all suspected and probable cases. When the causative pathogen remains unidentified, determining the optimal treatment duration can be challenging and often relies on clinical judgement and feasibility considerations. Therefore, the Guideline Development Group (GDG) emphasized the critical importance of providing updated recommendations for meningococcal and pneumococcal disease epidemics, including optimal antimicrobial treatment duration for suspected and probable cases of meningitis.
Desirable effects
Judgement: Moderate (Meningococcal meningitis); Trivial (Pneumococcal meningitis) *Meningococcal meningitis* Based on their clinical knowledge and experience, the GDG highlighted the advantages of a 5-day antibiotic regimen over single-dose therapy for suspected and probable meningitis cases during meningococcal disease outbreaks, including reduced morbidity, mortality, and risk of antimicrobial resistance. *Pneumococcal meningitis* Based on their clinical knowledge and experience, the GDG emphasized the benefits of 10–14-day treatment regimens for laboratory-confirmed pneumococcal meningitis in terms of patient outcomes and recommended a 10-day regimen as the most appropriate default for suspected and probable meningitis cases during pneumococcal disease outbreaks.
Source of evidence A systematic review was conducted to compare empiric antimicrobial treatment with ceftriaxone for 5 days with shorter or longer ceftriaxone regimens in epidemic settings.
Direct evidence

No relevant comparative studies were found. However, the desirable effects of single-dose vs 5-day ceftriaxone therapy were assessed in the 2014 *Meningitis outbreak response in sub-Saharan Africa: WHO guideline*s.

In 2005, a randomized non-inferiority trial conducted in Niger showed that single-dose ceftriaxone provided a suitable treatment for epidemic meningococcal meningitis compared to long-acting chloramphenicol (risk difference for treatment failure rate at 72 hours of 0.3%, 90% CI -3.8–4.5), with its effectiveness, ease of administration and low cost favouring its use (Nathan et al. 2005). Nonetheless, as part of the guidelines' evidence review, a total of 22 meningococcal meningitis epidemic events in countries within the African meningitis belt between 2002 and 2014 were investigated (11 *N. meningitidis* serogroup A [NmA] and 11 serogroup W/X [NmW/NmX] outbreaks). Overall, 12.9% (95% CI 8.6–19.1%) of cases (n = 1874) in NmA epidemics and 9% (95% CI 6.3–12.4%) of cases (n = 1880) in NmW and NmX outbreaks were due to *S. pneumoniae* or *H. influenzae* (very low certainty of evidence). Thus, during meningococcal disease outbreaks, the use of single-dose ceftriaxone may lead to suboptimal treatment for a substantial proportion of patients, including those affected by pneumococcal or *Haemophilus* meningitis, which are generally associated with a higher risk of long-term neurological complications and mortality.

Indirect evidence

As part of the current guidelines' development process, a systematic review was conducted to compare empiric antimicrobial treatment of 10 days with shorter or longer treatment regimens in non-epidemic settings. Overall, 2 randomized controlled trials (RCTs) were included, both of which were carried out among children and compared a 10-day antimicrobial treatment regimen with shorter therapy regimens.

All-cause mortality

Low-certainty evidence from 1 RCT with 330 children (aged 2 months to 12 years) revealed that empiric antimicrobial treatment for 10 days may have resulted in little to no difference in all-cause mortality compared to empiric treatment for less than 10 days. The events were very rare and the confidence interval was wide, ranging from important benefit to significant harm (RR 0.96, 95% CI 0.28–3.27).

Disease relapse

Low-certainty evidence from 1 RCT with 104 children (aged 3 months to 14 years) revealed that empiric antimicrobial treatment for 10 days may have resulted in little to no difference in disease relapse compared to empiric antimicrobial treatment for less than 10 days. The events were very rare and the confidence interval was wide, ranging from important benefit to appreciable harm (RR 0.86, 95% CI 0.31–2.38).

Disease complications

Low-certainty evidence from 2 RCTs with 434 children revealed that the empiric antimicrobial treatment for 10 days may have resulted in little to no difference in disease complications (i.e. neurological sequelae, hearing loss and hydrocephalus) compared to empiric antimicrobial treatment for less than 10 days. The confidence interval was wide, ranging from moderate benefit to harm (RR 0.85, 95% CI 0.58–1.23).

Undesirable effects

Judgement: Small (Meningococcal meningitis); Moderate (Pneumococcal meningitis)

Meningococcal meningitis

A 5-day treatment course might increase the risk of adverse effects or lead to undesirable consequences of hospitalization (e.g. nosocomial infection) when compared to single-dose therapy. Conversely, the risk of treatment failure may be higher if shorter treatment is inappropriately administered to patients with non-meningococcal acute bacterial meningitis.

Pneumococcal meningitis

As laboratory-confirmed pneumococcal meningitis usually require 10–14 days of treatment, the GDG highlighted that 5-day regimens may be associated with worse patient outcomes, including mortality and long-term complications.

Source of evidence

A systematic review was conducted to compare empiric antimicrobial treatment with ceftriaxone for 5 days with shorter or longer ceftriaxone regimens.

Direct evidence

No relevant comparative study was found.

Certainty of the evidence

Judgement: Very low

The certainty of evidence was considered very low due to the lack of direct evidence addressing the guideline question.

Values

Judgement: Possibly important uncertainty or variability

Based on the available evidence and their knowledge and experience, the GDG agreed that there might be important uncertainty or variability across settings in how much people value the main outcomes.

Source of evidence

A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.

Direct evidence

No direct evidence was identified regarding the uncertainty about or variability in how much people value the main outcomes. However, the included studies highlighted a complex landscape of values and beliefs surrounding the treatment of meningitis, underscoring the diversity in health-care decision-making processes across different communities in both low- and middle-income countries (LMICs) and high-income countries (HICs). Particularly, some insights into patient and caregiver values provided a nuanced understanding of treatment preferences and healthcare-seeking behaviours and are summarized as indirect evidence.

Indirect evidence

LMICs

Studies focused on patients'/caregivers' values related to meningitis treatment reported that biomedical treatments were most effective in diagnosing, treating and managing the disease. This acknowledgement reflected a value placed on conventional medical approaches when it came to addressing the physical aspects of the disease (2 studies, low confidence).

However, the choice of treatment was profoundly influenced by the perceived cause of the illness. A significant portion of patients and caregivers, especially those attributing the disease to supernatural forces, declared a preference for traditional and Islamic treatment methods (4 studies, moderate confidence).

The initial response to meningitis symptoms in caregivers and adult patients often involved a combination of self-medication and seeking advice or treatment from traditional healers and soothsayers, particularly to discern if the disease had supernatural origins (4 studies, moderate confidence). Patronage of government hospitals was considered the last resort when the illness became severe and not amenable to alternative care. This pattern of health-care utilization underscored the significant influence of cultural practices on health-care decisions, indicating a complex interplay between traditional beliefs, perceived efficacy of treatments and the severity of the disease in guiding treatment choices (1 study, low confidence).

Collective decision-making was also a barrier to timely help-seeking. As patients and caregivers were dependent on the community or senior household members to fund emergency care expenses, social validation of the illness severity was essential to warrant funding (2 studies, very low confidence).

Studies indicated that an increase in disease severity initiated help-seeking behaviour. The key factor at the household level was the ability to recognize when the illness had become severe enough to necessitate seeking treatment, rather than recognizing specific signs and symptoms of acute bacterial meningitis. Factors such as disruption of social life, weakness, loss of appetite and the inability to work were among the most cited reasons prompting individuals to seek help (2 studies, moderate confidence).

HICs

One study pointed out that health-care workers in primary care settings may have lacked experience with treating meningitis. As a result, they were more focused on getting a child hospitalized as early as possible rather than starting treatment on their own (1 study, moderate confidence).

The literature consistently indicated that caregivers' primary concern revolved around the survival of their child, with many expressing profound worry about this outcome (5 studies, low confidence).

Finally, one study highlighted that the complexity of treatment trajectories could be a source of dissatisfaction with health services (1 study, very low confidence).

Balance of effects

Judgement: Probably favours the intervention (Meningococcal meningitis); Probably favours the comparison (Pneumococcal meningitis)

Based on the evidence and judgements described above, the GDG agreed that a 5-day antibiotic regimen is likely preferable for suspected and probable meningitis cases during meningococcal disease outbreaks. Conversely, longer regimens are probably favoured for suspected and probable meningitis cases during pneumococcal disease outbreaks.

Resources required

Judgement: Varies

The GDG agreed that treatment costs are more likely to increase with regimens longer than 5 days and decrease with those shorter than 5 days, including single-dose approaches. In addition, the increased costs due to hospital care and antibiotic administration must be balanced against the potential savings related to the prevention of long-term complications and disability.

Source of evidence

A scoping review was undertaken to compile information regarding costs, resource utilization and cost-effectiveness associated with meningitis diagnosis, treatment and management of sequelae.

Direct evidence

The included studies found evidence of the unit cost of ceftriaxone in LMICs. One study conducted in Gambia reported the unit cost of each vial of ceftriaxone (2 ml/250mg) was US$ 2.5 (2010 US$). In another study conducted in Viet Nam, the unit cost of each vial of ceftriaxone (250 mg/vial) was US$ 4.24 (US$ 2006). None of the studies conducted in HICs were considered applicable to this guideline question.

Certainty of the evidence on resources required

Judgement: Very low

The judgement reflected the limited scope of the evidence and the potential variability in cost data across different LMICs.

Cost-effectiveness

Judgement: No included studies

A scoping review was undertaken to compile information regarding costs, resource utilization and cost-effectiveness associated with meningitis diagnosis, treatment and management of sequelae. However, no cost-effectiveness studies were found that would be applicable to this guideline question.

Health equity, equality and non-discrimination

Judgement: Varies

In resource-limited settings, including in the African meningitis belt region, a longer course of antimicrobial treatment may constitute a significant economic burden for families, especially where antibiotics are not provided free of charge during epidemics. Moreover, longer hospitalization stays and/or multiple journeys to health-care facilities may contribute to reducing access to treatment, disproportionally affecting rural, low-income and hard-to-reach communities. The intervention (5-day treatment) may therefore be associated with decreased equity when compared to shorter regimens or increased equity when compared with longer regimens.

Source of evidence

A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.

Direct evidence

None of the included qualitative studies directly focused on health equity, equality or non-discrimination in relation to empiric treatment duration. However, the main relevant findings on meningitis treatment in LMICs are summarized as part of the indirect evidence. None of the studies conducted in HICs were considered applicable to this guideline question.

Indirect evidence

LMICs

Reviewed evidence highlighted a lack of knowledge about meningitis symptoms in all stakeholder groups (caregivers, patients and communities), which was associated with a delay in timely help-seeking (2 studies, moderate confidence). Misdiagnosing meningitis with malaria also contributed to difficulties in the provision of prompt and appropriate care (2 studies, very low confidence).

As reported in most studies, orthodox treatment carried a great financial burden for both caregivers and adult patients. The lack of funds was the primary reason for seeking alternative types of treatment before going to the hospital. Interviews revealed that prescriptions were costly, resulting in increased financial dependency and substantial debts incurred by patients and caregivers to afford treatment expenses (2 studies, low confidence).

These factors collectively contributed to the majority of respondents favouring alternative medicine as a more affordable approach to seeking care (2 studies, low confidence). Additionally, gender disparities played a significant role in accessing care and its timeliness. Women often required the approval of family and community before deciding to seek help, in contrast to men, who generally made such decisions independently (2 studies, moderate confidence).

Feasibility

Judgement: Varies

Ceftriaxone should be used at maximum dosage and administered every 12 hours in an inpatient setting. However, during large-scale epidemics, a multiple-day treatment course may be particularly challenging to ensure among all suspected and probable cases, especially when health services are overstretched and/or when remote, underserved or marginalized communities are affected.

Based on feasibility considerations, the GDG therefore indicated that once-daily administration is acceptable as long as the same daily dosage is maintained. If the person is clinically stable and can return to the health-care facility every day, they can be discharged and given parenteral ceftriaxone at full dose once daily (4 g in adults and 100 mg/kg in children) to complete treatment in an outpatient setting.

During large-scale meningococcal disease epidemics in settings with weak infrastructure or health services stretched to capacity, single-dose treatment protocols may be implemented, provided

that there is laboratory confirmation that the epidemic is caused by *N. meningitidis* and the person can be reviewed after 24 and 48 hours

Source of evidence

A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.

Direct evidence

None of the included qualitative studies directly focused on the feasibility of empiric antimicrobial regimens based on duration. However, the main relevant findings on meningitis treatment in LMICs and HICs are summarized as part of the indirect evidence.

Indirect evidence

LMICs

The qualitative evidence review identified barriers potentially limiting the feasibility of timely care. Lack of knowledge about meningitis causes and symptoms among health-care workers was highlighted. Misdiagnosing meningitis with malaria also contributed to difficulties in the provision of prompt and appropriate care (2 studies, very low confidence).

Evidence showed elevated expenses incurred by households for medicines, despite the official government policy and the regular scarcity of complementary medicines supplied by ministries of health. If this happened, patients paid for their own medicines, including procuring them from costlier private pharmacies when they arrived outside the operating hours of the health centre's pharmacy (2 studies, very low confidence).

Reports among primary health-care workers and patients highlighted a lack of quality care, with long waiting times, presumptive diagnosis without examination, verbal mistreatment and underestimation of caregivers' concerns (2 studies, very low confidence).

Further to this, a significant barrier to effective management and treatment of meningitis in LMICs was the prevailing belief in supernatural explanations for the illness. This belief system was associated with a preference for alternative diagnostic and treatment approaches, often at the expense of seeking timely and appropriate medical care. The inclination towards alternative health-care providers, driven by cultural norms and low socioeconomic status, delayed the use of effective treatments that were crucial for mitigating the disease's impact (5 studies, moderate confidence).

HICs

Challenges faced by health-care workers in primary care settings were significant. These included the belief that antibiotics should be administered via injections in hospital settings, a hesitation to

administer injections in primary care due to a lack of experience and anxiety caused by a limited familiarity with the process. Difficulties with gaining intravenous access as a barrier to initiating antimicrobial treatment was also highlighted (2 studies, low confidence).

Organizational barriers also played a role in delaying antimicrobial treatment initiation among health-care workers. These included specific advice from emergency departments, perceived disapproval from national prescribing services regarding the general use of antibiotics and the unavailability of antibiotics (1 study, very low confidence).

One study pointed out that complex treatment paths could lead to discontent with health services and complicate prompt access to health care (1 study, very low confidence).

Two studies also found that general practitioners were inclined to start antimicrobial treatment when they were certain of the diagnosis. Failure to start treatment seemed to be related to uncertainty about the diagnosis, partly because of the tendency to focus on extreme signs (2 studies, moderate confidence). Early empirical treatment initiated by paediatricians could have saved time regardless of diagnostic certainty (1 study, very low confidence).

Human rights and sociocultural acceptability

Judgement: Varies

Based on their experience and the presented body of indirect evidence, the GDG agreed that the acceptability of the intervention (5-day treatment) compared to shorter or longer treatment regimens is likely to vary across settings, depending on cultural beliefs regarding conventional medicine and trust in the health-care system.

Source of evidence

A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.

Direct evidence

None of the included qualitative studies directly focused on the compliance of empiric antimicrobial regimens of different durations with universal human rights standards or their sociocultural acceptability. However, the main relevant findings on meningitis treatment in LMICs are summarized as part of the indirect evidence. None of the studies conducted in HICs were considered applicable to this guideline question.

Indirect evidence

LMICs

Some studies indicated a preference for conventional medicine as a treatment choice. Participants, including older patients and their caregivers, favoured medical interventions over traditional treatment practices. However, some patients and caregivers highlighted that "Western" practitioners typically focused on diagnosing peripheral causes and managing symptoms, whereas traditional healers addressed the root cause of the illness (4 studies, moderate confidence).

Narratives from caregivers of children who had encountered meningitis, as well as those whose neighbours' or relatives' children had previous meningitis episodes, underscored that health-care facilities were the primary point of care for meningitis, suggesting trust in the ability of formal health-care settings to provide necessary and effective treatment (2 studies, low confidence).

Two studies highlighted the ways that gender dynamics influenced decision-making processes in health care. Specifically, women often sought validation from their husbands, adult relatives or neighbours regarding the severity of health conditions before seeking care. This trend was exacerbated by the fact that many women had limited or no formal education and were unemployed, factors that constrained their capacity to make informed health decisions for their families. In contrast, men were more likely to make health-care decisions independently, underscoring a gender disparity in autonomy and access to health-care decision-making (2 studies, moderate confidence).

Another study reported that cultural beliefs and care-seeking behaviour related to meningitis in LMICs were still influenced by traditional thinking. However, despite the dominance of traditional views, there was a gradual shift towards embracing modern understandings of disease and, consequently, more contemporary approaches to care-seeking (2 studies, low confidence).

GDG: Guideline Development Group; HICs: high-income countries; LMICs: low- and middle-income countries; NmA/NmW/NmX: *Neisseria meningitidis* serogroup A/W/X; RCT: randomized controlled trial; WHO: World Health Organization.

10. Post-exposure antimicrobial prophylaxis

10.1 Guideline question

Should antimicrobial prophylaxis be provided to close contacts of cases of meningococcal disease?

Population: Close contacts, including household contacts and anyone directly exposed to oral secretions of patients with meningococcal disease

Subgroups: Epidemic versus non-epidemic settings, geographical region (in the African meningitis belt region versus outside the African meningitis belt)

Intervention: Antimicrobial prophylaxis (oral ciprofloxacin, parenteral ceftriaxone, oral rifampicin)

Comparator: No antimicrobial prophylaxis

Outcome:

Critical: Prevention of additional cases and meningococcal carriage

Important: Adverse effects

Full details of the evidence, including references, are provided in Web Annex A (10. Post-exposure antimicrobial prophylaxis) and Web Annex B (Qualitative and economic evidence reports).

10.2 Evidence-to-Decision framework

Priority of the problem
Judgement: Yes Meningococcal disease is a potentially life-threatening condition caused by the bacterium *Neisseria meningitidis* and transmitted through direct contact with large droplet respiratory secretions and/or saliva. The disease remains a major public health challenge worldwide, accounting for recurrent epidemics in the African meningitis belt region during the dry season (serogroups C, W, Y and X) as well as sporadic cases and small-scale outbreaks in Europe and North America (serogroups B, C and Y). The risk of infection is estimated to be substantially increased among individuals in close contact with patients with meningococcal disease, with the highest risk for household contacts. Although the definition of "close contact" has not been universally established and may vary across different settings, post-exposure antibiotic prophylaxis is widely used to prevent secondary cases and/or decrease asymptomatic nasopharyngeal carriage. However, the potential clinical benefits of prophylaxis have been primarily derived from studies that only address eradication of nasopharyngeal carriage through antimicrobials. In addition, while antibiotic prophylaxis is routinely used in high-income settings, there is no universal consensus on the opportunity to use it as part of the outbreak response within the African meningitis belt region, often resulting in different recommendations across similar settings. In 2014, the World Health Organization (WHO) published a guideline on outbreak response, which included evidence-based recommendations for antibiotic prophylaxis in the African meningitis belt during and outside epidemics. An update to these recommendations, incorporating the latest available evidence, was considered necessary.
Desirable effects
Judgement: Moderate The Guideline Development Group (GDG) discussed the findings from the 2 studies included in the systematic review and acknowledged the uncertainty regarding the effect of antibiotic prophylaxis in reducing secondary cases of meningococcal disease. Given the study design, the intervention used (i.e. single-dose ciprofloxacin) and the sample size, a 3-arm cluster randomized controlled trial (RCT) conducted in rural Niger during a meningococcal disease outbreak was thoroughly analysed. The GDG emphasized that the effect of antibiotic prophylaxis on prevention of secondary cases was uncertain when given to household contacts but highlighted the protective effect when administered to village-wide contacts. In addition, individual-level protective effectiveness of 82% (crude attack rate ratio 0.18, 95% CI 0.10–0.33) was demonstrated

when comparing all persons in the study area who received ciprofloxacin (in-household and village-wide prophylaxis arms) to those who did not receive ciprofloxacin.

Furthermore, the GDG discussed the evidence from the systematic review by Zalmanovici et al. (2013), which demonstrated the effectiveness of chemoprophylaxis (ciprofloxacin, rifampicin and ceftriaxone) in reducing meningococcal nasopharyngeal carriage. They agreed that nasopharyngeal carriage eradication is likely to reduce infection transmission and prevent secondary cases.

Overall, the GDG agreed that the desirable effects of antibiotic prophylaxis are moderate, indicating a potentially larger benefit when given to close contacts of laboratory-confirmed cases and tailored to antimicrobial susceptibility testing results. Moreover, while underscoring the importance of obtaining laboratory confirmation before administering antibiotic prophylaxis, the GDG acknowledged that close contacts of non-laboratory-confirmed cases may benefit from antibiotic prophylaxis, provided that antibiotic selection is guided by known antimicrobial susceptibility patterns prevalent in the community. Finally, they recognized that the desirable effects on prevention of secondary cases may vary depending on the level of vaccination coverage in the target population.

Source of evidence

A systematic review was conducted to assess the efficacy and safety of antibiotic prophylaxis among close contacts of patients with meningococcal disease.

Direct evidence

Two prospective studies directly addressed the guideline question and were included in the systematic review (one cluster randomized trial conducted in Niger and one prospective cohort study conducted in the United States of America). In the cluster randomized trial, single-dose ciprofloxacin was used as intervention. In the prospective cohort study, rifampicin, minocycline or sulphonamide were used. The main findings of these studies are summarized below.

Very-low-certainty evidence showed that the effect of antimicrobial prophylaxis for close contacts on secondary cases of meningococcal disease was uncertain (RR 0.47, 95% CI 0.10–2.15). The relative risk and confidence interval used in the Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment were calculated using design effect with respect to a cluster randomized trial. The incidence of secondary cases was 0.37% after chemoprophylaxis (91 of 24 297), and 0.45% without chemoprophylaxis (120 of 26 672).

A subgroup analysis was conducted to include studies conducted in the African meningitis belt. Very-low-certainty evidence from one 3-arm cluster-randomized trial conducted in Niger during a meningococcal disease outbreak showed that the effect of chemoprophylaxis with single-dose ciprofloxacin on secondary cases of meningococcal disease was uncertain (RR 0.85, 95% CI 0.65–1.12).

Additionally, evidence from retrospective studies, along with findings on village-wide prophylaxis and carriage eradication, is summarized as additional evidence.

Additional evidence

Retrospective studies on disease prevention

A retrospective cohort study was conducted in Denmark by interviewing 172 households that had a member diagnosed with meningococcal disease (Samuelsson et al. 2000). In total, the study examined 802 household-like contacts. Among the 724 (90%) who had received single-dose ciprofloxacin as chemoprophylaxis, no secondary cases occurred within 30 days. Among the 72 (9%) who had not received antimicrobial prophylaxis, 2 secondary cases occurred, 2 and 3 days after the primary cases, respectively. Therefore, chemoprophylaxis was associated with a reduced risk of secondary cases (RR 0.01, 95% CI 0.00–0.42). However, the risk of selection bias and the lack of adjustment for confounding were primary study limitations. In addition, it was not clear whether secondary cases were determined through interview, potentially accounting for further risk of recall bias.

Village-wide prophylaxis

Evidence on village-wide prophylaxis was derived from a 3-arm cluster RCT conducted in rural Niger during a meningococcal disease epidemic, which was also included in the systematic review with respect to household prophylaxis (Coldiron et al. 2018). The study showed a protective effect of village-wide prophylaxis on secondary cases when compared to placebo (aRR 0.40, 95% CI 0.19–0.97; RR adjusted for whether village was included after the first day of rainfall). Single-dose ciprofloxacin was administered within 72 hours of first case notification.

In addition, a secondary analysis comparing all persons in the study area who received single-dose ciprofloxacin (in household and village-wide prophylaxis arms) to those who did not receive ciprofloxacin showed an individual-level protective effectiveness of 82% (crude attack rate ratio 0.18, 95% CI 0.10–0.33).

Carriage eradication

Evidence informing the desirable effects of antimicrobial prophylaxis in preventing secondary cases is limited. However, the potential clinical benefit of prophylaxis may be derived from studies that address eradication of nasopharyngeal carriage through antimicrobials. Specifically, the systematic review by Zalmanovici et al. (2013) included 24 randomized or quasi-randomized clinical trials and assessed the effectiveness of antimicrobials in eradicating meningococcal carriage 1–2 weeks after treatment. The following findings regarding carriage eradication effectiveness were noted.

- Rifampicin (RR 0.20, 95% CI 0.14–0.29), ciprofloxacin (RR 0.03, 95% CI 0.00–0.42), and penicillin (RR 0.63; 95% CI 0.51–0.79) were shown to be effective in eradicating meningococcal carriage

compared to placebo at 1–2 weeks. Rifampicin was effective for up to 4 weeks after therapy, but resistant strains were isolated after prophylaxis administration.

- In a single study, ceftriaxone was shown to be more effective than rifampicin (RR 5.93, 95% CI 1.22–28.68) in eradicating carriage after 1–2 weeks of follow-up. There were no studies comparing ceftriaxone against placebo.
- Effectiveness in preventing secondary transmission could not be assessed since there were no cases of meningococcal disease following antibiotics or placebo.

Undesirable effects

Judgement: Varies

The GDG acknowledged the lack of direct evidence on adverse events from chemoprophylaxis for close contacts of people with meningococcal disease. They recognized that the safety profiles of ciprofloxacin and ceftriaxone are well known, and their administration as a single dose is likely to have limited side effects.

The GDG also emphasized that chemoprophylaxis can have an impact on the development of antimicrobial resistance. The increasing incidence of cases caused by ciprofloxacin-resistant strains in several regions worldwide has raised concerns about potential prophylaxis failure, particularly in areas with high levels of ciprofloxacin resistance. Consequently, the GDG agreed that antibiotic selection should be guided by the antimicrobial susceptibility patterns prevalent within the community and potentially adjusted as necessary based on susceptibility testing results from index cases. Finally, given the risk of resistance, the GDG agreed that rifampicin should be considered an alternative option when ciprofloxacin or cefriaxone are contraindicated or not available.

Source of evidence

A systematic review was conducted to assess the efficacy and safety of antibiotic prophylaxis among close contacts of patients with meningococcal disease.

Direct evidence

Two prospective studies directly addressed the guideline question and were included in the systematic review (one cluster randomized trial conducted in Niger and one prospective cohort study conducted in the United States of America).

In the cluster randomized trial, no serious adverse events were reported in the household prophylaxis or the placebo arm. In the cohort study, no information regarding adverse events was described.

Additional evidence

Village-wide prophylaxis

In the 3-arm cluster RCT by Coldiron et al. (2018), a sub-study was conducted to investigate faecal carriage of ciprofloxacin-resistant and extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae* in 2 arms (i.e. the village-wide ciprofloxacin prophylaxis and control arms; there were no data regarding the household prophylaxis arm). In both arms, the baseline prevalence of ciprofloxacin-resistant *Enterobacteriaceae* was 95% and of ESBL-producing *Enterobacteriaceae* was > 90%. There was no difference in the change of prevalence over time between the arms. However, the study was underpowered to show any changes, given the higher-than-expected baseline prevalence of antimicrobial resistance. In the same trial, no serious adverse events were reported in the village-wide prophylaxis or placebo arms.

Carriage eradication

Some evidence informing the undesirable effects of chemoprophylaxis may be derived from studies that address eradication of nasopharyngeal carriage through antimicrobials. Specifically, the systematic review by Zalmanovici et al. (2013) included 24 randomized or quasi-randomized clinical trials and assessed the effectiveness of antimicrobials in eradicating meningococcal carriage 1–2 weeks after treatment. The following findings regarding undesirable effects were noted.

- Among the 24 studies included in the systematic review, 11 trials reported the susceptibility of persistent isolates to at least 1 of the studied antibiotics (rifampicin, ciprofloxacin, sulphonamides, minocycline, cephalexin, ampicillin or ceftriaxone). The development of resistance was not detected for any antibiotic drug, with the exception of rifampicin. Six trials assessed the development of rifampicin resistance.
- In Guttler et al. (1971), rifampicin-resistant isolates requiring minimal inhibitory concentrations (MICs) of 100 to 200 µg/ml of rifampicin were seen in 20 of 75 isolates after treatment. Moreover, in 37 additional isolates, MICs increased from pre-treatment values of < 0.25 µg/ml to 2–6 µg/ml. All resistant isolates were detected among patients treated with rifampicin.
- In Munford et al. (1974), 7 resistant isolates were detected out of 37 isolates among 67 patients treated with rifampicin (MICs of 16 –256 µg/ml). All pre-treatment isolates were susceptible to rifampicin, with no rifampicin resistance detected among patients randomized to rifampicin in addition to minocycline.
- The meningococci identified in these two studies were serogroup B or C, with all resistant isolates identified as serogroup C.
- One additional study by Blakebrough et al. (1980) assessing group A meningococci found an increase in rifampicin MICs from < 0.1 µg/ml to 3.2 µg/ml (3 isolates) and 6.4 µg/ml (1 isolate) after treatment.

- In all trials 7 eradication failures were assessed for the presence of antibiotic resistance, which was not found.

Among the 24 included studies, 18 trials provided quantitative data regarding the occurrence of adverse effects. These were all mild in nature and included nausea, diarrhoea, abdominal pain, headaches, dizziness, skin rash and pain at injection site. One study comparing rifampicin to ceftriaxone resulted in an overall risk ratio for any clinical adverse effects of 1.39 (95% CI 1.10–1.75). Two studies comparing rifampicin to ciprofloxacin yielded an overall RR of 0.75 (95% CI 0.36–1.56).

Certainty of the evidence

Judgement: Very low

The certainty of evidence was very low for the critical outcome of interest.

Values

Judgement: Probably no important uncertainty or variability

The GDG discussed people's cultural values and how they can impact decisions regarding a preventive intervention aimed at reducing the spread of meningococcal disease and protect their community. Based on the available evidence and their knowledge and experience, the GDG agreed that there is probably no important uncertainty or variability across settings in how much people value the main outcomes.

Source of evidence

A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.

Direct evidence

No direct evidence was identified regarding the uncertainty about or variability in how much people value the main outcomes in relation to antibiotic prophylaxis. However, the included studies highlighted a complex landscape of values and beliefs surrounding the treatment of meningitis, underscoring the diversity in health-care decision-making processes across different communities in both low- and middle-income countries (LMICs) and high-income countries (HICs). Particularly, some insights into patient and caregiver values provided a nuanced understanding of treatment preferences and healthcare-seeking behaviours and are summarized as indirect evidence.

Indirect evidence

LMICs

Studies focusing on patients'/caregivers' values related to meningitis treatment reported that biomedical treatments are most effective in diagnosing, treating and managing the disease. This acknowledgement reflected a value placed on conventional medical approaches when it came to addressing the physical aspects of the disease (2 studies, low confidence). However, the choice of treatment was profoundly influenced by the perceived cause of the illness. A significant portion of patients and caregivers, especially those attributing the disease to supernatural forces, declared a preference for traditional and Islamic treatment methods (4 studies, moderate confidence).

The initial response to meningitis symptoms among caregivers and adult patients often involved a combination of self-medication and seeking advice or treatment from traditional healers and soothsayers, particularly to discern if the disease had supernatural origins (4 studies, moderate confidence).

Patronage of government hospitals was considered a last resort when the illness became severe and not amenable to alternative care. This pattern of health-care utilization underscored the significant influence of cultural practices on health-care decisions, indicating a complex interplay between traditional beliefs, perceived efficacy of treatments and the severity of the disease in guiding treatment choices (1 study, low confidence).

Collective decision-making was also a barrier to timely help-seeking. As patients and caregivers were dependent on the community or senior household members to fund the emergency care expenses, social validation of the illness severity was essential to warrant funding (2 studies, very low confidence).

Studies indicated that an increase in disease severity initiated help-seeking behaviour. The key factor at the household level was the ability to recognize when the illness had become severe enough to necessitate seeking treatment, rather than recognizing specific signs and symptoms of acute bacterial meningitis. Factors, such as disruption of social life, weakness, loss of appetite and the inability to work were among the most cited reasons prompting individuals to seek help (2 studies, moderate confidence).

HICs

One study pointed out that health-care workers in primary care settings may have lacked experience with treating meningitis, thus they were more focused on getting a child hospitalized as early as possible rather than starting treatment on their own (1 study, moderate confidence).

The qualitative evidence consistently indicated that caregivers' primary concern revolved around the survival of their child, with many expressing profound worry about this outcome (5 studies, low confidence).

One study also highlighted that the complexity of treatment trajectories could be a source of dissatisfaction with health services (1 study, very low confidence).

Balance of effects
Judgement: Probably favours the intervention Based on the available evidence and their clinical knowledge and experience, the GDG agreed that the benefits of antibiotic prophylaxis may outweigh the undesirable consequences in most settings, especially when antibiotic selection can be guided by the antimicrobial susceptibility patterns prevalent within the community or identified among index cases.
Resources required
Judgement: Varies The GDG acknowledged that the cost of chemoprophylaxis may vary depending on various factors, including the local cost of antibiotics, the choice of antibiotic (i.e. ciprofloxacin or ceftriaxone) and the amount of resources necessary to trace close contacts. Moreover, it was emphasized that the overall cost of such intervention varies based on whether it is implemented in the presence of sporadic cases, during small-scale outbreaks or large-scale epidemics.
Source of evidence A scoping review was undertaken to compile information regarding costs, resource utilization and cost-effectiveness associated with meningitis diagnosis, treatment and management of sequelae.
Direct evidence The scoping review identified two studies providing information on the cost of drugs used for chemoprophylaxis for contacts of cases of meningococcal disease in LMICs. None of the studies conducted in HICs were considered applicable to this guideline question. *LMICs* In Viet Nam, the unit cost of each vial of ceftriaxone (250 mg/vial) and ciprofloxacin (200mg/vial) was US$ 4.24 and 12.44 (2006 US$), respectively. One study conducted in Gambia reported that the unit cost of each vial of ceftriaxone (2ml/250mg) was US$ 2.5, while the unit cost for ciprofloxacin 100ml bottle (2mg/ml) and tablets (100/packet, 250mg) was US$ 3.93 and 2.71, respectively (2010 US$). None of the studies provided information on rifampicin.
Certainty of the evidence on resources required
Judgement: Very low The judgement reflected the limited scope of the evidence, the absence of comprehensive cost comparisons between different interventions and the potential variability in cost data across settings.

Cost-effectiveness
Judgement: No included studies A scoping review was undertaken to compile information regarding costs, resource utilization and cost-effectiveness associated with meningitis diagnosis, treatment and management of sequelae. However, no cost-effectiveness studies were found that would be applicable to this guideline question.
Health equity, equality and non-discrimination
Judgement: Probably increased Meningococcal disease is widely recognized by governments and communities as a severe condition associated with high healthcare costs, including in the African meningitis belt region. Therefore, low-income families may benefit from prevention measures, including antibiotic prophylaxis. However, the capacity to detect cases of meningococcal disease or respond to an outbreak is highly variable and largely depends on available technical, financial, and infrastructural resources. Based on the available evidence and their knowledge and experience, the GDG agreed that antibiotic prophylaxis may contribute to increased equity, especially when implemented in low-resource settings, vulnerable populations and marginalized, hard-to-reach communities.
Source of evidence A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.
Direct evidence None of the included qualitative studies directly focused on health equity, equality or non-discrimination in relation to post-exposure antibiotic prophylaxis.
Feasibility
Judgement: Varies The GDG discussed the feasibility of antibiotic prophylaxis in comparison to other public health measures for controlling meningococcal disease, including vaccination, which remains the primary recommended preventive intervention. Chemoprophylaxis presents several logistical advantages that may facilitate its implementation both during and outside of epidemic settings. Most antibiotics used for prophylaxis are often widely available, do not require cold chain storage and can be stockpiled in-country for rapid deployment. In addition, oral regimens (i.e., ciprofloxacin and

rifampicin) are easy to administer and prevent waste management challenges. Single-dose regimens (i.e., ciprofloxacin and ceftriaxone), on the other hand, can improve patient compliance and eliminate the need for continued therapy adherence. However, the feasibility of antibiotic prophylaxis can vary across settings based on the following considerations.

- Epidemic versus sporadic disease: Antimicrobial prophylaxis may be easily operationalized when given to close contacts of laboratory-confirmed cases in the presence of sporadic disease. On the other hand, it might be more challenging when given to contacts of suspected cases during large-scale epidemics, especially in resource-limited settings.
- Urban versus rural settings: The feasibility of antimicrobial prophylaxis, particularly during outbreaks, may largely vary based on the setting. In densely populated urban areas, extensive mobilization efforts and logistical arrangements would be required, alongside guarantees of access to high-quality and safe antibiotics. Conversely, among rural and underserved communities, financial constraints could limit the feasibility of chemoprophylaxis within households, which may depend critically on the provision of antibiotics at no cost.
- Antimicrobial resistance: Antimicrobial resistance rates and patterns within a community can hinder the rollout of chemoprophylaxis and/or dictate the choice of antimicrobial agent. For example, ciprofloxacin-resistant *N. meningitidis* isolates have been increasingly reported worldwide. In addition, the widespread use of antibiotics is associated with an increased risk of antimicrobial resistance among bacteria in the gastrointestinal tract, respiratory tract, and skin. The local emergence and spread of drug-resistant bacteria should therefore be closely monitored to ensure that antimicrobial prophylaxis regimens are appropriate to the epidemiological setting.
- Antibiotic contraindications: Contraindications to the use of antibiotics should be taken into consideration when addressing the feasibility of chemoprophylaxis in certain populations or age groups. For example, ciprofloxacin is contraindicated during pregnancy and its use in children varies worldwide. Also, rifampicin is a cornerstone drug in the treatment of tuberculosis, including active and latent infections. Therefore, the use of rifampicin-based regimens for meningococcal disease prophylaxis might be problematic in settings with high tuberculosis burden and is associated with an increased risk of developing rifampicin-resistant strains (especially when given as monotherapy).

Source of evidence

A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.

Direct evidence

None of the included qualitative studies directly focused on the feasibility of post-exposure antibiotic prophylaxis.
Human rights and sociocultural acceptability
Judgement: Probably yes Based on their knowledge and experience, the GDG agreed that antibiotic prophylaxis for the prevention of secondary cases of meningococcal disease is likely to be acceptable across settings, potentially with some variations depending on cultural beliefs regarding conventional medicine and trust in the healthcare system.
Source of evidence A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.
Direct evidence None of the included qualitative studies directly focused on the compliance of post-exposure antibiotic prophylaxis and universal human rights standards or its sociocultural acceptability

ESBL: extended-spectrum beta-lactamase; GDG: Guideline Development Group; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HICs: high-income countries; LMICs: low- and middle-income countries; MICs: minimal inhibitory concentrations; RCT: randomized controlled trial; WHO: World Health Organization.

11. Adjunctive corticosteroids

11.1 Guideline question

In individuals with suspected, probable or confirmed acute meningitis, should adjunctive corticosteroids (dexamethasone, hydrocortisone, methylprednisolone) be administered?

Population: Suspected, probable and confirmed cases of acute bacterial meningitis

Subgroups: Pathogen (*Neisseria meningitidis, Streptococcus pneumoniae, Haemophilus influenzae*, and Group B *Streptococcus*), age group (children, adults), World Bank income classification (High-income countries [HICs] and low and middle-income countries [LMICs]), disease severity (altered consciousness)

Intervention: Adjunctive corticosteroids (dexamethasone, hydrocortisone, methylprednisolone)

Comparator: Standard treatment without corticosteroids

Outcome:

Critical: Neurological sequelae,[9] mortality

Important: Time to resolution of symptoms, adverse effects, disease complications (sepsis, DIC, neurological complications, including neurological sequelae)

Full details of the evidence, including references, are provided in Web Annex A (11. Adjunctive corticosteroids) and Web Annex B (Qualitative and economic evidence reports).

[9] Neurological sequelae are defined as: hearing loss, speech and/or language impairment, seizures, neurocognitive impairment, psychological after-effects (stress, depression, behaviour), hydrocephalus, motor deficits, vision impairment.

11.2 Evidence-to-Decision framework

Priority of the problem
Judgement: Yes Acute bacterial meningitis is a life-threatening condition associated with a high risk of neurological sequelae and disability. Animal studies suggested that some disease outcomes, including hearing loss and other neurological complications, might be related to the host inflammatory response and the presence of cerebral oedema rather than the infection itself. These observations ultimately led to the clinical evaluation and use of corticosteroids as anti-inflammatory agents that can reduce the risk of death and neurological complications when used as adjunctive treatment for acute bacterial meningitis (i.e. in addition to antimicrobial treatment). Further studies in humans also indicated that beneficial effects of corticosteroids in high-income settings are more commonly associated with laboratory-confirmed *Streptococcus pneumoniae* and *Haemophilus influenzae* meningitis. Nonetheless, in resource-limited settings, the use of corticosteroids as adjunctive treatment for acute bacterial meningitis remains controversial. Access to health services might be delayed and pathogen identification is often challenging, leading to uncertainty and significant variations in clinical practice with respect to corticosteroid administration.
Desirable effects
Judgement: Moderate The Guideline Development Group (GDG) acknowledged the benefits of early corticosteroid administration on multiple critical outcomes when acute bacterial meningitis is clinically suspected or considered likely based on cerebrospinal fluid (CSF) characteristics. They also emphasized that there is some, albeit weak, evidence suggesting potential benefits of steroids among individuals with confirmed *S. pneumoniae* or *H. influenzae* type b meningitis, which is also consistent with a previous Cochrane systematic review (Brouwer et al. 2015). The GDG highlighted that all studies presented in the systematic review included individuals who underwent a lumbar puncture and emphasized the limited applicability of these findings to settings where a lumbar puncture is contraindicated, deferred or cannot be performed due to the lack of human and/or infrastructural resources. They also recognized that strong suspicion of acute meningitis based on clinical findings has suboptimal sensitivity and specificity and some concurrent conditions may contraindicate their use (e.g. cerebral malaria, invasive fungal infections, hypersensitivity reactions). Finally, the GDG discussed findings from 2 studies conducted in Malawi by Scarborough et al. (2007) and Molyneux et al. (2002), in which 90% and 34% of the study populations, respectively,

were HIV-positive. None of the adults or children in these studies were on antiretroviral treatment. As both studies demonstrated no benefit of dexamethasone in reducing mortality or morbidity in acute bacterial meningitis, intravenous corticosteroids administered as adjunctive treatment for suspected acute bacterial meningitis has not proven to be beneficial in individuals with advanced HIV disease.

Source of evidence

A systematic review was conducted to compare adjunctive corticosteroid therapy with standard care without corticosteroids.

Direct evidence

Overall, 26 randomized controlled trials (RCTs) were included. Seventeen studies were conducted in high-income countries (HICs), while 9 were conducted in low and middle-income countries (LMICs). Twenty-four studies reported on the age of patients, with 17 studies conducted in children. The main findings of the systematic review along with subgroup analyses are summarized below.

All-cause mortality

Moderate-certainty evidence from 26 RCTs with 4236 patients suggested that adjunctive corticosteroid therapy probably reduced mortality compared to placebo (RR 0.80, 95% CI 0.65–0.98).

Short-term neurological sequelae (within 6 weeks of discharge)

Low-certainty evidence from 12 RCTs in 1580 patients suggested that adjunctive corticosteroid therapy may reduce the risk of short-term neurological sequelae compared to placebo (RR 0.77, 95% CI 0.61–0.99). Short-term sequelae were defined as the presence of at least 1 neurological deficit except hearing loss until 6 weeks after discharge.

Long-term neurological sequelae (6 weeks to 12 months after discharge)

Very-low-certainty evidence from 12 RCTs with 1580 patients suggested that the effect of adjunctive corticosteroid therapy on long-term neurological sequelae compared to placebo was uncertain (RR 0.86, 95% CI 0.71–1.04). Long-term sequelae were defined as the presence of at least 1 neurological deficit between 6 weeks to 12 months after discharge.

Any hearing loss

High-certainty evidence from 19 RCTs with 2594 patients showed that adjunctive corticosteroid therapy reduced the risk of hearing loss compared to placebo (RR 0.66, 95% CI 0.51–0.86).

Severe hearing loss

Very-low-certainty evidence from 10 RCTs with 354 patients showed that the effect of adjunctive corticosteroid therapy on severe hearing loss compared to placebo was uncertain (RR 1.42, 95% CI 0.91–2.23).

Post-meningitis epilepsy

Low-certainty evidence from 8 RCTs with 1161 patients suggested that adjunctive corticosteroid therapy may have reduced post-meningitis epilepsy compared to placebo (RR 0.55, 95% CI 0.34–0.89).

Hydrocephalus

Very-low-certainty evidence from 8 RCTs with 1235 patients showed that the effect of adjunctive corticosteroid therapy on hydrocephalus compared to placebo was uncertain (RR 0.53, 95% CI 0.31–0.90).

Ataxia

Very-low-certainty evidence from 6 RCTs with 1009 patients showed that the effect of adjunctive corticosteroid therapy on ataxia compared to care without adjunctive corticosteroids was uncertain (RR 0.82, 95% CI 0.56–1.20).

Direct evidence (subgroup analyses)

All-cause mortality

- Causative pathogens: Low-certainty evidence from 5 RCTs suggested that the effect of adjunctive corticosteroid therapy on mortality in pneumococcal meningitis may have resulted in little to no difference when compared to placebo (RR 0.58, 95% CI 0.32–1.08). High-certainty evidence from 4 RCTs showed that corticosteroid therapy resulted in a mild reduction of mortality in *H. influenzae* type b meningitis (RR 0.71, 95% CI 0.50–1.00). Moderate-certainty evidence from 5 RCTs suggested that corticosteroid therapy probably resulted in little to no effect on mortality in meningococcal meningitis (RR 0.83, 95% CI 0.44–1.57). Given the limited data, this subgroup analysis was likely underpowered.
- Age groups: Low-certainty evidence from 8 RCTs suggested that adjunctive corticosteroid therapy may have reduced mortality in adults when compared to placebo (RR 0.61, 95% CI 0.42–0.88). Low-certainty evidence from 14 RCTs suggested that corticosteroid therapy may have resulted in little to no difference in mortality in children (RR 0.95, 95% CI 0.79–1.14).
- World Bank income classification: Low-certainty evidence from 14 RCTs suggested that the effect of adjunctive corticosteroid therapy on mortality may have resulted in little to no difference in HICs when compared to placebo (RR 0.84, 95% CI 0.66–1.07). Very-low-certainty evidence from 9 RCTs suggested that the effect of corticosteroid therapy on mortality in LMICs was uncertain (RR 0.75, 95% CI 0.51–1.12). There was no evidence of a difference in mortality between the two subgroups (P = 0.64).

Short-term neurological sequelae (within 6 weeks of discharge)

- Causative pathogens: Lack of data did not allow for a subgroup analysis of this outcome.
- Age groups: Low-certainty evidence from 2 RCTs suggested that adjunctive corticosteroid therapy may have reduced the risk of short-term neurological sequelae in adults when compared to placebo (RR 0.48, 95% CI 0.27–0.84). Low-certainty evidence from 10 RCTs suggested the effect of corticosteroid therapy may have resulted in little to no difference in short-term neurological sequelae in children (RR 0.86, 95% CI 0.67–1.11).
- World Bank income classification: Moderate-certainty evidence from 9 RCTs suggested that adjunctive corticosteroid therapy likely reduced the risk of short-term neurological sequelae in HICs when compared to placebo (RR 0.62, 95% CI 0.46–0.84). Moderate-certainty evidence from 5 RCTs suggested that corticosteroid therapy likely resulted in little to no difference in short-term neurological sequelae in LMICs (RR 1.09, 95% CI 0.82–1.45).

Long-term neurological sequelae (6 weeks to 2 months post-discharge)

- Causative pathogens: Lack of data did not allow for a subgroup analysis of this outcome.
- Age groups: Low-certainty evidence from 3 RCTs suggested that adjunctive corticosteroid therapy may have resulted in little to no difference in long-term neurological sequelae in adults when compared to placebo (RR 0.90, 95% CI 0.72–1.12). Low-certainty evidence from 9 RCTs suggested that corticosteroid therapy may have resulted in little to no difference in long-term neurological sequelae in children (RR 0.71, 95% CI 0.47–1.09). Given the limited data, this subgroup analysis was likely underpowered.
- World Bank income classification: Low-certainty evidence from 10 RCTs suggested that the effect of adjunctive corticosteroid therapy may have resulted in little to no difference in long-term neurological sequelae in HICs when compared to placebo (RR 0.80, 95% CI 0.61–1.05). Low-certainty evidence from 2 RCTs suggested that corticosteroid therapy may have resulted in little to no difference in long-term neurological sequelae in LMICs (RR 0.89, 95% CI 0.40–1.98).

Hearing loss

- Causative pathogens: Low-certainty evidence from 5 RCTs suggested that adjunctive corticosteroid therapy may have increased the risk of hearing loss in pneumococcal meningitis when compared to placebo (RR 1.40, 95% CI 0.99–1.98). Very-low-certainty evidence from 4 RCTs suggested that the effect of corticosteroid therapy on hearing loss in *H. influenzae* type b meningitis was uncertain (RR 1.38, 95% CI 0.55–3.44). Low-certainty evidence from 5 RCTs suggested that corticosteroid therapy may have resulted in little to no difference in hearing loss in meningococcal meningitis (RR 0.5, 95% CI 0.23–1.10). Noticeably, the samples used to conduct this subgroup analysis were limited in size.
- Age groups: Low-certainty evidence from 4 RCTs suggested that adjunctive corticosteroid therapy may have reduced the risk of hearing loss in adults when compared to placebo (RR

0.68, 95% CI 0.49–0.96). Moderate-certainty evidence from 15 RCTs suggested that corticosteroid therapy probably reduced the risk of hearing loss in children (RR 0.71, 95% CI 0.53–0.95).

- World Bank income classification: Moderate-certainty evidence from 14 RCTs suggested that adjunctive corticosteroid therapy likely reduced the risk of hearing loss in HICs when compared to placebo (RR 0.59, 95% CI 0.47–0.75). Low-certainty evidence from 5 RCTs suggested that corticosteroid therapy may have resulted in little to no difference in hearing loss in LMICs (RR 1.10, 95% CI 0.79–1.51).

Indirect evidence

The study by Scarborough et al. (2007) was excluded from the systematic review since the prevalence of HIV infection in the study population was 90%. Conducted in Blantyre, Malawi, the study was a randomized, double-blind, placebo-controlled trial of dexamethasone (16 mg twice daily for 4 days) and an open-label trial of intramuscular versus intravenous ceftriaxone (2 g twice daily for 10 days) in adults with an admission diagnosis of bacterial meningitis. The primary outcome was death at 40 days post-randomization. Out of 465 participants, 90% were HIV-positive. No HIV-positive patients were on antiretroviral treatment. Only 25.7% had information on their CD4 cell count, with a median value of 102 CD4 cells/μL (interquartile range [IQR] 51 to 169). Overall, there was no significant difference in the 40-day mortality rate between the dexamethasone group (129 out of 231 patients) and the placebo group (120 out of 228 patients), with an OR of 1.14 (95% CI 0.79–1.64). Moreover, adjunctive corticosteroid therapy did not reduce disability or death (OR 1.04, 95% CI 0.71–1.54) or hearing loss (OR 0.8, 95% CI 0.44–1.44) at 40 days. No significant difference was observed in adverse events among the 2 groups.

The systematic review by Brouwer et al. (2015) was conducted on the effects of corticosteroid therapy for acute bacterial meningitis versus placebo on mortality, hearing loss and neurological sequelae in adults and children. Overall, 25 studies involving 4121 participants were included, 9 of which were conducted in LMICs and 16 in HICs. The systematic review did not find a significant difference in mortality among adults and children who received corticosteroids for acute bacterial meningitis compared to placebo (RR 0.90, 95% CI 0.80–1.01). However, corticosteroids were associated with lower rates of neurological sequelae (RR 0.83, 95% CI 0.69–1.00), severe hearing loss (RR 0.67, 95% CI 0.5–0.88) and any hearing loss (RR 0.74, 95% CI 0.63–0.87). Subgroup analyses for causative pathogens showed that corticosteroids were associated with reduced mortality in pneumococcal meningitis (RR 0.84, 95% CI 0.72–0.98) and decreased severe hearing loss in children with *H. influenzae* type b meningitis (RR 0.34, 95% CI 0.20–0.59).

Undesirable effects

Judgement: Small

Based on the available evidence and their clinical knowledge and experience, the GDG emphasized that the undesirable effects of short-term corticosteroid therapy are small. While the evidence presented did not show a difference in adverse events between patients treated with steroids and those given a placebo, they emphasized that the studies may not have been sufficiently powered to detect adverse events. In addition, they acknowledged that potential adverse effects of short-term corticosteroid therapy may include hyperglycaemia, altered behaviour and upper gastrointestinal symptoms or bleeding (gastritis, gastric ulcer). In patients with bacterial meningitis, corticosteroids can also interfere with the ability to assess the clinical response upon initiation of antimicrobial treatment.

Source of evidence

A systematic review was conducted to compare adjunctive corticosteroid therapy with standard care without corticosteroids.

Direct evidence

Overall, 26 RCTs were identified. Twenty studies were conducted in HICs and 6 in LMICs. Only 21 studies reported on age of patients, with 11 conducted in children.

Adverse events

- Low-certainty evidence from 21 RCTs with 3943 patients suggested that adjunctive corticosteroid therapy may have resulted in little to no difference in adverse events compared to placebo (RR 1.26 95% CI 0.93–1.70).
- Low-certainty evidence from 15 RCTs with 2056 patients suggested that adjunctive corticosteroid therapy may have resulted in little to no difference in incidence of gastrointestinal bleed compared to placebo (RR 1.64, 95% CI 0.94–2.89).
- Low-certainty evidence from 5 RCTs with 967 patients suggested that adjunctive corticosteroid therapy may have resulted in little to no difference in the incidence of Herpes Zoster infection compared to placebo (RR 1.13, 95% CI 0.76–1.68)
- Low-certainty evidence from 5 RCTs with 619 patients suggested that adjunctive corticosteroid therapy did not result in increased arthritis compared to placebo (RR 0.68, 95% CI 0.18–2.63).
- One RCT compared the risk of fungal infections in adjunctive corticosteroid therapy with placebo (RR 2.06, 95% CI 0.65–6.65).

Certainty of the evidence

Judgement: Low

Mortality had moderate certainty of evidence. Any hearing loss had high certainty of evidence. Short-term neurological sequelae, post-meningitis epilepsy and adverse events had low certainty

of evidence. The remainder of critical outcomes had very low certainty of evidence. Overall, the certainty of evidence across all outcomes was considered low.

Values

Judgement: Possibly important uncertainty or variability

Based on the available evidence and their knowledge and experience, the GDG agreed that there might be important uncertainty or variability across settings in how much people value the main outcomes.

Source of evidence

A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.

Direct evidence

No direct evidence was identified regarding the uncertainty about or variability in how much people value the main outcomes. However, the included studies highlighted a complex landscape of values and beliefs surrounding the treatment of meningitis, underscoring the diversity in healthcare decision-making processes across different communities. While the direct valuation of treatment services for meningitis was not explicitly assessed within the reviewed evidence, some insights into patient and caregiver values provided a nuanced understanding of treatment preferences and care-seeking behaviours.

Indirect evidence

LMICs

Studies focused on patients'/caregivers' values related to meningitis treatment reported that biomedical treatments were most effective in diagnosing, treating and managing the disease. This acknowledgement reflected a value placed on conventional medical approaches when it came to addressing the physical aspects of the disease (2 studies, low confidence). However, the choice of treatment was profoundly influenced by the perceived cause of the illness. A significant portion of patients and caregivers, especially those attributing the disease to supernatural forces, declared a preference for traditional and Islamic treatment methods (4 studies, moderate confidence).

The initial response to meningitis symptoms among caregivers and adult patients often involved a combination of self-medication and seeking advice or treatment from traditional healers and soothsayers, particularly to discern if the disease had supernatural origins (4 studies, moderate confidence).

Patronage of government hospitals was considered a last resort when the illness became severe and not amenable to alternative care. This pattern of health-care utilization underscored the

significant influence of cultural practices on health-care decisions, indicating a complex interplay between traditional beliefs, perceived efficacy of treatments and the severity of the disease in guiding treatment choices (1 study, low confidence).

Collective decision-making was also a barrier to timely help-seeking. As patients and caregivers were dependent on the community or senior household members to fund emergency care expenses, social validation of the illness severity was essential to warrant funding (2 studies, very low confidence).

Studies indicated that an increase in disease severity initiated help-seeking behaviour. The key factor at the household level was the ability to recognize when the illness had become severe enough to necessitate seeking treatment, rather than recognizing specific signs and symptoms of acute bacterial meningitis. Factors, such as disruption of social life, weakness, loss of appetite and the inability to work were among the most cited reasons prompting individuals to seek help (2 studies, moderate confidence).

HICs

One study pointed out that health-care workers in primary care settings may have lacked experience with treating meningitis, thus they were more focused on getting a child hospitalized as early as possible rather than starting treatment on their own (1 study, moderate confidence).

The qualitative evidence consistently indicated that caregivers' primary concern revolved around the survival of their child, with many expressing profound worry about this outcome (5 studies, low confidence).

One study also highlighted that the complexity of treatment trajectories could be a source of dissatisfaction with health services (1 study, very low confidence).

Balance of effects

Judgement: Probably favours the intervention

Based on the available evidence, the GDG recognized that the beneficial effects of corticosteroids on multiple critical outcomes probably outweigh the risks in most settings.

Resources required

Judgement: Varies

The GDG acknowledged that administration of intravenous corticosteroids may contribute to increased treatment costs, especially in (but not limited to) LMICs, where steroid administration is not always part of standard clinical practice for the treatment of acute bacterial meningitis. On the other hand, increased direct costs related to corticosteroids must be balanced against the potential savings related to the prevention of long-term complications and disability related to meningitis.

Source of evidence

A scoping review was undertaken to compile information regarding costs, resource utilization and cost-effectiveness associated with meningitis diagnosis, treatment and management of sequelae.

Direct evidence

The included studies conducted did not directly address the cost of adjunctive corticosteroids.

Indirect evidence

The scoping review identified one population-based epidemiological study with information on the overall medical cost of hospitalization in children with acute bacterial meningitis, treated with or without corticosteroids between 2000 and 2013. The medical cost of hospitalization (median (IQR)) was NT$ 77 941 (26 647–237 540) and NT$ 26 653 (14 287–53 421) in the adjunctive corticosteroid and non-steroid groups, respectively.

Certainty of the evidence on resources required

Judgement: Very low

The judgement reflected the limited evidence provided, the absence of comprehensive cost comparisons between treatment options and the potential variability in cost data across settings.

Cost-effectiveness

Judgement: No included studies

A scoping review was undertaken to compile information regarding costs, resource utilization and cost-effectiveness associated with meningitis diagnosis, treatment and management of sequelae. However, no cost-effectiveness studies that would be applicable to this guideline question were identified.

Health equity, equality and non-discrimination

Judgement: Varies

Administration of intravenous corticosteroids can significantly increase the financial burden on patients or their families, particularly in resource-limited settings where treatment is not provided free of charge. Moreover, dexamethasone and other intravenous corticosteroids are not always readily available and/or affordable in resource-constrained environments, posing additional challenges in treatment access. On the other hand, the benefits related to corticosteroid treatment, in terms of reduced mortality and long-term complications in acute bacterial meningitis, are likely to reduce health inequalities and disparities.

Source of evidence

A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.

Direct evidence

None of the included qualitative studies directly focused on health equity, equality or non-discrimination in relation to corticosteroid therapy. However, the main relevant findings on health services for meningitis treatment are summarized as part of the indirect evidence.

Indirect evidence

LMICs

Reviewed evidence highlighted a lack of knowledge about meningitis symptoms in all stakeholder groups (caregivers, patients and communities), which was associated with a delay in timely help-seeking (2 studies, moderate confidence). Misdiagnosing meningitis with malaria also contributed to difficulties in the provision of prompt and appropriate care (2 studies, very low confidence).

As reported in most studies, orthodox treatment carried a great financial burden for both caregivers and adult patients. The lack of funds was the primary reason for seeking alternative types of treatment before going to the hospital. Interviews revealed that prescriptions were costly, resulting in increased financial dependency and substantial debts incurred by patients and caregivers to afford treatment expenses (2 studies, low confidence).

These factors collectively contributed to the majority of respondents favouring alternative medicine as a more affordable approach to seeking care (2 studies, low confidence). Additionally, gender disparities played a significant role in accessing care and its timeliness. Women often required the approval of family and community before deciding to seek help, in contrast to men, who generally made such decisions independently (2 studies, moderate confidence).

Feasibility

Judgement: Varies

Based on the available evidence and their knowledge and experience, the GDG agreed that the feasibility of corticosteroid therapy is likely to vary across settings, depending on the available human, financial and infrastructural resources. In particular, timely initiation and 6-hourly administration for multiple days might be challenging to implement in resource-limited settings and/or with health services stretched to capacity during large-scale epidemics.

Source of evidence

A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.

Direct evidence

None of the included qualitative studies directly focused on the feasibility of corticosteroid therapy. However, the main relevant findings on the feasibility of meningitis treatment are summarized as part of the indirect evidence.

Indirect evidence

LMICs

The qualitative evidence review identified barriers potentially limiting the feasibility of timely care.

Lack of knowledge about meningitis causes and symptoms among health-care workers was highlighted. Misdiagnosing meningitis with malaria also contributed to the difficulties in the provision of prompt and appropriate care (2 studies, very low confidence).

Evidence showed elevated expenses incurred by households for medicines, despite official government policy and the regular scarcity of complementary medicines supplied by ministries of health. If this happened, patients paid for their own medicines, including procuring them from costlier private pharmacies when they arrived outside the operating hours of the health centre's pharmacy (2 studies, very low confidence).

Reports among primary health-care workers and patients highlighted a lack of quality care, with long waiting times, presumptive diagnosis without examination, verbal mistreatment and underestimation of caregivers' concerns (2 studies, very low confidence).

Further to this, a significant barrier to effective management and treatment of meningitis in LMICs was the prevailing reliance on supernatural explanations for the illness. This belief system was associated with a preference for alternative diagnostic and treatment approaches, often at the expense of seeking timely and appropriate medical care. The inclination towards alternative health-care providers, driven by cultural norms and low socioeconomic status, delayed the use of effective treatments that were crucial for mitigating the disease's impact (5 studies, moderate confidence).

HICs

Challenges faced by health-care workers in primary care settings were significant. These included the belief that antibiotics should be administered via injections in hospital settings, a hesitation to administer injections in primary care due to a lack of experience and anxiety caused by a limited familiarity with the process. Difficulties with gaining intravenous access as a barrier to initiating antimicrobial treatment was also highlighted (2 studies, low confidence).

One study pointed out that complex treatment paths could lead to discontent with health services and complicate prompt access to health care (1 study, very low confidence).

Human rights and sociocultural acceptability

Judgement: Varies

Based on the available evidence and their knowledge and experience, the GDG agreed that the acceptability of the intervention is likely to vary across settings, depending on cultural beliefs regarding conventional medicine and trust in the health-care system.

Source of evidence

A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services

Direct evidence

None of the included qualitative studies directly focused on the compliance of corticosteroid therapy and universal human rights standards or its sociocultural acceptability. However, some aspects which influenced the ability of patients/caregivers to make a competent, informed and voluntary decision regarding meningitis treatment are summarized as part of the indirect evidence.

Indirect evidence

LMICs

Some studies indicated a preference for conventional medicine as a treatment choice. Participants, including older patients and their caregivers, favoured medical interventions over traditional treatment practices. However, some patients and caregivers highlighted that "Western" practitioners typically focused on diagnosing peripheral causes and managing symptoms, whereas traditional healers addressed the root cause of the illness (4 studies, moderate confidence).

Narratives from caregivers of children who had encountered meningitis, as well as those whose neighbours' or relatives' children had previous meningitis episodes, emphasized that health facilities were the primary point of care for meningitis, suggesting trust in the ability of formal health-care settings to provide necessary and effective treatment (2 studies, low confidence).

Two studies highlighted gender dynamics that had influenced decision-making processes in health care. Specifically, women often sought validation from their husbands, adult relatives or neighbours regarding the severity of health conditions before seeking care. This trend was exacerbated by the fact that many women had limited or no formal education and were unemployed, factors that constrained their capacity to make informed health decisions for their

families. In contrast, men were more likely to make health-care decisions independently, underscoring a gender disparity in autonomy and access to health-care decision-making (2 studies, moderate confidence).

Another study reported that cultural beliefs and care-seeking behaviour related to meningitis in LMICs were still influenced by traditional thinking. Yet despite the dominance of traditional views, there was a gradual shift towards embracing modern understandings of disease and, consequently, more contemporary approaches to care-seeking in society (2 studies, low confidence).

CSF: cerebrospinal fluid; GDG: Guideline Development Group; HICs: high-income countries; IQR: interquartile range; LMICs: low- and middle-income countries; RCT: randomized controlled trial.

12. Osmotic agents

12.1 Guideline question

In individuals with suspected, probable or confirmed acute bacterial meningitis, should osmotic agents be used?

Population: Suspected, probable or confirmed cases of acute bacterial meningitis

Subgroups: Pathogens (*Neisseria meningitidis, Streptococcus pneumoniae, Haemophilus influenzae* and Group B *Streptococcus*), age groups (children, adults), World Bank income classification (HIC, LMIC), disease severity (altered consciousness)

Intervention: Adjunctive osmotic agent (glycerol, mannitol, sorbitol, hypertonic saline, sodium lactate)

Comparator: Standard care without adjunctive osmotic agent

Outcome:

Critical: Neurological complications (neurological sequelae,[10] hearing loss); mortality; adverse effects

Important: Impact on disease course (time to resolution of symptoms, persistent fever)

Full details of the evidence, including references, are provided in Web Annex A (12. Osmotic agents) and Web Annex B (Qualitative and economic evidence reports).

[10] Neurological sequelae defined as any of the following: Hearing loss, speech and/or language impairment, seizures, neurocognitive impairment, psychological after-effects (stress, depression, altered behaviour), hydrocephalus, motor deficits, vision impairment.

12.2 Evidence-to-Decision framework

Priority of the problem
Judgement: Yes Cerebral oedema is a serious complication of acute meningitis that can lead to increased intracranial pressure, brain herniation and potentially fatal outcomes. Effective management of cerebral oedema is thus crucial for reducing morbidity and mortality associated with acute meningitis. Although commonly used in treating raised intracranial pressure, the effectiveness and safety of osmotic agents among patients with acute bacterial meningitis remains uncertain.
Desirable effects
Judgement: Varies The Guideline Development Group (GDG) acknowledged that the desirable effects of oral glycerol are limited when used routinely in people with acute meningitis. They also agreed that although all studies were conducted in children and adolescents (up to 16 years of age), their findings could be generalized to adults. Moreover, they noted that other osmotic agents (but not glycerol) may be used as a temporary intervention in selected individuals to treat increased intracranial pressure and avert impending brain herniation.
Source of evidence A systematic review was conducted to compare adjunctive osmotic therapy with standard care without osmotic therapy in acute bacterial meningitis.
Direct evidence Overall, 4 randomized controlled trials (RCTs) conducted in children and adolescents (up to 16 years of age) were included. Glycerol was the only osmotic agent included in these studies. The main findings are summarized below. No data were available for some subgroups of interest, including age groups, World Bank income classification and disease severity. *All-cause mortality* Low-certainty evidence from 4 RCTs with 1011 children suggested that glycerol may have resulted in little to no difference in mortality at 1-month follow-up compared with care without osmotic therapy (RR 0.84, 95% CI 0.62–1.15). *Neurological sequelae* Low-certainty evidence from 4 RCTs with 1011 children suggested that glycerol may have resulted in little to no difference in neurological sequelae at 2-month follow-up compared with care

without osmotic agents (RR 0.77, 95% CI 0.38–1.53). Neurological sequelae included hemiplegia, quadriparesis, ataxia, blindness, hearing loss, seizures, developmental delay, severe psychomotor retardation and hydrocephalus requiring a shunt.

Hearing loss

Low-certainty evidence from 4 RCTs with 874 children suggested that glycerol may have resulted in little to no difference in hearing loss at 1.5-month follow-up compared with care without osmotic agents (RR 0.70, 95% CI 0.47–1.04).

Post-meningitis epilepsy or symptomatic seizures

Low-certainty evidence from 3 RCTs with 839 children suggested that glycerol may have resulted in little to no difference in post-meningitis epilepsy or symptomatic seizures at 1-month follow-up compared with care without osmotic agents (RR 0.89, 95% CI 0.71–1.12).

Direct evidence (subgroup analyses)

All-cause mortality

- Causative pathogens*:* No significant difference in mortality was observed between osmotic therapy and placebo in *Haemophilus influenzae* type b meningitis (RR 0.87, 95% CI 0.37–2.05), pneumococcal meningitis (RR 0.72, 95% CI 0.3–1.75) or meningococcal meningitis (RR 0.85, 95% CI 0.09–8.28).
- Adjunctive corticosteroids vs no corticosteroids: Among patients who received corticosteroids, no significant difference was observed between osmotic therapy and placebo (RR 0.83, 95% CI 0.57–1.21). Among patients who did not receive corticosteroids, no significant difference in mortality was observed between osmotic therapy and placebo (RR 0.88, 95% CI 0.51–1.52). There was no evidence of a difference in mortality between patients who received corticosteroids and those who did not (*P* = 0.84).

Neurological sequelae

- Adjunctive corticosteroids vs no corticosteroids: Among patients who received corticosteroids, no significant difference in neurological sequelae was observed between osmotic therapy and placebo (RR 0.82, 95% CI 0.23–2.94). Among patients who did not receive corticosteroids, no significant difference in neurological sequelae was observed between osmotic therapy and placebo (RR 0.73, 95% CI 0.26–2.06). There was no evidence of a difference in neurological sequelae between patients who received corticosteroids and those who did not (*P* = 0.89).

Hearing loss

- Causative pathogens: No significant difference in hearing loss was observed between osmotic therapy and placebo in pneumococcal meningitis (RR 0.62, 95% CI 0.06–6.43) and *H. influenzae* meningitis (RR 0.79, 95% CI 0.28–2.23).

- Adjunctive corticosteroids vs no corticosteroids: Among patients who received corticosteroids, no significant difference in hearing loss was observed between osmotic therapy and placebo (RR 0.66, 95% CI 0.32–1.35). Among patients who did not receive corticosteroids, no significant difference in hearing loss was observed between osmotic therapy and placebo (RR 0.72, 95% CI 0.45–1.16). There was no evidence of a difference in hearing loss between patients who received corticosteroids and those who did not (*P* = 0.84).

Post-meningitis epilepsy or symptomatic seizures

- Adjunctive corticosteroids vs no corticosteroids: Among patients who received corticosteroids, no significant difference in post-meningitis epilepsy or symptomatic seizures was observed between osmotic therapy and placebo (RR 0.96, 95% CI 0.70–1.33). Among patients who did not receive corticosteroids, no significant difference in post-meningitis epilepsy or symptomatic seizures was observed between osmotic therapy and placebo (RR 0.82, 95% CI 0.60–1.14). There was no evidence of a difference in post-meningitis epilepsy or symptomatic seizures between patients who received corticosteroids and those who did not (*P* = 0.50).

Indirect evidence

Two studies provided evidence on glycerol therapy for acute bacterial meningitis in settings with high HIV prevalence and were considered relevant to the scope of the guidelines. The main findings are summarized below.

A double-blind, randomized placebo-controlled trial was conducted in a setting with high HIV seroprevalence in Malawi to investigate the effect of oral glycerol as adjunctive therapy in adults with bacterial meningitis (Ajdukiewicz et al. 2011). Overall, 83% of the population had HIV infection. The most common cause of bacterial meningitis was *Streptococcus pneumoniae* (cryptococcal and lymphocytic meningitis were exclusion criteria). The trial was stopped early following a planned interim analysis. Mortality by day 40 was 61 of 125 (49%) in the placebo and 86 of 136 (69%) in the glycerol arms (adjusted OR 2.4, 95% CI 1.3–4.2). There was no benefit from glycerol in terms of death or disability by day 40 by intention-to-treat or in predefined subgroups.

A study analysed the evidence from all clinical trials investigating bacterial meningitis from 1990 in Blantyre, Malawi, and combined the data from all included trial datasets into one database (Wall et al. 2013). Overall, 715 episodes of bacterial meningitis were evaluated. The most common pathogens were *S. pneumoniae* (84% of positive cerebrospinal fluid isolates) and *Neisseria meningitidis* (4%). Notably, 87% of participants tested were HIV antibody positive. The mortality rate was 45% at day 10 and 54% at day 40. With respect to osmotic therapy, glycerol was independently associated with mortality (adjusted OR 1.88, 95% CI 1.09–3.25).

Undesirable effects

Judgement: Trivial

The GDG acknowledged that potential adverse effects of oral glycerol include (but may not be limited to) headache, nausea, vomiting, diarrhoea and dizziness. As nausea and vomiting are generally considered the 2 most common adverse events, the GDG indicated that the undesirable effects resulting from glycerol administration should be considered trivial.
Source of evidence A systematic review was conducted to compare adjunctive osmotic therapy with standard care without osmotic therapy in acute bacterial meningitis.
Direct evidence The studies included in the systematic review described above did not assess adverse events of glycerol.
Certainty of the evidence
Judgement: Low The certainty of evidence was low for all critical outcomes.
Values
Judgement: Probably no important uncertainty or variability Based on the available evidence and their knowledge and experience, the GDG agreed that there might be important uncertainty or variability across settings in how much people value the main outcomes.
Source of evidence A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.
Direct evidence No direct evidence was identified regarding the uncertainty about or variability in how much people value the main outcomes. However, the included studies highlighted a complex landscape of values and beliefs surrounding the treatment of meningitis, underscoring the diversity in healthcare decision-making processes across different communities. While the direct valuation of treatment services for meningitis was not explicitly assessed within the reviewed evidence, some insights into patient and caregiver values provided a nuanced understanding of treatment preferences and care-seeking behaviours.

Indirect evidence

Low and middle-income countries (LMICs)

Studies focused on patients'/caregivers' values related to meningitis treatment reported that biomedical treatments were most effective in diagnosing, treating and managing the disease. This acknowledgement reflected a value placed on conventional medical approaches when it came to addressing the physical aspects of the disease (2 studies, low confidence). However, the choice of treatment was profoundly influenced by the perceived cause of the illness. A significant portion of patients and caregivers, especially those attributing the disease to supernatural forces, declared a preference for traditional and Islamic treatment methods (4 studies, moderate confidence).

The initial response to meningitis symptoms among caregivers and adult patients often involved a combination of self-medication and seeking advice or treatment from traditional healers and soothsayers, particularly to discern if the disease had supernatural origins (4 studies, moderate confidence).

Patronage of government hospitals was considered a last resort when the illness became severe and not amenable to alternative care. This pattern of health-care utilization underscored the significant influence of cultural practices on health-care decisions, indicating a complex interplay between traditional beliefs, perceived efficacy of treatments and the severity of the disease in guiding treatment choices (1 study, low confidence).

Collective decision-making was also a barrier to timely help-seeking. As patients and caregivers were dependent on the community or senior household members to fund emergency care expenses, social validation of the illness severity was essential to warrant funding (2 studies, very low confidence).

Studies indicated that an increase in disease severity initiated help-seeking behaviour. The key factor at the household level was the ability to recognize when the illness had become severe enough to necessitate seeking treatment, rather than recognizing specific signs and symptoms of acute bacterial meningitis. Factors, such as disruption of social life, weakness, loss of appetite and the inability to work were among the most cited reasons prompting individuals to seek help (2 studies, moderate confidence).

High-income countries (HICs)

One study pointed out that health-care workers in primary care settings may have lacked experience with treating meningitis, thus they were more focused on getting a child hospitalized as early as possible rather than starting treatment on their own (1 study, moderate confidence).

The qualitative evidence consistently indicated that caregivers' primary concern revolved around the survival of their child, with many expressing profound worry about this outcome (5 studies, low confidence).

One study also highlighted that the complexity of treatment trajectories could be a source of dissatisfaction with health services (1 study, very low confidence).
Balance of effects
Judgement: Varies The judgement was based on the evidence and judgements presented above.
Resources required
Judgement: Negligible costs and savings Based on their knowledge and experience, the GDG indicated that the cost of oral glycerol can be considered negligible in most countries.
Source of evidence A scoping review was undertaken to compile information regarding costs, resource utilization and cost-effectiveness associated with meningitis diagnosis, treatment and management of sequelae.
Direct evidence None of the identified cost and resource utilization studies were considered applicable to this guideline question.
Certainty of the evidence on resources required
Judgement: No included studies
Cost-effectiveness
Judgement: No included studies A scoping review was undertaken to compile information regarding costs, resource utilization and cost-effectiveness associated with meningitis diagnosis, treatment and management of sequelae. However, no cost-effectiveness studies that would be applicable to this guideline question were identified.
Health equity, equality and non-discrimination
Judgement: Probably no impact Based on the available evidence showing little to no effect on critical outcomes among children with acute bacterial meningitis, the GDG agreed that osmotic therapy with oral glycerol is not likely to reduce or increase health inequities or discrimination.

Source of evidence

A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.

Direct evidence

None of the included qualitative studies directly focused on health equity, equality or non-discrimination in relation to osmotic therapy. However, the main relevant findings on health services for meningitis treatment are summarized as part of the indirect evidence.

Indirect evidence

LMICs

Reviewed evidence highlighted a lack of knowledge about meningitis symptoms in all stakeholder groups (caregivers, patients and communities), which was associated with a delay in timely help-seeking (2 studies, moderate confidence). Misdiagnosing meningitis with malaria also contributed to difficulties in the provision of prompt and appropriate care (2 studies, very low confidence).

As reported in most studies, orthodox treatment carried a great financial burden for both caregivers and adult patients. The lack of funds was the primary reason for seeking alternative types of treatment before going to the hospital. Interviews revealed that prescriptions were costly, resulting in increased financial dependency and substantial debts incurred by patients and caregivers to afford treatment expenses (2 studies, low confidence).

These factors collectively contributed to the majority of respondents favouring alternative medicine as a more affordable approach to seeking care (2 studies, low confidence). Additionally, gender disparities played a significant role in accessing care and its timeliness. Women often required the approval of family and community before deciding to seek help, in contrast to men, who generally made such decisions independently (2 studies, moderate confidence).

Feasibility

Judgement: Varies

Based on the available evidence and their knowledge and experience, the GDG agreed that the feasibility of osmotic therapy varies across settings, depending on available drugs, existing clinical capacity and trained health-care workforce. Noticeably, mannitol is the only osmotic agent included in the WHO Essential Medicines List and is widely accessible and affordable across most settings.

Source of evidence

A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.

Direct evidence

None of the included qualitative studies directly focused on the feasibility of osmotic therapy. However, the main relevant findings on the feasibility of meningitis treatment are summarized as part of the indirect evidence.

Indirect evidence

LMICs

The qualitative evidence review identified barriers potentially limiting the feasibility of timely care.

Lack of knowledge about meningitis causes and symptoms among health-care workers was highlighted. Misdiagnosing meningitis with malaria also contributed to difficulties in the provision of prompt and appropriate care (2 studies, very low confidence).

Households incurred elevated expenses for medicines despite official government policy and the regular scarcity of complementary medicines supplied by ministries of health (2 studies, very low confidence).

A significant barrier to effective management and treatment of meningitis in LMICs was a prevailing reliance on supernatural explanations for the illness. This belief system was associated with a preference for alternative diagnostic and treatment approaches, often at the expense of seeking timely and appropriate medical care. The inclination towards alternative health-care providers, driven by cultural norms and low socioeconomic status, delayed the use of effective treatments that were crucial for mitigating the disease's impact (5 studies, moderate confidence).

HICs

Challenges faced by health-care workers in primary care settings were significant. These included the belief that antibiotics should be administered via injections in hospital settings, a hesitation to administer injections in primary care due to a lack of experience and anxiety caused by a limited familiarity with the process. Difficulties with gaining intravenous access as a barrier to initiating antimicrobial treatment was also highlighted (2 studies, low confidence).

Organizational barriers also played a role in delaying antimicrobial treatment initiation among health-care workers. These included specific advice from emergency departments, perceived disapproval from national prescribing services regarding the general use of antibiotics and the unavailability of antibiotics (1 study, very low confidence).

Human rights and sociocultural acceptability

Judgement: Probably yes

Based on the available evidence and their knowledge and experience the GDG agreed that osmotic therapy is likely to be acceptable across settings, potentially with some variations depending on cultural beliefs regarding conventional medicine and trust in the health-care system.

Source of evidence

A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services

Direct evidence

None of the included qualitative studies directly focused on the on the compliance of osmotic therapy with universal human rights standards or its sociocultural acceptability. However, some aspects which influenced the ability of patients/caregivers to make a competent, informed and voluntary decision regarding meningitis treatment are summarized as part of the indirect evidence.

Indirect evidence

LMICs

Some studies indicated a preference for conventional medicine as a treatment choice. Participants, including older patients and their caregivers, favoured medical interventions over traditional treatment practices. However, some patients and caregivers highlighted that "Western" practitioners typically focused on diagnosing peripheral causes and managing symptoms, whereas traditional healers addressed the root cause of the illness (4 studies, moderate confidence).

Narratives from carers of children who had experienced meningitis, as well as those whose neighbours' or relatives' children had experienced meningitis, emphasized that health facilities were the primary point of care for meningitis, suggesting trust in the ability of formal health-care settings to provide necessary and effective treatment (2 studies, low confidence).

Gender dynamics were highlighted as factors that influenced decision-making processes in health care. Specifically, women often sought validation from their husbands, adult relatives or neighbours regarding the severity of health conditions before seeking care. This trend was exacerbated by the fact that many women had limited or no formal education and were unemployed, factors that constrained their capacity to make informed health decisions for their families. In contrast, men were more likely to make health-care decisions independently,

underscoring a gender disparity in autonomy and access to health-care decision-making (2 studies, moderate confidence). Another study reported that cultural beliefs and care-seeking behaviour related to meningitis in LMICs were still influenced by traditional thinking. Yet despite the dominance of traditional views, there was a gradual shift towards embracing modern understandings of disease and, consequently, more contemporary approaches to care-seeking in society (2 studies, low confidence).

GDG: Guideline Development Group; HICs: high-income countries; LMICs: low- and middle-income countries; RCT: randomized controlled trial; WHO: World Health Organization.

13. Fluid management

13.1 Guideline question

In individuals with suspected, probable or confirmed acute bacterial meningitis, should fluid restriction be implemented?

Population: Suspected, probable or confirmed cases of acute bacterial meningitis

Subgroups: Pathogens (*Neisseria meningitidis, Streptococcus pneumoniae, Haemophilus influenzae* and Group B *Streptococcus*), age groups (children, adults), World Bank income classification (HIC, LMIC), disease severity (altered consciousness)

Intervention: Fluid restriction

Comparator: Standard care without fluid restriction

Outcome:

Critical: Neurological complications (neurological sequelae,[11] hearing loss), mortality, adverse effects

Important: Impact on disease course (time to resolution of symptoms, persistent fever)

Full details of the evidence, including references, are provided in Web Annex A (13. Fluid management) and Web Annex B (Qualitative and economic evidence reports).

[11] Neurological sequelae defined as: Hearing loss, speech and/or language impairment, seizures, neurocognitive impairment, psychological after-effects (stress, depression, behaviour), hydrocephalus, motor deficits, vision impairment.

13.2 Evidence-to-Decision framework

Priority of the problem
Judgement: Yes Acute bacterial meningitis is a medical emergency that requires timely and accurate treatment to reduce morbidity and mortality. Management of fluid and electrolyte balance plays a crucial role in meningitis treatment as both over-hydration and under-hydration may be associated with adverse outcomes. Fluid restriction in the management of bacterial meningitis has been widely advocated and often used in children based on reports of hyponatraemia, which is generally attributed to increased circulating antidiuretic hormone (ADH) levels. While hyponatraemia has been associated with disease severity and adverse neurological outcomes, the effectiveness and safety of fluid restriction in the management of people with acute bacterial meningitis remains controversial.
Desirable effects
Judgement: Trivial The Guideline Development Group (GDG) emphasized that both studies were conducted in low and middle-income countries (LMICs) more than 2 decades prior to the publication of these guidelines and used maintenance fluids in the comparator arms that are no longer considered the standard of care (fifth-normal saline and half-normal saline, respectively, with 5% dextrose).
Source of evidence A systematic review was conducted to compare fluid restriction with standard care without fluid restriction for acute bacterial meningitis.
Direct evidence Overall, two randomized controlled trials (RCTs) conducted in children in LMICs were included. The main findings on mortality and neurological sequelae are summarized below. There was no evidence on the impact of fluid restriction on disease course (i.e. time to resolution of symptoms, persistent fever). *Mortality* Very-low-certainty evidence from two RCTs with 407 children suggested that the effect of fluid restriction on mortality at admission compared with normal fluid maintenance was uncertain (RR 1.19, 95% CI 0.77–1.85). *Neurological sequelae*

Very-low-certainty of evidence from 2 RCTs with 482 children suggested that the effect of fluid restriction on neurological sequelae compared with normal fluid maintenance was uncertain (RR 1.31, 95% CI 0.74–2.30). Neurological sequelae included hemiplegia, hypotonia, spasticity, sensory deficits, cranial neuropathy, seizures and coma.

Direct evidence (outcomes based on hyponatraemia status)

Mortality

One RCT reported on mortality based on hyponatraemia status. No evidence of a difference in mortality among those with or without hyponatraemia was shown between the fluid-restricted group and standard maintenance group (4 of 15 [27%] vs 0 of 11 [0%] in the hyponatraemia groups and 3 of 13 [23%] vs 2 of 11 [18%] in the groups without hyponatraemia, $P = 0.48$).

Neurological sequelae

One RCT reported on neurological sequelae based on hyponatraemia status. No evidence of a difference in sequelae among those with or without hyponatraemia was shown between the fluid-restricted group and standard maintenance group (6 of 15 [40%] vs 4 of 11 [36%] in the hyponatraemia groups, respectively; 4 of 13 [23%] vs 2 of 11 [18%] in the groups without hyponatraemia, respectively; $P = 0.48$).

Undesirable effects

Judgement: Moderate

Known side effects associated with fluid restriction in adults and children include dehydration and hypernatraemia, especially in selected groups (e.g. older adults).

Although adverse events related to fluid restriction were not reported, the GDG considered the direction of the relative and absolute effect for the critical outcomes, suggesting a lower risk of death and neurological sequelae in the comparator arm (no fluid restriction). Moreover, the GDG highlighted that one of the included studies suggested a higher risk of adverse outcome, defined as death or severe neurological sequelae (RR 0.75, 95% CI 0.53–1.04).

Based on the available evidence and their clinical knowledge and expertise the GDG indicated that the undesirable effects resulting from fluid restriction should be considered moderate.

Source of evidence

A systematic review was conducted to compare fluid restriction with standard care without fluid restriction in acute bacterial meningitis.

Direct evidence

The studies included in the systematic review did not assess adverse events of fluid restriction.

Certainty of the evidence
Judgement: Very low The evidence was very low for all critical outcomes.
Values
Judgement: no important uncertainty or variability The GDG discussed people's cultural values and how they can impact decisions regarding a potentially life-threatening disease with a high risk of neurological sequelae. They also indicated that people in traditional societies are often pragmatic when it comes to combining religious and spiritual beliefs with available medical care. Based on the available evidence and their knowledge and experience, the GDG agreed that there probably is no important uncertainty or variability across settings in how much people value the main outcomes.
Source of evidence A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.
Direct evidence No direct evidence was identified regarding the uncertainty about or variability in how much people value the main outcomes. However, the included studies highlighted a complex landscape of values and beliefs surrounding the treatment of meningitis, underscoring the diversity in healthcare decision-making processes across different communities. While the direct valuation of treatment services for meningitis was not explicitly assessed within the reviewed evidence, some insights into patient and caregiver values provided a nuanced understanding of treatment preferences and care-seeking behaviours.
Indirect evidence *LMICs* Studies focused on patients'/caregivers' values related to meningitis treatment reported that biomedical treatments were most effective in diagnosing, treating and managing the disease. This acknowledgement reflected a value placed on conventional medical approaches when it came to addressing the physical aspects of the disease (2 studies, low confidence). However, the choice of treatment was profoundly influenced by the perceived cause of the illness. A significant portion of patients and caregivers, especially those attributing the disease to supernatural forces, declared a preference for traditional and Islamic treatment methods (4 studies, moderate confidence).

The initial response to meningitis symptoms among caregivers and adult patients often involved a combination of self-medication and seeking advice or treatment from traditional healers and soothsayers, particularly to discern if the disease had supernatural origins (4 studies, moderate confidence).

The initial response to meningitis symptoms among caregivers and adult patients often involved a combination of self-medication and seeking advice or treatment from traditional healers and soothsayers, particularly to discern if the disease had supernatural origins. Despite these initial preferences, severe progression of the disease tended to shift care-seeking behaviour towards government hospitals (5 studies, moderate confidence).

In 1 study, most of the interviewed caregivers sought orthodox care when the disease became severe, while alternative care sources, such as patent medicine vendors/chemists, unlicensed health workers and traditional healers were the first choice (1 study, low confidence).

Collective decision-making was also a barrier to timely help-seeking. As patients and caregivers were dependent on the community or senior household members to fund emergency care expenses, social validation of illness severity was essential to warrant funding (2 studies, very low confidence).

High-income countries (HICs)

Health-care workers in primary care settings may have lacked experience with treating meningitis, thus they were more focused on getting a child hospitalized as early as possible rather than starting treatment on their own (1 study, moderate confidence).

The qualitative evidence consistently indicated that caregivers' primary concern revolved around the survival of their child, with many expressing profound worry about this outcome (5 studies, low confidence).

Balance of effects

Judgement: Probably favours the comparison

The judgement was based on the evidence and judgements presented above.

Resources required

Judgement: Negligible costs and savings

Based on their knowledge and experience, the GDG indicated that the savings resulting from fluid restriction can mostly be considered negligible.

Source of evidence

A scoping review was undertaken to compile information regarding costs, resource utilization and cost-effectiveness associated with meningitis diagnosis, treatment and management of sequelae.

Direct evidence

The scoping review identified 1 study that provided information on the cost of IV fluids in Gambia. The unit cost of a 500 ml bottle of Ringer's lactate, normal saline and 5% glucose was US$ 0.55, 0.50 and 0.55 (2010 US$), respectively. None of the studies conducted in HICs were considered applicable to this guideline question.

Certainty of the evidence on resources required

Judgement: Very low

The judgement reflected the limited scope of the evidence, the absence of comprehensive cost comparisons between interventions and the potential variability in cost data across settings.

Cost-effectiveness

Judgement: No included studies

A scoping review was undertaken to compile information regarding costs, resource utilization and cost-effectiveness associated with meningitis diagnosis, treatment and management of sequelae. However, no cost-effectiveness studies that would be applicable to this guideline question were identified.

Health equity, equality and non-discrimination

Judgement: Probably reduced

The GDG emphasized that that prevention of neurological sequelae leads to improved health equity and less stigma burden. However, based on the available evidence showing little to no effect on critical outcomes among children with acute bacterial meningitis, the GDG agreed that osmotic therapy with oral glycerol is not likely to reduce or increase health inequities or discrimination.

Source of evidence

A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.

Direct evidence

None of the included qualitative studies directly focused on health equity, equality or non-discrimination in relation to fluid restriction. However, the main relevant findings on health services for meningitis treatment are summarized as part of the indirect evidence.

Indirect evidence

LMICs

Reviewed evidence highlighted a lack of knowledge about meningitis symptoms in all stakeholder groups (caregivers, patients and communities), which was associated with a delay in timely help-seeking (2 studies, moderate confidence). Misdiagnosing meningitis with malaria also contributed to the difficulties in the provision of prompt and appropriate care (2 studies, very low confidence).

As reported in most studies, orthodox treatment carried a great financial burden for both caregivers and adult patients. The lack of funds was the primary reason for seeking alternative types of treatment before going to the hospital. Interviews revealed that prescriptions were costly, resulting in increased financial dependency and substantial debts incurred by patients and caregivers to afford treatment expenses (2 studies, low confidence).

These factors collectively contributed to the majority of respondents favouring alternative medicine as a more affordable approach to seeking care (2 studies, low confidence). Additionally, gender disparities played a significant role in accessing care and its timeliness. Women often required the approval of family and community before deciding to seek help, in contrast to men, who generally made such decisions independently (2 studies, moderate confidence).

Feasibility

Judgement: Probably yes

Based on the available evidence and their knowledge and experience, the GDG agreed that the feasibility of fluid restriction varies across settings, depending on available drugs, existing clinical capacity and trained health-care workforce. Noticeably, mannitol is the only osmotic agent included in the WHO Essential Medicines List and is widely accessible and affordable across most settings.

Source of evidence

A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.

Direct evidence

None of the included qualitative studies directly focused on the feasibility of osmotic therapy. However, the main relevant findings on the feasibility of meningitis treatment are summarized as part of the indirect evidence.

Indirect evidence

LMICs

The qualitative evidence review identified barriers potentially limiting the feasibility of timely care.

Lack of knowledge about meningitis causes and symptoms among health-care workers was highlighted. Misdiagnosing meningitis with malaria also contributed to difficulties in the provision of prompt and appropriate care (2 studies, very low confidence).

Households incurred elevated expenses for medicines despite official government policy and the regular scarcity of complementary medicines supplied by ministries of health (2 studies, very low confidence).

A significant barrier to effective management and treatment of meningitis in LMICs was a prevailing reliance on supernatural explanations for the illness. This belief system was associated with a preference for alternative diagnostic and treatment approaches, often at the expense of seeking timely and appropriate medical care. The inclination towards alternative health-care providers, driven by cultural norms and low socioeconomic status, delayed the use of effective treatments that were crucial for mitigating the disease's impact (5 studies, moderate confidence).

HICs

Challenges faced by health-care workers in primary care settings were significant. These included the belief that antibiotics should be administered via injections in hospital settings, a hesitation to administer injections in primary care due to a lack of experience and anxiety caused by a limited familiarity with the process. Difficulties with gaining intravenous access as a barrier to initiating antibiotic treatment was also highlighted (2 studies, low confidence).

Organizational barriers also played a role in delaying antibiotic treatment initiation among health-care workers. These included specific advice from emergency departments, perceived disapproval from national prescribing services regarding the general use of antibiotics and the unavailability of antibiotics (1 study, very low confidence).

Human rights and sociocultural acceptability

Judgement: Varies

Based on the available evidence and their knowledge and experience the GDG agreed that osmotic therapy is likely to be acceptable across settings, potentially with some variations depending on cultural beliefs regarding conventional medicine and trust in the health-care system.

Source of evidence

A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services

Direct evidence

None of the included qualitative studies directly focused on the compliance of fluid restriction with universal human rights standards or its sociocultural acceptability. However, some aspects which influenced the ability of patients/caregivers to make a competent, informed and voluntary decision regarding meningitis treatment are summarized as part of the indirect evidence.

Indirect evidence

LMICs

Some studies indicated a preference for conventional medicine as a treatment choice. Participants, including older patients and their caregivers, favoured medical interventions over traditional treatment practices. However, some patients and caregivers highlighted that "Western" practitioners typically focused on diagnosing peripheral causes and managing symptoms, whereas traditional healers addressed the root cause of the illness (4 studies, moderate confidence).

Narratives from carers of children who had experienced meningitis, as well as those whose neighbours' or relatives' children had experienced meningitis, emphasized that health facilities were the primary point of care for meningitis, suggesting trust in the ability of formal health-care settings to provide necessary and effective treatment (2 studies, low confidence).

Gender dynamics were highlighted as factors that influenced decision-making processes in health care. Specifically, women often sought validation from their husbands, adult relatives or neighbours regarding the severity of health conditions before seeking care. This trend was exacerbated by the fact that many women had limited or no formal education and were unemployed, factors that constrained their capacity to make informed health decisions for their families. In contrast, men were more likely to make health-care decisions independently, underscoring a gender disparity in autonomy and access to health-care decision-making (2 studies, moderate confidence).

Another study reported that cultural beliefs and care-seeking behaviour related to meningitis in LMICs were still influenced by traditional thinking. Yet despite the dominance of traditional views, there was a gradual shift towards embracing modern understandings of disease and, consequently, more contemporary approaches to care-seeking in society (2 studies, low confidence).

GDG: Guideline Development Group; HICs: high-income countries; LMICs: low- and middle-income countries; RCT: randomized controlled trial; WHO: World Health Organization.

14. Anti-seizure medicines

14.1 Guideline question

In children and adults with acute symptomatic seizures from meningitis, should anti-seizure medicines be stopped before 3 months?

Population: People with acute meningitis and acute symptomatic seizures

Subgroup: Age group (children, adults)

Intervention: Duration of anti-seizure medicine up to 3 months

Comparison: More than 3 months duration of anti-seizure medicine

Outcome: *Critical:* Development of epilepsy, adverse effects of medicines, mortality

Full details of the evidence, including references, are provided in Web Annex A (14. Anti-seizure medicines) and Web Annex B (Qualitative and economic evidence reports).

14.2 Evidence-to-Decision framework

Priority of the problem
Judgement: Yes Acute symptomatic seizures frequently occur as a complication of acute meningitis. While anti-seizure medicines (ASMs) are commonly prescribed to control seizures and prevent recurrent episodes, the optimal duration of their use in individuals with meningitis remains unclear. The inappropriate and prolonged use of ASMs may contribute to unnecessary side effects, drug interactions and increased health-care costs. Conversely, discontinuation of these medicines can lead to recurrent seizures, with detrimental medical, social and economic implications.
Desirable effects
Judgement: Trivial Based on the indirect evidence and their clinical knowledge and expertise, the Guideline Development Group (GDG) agreed that the desirable effects on critical outcomes resulting from a short ASM treatment duration may be considered trivial when compared to later discontinuation.
Source of evidence A systematic review was conducted to compare duration of ASM treatment up to three months to longer treatment durations.
Direct evidence The systematic review did not find any comparative studies directly addressing the guideline question.
Indirect evidence Two studies were considered as sources of indirect evidence: 1 randomized controlled trial (RCT) conducted in children with acute encephalitis syndrome and 1 cohort study conducted in adults with a variety of structural and non-structural brain conditions, including meningitis and meningoencephalitis. In the cohort study, the proportion of evidence from people with meningitis or meningoencephalitis was limited and has not been disaggregated (5 of 141 or 3.5% of participants). *Seizure recurrence*

- Very-low-certainty evidence from 1 RCT including 60 children with acute encephalitis syndrome showed that the effect of 4 weeks of ASM on seizure recurrence at 12 months compared with 12 weeks of ASM was uncertain (RR 1.00, 95% CI 0.06–16.68).
- Very-low-certainty evidence from one cohort study including 141 adults with various structural and non-structural brain conditions showed that the effect of less than 100 days of ASMs on seizure recurrence at 12 months compared with more than 100 days of ASMs was uncertain (RR 1.20, 95% CI 0.21–6.84).
- The pooled RR across the 2 studies was 1.14 (95% CI 0.26–5.01).

Undesirable effects

Judgement: Trivial

The GDG recognized that a shorter treatment regimen could result in fewer undesirable effects due to the reduced duration of therapy.

Source of evidence

A systematic review was conducted to compare duration of anti-seizure medicines up to three months to longer treatment durations.

Direct evidence

The systematic review did not find any comparative studies directly addressing the guideline question.

Indirect evidence

Adverse events

One RCT including 60 children with acute encephalitis syndrome receiving either 4 weeks of anti-seizure medicines or 12 weeks of anti-seizure medicines reported that no patients in either arm had adverse events.

Certainty of the evidence

Judgement: Very low

The certainty of evidence was considered very low due to the lack of direct evidence addressing the guideline question.

Values

Judgement: Possibly important uncertainty or variability

The GDG discussed people's cultural values and how they can impact decisions regarding a potentially life-threatening disease with a relatively high risk of recurrent seizures and epilepsy. They indicated that people in traditional societies are often pragmatic when it comes to combining religious and spiritual beliefs with available medical care.

On the other hand, fear of seizure recurrence can indicate that adverse effects of medicines are considered an indicator of treatment efficacy and valued differently depending on how this is understood. In addition, stigma associated with ASM treatment may further add variation in how treatment outcomes are valued. Therefore, the GDG agreed that there may be important uncertainty or variability in the value of outcomes.

Source of evidence

A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.

Direct evidence

No direct evidence was identified regarding the uncertainty about or variability in how much people value the main outcomes. However, the included studies highlighted a complex landscape of values and beliefs surrounding the treatment of meningitis, underscoring the diversity in health-care decision-making processes across different communities. While the direct valuation of treatment services for meningitis was not explicitly assessed within the reviewed evidence, some insights into patient and carer values provided a nuanced understanding of treatment preferences and care-seeking behaviours. This evidence is summarized as indirect evidence.

Indirect evidence

Low and middle-income countries (LMICs)

Studies focusing on values related to meningitis treatment reported that medical treatments were most effective in diagnosing, treating and managing the disease. This acknowledgement reflected a value placed on conventional medical approaches when it came to addressing the physical aspects of the disease (2 studies, low confidence). However, the choice of treatment was influenced by the perceived cause of the illness, with a value system where spiritual or supernatural interpretations of illness played a role in determining the approach to treatment (5 studies, moderate confidence).

The initial response to meningitis symptoms among carers and adult patients often involved a combination of self-medication and seeking advice or treatment from traditional healers and soothsayers, particularly to discern if the disease had supernatural origins. Despite these initial preferences, severe progression of the disease tended to shift care-seeking behaviour among

carers of younger patients towards hospitals and outpatient clinics (5 studies, moderate confidence).

In 1 study, most of the interviewed carers sought medical care when the disease became severe, while alternative care sources, such as patent medicine vendors/chemists, unlicensed health workers and traditional healers, were the first choice. Furthermore, patronage of government hospitals was considered a last resort when the illness became severe and not amenable to alternative care. This pattern of health-care utilization underscored the impact of cultural practices on health-care decisions, indicating a complex interplay between traditional beliefs, perceived efficacy of treatments and the severity of the disease in guiding treatment choices (1 study, low confidence).

Collective decision-making was also a barrier to timely help-seeking. Even when a patient was sufficiently well to make their own medical decisions, family consensus may have over-ruled patient wishes (2 studies, very low confidence).

High-income countries (HICs)

Health-care workers in primary care settings may have lacked experience with treating meningitis, thus they were more focused on getting a child hospitalized as early as possible rather than starting treatment on their own (1 study, moderate confidence).

The qualitative evidence consistently indicated that carers' primary concern focused on the survival of their child, with many expressing profound worry about this outcome (5 studies, low confidence).

Balance of effects

Judgement: Probably favours the comparison

Based on the available evidence and their knowledge and experience the GDG agreed that short duration of ASM treatment is likely to have similar beneficial effects and fewer adverse events when compared to longer regimens.

Resources required

Judgement: Moderate savings

As the intervention involves a shorter treatment duration, the GDG anticipated moderate cost savings compared to longer treatment regimens with ASMs.

Source of evidence

A scoping review was undertaken to compile information regarding costs, resource utilization and cost-effectiveness associated with meningitis diagnosis, treatment and management of sequelae.

Direct evidence

None of the identified cost and resource utilization studies were considered applicable to this guideline question.

Certainty of the evidence on resources required

Judgement: No included studies

Cost-effectiveness

Judgement: No included studies

A scoping review was undertaken to compile information regarding costs, resource utilization and cost-effectiveness associated with meningitis diagnosis, treatment and management of sequelae. However, no cost-effectiveness studies that would be applicable to this guideline question were identified.

Health equity, equality and non-discrimination

Judgement: Probably increased

Based on the indirect evidence as well as the stigma associated with epilepsy treatment, the GDG considered that health equity, equality and non-discrimination will probably increase with shorter duration of treatment with ASMs.

Source of evidence

A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.

Direct evidence

None of the included qualitative studies directly focused on health equity, equality or non-discrimination in relation to ASM treatment duration. However, the main relevant findings on health services for meningitis treatment are summarized as part of the indirect evidence.

Indirect evidence

LMICs

As reported in most studies, medical treatment carried a great financial burden. Lack of funds was the primary reason for seeking alternative types of treatment before going to the hospital. Interviews revealed that prescriptions were costly, resulting in increased financial dependency and substantial debts incurred by patients and caregivers to afford treatment expenses.

These factors collectively contributed to the majority of respondents favouring alternative medicine as a more affordable approach to seeking care (2 studies, low confidence). Additionally, gender disparities played a role in accessing care and its timeliness. Women often required the approval of family and community before deciding to seek help, in contrast to men, who generally made such decisions independently (2 studies, moderate confidence).

Feasibility

Judgement: Probably yes

The GDG discussed potential barriers to the implementation of the intervention. They concluded that shorter treatment regimens with ASMs can be more easily operationalized by health-care providers and would contribute to enhanced therapy adherence among patients.

Source of evidence

A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.

Direct evidence

None of the included qualitative studies directly focused on the feasibility of ASM treatment. However, the main relevant findings on the feasibility of meningitis treatment are summarized as part of the indirect evidence.

Indirect evidence

LMICs

The qualitative evidence review identified barriers potentially limiting the feasibility of timely care.

Elevated expenses were incurred by households for medicines despite official government policy and the regular scarcity of complementary medicines supplied by the ministries of health. If this happened, patients paid for their own medicines, including procuring them from costlier private pharmacies when they arrived outside the operating hours of the health centre's pharmacy. Consequently, this led to a reduction in health-care utilization (2 studies, very low confidence).

The underestimation of carers' concerns by health-care workers was also highlighted, which led to the decreased uptake of health care. Reports among primary health-care workers and patients highlighted a lack of quality care, with long waiting times, presumptive diagnosis without examination and verbal mistreatment (2 studies, very low confidence).

HICs

Challenges faced by health-care workers in primary care settings were significant. These included the belief that antibiotics should be administered via injections in hospital settings, a hesitation to

administer injections in primary care due to a lack of experience and anxiety caused by a limited familiarity with the process. Difficulties with gaining intravenous access as a barrier to initiating antibiotic treatment was also highlighted (2 studies, low confidence).

Organizational barriers also played a role in delaying antibiotic treatment initiation among health-care workers. These included specific advice from emergency departments, perceived disapproval from national prescribing services regarding the general use of antibiotics and the unavailability of antibiotics (1 study, very low confidence).

Human rights and sociocultural acceptability

Judgement: Varies

Based on the available evidence and their knowledge and experience the GDG agreed that osmotic therapy is likely to be acceptable across settings, potentially with some variations depending on cultural beliefs regarding conventional medicine and trust in the health-care system.

Source of evidence

A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services

Direct evidence

None of the included qualitative studies directly focused on the compliance of ASM treatment with universal human rights standards or its sociocultural acceptability. However, some aspects which influenced the ability of patients/caregivers to make a competent, informed and voluntary decision regarding meningitis treatment are summarized as part of the indirect evidence.

Indirect evidence

LMICs

Some studies indicated a preference for conventional medicine as a treatment choice. Participants, including older patients and their caregivers, favoured medical interventions over traditional treatment practices. However, some patients and caregivers highlighted that "Western" practitioners typically focused on diagnosing peripheral causes and managing symptoms, whereas traditional healers addressed the root cause of the illness (4 studies, moderate confidence).

Narratives from carers of children who had experienced meningitis, as well as those whose neighbours' or relatives' children had experienced meningitis, emphasized that health facilities

were the primary point of care for meningitis, suggesting trust in the ability of formal health-care settings to provide necessary and effective treatment (2 studies, low confidence).

Gender dynamics were highlighted as factors that influenced decision-making processes in health care. Specifically, women often sought validation from their husbands, adult relatives or neighbours regarding the severity of health conditions before seeking care. This trend was exacerbated by the fact that many women had limited or no formal education and were unemployed, factors that constrained their capacity to make informed health decisions for their families. In contrast, men were more likely to make health-care decisions independently, underscoring a gender disparity in autonomy and access to health-care decision-making (2 studies, moderate confidence).

Another study reported that cultural beliefs and care-seeking behaviour related to meningitis in LMICs were still influenced by traditional thinking. Yet despite the dominance of traditional views, there was a gradual shift towards embracing modern understandings of disease and, consequently, more contemporary approaches to care-seeking in society (2 studies, low confidence).

ASM(s): anti-seizure medicine(s); GDG: Guideline Development Group; HICs: high-income countries; LMICs: low- and middle-income countries; RCT: randomized controlled trial.

15. Clinical assessment of sequelae

15.1 Guideline questions

Should children with acute meningitis from any cause be reviewed by a health-care provider before discharge from hospital or at follow-up to identify sequelae?

Population: Children with acute meningitis from any cause

Intervention: Review by a health-care provider (before or at discharge from hospital versus post-discharge)[12] to identify sequelae[13]

Comparator: No review by a health-care provider before discharge from hospital to identify sequelae; head-to-head comparison of review time periods

Outcome:

Critical: Detection of sequelae; mortality

Important: Loss to follow-up

Should adults with acute meningitis from any cause be reviewed by a health-care provider before discharge from hospital or at follow-up to identify sequelae?

Population: Adults with acute meningitis from any cause

Intervention: Review by a health-care provider (before or at discharge from hospital versus post-discharge)[14] to identify sequelae[15]

Comparator: No review by a health-care provider before discharge from hospital to identify sequelae; head-to-head comparison of review time periods

Outcomes:

Critical: Detection of sequelae; mortality

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[12] Potential stratification of post-discharge time period in presentation of results (4–6 weeks, up to 2 years etc.).

[13] Sequelae defined as: Hearing loss, speech and/or language impairment, seizures, neurocognitive impairment, psychological after-effects (stress, depression, behaviour), hydrocephalus, motor deficits, vision impairment, digit or limb amputation.

[14] Potential stratification of post-discharge time period in presentation of results (4–6 weeks, up to 2 years etc.).

[15] Sequelae defined as: Hearing loss, speech and/or language impairment, seizures, neurocognitive impairment, psychological after-effects (stress, depression, behaviour), hydrocephalus, motor deficits, vision impairment, digit or limb amputation.

Important: Loss to follow-up

Full details of the evidence, including references, are provided in Web Annex A (15. Clinical assessment of sequelae) and Web Annex B (Qualitative and economic evidence reports).

15.2 Evidence-to-Decision framework

Priority of the problem
Judgement: Yes The consequences of acute meningitis in children and adults can be profound, with a wide spectrum of sequelae, including cognitive deficits, motor impairment, speech and language difficulties, sensory impairments and psychological challenges. Performing a clinical review to identify sequelae following specific neurological conditions (e.g. stroke, traumatic brain injury) is generally considered an effective intervention to reduce the burden of unaddressed sequelae and allow timely initiation of rehabilitation. However, whether a formal review should be performed following acute meningitis and its optimal timing are not yet well defined.
Desirable effects
Judgement: Moderate The Guideline Development Group (GDG) highlighted that a clinical assessment by a health-care provider to identify sequelae can allow early detection of sequelae. This enables early initiation of rehabilitation with positive effects on sequelae-related morbidity and mortality. However, the GDG acknowledged that not all functional deficits will benefit from rehabilitation equally, even when initiated early.
Source of evidence A systematic review was conducted to compare a formal clinical review to identify sequelae in children and adults following acute meningitis to no review.
Direct evidence The systematic review did not find any evidence comparing clinical review to identify sequelae to no review. Moreover, no study comparing different time points (i.e. before or at discharge vs post-discharge) was identified.
Indirect evidence The review identified 30 and 62 observational studies providing evidence on clinical assessment for sequelae in children and adults, respectively. These studies were limited by numerous factors, including lack of evaluation of sequelae across varying time points in the post-acute meningitis period, variability in diagnostic certainty due to a lack of case definitions and some studies

reporting pooled unstratified data on sequelae. The evidence from these observational studies is summarized below.

Adults

- Thirty studies including a total of 9311 adults with confirmed diagnosis of meningitis were identified. Three studies included both children and adults. The studies showed that 99.7% of the included adults had bacterial meningitis; 7301 (78.4%) of adults underwent audiological screening; and 1339 (14.4%) were found to have meningitis-related sequelae.
- Clinical assessments to identify sequelae were conducted before discharge in 1 study, at discharge in 17 studies and after discharge in 18 studies. Of adults assessed before discharge (including those assessed during hospitalization and at discharge), 16% (814 of 5270) were found to have sequelae; among those assessed after discharge, 29% (785 of 2711) were found to have at least 1 sequela.

Children

- Sixty-two studies including 18 658 children with a confirmed diagnosis of meningitis were identified. Three studies included both adults and children. Within the 62 studies, 94% of children had bacterial meningitis; 14 826 (79%) underwent clinical assessment by a health-care provider; and 3484 (19%) were diagnosed with meningitis-related sequelae.
- Clinical assessments to identify sequelae were conducted before discharge in 4 studies, at discharge in 27 studies and after discharge in 37 studies. Of children assessed before discharge, 34% (2473 of 7180) were found to have sequelae; among those assessed after discharge, 17% (1406 of 8298) were found to have at least 1 sequela.

Additional evidence

WHO *Package of interventions for rehabilitation* (PIR)

The WHO PIR provides information on both interventions and the related assessments for 20 health conditions, including neurological and sensory conditions. This is to provide rehabilitation plans that are tailored to an individual's needs and based on initial assessment.

Undesirable effects

Judgement: Small

The GDG recognized that clinical review can prompt further investigations that may lead to increased anxiety among the individual assessed and caregivers. The GDG acknowledged that the thoroughness of the clinical assessment can vary depending on the expertise of the health-care provider. They also acknowledged that the intervention is likely to increase the workload of health-care providers, with a negative impact on other clinical activities, especially when staff numbers are limited.

Source of evidence A systematic review was conducted to compare a formal clinical review to identify sequelae in children and adults following acute meningitis to no review.
Direct evidence The systematic review did not find any evidence comparing clinical review to identify sequelae to no review.
Indirect evidence The indirect evidence from the observational studies did not report on adverse effects of formal audiological screening.
Certainty of the evidence
Judgement: Very low The certainty of evidence was considered very low due to the lack of direct evidence addressing the guideline question.
Values
Judgement: Probably no important uncertainty or variability Based on the body of indirect evidence as well as their knowledge and experience, the GDG agreed that there is probably no important variability in how people value the main outcomes.
Source of evidence A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.
Direct evidence No direct evidence was identified regarding the uncertainty about or variability in how much people value the main outcomes related to a clinical review by a health-care provider to identify sequelae. However, the included studies highlighted a complex landscape of values and beliefs associated with meningitis sequelae and caregiving for children and adults. This evidence is summarized as indirect evidence.
Indirect evidence *Low and middle-income countries (LMICs)*

In 1 study, the authors reflected on the experiences and values of older adults with sequelae and their caregivers. People reported persistent disability interfering with social and personal activities, leading to increased dependency of older adults on family members (1 study, moderate confidence). Despite caregivers' willingness to provide aftercare, financial constraints and work commitments often limited their ability to cover the costs of necessary medicines and supplies (1 study, moderate confidence).

One study explored community perceptions of meningitis and highlighted the significant concern among carers about the sequelae of meningitis in children. They feared that such impairments could hinder a child's development and potentially limit their future ability to work, thus imposing an additional financial strain on families (1 study, low confidence).

High-income countries (HICs)

People who had experienced meningitis reported long-term mental consequences including cognitive and memory impairment, and physical sequelae including limb loss, heart problems and hearing and visual impairments. Meningitis sequelae, both mental and physical, interfered with people's social and personal lives, sometimes drastically changing their life course and causing considerable distress. Long periods of rehabilitation were cited as an additional source of frustration. Most individuals affected by meningitis shared the perception of the disease as serious and disabling (2 studies, low confidence). Fear of meningitis sequelae was highlighted along with its perception as a financial burden (3 studies, moderate confidence).

Several studies identified the impact of meningitis sequelae on parents' emotional well-being. Parents reported having long-lasting concerns and anxiety about possible sequelae of meningitis in their children. Some parents experienced long-term consequences of their child's meningitis, including depressive symptoms and depression requiring medication, abandoning their job to provide care and distress due to their child's sequelae (6 studies, low confidence).

Balance of effects

Judgement: Probably favours the intervention

Based on the available evidence and their knowledge and experience the GDG agreed that a review by a health-care provider can facilitate early identification of sequelae, enable prompt initiation of rehabilitation, and reduce the risk of further complications and death.

Resources required

Judgement: Varies

Although the scoping review did not identify any cost and resource utilization studies on the cost of conducting a clinical review to identify sequelae the GDG acknowledged its cost is likely to vary depending on the type of assessment, the time required to conduct it, the expertise of the health-

care provider, the additional examinations needed to confirm a clinical suspicion and the extent to which the health system covers medical expenses.

Source of evidence

A scoping review was undertaken to compile information regarding costs, resource utilization and cost-effectiveness associated with meningitis diagnosis, treatment and management of sequelae.

Direct evidence

None of the identified cost and resource utilization studies addressed the cost of conducting a clinical review to identify sequelae following acute meningitis in adults.

Certainty of the evidence on resources required

Judgement: No included studies

Cost-effectiveness

Judgement: No included studies

A scoping review of economic evidence was undertaken on all topics included in the guidelines. However, none of the cost-effectiveness studies identified were considered applicable to this guideline question.

Health equity, equality and non-discrimination

Judgement: Probably increased

The GDG highlighted that a clinical assessment before or at discharge and at follow-up is a crucial intervention to reduce the burden of unaddressed sequelae in children and adults. As sequelae are identified, rehabilitation can be initiated, which has a positive impact on mortality, morbidity and quality of life, as well as leading to fewer health inequities.

Source of evidence

A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.

Direct evidence

None of the included qualitative studies directly focused on health equity, equality or non-discrimination in relation to conducting a clinical review to identify sequelae. However, the main relevant findings related to meningitis aftercare affordability and accessibility are summarized as part of the indirect evidence.

Indirect evidence

LMICs

The synthesis of caregivers' experiences with meningitis sequelae indicated that financial barriers significantly limit the accessibility of aftercare services for both adults and children. Some caregivers reported discontinuing conventional aftercare services due to lack of funds for consultations and transportation to health-care facilities (2 studies, moderate confidence).

One study reported that sociocultural traditions played a big part in shaping attitudes towards providing aftercare for old or ageing parents. Female adults were expected to act as the main caregivers for their parents. However, most female participants reported that marriage and its associated responsibilities adversely affected the ability to provide care. Conversely, 2 male participants indicated a greater capacity to care for their ailing parents (1 study, low confidence). While there were reports from some adult children that caring for their older parents was a form of gratitude for their own upbringing, aftercare provision was also linked to psychological stress among caregivers. Both patients and caregivers expressed a need for support services to support family caregiving (1 study, low confidence).

Aftercare for disabled children with meningitis sequelae was associated with parental loss of productivity due to shortage of time. Additionally, a single carer cited the need to pay for caring staff in order to continue working (1 study, very low confidence).

HICs

One study reported that some caregivers experienced organizational barriers to accessing support services as well as applying for disability living allowance. They also reported a lack of communication between different members of staff involved in the aftercare process. Carers also highlighted that limited criteria for gaining support services and lack of obvious impairments were barriers to accessing aftercare for their children. Other factors limiting the uptake of aftercare included a restricted budget and a lack of medical staff. At the same time, parents stated that proactive behaviour helped them overcome organizational barriers (1 study, moderate confidence).

The evidence also identified limitations in access to information. Caregivers reported a lack of knowledge about meningitis sequelae and highlighted the need for accessible information on potential outcomes of meningitis (1 study, low confidence).

Additional evidence

WHO Global report on health equity for persons with disabilities

The report calls on WHO Member States to take action to advance health equity for persons with disabilities (WHO, 2022). It also invites civil society, including organizations of persons with disabilities, and other health partners, to collaborate and advocate for the implementation of the

recommendations included in the report and achieve the highest attainable standard of health for all.

Feasibility

Judgement: Varies

The GDG discussed potential barriers to the implementation of the intervention. They agreed that the feasibility of a clinical assessment to identify sequelae before or at discharge and at follow-up varies among different contexts depending on the expertise of the health-care providers and the resources available.

Source of evidence

A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.

Direct evidence

None of the included qualitative studies directly focused on the feasibility of conducting a clinical review to identify sequelae. However, the main findings related to meningitis aftercare barriers potentially limiting the feasibility of meningitis sequelae care for children and adults are summarized as part of the indirect evidence.

Indirect evidence

LMICs

Inability to provide care due to work commitments and associated hospital bills and medicine costs were barriers for caregivers to provide care for adults with meningitis sequelae. One caregiver reported resigning from her job to take care of her sick mother (1 study, moderate confidence).

Both people affected and caregivers expressed a need for services to support family caregiving (1 study, moderate confidence).

Aftercare costs were reported as a significant financial burden by parents taking care of children with meningitis sequelae. Carers could not afford hospital visits and related care for their children with sequelae due to the high costs of consultations, treatments and transport. While some patients had to stop attending hospital appointments, others could not even begin consultations because their carers' financial resources were limited (2 studies, moderate confidence).

Work commitments were also a barrier for carers providing care for their parents with meningitis sequelae. Carers stated that they had to work to be able to afford medicines and pay hospital

bills. Many participants underscored the importance of additional support services, such as counselling and meal programmes, to ease the burden of caregiving (1 study, moderate confidence).

HICs

Factors limiting the uptake of aftercare included a restricted budget and a lack of medical staff. Further to this, some caregivers experienced organizational barriers to accessing support services (1 study, moderate confidence).

Evidence from the reviewed studies pointed to a lack of knowledge about meningitis etiology and symptoms among carers of children. This led to delays in help-seeking behaviour, which was associated with an increased risk of developing sequelae (2 studies, moderate confidence).

A single study further highlighted difficulties in accessing support services for carers of young children affected by meningitis. According to data from the study, health-care professionals experienced difficulties with hearing assessments and with predicting cognitive after-effects of meningitis in young children (1 study, moderate confidence).

Two of the studies indicated gaps in the care continuum for children affected by meningitis in HICs. Carers of children reported a lack of follow-up appointments after discharge (2 studies, low confidence). In addition, one study noted a misunderstanding of the specific needs of young children with disabilities, as their needs were perceived to be similar to those of very young children. This posed a challenge to parents in terms of accessing adequate support (1 study, moderate confidence).

Additionally, parents reported poor communication between different members of staff involved in the aftercare process, delaying timely and sufficient care. The active involvement of a consultant and multidisciplinary team meetings that included parents, school staff and health visitors were cited as factors that helped to overcome this barrier (1 study, moderate confidence).

Carers also reported that limited criteria for accessing support services and lack of obvious impairments were barriers to accessing aftercare for their children. Other factors limiting the uptake of aftercare included a restricted budget and a lack of medical staff (1 study, moderate confidence).

At the same time, parents stated that proactive behaviour helped them overcome organizational barriers (1 study, moderate confidence).

Finally, some carers experienced organizational barriers to accessing support services. Parents cited difficulties with accessing and navigating support systems as well as applying for disability living allowance (1 study, moderate confidence).

Human rights and sociocultural acceptability

Judgement: Probably yes

Based on their experience and the presented body of indirect evidence, the GDG agreed that clinical assessment before or at discharge and at follow-up is likely to be acceptable across different settings. However, the GDG highlighted that the review from a health-care provider should be considered the initial step in the comprehensive management of sequelae, rather than an isolated intervention.

Source of evidence

A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.

Direct evidence

None of the included qualitative studies directly focused on relationship between conducting a clinical review to identify sequelae and universal human rights standards or its sociocultural acceptability. However, some aspects which influenced the ability of patients/caregivers to make a competent, informed and voluntary decision regarding meningitis aftercare are summarized as part of the indirect evidence.

Indirect evidence

LMICs - Adults

One study emphasized some sociocultural aspects influencing caregivers' ability to provide aftercare for adults with meningitis sequelae. Caregivers reported their experience with difficulties in providing aftercare for their ailing parents. The different expectations of women and men in providing care for parents were highlighted, particularly in Nigeria where female adults were seen as the ultimate caregivers (1 study, low confidence).

LMICs - Children

Despite many challenges of caregiving, there was a marked preference among caregivers for home care rather than institutionalization. There was widespread scepticism about the benefits of professional aftercare services, with many caregivers fearing that institutional care could further deteriorate their loved ones' health. This led to a consensus that care should ideally be managed within the family, highlighting the need for enhanced support and resources to facilitate effective home-based care (1 study, low confidence).

HICs - Children

Carers also noted misunderstandings of the specific needs of young children with disabilities, as their needs were perceived to be similar to those of very young children. This posed a challenge to parents in terms of accessing adequate support (1 study, moderate confidence).

Additional evidence

The United Nations Convention on the Rights of Persons with Disabilities (CRPD)

The CRPD (2007) emphasizes the right of persons with disabilities to the highest attainable standard of health without discrimination. It requires states to offer accessible health services, including early diagnosis and intervention, designed to meet the needs of people with disabilities. The CRPD calls for equitable health-care access, ensuring that individuals with disabilities receive the same range, quality and standard of health services as others, either free or at an affordable cost. It also mandates training for health-care professionals on disability rights and prohibits discriminatory practices within the health sector.

CRPD: The United Nations Convention on the Rights of Persons with Disabilities; GDG: Guideline Development Group; HICs: high-income countries; LMICs: low- and middle-income countries; PIR: WHO Package of interventions for rehabilitation; WHO: World Health Organization..

16. Rehabilitation for sequelae (children and adults)

16.1 Guideline questions

In children with sequelae[16] following acute meningitis from any cause (excluding isolated hearing loss), should rehabilitation for sequelae be provided?

Population: Children with acute meningitis from any cause with sequelae (excluded if isolated hearing loss)

Intervention: Rehabilitation (neurological, psychological or physical rehabilitation/occupational therapy/assistive technology/speech and language therapy/vision)

Comparator: Care without rehabilitation

Outcome:

Critical: Quality of life, functioning and participation[17] caregiver burden

Important: Mortality, secondary consequences (including cognitive and psychological consequences, social and behavioural changes and economic impact)

In adults with sequelae[18] following acute meningitis from any cause (excluding isolated hearing loss), should rehabilitation for sequelae be provided?

Population: Adults with acute meningitis from any cause with sequelae (excluded if isolated hearing loss)

Intervention: Rehabilitation (neurological, psychological or physical rehabilitation/occupational therapy/assistive technology/speech and language therapy/vision)

Comparator: Care without rehabilitation

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[16] Sequelae are defined as: Hearing loss, speech and/or language impairment, seizures, neurocognitive impairment, psychological after-effects (stress, depression, behaviour), hydrocephalus, motor deficits, vision impairment, digit or limb amputation.

[17] Participation is defined as the involvement in a life situation (e.g. going to school, undertaking work, having a family).

[18] Sequelae are defined as: Hearing loss, speech and/or language impairment, seizures, neurocognitive impairment, psychological after-effects (stress, depression, behaviour), hydrocephalus, motor deficits, vision impairment, digit or limb amputation.

Outcome:

Critical: Quality of life, functioning and participation,[19] caregiver burden

Important: Mortality, secondary consequences (including cognitive and psychological consequences, social and behavioural changes and economic impact).

Full details of the evidence, including references, are provided in Web Annex A (16a and 16b. Rehabilitation for sequelae) and Web Annex B (Qualitative and economic evidence reports).

[19] Participation is defined as the involvement in a life situation (e.g. going to school, undertaking work, having a family).

16.2 Evidence-to-Decision framework

Priority of the problem
Judgement: Yes The consequences of acute meningitis can be profound, with a wide spectrum of sequelae, including cognitive deficits, motor impairment, speech and language difficulties, sensory impairments and psychological challenges. Rehabilitation plays a crucial role in addressing the diverse and complex sequelae following various neurological conditions (e.g. stroke). As outlined in the WHO *Package of interventions for rehabilitation* (PIR), sequelae rehabilitation includes a variety of interventions such as physical therapy, occupational therapy, speech and language therapy, neuropsychological rehabilitation and psychological support. Despite the wide array of rehabilitation interventions available, the optimal strategy for sequelae rehabilitation in the context of acute meningitis in children and adults is not yet well defined.
Desirable effects
Judgement: Moderate The Guideline Development Group (GDG) acknowledged the lack of comparative and observational studies on rehabilitation for sequelae due to meningitis in children and adults. Members with clinical expertise as well as members with lived experience highlighted the large positive impact of rehabilitation in improving quality of life, functioning and participation and reducing caregiver burden. However, the GDG acknowledged the lack of interventions that allow an almost complete functional recovery, as experienced with cochlear implants in people with hearing loss. The GDG emphasized that the beneficial effect of rehabilitation is larger when initiated as soon as possible. Early rehabilitation facilitates neuroplasticity, prevents complications and helps in rapidly reacquiring functionality or avoiding further functional loss. The GDG also highlighted the long-term beneficial effects of rehabilitation as this is likely to make individuals more independent and reduce caregiver burden over time.
Source of evidence A systematic review was conducted to compare rehabilitation for sequelae in children and adults following acute meningitis to no rehabilitation.
Direct evidence

The systematic review did not identify any evidence comparing rehabilitation for sequelae to no rehabilitation.

Indirect evidence

A systematic review of 20 studies on rehabilitation outcomes in cases of infectious encephalitis, which included 37 adults and 5 children, was identified. The review included studies describing a variety of interventions to alleviate sequelae from infectious encephalitis, including cognitive therapy (9 studies), behavioural therapy (5 studies) and physical therapy (2 studies), or a combination (4 studies).

Studies with adults included 1 crossover randomized controlled trial (RCT), 2 cohort studies, 2 case series and 14 case reports. Half (50%) of the studies were assessed as having a high risk of bias. The majority of studies (which included 15 of the total 37 adults in the review) examined the effectiveness of interventions targeting sequelae of herpes simplex virus (HSV) encephalitis.

The evidence indicated that rehabilitation interventions may have positive effects on individuals with infectious encephalitis across various outcomes. These outcomes include functional, neuropsychological and behavioural measures, or a combination of these. However, due to differences in study designs and inconsistencies in outcome measures, a meta-analysis was not performed.

Three studies in the systematic review included children (with only 5 participants in total across these studies): 1 cohort study and 2 case series. Baseline assessments differed among the 3 studies. One study utilized 2 neuropsychological tests, the Children's Orientation and Amnesia Test and the McCarthy Scale of Children's Abilities, to evaluate cognitive status. The other 2 studies did not specify any standardized tools for measuring the severity of encephalitis sequelae at baseline.

The rehabilitation outcomes for these children were documented using functional measures. However, since none of the studies included follow-up assessments after discharge, long-term improvements from the rehabilitation interventions were not evaluated.

Additional evidence

WHO PIR

The WHO PIR outlines the most essential interventions for rehabilitation for 20 health conditions, including neurological and sensory conditions. Although meningitis sequelae are not directly addressed, conditions with similar limitations in functioning are included. Interventions for motor deficits occurring in cerebral palsy, stroke or traumatic brain injury include the following:

- Muscle strengthening exercises
- Oral muscle relaxants

- Chemodenervation
- Antispastic pattern positioning
- Range of motion exercises
- Provision and training in the use of orthoses
- Referral to selective dorsal rhizotomy
- Stretching
- Positioning for the prevention of contractures
- Mirror therapy
- Balance training
- Neuromuscular electrical stimulation
- Gait training
- Provision and training in the use of lower limb prosthesis
- Bimanual therapy
- Constraint induced movement therapy
- Functional training for hand and arm use
- Provision and training in the use of upper limb prosthesis
- Mobility training
- Functional positioning.

Undesirable effects

Judgement: Varies

The GDG agreed that there are few undesirable effects of rehabilitation. The GDG acknowledged that rehabilitation can indirectly impact carers and family members by increasing caregiver burden (e.g. time and resources required to accompany the child to the rehabilitation facility). However, they highlighted that caregiver burden can also vary over time as rehabilitation increases independence in the long term, eventually resulting in a reduced caregiver burden. The GDG also noted that caregiver burden varies depending on the type of functional deficit (i.e. physical disability compared to cognitive disability).

Source of evidence

A systematic review was conducted to compare rehabilitation for sequelae in children and adults following acute meningitis to no rehabilitation.

Direct evidence

The systematic review did not identify any studies comparing rehabilitation for sequelae to no rehabilitation.

Indirect evidence

The indirect evidence derived from a systematic review of rehabilitation intervention outcomes of adults and children with infectious encephalitis is summarized as part of the indirect evidence in the previous section on desirable anticipated effects. Indirect evidence derived from a qualitative evidence synthesis on caregiver burden is summarized below.

Research evidence from a qualitative evidence synthesis identified the negative influence of meningitis sequelae care on family members. Specifically, caregivers frequently reported having to leave their jobs or alter their personal lives to provide necessary care for their family members with meningitis sequelae. The task of caring for adults with these conditions often led to psychological distress among caregivers. Some mentioned specific factors, including isolation from friends and frustration from care experiences (3 studies, low confidence).

Several studies identified the impact of meningitis sequelae on parents' emotional well-being. Parents reported having long-lasting concerns and anxiety about possible sequelae of meningitis in their children. Some parents experienced long-term consequences of their child's meningitis, including depressive symptoms and depression requiring medication, abandoning their job to provide care and distress due to a child's sequelae (6 studies, low confidence).

Certainty of the evidence

Judgement: Very low

The certainty of evidence was considered very low due to the lack of direct evidence addressing the guideline question.

Values

Judgement: Probably no important uncertainty or variability

The GDG acknowledged that the qualitative evidence synthesis focused on the impact of meningitis on caregivers rather than on the impact of rehabilitation on the functioning limitations. However, based on the body of indirect evidence as well as their knowledge and experience, the GDG agreed that there is probably no important variability in how children and adults with sequelae value the main outcomes.

Source of evidence

A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.

Direct evidence

No direct evidence was identified regarding the uncertainty about or variability in how much people value the main outcomes related to sequelae rehabilitation. However, several studies reported experiences and values associated with meningitis sequelae and caregiving for children and adults. The relevant themes are summarized as indirect evidence.

Indirect evidence

Low and middle-income countries (LMICs)

One study explored community perceptions of meningitis and highlighted the significant concern among carers about the sequelae of meningitis in children. They feared that such impairments could hinder a child's development and potentially limit their future ability to work, thus imposing an additional financial strain on families (1 study, low confidence).

In 1 study, the authors reflected on the experiences and values of older adults and their caregivers related to meningitis sequelae. Persistent disability was reported to interfere with social and personal activities, leading to increased dependency of older adults on family members (1 study, moderate confidence). Despite caregivers' willingness to provide aftercare, financial constraints and work commitments often limited their ability to cover the costs of necessary medicines and supplies (1 study, moderate confidence).

High-income countries (HICs)

People with meningitis reported long-term consequences of meningitis, including cognitive and memory impairment and physical sequelae, including limb loss, heart problems and hearing and visual impairments. Meningitis sequelae, both mental and physical, interfered with peoples' social and personal lives, sometimes drastically changing their life course and causing considerable distress. Long periods of rehabilitation were cited as an additional source of frustration. Most people affected by meningitis shared the perception of the disease as serious and disabling (2 studies, low confidence).

Several studies identified the impact of meningitis sequelae on parents' emotional well-being. Parents reported having long-lasting concerns and anxiety about possible sequelae of meningitis in their children. Some parents experienced long-term consequences of their child's meningitis, including depressive symptoms and depression requiring medication, abandoning their job to provide care and distress due to a child's sequelae (6 studies, low confidence).

Balance of effects

Judgement: Probably favours the intervention

Based on the available evidence and their knowledge and experience the GDG agreed that providing sequelae rehabilitation will probably improve reacquisition of functionality, avoid further functional loss, facilitate neuroplasticity and prevent complications.

Resources required

Judgement: Varies

The GDG acknowledged that rehabilitation interventions for sequelae generally incur moderate to large costs. However, the cost of rehabilitation can vary depending on the setting, the type of rehabilitation intervention and the extent to which the health system covers medical expenses. The GDG also highlighted the indirect costs of rehabilitation, for example, training relevant professionals such as rehabilitation specialists.

Source of evidence

A scoping review was undertaken to compile information regarding costs, resource utilization and cost-effectiveness associated with meningitis diagnosis, treatment and management of sequelae.

Direct evidence

None of the identified cost and resource utilization studies addressed the cost of rehabilitation but found evidence of the cost of follow-up for people with sequelae in HICs. The evidence was considered indirect since the cost of rehabilitation was aggregated with the cost of other health services.

Indirect evidence

HICs

The scoping review identified 4 studies with information on the cost of sequelae in cases of acute meningitis in HICs. Study populations included adults, children and infants. In the United States of America, subjects with at least one sequela experienced US$ 26 950 (95% CI US$ 20 807 –33 094) additional costs (2009 US$) compared to people without invasive meningococcal disease (IMD) sequelae. In addition, when considering the period from admission through the following 12 months, mean predicted costs were approximately US$ 97 000 (2009 US$), almost 3 times higher compared to uncomplicated IMD. In France, the cost of 1-year follow-up of neonates, children and adults with at least one IMD-related sequela was 2.48 (95% CI 2.20–2.83) higher than in people without sequelae. Furthermore, the reported annual cost associated with IMD in adults was € 4254 in cases without sequelae, € 10 799 in cases with one sequela and € 20 096 in cases with more than one sequela (2009 €).

Certainty of the evidence on resources required
Judgement: Very low The judgement reflected the limited scope of the evidence, the absence of comprehensive cost comparisons between interventions and the potential variability in cost data across settings.
Cost-effectiveness
Judgement: No included studies A scoping review of economic evidence was undertaken on all topics included in the guidelines. However, none of the cost-effectiveness studies identified were considered applicable to this guideline question.
Health equity, equality and non-discrimination
Judgement: Probably increased Although the evidence on the impact of rehabilitation on equity for individuals with acute meningitis mainly focused on caregiver burden, the GDG emphasized the role of rehabilitation in enabling people living with disabilities to live more independent and fuller lives. Rehabilitation facilitates their ability to contribute to their families and communities, thereby increasing equity, equality and non-discrimination.
Source of evidence A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services. The review identified themes related to meningitis aftercare affordability and accessibility. The available evidence is summarized below for LMICs and HICs.
Direct evidence *LMICs* The synthesis of caregivers' experiences with meningitis sequelae indicated that financial barriers significantly limited the accessibility of aftercare services for adults. Some caregivers reported discontinuing conventional aftercare services due to lack of funds for consultations and transportation to health-care facilities (2 studies, moderate confidence). One study reported that sociocultural traditions played a big part in shaping attitudes towards providing aftercare for older, ailing parents. Female adults were expected to act as the main caregivers for their parents. However, most female participants reported that marriage and its

associated responsibilities adversely affected the ability to provide care. Conversely, 2 male participants indicated a greater capacity to care for their ailing parents (1 study, low confidence).

Despite reports from some adult children that caring for their older parents was seen as a form of gratitude for their own upbringing, aftercare provision was also linked to psychological stress among caregivers. A need for services to support family caregiving was highlighted (1 study, low confidence).

Aftercare for disabled children with meningitis sequelae was associated with parental loss of productivity due to shortage of time**.** Additionally, a single carer cited the need to pay for caring staff in order to continue working (1 study, very low confidence).

HICs

One study reported that some carers experienced organizational barriers to accessing support services. Parents cited difficulties with accessing and navigating support systems as well as applying for disability living allowance. They also reported a lack of communication between different members of staff involved in the aftercare process. Carers also reported that limited criteria for gaining support services and lack of obvious impairments were barriers to accessing aftercare for their children. Other factors limiting the uptake of aftercare included a restricted budget and a lack of medical staff. At the same time, parents stated that proactive behaviour helped them overcome organizational barriers (1 study, moderate confidence).

Multidisciplinary team meetings between members of staff involved in the aftercare process, including parents, school staff and health visitors, were found to facilitate customized aftercare (1 study, low confidence).

Evidence identified limitations to informational access. Carers reported a lack of knowledge about meningitis sequelae and highlighted the need for accessible information on potential outcomes of meningitis (1 study, low confidence).

Additional evidence

WHO Global report on health equity for persons with disabilities

The report calls on WHO Member States to take action to advance health equity for persons with disabilities (WHO, 2022). It also invites civil society, including organizations of persons with disabilities, and other health partners, to collaborate and advocate for the implementation of the recommendations included in the report and achieve the highest attainable standard of health for all.

Feasibility

Judgement: Varies

The GDG agreed that rehabilitation for sequelae comprises a wide range of interventions. They highlighted that the feasibility of rehabilitation for sequelae may vary among different contexts, depending on the expertise and training of specialized personnel as well as the availability of the necessary infrastructure dedicated to rehabilitation within health-care facilities.

Source of evidence

A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.

Direct evidence

The review identified themes related to meningitis aftercare barriers potentially limiting the feasibility of meningitis sequelae care for children and adults. The available evidence is summarized below for LMICs and HICs.

LMICs

Inability to provide aftercare due to work commitments and associated needs to finance hospital bills and medicines was a barrier for caregivers to providing care for adults with meningitis sequelae. Carers stated that they must work to be able to afford medicines and pay hospital bills. One caregiver reported resigning from her job to take care of her sick mother (1 study, moderate confidence). Many participants underscored the importance of additional support services, such as counselling and meal programmes, to ease the burden of caregiving (1 study, moderate confidence).

Aftercare costs were also reported by parents taking care of children with meningitis sequelae as a significant financial burden. Carers could not afford hospital visits and other related care for their children with sequelae due to the high costs of consultations, treatments and transport. While some had to stop attending hospital appointments, others could not even begin consultations because their carers' financial resources were limited (2 studies, moderate confidence).

Both individuals affected and caregivers expressed a need for services to support family caregiving (1 study, moderate confidence).

HICs

Factors limiting the uptake of aftercare included a restricted budget and a lack of medical staff. Further to this, some caregivers experienced organizational barriers to accessing support services (1 study, moderate confidence).

One study highlighted a lack of knowledge about meningitis etiology and symptoms among carers of children. This delayed help-seeking behaviour, which was associated with an increased risk of developing sequelae (2 studies, moderate confidence). A single study further highlighted

difficulties in accessing support services for carers of young children affected by meningitis. According to data from the study, health-care professionals experienced difficulties with hearing assessments and with predicting cognitive after-effects of meningitis in young children (1 study, moderate confidence).

Two of the studies indicated gaps in the care continuum for children affected by meningitis in HICs. Carers of children reported a lack of follow-up appointments after discharge (2 studies, low confidence).

Additionally, parents reported poor communication between different members of staff involved in the aftercare process, delaying timely and sufficient care. The active involvement of a consultant and multidisciplinary team meetings including parents, school staff and health visitors were cited as factors that helped overcome this barrier (1 study, moderate confidence).

Carers also reported that limited criteria for gaining support services and lack of obvious impairments were barriers to accessing aftercare for their children. Other factors limiting the uptake of aftercare included a restricted budget and a lack of medical staff (1 study, moderate confidence).

At the same time, parents stated that proactive behaviour helped them overcome organizational barriers (1 study, moderate confidence).

Finally, some carers experienced organizational barriers to accessing support services. Parents cited difficulties with accessing and navigating support systems as well as applying for disability living allowance (1 study, moderate confidence).

Human rights and sociocultural acceptability

Judgement: Varies

The GDG noted that providing rehabilitation for sequelae is in line with the "United Nations Convention on the Rights of Persons with Disabilities". The convention has led to improved legislation and policies regarding the rights of people with disabilities in many countries. However, the GDG highlighted that the implementation and enforcement of these policies significantly varies among the 164 countries that have signed the treaty. The GDG also highlighted that people with sequelae and functional deficits often experience stigma. However, the GDG recognized the role of rehabilitation as a measure to fight stigma and empower individuals, although this can vary across different settings due to social and cultural barriers.

Source of evidence

A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.

Direct evidence

LMICs

One study emphasized some sociocultural aspects influencing caregivers' ability to provide aftercare for adults with meningitis sequelae. Caregivers reported their experience with difficulties in providing aftercare for their older, ailing parents. The different expectations of women and men in providing care for parents were highlighted, particularly in Nigeria where female adults were seen as the ultimate caregivers (1 study, low confidence).

Despite many challenges of caregiving, there was a marked preference among caregivers for home care rather than institutionalization. There was widespread scepticism about the benefits of professional aftercare services, with many caregivers fearing that institutional care could further deteriorate their loved ones' health. This led to a consensus that care should ideally be managed within the family, highlighting the need for enhanced support and resources to facilitate effective home-based care (1 study, low confidence).

HICs

In a single qualitative study caregivers of children with meningitis sequelae reported experiences with rehabilitation services. Parents were dissatisfied with inadequate customization of prosthetic limbs and orthopaedic devices. Additionally, parents reported poor communication between different members of staff involved in the aftercare process, delaying timely and sufficient care (1 study, moderate confidence). Carers also noted a misunderstanding of the specific needs of young children with disabilities, as their needs were perceived to be similar to those of very young children. This posed a challenge to parents in terms of accessing adequate support (1 study, moderate confidence).

Additional evidence

The United Nations Convention on the Rights of Persons with Disabilities (CRPD)

The CRPD (2007) emphasizes the right of persons with disabilities to the highest attainable standard of health without discrimination. It requires states to offer accessible health services, including early diagnosis and intervention, designed to meet the needs of people with disabilities. The CRPD calls for equitable health-care access, ensuring that individuals with disabilities receive the same range, quality and standard of health services as others, either free or at an affordable cost. It also mandates training for health-care professionals on disability rights and prohibits discriminatory practices within the health sector.

CRPD: The United Nations Convention on the Rights of Persons with Disabilities; GDG: Guideline Development Group; HICs: high-income countries; IMD: invasive meningococcal disease; LMICs: low- and middle-income countries; PIR: WHO Package of interventions for rehabilitation; RCT: randomized controlled trial; WHO: World Health Organization.

17. Hearing loss screening

17.1 Guideline question

In children and adults with acute meningitis from any cause, should a formal audiological screening test be conducted before discharge or within 4 weeks of discharge?

Population: People with acute meningitis from any cause with hearing loss

Subgroup: Age group (children, adult)

Intervention: Formal audiological screening test before discharge or within 4 weeks of discharge

Comparator: No formal audiological screening test before discharge or within 4 weeks of discharge

Outcome:

Critical: Detection of hearing loss, time to access hearing rehabilitation services where indicated

Important: Quality of life, functioning (including developmental outcomes for children) and participation,[20] loss to follow-up

Full details of the evidence, including references, are provided in Web Annex A (17. Hearing loss screening) and Web Annex B (Qualitative and economic evidence reports).

[20] Participation is defined as the involvement in a life situation (e.g. going to school, undertaking work, having a family).

17.2 Evidence-to-Decision framework

Priority of the problem
Judgement: Yes Hearing loss is one of the most common sequelae of acute meningitis and can significantly impact the quality of life of affected individuals. Unaddressed hearing loss in individuals with acute meningitis has a potentially devastating impact on an individual's communication, education, employment and social well-being. The Guideline Development Group (GDG) highlighted the critical importance of reducing the burden of unaddressed hearing loss in individuals with acute meningitis. Formal audiological screening can detect hearing loss and minimize the time to access hearing rehabilitation services. As hearing rehabilitation tends to be more effective when initiated promptly, timely audiological screening is crucial to capture the largest number of people with hearing impairment due to acute meningitis. However, whether formal audiological screening should be performed following acute meningitis, and its optimal timing, is not yet well defined.
Desirable effects
Judgement: Large The GDG emphasized that formal audiological screening is the optimal diagnostic method for detecting hearing loss, enabling the early initiation of hearing rehabilitation. Since interventions for hearing loss tend to be more effective when started promptly, early detection before discharge or within 4 weeks of discharge is likely to have a significant beneficial effect on the time to access rehabilitation services. This leads to better outcomes in terms of quality of life, functioning and participation compared to those diagnosed and treated later.
Source of evidence A systematic review was conducted to compare formal audiological screening before discharge or within 4 weeks of discharge to no formal audiological screening.
Direct evidence The review did not identify any evidence comparing formal audiological screening tests conducted before discharge or within 4 weeks of discharge versus no audiological screening.
Indirect evidence

The review identified 41 observational studies providing evidence on audiological screening. These studies were limited by numerous factors, including variability in the time points when hearing loss was assessed, differences in screening tests and lack of clarity in determining whether the hearing loss developed after acute meningitis or was an ongoing condition. The evidence from these observational studies is summarized below.

Adults

Six studies including a total of 1397 adults with acute meningitis were identified. Two studies included both adults and children. All included adults had bacterial meningitis, with 1046 (75%) of adults with pneumococcal meningitis and 264 adults with meningococcal meningitis (19%). Nearly half (675, or 48%) of adults underwent audiological screening and 291 (43%) were found to have meningitis-related hearing loss. Of these, 234 (80%) had pneumococcal meningitis.

Five studies used pure-tone audiometry as the primary audiological screening test. Auditory Brainstem Response Audiometry and Distortion Product Otoacoustic Emissions were each used in 1 study, while 1 study utilized both methods.

An audiological screening test was conducted before discharge in 3 studies and after discharge in 5 studies, while 2 studies conducted the test at both time points.

Of the 145 adults screened before discharge, 66 (46%) were found to have hearing loss. Of the 530 adults screened after discharge, 225 (43%) were found to have hearing loss.

Children

Thirty-seven studies including a total of 6708 children with acute meningitis were identified. Two studies included both adults and children. Among the children included in the studies, 90.4% had bacterial meningitis; 5351 children (80%) underwent audiological screening; and 1198 (22%) were found to have meningitis-related hearing loss. 95% of them had bacterial meningitis, with *Streptococcus pneumoniae* being isolated in 32% of cases.

Thirteen audiological screening tests were used, with multiple studies using more than 1 screening test. Of the 37 studies included, 25 implemented 2 or more types of audiological tests and 12 studies implemented only 1 type of audiological test.

Auditory Brainstem Response Audiometry was used in 22 studies, while pure-tone audiometry and transient-evoked otoacoustic emissions were used in 16 and 12 studies, respectively.

Audiological screening tests were conducted before discharge in 18 studies and after discharge in 24 studies, while 2 studies conducted the test at both time points.

Of the 1975 children screened before discharge, 611 (31%) were found to have hearing loss. Of the 3340 children screened after discharge, 756 (23%) were found to have hearing loss.

Additional evidence

WHO World report on hearing

The WHO World report on hearing (2021) recommends a series of interventions for hearing care. These are summarized in the H.E.A.R.I.N.G. set of interventions where the "H" stands for "Hearing screening across the life course".

WHO Hearing screening: considerations for implementation

The report builds on the *WHO World report on hearing* with the objective of guiding the implementation of hearing screening programmes at national or subnational levels (WHO, 2021). In the report, meningitis is listed as one of the conditions that should lead to immediate referral for diagnostic audiology in infants.

Undesirable effects

Judgement: Small

The GDG recognized that false positive hearing test results may occur, causing unnecessary anxiety among the individuals being misdiagnosed and their carers. False positive results also lead to additional health system costs due to confirmatory tests. However, the GDG highlighted that the rate of false positives is generally very low and varies depending on the screening test. The GDG also acknowledged that some individuals may develop hearing loss after being screened for audiological impairment.

Source of evidence

A systematic review was conducted to compare formal audiological screening before discharge or within 4 weeks of discharge to no formal audiological screening.

Direct evidence

The review did not identify any evidence comparing formal audiological screening tests conducted before discharge or within 4 weeks of discharge versus no audiological screening. The indirect evidence from observational studies did not report on adverse effects of formal audiological screening.

Indirect evidence

The indirect evidence derived from a systematic review of rehabilitation intervention outcomes of adults and children with infectious encephalitis is summarized as part of the indirect evidence in the previous section on desirable anticipated effects. Indirect evidence derived from a qualitative evidence synthesis on caregiver burden is summarized below.

Research evidence from a qualitative evidence synthesis identified the negative influence of meningitis sequelae care on family members. Specifically, caregivers frequently reported having to leave their jobs or alter their personal lives to provide necessary care for their family members with meningitis sequelae. The task of caring for adults with these conditions often led to

psychological distress among caregivers. Some mentioned specific factors, including isolation from friends and frustration from care experiences (3 studies, low confidence).

Several studies identified the impact of meningitis sequelae on parents' emotional well-being. Parents reported having long-lasting concerns and anxiety about possible sequelae of meningitis in their children. Some parents experienced long-term consequences of their child's meningitis, including depressive symptoms and depression requiring medication, abandoning their job to provide care and distress due to a child's sequelae (6 studies, low confidence).

Certainty of the evidence

Judgement: Very low

The certainty of evidence was considered very low due to the lack of direct evidence addressing the guideline question.

Values

Judgement: Probably no important uncertainty or variability

Based on the body of indirect evidence from low and middle-income countries (LMICs) and high-income countries (HICs) as well as their knowledge and clinical experience, the GDG agreed that there is probably no important variability in how children and adults with sequelae value the main outcomes.

Source of evidence

A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.

Direct evidence

No direct evidence was identified regarding the uncertainty about or variability in how much people value the main outcomes related to hearing screening. However, the included studies highlighted a complex landscape of values and beliefs associated with meningitis sequelae and caregiving for children and adults. This evidence is summarized as indirect evidence.

Indirect evidence

LMICs

One study explored community perceptions of meningitis and highlighted the significant concern among caregivers about the sequelae of meningitis in children. They feared that such impairments could hinder a child's development and potentially limit their future ability to work, thus imposing an additional financial strain on families (1 study, low confidence).

In another study, the authors reflected the experiences and values of older adults and their carers related to meningitis sequelae. The patients reported persistent disability interfering with social and personal activities, leading to increased dependency of older adults on family members. Despite caregivers' willingness to provide aftercare, financial constraints and work commitments often limited their ability to cover the costs of necessary medicines and supplies (1 study, moderate confidence).

HICs

Meningitis survivors reported long-term mental consequences of meningitis, including cognitive and memory impairment, and physical sequelae including limb loss, heart problems and hearing and visual impairments. Meningitis sequelae, both mental and physical, interfered with patients' social and personal lives, sometimes drastically changing their life course and causing considerable distress. Long periods of rehabilitation were cited as an additional source of frustration (2 studies, low confidence). Fear of meningitis sequelae was highlighted along with its perception as a financial burden (3 studies, moderate confidence).

Several studies identified the impact of meningitis sequelae on parents' emotional well-being. Parents reported having long-lasting concerns and anxiety about possible sequelae of meningitis in their children. Some parents experienced long-term consequences of their child's meningitis, including depressive symptoms and depression requiring medication, abandoning their job to provide care and distress due to a child's sequelae (6 studies, low confidence).

Balance of effects

Judgement: Probably favours the intervention

Based on the available evidence and their knowledge and experience the GDG agreed that conducting formal audiological screening at the appropriate time allows for early diagnosis, reduces the time to access hearing rehabilitation services and contributes to mitigating the impact of long-term complications. In individuals potentially eligible for cochlear implants, unnecessary delays may increase the likelihood of cochlear ossification, affecting the feasibility and auditory performance of cochlear implants.

Resources required

Judgement: Varies

The GDG acknowledged that the cost of audiological screening is generally moderate to large. However, they highlighted that its cost could vary depending on the setting, the type of test used and the extent to which the health system covers medical expenses. The GDG emphasized the indirect costs of audiological screening, such as training of relevant professionals (i.e. technicians, audiologists) as well as the establishment of the necessary infrastructure dedicated to audiological screening testing within health-care facilities (i.e. soundproofing of rooms).

Source of evidence

A scoping review was undertaken to compile information regarding costs, resource utilization and cost-effectiveness associated with meningitis diagnosis, treatment and management of sequelae.

Direct evidence

None of the identified cost and resource utilization studies directly addressed the cost of audiological screening. One additional study that did not meet the criteria to be included as part of the research evidence but provided evidence on resources required for hearing loss screening is summarized as additional evidence.

Additional evidence

A modelling study was conducted to analyse the return on investment (ROI) and cost-effectiveness of WHO's HEAR interventions for hearing loss, including audiological screening (Tordrup et al. 2022). It provided lower and upper bound estimates based on expert opinion of commodities used in audiological screening (cost per unit/use/procedure, 2018 US$). The estimates for the cost of personnel were based on WHO CHOICE salary data. Costs of the most relevant items are reported below.

- Otoacoustic emissions: US$ 0.50–0.69
- Otoacoustic emissions testing device:
    - US$ 0.19–0.33 (cost per procedure)
    - US$ 3500–6000 (unit cost)
    - Assumed uses: US$ 18 250
    - Life span 7–10 years
- Auditory brainstem response: US$ 1.35–1.43
- Auditory brainstem response machine:
    - US$ 0.55–0.63 (cost per procedure)
    - US$ 10 000–11 500 (unit cost)
    - Assumed uses: US$ 18 250
    - Life span 7–10 years
- Otoscope: US$ 0.01–0.02
- Tympanometer: US$ 0.19–0.27
- App screening: US$ 0–0
- Screening audiometer: US$ 0.03–0.08.

Certainty of the evidence on resources required
Judgement: Very low The GDG acknowledged that the evidence presented captures the cost of the technical instruments as well as the cost of the specialized personnel. However, the cost estimates were mainly based on expert opinion.
Cost-effectiveness
Judgement: Probably favours the intervention Although the review of the economic evidence did not include any cost-effectiveness studies relevant for this question, the additional evidence presented showed that hearing screening is probably cost-effective, especially when integrated into WHO's HEAR interventions.
Source of evidence A scoping review was undertaken to compile information regarding costs, resource utilization and cost-effectiveness associated with meningitis diagnosis, treatment and management of sequelae.
Direct evidence None of the cost-effectiveness studies identified were considered applicable to this guideline question. However, evidence that did not meet the criteria to be included as part of the research evidence but provided relevant information on cost-effectiveness of hearing loss screening is summarized as additional evidence below.
Additional evidence *WHO World report on hearing* A comprehensive report was developed to promote equitable access to ear and hearing care for all populations across the world and its integration as part of universal health coverage and the Sustainable Development Goals agenda (WHO, 2021). The cost-effectiveness of screening was assessed. Costs are reported below as 2019 International dollars (Int$). In a low-income setting (Philippines), universal newborn audiological screening was conservatively estimated to yield a ROI per 1000 newborns of Int$ 1.67 per dollar invested, with the lifetime value of Disability-Adjusted Life Years (DALYs) averted reaching Int$ 21 266. In a high-income setting (France), universal newborn audiological screening was conservatively estimated to yield a ROI per 1000 newborns of Int$ 6.53 per dollar invested, with the lifetime value of DALYs averted reaching Int$ 523 251.

In a high-income setting (the United Kingdom of Great Britain and Northern Ireland) school entry audiological screening was conservatively estimated to yield a ROI per 1000 school children of Int$ 0.03 per dollar invested, with the lifetime value of DALYs averted reaching Int$ 5004.

In a high-income setting (the Kingdom of the Netherlands) an adult universal audiological screening was conservatively estimated to yield a ROI per 10 000 adults (aged 50 years) of Int$ 1.16 per dollar invested, with the lifetime value of DALYs averted reaching Int$ 788 605.

In a middle-income setting (China), an adult universal audiological screening was conservatively estimated to yield a ROI per 10 000 adults (aged 50 years) of Int$ 0.28 per dollar invested, with the lifetime value of DALYs averted reaching Int$ 8 877 785.

Tordrup et al. (2022)

The study evaluated the cost-effectiveness and ROI of the WHO's HEAR interventions for hearing loss. The HEAR interventions encompass hearing screening for various age groups as well as ear disease prevention and management. Using modelling, the study assessed the financial and health impacts of increasing service coverage to recommended levels in 172 countries from 2020 to 2030. The study concluded that a global investment of US$ 238.8 billion could result in health benefits valued at over US$ 1.3 trillion and productivity gains of more than US$ 2 trillion, equating to a return of nearly US$ 15 for every US$ 1 invested (2018 US$). However, the cost-effectiveness of all HEAR interventions were considered together and the specific ROI of hearing aids and cochlear implants could not be assessed separately from the global estimates.

WHO Global costs of unaddressed hearing loss and cost-effectiveness of interventions

In the report, the following conclusions were formulated (WHO, 2017).

- Unaddressed hearing loss poses substantial costs to the health system and to the economy as a whole.
- Current estimates show that most global health-care and education costs linked to hearing loss are incurred in LMICs.
- Public health interventions for prevention and early identification of hearing loss are cost-effective.

Health equity, equality and non-discrimination

Judgement: Probably increased

The GDG highlighted that timely audiological screening is a crucial intervention to reduce the burden of unaddressed hearing loss. As hearing loss is identified, hearing rehabilitation can be initiated, with a positive impact on individuals' quality of life, functioning and participation, leading to reduced health inequalities.

The GDG recognized that access to audiological screening can vary among different countries and health systems. However, the GDG emphasized that hearing screening is part of universal health coverage and guaranteeing universal access to this intervention contributes to reducing health inequalities.

Source of evidence

A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.

Direct evidence

None of the included qualitative studies directly focused on health equity, equality or non-discrimination in relation to conducting a formal audiological screening. However, the main relevant findings related to meningitis aftercare affordability and accessibility are summarized as part of the indirect evidence.

Indirect evidence

LMICs

Studies on carers' experiences with meningitis sequelae indicated that financial barriers significantly limited the accessibility of aftercare services for adults. Some carers reported discontinuing conventional aftercare services due to lack of funds for consultations and transportation to health-care facilities (2 studies, moderate confidence).

One study reported that sociocultural traditions played a big part in shaping attitudes towards providing aftercare for older, ailing parents. Female adults were expected to act as the main carers for their parents. However, most female participants reported that marriage and its associated responsibilities adversely affected the ability to provide care (1 study, low confidence).

While there were reports from some adult children that they saw caring for their older parents as a form of gratitude for their own upbringing, aftercare provision was also linked to psychological stress among carers (1 study, low confidence).

HICs

One study reported that some carers experienced organizational barriers to accessing support services. Other factors limiting the uptake of aftercare included a restricted budget and a lack of medical staff (1 study, moderate confidence).

Multidisciplinary team meetings between members of the aftercare process, including parents, school staff and health visitors, were found to facilitate customized aftercare (1 study, moderate confidence).

Evidence identified limitations to informational access. Carers reported a lack of knowledge about meningitis sequelae and highlighted the need for accessible information on the potential outcomes of meningitis (1 study, low confidence).

Additional evidence

WHO Global report on health equity for persons with disabilities

The report calls on WHO Member States to take action to advance health equity for persons with disabilities (WHO, 2022). It also invites civil society, including organizations of persons with disabilities, and other health partners, to collaborate and advocate for the implementation of the recommendations included in the report and achieve the highest attainable standard of health for all.

Feasibility

Judgement: Varies

The GDG agreed that audiological screening comprises a range of tests for different age groups. They highlighted that the feasibility of hearing tests may vary among different contexts, depending on the expertise and training of specialized personnel as well as the availability of the necessary infrastructure dedicated to audiological screening testing within health-care facilities.

Source of evidence

A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.

Direct evidence

None of the included qualitative studies directly focused on the feasibility of conducting a formal audiological screening. However, the main findings related to meningitis aftercare barriers potentially limiting the feasibility of meningitis sequelae care for children and adults are summarized as part of the indirect evidence.

Indirect evidence

LMICs

The inability of carers to provide aftercare due to work commitments and associated needs to finance hospital bills and medicines were barriers to providing care for adults with meningitis sequelae. One carer reported resigning from her job to take care of her sick mother (1 study, moderate confidence).

Both patients and caregivers expressed a need for services to support family caregiving (1 study, moderate confidence).

HICs

Factors limiting the uptake of aftercare included a restricted budget and a lack of medical staff. Moreover, health-care professionals experienced difficulties with hearing assessments and predicting cognitive after-effects of meningitis in young children. In addition, the study noted a misunderstanding of the specific needs of young children with disabilities, as their needs were perceived to be similar to those of very young children. This posed a challenge to parents in terms of accessing adequate support (1 study, moderate confidence). Some carers also experienced organizational barriers to accessing support services (1study, moderate confidence).

Human rights and sociocultural acceptability

Judgement: Probably yes

Based on their experience and the presented body of indirect evidence, the GDG agreed that audiological screening is likely to be acceptable across different settings. However, the GDG highlighted that audiological screening should be considered the initial step in the comprehensive management of hearing impairment, rather than an isolated intervention.

Source of evidence

A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.

Direct evidence

None of the included qualitative studies directly focused on relationship between conducting a clinical review to identify sequelae and universal human rights standards or its sociocultural acceptability. However, some aspects which influenced the ability of patients/caregivers to make a competent, informed and voluntary decision regarding meningitis aftercare are summarized as part of the indirect evidence.

Indirect evidence

LMICs

One study emphasized some sociocultural aspects influencing caregivers' ability to provide aftercare for adults with meningitis sequelae (1 study, low confidence). Caregivers reported their experience with difficulties in providing aftercare for their older, ailing parents. The different expectations of women and men in providing care for parents were highlighted, particularly in Nigeria where female adults were seen as the ultimate caregivers (1 study, low confidence).

HICs

In a single qualitative study, caregivers of children with meningitis sequelae reported experiences with rehabilitation services. Parents were dissatisfied with inadequate customization of prosthetic limbs and orthopaedic devices. Additionally, parents reported poor communication between different members of staff involved in the aftercare process, delaying timely and sufficient care (1 study, moderate confidence). Caregivers also noted misunderstandings of the specific needs of young children with disabilities, as their needs were perceived to be similar to those of very young children. This posed a challenge to parents in terms of accessing adequate support (1 study, moderate confidence).

Additional evidence

The United Nations Convention on the Rights of Persons with Disabilities (CRPD)

The CRPD (2007) emphasizes the right of persons with disabilities to the highest attainable standard of health without discrimination. It requires states to offer accessible health services, including early diagnosis and intervention, designed to meet the needs of people with disabilities. The CRPD calls for equitable health-care access, ensuring that individuals with disabilities receive the same range, quality and standard of health services as others, either free or at an affordable cost. It also mandates training for health-care professionals on disability rights and prohibits discriminatory practices within the health sector.

CRPD: The United Nations Convention on the Rights of Persons with Disabilities; DALY: disability-adjusted life year; GDG: Guideline Development Group; HICs: high-income countries; LMICs: low- and middle-income countries; ROI: return on investment; WHO: World Health Organization.

18. Rehabilitation for hearing loss

18.1 Guideline question

In children and adults with hearing loss following acute meningitis, should hearing rehabilitation be provided?

Population: Children and adults with acute meningitis from any cause with hearing loss

Subgroup: Age group (children, adult)

Intervention: Hearing rehabilitation[21]

Comparator: Care without hearing rehabilitation

Outcome:

Critical: Quality of life, functioning and participation,[22] caregiver burden

Important: Secondary consequences (including speech delays or regression, behavioural issues)

Full details of the evidence, including references, are provided in Web Annex A (18. Rehabilitation for hearing loss) and Web Annex B (Qualitative and economic evidence reports).

[21] May include interventions to support optimal hearing and communication including provision and training in the use of assistive products for communication or hearing, education, counselling and support, communication skills training, education for caregivers, etc.

[22] Participation is defined as the involvement in a life situation (e.g. going to school, undertaking work, having a family).

18.2 Evidence-to-Decision framework

Priority of the problem
Judgement: Yes Hearing loss is one of the most common sequelae of acute meningitis and can significantly impact the quality of life of affected individuals. Unaddressed hearing loss in individuals with acute meningitis has a potentially devastating impact on an individual's communication, education, employment and social well-being. The Guideline Development Group (GDG) highlighted the critical importance of reducing the burden of unaddressed hearing loss in individuals with acute meningitis. Formal audiological screening can detect hearing loss and minimize the time to access hearing rehabilitation services. As hearing rehabilitation tends to be more effective when initiated promptly, timely audiological screening is crucial to capture the largest number of people with hearing impairment due to acute meningitis. However, whether formal audiological screening should be performed following acute meningitis, and its optimal timing are not yet well defined.
Desirable effects
Judgement: Large The GDG emphasized that the beneficial effect of hearing rehabilitation is larger when initiated early. This is due to a loss of auditory feedback leading to loss of speech. This is also the case for cochlear implants, as early cochlear ossification can greatly affect their auditory performance. The GDG highlighted that hearing loss following acute bacterial meningitis is generally profound, and the impact of certain interventions (i.e. cochlear implants) is larger than in cases of mild or moderate hearing loss. The GDG discussed the evidence from the WHO package of interventions for rehabilitation (PIR). While the hearing rehabilitation interventions in the package are not specifically targeted at hearing loss resulting from acute meningitis, the GDG concurred that these interventions are applicable to this population. Once hearing loss is established, it is similar to any other form of post-lingual hearing loss that may develop due to various infectious or non-infectious causes. However, the GDG agreed that the evidence from the WHO PIR followed a different methodology than the present guideline, relying primarily on expert opinion and recommendations from two adult guidelines from high-income countries (HICs).
Source of evidence

A systematic review was conducted to compare hearing rehabilitation in children and adults following acute meningitis to no hearing rehabilitation.

Direct evidence

The review did not identify any comparative evidence on hearing rehabilitation versus care without hearing rehabilitation

Indirect evidence

Twenty-six case series (with 715 participants) only including people who had undergone cochlear implantation were identified. All except 2 studies were conducted exclusively with children, and 1 study included both children and adults. The evidence from these case series, which report pretest and post-test outcomes of implantation, is summarized below.

Auditory performance

Across all 26 studies reporting audiological outcomes, cochlear implantation was consistently shown to improve auditory outcomes post-intervention. However, the reporting methods and follow-up durations varied considerably across the studies.

The most commonly utilized outcome measures were open set speech perception scores (16 studies, n = 520) and Categorised Auditory Performance (CAP) (8 studies, n = 204). Notably, 2 studies indicated a statistically significant inclination towards better audiological outcomes with full electrode insertion compared to partial insertion. While all studies enrolled people with hearing loss and reported audiological outcomes after cochlear implantation, 10 studies (n = 322) documented change in measures in terms of scale scores, allowing a comparison of pre- and post-implantation status.

Participation

Educational outcomes following cochlear implantation were reported in 4 studies (n = 169 children), specifically participation in mainstream schooling or specialized educational settings. In studies that reported participation, the majority of children transitioned to mainstream education, with some progressing to higher-level education and securing full-time employment after more than 10 years of cochlear implant use.

Quality of life

One study with 61 people – 44 of whom had hearing loss,,but only 3 of which were due to meningitis – reported on quality of life after cochlear implantation. This study included 3 groups: prelingual implanted deaf children and adolescents, prelingual deaf children, adolescents without implants, and normal-hearing children and adolescents. All were between 8 and 18 years old and attended school in Portugal. Kidscreen 52 was used to assess health-related quality of life, with the conclusion that cochlear implantation appeared to favour the perception of improved quality of life among children and adolescents. The health-related quality of life scores reported were

higher in hearing children, followed by deaf children with implant and finally by deaf children without implant, in almost all dimensions.

Complications

Post-operative complications were rare. Five studies (n = 142 children) documented complications such as implant infection (n = 1), facial nerve stimulation (n = 2), and otitis media (n = 16). Device failure (n = 13) and reimplantation (n = 15) were also rare.

Evidence on other hearing rehabilitation interventions, such as hearing aids, assistive listening devices and bone conduction hearing devices was not reported in these studies. Indirect evidence from other causes of hearing loss, such as congenital aural atresia and cerebral palsy, supported the use of these interventions.

Additional evidence

WHO Package of interventions for rehabilitation

The WHO PIR outlines assessments and interventions for hearing loss including recommendations in the following areas.

- Assessment of hearing functions
- Referral to cochlear implant or hearing aids
- Provision and training in the use of assistive products for hearing
- Assessment of auditory perception and auditory training
- Assessment of language and language therapy
- Assessment of speech functions and speech therapy
- Assessment of communication and verbal and/or sign language training
- Communications skills training and provision and training in the use of assistive products for communication
- Educational assessment, counselling, training and support
- Vocational assessment counselling, training and support
- Assessment of participation in community and social life and focused interventions
- Self-management
- Carer and family support.

Undesirable effects

Judgement: Small

The GDG discussed the undesirable effects of hearing rehabilitation and agreed that these are limited. However, hearing rehabilitation can indirectly affect carers and family members, thereby increasing the caregiver burden.
Source of evidence A systematic review was conducted to compare hearing rehabilitation in children and adults following acute meningitis to no hearing rehabilitation.
Direct evidence The review did not identify any comparative evidence on hearing rehabilitation versus care without hearing rehabilitation.
Indirect evidence Research evidence from a qualitative evidence synthesis identified themes related to the negative influence of meningitis sequelae care on family members. Parents have reported prioritizing the care of their children's meningitis sequelae over their professional commitments, including their job. Some parents taking care of their children with meningitis sequelae were unable to continue working. Others had to pay someone else to look after their disabled children and, as a result, could not save money (1 study, very low confidence). Caregivers frequently reported that they needed to leave their jobs or significantly alter their personal lives to provide necessary care for their parents with meningitis sequelae. The task of caring for adults with these conditions often led to psychological distress among caregivers. Some mentioned specific factors, including isolation from friends and frustration related to the care experience (3 studies, low confidence). The themes related to caregiver burden are further summarized below in the sections of this table addressing feasibility and sociocultural acceptability.
Certainty of the evidence
Judgement: Very low The certainty of evidence was considered very low due to the lack of direct evidence addressing the guideline question.
Values
Judgement: Probably no important uncertainty or variability Based on the body of indirect evidence from low and middle-income countries (LMICs) and high-income countries (HICs) as well as their knowledge and clinical experience, the GDG agreed that

there is probably no important variability in how children and adults with sequelae value the main outcomes.

Source of evidence

A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.

Direct evidence

No direct evidence was identified regarding the uncertainty about or variability in how much people value the main outcomes related to hearing rehabilitation. However, the included studies highlighted a complex landscape of values and beliefs associated with meningitis sequelae and caregiving for children and adults. This evidence is summarized as indirect evidence.

Indirect evidence

LMICs

One study explored community perceptions of meningitis and highlighted the significant concern among caregivers about the sequelae of meningitis in children. They feared that such impairments could hinder a child's development and potentially limit their future ability to work, thus imposing an additional financial strain on families (1 study, low confidence).

In another study, the authors reflected the experiences and values of older adults and their carers in relation to meningitis sequelae. The patients reported persistent disability interfering with social and personal activities, leading to increased dependency of older adults on family members. Despite caregivers' willingness to provide aftercare, financial constraints and work commitments often limited their ability to cover the costs of necessary medicines and supplies (1 study, moderate confidence).

HICs

People with meningitis reported long-term mental consequences of meningitis, including cognitive and memory impairment, and physical sequelae including limb loss, heart problems and hearing and visual impairments. Meningitis sequelae, both mental and physical, interfered with peoples' social and personal lives, sometimes drastically changing their life course and causing considerable distress. Long periods of rehabilitation were cited as an additional source of frustration (2 studies, low confidence).

Several studies identified the impact of meningitis sequelae on parents' emotional well-being. Parents reported having long-lasting concerns and anxiety about possible sequelae of meningitis in their children. Some parents experienced long-term consequences of their child's meningitis,

including depressive symptoms and depression requiring medication, abandoning their job to provide care and distress due to child's sequelae (6 studies, low confidence).

Balance of effects

Judgement: Probably favours the intervention

Based on the available evidence and their knowledge and experience the GDG agreed that hearing rehabilitation, including cochlear implants, probably has a beneficial effect on auditory performance in people with severe hearing loss.

Resources required

Judgement: Varies

The GDG acknowledged that rehabilitation interventions for hearing loss generally incur moderate to large costs. The GDG also emphasized the indirect costs of hearing rehabilitation, for example, training relevant professionals such as audiologists, speech therapists and surgeons. The GDG agreed that cochlear implantations are generally very expensive and require highly specialized personnel, while other types of hearing devices are more accessible. However, the GDG agreed that there is large variability in the resources required, and this also depends on the setting and the extent to which the health system covers medical expenses.

Source of evidence

A scoping review was undertaken to compile information regarding costs, resource utilization and cost-effectiveness associated with meningitis diagnosis, treatment and management of sequelae.

Direct evidence

None of the identified cost and resource utilization studies directly addressed the cost of hearing rehabilitation, but evidence of the cost of hearing implants and management of hearing loss sequelae was reported.

LMICs

The scoping review identified 1 study providing information on the cost of hearing devices in Senegal. The reported cost of one pair of hearing devices was US$ 1234 (US$ 2010). The evidence from qualitative evidence synthesis further reported that this price was viewed as unaffordable for families.

HICs

The scoping review identified 1 study providing information on the cost of management of hearing loss in France. The mean annual cost per capita of hearing loss requiring cochlear

implant, unilateral hearing loss and bilateral hearing loss was € 9785, € 7426 and € 25 093 after one year and € 1922, € 1460, € 3464 in subsequent years, respectively (€ 2019).

Additional evidence

Tordrup et al. (2022)

A modelling study was conducted to analyse the return on investment (ROI) and cost-effectiveness of WHO's HEAR interventions for hearing loss, including hearing aids and cochlear implants. It provided lower and upper bound estimates of the costs of hearing aids and cochlear implants in 2018 US$ based on expert opinion.

- Hearing aids: Low power (US$ 50–306); High power (US$ 100–306)
- Cochlear implants: US$ 6011.43–6056.75

WHO Global costs of unaddressed hearing loss and cost-effectiveness of interventions

In the report, the following conclusions were formulated (WHO, 2017).

- Unaddressed hearing loss poses substantial costs to the health-care system and to the economy as a whole.
- Current estimates show that most global health-care and education costs linked to hearing loss are incurred in LMICs.
- Public health interventions for prevention and early identification of hearing loss are cost-effective.
- Provision of hearing devices is a cost-effective strategy, especially when used regularly and supported with rehabilitation services.

While cochlear implantation is the gold standard, it is not the only option. The high cost and lack of availability of cochlear implants put it out of reach of the majority of people in LMICs. Use of other assistive technologies such as hearing aids is relevant and useful for those unable to access cochlear implants.

Certainty of the evidence on resources required

Judgement: Very low

The judgement reflected the limited scope of the evidence, the absence of comprehensive cost comparisons between interventions and the potential variability in cost data across settings.

Cost-effectiveness

Judgement: Probably favours the intervention

Although the review of the economic evidence did not include any cost-effectiveness studies relevant for this question, the additional evidence presented showed that interventions for hearing loss are probably cost-effective, especially when integrated into WHO's HEAR interventions.

Source of evidence

A scoping review was undertaken to compile information regarding costs, resource utilization and cost-effectiveness associated with meningitis diagnosis, treatment and management of sequelae.

Direct evidence

None of the cost-effectiveness studies identified were considered applicable to this guideline question. However, evidence that did not meet the criteria to be included as part of the research evidence but provided relevant information on cost-effectiveness of hearing rehabilitation is summarized as additional evidence below.

Additional evidence

WHO World report on hearing

A comprehensive report was developed to promote equitable access to ear and hearing care for any population across the world and as part of universal health coverage and the Sustainable Development Goals agenda (WHO, 2021).

The report assessed the cost-effectiveness of hearing aids and implants. In high-income settings, unilateral hearing aids were conservatively estimated to yield a return of Int$ 1.84 for every dollar invested, with the lifetime value of disability-adjusted life years (DALYs) averted reaching Int$ 60 183 per person. In lower-middle-income contexts, the ROI was Int$ 1.62, with a lifetime DALYs averted value of Int$ 3564.

For unilateral cochlear implants, estimates based on real costs in high-income areas indicated a return of Int$ 2.59 per dollar invested, with a lifetime DALYs averted value of Int$ 38 153 per individual. In lower-middle-income settings, the ROI was Int$ 1.46 and the lifetime value of DALYs averted was Int$ 6907. In upper-middle-income regions, the ROI was estimated at Int$ 4.09, with a lifetime DALYs averted value of Int$ 24 161.

Tordrup et al. (2022)

The study evaluated the cost-effectiveness and ROI of the WHO's HEAR interventions for hearing loss. The HEAR interventions encompass screening and treatment for various age groups, ear disease prevention and access to hearing technologies, such as hearing aids and cochlear implants. Using modelling, the study assessed the financial and health impacts of increasing service coverage to recommended levels in 172 countries from 2020 to 2030. The study concluded that a global investment of US$ 238.8 billion could result in health benefits valued at over US$ 1.3 trillion and productivity gains of more than US$ 2 trillion, equating to a return of nearly US$ 15 for

every US$ 1 invested. However, the cost-effectiveness of all HEAR interventions were considered together and the specific ROI of hearing aids and cochlear implants could not be assessed separately from the global estimates.

Health equity, equality and non-discrimination

Judgement: Probably increased

Although evidence on the impact of hearing rehabilitation on equity for individuals with acute meningitis is limited, the GDG emphasized the consistent body of evidence demonstrating how rehabilitation can enable people living with disabilities to live more independent and fuller lives. Rehabilitation facilitates the ability to contribute to families and communities, thereby increasing equity, equality and non-discrimination.

Source of evidence

A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.

Direct evidence

None of the included qualitative studies directly focused on health equity, equality or non-discrimination in relation to hearing rehabilitation. However, the main relevant findings related to meningitis aftercare affordability and accessibility are summarized as part of the indirect evidence.

Indirect evidence

LMICs

The synthesis of caregivers' experiences with meningitis sequelae indicated that financial barriers significantly limited the accessibility of aftercare services for both adults and children. Caregivers could not afford hospital visits and other care of their children with sequelae due to the high costs of consultations, treatments and transport. Specifically, 1 mother reported that the price of a hearing device (US$ 1234) was unaffordable for her. While some patients had to stop attending hospital appointments, others could not even begin consultations because their carers' financial resources were limited (2 studies, moderate confidence).

Aftercare for disabled children with meningitis sequelae was associated with parental loss of productivity due to shortage of time**.** Additionally, a single caregiver cited the need to pay for caring staff in order to continue working. One caregiver specifically reported unaffordability of hearing devices for her child (2 studies, moderate confidence).

One study reported that sociocultural traditions played a big part in shaping attitudes towards providing aftercare for older, ailing parents. Female adults were expected to act as the main

caregivers for their parents. However, most female participants reported that marriage and its associated responsibilities adversely affected the ability to provide care. Conversely, 2 male participants indicated a greater capacity to care for their ailing parents (1 study, low confidence).

Despite reports from some adult children that caring for their older parents was a form of gratitude for their own upbringing, aftercare provision was also linked to psychological stress among caregivers. Both patients and caregivers expressed a need for services to support family caregiving (1 study, low confidence).

HICs

One study reported that some caregivers experienced organizational barriers to accessing support services (1 study, moderate confidence).

Parents cited difficulties with accessing and navigating support systems as well as applying for disability living allowance. They also reported a lack of communication between different members of staff involved in the aftercare process. Caregivers also highlighted that limited criteria for gaining support services and lack of obvious impairments were barriers to accessing aftercare for their children. Other factors limiting the uptake of aftercare included a restricted budget and a lack of medical staff. At the same time, parents stated that proactive behaviour helped them overcome organizational barriers (1 study, moderate confidence).

Multidisciplinary team meetings between members of the aftercare process, including parents, school staff and health visitors, were found to facilitate customised aftercare (1 study, low confidence).

Evidence identified limitations to informational access. Caregivers reported a lack of knowledge about meningitis sequelae and highlighted the need for accessible information on potential outcomes of meningitis (1 study, low confidence).

Additional evidence

WHO Global report on health equity for persons with disabilities

The report calls on WHO Member States to take action to advance health equity for persons with disabilities (WHO, 2022). It also invites civil society, including organizations of persons with disabilities, and other health partners, to collaborate and advocate for the implementation of the recommendations included in the report and achieve the highest attainable standard of health for all.

Feasibility

Judgement: Varies

The GDG agreed that hearing rehabilitation comprises a wide range of interventions. They highlighted that the feasibility of hearing rehabilitation may vary among different contexts,

depending on the expertise and training of specialized personnel as well as the availability of the necessary infrastructure dedicated to hearing rehabilitation within health-care facilities.

Source of evidence

A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.

Direct evidence

None of the included qualitative studies directly focused on the feasibility of hearing rehabilitation. However, the main relevant findings related to meningitis aftercare affordability and accessibility are summarized as part of the indirect evidence.

Indirect evidence

LMICs

Aftercare costs were reported by parents taking care of children with meningitis sequelae as a significant financial burden. Caregivers could not afford hospital visits and other care of their children with sequelae due to the high costs of consultations, treatments and transport. Specifically, 1 mother reported that the price of a hearing device (US$ 1234) was unaffordable for her. While some patients had to stop attending hospital appointments, others could not even begin consultations because their carers' financial resources were limited (2 studies, moderate confidence).

Work commitment was another barrier for caregivers to providing care for their parents with meningitis sequelae (1 study, moderate confidence).

Both patients and caregivers expressed a need for services to support family caregiving (1 study, moderate confidence).

HICs

The evidence from the reviewed studies pointed to a lack of knowledge about meningitis etiology and symptoms among caregivers of children. This delayed help-seeking behaviour, which was associated with an increased risk of developing sequelae (2 studies, moderate confidence). A single study further highlighted difficulties in accessing support services for caregivers of young children affected by meningitis. According to data from the study, health-care professionals experienced difficulties with hearing assessments and predicting cognitive after-effects of meningitis in young children (1 study, moderate confidence).

Two of the studies indicated gaps in the care continuum for children affected by meningitis in HICs. Caregivers of children reported a lack of follow-up appointments after discharge (2 studies, low confidence).

Additionally, parents reported poor communication between different members of staff involved in the aftercare process, which delayed timely and sufficient care. The active involvement of a consultant and multidisciplinary team meetings including parents, school staff and health visitors were cited as factors that helped overcome this barrier (1 study, moderate confidence).

Caregivers also highlighted that limited criteria for gaining support services and lack of obvious impairments were barriers to accessing aftercare for their children (1 study, moderate confidence).

Other factors limiting the uptake of aftercare included a restricted budget and a lack of medical staff. At the same time, parents stated that proactive behaviour helped them overcome organizational barriers (1 study, moderate confidence).

Finally, some caregivers experienced organizational barriers to accessing support services. Parents cited difficulties with accessing and navigating support systems as well as applying for disability living allowance (1 study, moderate confidence).

Human rights and sociocultural acceptability

Judgement: Varies

The GDG noted that providing hearing rehabilitation is in line with the CRPD. The convention has led to improved legislation and policies regarding the rights of people with disabilities in many countries. However, the GDG noted that the implementation and enforcement of these policies significantly varies among the 164 countries that have signed the treaty.

The GDG also noted the potential stigma experienced by people with hearing loss who use hearing aids. However, they agreed that this stigma can vary across settings due to different social and cultural barriers. Additionally, the GDG noted that the quality of hearing devices, particularly regarding feedback sound cancellation, has improved substantially. This improvement has led to increased acceptability of hearing devices among people with hearing loss.

Source of evidence

A qualitative evidence review focused on end users' values and experiences of diagnosis, treatment and long-term care for meningitis and addressed factors influencing the uptake of related health services.

Direct evidence

None of the included qualitative studies directly focused on relationship between conducting a clinical review to identify sequelae and universal human rights standards or its sociocultural acceptability. However, some aspects which influenced the ability of patients/caregivers to make a competent, informed and voluntary decision regarding meningitis aftercare are summarized as part of the indirect evidence.

Indirect evidence

LMICs

One study emphasized some sociocultural aspects influencing caregivers' ability to provide aftercare for adults with meningitis sequelae (1 study, low confidence). Caregivers reported their experience with difficulties in providing aftercare for their older, ailing parents. The different expectations of women and men in providing care for parents were highlighted, particularly in Nigeria where female adults were seen as the ultimate caregivers (1 study, low confidence).

HICs

In a single qualitative study, caregivers of children with meningitis sequelae reported experiences with rehabilitation services. Parents were dissatisfied with inadequate customization of prosthetic limbs and orthopaedic devices. Additionally, parents reported poor communication between different members of staff involved in the aftercare process, delaying timely and sufficient care (1 study, moderate confidence). Caregivers also noted misunderstandings of the specific needs of young children with disabilities, as their needs were perceived to be similar to those of very young children. This posed a challenge to parents in terms of accessing adequate support (1 study, moderate confidence).

Additional evidence

The United Nations Convention on the Rights of Persons with Disabilities (CRPD)

The CRPD (2007) emphasizes the right of persons with disabilities to the highest attainable standard of health without discrimination. It requires states to offer accessible health services, including early diagnosis and intervention, designed to meet the needs of people with disabilities. The CRPD calls for equitable health-care access, ensuring that individuals with disabilities receive the same range, quality and standard of health services as others, either free or at an affordable cost. It also mandates training for health-care professionals on disability rights and prohibits discriminatory practices within the health sector.

CRPD: The United Nations Convention on the Rights of Persons with Disabilities; DALY: disability-adjusted life year; GDG: Guideline Development Group; HICs: high-income countries; LMICs: low- and middle-income countries; PIR: WHO Package of interventions for rehabilitation; ROI: return on investment; WHO: World Health Organization.

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