IQWiG

ThemenCheck Medizin

Antibiotic therapy[1]

Does shorter compared to longer-duration therapy lead to comparable treatment results?

Health technology assessment commissioned by IQWiG

EXTRACT OF THEMENCHECK REPORT

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- Claudia Breuer, Cochrane Germany Foundation, Freiburg, Germany

Patient involvement

Patients were consulted as part of the report preparation process. The aim of the consultation was to obtain information on the following topics: the the impact of the disease on life and daily activities and how the patient copes with it, treatment preferences including treatment goals, and experiences and concerns about treatment. Two people took part in the consultation; they were not involved in the report preparation. The authors of the report would like to thank them for their participation.

The Institute for Quality and Efficiency in Health Care (IQWiG) was responsible for coordinating the project, conducting information retrieval for the domains “Benefit assessment“ and “Health economic evaluation”, and preparing the easy-to-understand summary (ThemenCheck kompakt).

The authors of the report would also like to thank Eberhard Thörel for his support in preparing the ThemenCheck report protocol.

According to §139b (3) No. 2 of Social Code Book (SGB) V, SHI, external experts who are involved in the Institute's research commissions must disclose "all connections to interest groups and contract organizations, particularly in the pharmaceutical and medical devices industries, including details on the type and amount of any remuneration received". The Institute received the completed *Form for disclosure of potential conflicts of interest* from each external expert. The information provided was reviewed by a Committee of the Institute specifically established to assess conflicts of interests. The information on conflicts of interest provided by the external experts and external reviewers is presented in Chapter A12 of the full report. No conflicts of interest were detected that could endanger professional independence with regard to the work on the present commission.

Publisher's comment

What is the background of the ThemenCheck report?

Persons insured in statutory health insurance (SHI) and other interested persons can propose topics for the assessment of medical interventions and technologies to the Institute for Quality and Efficiency in Health Care (IQWiG) as part of the ThemenCheck Medizin. The assessment is done in the form of a comprehensive health technology assessment (HTA) report. Comprehensive HTA reports include an assessment of medical benefit and health economics as well as an investigation of ethical, social, legal, and organizational aspects of a technology.

In a 2-stage selection procedure, which also involves members of the public, up to 5 new topics are selected each year from all submitted proposals. According to the legal mandate, these should be topics that are of particular importance for patient care [1]. IQWiG then commissions external teams of researchers to investigate the topics in accordance with IQWiG methods, and it publishes the ThemenCheck reports.

In 2023, IQWiG commissioned a team of researchers led by the University of Freiburg to investigate the selected topic "T23-04: Antibiotic therapy". The team consisted of methodologists experienced in preparing HTA reports, experts with expertise in investigating health economic, ethical, social, legal and organizational issues, and an internal medicine and infectious diseases specialist.

Why is the ThemenCheck report important?

The ThemenCheck report T23-04 deals with the duration of antibiotic treatment. The duration of antibiotic treatment can affect the health of the patients as well as their social participation. The duration of antibiotic treatment is also relevant for society as a whole in terms of preventing the development of resistance. The costs of antibiotic treatment, which also depend on its duration, affect both patients and health insurance funds.

Antibiotics are drugs that are used to treat diseases caused by bacteria. They alleviate the symptoms of the disease and speed up recovery by inhibiting bacterial growth or killing bacteria. However, taking antibiotics can also lead to side effects such as nausea or diarrhoea [2]. The optimal duration of antibiotic treatment for patients improves or cures the disease while causing as few side effects as possible.

The use of antibiotics can lead to resistance. To avoid resistance, antibiotics must be used judiciously and appropriately [2]. This also includes deciding how long an antibiotic should be taken.

The duration of antibiotic treatment is also interesting from a financial perspective, as longer-duration antibiotic therapy may increase drug costs. However, these costs have to be compared with other disease costs, such as those caused by sick days or recurrence of the disease.

This ThemenCheck report investigated the comparison of shorter-duration antibiotic therapy with longer-duration antibiotic therapy for the bacterial infectious diseases acute otitis media (AOM) in children and community-acquired pneumonia (CAP) in children and adults. Both diseases are widespread and, if left untreated, can have serious health consequences in rare cases, e.g. meningitis in the case of AOM, or potentially life-threatening acute cardiac complications in older people with CAP. Both AOM and CAP are more common in children than in adults [3,4].

Concerns of the individual proposing the topic

The topic proposer recognizes the importance of antibiotics in the treatment of diseases, but suspects that antibiotics are often still used even when they are no longer necessary, for example because symptoms have already subsided and the patient feels healthy again. This potentially unnecessarily long treatment period could lead to long-term side effects such as the development of resistance. This gives rise to the question of whether shorter compared to longer-duration (conventional) antibiotic therapy leads to comparable treatment results.

Aim of the ThemenCheck report

To answer the question posed by the person who proposed the topic, the commissioned research team investigated, from the various perspectives of a ThemenCheck report, whether both children with AOM and children and adults with CAP can expect comparable treatment results from a shorter-duration antibiotic therapy. To this end, they investigated the non-inferiority of shorter-duration antibiotic therapy in comparison with longer-duration therapy. “Non-inferiority” means that the shorter-duration antibiotic therapy is not worse than the longer-duration therapy in terms of patient-relevant outcomes, within an acceptable, clinically irrelevant range. Key patient-relevant outcomes are treatment success, recurrence of the infectious disease, and health-related quality of life.

The researchers decided to investigate non-inferiority because there may be advantages in terms of resistance development or treatment adherence, treatment-associated adverse events (AEs) or treatment costs, even if a shorter-duration antibiotic therapy is no expected to have better effectiveness from a medical-biological pBoint of view.

Which questions were answered - and which were not?

Benefit assessment

With regard to both bacterial diseases, the included studies did not report any results on the outcome quality of life, and used different operationalizations for the outcome treatment success. Since the studies investigated different definitions of short and long-duration antibiotic therapy, the research team presented these study results separately.

AOM

The research team identified 12 suitable studies that investigated 7 different antibiotics approved in Germany (e.g. penicillin or amoxicillin) with regard to the effects of different treatment durations in children between 1 month and 14 years of age. The studies investigated 5 different comparisons of short and long-duration antibiotic treatments (e.g. 5 versus 10 days or 2 versus 7 days).

The results can be summarized simply: There was no hint of non-inferiority of the shorter-duration treatment for any of the antibiotics investigated, neither for the outcome treatment success nor for the outcomes recurrence, AEs or mortality. However, a lacking hint of non-inferiority cannot generally be used to conclude an inferiority of the shorter-duration antibiotic therapy. In 5 of the 9 studies that investigated the outcome treatment success, a statistically significant lower rate of treatment success was observed shortly after the end of treatment with a shorter treatment duration, although the disadvantage of shorter antibiotic treatment was no longer apparent at later recording times.

There was a high risk of bias across outcomes and a high outcome-specific risk of bias in 11 of the 12 studies. Only one study and its results on the outcomes treatment success and AEs had a low risk of bias. The potential for publication bias was assessed as low.

It is not possible to say whether these results can be transferred from children to adolescents over the age of 14, as there are neither studies with adolescents nor analyses of age-stratified approaches. There is also a lack of high-quality studies on the antibiotic amoxicillin, which is currently the first choice for antibiotic therapy in Germany.

CAP

Seven studies investigated the duration of amoxicillin treatment in CAP in children. The average age of the children included in most studies was 1 to 2 years, with the maximum age limit for study inclusion ranging from 5 to 10 years in most studies. The included studies investigated 5 different comparisons of short and long-duration antibiotic treatments (e.g. 3 versus 5 days or 5 versus 10 days).

The results can be summarized simply: For the outcome treatment success, there was proof of non-inferiority for both a treatment duration of 5 days compared with 10 days, and for a

treatment duration of 3 days compared with 5, 7 or 10 days. In addition, for the outcome AEs, a 3-day course of antibiotics was superior to a 5-day course; this did not apply to the other comparisons of short vs. long-duration antibiotic therapy. There was no hint of non-inferiority of the shorter-duration antibiotic therapy for the outcomes recurrence and mortality.

The certainty of results was high because both the risk of bias across outcomes and the outcome-specific risk of bias was low in most of the studies. The potential for publication bias was assessed as low.

Questions about non-inferiority with regard to other antibiotics (e.g. amoxicillin-clavulanic acid or doxycycline) or in older children, adolescents and adult patients cannot be answered directly with this ThemenCheck report, as no studies were available on these topics.

Health economics

In order to compare the costs of shorter-duration antibiotic treatment with those of a longer-duration treatment, examples were calculated for 3 antibiotics independently of the underlying disease. Since the dosage for children under 40 kg depends on body weight, the costs were calculated for a 5 kg infant, a 19 kg child, a 30 kg child and a person weighing over 40 kg, for courses of treatment of 3, 5, 7 and 10 days, respectively. The available pack sizes and administration forms also influenced the calculated costs. For SHI funds, the range of cost reduction for a 3-day antibiotic therapy compared with a 10-day antibiotic therapy was up to about 35 €. The research team showed in summary that the costs for all 3 age categories increased with longer treatment durations for the majority of the antibiotics investigated. For adult patients, the costs to be borne privately arise from the flat-rate co-payment of 5 € per pack. The number of packs required for the antibiotic treatment depends on the treatment duration and the pack size of the respective antibiotic. It is therefore not possible to make a general conclusion about the costs for patients.

The report also presents one health economic study each on AOM and on CAP. For AOM, the study from the United States showed that although drug costs were reduced with a 5-day course of antibiotic therapy, other disease costs, such as those due to absence from work, increased. Overall, the disease costs for longer-duration antibiotic therapy were lower than for short-duration antibiotic therapy. With regard to CAP, the study from India showed that medical costs were reduced due to the comparable effectiveness of a shortened course of antibiotic treatment. Due to differences in cost regulations for disease costs in Germany compared with India and the United States, these results were only transferable to Germany to a limited extent.

Further aspects

In ethical terms, the autonomy of the patients plays a special role: The patient population affected mostly includes children and older adults, whose freedom of choice may be limited.

This autonomy can also be influenced by social interests. With regard to autonomy and the social aspect of societal acceptance of shorter antibiotic therapy, the research team concluded that comprehensive and age-appropriate information was important. From an organizational perspective, acceptance of the duration of antibiotic treatment could also be increased through uniform professional standards based on evidence-based findings on the duration of treatment, the researchers added. From a legal perspective, when prescribing a shortened course of antibiotic therapy that deviates from the professional standard for the prescribed drug, doctors are required to weigh up the individual circumstances and provide detailed information. The investigation of environmental and climate aspects showed that shorter-duration antibiotic therapy with adapted pack sizes may lead to lower CO_2 emissions and environmental pollution.

Summarized conclusion from IQWiG's perspective

It is not possible to make a general conclusion about a shortened duration of treatment. Even for the diseases investigated in the ThemenCheck report, the picture is not clear:

In children with CAP, it can be safely derived from studies of sufficient quality that a 3-day course of antibiotic therapy with amoxicillin is not inferior to a 5-day course. The results support a shorter course of therapy for CAP.

With a predominantly insufficient evidence base, there are heterogeneous results in children with AOM: Non-inferiority could not be demonstrated for any of the outcomes investigated. This result does not mean that shorter-duration therapy is inferior, but only that it cannot be said with certainty whether it is equivalent. Further studies with a low risk of bias, including on the antibiotic amoxicillin, would be necessary for the benefit assessment in AOM. Given the uncertainty in the results, the choice of treatment regimen for AOM requires shared decision-making, in which not only individual factors (e.g. adverse effects, treatment adherence, treatment success) but also public health aspects may play a role:

Shorter-duration antibiotic therapy is environmentally and resource-friendly as well as ethically, legally and socially acceptable. In particular, the principle of antibiotic stewardship, which aims to minimize the risk of resistance, could be an argument in favour of shorter therapy.

At the same time, questions remain: What is the optimal duration of treatment for other antibiotics, age groups and therapeutic indications from the perspective of the benefit assessment and health economic evaluation? Which shorter-duration antibiotic therapy is most suitable? With regard to this last question, the ongoing study from Australia identified in the ThemenCheck report, which compares treatment with amoxicillin over 2, 3, 4 and 5 days in children with CAP, could provide results and insights.

ThemenCheck key statements

Research question of the ThemenCheck report

The aims of this investigation are

- the benefit assessment of shorter-duration compared to longer-duration (conventional) treatment with oral antibiotics in children with AOM and children and adults with CAP,
- the determination of costs (intervention costs) and the assessment of cost effectiveness, and
- a review of ethical, social, legal, and organizational as well as environmental and climate aspects associated with the medical intervention.

Conclusion of the ThemenCheck report

To summarize, it can be said that the costs increase notably with longer treatment with the difference varying depending on body weight, drug, dosage form and available pack sizes. For the paediatric antibiotic Amoxicillin Oral Suspension, there is no difference in cost from an SHI perspective for the treatment of a child weighing 5 kg due to the available pack size of 100 mL. For both 3 and 10 days of treatment, this amounts to exactly the cost of one pack (€10.17). For a child weighing 19 kg, the costs for the SHI funds increase by €20.34 from €20.34 for 3 days (2 bottles) to €40.68 for 10 days (4 bottles). Cefpodoxime shows similar increases in the paediatric setting: For a child weighing 5 kg, the cost for both 3 days and 10 days of treatment is €14.79 for the smallest available pack size of 50 mL. For a child weighing 19 kg, the costs from an SHI perspective would amount to €19.02 for a 100 mL pack for 3 days of treatment, and to €25.27 for a 200 mL pack for 10 days of treatment. This corresponds to a difference of € 6.25. The cost of treatment of a child weighing 30 kg with the selected product for amoxicillin/clavulanic acid showed no difference in cost (€21.74), as one pack of 10 film-coated tablets is sufficient for both 3 days and 10 days of treatment.

From an SHI perspective, the difference in costs between a 3-day and a 10-day treatment with amoxicillin for adult patients corresponds to €20.68 (amoxicillin oral suspension) and €5.92 (Amoxicillin AL 1000). The cost of cefpodoxime film-coated tablets increases by €19.42, i.e. by 1 pack of 10 film-coated tablets. Amoxicillin/clavulanic acid shows the highest difference of €34.71, with costs of €21.74 (3 days, 1 pack of 10 film-coated tablets) and €56.45 (10 days, 1 pack of 10 film-coated tablets and 1 pack of 20 film-coated tablets).

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List of abbreviations

Abbreviation	Meaning
AE	adverse event
AOM	acute otitis media
BW	body weight
CAP	community-acquired pneumonia
CI	confidence interval
EMA	European Medicines Agency
HTA	Health technology assessment
ICD	International Classification of Diseases
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ITT	Intention to treat
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SHI	statutory health insurance

ThemenCheck Overview

1 Background

1.1 Health policy background and commission

According to §139b (5) of Social Code Book V, Statutory Health Insurance (SHI) (SGB V), SHI *members, and other interested people may suggest topics for the scientific assessment of medical interventions and technologies to the Institute for Quality and Efficiency in Health Care (IQWiG). The topics for these ThemenCheck reports can be submitted on the IQWiG website.

ThemenCheck Medizin aims to promote the involvement of the public in evidence-based medicine and answer questions which are particularly relevant in patient care.

Once a year, IQWiG, in collaboration with patient representatives and members of the public, selects up to 5 topics on which ThemenCheck reports are to be prepared. IQWiG then commissions external experts to investigate the research question. The results prepared by the external experts are published together with a publisher’s comment by IQWiG .

IQWiG forwards ThemenCheck reports to German institutions, for instance those deciding about health care services and structures. The ThemenCheck report is made available to the professional community through the IQWiG website (www.iqwig.de). In addition, a lay summary of the results is published under the title “ThemenCheck compact: The most important points clearly explained”.

1.2 Medical background

1.2.1 Controversy: Duration of antibiotic therapy

The use of antibiotics is always associated with the risk of resistance developing. In order to reduce this risk, many physicians practising infectious disease medicine assumed that sufficiently long treatment was necessary - even if the patient's symptoms had already subsided [5]. Many scientists are now propagating the "shorter is better" approach. For example, a publication which appeared in the specialist journal "JAMA Internal Medicine" as early as in 2016 pointed out that extensive antibiotic therapy does not prevent the development and spread of resistance in most cases [6]. Any single administration of antibiotics can induce resistance [7], so any omitted dose of antibiotics can potentially reduce the resistance pressure. It is therefore not essential to continue treatment after the symptoms have subsided. One year later - in 2017 - the "British Medical Journal" also called for a general revision of the recommendations on the duration of antibiotic therapy [8]. Besides the risk of resistance development, these calls were also made against the background that a shorter

antibiotic therapy duration decreases the risk of treatment-associated adverse effects (e.g. intestinal infections). In the meantime, a large number of randomized controlled trials (RCTs) have compared shorter with longer-duration (conventional) antibiotic therapy for various infectious diseases [9-11].

Given the widespread prevalence of bacterial infectious diseases such as AOM (AOM; see Section 1.2.2) and pneumonia acquired on an outpatient basis (community-acquired pneumonia [CAP]; see Section 1.2.3), which can be associated with serious health consequences, adequate treatment is of major importance both for those affected and for public health. The planned ThemenCheck report will therefore investigate whether a shorter antibiotic therapy is equally effective compared to a longer, conventional therapy duration for the frequently occurring infectious diseases mentioned above and whether it potentially minimizes the risk of adverse effects and the development of antibiotic resistance.

1.2.2 AOM

Aetiology

AOM is an acute inflammatory disease of the middle ear with particular involvement of the tympanic cavity, which often occurs in the context of an upper respiratory tract infection [12]. Because the auditory tube (the tube that connects the tympanic cavity with the nasopharynx) is shorter and more horizontal in children, pathogens can more easily penetrate the middle ear and cause an infection as a result of rhinitis (cold) or tonsillopharyngitis (throat inflammation, often with a sore throat) when the mucous membranes swell and drainage is impaired. In addition, the mucous membrane of the nasopharynx swollen in the course of the infection impairs ventilation of the middle ear with negative pressure, thus promoting the spread of pathogens into the middle ear.

Depending on the detection method, bacteria can be isolated in up to 900 out of 1000 patients during the course of AOM [13]. The most common bacterial pathogens causing AOM are *Streptococcus pneumoniae* (pneumococci) and *Haemophilus influenzae*, followed by *Moraxella catarrhalis* [14].

Epidemiology

In total, around 709 million cases of AOM occur worldwide every year [15,16]. Half of these infections affect children under the age of 5. In Germany, the prevalence in children in the first year of life is around 200 out of 1000 children, in the second and third year of life around 300 out of 1000 and in children up to the age of 6 around 600 out of 1000 [17,18]. AOM is therefore also one of the most common reasons for visits to the doctor and antibiotic prescriptions in childhood [19,20].

Clinical symptoms and diagnosis

The cardinal symptoms of AOM are acute onset earache (usually unilateral) in conjunction with a reduced general health (including fever) and hearing impairment. A compulsion to reach for the ear is frequently observed in infants, but this alone is not specific [21]. For example, only 100 out of 1000 of all children with such compulsion suffer from AOM [22]. In older children and adolescents, earache, headache and hearing impairment in the affected ear are usually more definite symptoms [23]. The following criteria are required to make a diagnosis of AOM [24,25]:

- acute onset of symptoms with fever, restlessness and reduced general health
- otalgia (earache) and reddening of the eardrum
- otoscopically (with otoscopy) proven tympanic effusion and protrusion of the eardrum (possibly mirroring, blistering, occurrence of otorrhoea [ear discharge])

It should also be noted that the acute occurrence of clinical symptoms (such as earache, otorrhoea, fever) and/or reddening of the eardrum supports the diagnosis of AOM, but is not sufficient in itself [21,26]. The diagnosis of AOM should only be made if a tympanic effusion is also present.

Similar diagnostic criteria are also recommended by international guidelines, such as the American Academy of Pediatrics (AAP) guideline [27].

Therapy

Since respiratory viruses are the main cause in the initial phase of AOM, it is recommended that earache in otherwise healthy children be treated initially with standard analgesics (paracetamol or ibuprofen) [27]. In addition, decongestant nasal drops can be used in the case of rhinosinusitis (cold). Direct administration of antibiotics should take place in the following cases [25,28]:

- age: < 6 months
- age: < second year of life with bilateral AOM with fever (with/without otorrhoea) or no improvement in symptoms after 24 hours
- AOM with moderate to severe earache or temperature ≥ 39.0 °C
- severe or protracted course (48 to 72 hours after symptom onset)
- persistent, purulent otorrhoea
- in the presence of risk factors (e.g. otogenic complication, immunodeficiency, Down's syndrome, cleft lip and palate, cochlear implant wearer, influenza)
- no improvement in symptoms within 48 hours of first medical consultation

- follow-up within the first 3 days not possible with certainty

The antibiotic of first choice is amoxicillin at a dose of 50 mg/kg per day in 3 single doses [27]. Cefuroxime or cefpodoxime can be prescribed if a patient is allergic to penicillin [22]. A treatment period of 10 days is recommended for children up to and including the age of 2 and for children with serious illnesses (no age limit). For 3 to 6-year-olds, the recommended treatment duration is 7 days, and for children from the age of 6 it is between 5 and 7 days [27,29]. However, the recommended treatment duration varies around the world. Moreover, antibiotic therapy is often not prescribed [30].

Disease burden

The spontaneous recovery rate for AOM is high and complications are rare. Complications are categorized as extracranial (outside the skull, e.g. mastoiditis) and intracranial (inside the skull, e.g. otogenic meningitis). In addition, the hearing loss associated with AOM can lead to behavioural changes and delays in communication [28]. The illness can also lead to missed days at school or day care, which can have an impact on the child's education and social interaction. In addition, parents whose children are frequently affected by AOM could be additionally burdened by numerous visits to the doctor [31].

1.2.3 CAP

Aetiology

Pneumonia (lung inflammation) is an infectious inflammation of the lung parenchyma (lung tissue, functional component of the lungs responsible for gas exchange between the air we breathe and the blood) caused by viral or bacterial pathogens or fungi [32]. Due to the consequences for the diagnostic and therapeutic procedure, a distinction is made between CAP and hospital-acquired pneumonia (HAP). The decisive factor for CAP is that the symptoms begin outside of a hospital stay or (due to the incubation period) within 48 hours of admission to hospital [33,34]. In addition to a generally increased susceptibility to infections, which can also be expressed in a reduced antibody response after pneumococcal vaccination, polymorbidity in old age and the restricted functional status of many senior citizens play an important role [32].

The CAP pathogen spectrum in Central Europe has remained relatively constant over the last few decades. The most frequently identified pathogens (disease-causing bacteria) in CAP are *Streptococcus pneumoniae* (pneumococci), *Haemophilus influenzae*, atypical bacteria (e.g. mycoplasma) and viruses (including respiratory syncytial virus [RS virus] and influenza [flu] A and B viruses) [35]. Differentiating between bacterial and viral CAP is a challenge, as even the detection of a virus does not rule out a simultaneous infection with bacteria [34].

Epidemiology

CAP is a common infectious disease in Western industrialized countries and is associated with the highest mortality rate of all infectious diseases [36]. It occurs mainly in children up to the age of 10 and in older adults between the ages of 60 and 90 [37]. In Germany, around 500,000 cases of CAP occur each year, with the incidence increasing with advancing age [38]. In 2019, 255,000 patients were hospitalized with CAP, of which 130 out of every 1,000 patients died during their hospital stay [36]. In comparison, the mortality rate for patients who do not show a severe disease progression is less than 10 out of 1000 patients [38]. According to the World Health Organization (WHO), if only children under the age of 5 are considered, around 200 out of every 1000 deaths in this age group worldwide are due to a lower respiratory tract infection (90% of which are due to pneumonia) [34]. Children from resource-poor countries are the most affected. In Central and Northern Europe, 3 out of 1000 children aged 0 to 16 years suffer from pneumonia every year [39-41]. Even though the prognosis for children with CAP is comparatively good in Western countries [35], CAP is a common reason for outpatient presentations and antibiotic therapy [42].

Clinical symptoms and diagnosis

The symptoms of pneumonia can vary depending on the age of the patient and are often non-specific. The diagnosis of pneumonia is primarily made clinically. Diagnostic criteria according to corresponding S3 guidelines are [33,34]:

- General symptoms such as fever (may be absent in older patients)
- respiratory symptoms such as cough, but also tachypnoea (accelerated breathing), dyspnoea (shortness of breath) and respiratory chest pain with pleural involvement (involvement of the visceral pleura)
- neurological symptoms such as disorientation, especially in older patients

The diagnosis is confirmed by new or progressive X-ray infiltrates. If it is in practice not possible to perform the X-ray examination, clear focal auscultation findings, which are characterized by abnormal breathing noises in the form of fine-bubble rales, can be considered equivalent. An X-ray examination can then initially be omitted. The essential aim of the clinical diagnosis is to differentiate CAP from the much more common acute bronchitis: only around 50 out of 1000 patients with respiratory symptoms suggesting a lower respiratory tract infection were diagnosed with CAP in practice [32]. This distinction is important because, unlike CAP, acute bronchitis should not be treated with antibiotics. In addition, the diagnosis of CAP requires increased monitoring.

Therapy

The symptoms of patients with CAP are alleviated with supportive measures. These include the administration of sufficient fluids, antipyretics, analgesics and possibly oxygen [33,34]. In addition, in most cases antibiotics are used, usually without detection of the pathogen [43]. Current national and international guidelines uniformly recommend amoxicillin as the antibiotic of first choice for both children and adults [33,34,44]. If an atypical pathogen cannot be ruled out as the cause, a macrolide (e.g. azithromycin or clarithromycin) can be used. If there is a penicillin allergy or intolerance, macrolides (preferably in children) or fluoroquinolones, e.g. moxifloxacin or levofloxacin are recommended. antibiotic therapy for CAP is administered orally for 5 to 7 days in patients with no previous illness [45]. However, the recommendations on treatment duration are not consistent, even if there has been a general trend towards shorter treatment durations in recent years.

Disease burden

CAP contributes significantly to incapacity for work, especially in younger people [46-48]. Older and multimorbid patients often have to be hospitalized due to hypoxaemia (oxygen deficiency) and there is a risk of life-threatening acute cardiac complications [49,50].

1.3 Health care situation

1.3.1 AOM

AOM is one of the most common illnesses that paediatricians are confronted with. Although the spontaneous recovery rate is high, there is a concern of serious complications. A total of 900 out of 1000 drug prescriptions in the first and second year of life are based on an AOM diagnosis. The direct treatment costs alone amount to over 50 million euros per year in Germany [51].

Although the disease and its treatment have been investigated in a large number of studies, the therapeutic approach in the care of patients appears to be inconsistent with regard to the duration of antibiotic therapy, if this is necessary.

1.3.2 CAP

The need for care for respiratory diseases is subject to seasonal fluctuations [52]. In 2015, 12 out of 100 of all deaths in Germany were due to respiratory diseases (International Classification of Diseases [ICD]-10: J00-J99 including C33-C34) [53]. In Europe, the total annual cost of pneumonia is estimated at €10.1 billion [46]. Costs caused solely by the diagnosis of CAP could not be identified for Germany.

General practitioners play a key role in CAP. Assuming that the ratio between treated outpatients and inpatients with CAP is 2:1, over 500,000 CAP diagnoses are to be expected in Germany every year [36,38,47].

Children with non-severe CAP can be treated as outpatients if their medical care is assured, the caregivers have been instructed on treatment measures and informed about possible warning signs (treatment failure and complications) [34]. In addition, caregivers should be asked to re-present at short notice if the patient's general condition has not improved or has even deteriorated within 48 hours. In this case, the patient’s admission to hospital should be considered.

Older patients (≥ 65 years) have a higher risk of mortality, but older age is not sufficient as the sole criterion for hospitalization. Further criteria, including (i) hypoxaemia, (ii) unstable comorbidities, (iii) complications (e.g. pleural effusion) and (iv) social factors (e.g. lack of home care) that may require hospitalization must therefore also be taken into account [33,34].

1.4 Concerns of the individual proposing the topic

The topic proposer recognizes the importance of antibiotics in the treatment of diseases, but suspects that antibiotics are often still used even when they are no longer necessary, for example because symptoms have already subsided and the patient feels healthy again. This potentially unnecessarily long treatment period could lead to long-term side effects such as the development of resistance. This gives rise to the question of whether shorter compared to longer-duration (conventional) antibiotic therapy leads to comparable treatment results.

The *ThemenCheck Medizin* staff at IQWiG developed a Health Technology Assessment (HTA) research question on the basis of this suggestion.

2 Research questions

The aims of this investigation are to

- the benefit assessment of a shorter compared to a longer (conventional) treatment period with oral antibiotics in children with AOM and children and adults with CAP,
- the determination of costs (intervention costs) and the assessment of cost effectiveness, and
- a review of ethical, social, legal, and organizational as well as environmental and climate aspects associated with the medical intervention.

3 Methods

3.1 Methods – benefit assessment

The target population of the benefit assessment consisted of patients with either AOM or CAP. Only studies in which children (up to the age of 18) were treated with antibiotics were considered for the indication AOM. Both children and adults (without age restrictions) were considered for the indication CAP. The intervention to be tested was treatment with oral antibiotics for shorter treatment periods. Administration of oral antibiotics with a longer (conventional) treatment duration was used as a comparator intervention. The comparator intervention had to be identical to the experimental intervention except for the duration of intake. Only antibiotics approved in Germany were considered.

The following patient-relevant outcomes were taken into account for the assessment:

- treatment success
- recurrence of the infectious disease
- mortality
- AEs (including hospitalization)
- health-related quality of life

Microbiological outcomes (microbiological cure rate/eradication, evidence of antibiotic resistance/evidence of multi-resistant pathogens) and treatment adherence were also considered. However, non-inferiority or superiority cannot be determined on the basis of these outcomes alone.

Only RCTs were included in the benefit assessment. There were no restrictions regarding the study duration.

Parallel to the preparation of the ThemenCheck report protocol, a systematic search for systematic reviews was carried out in the MEDLINE database (also includes the Cochrane Database of Systematic Reviews) and the HTA Database. An exploratory search was also carried out on the websites of the National Institute for Health and Care Excellence (NICE) and the Agency for Healthcare Research and Quality (AHRQ).

It was ascertained whether at least one high-quality, current systematic review existed whose information retrieval was a suitable basis for the assessment (hereinafter: basic SR).

If such a basic SR had been available, a supplementary search for studies covering the period not covered by the basic SR would have been carried out in a second step. As no basic SR could be identified, the search for studies was conducted without restricting the time period.

A systematic literature search for studies was conducted in the following databases: MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials.

The following sources of information and search techniques were additionally used: trial registries and the review of reference lists.

Relevant studies were selected by 2 persons independently from one another. Any discrepancies were resolved by discussion between them. Data were extracted into standardized tables. To assess the qualitative certainty of results, risk of bias criteria across outcomes and outcome-specific risk of bias criteria were assessed, and the risk of bias was rated as high or low in each case. The results of the individual studies were described according to outcomes.

In addition to comparing the results of the individual studies, meta-analyses (separated by infectious disease and antibiotics (groups) used) and sensitivity analyses were conducted and effect modifiers were investigated, provided that the methodological prerequisites had been met.

With regard to the clinical outcomes treatment success, recurrence of infection, mortality and AEs caused by the disease (e.g. hospitalization), it is not to be expected from a medical-biological perspective that a shorter-duration antibiotic therapy will be more effective. Due to possible advantages in terms of resistance development, treatment adherence or treatment-associated AEs or regarding treatment costs, even non-inferiority of shorter-duration antibiotic therapy can therefore mean an individual and social advantage for the outcomes mentioned [9,54]. With regard to these outcomes, the inferiority of the shortened treatment period must be at most acceptable and clinically irrelevant compared to the longer antibiotic therapy duration [55]. The non-inferiority of shorter compared to longer-duration antibiotic therapy was therefore investigated using a predefined threshold (non-inferiority threshold), which is generally defined according to clinical and statistical criteria [55,56].

The guidelines of the European Medicines Agency (EMA) on the assessment of medical devices for the treatment of bacterial infections for AOM [57] and CAP [58] recommend 10% deviations as non-inferiority boundaries for the treatment result for both pathologies. Based on these recommendations, a maximum worse effectiveness of 10% was considered clinically acceptable for all outcomes in this ThemenCheck report. Therefore, the non-inferiority boundaries of the relative risk (RR) were set at 0.9 (positive event) and 1.1 (negative event). Accordingly, non-inferiority can only be assumed if the (pooled) 95% confidence interval (CI) is completely above an RR of 0.9 (positive event) or below an RR of 1.1 (negative event). If the 95% CI is completely below an RR of 0.9 (positive event) or above an RR of 1.1 (negative event) or intersects the non-inferiority boundary, i.e. is partly above and partly below the non-

inferiority boundary, no non-inferiority can be assumed regardless of the position of the effect estimator.

In case of several analysis dates, the EMA's guideline stipulated that the primarily considered analysis point was 5 to 10 days after the end of treatment for CAP and 1 to 2 days after the end of treatment (and possibly 14 to 21 days after the start of treatment) for AOM [57].

For each outcome, a conclusion was drawn on the evidence base for non-inferiority, with 4 levels of certainty of conclusions: There was either proof (highest certainty of conclusions), indication (moderate certainty of conclusions), hint (lowest certainty of conclusions), or none of the above. The latter was the case if either no data were available or the available data did not allow any of the other 3 conclusions to be drawn. In this case, the conclusion “There is no hint of non-inferiority” was drawn.

In addition, a test for superiority of the shorter-duration antibiotic therapy compared with the longer-duration antibiotic therapy was conducted for the outcome "AEs" in the event of non-inferiority. Supplementary outcomes were only reported as descriptive information.

Finally, the results were assessed across outcomes.

3.2 Methods – health economic assessment

To calculate intervention costs, the average resources directly required for the application of the experimental and comparator intervention were estimated. For this purpose, in addition to the experimental and comparator interventions, the services additionally associated with the intervention were taken into account. If the experimental or comparator intervention consisted of several services, all components were presented. For the services provided, wherever possible, the relevant regulated or negotiated prices were applied, e.g. from the database of the Information Centre for Specialized Medicines (Informationsstelle für Arzneispezialitäten, IFA), the German Uniform Assessment Standard (Einheitlicher Bewertungsmaßstab, EBM), the Diagnosis-Related Groups (DRG) catalogue or similar suitable listings from the pension insurance or the Federal Statistical Office. Where necessary, alternative approaches for determining the intervention costs were presented transparently. Reimbursable and non-reimbursable costs as well as copayments were listed separately.

The systematic review of health economic studies included comparative studies drawing conclusions on cost effectiveness [59], i.e. cost–effectiveness analyses, efficacy analyses, cost-utility analyses, or cost-benefit analyses (in the narrower sense). Both health economic analyses from clinical studies and health economic modelling were included [60]. If no such study types had been identified in the search, comparative health economic studies drawing conclusions on the cost of the experimental intervention and the comparator intervention, i.e. cost-cost analyses, would have been included.

The publication had to be in German or English.

The systematic review of health economic studies was not limited to studies from a specific health system or country.

- For the assessment of health economic aspects, a systematic search was conducted in the form of a focussed information retrieval in the MEDLINE and Embase databases as well as the HTA Database. Moreover, the reference lists of identified systematic reviews were screened.

The citations identified by the search were selected by one person based on the inclusion criteria. A second person assured the quality of the result.

All information necessary for the assessment was extracted from the documents on the included publications into standardized tables.

The assessment of the reporting quality of the health economic studies considered was based on the criteria of the Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022 statement) [61].

The assessment of the transferability of the results was based on the criteria of the European network for Health Technology Assessment (EUnetHTA) HTA adaptation toolkit [62].

Health economic studies were considered which drew conclusions on the cost effectiveness of the technology versus the comparator intervention.

The results of the cost-effectiveness reported in the studies and the costs reported in the studies, and the authors' conclusions were described comparatively. In doing so, quality aspects of the presented studies and their transferability to the German health care system were discussed in particular.

3.3 Methods – ethical aspects

For the information retrieval, an exploratory search was conducted in Ethics in Medicine (ETHMED), Philosopher's Index, MEDLINE and Google Scholar (search strategy in Section A10.3 in Appendix B) and the results of the benefit assessment, the health economic assessment, the assessment of social and legal aspects as well as the protocol documenting the discussion with the surveyed patients were examined for ethical arguments.

The documents were checked by one person. A second person assured the quality of the result.

"Reflective thoughts" [63], i.e. reflections on possible ethical arguments and aspects based on the knowledge of the report authors were used as an additional source of information.

During the preparation of information on ethical aspects, social and moral norms and values related to the technology of the ThemenCheck report were analysed. Information processing on ethical aspects was based on Marckmann (2015) [64]. The results were presented in tabular form.

3.4 Methods - social, legal and organizational aspects as well as environmental and climate aspects

For the examination of social, legal and organizational aspects as well as environmental and climate aspects, exploratory searches were conducted in various sources of information listed (search strategies in Section A10.3 of Appendix B) and other documents cited were examined for possible social, legal and/or organizational arguments as well as environmental and climate aspects:

- Social aspects: the MEDLINE database; interest-based sources of information (e.g. websites of interest groups); studies included in the benefit assessment; studies included in the health economic assessment; the protocol documenting the discussion with the surveyed patients
- Legal aspects: laws, regulations or directives including commentary literature using the JURIS and beck-online databases
- Organizational aspects: the databases MEDLINE, Google Scholar, AWMF guideline database; studies included in the benefit assessment; studies included in the health economic assessment; studies included in the assessment of ethical or social aspects; the protocol for documenting the discussion with the surveyed patients
- Environmental and climate aspects: the databases MEDLINE, Google Scholar, AWMF guideline database, HealthcareLCA database; the protocol documenting the discussion with the surveyed patients

The documents were checked by one person. A second person assured the quality of the result.

"Reflective thoughts" [63], i.e. reflections on possible social or organizational arguments aspects as well as environmental and climate aspects based on the knowledge of the report authors were used as an additional source of information.

All arguments and aspects necessary for information processing were extracted into tables.

Social aspects

Social and sociocultural aspects in the ThemenCheck report address the reciprocal interactions between the examination or treatment method and the social environment (e.g. distribution of resources in a society, access to technologies, patient preferences, social norms, and values).

The information processing on social aspects was based on the comprehensive conceptional framework proposed by Mozygemba in 2016 [65].

Legal aspects

Legal aspects discussed in the ThemenCheck report relate, firstly, to the legal framework in which the examination or treatment method and its assessment are embedded (e.g. marketing authorization, reimbursement status), and, secondly, to legal aspects associated with the implementation and use of the healthcare technology (e.g. autonomy of patients). Technology-related legal aspects are distinguished from patient-related ones.

The information processing on legal aspects is based on the guideline for the identification of legal aspects developed by Brönneke 2016 [66].

Organizational aspects

Organizational aspects comprise the interactions resulting from an examination or treatment method on the organization of care.

The information processing of organizational aspects followed the grid template proposed by Perleth 2014 [67] for the assessment of the organizational consequences of examination and treatment methods.

Environmental and climate aspects

Environmental and climate aspects include the impact that health technologies have on the environment, for example due to Co_2 emissions during production and transport, due to toxic substances (especially during the manufacturing process) or due to waste (e.g. when disposing of the product or packaging materials). In addition, the development of antibiotic resistance can have an impact on the environment, for example through the transfer of resistant bacteria via human faeces.

The information processing included a descriptive presentation of possible environmental and climate aspects

- on greenhouse gas emissions (e.g. during production, use and disposal, during transport),
- on toxic substances (e.g. metabolic byproducts),

- on waste management (e.g. recyclability, amount of waste, improper disposal of drugs)

as well as, if applicable, on other aspects (e.g. antibiotic resistance).

3.5 Interviews with affected people

Five patients were involved in order to gain an impression of how patients (or their relatives) experience the disease, the treatment experiences they have had, and what they would like from treatment.

A total of 2 patients (one adult and one adolescent) were surveyed in a one-on-one interview using an interview guide. The impressions and experiences reported by the patients were used for the preparation of the report (especially for the definition of patient-relevant outcomes, but also for the ethical, social, legal, and organizational aspects).

4 Results: Benefit assessment

4.1 Results of the comprehensive information retrieval

No systematic reviews were rated as being current and of high quality, and none were taken into account as a basic systematic review for the identification of primary studies.

Information retrieval from bibliographical databases, trial registries and other search techniques yielded a total of 19 RCTs (22 publications) that were relevant to the research questions and met the inclusion criteria. Of these, 12 studies (12 publications) related to the indication AOM and 7 studies (10 publications) to the indication CAP. One ongoing study [68] was identified for the indication CAP.

The search strategies for bibliographic databases and trial registries are found in the Appendix. The most recent search was conducted on 6 February 2024.

Table 1: Study pool of the benefit assessment (multipage table)

Study	**Available documents**		
	Full publication (in scientific journals)	**Registry entry**	**Other documents**
AOM - children			
2 vs. 7 days penicillin V			
Meistrup-Larsen (1983)	Yes [69]	No	No
5 vs. 10 days penicillin V			
Ingvarsson (1982)	Yes [70]	No	No
3 vs. 10 days amoxicillin			
Chaput de Saintonge (1982)	Yes [71]	No	No
10 vs. 20 days amoxicillin			
Mandel (1995)	Yes [72]	No	No
5 vs. 10 days amoxicillin -clavulanic acid			
Hoberman (1997)	Yes [73]	No	No
Cohen (1998)	Yes [74]	No	No
Hoberman (2016)	Yes [75]	Yes [NCT01511107] [76]	No
3 vs. 7 days first-generation cephalosporin (cefaclor)			
Jones (1986)	Yes [77]	No	No
5 vs. 10 days first generation cephalosporin (cefaclor)			
Hendrickse (1988)	Yes [78]	No	No
5 vs. 10 days second-generation cephalosporin (cefuroxime)			
Gooch (1996)	Yes [79]	No	No
5 vs. 10 days third-generation cephalosporin (cefixime, cefpodoxime)			
Adam (2000)	Yes [80]	No	No
Cohen (2000)	Yes [81]	No	No

Table 1: Study pool of the benefit assessment (multipage table)

Study	Available documents		
	Full publication (in scientific journals)	**Registry entry**	**Other documents**
CAP – children			
3 vs. 5 days amoxicillin			
MASCOT (2002)	Yes [82]	No	No
ISCAP (2004)	Yes [83]	No	No
Ginsburg (2020) Ginsburg (2022)	Yes [84] yes [86]	Yes [NCT02678195] [85]	1 study (2 publications)
3 vs. 7 days amoxicillin			
Bielicki (2021) Barratt (2021)	Yes [87] yes [89]	Yes [ISRCTN76888927] [88]	1 study (2 publications)
3 vs. 10 days amoxicillin			
Greenberg (2014) – 1[a]	Yes [90]	Yes [ISRCTN59218653] [91]	No
5 vs. 10 days amoxicillin			
Greenberg (2014) – 2[a]	Yes [90]	Yes [ISRCTN59218653] [91]	No
Pernica (2021)	Yes [92]	Yes [NCT02380352] [93]	No
Williams (2022) Pettigrew (2022)	Yes [94] yes [96]	Yes [NCT02891915] [95]	1 study (2 publications)

a. Greenberg (2014) consisted of 2 independent phases, the first investigated a treatment duration of 3 days of amoxicillin, the second phase a treatment duration of 5 days of amoxicillin, in each case against 10 days of amoxicillin control.

Abbreviations: ***ISCAP***: Indian Study for CAP; ***MASCOT***: Pakistan Multicentre Amoxicillin Short Course Therapy; ***vs***: versus

4.2 Characteristics of the studies included in the assessment

4.2.1 AOM

Table 1 shows the relevant study pool for the AOM indication stratified by the antibiotic used (penicillin V [69,70], amoxicillin [71,72], amoxicillin clavulanic acid [73-75], first-generation cephalosporins (cefaclor [77,78]), second-generation cephalosporins (cefuroxime [79]) and third-generation cephalosporins (cefixime [80], cefpodoxime [81])) and the compared antibiotic therapy durations (2 vs. 7 days [69], 3 vs. 7 days [77], 3 vs. 10 days [71], 5 vs. 10 days [70,73-75,78-81], 10 vs. 20 days [72]). Three further studies investigating the antibiotics cefprozil [97] and ceftibuten [98,99] were excluded due to the lack of marketing authorization of these antibiotics in Germany. The results of these studies are discussed in Section 8.3. The 12 studies included comprised a total of 3409 randomized participants. All studies were conducted in Europe (n=7) or North America (n=5). The oldest study began with recruitment

in 1977 [70]. With the exception of one study that ended recruitment in 2015 [75], the studies were ended before the year 2000.

The lower age limit of the study participants ranged between 1 month [78] and 3 years [77] (2 studies do not specify a lower age limit [74,81]), the upper age limit between just under 2 years [75] and 14 years [80]. In the majority of RCTs (n=11), the diagnosis of AOM was based on typical findings from otoscopies and potentially additional pain (n=10). Important exclusion criteria in the studies were allergies/intolerance to the antibiotic class (n=10), previous treatment with antibiotics within the last 3 to 30 days (n=10), history of AOM (n=3, various criteria and time periods mentioned) or other severe concomitant diseases (n=9, e.g. pneumonia, tonsillitis, craniofacial anomaly or immunodeficiency). Moreover, 7 studies excluded patients with eardrum perforation, and 3 studies excluded patients with tympanostomy tubes.

The outcomes treatment success (n=9), recurrence (n=10), AEs (n=8), treatment adherence (n=4) and microbiological outcomes (n=4) were reported. Data on mortality could also be derived from 2 studies. Data on health-related quality of life, severe AEs or hospitalization were not reported in any study. The analysis dates varied between the studies and the outcomes. In 7 studies, the analysis date for the outcome treatment success was shortly after the end of treatment, 5 studies (additionally) reported a later analysis date of up to 42 days after the start of treatment, in which recurrence was then included as treatment failure. The analysis periods for recurrence also differed significantly, from 14 days to 18 months. In 3 studies, a distinction was also made between relapse (up to Day 14) and recurrence (from day 14) [74,78,81].

Detailed information on the study characteristics including the doses of antibiotics used, detailed inclusion and exclusion criteria and information on the characteristics of the patients in the individual study arms can be found in Table 12, Table 14 and Table 15 in the ThemenCheck details in Section A3.2.1.1 of the full report.

Penicillin V

Two studies investigated penicillin V. One placebo-controlled study compared a treatment duration of 2 vs. 7 days [69] and the other study (without placebo) compared 5 vs. 10 days [70]. No additional medication other than acetylsalicylic acid (ASA) was allowed in the study that compared 2 vs. 7 days [69]. The study that compared 5 vs. 10 days [70] consisted of 2 phases. Only the second phase investigated penicillin V at the same dosage and was included.

Amoxicillin

Two placebo-controlled studies investigated amoxicillin as an antibiotic, 3 vs. 10 days [71] and 10 vs. 20 days [72]. The study comparing 10 vs. 20 days also had a third study arm, which investigated the antibiotic amoxicillin-clavulanic acid for 10 days, but this was not included

here due to the comparison of different drugs. In addition, in this study it was unclear for a small proportion (n=19) of the participants in these study arms whether they were outpatients or inpatients [72]. As this corresponded to less than 20% of the randomized participants in the study arms under consideration, the study was nevertheless included.

Amoxicillin-clavulanic acid

Three studies investigated 5 vs. 10 days of amoxicillin-clavulanic acid – 2 studies were placebo-controlled [74,75], 1 study was conducted without placebo [73]. Hoberman (1997) [73] additionally investigated a third study arm, in which the focus was on different dosages and which was therefore not included in this report. In Hoberman (2016), only patients who had received at least 2 doses of pneumococcal conjugate vaccine were included [75].

First-generation cephalosporins (cefaclor)

Two placebo-controlled studies investigated cefaclor, 3 vs. 7 days [77] and 5 vs. 10 days [78].

Second-generation cephalosporins (cefuroxime)

Cefuroxime was investigated in 1 study by Gooch (1996) comparing 5 vs. 10 days [79]. A third study arm, in which amoxicillin-clavulanic acid was administered for 10 days, was not included here due to the comparison of different drugs. However, as the analysis of the outcomes treatment success and recurrence in the relevant study arms was based on < 70% of the patients included, the study was not included in the derivation of the evidence base for these outcomes.

Third-generation cephalosporins (cefixime, cefpodoxime)

Two studies used a third-generation cephalosporin: The study by Adam (2000) investigated cefixime 5 vs. 10 days [80] and the study by Cohen (2000) investigated cefpodoxime 5 vs. 10 days [81].

4.2.2 CAP

Children

Table 2 shows the relevant study pool for the indication CAP. Seven studies with 10 publications investigated CAP in children [82-84,86,87,89,90,92,94,96]. A total of 8590 patients were randomized in the studies. All of these studies were placebo-controlled and used amoxicillin as the antibiotic. In the study by Williams (2022), amoxicillin-clavulanic acid (5%) and cefdinir (4%) were used in addition to amoxicillin without a separate analysis on these antibiotics [94]. As these drugs were administered to < 20% of the study participants, these studies were nevertheless included and analysed together with the studies on amoxicillin. Three studies investigated 3 vs. 5 days [82-84], 1 study investigated 3 vs. 7 days [89], 2 studies investigated 5 vs. 10 days [92,94] and 1 study investigated both 3 vs. 10 days in the first study phase and 5 vs. 10 days in the second study phase [90]. These study phases

were conducted independently of each other and were considered separately in the benefit assessment.

Three studies were conducted in low income and lower middle-income countries (Pakistan [82], India [83], Malawi [84]) and 4 studies were conducted in upper middle-income countries (UK/Ireland [89], Israel [90], Canada [92], USA [94]). The oldest study started recruitment in October 1999 [82], while the most recent studies ended recruitment in December 2019 [92,94]. The lower age limit of the included children with CAP was 2 months [82-84] or 6 months [87,90,92,94], the upper age limit between just under 5 years [82-84,90] and 10 years [92] (1 study only stated the upper limit as weight < 24 kg [89]).

In 4 studies, the diagnosis was based solely on clinical signs such as cough, increased respiratory rate, fever or chest wall retractions [82-84,89]. In 2 studies, an abnormal X-ray image was a prerequisite in addition to clinical signs [90,92]. The study by Williams (2022) only recruited children who had already been diagnosed and started antibiotic therapy (which was included in the treatment duration of 5 or 10 days), without providing further details on the diagnosis [94]. Important exclusion criteria in the studies were severe pneumonia or complications (n=7), severe concomitant diseases (n=5), chronic diseases (n=6), hospitalization within the last 7 days to 2 months (n=4), pretreatment with antibiotics within the last 2 to 14 days (n=5) and known allergies to the antibiotic class (n=6). The study by Bielicki (2021) also included a proportion > 20% of patients who had initially required inpatient treatment, but provided a stratified analysis for children treated exclusively as outpatients for the outcome treatment success/treatment failure, for which the study was then also taken into account [89]. This study could also be taken into account for the mortality outcome, as there were no deaths overall [87]. The study by Ginsburg (2020) monitored the patients for 2 days in a hospital. This study was nevertheless included [84] as the monitoring was only carried out for safety reasons and without special therapy, and severe pneumonia, complications and severe concomitant diseases were exclusion criteria.

The outcomes treatment success (n=7), recurrence (n=5), mortality (n=7), (severe) AEs (n=6, including hospitalization), treatment adherence (n=4) and microbiological outcomes (n=1) were reported in a usable way. Data on health-related quality of life were not reported in any of the studies. In 5 studies, the analysis date for the outcome treatment success was immediately after the end of treatment, 6 studies (additionally) reported an analysis date of up to 28 days after the start of treatment, in which recurrence was then included as treatment failure. The analysis dates for recurrence also differed and varied between 14 and 35 days after the start of treatment. Adverse events were recorded up to the last analysis date.

Detailed information on the study characteristics including the doses of antibiotics used, detailed inclusion and exclusion criteria and information on the characteristics of the patients

in the individual study arms can be found in Table 16, Table 18 and Table 19 in the ThemenCheck details in Section A3.2.1.2 of the full report.

Adults

For the comparison of shorter with longer-duration antibiotic therapy for CAP in adults, no studies were identified that met the inclusion criteria for this report. Two further studies investigating the antibiotics telithromycin [100] and gemifloxacin [101] were excluded due to the lack of marketing authorization of these medications in Germany. The results of these studies are discussed in Section 8.3.

4.3 Overview of patient-relevant outcomes

4.3.1 AOM

Data on patient-relevant outcomes could be extracted from 12 studies [69-75,77-81]. Table 2 shows an overview of the available data on patient-relevant outcomes from the included AOM studies.

Table 2: Matrix of patient-relevant outcomes in AOM

Study	Outcomes						
				Adverse events			
	Therapy success	Recurrence	Mortality	Serious adverse events (SAEs)	Hospitalization	Adverse events (any)	Health-related quality of life
AOM - children							
2 vs. 7 days penicillin V							
Meistrup-Larsen (1983)	●	●	–	–	–	–	–
5 vs. 10 days penicillin V							
Ingvarsson (1982)[a]	●	●	–	–	–	○	–
3 vs. 10 days amoxicillin							
Chaput de Saintonge (1982)	●	●	●	–	–	●	–
10 vs. 20 days amoxicillin							
Mandel (1995)	○	●	–	–	–	●	–
5 vs. 10 days amoxicillin -clavulanic acid							
Hoberman (1997)	●	●	–	–	–	●	–
Cohen (1998)	●	●	–	–	–	●	–
Hoberman (2016)	●	●	–	–	–	●	–
3 vs. 7 days first-generation cephalosporin (cefaclor)							
Jones (1986)	○	●	●	–	–	–	–
5 vs. 10 days first-generation cephalosporin (cefaclor)							
Hendrickse (1988)	●	●	–	–	–	○	–
5 vs. 10 days second-generation cephalosporin (cefuroxime)							
Gooch (1996)	○	○	–	–	–	●	–
5 vs. 10 days third-generation cephalosporin (cefixime, cefpodoxime)							
Adam (2000)	●	x	–	–	–	●	–
Cohen (2000)	●	●	–	–	–	●	–

●: Data were reported and usable.
○: Data were reported but unusable for the benefit assessment.
x: Data were not reported despite the collection of these data being pre-specified.
-: The outcome was not surveyed and/or no data were reported.

a. Ingvarsson (1982) consisted of 2 phases. Only the second phase investigated penicillin V 5 versus 10 days at the same dosage and was considered here.

Abbreviations: ***AOM***: acute otitis media (acute inflammation of the middle ear); ***SAE***: serious adverse event

Nine of the 12 studies that investigated children with AOM reported data on the outcome treatment success in a usable form [69-71,73-75,78,80,81]. Two further studies only reported this outcome in a non-usable form (the studies only reported on the period until the disappearance of individual symptoms [77] or treatment failure at a time when both the intervention and the control group were still receiving antibiotics [72]). The results of the study by Gooch (1996) were not used to derive the evidence base for this outcome because the number of dropouts was too high (n=157; 32.9%) [79].

Ten of the 12 studies reported data on the outcome recurrence in a usable form [69-75,77,78,81]. The observed analysis date differed significantly in some cases (see Section A3.3.2.2 of the full report). One further study reports no data on this outcome despite mentioning recurrence as an outcome in the methods section [80]. The results of the study by Gooch (1996) were not used to derive the evidence base because the number of dropouts for this outcome was too high [79].

Only in 2 of the 12 studies could a conclusion on mortality be derived from the data on AEs [71,77].

AEs were reported in 8 of 12 studies in a usable form [71-75,79-81]. Three of these studies also reported dropouts due to AEs [74,75,81]. Two other studies only reported AEs across groups and were therefore not usable for this outcome [70,78], and a further 2 studies did not provide any data on this outcome [69,77]. None of the included studies reported data on severe AEs, hospitalization or health-related quality of life.

4.3.2 CAP

Data on patient-relevant outcomes could be extracted from 7 studies [82-84,87,90,92,94]. Table 2 shows an overview of the data available on patient-relevant outcomes from the included CAP studies.

Table 3: Matrix of patient-relevant outcomes in CAP

Study	Outcomes						
				Adverse events			
	Therapy success	Recurrence	Mortality	Serious adverse events (SAEs)	Hospitalization	Adverse events (other)	Health-related quality of life
CAP – children							
3 vs. 5 days amoxicillin							
MASCOT* (2002)	●	●	●	●	–	●	–
ISCAP (2004)	●	●	●	●	●	○	–
Ginsburg (2020) / Ginsburg (2022)	●	●	●	●	–	●	–
3 vs. 7 days amoxicillin							
Bielicki (2021) / Barratt (2021) (CAP-IT-RCT)	●	–	●	○	○	○	–
3 vs. 10 days amoxicillin							
Greenberg (2014) – 1[a]	●	x	●	–	●	–	–
5 vs. 10 days amoxicillin							
Greenberg (2014) – 2[a]	●	●	●	–	–	–	–
Pernica (2021)	●	●	●	●	○	○	–
Williams (2022) / Pettigrew (2022) (SCOUT-CAP study)	●	–	●	●	●	●	–

●: Data were reported and usable.
○: Data were reported but unusable for the benefit assessment.
x: Data were not reported despite the collection of these data being pre-specified.
-: The outcome was not recorded and/or not reported.

a. Greenberg (2014) consisted of 2 independently conducted phases. The first one investigated a treatment duration of 3 days of amoxicillin, the second phase a treatment duration of 5 days of amoxicillin, each compared with 10 days of amoxicillin control.

Abbreviations: AE: adverse event; ***CAP*****:** community-acquired pneumonia; ***CAP-IT***: CAP: a protocol for a randomized controlled trial; ***ISCAP***: Indian Study for CAP, ***MASCOT***: Pakistan Multicentre Amoxicillin Short Course Therapy; ***SCOUT-CAP***: Short-Course Outpatient Therapy of Community-Acquired Pneumonia; ***SAE***: serious adverse event

All 7 studies reported data on treatment success.

Recurrence was described in 5 studies [82-84,92] (in the study by Greenberg [2014], however, despite being mentioned in the methods section, only in the second study phase [90]). Two studies did not report this outcome [87,94].

Five studies reported on mortality [82-84,87,94], and in 2 further studies a conclusion on mortality could be derived from data on AEs [90,92].

AEs were reported very heterogeneously. Five studies provided usable data on severe AEs [82-84,92,94] and 3 studies on other AEs [82,84,94]. ISCAP (2004) only reported comparable rates of AEs without giving numbers [83], and Pernica (2021) only reported days with AEs, so these studies were not usable for the benefit assessment for this outcome [92]. Hospitalization was only reported in a usable form in ISCAP (2004), Williams (2022) and Greenberg (2014) (in the first study phase) [83,90,94]. In the study by Ginsburg (2020), hospitalization was also explicitly included in the operationalization of severe AEs, but not listed separately [84]. In the study by Bielicki (2021), the data on AEs were not usable because there were too many initially hospitalized patients in the study population and the result was not listed in a stratified manner [87].

None of the studies reported data on health-related quality of life.

4.4 Assessment of the risk of bias of the results

4.4.1 AOM

Risk of bias across outcomes

Table 20 in the ThemenCheck details in Section A3.2.2 of the full report provides a detailed overview of the risk of bias across outcomes. Although both patients and treating physicians were blinded in 10 studies, the risk of bias for the studies on AOM in children was only rated as low across outcomes for the study by Hoberman (2016) [75], and was rated as high for the other 11 studies [69-74,77-81]. This was mainly due to the lack of description of the random sequence generation (n=9) and the lack of description of the group allocation concealment (n=9). For 11 studies, study protocols or trial registry entries were also lacking. In addition, in 7 studies, study discontinuations were not adequately reported.

Outcome-specific risk of bias

A detailed presentation of the outcome-specific risk of bias for the outcomes treatment success, recurrence, mortality and AEs can be found in Table 21, Table 24, Table 27 and Table 30 in the ThemenCheck details in Section A3.3 of the full report.

Hoberman (2016) found a low outcome-specific risk of bias for the outcomes treatment success and AEs. Only for the outcome recurrence there was a high outcome-specific risk of bias for this study. This was mainly due to the fact that the ITT (intention to treat) principle

was not adequately implemented here, as less than 90% of the included study participants were considered for this outcome recording and the difference in study discontinuations between the study arms was > 5 percentage points. In addition, an analysis date for recurrence prospectively defined in the study protocol was not reported. Data on the outcome mortality were not reported in the study. In the other studies, there was also a high risk of bias for each outcome due to the high risk of bias across outcomes.

4.4.2 CAP

Risk of bias across outcomes

A detailed overview of the risk of bias across outcomes is provided in Table 20 in the ThemenCheck details in Section A3.2.2 of the full report. The risk of bias was rated as low across outcomes for 6 studies [82-84,87,92,94] and as high for 1 study [90]. The high risk of bias in the study by Greenberg (2014) was due to the fact that the trial registry entry only comprised the study design of the first study phase and changes in the definition of the primary outcome as well as additional secondary outcomes occurred in the comparison of the registry entry with the publication. In addition, the study was discontinued prematurely in both study phases without a prospectively planned interim analysis, based on knowledge of the results (first due to treatment failure, then due to study success) [90].

Outcome-specific risk of bias

A detailed presentation of the outcome-specific risk of bias for the outcomes treatment success, recurrence, mortality and AEs can be found in Table 21, Table 24, Table 27 and Table 30 in the ThemenCheck details in Section A3.3 of the full report.

For the study by Greenberg (2014), the high risk of bias across outcomes resulted in high outcome-specific risks of bias for all reported outcomes [90]. The outcome-specific risk of bias for the outcome treatment success was rated as low for the other 6 studies [82-84,87,92,94].

For the outcome recurrence, low outcome-specific risks of bias resulted for ISCAP (2004) and Pernica (2021) [83,92]. In MASCOT (2002) and Ginsburg (2020), on the other hand, there was a high outcome-specific risk of bias for the outcome recurrence [82,84]. The reason for this was that in both studies only patients with treatment success (at the earlier analysis date) were considered in the analysis for this outcome, which meant that the ITT principle was not adequately implemented for this outcome. The outcome recurrence was not reported in Bielicki (2021) and Williams (2022) [87,94].

For the results on the outcome mortality, all 6 studies with a low risk of bias across outcomes were also assessed as having a low outcome-specific risk of bias [82-84,87,92,94].

Four studies with a low risk of bias across outcomes were also rated with a low outcome-specific risk of bias for the outcome AEs [82,84,92,94]. In contrast, the outcome-specific risk

of bias for AEs was rated as high for the ISCAP (2004) study, as only part of the data was presented in a usable form [83]. Bielicki (2021) reported no data on AEs stratified by outpatient and inpatient settings [87]. An assessment of this study therefore proved to be redundant.

4.5 Results on patient-relevant outcomes

4.5.1 Results on the outcome treatment success

4.5.1.1 AOM

Nine studies reported usable data on the outcome treatment success in children with AOM [69-71,73-75,78,80,81]. Since in the study by Gooch (1996) the analysis of the outcome treatment success was based on less than 70% of the included study participants, the results of this study for this outcome were not considered for the derivation of the evidence base [79]. The studies by Mandel (1995) and Jones (1986) did not provide any usable results on the treatment success [72,77]. For a detailed presentation of the results for this outcome, please refer to Table 22 in the ThemenCheck details in Section A3.3.1.2 of the full report. The outcome treatment success is a composite outcome that was partially defined differently in the studies. The respective definitions are listed in Table 13 in the ThemenCheck details in Section A3.2.1.1 of the full report. Based on the recommendations of the EMA [57], an analysis date of approximately 1 to 2 days after the end of treatment (or 14 to 21 days after the start of treatment) was considered more relevant for AOM and prioritized for data collected on several analysis dates.

Penicillin V

2 vs. 7 days

One study (Meistrup-Larsen (1983)) compared 2 vs. 7 days of penicillin V [69]. This study was assessed as having a high outcome-specific risk of bias. There was no statistically significant difference between the 2-day treatment and the 7-day treatment (RR with 95% CI: 0.94 [0.74; 1.19]; p-value: 0.600). Since the CI intersected the non-inferiority boundary of the RR of 0.9, no hint of non-inferiority of the shorter-duration antibiotic therapy could be derived for this outcome. However, the absence of a hint of non-inferiority cannot be used to conclude an inferiority of the shorter-duration antibiotic therapy.

5 vs. 10 days

Ingvarsson (1982) compared the treatment success of 5 vs. 10 days of therapy with penicillin V [70]. This study was assessed as having a high outcome-specific risk of bias. The outcome was recorded 30 days after the start of treatment. No statistically significant difference was shown between the study arms (RR [95% CI]: 1.01 [0.88; 1.16], p = 0.859). Since the CI intersected the non-inferiority boundary of the RR of 0.9, no hint of non-inferiority of the shorter-duration antibiotic therapy could be derived for this outcome. However, the absence

of a hint of non-inferiority cannot be used to conclude an inferiority of the shorter-duration antibiotic therapy.

Amoxicillin

3 vs. 10 days

Chaput de Saintonge (1982) investigated a treatment duration of 3 days of amoxicillin vs. 10 days of amoxicillin [71]. This study was assessed as having a high outcome-specific risk of bias. Treatment success was similar in both groups at around 90% without a statistically significant difference (RR [95% CI]: 0.95 [0.83; 1.09]; p=0.459). Since the CI intersected the non-inferiority boundary of the RR of 0.9, no hint of non-inferiority of the shorter-duration antibiotic therapy could be derived for this outcome. However, the absence of a hint of non-inferiority cannot be used to conclude an inferiority of the shorter-duration antibiotic therapy.

Amoxicillin-clavulanic acid

5 vs. 10 days

Three studies compared the 5-day use of amoxicillin-clavulanic acid with a 10-day use [73-75]. Only the study by Hoberman (2016) showed a low risk of bias for this outcome [75]. This study reported a statistically significantly lower rate of treatment success in the group with shorter-duration antibiotic therapy for the period of 12 to 14 days after the start of antibiotic therapy (RR [95% CI]: 0.79 [0.71; 0.88]; p<0.001). At this time, this effect was also statistically significant in the other 2 studies (Hoberman (1997) and Cohen (1998)), both of which included a high risk of bias for this outcome (Hoberman (1997): RR [95% CI]: 0.89 [0.82; 0.97]; p=0.006; Cohen (1998): RR [95% CI]: 0.86 [0.78; 0.96]; p=0.006) [73,74]. Since the effect estimates of the 3 studies were already below the non-inferiority boundary of the RR of 0.9, no hint of non-inferiority of the shorter treatment duration could be derived for this analysis date, which was considered relevant (according to EMA recommendations [57]). However, all 3 studies showed statistically significantly worse treatment results in terms of treatment success with a 5-day antibiotic therapy compared to a 10-day therapy. A graphical representation of the studies at this analysis date can be found in Figure 3 in the ThemenCheck details in Section A3.3.1.2 of the full report. A pooled effect estimate in the form of a meta-analysis was intentionally omitted, as the estimate of the CI according to Knapp-Hartung was not informative (see Section A2.1.3 of the full report).

Data for a second, later analysis date were only available for the 2 studies with a high risk of bias for this outcome [73,74]. At this time, recurrence was included in this outcome as treatment failure. With periods of 32 to 38 days and 28 to 42 days after the start of treatment, the time points of the data recording by Hoberman (1997) and Cohen (1998) were beyond the second analysis date of 14 to 21 days after the start of treatment recommended by the EMA [57]. At this time, neither study found a statistically significant difference between the 2 treatment regimens (Hoberman (1997): RR [95% CI]: 0.97 [0.85; 1.11]; p=0.640; Cohen (1998):

RR [95% CI]: 0.92 [0.77; 1.10]; p=0.360). The pooled results of the meta-analysis also showed no statistically significant difference (RR [95% CI]: 0.95 [0.85; 1.06]. However, since the CI intersected the non-inferiority boundary of the RR of 0.9, no hint of non-inferiority of the shorter-duration antibiotic therapy could not be derived for this time point either. However, the absence of a hint of non-inferiority cannot be used here to conclude inferiority of the shorter-duration antibiotic therapy at this analysis date. The meta-analysis of the studies at this analysis date can be found in Figure 4 in the ThemenCheck details in Section A3.3.1.2 of the full report.

First-generation cephalosporin

5 vs. 10 days

Hendrickse (1988) investigated a treatment duration of 5 vs. 10 days of cefaclor and the risk of bias for this outcome was rated as high [78]. There was a statistically significantly lower rate of treatment success (81.1% vs. 93.5%) in the group with the shorter-duration antibiotic therapy (RR [95% CI]: 0.87 [0.77; 0.98]; p=0.025). As the CI intersected the non-inferiority boundary of the RR of 0.9 with this statistically significantly worse result of the shorter-duration therapy, no hint of non-inferiority of the shorter-duration antibiotic therapy could be derived for this outcome.

Third-generation cephalosporins

5 vs. 10 days

Two studies reported the comparison of 5 vs. 10 days of therapy with a third-generation cephalosporin (Adam (2000): cefixime [80]; Cohen (2000): cefpodoxime [81]). Both of them were assessed as having a high outcome-specific risk of bias. While in the study by Cohen (2000) statistically significantly fewer patients in the shorter-duration antibiotic therapy group experienced successful treatment shortly after the end of therapy (Days 12 to 14 after the start of therapy) (RR [95% CI]: 0.89 [0.82; 0.96]; p=0.004), the effect was not statistically significant in the study by Adam (Day 11 after the start of treatment) (RR [95% CI]: 0.95 [0.89; 1.01]; p=0.102). However, the meta-analysis conducted showed a statistically significantly lower rate of treatment success in the shorter-duration antibiotic therapy group for this analysis date (RR [95% CI]: 0.91 [0.86; 0.96]), which was considered more relevant (according to EMA recommendations [57]). Cohen (2000) could not demonstrate any statistically significant difference for the later analysis date on Days 28 to 42 after the start of treatment (RR [95% CI]: 0.93 [0.81; 1.07]; p=0.295). However, since the CIs intersected the non-inferiority boundary of the RR of 0.9 at both time points, no hint of non-inferiority of the shorter-duration antibiotic therapy could be derived for this outcome for either analysis date. The meta-analysis of the studies at the earlier, more relevant analysis date can be found in Figure 5 in the ThemenCheck details in Section A3.3.1.2 of the full report.

4.5.1.2 CAP

The benefit assessment for the outcome treatment success included the results of 7 studies for CAP, all of which investigated the treatment of children with amoxicillin [82-84,87,90,92,94]. For a detailed presentation of the results for this outcome, please refer to Table 23 in the ThemenCheck details in Section A3.3.1.3 of the full report. The outcome treatment success is a composite outcome that was partially defined differently in the studies. The respective definitions are listed in Table 17 in the ThemenCheck details in Section A3.2.1.2 of the full report. Based on the recommendations of the EMA [57], an analysis date of approximately 5 to 10 days after the end of treatment was considered more relevant for CAP and prioritized for data relating to several analysis dates.

Amoxicillin

3 vs. 5/7/10 days

Three studies with a low outcome-specific risk of bias by MASCOT (2002), ISCAP (2004) and Ginsburg (2020) investigated 3-day versus 5-day duration of treatment with amoxicillin [82-84], 1 study with a low outcome-specific risk of bias by Bielicki (2021) investigated an amoxicillin treatment duration of 3 vs. 7 days [87] and 1 study (Greenberg 2014) with a high outcome-specific risk of bias in the first study phase investigated 3 vs. 10 days of treatment with amoxicillin [90]. In the first Greenberg 2014 study phase, 2 (16.6%) patients in the intervention group and 5 (38.5%) patients in the control group were not included in the analysis. As the absolute difference in drop-outs is therefore minor, this study was used to derive the evidence base despite the large percentage difference in study discontinuations.

Each of the 3 studies comparing 3 days with 5 days of amoxicillin, included both an earlier (Day 5 or 6 after the start of treatment) and a later analysis date (Days 12 to 14 after the start of treatment). In the study by Bielicki (2021), only the data for the period up to 28 days after the start of treatment were reported as usable, and the analysis date in the Greenberg study (2014) was Day 10 after the start of treatment.

Following the EMA recommendations [57], the analysis date on Day (12 to) 14 was considered more relevant in the studies by MASCOT (2002), ISCAP (2004) and Ginsburg (2020) and was primarily used to assess the success of the therapy. There was no difference between the treatment groups of 3 vs. 5 days of amoxicillin in the studies by MASCOT (2002) (RR [95% CI]: 0.99 [0.95; 1.04]; p=0.698), ISCAP (2004) (RR [95% CI]: 0.99 [0.96; 1.02]; p=0.624) and Ginsburg (2020) (RR [95% CI]: 0.98 [0.96; 1.01]; p=0.159).

In the study by Bielicki (2021) (3 vs. 7 days of amoxicillin), outpatients and inpatients were analysed together. For the outcome treatment success, only the data for the period up to 28 days after the start of treatment were presented in a usable stratified form. No difference between the treatment regimens was found here and the CI was above the non-inferiority

boundary (RR [95% CI]: 1.01 [0.96; 1.08]; p=0.627). A graph also suggests that there was no relevant difference between the groups at previous time points.

Only the first phase of the study by Greenberg (2014) found a statistically significant difference between treatment with 3 vs. 10 days of amoxicillin up to Day 10 after the start of treatment (RR [95% CI]: 0.62 [0.39; 0.99]; p=0.048).

Considered together, this resulted in an RR [95% CI] of 0.99 [0.96; 1.02] with a prediction interval of 0.96 to 1.02 for the comparison of 3 days of amoxicillin therapy with 5/7/10 days of amoxicillin therapy when considering the analysis date in the studies that was considered more relevant (according to EMA recommendations [57]) (see Figure 6 in the ThemenCheck details in Section A3.3.1.3 of the full report). When considering only the studies with a low outcome-specific risk of bias, the RR [95% CI] was also 0.99 [0.96; 1.02]. The sensitivity analysis conducted without the MASCOT (2002) study due to doubts about the transferability also yielded an RR [95% CI] of 0.99 [0.95; 1.03] and a prediction interval of 0.95 to 1.03 (see Figure 9 in the ThemenCheck details in Section A3.3.1.3 of the full report).

Even at the analysis date directly following the end of treatment on Day 5 or Day 6 there was no difference between the treatment regimens, neither in MASCOT (2002) (RR [95% CI]: 0.99 [0.95; 1.03]; p=0.650), nor in ISCAP (2004) (RR [95% CI]: 1.00 [0.97; 1.02]; p=0.736) or Ginsburg (2020) (RR [95% CI]: 0.99 [0.97; 1.01]; p=0.381). The pooled result yielded an effect estimate RR [95% CI]: 0.99 [0.96; 1.02] (see Figure 7 in the ThemenCheck details in Section A3.3.1.3 of the full report). Here too, a sensitivity analysis conducted without MASCOT (2002) showed a similar result with an RR [95% CI] of 0.99 [0.98; 1.01] (see Figure 10 in the ThemenCheck details in Section A3.3.1.3 of the full report).

The CI of the pooled effect was completely above the non-inferiority boundary of the RR of 0.9 at each of the analysis dates, resulting in proof of non-inferiority of treatment with amoxicillin for 3 days compared with a longer treatment duration of 5/7/10 days in children with CAP. The transferability of the results to the German health care context was recognized in the case of a purely clinical diagnosis of CAP and is discussed in Section 8.2.2.

5 vs. 10 days

3 studies investigated a treatment duration of 5 vs. 10 days of amoxicillin in children with CAP [90,92,94]. The second phase of the study by Greenberg (2014) had a high outcome-specific risk of bias and the studies by Pernica (2021) and Williams (2022) had a low one. The study by Pernica (2021) considered an analysis date of 14 to 21 days after the start of treatment (whereby earlier time points from Day 4 after the start of treatment were also included in the definition of treatment success) [92]. No statistically significant difference was shown between the groups (RR [95% CI]: 1.02 [0.92; 1.13], p = 0.725). In Williams (2022), no difference was found both directly after the end of treatment (on Days 11 to 15 after the start

of treatment, primarily considered) and on Days 24 to 30 after the start of treatment (Days 11 to 15: RR [95% CI]: 1.00 [0.95; 1.07]; p=0.875; Days 24 to 30: RR [95% CI]: 1.00 [0.95; 1.06]; p=0.864) [94]. Greenberg (2014) also showed no difference on Day 10 after the start of treatment (RR [95% CI]: 1.00 [0.96; 1.04]; p>0.999) [90]. In all these studies, as well as in the associated joint effect estimate for the analysis date considered more relevant (according to EMA recommendations [57]) (RR [95% CI]: 1.00 [0.93; 1.08]; studies with a low risk of bias: RR [95% CI]: 1.01 [0.93; 1.09]), the CI was completely above the non-inferiority boundary of the RR of 0.9 (see Figure 8 in the ThemenCheck details in Section A3.3.1.3 of the full report)

This proved that the duration of 5-day amoxicillin therapy was not inferior to 10 days in children with CAP.

4.5.2 Results for the outcome recurrence of infection

4.5.2.1 AOM

Results of 10 studies were included in the benefit assessment on the outcome recurrence of infection in children with AOM (for Ingvarsson (1982) only the second study phase was considered) [69-75,77,78,81] with the survey periods differing significantly in some cases. While in most cases all children who underwent a follow-up examination were included in the analysis, the study by Cohen (1998) only used the children with therapy success on Days 12 to 14 as the reference group [74]. The study by Jones (1986) only mentions episodes of AOM recurrence of without providing the number of children affected [77]. Since in the study by Gooch (1996) the analysis was based on less than 70% of the included study participants, this study was not considered for the derivation of the evidence base for this outcome [79]. A detailed presentation of the results for this outcome can be found in Table 25 in the ThemenCheck details in Section A3.3.2.2 of the full report.

Penicillin V

2 vs. 7 days

Meistrup-Larsen (1983) compared the recurrence after 2 days of antibiotic therapy and 7 days of penicillin V [69]. This study was assessed as having a high outcome-specific risk of bias. There was no statistically significant difference between 2-day treatment and 7-day treatment up to Day 14 (RR [95% CI] (95% CI): 1.99 [0.50; 7.90]; p-value: 0.326). Since the CI intersected the non-inferiority boundary of the RR of 1.1, no hint of non-inferiority of the shorter-duration antibiotic therapy could be derived for this outcome. However, the absence of a hint of non-inferiority cannot be used to conclude an inferiority of the shorter-duration antibiotic therapy.

5 vs. 10 days

Ingvarsson (1982) compared the recurrence after 5 vs. 10 days of antibiotic therapy with penicillin V [70]. This study was assessed as having a high outcome-specific risk of bias. There

was no statistically significant difference between the study arms either in the period from Day 10 to 1 month after the start of treatment or up to 6 months after the start of treatment, (up to 1 month: RR [95% CI]: 1.03 [0.27; 3.95]; p=0.965; up to 6 months: RR [95% CI]: 1.08 [0.64; 1.84]; p=0.764). Since the CIs intersected the non-inferiority boundary of the RR of 1.1, no hint of non-inferiority of the shorter-duration antibiotic therapy could be derived for this outcome for either period. However, the absence of a hint of non-inferiority cannot be used to conclude an inferiority of the shorter-duration antibiotic therapy.

Amoxicillin

3 vs. 10 days

Chaput de Saintonge (1982) investigated a treatment duration of 3 days vs. 10 days of amoxicillin [71]. This study was assessed as having a high outcome-specific risk of bias. Recurrence was considered in the follow-up period up to a maximum of 18 months (median 12 months) after the start of treatment. No statistically significant difference was shown between the groups (RR [95% CI]: 1.14 [0.46; 2.87], p = 0.776). Since the CI intersected the non-inferiority boundary of the RR of 1.1, no hint of non-inferiority of the shorter-duration antibiotic therapy could be derived for this outcome. However, the absence of a hint of non-inferiority cannot be used to conclude an inferiority of the shorter-duration antibiotic therapy.

10 vs. 20 days

Mandel (1995) investigated recurrence after 10 vs. 20 days of amoxicillin therapy. This study was assessed as having a high outcome-specific risk of bias. There was no statistically significant difference between the groups either between Day 10 and Day 20 (when one group was still receiving antibiotic therapy) nor up to Day 90 after the start of therapy (Day 10-20: RR [95% CI]: 1.58 [0.39; 6.40]; p=0.524; Day 10-90: RR [95% CI]: 1.17 [0.82; 1.66]; p=0.389). Due to the limited transferability of the long treatment duration of 20 days analysed, no benefit conclusion was derived for the outcome.

Amoxicillin-clavulanic acid

5 vs. 10 days

Three studies reported recurrence of infection after 5 days of antibiotic therapy with amoxicillin-clavulanic acid compared with 10 days of therapy. All 3 studies were assessed as having a high outcome-specific risk of bias. While Hoberman (1997) and Cohen (1998) recorded recurrences from Day 10 and Day 14 after the start of treatment to Day 38 and Day 42 respectively, Hoberman (2016) recorded recurrences over the entire season of acute respiratory infections (1 October to 31 May).

In all 3 studies, there was no statistically significant increase in recurrence in the 5-day treatment group. In the study by Hoberman (1997), there were even statistically significant fewer cases of disease recurrence (RR [95% CI]: 0.61 [0.41; 0.93]; p=0.020). In the studies by

Cohen (1998) (RR [95% CI]: 0.70 [0.42; 1.19]; p=0.189) and Hoberman (2016) (RR [95% CI]: 0.91 [0.73; 1.13]; p=0.386), however, there was no statistically significant difference and the CI intersected the non-inferiority boundary of the RR of 1.1. Since no conclusive effects resulted in relation to the non-inferiority boundary of the RR of 1.1, no hint of non-inferiority of the shorter-duration antibiotic therapy could be derived for this outcome. However, the absence of a hint of non-inferiority cannot be used to conclude an inferiority of the shorter-duration antibiotic therapy. A pooled effect estimate in the form of a meta-analysis was not performed, as the CI estimate according to Knapp-Hartung was not informative. A graphical representation of the studies can be found in Figure 11 in the ThemenCheck details in Section A3.3.2.2 of the full report.

First-generation cephalosporins

3 vs. 7 days

Jones (1986) investigated a cefaclor treatment duration of 3 vs. 7 days [77]. This study was assessed as having a high outcome-specific risk of bias. Recurrence was recorded from the end of treatment until Day 42 and occurred with approximately equal frequency in both groups with 8 cases each, with no statistically significant difference (RR [95% CI]: 1.13 [0.46; 2.77]; p=0.784). Since the CI intersected the non-inferiority boundary of the RR of 1.1, no hint of non-inferiority of the shorter-duration antibiotic therapy could be derived for this outcome. However, the absence of a hint of non-inferiority cannot be used to conclude an inferiority of the shorter-duration antibiotic therapy.

5 vs. 10 days

Hendrickse (1988) investigated a cefaclor treatment duration of 5 vs. 10 days for this outcome from the end of treatment to Day 13, from Day 14 to Day 30, from Day 31 to Day 60 and from Day 61 to Day 90 after the start of antibiotic therapy [78]. This study was assessed as having a high outcome-specific risk of bias. There was no statistically significant difference in the rate of recurrence in any of the time periods (the RR values with 95% CI and p-values are shown in Table 25 in the ThemenCheck details in Section A3.3.2.2 of the full report). Since the CIs for all time periods intersected the non-inferiority boundary of the RR of 1.1, no hint of non-inferiority of the shorter antibiotic therapy duration could be derived for this outcome. However, the absence of a hint of non-inferiority cannot be used to conclude an inferiority of the shorter-duration antibiotic therapy.

Third-generation cephalosporins

5 vs. 10 days

Cohen (2000) compared antibiotic therapy with cefpodoxime for 5 vs. 10 days [81]. This study was assessed as having a high outcome-specific risk of bias. Recurrence was recorded up to 42 days after the start of antibiotic therapy and a comparable number of cases occurred in

both groups without a statistically significant difference (RR [95% CI]: 0.90 [0.54; 1.49]; p=0.684). Since the CI intersected the non-inferiority boundary of the RR of 1.1, no hint of non-inferiority of the shorter-duration antibiotic therapy could be derived for this outcome. However, the absence of a hint of non-inferiority cannot be used to conclude an inferiority of the shorter-duration antibiotic therapy.

4.5.2.2 CAP

Recurrence of the infection was described in 5 studies [82-84,92] (in the study by Greenberg (2014) only in the second study phase [90]). While in most cases all participants who received a follow-up examination were included in the analysis, the studies by MASCOT (2002) and Ginsburg (2020) used only the children with treatment success on Day 5 and Day 6 respectively as the reference group [82,84]. A detailed presentation of the results for this outcome can be found in Table 26 in the ThemenCheck details in Section A3.3.2.3 of the full report.

Amoxicillin

3 vs. 5/7/10 days

Three studies yielded recurrence data on 3 days of amoxicillin compared with longer therapy in children with CAP. All 3 studies used 5 days of amoxicillin as the control group and recorded recurrence from the end of treatment to Day 14 after the start of therapy. The study by ISCAP (2004) had a low outcome-specific risk of bias and showed no statistically significant difference between the groups (RR [95% CI]: 1.21 [0.83; 1.75]; p=0.325). Both the studies by MASCOT (2002) and Greenberg (2020) had high outcome-specific risks of bias, but here as well, there were no statistically significant differences (MASCOT (2002): RR [95% CI]: 0.93 [0.43; 2.03]; p=0.860; Ginsburg (2020): RR [95% CI]: 1.18 [0.88; 1.57]; p=0.276). There was also no statistically significant effect in the joint effect estimate of the 3 studies (RR [95% CI]: 1.16 [0.72; 1.89]). The meta-analysis is represented in Figure 12 in the ThemenCheck details in Section A3.3.2.3 of the full report. Since the CI intersected the non-inferiority boundary of the RR of 1.1, no hint of non-inferiority of the shorter-duration antibiotic therapy could be derived for this outcome. However, the absence of a hint of non-inferiority cannot be used to conclude an inferiority of the shorter-duration antibiotic therapy.

5 vs. 10 days

Two studies reported data on recurrence after a 5-day compared to a 10-day amoxicillin therapy in children with CAP [90,92]. The study by Pernica (2021) had a low risk of bias for this outcome, while the second study phase by Greenberg (2014) had a high risk of bias. Pernica (2021) did not show any statistically significant difference between the treatment regimens up to Day 30 after the start of treatment (RR [95% CI]: 0.89 [0.41; 1.94]; p=0.766) and Greenberg (2014) did not observe a single case of recurrence up to Day 35 after the start of treatment (calculation of RR and CI not possible). Since the non-inferiority threshold of the RR

of 1.1 was intersected, no hint of non-inferiority of the shorter-duration antibiotic therapy could be derived for this outcome. However, the absence of a hint of non-inferiority cannot be used to conclude an inferiority of the shorter-duration antibiotic therapy.

4.5.3 Results on the outcome mortality

4.5.3.1 AOM

Table 28 in the ThemenCheck details in Section A3.3.3.2 of the full report shows the study results on the outcome mortality. Ten of the included studies did not provide any information on deaths and did not allow any conclusions on deaths [69,70,72-75,78-81]. Only from the studies by Chaput de Saintonge (1982), which investigated 3 vs. 10 days of amoxicillin [71], and by Jones (1986), which investigated 3 vs. 7 days of cefaclor [77], could it be deduced that there were no deaths during the intervention period. Both studies were assessed as having a high outcome-specific risk of bias. Overall, no hint of non-inferiority of the treatment options could be derived. However, the absence of a hint of non-inferiority cannot be used to conclude an inferiority of the shorter-duration antibiotic therapy.

4.5.3.2 CAP

Table 29 in the ThemenCheck details in Section A3.3.3.3 of the full report shows the study results on the outcome mortality. A total of 5 studies explicitly reported results on mortality [82-84,87,94], and 2 other studies allowed the derivation of mortality data [90,92]. Deaths occurred in 2 studies. Both studies compared a treatment duration of 3 days with 5 days of amoxicillin [82,84] and were assessed as having a low outcome-specific risk of bias. In the MASCOT (2002) study, one child died in the longer-duration therapy group (RR [95% CI]: 0.33 [0.01; 8.17]; p=0.501) [82] and in the study by Ginsburg (2020), one child died in the shorter-duration therapy group and two children died in the longer therapy group (RR [95% CI]: 0.50 [0.05; 5.53]; p=0.573) [84]. The pooled effect estimate for the RR [95% CI] was 0.43 [0.06; 2.91]. The meta-analysis is presented in Figure 13 in the ThemenCheck details in Section A3.3.3.3 of the full report.

No deaths occurred in the other 5 studies comparing treatment durations with amoxicillin of 3 vs. 5 days [83], 3 vs. 7 days [87], 3 vs. 10 days [90], or 5 vs. 10 days [90,92,94]. Due to the rare occurrence of deaths within the reported studies and the CI of the pooled result, which intersected the non-inferiority boundary of the RR of 1.1, no hint of non-inferiority of the shorter-duration therapy could be derived for the outcome mortality for any comparison. However, the absence of a hint of non-inferiority cannot be used to conclude an inferiority of the shorter-duration antibiotic therapy.

4.5.4 Results for the outcome AEs

The outcome AEs was reported very differently in the various studies. Some of the AEs were stratified according to their severity, with the definition of severe AEs varying widely. In some cases, study discontinuations due to AEs were added to the severe AEs, in others they were reported separately. There were also differences in whether only medication-associated AEs or all AEs were recorded. This was unclear in some studies. The individual AEs were also grouped and recorded differently in the studies.

The studies reported data on deaths, hospitalizations and outpatient visits together with AE. As some of these outcomes were described as being related to side effects, they were also considered here. Only the data on mortality were excluded (if necessary) and are reported as a separate outcome (see Section 4.5.3).

4.5.4.1 AOM

Eight studies reported AEs in a usable manner [71-75,79-81]. Two studies did not report AEs at all [69,77] and 2 studies reported AEs only collectively across all groups (and study phases) [70,78]. For a detailed presentation of the results for this outcome, please refer to Table 31 in the ThemenCheck details in Section A3.3.4.2 of the full report.

Amoxicillin

3 vs. 10 days

Chaput de Saintonge (1982) reported any side effects occurring in the first 10 days after starting antibiotic therapy (3 vs. 10 days of amoxicillin) [71]. This study was assessed as having a high outcome-specific risk of bias. The difference between the groups was not statistically significant (RR [95% CI]: 4.00 [0.47; 34.31]; p=0.206). Since the CI intersected the non-inferiority boundary of the RR of 1.1, no hint of non-inferiority of the shorter-duration antibiotic therapy could be derived for this outcome. However, the absence of a hint of non-inferiority cannot be used to conclude an inferiority of the shorter-duration antibiotic therapy.

10 vs. 20 days

Mandel (1995) investigated 10 vs. 20 days of treatment with amoxicillin [72]. In doing so, the side effects were reported from Day 11 to Day 20 after the start of antibiotic therapy. This study was assessed as having a high outcome-specific risk of bias. Overall, in this study, statistically significant more AEs occurred in the group with shorter-duration antibiotic therapy than in the one with longer antibiotic therapy (RR [95% CI]: 5.34 [1.21; 23.49]; p=0.027). However, the differences were not statistically significant for the individual side effects (diarrhoea, nausea/vomiting, rash, appetite loss, constipation) (the RR values with 95% CI and p-values are shown in Table 31 in the ThemenCheck details in Section A3.3.4.2 of the

full report). Due to the limited transferability of the investigated long treatment duration of 20 days, no benefit conclusion was derived for this outcome.

Amoxicillin-clavulanic acid

5 vs. 10 days

All 3 studies comparing 5 vs. 10 days of amoxicillin-clavulanic acid also provided information on AEs [73-75]. The study by Hoberman (2016) had a low outcome-specific risk of bias, while the studies by Hoberman (1997) and Cohen (1998) had a high one. Only the study by Cohen (1998) reported a total number of patients with AEs and study discontinuations due to AEs, which were not subject to statistically significant differences between the treatment regimens (total AEs: RR [95% CI]: 1.06 [0.78; 1.44]; p=0.722; study discontinuations due to AEs: RR [95% CI]: 1.94 [0.59; 6.33]; p=0.273). Diarrhoea and rash (in Hoberman (2016) only skin rash in the nappy region) were reported in all 3 studies (the RR values with 95% CI and p-values are shown in Table 31 in the ThemenCheck details in Section A3.3.4.2 of the full report). None of the studies showed a statistically significant difference between the shorter and longer treatment duration. A meta-analysis of the results on diarrhoea (RR [95% CI]: 0.92 [0.60; 1.40]) and a graphical representation of the results on skin rash can be found in Figure 14 and Figure 15 in the ThemenCheck details in Section A3.3.4.2. A meta-analysis of the studies on the skin rash AE was not conducted, as the estimate of the CI according to Knapp-Hartung was not informative. Hoberman (1997) additionally reported vomiting, which also showed no statistically significant difference between the treatment groups (RR [95% CI]: 0.71 [0.41; 1.21]; p=0.210). A hint of non-inferiority of the shorter-duration antibiotic therapy could not be derived for this outcome since the CIs intersected the non-inferiority boundary of the RR of 1.1. However, the absence of a hint of non-inferiority cannot be used to conclude an inferiority of the shorter-duration antibiotic therapy.

Second-generation cephalosporins

5 vs. 10 days

Gooch (1996) investigated a treatment duration of 5 vs. 10 days of cefuroxime [79]. This study was assessed as having a high outcome-specific risk of bias. Overall, there was no statistically significant difference in drug-associated AEs between the 2 study arms up to Day 28 (RR [95% CI]: 1.26 [0.85; 1.86]; p=0.245). For the individual side effects (diarrhoea/soft stools, vomiting, other), the differences were also not statistically significant (the RR values with 95% CI and p-values are shown in Table 31 in the ThemenCheck details in Section A3.3.4.2 of the full report). There was also no statistically significant difference for the side effects that led to study discontinuation (RR [95% CI]: 1.58 [0.67; 3.74]; p=0.300). A hint of non-inferiority of the shorter-duration antibiotic therapy could not be derived for this outcome since the CIs intersected the non-inferiority boundary of the RR of 1.1. However, the absence of a hint of

non-inferiority cannot be used to conclude an inferiority of the shorter-duration antibiotic therapy.

Third-generation cephalosporins

5 vs. 10 days

The study by Adam (2000) observed AEs from cefixime up to Day 28 [80], and Cohen (2000) observed AEs from cefpodoxime up to Day 28 [81]. Both studies were assessed as having a high outcome-specific risk of bias. In both studies, the overall assessment of AEs did not reveal any statistically significant difference between the treatment groups (Adam (2000): RR [95% CI]: 1.97 [0.61; 6.34]; p=0.258; Cohen (2000): RR [95% CI]: 0.72 [0.45; 1.14]; p=0.162). There was also no statistically significant difference in the meta-analysis (RR [95% CI]: 0.84 [0.55; 1.29]). The meta-analysis of the AEs can be found in Figure 16 in the ThemenCheck details in Section A3.3.4.2 of the full report. There were no statistically significant differences between the treatment groups, even when taking into account study discontinuations due to ÄEs in Cohen (2000) (RR [95% CI]: 0.99 [0.14; 6.97]; p=0.993) or the affected body systems (gastrointestinal tract, mind, urinary tract, other) in Adam (2000) (the RR values with 95% CI and p-values are listed in Table 31 in the ThemenCheck details in Section A3.3.4.2 of the full report). A hint of non-inferiority of the shorter-duration antibiotic therapy could not be derived for this outcome since the CIs intersected the non-inferiority boundary of the RR of 1.1. However, the absence of a hint of non-inferiority cannot be used to conclude an inferiority of the shorter-duration antibiotic therapy.

4.5.4.2 CAP

Five studies reported data on AEs [82-84,87,90,92,94]. One study reported study discontinuations due to AEs [92]. Three studies reported data on hospitalization [83,90,94] and a further study reported hospitalization only in aggregated form across both study arms and was therefore not usable [92]. One study also reported outpatient visits [94]. The study by Bielicki (2021) reported AEs in a manner not stratified by outpatient and inpatient treatment and was therefore not usable for this outcome [87]. A detailed list on this outcome can be found in Table 32 in the ThemenCheck details in Section A3.3.4.3 of the full report.

Amoxicillin

3 days versus 5/7/10 days

Three studies comparing 3 days of amoxicillin therapy with a longer treatment duration provided data on severe AEs, 2 with a low outcome-specific risk of bias [82,84], 1 with a high outcome-specific risk of bias [83]. The studies MASCOT (2002) and ISCAP (2004) each reported that no severe AEs had occurred (one death in MASCOT (2002) was not included here by the study authors). Severe AEs only occurred in the study by Ginsburg (2020), and there was no

statistically significant difference between the 2 treatment groups after deaths were factored out (RR [95% CI]: 1.43 [0.73; 2.83]; p=0.298).

Other AEs were only reported in a usable manner in the studies by MASCOT (2002) and Ginsburg (2020), each with a low outcome-specific risk of bias [82,84]. MASCOT (2002) was unable to determine a statistically significant difference between the 2 treatment groups (RR [95% CI]: 0.86 [0.68; 1.09]; p=0.223) and the individual symptoms were only reported jointly across both groups. In contrast, Ginsburg (2020) was able to demonstrate a statistically significant reduction in other AEs in favour of the shorter-duration therapy duration (RR [95% CI]: 0.87 [0.78; 0.97]; p=0.016). In particular, gastrointestinal infections (RR [95% CI]: 0.79 [0.66; 0.95]; p=0.013) and skin rash (RR [95% CI]: 0.64 [0.41; 1.00]; p=0.048) occurred less frequently in the shorter-duration antibiotic therapy group. The meta-analysis conducted also showed a statistically significant reduction in other AEs during a 3-day treatment period (RR [95% CI]: 0.87 [0.78; 0.96]). The conducted meta-analysis is shown in Figure 17 in the ThemenCheck details in Section A3.3.4.3 of the full report.

Only 2 studies with a high outcome-specific risk of bias reported hospitalization [83,90]. Neither ISCAP (2004) nor Greenberg (2014) were able to determine a statistically significant difference between the treatment regimens (ISCAP (2014): RR [95% CI]: 0.78 [0.42; 1.44]; p=0.428; Greenberg (2014): RR [95% CI]: 0.36 [0.02; 8.05]; p=0.519). The pooled result was also not statistically significant (RR [95% CI]: 0.76 [0.42; 1.38]). The meta-analysis on hospitalization is shown in Figure 18 in the ThemenCheck details in Section A3.3.4.3 of the full report.

Overall, this not only demonstrated proof of non-inferiority for other AEs (the overall pooled 95% CI was below the non-inferiority boundary of the RR of 1.1), but also proof of superiority (the overall pooled 95% CI was below an RR of 1.0) of 3-day versus 5-day antibiotic therapy with amoxicillin. However, no hint of non-inferiority of the shorter-duration antibiotic therapy could be derived for severe AEs and hospitalization, although the absence of a hint of non-inferiority cannot be used to conclude an inferiority of the shorter-duration antibiotic therapy.

5 vs. 10 days

The studies by Pernica (2021) and Williams (2022) reported severe AEs [92,94], each with a low outcome-specific risk of bias. Williams (2022) reported this in 2 periods – the first period from Day 5 to Day 15 after the start of treatment, and the second period additionally until Day 30 after the start of treatment. There was no statistically significant difference in severe AEs between the 2 groups in any period (up to Day 15: RR [95% CI]: 0.51 [0.05; 5.53]; p=0.576; up to Day 30 including events up to Day 15: RR [95% CI]: 1.01 [0.26; 3.98]; p=0.988). In the study by Pernica (2021), no severe AEs occurred up to Day 30.

Study discontinuations due to AEs were only reported by Pernica (2021) [92]. Here as well, no statistically significant difference was shown between the treatment groups (RR [95% CI]: 0.25 [0.03; 2.22], p = 0.215). Hospitalization was only reported jointly across both groups in Pernica (2021) and did not occur in Williams (2022). Outpatient clinic visits were reported by Williams (2022) and were not subject to statistically significant differences in the 2 analysis periods (up to Day 15: RR [95% CI]: 2.02 [0.18; 22.10]; p=0.564; up to Day 30 including events up to Day 15: RR [95% CI]: 1.35 [0.31; 5.94]; p=0.694) [94].

The total AEs (and individual symptoms) were also reported by Williams (2022) and did not differ statistically significantly between the treatment groups in any time period (total AEs: up to Day 15: RR [95% CI]: 1.08 [0.84; 1.40]; p=0.543; up to Day 30 incl. events up to Day 15: RR [95% CI]: 1.05 [0.86; 1.29]; p=0.609) [94].

Since the CI intersected the non-inferiority boundary of the RR of 1.1, no hint of non-inferiority of the shorter-duration antibiotic therapy could be derived for any of the AE outcomes. However, the absence of a hint of non-inferiority cannot be used to conclude an inferiority of the shorter-duration antibiotic therapy.

4.5.5 Results for the outcome of health-related quality of life

None of the studies reported results on the outcome health-related quality of life – neither for the therapeutic indication AOM nor for the therapeutic indication CAP.

4.5.6 Results on the supplementary outcome treatment adherence

Adherence to treatment was in part recorded very heterogeneously in the studies. In some cases, the parents' information [71-74,81,84,87,90,92,94] and/or the amount of medication missing in the packaging [71,72,74,78,79,81,83,87,90,92,94] provided the basis for the recording, in some cases intake was checked with a urine test [72,78,79].

4.5.6.1 AOM

Table 33 in the ThemenCheck details in Section A3.3.6.1 of the full report presents the study results on the outcome treatment adherence in AOM. Only 4 studies compared the treatment adherence of shorter with longer-duration antibiotic therapy [72-74,79]. Another 3 studies only reported treatment adherence at a single time point and collectively for the intervention and control groups [71,78,81]. Five studies on AOM provided no results on the outcome treatment adherence [69,70,75,77,80], 1 of the studies them despite having previously mentioned treatment adherence as an outcome in the methods section [69].

The study by Mandel (1995) compared treatment adherence for a treatment duration of 10 days of amoxicillin with 20 days of amoxicillin [72]. At all time points (Day 10 and Day 20), treatment adherence (measured by amount of medication used and self-reporting) was

comparable between treatment groups at around 95%. In addition, the number of patients with antibiotics detected in their urine did not differ notably between the groups on Day 10, but only on Day 20, as one group was already receiving placebo (78.8% vs. 7.7%). However, when comparing Day 10 to Day 20, there was a clear change in treatment adherence in the 20-day treatment group after the urine sample was taken (difference 18.9%). No CIs could be calculated for the differences due to missing data. In addition, the long treatment duration of 20 days for AOM can only be transferred to the German health care context to a limited extent.

Two studies investigating 5 vs. 10 days of amoxicillin-clavulanic acid also provided data on treatment adherence [73,74]. Hoberman (1997) was conducted without placebo and without blinding of the patients, and defined treatment adherence as self-reported adherence to at least 80% of the prescribed medication [73]. In the 5-day group, 96.9% reached this threshold value, while in the 10-day group the percentage was statistically significantly lower at 89.6% (RR [95% CI]: 1.08 [1.04; 1.13]; p<0.001). In the study by Cohen (1998), treatment adherence (not further defined) was recorded by the amount of medication returned and self-reporting [74]. At 93% and 94.2% respectively, a similar number of patients in both groups were rated as adherent to treatment (RR [95% CI]: 0.99 [0.93; 1.04]; p=0.649). This study was placebo-controlled and patients and treating physicians were blinded.

The study by Gooch (1996) investigated treatment adherence in a placebo-controlled comparison of 5 vs. 10 days of cefuroxime [79]. Therefore, both groups had to take medication for 10 days. Adherence to treatment was recorded by the amount of medication returned and urine samples, and 92% of patients in the shorter-duration therapy group and 96% in the longer therapy group were rated as adherent to therapy. Exact effect measures could not be calculated because only percentages were provided.

4.5.6.2 CAP

Table 34 in the ThemenCheck details in Section A3.3.6.2 of the full report presents the study results on the outcome treatment adherence in CAP. Four studies reported usable data on treatment adherence in children with CAP [83,84,92,94]. The study by Bielicki (2021) did not report treatment adherence stratified by outpatients and inpatients and was therefore not included [87]. Treatment adherence was recorded by the amount of medication returned and/or the parents' report. All studies were placebo-controlled trials with the same intake duration of a study drug. Treatment adherence was similar between the intervention and control groups in all studies:

3 vs. 5 days: ISCAP (2004): 94.2% and 93.9% respectively (up to Day 3; RR [95% CI]: 1.00 [0.98; 1.02]; p=0.779) and 85.6% and 84.9% respectively (up to Day 5; RR [95% CI]: 1.01 [0.97; 1.04]; p=0.660);

5 vs. 10 days: Pernica (2021) 90.4% and 86.4% respectively (recorded on Days 14-21; RR [95% CI]: 1.05 [0.96; 1.14]; p=0.309); Williams (2022) 84% and 80% respectively (recorded on Days 11-15; RR [95% CI]: 1.06 [0.96; 1.16]; p=0.251).

Ginsburg (2020) reported treatment adherence of 91.6% in the 3-day therapy group and 91.8% in the 5-day therapy group, recorded at all examination dates up to Day 6 without indicating the exact number of analysed patients [84].

In the ISCAP study (2004), it was possible to see from the different observation times that treatment adherence also decreases with increasing treatment duration [83]. The difference [95% CI] from Day 5 compared to Day 3 was 8.58% [6.08%; 11.09%] in the intervention group with placebo from Day 3, and 8.97% [6.41%; 11.52%] in the control group with 5 days of amoxicillin therapy.

4.5.7 Results on supplementary microbiological outcomes

4.5.7.1 AOM

Table 35 and Table 36 in the ThemenCheck details in Section A3.3.7.1 of the full report present the study results on microbiological outcomes in AOM. Only 4 studies provided usable data on microbiological outcomes: 1 study provided data on antibiotic resistance [75], 2 studies provided data on microbiological treatment failure [70] or persistent detection of bacteria [74], and 1 study combined microbiological treatment failure and antibiotic resistance [79]. Two studies reported microbiological data only for the period before the start of antibiotic therapy or only collectively for the intervention group and the comparator group and were therefore not usable [78,81]. Six studies reported no data on microbiological outcomes [69,71-73,77,80].

Ingvarsson (1982) reported evidence of pathogenic bacteria on Day 10 for the comparison of treatment with penicillin V for 5 days or 10 days [70]. At this time, pathogenic bacteria were proven in 47% of patients treated in the 5-day therapy group and 56% of those treated in the 10-day therapy group. No statistically significant difference was shown between the study arms (RR [95% CI]: 0.84 [0.60; 1.17], p = 0.305).

Cohen (1998) reported evidence of various bacterial strains on Days 12 to 14 after the start of 5-day or 10-day therapy with amoxicillin-clavulanic acid [74]. However, most bacterial strains were only described across groups or the comparisons between groups were only described as "non-significant". After the end of treatment, only the bacterial genus Moraxella catarrhalis was statistically significantly more frequently detected in the group receiving shorter-duration antibiotic therapy (RR [95% CI]: 2.23 [1.37; 3.63]; p=0.001).

Hoberman (2016) reported on recolonization with penicillin-resistant bacterial strains on Days 12 to 14 after starting antibiotic therapy with amoxicillin-clavulanic acid (5 vs. 10 days) and

the proportion of penicillin-resistant bacterial strains of *Streptococcus pneumoniae* and *Haemophilus influenzae* on Days 12 to 14 and up to the following September. None of the recorded outcomes provided statistically significantly different results between the different treatment durations (the different results with RR, 95% CI and p-value are presented in Table 35 in the ThemenCheck details in Section A3.3.7.1 of the full report).

Gooch (1996) reported bacteriological treatment failure (as a combination of clinical failure and detection of bacteria) on Days 11 to 14 (after 5 vs. 10 days of cefuroxime), subdivided into clinical failure, clinical failure with resistance and cure with superinfection. None of the data showed a statistically significant difference between the shorter and longer treatment duration (the various results with RR, 95% CI and p-value are shown in Table 36 in the ThemenCheck details in section A3.3.7.1 of the full report).

4.5.7.2 CAP

Table 37 in the ThemenCheck details in Section A3.3.7.2 of the full report presents the study results on microbiological outcomes in CAP. Only 1 study provided usable data on microbiological antibiotic resistance after antibiotic therapy in children with CAP [83]. Data on persistent bacterial detection/bacterial eradication were not available in the included studies on CAP.

The study by ISCAP (2004) compared resistance of the bacterial strains *Streptococcus pneumoniae* and *Haemophilus influenzae* to various antibiotics on Day 14 after the start of a 3-day or 5-day antibiotic therapy with amoxicillin. Only the proportion of *Streptococcus pneumoniae* strains that were resistant to co-trimoxazole on Day 14 differed statistically significantly between the groups. Here, resistance was rarer in the group treated with amoxicillin for 3 days (RR [95% CI]: 0.85 [0.74; 0.98]; p=0.026). There was no statistically significant difference between the treatment durations in the resistance of Streptococcus pneumoniae to chloramphenicol, oxacillin or erythromycin or in the resistance of Haemophilus influenzae to co-trimoxazole, chloramphenicol, ampicillin or erythromycin. For a detailed presentation of the results, please refer to Table 37 in the ThemenCheck details in Section A3.3.7.2 of the full report.

4.6 Summarized assessment of the results

4.6.1 AOM

Evidence map

Table 4 shows the evidence map regarding patient-relevant outcomes in AOM.

Table 4: Evidence map regarding patient-relevant outcomes in AOM

	Therapy success	Recurrence	Mortality	Adverse events			Health-related quality of life
				Serious adverse events (SAEs)	Hospitalization	Other adverse events	
AOM - children							
Penicillin V							
2 vs. 7 days	⇔	(⇔)	–	–	–	–	–
5 vs. 10 days	⇔	(⇔)	–	–	–	–	–
Amoxicillin							
3 vs. 10 days	⇔	(⇔)	–[a]	–	–	(⇔)	–
10 vs. 20 days	–	(–)	–	–	–	(–)	–
Amoxicillin-clavulanic acid							
5 vs. 10 days	⇑⇓[b]	⇑⇓[c]	–	–	–	⇔	–
First-generation cephalosporin (cefaclor)							
3 vs. 7 days	–	(⇔)	–[a]	–	–	–	–
5 vs. 10 days	⇔[d]	(⇔)	–	–	–	–	–
Second-generation cephalosporin (cefuroxime)							
5 vs. 10 days	–	–	–	–	–	⇔	–
Third-generation cephalosporins (cefixime, cefpodoxime)							
5 vs. 10 days	⇔[e]	⇔	–	–	–	⇔	–

⇔: no hint, indication or proof of non-inferiority of the shorter-duration treatment. Homogeneous results (the 95% CIs of all studies intersect the non-inferiority boundary)

⇑⇓:no hint, indication or proof of non-inferiority of the shorter treatment duration. Heterogeneous results (regarding to the non-inferiority boundary)

(⇔): no hint, indication or proof of non-inferiority of the shorter treatment duration. Homogeneous, imprecise results (for at least one analysis date, neither a halving nor a doubling of the effect can be ruled out).

–: No usable data reported

(–): Although usable data were reported, no benefit conclusion was derived due to limited transferability

a. For this comparison, no event occurred in either group; it was therefore not possible to calculate the relative risk and the 95% CI.

b. The results of the individual studies all showed a statistically significantly worse effect of shorter-duration antibiotic therapy at the analysis date considered to be of primary importance. The 95% CIs of 2 studies intersected the non-inferiority boundary at this analysis date, the 95% CI of one further study was completely below the non-inferiority boundary.

c. One study showed non-inferiority in terms of recurrence, but in 2 others the 95% CIs of the individual studies intersected the non-inferiority boundary.

d. The result of the study showed a statistically significantly worse effect of shorter-duration antibiotic therapy. The 95% CI intersected the non-inferiority boundary.

e. The result of the meta-analysis showed a statistically significant worse effect of a shorter-duration antibiotic therapy at the analysis date considered to be of primary importance. The 95% CI intersected the non-inferiority boundary.

Assessment of the volume of unpublished data

Due to the heterogeneity of the published studies and the small number of studies in each comparator category (<10 studies), it proved impractical to investigate the publication bias by means of a Funnel plot.

The registry search identified no studies which had been completed but not published. In one of the studies included, the outcome recurrence was not reported despite being mentioned in the methods section [80], and in one other included study, a predefined analysis period for recurrence was not reported [75]. Overall, however, the potential for publication bias appears low for the shorter-duration antibiotic therapy in children with AOM.

Weighing up of benefits versus harms

Most of the available studies on AOM had a high risk of bias, which reduces their informative value. Only 1 more recent and higher-quality study could be identified [75]. The overall picture is heterogeneous due to the different antibiotics used and the different treatment durations tested. Amoxicillin, which is the antibiotic of choice for bacterial otitis media [102], was only investigated in 2 studies, one of which compared an irrelevantly long period of 10 vs. 20 days. No conclusion on the benefit was derived in this study due to a lack of transferability to the German context.

No hint of non-inferiority in terms of treatment success could be derived for any of the antibiotics investigated in the comparison of different treatment durations. In a total of 5 of the 9 studies (on amoxicillin-clavulanic acid, a first-generation cephalosporin, and third-generation cephalosporins) that reported treatment success in a usable way, the results of the individual studies even showed a statistically significantly lower rate of treatment success in the shorter-duration treatment group for one analysis date.

Due to the rareness of the events, no hints of non-inferiority could be derived for the outcomes recurrence or mortality for the antibiotics and treatment durations investigated. Even for AEs, there was no hint of non-inferiority or superiority of shorter-duration antibiotic treatment for any comparison. However, the absence of a hint of non-inferiority does not necessarily mean that proof of inferiority of the shorter-duration antibiotic treatment can be inferred.

With regard to the supplementary outcomes, the only finding was that treatment adherence decreased with longer treatment duration in the unblinded comparison and in the comparison of multiple time points in a study. One bacterial strain, which was detected more frequently after antibiotic treatment in the group with shorter-duration antibiotic treatment in one study, can be interpreted as an incidental finding (<2431>Moraxella catarrhalis</2431> at 5 vs. 10 days of amoxicillin-clavulanic acid).

Overall, therefore, no non-inferiority of shorter-duration treatment for AOM can be demonstrated. The results show that a shorter treatment duration leads to poorer treatment results in some comparisons. The only possible advantage of a shorter-duration treatment is improved treatment adherence. A non-placebo-controlled study on AOM showed that with increasing duration of therapy, fewer patients take the medication as prescribed. The other studies that reported treatment adherence were placebo-controlled, so that both groups had to take medication for the same length of time.

However, there is a lack of high-quality studies that investigate the treatment durations currently used with a sufficient number of subjects, particularly for amoxicillin therapy (first-choice drug) in children with a therapeutic indication for antibiotic treatment.

4.6.2 CAP

Evidence map

The following Table 5 shows the evidence map regarding patient-relevant outcomes in CAP.

Table 5: Evidence map regarding patient-relevant outcomes in CAP

	Therapy success	Recurrence	Mortality	Adverse events: Serious adverse events (SAEs)	Adverse events: Hospitalization	Adverse events: Other adverse events	Health-related quality of life
CAP – children							
Amoxicillin							
3 vs. 5/7/10 days	⇑⇑	⇔	(⇔)	⇔	⇔	⇑⇑[a]	–
5 vs. 10 days	⇑⇑	⇔	–[b]	(⇔)	(⇔)	⇔	–

⇑⇑: Proof of non-inferiority of the shorter treatment duration (at all analysis dates).
⇔: no hint, indication or proof of non-inferiority of the shorter-duration treatment. Homogeneous results (the 95% CIs of all studies intersect the non-inferiority boundary).
(⇔): no hint, indication or proof of non-inferiority of the shorter treatment duration. Homogeneous, imprecise results (for all analysis dates, neither a halving nor a doubling of the effect can be ruled out).
-: no data reported

a. For this comparison, there was proof of non-inferiority of the shorter treatment duration as well as proof of superiority of the shorter treatment duration.
b. For this comparison, no event occurred in either group; it was therefore impossible to calculate the relative risk and the 95% CI.

Assessment of the volume of unpublished data

Due to the heterogeneity of the published studies and the small number of studies in each comparator category (<10 studies), it proved impractical to investigate the publication bias by means of a Funnel plot.

Searches in the trial registries did not identify any studies that had been completed but not published. However, 2 studies with published results on the antibiotic co-trimoxazole were identified for which no full-text publication was available [103,104]. In addition, the outcome recurrence of infection in the study by Greenberg (2014) was only reported in the second study phase [90]. Overall, however, the risk of publication bias is considered to be low.

Weighing up of benefits versus harms

A total of 7 studies that investigated different durations of treatment with amoxicillin were available for children with CAP. Most of these studies were assessed as having a low risk of bias. The transferability of the individual studies to the German health care context was largely considered to be given in view of the patient characteristics and is discussed in Section 8.2.2.

For children, the comparison of the amoxicillin treatment duration of 5 days with 10 days provided proof that the shorter-duration therapy is not inferior to the longer-duration therapy in terms of therapeutic success. Proof of non-inferiority was also found in the comparison of 3-day amoxicillin therapy versus a longer treatment duration of 5/7/10 days.

No hint of non-inferiority could be derived for recurrence due to the lower number of events and the resulting greater statistical uncertainty. Due to the rare number of deaths, no hint of non-inferiority could be derived for mortality either. However, the absence of a hint of non-inferiority does not necessarily mean that proof of inferiority of the shorter-duration antibiotic treatment can be inferred. With regard to other AEs, a comparison of 3 vs. 5 days of amoxicillin provided proof of the superiority of the shorter-duration therapy. Other comparisons yielded no hint of non-inferiority of the shorter-duration antibiotic therapy in each case, often due to wide CIs.

With regard to the supplementary outcomes, the analysis of various time points within the ISCAP (2004) study points to a decline in treatment adherence with longer treatment. With regard to microbiological outcomes, only in one study was one bacterial strain statistically significantly more rarely resistant to one antibiotic tested when amoxicillin was administered for only 3 days (compared to 5 days).

Overall, it can therefore be assumed that for the treatment of clinically diagnosed CAP in children, treatment with amoxicillin for 3 days is not inferior to longer therapy (for 5, 7 or 10 days) and, accordingly, 5-day therapy is not inferior to 10-day therapy. Although non-inferiority in terms of recurrence and mortality could not be demonstrated, recurrence up to

the respective analysis date was also included in the results for the outcome treatment success in the studies analysed. Overall, deaths are rare in children with CAP treated on an outpatient basis. The comparison of 3 days versus 5 days of amoxicillin therapy even resulted in a superiority of a shorter-duration therapy for the outcome (other) AEs. In addition, treatment adherence may be higher with shorter treatment duration. A placebo-controlled study on CAP, which investigated treatment adherence at several points in time, showed that fewer people take the medication as prescribed as the duration of treatment increases. The other studies that reported treatment adherence were placebo-controlled and reported treatment adherence at only one time point. Effects on resistance in bacteria remain unclear.

For shorter-duration antibiotic treatment for CAP in adults, only studies that investigated drugs without valid marketing authorisation status in Germany could be identified. This also applies to an identified discontinued study. Hence, no usable data are available for the German health care context. There is a lack of high-quality studies that investigate different outpatient treatment durations with currently used approved drugs (e.g. amoxicillin, amoxicillin-clavulanic acid, doxycycline, clarithromycin or levofloxacin) in adults with a sufficient number of subjects.

5 Results: Health economic assessment

5.1 Intervention costs

The central intervention costs of the experimental and comparator interventions are limited to the costs of drug treatment, which differs only in terms of duration, but not in terms of dosage. The other treatment costs are considered equivalent due to the short treatment duration of a few days and the consideration of non-severe courses of disease in the included studies. Each intervention is based on one visit to the doctor at the onset of the illness and one follow-up visit. Relevant differences in intervention costs therefore arise primarily from the differences in treatment duration.

The assessment of the costs from the perspective of the SHI funds is based on the pharmacy retail prices or the reference price. The reference price for a drug corresponds to the maximum drug costs that are covered by the SHI in Germany. These fixed drug costs are determined for a group of drugs that are comparable in terms of effect, use and quality. If the pharmacy retail price exceeds this reference price, patients must pay the remaining difference themselves [105]. This is to ensure that the more cost-effective drug is favoured when equivalent alternative drugs are available [106]. If the reference price for a drug is higher than the pharmacy retail price, the SHI only reimburses the actual selling price. To determine the costs from the SHI perspective, the statutory pharmacy discount, which is currently €2 (Section 130 Social Code Book V), a possible manufacturer discount and any potential co-payment due from the patient must also be deducted. Individual discount contracts for drugs between SHI funds and pharmaceutical companies cannot be included in the calculation, as the terms of these contracts are confidential and may vary depending on the SHI fund [105]. Co-payments for prescription drugs are to be borne by the insured person for adults over the age of 18. The co-payment is generally 10% of the pharmacy dispensing price (Section 61 Social Code Book V) [107]. However, it amounts to a minimum of €5 and a maximum of €10 per pack and may not exceed the actual cost of the drug (Section 61 SBG V) [107]. There is no co-payment for drugs for children and adolescents up to their 18th birthday. There are also other exceptions, for example for chronically ill people and co-payment exemptions for inexpensive drugs (Section 31 (3) Social Code Book V) [106].

The list of reference price drugs according to §35 Social Code Book V of the Federal Institute for Drugs and Medical Devices (BfArM) [108], the German Uniform Assessment Standard of the National Association of SHI Physicians (EBM) [109] and the Lauer-Taxe [110] were used as sources for cost determination. The reference price or the pharmacy retail price (whichever is lower) of the largest available pack minus the pharmacy discount, the manufacturer discount and the co-payment by patients is used for the assessment of costs from the SHI perspective [105]. The calculation of costs is mainly approached on the basis of the actual dose or number of tablets and therefore does not explicitly take into account the wastage of excessively large

packs. However, the necessary pack size and any resulting changes are referred to in the further consideration of the interventions [105].

As a large number of antibiotics are available, the treatment costs in this project are presented as examples using 2 preparations each for amoxicillin and cefpodoxime (third-generation cephalosporin) and one preparation for amoxicillin-clavulanic acid. Amoxicillin was used both in the included studies from both the benefit assessment (2 on AOM, 7 on CAP) and from the domain of Health Economics (1 on AOM, 1 on CAP). The other antibiotics were analysed in a total of 4 studies (all AOM) in the benefit assessment domain. The following products were selected as examples for the information on cost parameters in Table 5: (i) amoxicillin 250 mg/5 mL oral suspension, BP Ireland (100 mL powder for the preparation of a suspension; pharmaceutical central number (Pharmazentralnummer, PZN): 18890477), (ii) Amoxicillin AL 1000, ALIUD Pharma GmbH (30 film-coated tablets; PZN: 00038706), (iii) Cefpodoxim-ratiopharm 40 mg/5 mL, ratiopharm GmbH (200 mL powder for the preparation of a suspension; PZN: 09124726), (iv) Cefpodoxim-ratiopharm 200 mg, ratiopharm GmbH (15 film-coated tablets, PZN: 04478483) and (v) Amoxicillin/Clavulanic Acid Micro Labs 875 mg/125 mg, Micro Labs GmbH (20 film-coated tablets; PZN: 14334414).

The drug costs for adults and children over 40 kg body weight (BW) are calculated based on the manufacturer's recommended dosage according to the package insert or Lauer-Taxe [110]. Since the dosage for children under 40 kg depends on their body weight, the subsequent calculations for paediatric use are also based on the recommended dosage adjusted to body weight [110] using the following 2 examples: (i) infant with 5 kg body weight; (ii) child with 19 kg body weight (average body weight of a 5-year-old child [111]).

The cost parameters for the 5 selected preparations are summarized in Table 6 below. Detailed calculations of the treatment costs are shown in Table 38 to Table 47 in the ThemenCheck details in Section A4.1 of the full report.

Table 6: Particularities of the legal aspects of a shorter-duration antibiotic therapy for AOM/CAP

	Amoxicillin 250 mg/5 mL Amoxicillin Oral Suspension, BP Irland	**Amoxicillin AL 1000, ALIUD Pharma GmbH**	**Cefpodoxim-ratiopharm 40 mg/5 mL TS**	**Cefpodoxim-ratiopharm 200 mg**	**Amoxicillin/Clavulanic acid Micro Labs 875mg/125mg**
PZN	18890477	00038706	09124726	04478483	14334414
Pack size	100 mL powder for the preparation of an oral suspension (250 mg per 5 ml)	30 film-coated tablets of 1000 mg amoxicillin each	200 mL powder for the preparation of an oral suspension (40 mg per 5 mL)	15 film-coated tablets	20 film-coated tablets
Dosage	Children under 40 kg: 20 - 90 mg/kg of body weight/day persons over 40 kg of body weight: 1500 mg to 3000 mg daily	Persons over 40 kg: 1500 to 3000 mg of amoxicillin daily	Children up to 12 years: 5 to 12 mg kg of body weight/day adults: N D	Persons aged 12 years and older: 2 film-coated tablets daily	Children from 6 years of age > 25 kg and < 40 kg: 25/3.6-70/10 mg/kg of body weight/day persons ≥ 40 kg of body weight: 3 film-coated tablets daily
AAP	€ 29.85	€ 19.33	€ 28.06	€ 33.03	€ 36.71
Reference price	€ 13.64	€ 20.28	-	€ 33.05	€ 53.20
Additional costs[a]	€ 16.21	-	-	-	-
Pharmacy discount	€ 2.00	€ 2.00	€ 2.00	€ 2.00	€ 2.00
Manufacturer's discount	€ 1.47	€ 0.00	€ 0.79	€ 0.00	€ 0.00
Co-payment[a]	Children: € 0.00 adults: € 5.00				Children and adults: € 0.00 (no co-payment)
SHI costs[b]	Children: € 10.17 adults: € 5.17	Children: € 17.33 adults: € 12.33	Children: € 25.27	Children: € 31.03 adults: € 26.03	Children and adults: € 34.71

a. Non-reimbursable costs that must be borne by the patient.
b. Reimbursable costs covered by the SHI.

Amoxicillin

For the antibiotic Amoxicillin Oral Suspension (BP Ireland), the manufacturer's instructions state a necessary daily dose of between 2 mL (at 20 mg/kg BW/day) and 9 mL (at 90 mg/kg BW/day) for an infant of 5 kg body weight. The daily costs range from €0.20 (at 20 mg/kg BW/day) to €0.92 (at 90 mg/kg BW/day) based on the SHI costs (reference price less pharmacy discount, manufacturer discount and co-payment). With an average dosage, this results in daily costs of €0.56. One packaging unit (100 mL) is therefore sufficient for treatment lasting between 11 days (at 90 mg/kg BW/day) and 50 days (at 20 mg/kg BW/day). At an average dosage, the corresponding total costs amount to €1.68 for 3 days, €2.80 for 5 days, €3.92 for 7 days and €5.59 for 10 days of treatment. However, as mentioned above, it is assumed that the pack sizes can be customized as required at these price conditions. Otherwise, the costs for the SHI would amount to the respective price of the drug, i.e. in this example €10.17 for one bottle, regardless of the treatment duration.

Based on a child with a body weight of 19 kg, the daily dose required is between 7.60 mL (at 20 mg/kg BW/day) and 34.20 mL (at 90 mg/kg BW/day). Thus, the daily costs for the SHI range between €0.77 and €3.48 depending on the dosage (20 vs. 90 mg/kg BW/day). Assuming an average cost per day of € 2.13, this results in a total cost of € 6.38 for 3 days, € 10.63 for 5 days, € 14.88 for 7 days and € 21.26 for 10 days of treatment. The above assumption regarding the fully customizable pack size also applies in this scenario. One packaging unit would last between 2.9 and 13 days for a child weighing 19 kg. Based on a non-variable pack size of 100 mL, the costs would therefore increase accordingly to up to €40.68 for 10 days of treatment at a dose of 90 mg/kg BW/day (SHI costs for 4 packs of the product). In both of the paediatric application examples presented, patient-relevant costs are also incurred in the form of the difference between the pharmacy retail price and the reference price of €16.21 per bottle. For 10 days of treatment, this results in a cost of €16.21 for 1 bottle for an infant weighing 5kg, and up to €64.84 for 4 bottles for a child weighing over 19kg.

In principle, the drug Amoxicillin Oral Suspension can also be used for adults, although the costs are higher than alternatives in tablet form. The costs for a patient over 18 years of age (and a body weight of over 40 kg) amount to €3.10 for the SHI at a daily dose of 3000 mg (60 ml). For treatments lasting 3, 5, 7 and 10 days, the costs for the SHI funds therefore add up to €9.31, €15.51, €21.71 and €31.02 respectively. One packaging unit of 100 ml covers a treatment period of 1.67 days. Ten-day treatment requires exactly 6 bottles (600 mL). Therefore, the total costs amount to €31.02 from an SHI perspective. The costs to be borne by the patient for a 10-day treatment add up to €127.26 from the difference between the pharmacy retail price and the reference price of €16.21 per bottle and the co-payment of €5 per bottle (i.e. a total of €21.21 per bottle) for 6 bottles.

The second product under consideration, Amoxicillin AL 1000 (ALIUD Pharma GmbH), is available as a film-coated tablet. The costs listed in Table 6 refer to a pack of 30 film-coated tablets containing 1000 mg amoxicillin each. A daily dose of 3 tablets (3000 mg amoxicillin) is assumed in accordance with the guidelines for CAP [33]. The daily costs for the SHI funds thus amount to €1.23 for a person not exempt from co-payment (€1.73 for persons exempt from co-payment and children). Based on a treatment duration of 3, 5, 7 or 10 days, the costs for the SHI funds thus add up to €3.70, €6.17, €8.63 and €12.33 respectively. The pack of 30 film-coated tablets corresponds exactly to a 10-day treatment duration at the dosage investigated. Alternatively, packs of 10, 16 and 20 film-coated tablets are also available for this drug, which are relatively more expensive at a daily cost of €1.92 (10 film-coated tablets), €1.57 (16 film-coated tablets) and €1.35 (20 film-coated tablets). If one now considers the prices for the pack sizes corresponding to the treatment duration, the costs for SHI for adult patients (those exempt from co-payment) would amount to €6.41 (€11.41) for a pack of 10 film-coated tablets for a 3-day treatment, €8.39 (€13.39) for a pack of 16 film-coated tablets for a 5-day treatment and €12.33 (€17.33) for a pack of 30 film-coated tablets for a 7-day treatment and longer. The costs for patients are the co-payment of €5 per pack for adults and €0 for minors or patients exempt from co-payment for all variants considered.

Cefpodoxime

Based on the manufacturer's information on the normal dose [112], a dose of 8 mg/kg BW per day (corresponding to 1 mL/kg BW/day) is assumed for the calculations of the costs for the product Cefpodoxim-ratiopharm 40 mg/5 mL (paediatric antibiotic oral suspension). Available packaging sizes are bottles of 200 mL (see Table 6), 100 mL and 50 mL. For the example of an infant with a body weight of 5 kg, this results in a daily dose of 40 mg or 5 ml. Based on the SHI costs of the largest pack (€25.27 per 200 mL, €0.13/mL), the total daily costs therefore amount to €0.63. For a treatment duration of 3 days, this results in costs of €1.90, for 5 days €3.16, for 7 days €4.42 and for 10 days €6.32. This does not take into account wastage, otherwise the cost of each intervention would be €25.27, which is exactly the cost of a 200 mL bottle. The amount of medicine required for a child weighing 5 kilograms amounts to a total of 50 ml for a maximum of 10 days of treatment. This makes a comparison with the costs for the smallest available bottle (50 mL) interesting, which in total costs the SHI €14.79 (€0.30 per mL), which is less than a bottle of 200 mL.

Considering a child with a body weight of 19 kg, this results in a daily dose of 19 mL (152 mg) and daily drug costs of €2.40. Assuming the cost per mL of the largest available pack can be, this results in drug costs of €7.20 for treatment over 3 days, €12.00 over 5 days, €16.80 over 7 days and €24.01 over 10 days. Taking the wastage into account, all 4 treatment strategies would incur total drug costs of €25.27 from an SHI perspective. In this case, for a treatment

duration of up to 5 days, it would be advisable to use the medium pack size (100 ml), which costs €19.02 from an SHI perspective.

For the treatment of adults with cefpodoxime, reference is made to the use of film-coated tablets with the dosage adjusted accordingly. The costs for the product Cefpodoxim-ratiopharm 200 mg were applied here, which from an SHI perspective amount to €26.03 for a pack size of 15 film-coated tablets (PZN: 04478483) and €19.42 for a pack size of 10 film-coated tablets (PZN: 04478477). In both cases, the costs from the patient's perspective amount to the co-payment of €5 per pack (unless exempt from co-payment). Based on a daily dose of 2 film-coated tablets (2 x 200 mg), this results in daily costs (SHI) of €3.47 or €3.88, depending on the pack size (15 vs. 10 film-coated tablets). The costs based on the larger pack therefore amount to €10.41 (3 days), €17.35 (5 days), €24.29 (7 days) and €34.71 (10 days) for the 4 treatment durations considered. It should again be noted that, due to wastage, the use of the smaller pack size for treatment over 3 and 5 days (€19.42 vs. €26.03) and over 10 days (€38.84 vs. €52.06) results in lower costs for the SHI system. The larger pack would only be cheaper (€26.03 vs. €38.84) in the case of a 7-day treatment. For patients, on the other hand, the larger pack can be regarded as advantageous (only 1 pack required for 7 days) or at least equivalent, as the co-payment of €5 per pack is incurred regardless of the pack size.

Amoxicillin/clavulanic acid

The last drug selected is the co-payment-free product Amoxicillin/Clavulanic Acid Micro Labs 875 mg/125 mg, which can be used for adults and children over 6 years of age and 25 kg body weight. A daily dose of 3 film-coated tablets is assumed for patients with body weights > 40 kg; a dose of between 25 mg/3.6 mg and 70 mg/10 mg/kg BW per day is recommended for children between 25 kg and 40 kg body weight. For the further calculations in the paediatric setting, a child with a body weight of 30 kg and a daily dose corresponding to the manufacturer's recommendations of 29.2 mg/4.2 mg/kg body weight and thus 876 mg/126 mg/day is used as an example. This corresponds to about 1 film-coated tablet per day and thus to exactly 10 film-coated tablets for a maximum treatment duration of 10 days. The daily costs from an SHI perspective of €2.17 are based on a pack of 10 film-coated tablets (PZN: 14334383; pack cost: €21.74). The exact dose costs for the treatment of a child weighing 30 kg with this product therefore range between €6.52 (3 days), €10.87 (5 days), €15.22 (7 days) and €21.74 (10 days).

The daily cost for an adult is €5.21 based on a pack of 20 film-coated tablets (pack cost: €34.71). The costs for the SHI funds are therefore €15.62 (9 film-coated tablets) for 3 days, €26.03 (15 film-coated tablets) for 5 days, €36.45 (21 film-coated tablets) for 7 days and €52.07 (30 film-coated tablets) for 10 days. Depending on the treatment duration, an adjustment of the pack size should again be considered for the cost calculation for adult patients. For a 3-day treatment and thus 9 film-coated tablets, the costs for the SHI would

amount to €21.74 for a pack of 10 film-coated tablets. For a 5-day treatment and 15 film-coated tablets, the costs for the SHI would correspond to €34.71 for a pack of 20 film-coated tablets. For 7 days of treatment and 21 film-coated tablets or more, costs totalling €56.45 are incurred for a pack of 20 film-coated tablets and a pack of 10 film-coated tablets. As this product is exempt from co-payment, no further costs arise from the patient's perspective.

Conclusion

To summarize, it can be said that the costs increase notably with longer treatment with the difference varying depending on body weight, drug, dosage form and available pack sizes. For the paediatric antibiotic Amoxicillin Oral Suspension, there is no difference in cost from an SHI perspective for the treatment of a child weighing 5 kg due to the available pack size of 100 mL. For both 3 and 10 days of treatment, this amounts to exactly the cost of one pack (€10.17). For a child weighing 19 kg, the costs for the SHI funds increase by €20.34 from €20.34 for 3 days (2 bottles) to €40.68 for 10 days (4 bottles). Cefpodoxime shows similar increases in the paediatric setting: For a child weighing 5 kg, the cost for both 3 days and 10 days of treatment is €14.79 for the smallest available pack size of 50 mL. For a child weighing 19 kg, the costs from an SHI perspective would amount to €19.02 for a 100 mL pack for 3 days of treatment, and to €25.27 for a 200 mL pack for 10 days of treatment. This corresponds to a difference of € 6.25. The cost of treatment of a child weighing 30 kg with the selected product for amoxicillin/clavulanic acid showed no difference in cost (€21.74), as one pack of 10 film-coated tablets is sufficient for both 3 days and 10 days of treatment.

From an SHI perspective, the difference in costs between a 3-day and a 10-day treatment with amoxicillin for adult patients corresponds to €20.68 (amoxicillin oral suspension) and €5.92 (Amoxicillin AL 1000). The cost of cefpodoxime film-coated tablets increases by €19.42, i.e. by 1 pack of 10 film-coated tablets. Amoxicillin/clavulanic acid shows the highest difference of €34.71, with costs of €21.74 (3 days, 1 pack of 10 film-coated tablets) and €56.45 (10 days, 1 pack of 10 film-coated tablets and 1 pack of 20 film-coated tablets).

5.2 Systematic review of health economic evaluations

5.2.1 Results of the information retrieval

As part of the systematic search, 2 studies were identified from a total of 387 hits to be screened after title and abstract screening as well as full-text screening that corresponded to the inclusion criteria for the health economic evaluation of shorter-duration antibiotic use: Coco (2007) for AOM and ISCAP (2004) for CAP in children.

The search strategies for bibliographic databases are listed in the Appendix of the full report. T*he last search took place on 14 February 2024.

Table 7: Study pool of the health economic assessment

Study	Available documents [reference]
Coco (2007)	Full publication [113]
ISCAP (2004)	Full publication [83]

5.2.2 Characteristics of the studies included in the assessment

The 2 included studies investigate different therapeutic indications, which are discussed in this report.

Coco (2007)

The study by Coco (2007) [113] examined children between 6 months and 12 years of age with AOM. This modelling study compares 5-day treatment with amoxicillin (experimental intervention) with 7 to 10-day treatment with amoxicillin (comparator intervention). The study also presents comparisons with the strategies watchful waiting (i.e. 72 hours of monitoring and waiting for symptom improvement before starting treatment with amoxicillin) and delayed prescription (treatment with amoxicillin is prescribed if patients continue to complain about symptoms after 48 to 72 hours). For this purpose, the study conducts an incremental cost-utility analysis of the 4 strategies and compares the cost-utility ratio measured in cost per quality-adjusted life year (QALY) gained using a deterministic decision tree analysis. In addition, one-way sensitivity analyses were carried out for all model variables as well as probabilistic sensitivity analyses based on the normal distribution for the cost data and the beta distribution for probabilities and utilities. The utilities were taken from the secondary literature, in which the visual analogue scale (VAS) and a survey of paediatricians were used [114]. In addition to the cost of drugs, the costs also include non-health-related care costs, costs for the carer's absence from work and visits to the doctor. The costs are stated in US dollars for 2001 on the basis of the U.S. Medical Consumer Price Index. The costs were not discounted due to the short time horizon of 30 days. The data sources for the costs are publications by Staff (2002) [115], Marx (2002) [116] and Capra (2000) [117] as well as the databases of the Pennsylvania Department of Public Welfare [118], Medicare and Medicaid [119], the Healthcare Cost and Utilization Project 2000 database [120] and the 2001 National Compensation Survey [121]. A social perspective is assumed for the analyses. The study received financial support by the Lancaster General Hospital and the American Academy of Family Practice Grant.

ISCAP (2004)

The study by ISCAP (2004) [83] examined the outpatient treatment of children between 2 and 59 months of age with CAP (CAP in children). ISCAP (2004) is a health economic evaluation accompanying a randomized, double-blind, controlled trial in India comparing 3-day treatment with amoxicillin with 5-day treatment. The study compares the benefits and direct

medical costs of the 2 treatment strategies, but one after the other and separately. The data were recorded between August 2000 and December 2002. The study included a total of 2188 patients, of whom 1095 children received shorter-duration treatment with amoxicillin (3 days) (experimental intervention) and 1093 children received amoxicillin for 5 days (comparator intervention). The clinical outcomes of the study include treatment success and recurrence. The cost parameters were transmitted by hospitals and were used in the study as mean values of the participating hospitals. The analyses were conducted from the payers' perspective. Direct medical costs are taken into account, which are stated in Indian rupees (INR). Information on the index year and the discount rate (if applicable) is missing. The study was supported by US AID via INCLEN and IndiaClen.

5.2.3 Results of health economic evaluations

Coco (2007)

After conversion from US dollars to euros with the CCEMG - EPPI-Centre Cost Converter [122] for Germany and after adjustment for inflation for the base year 2022, the deterministic decision tree analysis by Coco (2007) [113] resulted in costs totalling €173.76 per patient (US$156.90) for the shorter-duration treatment strategy (5 days of amoxicillin) and costs totalling €171.98 per patient (US$155.30) for the longer-duration treatment strategy (7 to 10 days of amoxicillin). Although the costs for drugs are higher for the longer comparator intervention (€2.43), the costs for lost working hours (-€2.92) and visits to the doctor (-€0.86) are lower. In total, this results in additional costs of €1.77 per patient (US$1.60) for the shorter experimental intervention compared to the longer comparator intervention.

With regard to the utility values, which Coco (2007) [113] stated in quality-adjusted life years (QALY), the experimental intervention (5 days of amoxicillin) has a QALY value of 0.99487 and the comparator intervention has a QALY value of 0.99501. This results in a lesser benefit for the shorter-duration treatment strategy (-0.00014). As the experimental intervention in this model is now more expensive (cost difference = €1.77) and provides less benefit (utility difference = -0.00014), Coco's (2007) experimental intervention is considered to be dominated. The conclusion from the study by Coco (2007), which investigated a total of 4 treatment strategies for AOM in children as described above, thus does not result in a further comparison of the 2 strategies analysed in this report, but in an analysis of the trade-off between 7 to 10-day treatment with amoxicillin and the treatment strategy of delayed prescription. While treatment over 7 to 10 days is the most efficient option with the highest utility (QALY), the "delayed prescription" strategy can be identified as the most cost-effective option (cost = €146.62 US$132.40)). Finally, the further sensitivity analyses cited by Coco (2007) refer only to the comparison between these 2 strategies and the incremental cost-utility ratio (ICUR) of € 61 854 (US$ 55 853) per QALY gained.

ISCAP (2004)

The comparison of the 2 investigated treatment strategies for children with CAP in India in the ISCAP (2004) study [83] shows no statistically significant differences in the 2 clinical outcomes treatment success after 5 days (89.5% at 3 days vs. 89.9% at 5 days of treatment, difference [95% CI] = 0.4 [-2.1; 3.0]) and recurrence after 14 days (5.3% at 3 vs. 4.4% at 5 days of treatment; difference [95% CI] = 1.0 [-1.0; 3.0]) (see Section 4.5). The direct medical costs, converted into euros using the CCEMG - EPPI-Centre Cost Converter for Germany and adjusted for inflation for 2022, are stated as €1.15 (11 INR) for the experimental intervention over 3 treatment days and €1.99 (19 INR) for the comparator intervention over 5 treatment days, assuming successful treatment (cure). This results in a difference of - € 0.84 (- 8 INR) in favour of a shorter-duration treatment over 3 days (experimental intervention). In their conclusions, the group of authors of the ISCAP (2004) study thus recommend to shorten the treatment with amoxicillin to 3 days, as this strategy proves to be equally effective but less expensive. In addition, a statistically significant increase in the resistance of *Streptococcus pneumoniae* to co-trimoxazole was observed from the start of the study to the end of the observation period after 14 days in children who had been treated over 5 days. According to the study group, antibiotic resistance could also be reduced by shortening the duration of administration. The authors also cite as limitations the fact that this was a hospital-based study in which the causes of infection were not investigated, the follow-up period was only 15 days and children with asthma were excluded.

It must be critically noted that the publication provides no information on the discount rate and the cost year. For the inflation adjustment carried out above, the cost year 2004, the year of the study publication, was assumed. In addition, no sensitivity analyses are reported for the study and therefore no information is provided on how to deal with uncertainties. The results and costs result from the Indian health care system and are therefore not directly transferable to Germany.

Conclusion

In summary, the available literature shows that, from a cost perspective, no general recommendation can be made in favour of shortening the duration of treatment with antibiotics in AOM [113]. The strategy of a shorter-duration treatment of 5 days compared to 7 to 10 days reduces drug costs, but further costs for e.g. loss of working hours or transport appear to be higher. In addition, shortening the treatment duration to 5 days in Coco (2007) leads to a reduction in the QALYs gained compared to treatment over 7 to 10 days. Coco (2007) thus considers the longer-duration treatment to be the dominant strategy versus the shorter-duration treatment. From a payers perspective, shortening the duration of antibiotic treatment in CAP appears to be an interesting alternative, as the cost of drugs can be reduced while maintaining comparable effectiveness (treatment success and recurrence) [83]. However, due to the limited transferability of the health economic aspects to the German health care system, these results can only be used to a limited extent for the assessment in this ThemenCheck report.

6 Results: Ethical, social, legal and organizational aspects as well as environmental and climate aspects

6.1 Results on ethical aspects

The ethical aspects were analysed on the basis of an established ethical framework for the assessment of interventions in the health care sector according to Marckmann (2015) [64], which was modified accordingly (see Table 58 of the full report).

The exploratory search of scientific and non-scientific literature identified few publications which explicitly investigated ethical aspects of (shorter-duration) antibiotic therapy for AOM or CAP in children and adolescents as well as in adults. Rather, literature permitting an ethical assessment was found with regard to shorter-duration antibiotic treatment in general. A total of 26 publications were included in the ethical assessment. Based on the specified criteria, the ethical aspects were evaluated analytically and argumentatively. The results of the other domains, in particular of the legal (Section 6.3 and social aspects (Section 6.2) as well as the preparatory interviews with patients (ThemenCheck details Chapter A11 of the full report) were used and "reflective thoughts" of the report authors [63] were integrated.

Overview

AOM has a major impact on children and is a major burden for both the children affected and their families (custodians) (see Section 1.2.2). Possible consequences for the psychosocial development, education and social interaction of children and adolescents are discussed in detail in Section 6.2. However, the burden of AOM in children goes beyond the immediate health and social impact on the children affected. It is common for parents to be faced with repeated visits to health care providers and recurring antibiotic therapies. This cycle of disease and treatment can disrupt everyday life and employment and lead to (psychological) stress. CAP can affect children and adolescents as well as adults. Two of these population groups can be particularly affected by CAP: In younger people, CAP is a major contributor to incapacity to work and in older and multimorbid patients there is a particular risk of potentially fatal hypoxia and acute cardiac complications (see Section 1.2.3). CAP therefore also has the potential for socio-economic burdens (see also Section 6.2 for more details).

Antibiotic therapy for CAP as well as AOM raises ethical questions regarding the duration of treatment, ranging from the responsibility to maintain individual patient care to public health. The focus of this ethical analysis is therefore on the consequences of (shortened) outpatient antibiotic treatment for both diagnoses. Ethical considerations include the appropriate use (prescription) of antibiotics, the prevention of antibiotic resistance and ensuring fair health care.

Expected health benefit for the target group

The expected benefits of shorter-duration antibiotic therapy in AOM and CAP for the groups of patients are described in detail in Chapter 1. In Chapter 4, 2 studies suggested that improved treatment adherence may be an identifiable advantage of shorter-duration antibiotic therapy in AOM and CAP. In both cases, a shortened treatment duration led to better patient adherence to the therapy. All other studies that evaluated treatment adherence were placebo-controlled and only investigated one time point. Patients are also generally more willing to take a shorter course of antibiotics in full, which can lead to greater adherence [123]. This connection is also confirmed in an interview with a patient (ThemenCheck details, Chapter A11 of the full report). A high level of adherence is crucial for the effectiveness of the therapy, as incomplete treatment harbours the risk that the infection will not heal completely. In their studies, Kardas (2013) and Hoppe (1999) determined that shorter therapies and thus milder treatment burdens lead to a higher overall effectiveness of the treatment due to increased adherence [123,124].

Garau (2006) and Spellberg (2016) emphasize that shorter-duration treatment not only accelerates physical recovery, but also reduces the psychosocial impact of the disease [6,125]. A shorter treatment duration can also lead to a faster recovery of the patients, enabling them to return to their normal lives more quickly. This is particularly important for working adults and schoolchildren, who may experience less downtime.

From a public health perspective, it should be noted that the length of antibiotic therapy can influence the development of resistance, which is not only important for immediate patient care, but also for long-term public health and the sustainability of antibiotic effectiveness (for details see [126], see also Section 1.2.1). This argument is also articulated in an interview with a patient, in which the effectiveness of antibiotics for future bacterial infections was categorized as very important (ThemenCheck details Chapter A11 of the full report).

Potential harm and burden

A substantial burden of shorter-duration antibiotic therapy can be the risk of inadequate treatment. Inadequate treatment duration bears the risk of incomplete healing of the infection, which can lead to recurrent or chronic conditions. If children and adults contract the same infections again, this could lead to repeated treatments, further health impairments and additional burdens on the health care system [6,127]. This additional burden can be both physically and psychologically stressful, especially for children who may suffer from recurring pain and symptoms. These possible consequences of shorter-duration antibiotic treatment are also expressed in the patient interviews, in which insufficient effectiveness, no improvement in symptoms and a long course of disease (possible recurrence after short-term improvement) are addressed (ThemenCheck details, Chapter A11 of the full report).

From an ethical point of view, it is also important to consider not only the potential harm of inadequate treatment, but also the burden of adverse drug reactions associated with antibiotic therapy, which can affect patients' quality of life. In relation to CAP, Chapter 4 shows that shorter-duration antibiotic therapy has an advantage in terms of AEs when comparing 3 versus 5 days of amoxicillin. However, this could not be shown for other comparisons (AOM or other treatment durations).

Effects on autonomy

The ability and right to make self-determined decisions about health care are central ethical principles in medical practice (see Section 6.3 for the legal localization of patient autonomy and the associated capacity to consent, and Section 6.2 for the health literacy that is fundamentally necessary for this).

The concept of informed consent basically assumes that patients are fully informed about the advantages and disadvantages, risks and alternatives of a treatment before they make a decision about the treatment [128]. This concept of informed consent should be supplemented with shared decision-making. It is a collaborative process in which patients and health care professionals make decisions together, taking into account patient preferences and values as well as medical information and recommendations [129].

The implementation of patient autonomy in the sense of informed consent is based on the components of information, voluntariness, legal competence and consent. In the course of providing information, health care professionals should provide the patient with clear and understandable information about the (shorter-duration) antibiotic therapy and, above all, about possible risks and adverse effects as well as alternative treatment options. In the context of shorter-duration antibiotic therapy, the limited knowledge of patients with regard to shorter-duration antibiotic therapy, as described in Section 6.2, must be taken into account here, as well as the application of relevant guidelines from the physicians’ point of view. Accordingly, patients should be informed about the possibility of shorter-duration antibiotic therapy so that they can make a decision based on their own preferences in the sense of self-determination. Kardas (2013) and Spellberg (2016) point out that well-informed patients are more likely to follow medical advice and adhere to treatment plans, which subsequently increases the effectiveness of therapy [6,123].

The interviews with patients show that the decision on the duration of antibiotic therapy should be made by the patients themselves on an informed basis within the scope of what is medically appropriate (ThemenCheck details Chapter A11 of the full report). However, they also express concerns about the development of resistance, which could restrict self-determined decisions. This illustrates the need for thorough information and careful balancing of the individual and social implications.

In the context of the present analysis, particular attention must be paid to the rights and needs of vulnerable patient groups such as children and the elderly. These groups may need (legally required) decision-making support from parents, guardians or adult representatives, as well as specific information that takes account of individual characteristics while ensuring that the autonomy of the patients is preserved. The patient interviews show that such support is essential in order to make an informed decision (ThemenCheck details Chapter A11 of the full report).

Children and adolescents should be involved in the process of shared decision-making according to their stage of development, especially to promote their adherence versus the therapy form [123]. In an interview with one of the affected adolescents, he said that he would always take a prescribed antibiotic for as long as the doctor prescribed it. When asked what information he would need to make an informed decision about the duration of antibiotic therapy, he replied that he would consider recommendations from both his doctor and his parents. Age-appropriate information and a participatory decision-making process can help to improve the acceptance and effectiveness of treatment. Parents or guardians of children and adolescents should be given appropriate information about the opportunities and risks so that they can make an informed decision about the use of (short-duration) antibiotic therapy (also in combination with standard therapies).

Finally, the tension between the described individual autonomy and the protection of public health from a public health perspective should be addressed. The spread of antibiotic resistance poses a major risk to the general public. Therefore, decisions on antibiotic administration should not only take into account the individual preferences and rights of current patients, but also the potential impact on public health and thus on future patients [125,129,130]. Responsible use of antibiotics is crucial to prevent the development and spread of resistant bacteria [127]. The WHO (2000) and Davey (2002) emphasize the importance of educating the public and health care professionals about the risks and consequences of antibiotic resistance [129,131]. Especially in the context of shared decision-making, doctors can therefore help to strike a balance between respecting patient autonomy and avoiding excessive or inappropriate use of antibiotics that could harm public health when prescribing antibiotics. This balancing process is given great attention in current guidelines [33,34,102] and is also addressed by national and international antibiotic resistance strategies (for example [132]). For specific prescribing practices and the relevant relationships between professionals, see Section 6.2.

Ethics of justice

Considerations regarding the ethics of justice play a central role in the discussion about planning and implementing antibiotic therapies, above all to ensure that medical resources are distributed fairly, that current and future needs are met and that no generation is

disadvantaged [133-135]. Distributive justice demands that health care resources are distributed according to need and not according to the ability to pay for them. Littmann and Buyx (2015) chiefly emphasize the need to ensure that all patients have equal access to effective and necessary treatment, especially in times when medical resources are scarce [130]. Furthermore, the responsibility towards future patients must be considered in the sense of future justice. Today effective antibiotic therapy must not be at the expense of the effectiveness of antibiotics tomorrow. Laxminarayan (2013), Littmann (2015, 2018) and Amente (2023) emphasize that measures must be taken to minimize the spread of resistance and maintain the effectiveness of antibiotics in the long term [130,136-138]. Among other things, it is pointed out that antibiotics should only be used when they are really necessary and that treatments should be as short as possible but as long as necessary to prevent the development and spread of resistance. "Antimicrobial stewardship" involves coordinated measures to promote the appropriate use of antimicrobial drugs in order to maximize the effectiveness of treatment and minimize the development of antibiotic resistance. These programmes include monitoring, evidence-based guidelines, training of medical staff and interdisciplinary collaboration (for more details see [139,140]).

Finally, intergenerational aspects should also be considered in this context, which primarily refer to the fair distribution of resources and opportunities between different generations [134]. With regard to antibiotics, this means that current generations have a responsibility to preserve the effectiveness of these drugs for future generations. Sustainable use of antibiotics helps to ensure that future generations will also have access to effective treatments. The ethical challenge also lies in incorporating the long-term needs and rights of future patients into current decision-making processes.

Expected efficiency

As discussed in detail in Chapter 5, the relevant health economic literature shows that shortening antibiotic therapy in AOM reduces drug costs, but is characterized by higher follow-up costs such as loss of working hours and a reduction in QALYs gained. In CAP, shorter-duration treatment can be potentially beneficial due to comparable effectiveness, lower drug costs and reduction of AEs. The societal advantages of shorter-duration antibiotic therapies can thus be seen in various aspects, from direct cost savings and efficient use of resources to the avoidance of AEs, while maintaining comparable effectiveness. The fair distribution of therapies, the avoidance of inappropriate differentiation and responsibility towards future generations are central aspects that must be taken into account when planning and implementing antibiotic therapies. These approaches have the potential to promote not only individual but also public health and trust in the health care system as a whole.

6.2 Results on social aspects

The information processing is based on the comprehensive conceptual framework proposed by Mozygemba (2016) [65] (see also Table 59 of the full report).

The analysis of social aspects is based on the interviews with patients, "reflective thoughts" [63] and a total of 51 publications included. In addition to the ethical aspects outlined above (Section 6.1), this subchapter focuses on the following social aspects: social construct and understanding of AOM and CAP, understanding of shorter-duration antibiotic treatment for AOM and CAP and its use in society and science, sociocultural aspects of intervention implementation and organization of use.

Social construct and understanding of AOM and CAP

With regard to children and adolescents, the primary national and international discussion on AOM is the impact on development and education. Hearing impairment and hearing loss in particular can therefore lead to socially relevant delays, e.g. in speech and language development, emotional and psychosocial development and school readiness [141-149]. Less clear literature could be found on the social understanding and consequences of CAP in children. In principle, there is a great need for research to improve the selection and dosage of drugs for CAP [150]. Individual authors identify a connection between social disadvantage and higher case numbers as well as hospital admissions [151,152]. The publications identified on the social risks of CAP in adults primarily address risk factors and predictors of the disease. The risk of CAP is thus increased by: living alone, contact with children, contact with pets, male sex, ex-smoker status, chronic pre-existing conditions, hospitalization in the last 5 years, a low level of education and living together with more than 10 people [153-155]. The risk of mortality from CAP disease may be increased by older age, non-white ethnicity and low income [156,157]. The risk of readmission to hospital after CAP treatment may be increased by older age, low income, non-white ethnicity, low education and unemployment [156,157]. Fernandez (2010) and Izquierdo (2020), on the other hand, found no correlation between socioeconomic factors and CAP development or recovery [158,159].

Understanding shorter-duration antibiotic therapy in AOM and CAP and its use in society and science

The perceived benefits of shorter-duration antibiotic therapy in children with AOM include many of the aspects already mentioned in Chapter 1: These include the potential reduction in the risk of allergic reactions/side effects, the potential reduction in the risk of resistance development, the reduction in total antibiotic consumption and thus reduction in the cost of antibiotics as well as greater treatment adherence ([69,160], see also the results of the benefit assessment in Section 4.5 and the health economic evaluation in Chapter 5, which do not provide consistent and/or statistically significant results in this respect). However, Vernon-Feagans (1996) [149] point out that antibiotics and other forms of treatment are effective in

eliminating bacterial infections, but there is no evidence that they reduce fluid in the middle ear. However, it is the middle ear effusion and not the infection that causes the hearing loss [149] and - as outlined above - can lead to social consequences. With regard to CAP in children and adults, there are sometimes contradictory results on treatment adherence, side effects and the socio-economically relevant absence from work of parents/childcarers [84,87,89,92,94]. At the same time, the sometimes difficult differentiation from viral infections makes it difficult to weigh up whether antibiotics should be used at all [150]. Overall, Bielicki (2021) and Barratt (2021) conclude that the data situation points to a complex and dynamic relationship between duration, dose, treatment success and resistance development in antibiotic therapies [87,89]. In this context, the Federal Cabinet adopted the German Antibiotic Resistance Strategy 2030 (DART 2030 [132]) in April 2023. To combat the development of antibiotic resistance, the G7 health and agriculture ministers have committed to establishing and expanding integrated surveillance systems on antibiotic use and resistance. The long-term goal is to link (molecular) data from the human and veterinary fields, the environment, epidemiological data and other context-relevant data with socio-medical data [132]. The German Professional Association of Otorhinolaryngologists is also aware of the issue and, for example, held a congress on the topic of antibiotic avoidance in 2021 [161].

Explicit sources on the knowledge and understanding of shorter-duration antibiotic administration in AOM and CAP in adults or children could not be identified. However, there are relevant publications on the avoidance of antibiotics and resistance in general: Since preschool children with mild CAP are routinely administered antibiotics in the United States, the "no-antibiotics" strategy was developed there. An evaluation by Szymczak (2024) [162] showed that none of the parents had previously heard of the "no-antibiotics" strategy and that the degree of support for the strategy also varied. In DART 2030 [132], strengthening health literacy in the population, for which access routes must be developed and evaluated, is generally named as being of central importance to ensure compliance with preventive measures. In this context, it should be noted that no information on the advantages and disadvantages of shorter-duration antibiotic use could currently be found on common German health information portals such as the website of the Federal Centre for Health Education [163] and Gesundbund.de [164], neither with regard to the avoidance of antibiotic resistance development nor with regard to information on AOM and CAP. Instead, it is pointed out that the antibiotic should be used for as long as prescribed by the physician [163-166].

With regard to the acceptance of a shorter-duration antibiotic therapy, it was generally stated in the patient interview (ThemenCheck details, Chapter A11 of the full report) that a shorter-duration treatment is fine if it is equally effective. It is emphasized that the chances of success must be balanced against the risks. Patients define treatment success as an improvement in symptoms. This should not be worse than the standard treatment, i.e. the longer-duration treatment. No other explicit publications on the acceptance of a shorter-duration of

antibiotics administration in AOM and CAP could be identified apart from the findings from the patient interviews. Two publications are interesting in connection with the general treatment of AOM in children: Gooch (1996) [167] focuses on the taste of the antibiotic as being decisive for its acceptance by children. Chando (2016) [31] concludes that treatment of AOM in children that supports parents' confidence and addresses their concerns about the child's development can improve treatment results in children with otitis media. One of the identified publications addresses the acceptance and adherence to treatment in children with CAP: In ISCAP (2004) [168] there were discrepancies between the assessment of the practitioners and the assessment of the parents regarding cure and improvement. The authors therefore conclude that parents could possibly benefit from counselling or a second opinion.

When asked whether he was concerned about possible negative aspects of a shorter course of antibiotic therapy, one affected adolescent replied that he was worried about insufficient effectiveness, the failure of symptoms to subside, a long course of disease and a possible relapse after a short-term improvement. In addition, when asked whether the respondents have (social) obligations for which a longer absence or sick leave due to a recurrence of the disease could have negative consequences as a result of an antibiotic therapy period that is too short, the answer was that a recurrence could have a negative impact on school education or work (ThemenCheck details, Chapter A11 of the full report).

Sociocultural aspects of the intervention’s implementation and organization of use

For both AOM and CAP, numerous issues can be found on socio-cultural aspects of the target group or social inequality and the use of (shorter-duration) antibiotic therapy. Two aspects of social inequality are discussed in relation to AOM in children: (1) the likelihood of developing the disease (according to [144,169], children from a low social class, children of North African or Asian origin and children whose parents have a low level of education are more likely to develop the disease) and (2) the subsequent treatment (here too, children from socially disadvantaged backgrounds have less chances of treatment, are more likely to experience complications due to inadequate treatment, are hospitalized more often and receive tympanostomy tubes less frequently [170,171]). Young age and attendance at a day care centre also have an effect in the form of an increased illness rate and a lower treatment success rate [172,173]. With regard to antibiotic therapy in children with CAP, the influence of socioeconomic factors on treatment success or failure is discussed in particular [82,84].

Another relevant sociocultural aspect is the decision-making process between patients and those treating them. In the interview conducted with a patient (ThemenCheck details, Chapter A11), one adolescent stated that he would always take a prescribed antibiotic for as long as prescribed by the doctor. The doctor's recommendation and the opinion of the parents are therefore important when making medical decisions. Another patient specified that the medical recommendation should also be based on scientific findings. Szymczak (2024) [162],

who interviewed outpatient physicians from (paediatric) emergency departments and paediatric practices, also concludes that interventions for the prudent use of antibiotics in children with CAP must take emotional, social and logistical aspects into account.

The prescribing practices and relationships between professionals providing the intervention are also fundamental to the treatment success. In the updated S2k guideline on antibiotic therapy for ENT infections, in the S2k guideline on the management of CAP in children and adolescents, as well as in the S3 guideline on the treatment of adults with CAP, the topics of "duration of antibiotic therapy" and "development of resistance" are assigned great relevance [33,34,102]. For guidelines to result in successful treatment, they must in turn be implemented by practitioners. For Germany, Kohlhammer (2007) attested a great variance in the implementation of guidelines in the treatment of CAP, which is within the specified directives, but should be more closely aligned with the guidelines in order to avoid potential negative clinical or economic consequences [174]. There are also international investigations into guideline compliance in the antibiotic therapy of CAP in children and adults: All of them identify inadequate guideline compliance [175-177]. Sedrak (2017) [178] investigated factors favouring and hindering compliance with guidelines by physicians in CAP. It was found that the acceptance and accessibility of the guidelines by physicians are favourable factors. A generally positive attitude towards antibiotic stewardship services was also helpful, as it provides personalized feedback and updates to practitioners. The study concludes accordingly that a more social and personalized approach could lead to a gradual improvement in guideline-compliant practice in the assessment and treatment of CAP [178].

Summary of social aspects

Overall, the data situation indicates a complex and dynamic relationship between social aspects, specific disease, duration of antibiotic therapy as well as reasons and (social) consequences of treatment failure and success. Even if the data situation is not optimal, there are numerous indications of social disadvantage and other social factors having a negative impact on the likelihood of developing the disease, the consequences of the disease and the success of treatment for AOM and CAP. In addition, there are findings suggesting that a shorter-duration antibiotic therapy could in principle reduce the risk of allergic reactions and side effects, the development of resistance and the overall antibiotic consumption, and lead to greater treatment compliance. The latter in particular seems to be very relevant for successful treatment. The results also make it clear that not only the duration of antibiotic therapy, but also the decision in favour of or against antibiotic therapy should be examined more closely.

From a social perspective, the fundamental goal should be to ensure informed and successful treatment in which sociocultural aspects have as little as possible or no influence on the likelihood of developing the disease and the content or success of treatment. The analysis

shows that this may currently not be sufficiently ensured in the case of AOM and CAP: Although "antibiotic treatment" in relation to both diseases is often discussed among experts and in guidelines, e.g. given the threat of resistance, knowledge of the advantages and disadvantages of (shorter-duration) antibiotic treatment among patients appears to be limited. Rather, the treating physicians appear to be their main source of information. Internationally, however, these doctors do not appear to be providing treatment with satisfactory compliance to the guidelines, and treatment in Germany appears to be provided with a major amount of variance within the guidelines. More recent and disease-specific investigations are needed in order to be able to assess this more accurately. Against this background, particular importance should be attached to (increased) compliance with current, evidence-based guidelines on antibiotic therapy and its duration. A more social and personalized approach to information could lead to a gradual improvement in guideline-compliant practice. In order to address the currently limited knowledge of users, their health literacy should additionally be improved. Socially disadvantaged groups and parents in particular should be focussed on. As a first step, the topic of shorter-duration antibiotic administration could be addressed more frequently in common health portals, for example.

6.3 Results on legal aspects

The legal research questions on the topic "antibiotic therapy: Does shorter-duration administration yield comparable results?" were analysed using the existing legal regulations. This concerns the points outlined in the guidelines for identifying legal aspects developed by Brönneke (2016) [66], in particular the nature of the contractual relationship between the actors and liability aspects in the use of the method, as well as social law issues and those relating to patient consent and information by the physician (see Table 60 of the full report).

The relevant laws and standards (from the German Civil Code [BGB], Criminal Code [StGB], Medicinal Products Act [AMG], Ordinance on Prescription-Only Medicinal Products [AMVV], Social Code Book V) and the relevant commentary literature were investigated and analysed. The legal databases "juris" and "beck-online" were used as search sources and 25 publications were included. The literature was analysed to determine whether it was written by recognized authors, i.e. experts with corresponding specialist knowledge, and whether the content of the publication was meaningful to the research question.

Summary of legal aspects

To summarize, it can be stated that the administration of antibiotics is a treatment contract in the sense of §630a BGB. The main obligation of those providing treatment is the medical treatment of the patient. Those providing treatment also have a number of other obligations, such as documentation, information and due care obligations. In the event of incorrect treatment, civil and criminal liability claims as well as consequences under professional law may be considered.

When prescribing antibiotics, it should always be ensured that antibiotics are to be used as sparingly as possible. An antibiotic should only be prescribed if medically indicated. The patient's consent must be obtained before any medical treatment is carried out. This presupposes their ability to give consent. In the case of minors who are incapable of giving consent, the parents give their consent or refuse treatment. This is generally the case for children < 14 years of age and must be decided individually for children between 14 and 18 years of age, depending on the child's personality and the severity of the intervention. The patient must be informed of alternative methods during the consultation. The practitioner must also provide information about the costs, diagnosis, risks and treatment options. Administration of antibiotics requires information about a possible shorter duration of use and the related risks. Inadequate information may invalidate the effectiveness of the patient's consent.

The standard of due care to be observed for treatment is based on the professional standard recognized at the time. This can be specified through guidelines. The guideline on antibiotic therapy for ENT infections or for the treatment of CAP or AOM indicates the duration of

treatment that should be used as a guide for the treating staff [24,33,34,102]. The following applies with regard to the legal liability implications of prescribing shorter-duration antibiotic therapy: Irrespective of the fact that evidence suggests that a shorter-duration treatment provides equally good therapeutic results for the patient in certain situations, a more differentiated approach is required from those treating the patient. According to the current state of knowledge, it must be assessed on an individual basis whether an antibiotic can be discontinued as soon as the symptoms have subsided or not. The type of disease, the severity, the individual course and the respective type of bacteria must be taken into account.

A treatment error can then result from a negligently taken medical history and the resulting incorrect duration of treatment and the failure to inform the patient about the shorter use of the antibiotic and the associated advantages and risks. If one of the obligations is breached by the treating medical staff, a claim for damages for financial loss and compensation for pain and suffering may be considered in the event of malpractice. In addition, criminal liability may also be considered under certain circumstances. Both civil and criminal liability can be considered in the event of missing or incorrect information.

The costs of antibiotic therapies, both in the prescribed duration and in shortened form, are covered by the health insurance funds.

The special features of the legal aspects relating to the administration of antibiotics can be found in the following Table 8. A detailed presentation of the individual aspects is shown in Table 60 in the ThemenCheck details in Section A5.3 of the full report.

Table 8: Particularities o*f the legal aspects of a shorter-duration antibiotic therapy for AOM/CAP (multipage table)

Legal aspect	**Particularities of a shorter-duration antibiotic therapy for AOM/CAP**	**Standards**	**(Further) literature**
Treatment contract	Treatment contract on the administration of antibiotics for the treatment of AOM/CAP relevant: specific anamnestic, diagnostic and individual therapeutic approach consequence of the categorization as a treatment contract: duty to provide information, duty of documentation, simplified termination without notice special duties of to provide information about the possible alternative methods if there are several treatment options to choose from, the risks, the prospects of success	§ 611 BGB § 627 BGB § 630a BGB § 630d BGB § 630e BGB § 630h BGB	[179-185]
Civil and criminal liability	Possibly compensation for financial losses and compensation for pain and suffering in the event of malpractice malpractice may be present if the necessary medical history was negligently omitted and an antibiotic was consequently prescribed for too short a period of time possibly Criminal liability for simple or negligent bodily harm consent must be given before any medical treatment is carried out effective consent requires the patient's capacity to consent capacity to consent means the natural capacity of will patients who are minors and incapable of giving consent (usually < 14 years, between 14 and 18 years depending on developmental stage and type of intervention): parents or custodial parent as legal representative authorized to give or withhold consent information must include details on diagnosis, risk, therapy and costs the scope of information depends on risk and therapeutic indication: information on shorter-duration use and the risks is required	§ 278 BGB §§ 280 ff. BGB §§ 823 ff. BGB § 223 StGB § 229 StGB	[179,180,186-189]

Table 8: Particularities o*f the legal aspects of a shorter-duration antibiotic therapy for AOM/CAP (multipage table)

Legal aspect	Particularities of a shorter-duration antibiotic therapy for AOM/CAP	Standards	(Further) literature
	The respective treatment option depends on the course and severity of the disease: priority of standard analgesics over antibiotics treating physician must provide information on all available forms of treatment as a general rule: treating physicians decide on suitable treatment options patients can choose the form of treatment from several options (patient autonomy) treating physicians suggest measures they believe to be necessary and patients reject them: patients act at their own risk standard of due care: so-called medical guidelines of the scientific-medical societies are used as a supplement if the patient waives the right to information, this still constitutes effective consent and criminal liability under §§223, 229 of the German Criminal Code is ruled out insufficient information can invalidate the effectiveness of consent consequences under professional law: professional tribunals may issue warnings, reprimands and disqualifications from membership of chamber's bodies and the right to vote, and impose fines		
SHI: **Antibiotic therapy for CAP/AOM**	The insured person must have a disease to be entitled to services from the SHI scheme CAP/AOM are diseases the administration of antibiotics is a medical treatment the principle of economic efficiency must always be observed, §12 SGB V the directives of the G-BA determine which services are covered by the SHI, §92 SGB V the administration of antibiotics is covered by the SHI	§ 2 I a SGB V § 11 V SGB V § 11 VI SGB V § 12 SGB V § 27 I No. 1 SGB V § 28 I SGB V	[190,191]

Table 8: Particularities o*f the legal aspects of a shorter-duration antibiotic therapy for AOM/CAP (multipage table)

Legal aspect	**Particularities of a shorter-duration antibiotic therapy for AOM/CAP**	**Standards**	**(Further) literature**
		§ 92 SGB V	
Private health insurance: reimbursement of antibiotic therapy for CAP/AOM	Medically necessary treatments are covered medically necessary: if necessary according to objective findings and scientific knowledge for CAP/AOM: antibiotics are necessary to cure/alleviate and therefore for treatment of the disease antibiotic therapies are covered by private health insurance	§ 192 VVG GOÄ	[192]

6.4 Results on organizational aspects

The information processing of organizational aspects followed the grid template proposed by Perleth 2014 [67] for the assessment of the organizational consequences of examination methods (see also Table 61 of the full report).

A total of 19 publications were included for the content analysis of the organizational aspects in this ThemenCheck report. Most of the publications addressed general organizational aspects of antibiotic therapy, which are also relevant in the context of shorter-duration antibiotic therapy. In addition, the results of the patient interviews and the "reflective thoughts" of the report authors [63] were integrated into the organizational analysis.

Influence on the prerequisites of service provision

AOM and CAP are common medical conditions, especially in children, and the outpatient treatment of these conditions is part of basic (paediatric) care [15-20,24,33,34,36-38,42]. Shorter-duration antibiotic therapy would not require a change of the place of treatment or the qualifications of the practitioners.

However, the implementation of antibiotic therapy in AOM and CAP is not always consistent with professional standards [174]. In order to increase evidence-based prescribing of antibiotics, guidelines and practice-based professional standards should be adapted to scientific findings with the involvement of stakeholders and taking into account other factors, such as the clinical expertise of practitioners or the needs of patients [178,193]. Training and further education for practitioners can also be important [193-195]. Programmes for the appropriate prescription and use of antibiotics in the sense of "antibiotic stewardship" with low-threshold information and advice services also increase the conscious and correct use of antibiotics [132,178,193,195]. They also create opportunities for exchange between practitioners [194] as well as clear responsibilities [195,196]. Monitoring of correct antibiotic prescription should also take place [194].

Influence on processes

Even with shorter-duration antibiotic therapy, it must still be carefully checked whether antibiotic therapy is indicated at all in the individual case. For both CAP and especially AOM, symptomatic therapy without the use of antibiotics is also sufficient under certain circumstances, especially in children [24,33,34,102]. In cases of good effectiveness and acceptance, shorter-duration antibiotic therapy can save resources [83]; in cases of lower effectiveness (due to increased complications) or lower acceptance (due to more frequent follow-up appointments and longer consultations in the sense of shared decision-making), the opposite may be the case [113]. Risks, reservations or poorer acceptance (see below) may require increased information and follow-up (ThemenCheck details Chapter A11 of the full report [113,194]). There is also a desire for shared decision-making on the part of the patients,

which can increase treatment adherence and the treatment result (ThemenCheck details Chapter A11 of the full report, [6,123,178]).

Further aspects

It is possible that the interests of different stakeholders differ with regard to the duration of antibiotic therapy. While patients are interested in quick and safe healing, avoidance of recurrences and AEs and a quick return to various areas of life (ThemenCheck details in Chapter A11 of the full report), resource-saving treatment, avoidance of resistance and a quick return to work/school are important factors for public health. Practitioners have the task of mediating between these interests and, in compliance with the requirements of the health care system, making a decision on the approach together with the patient [178,196].

The benefit assessment showed that shorter-duration antibiotic therapy can lead to greater treatment adherence [72,79,83]. The patients also stated in the survey that taking medication over a shorter period of time would be easier for them than over a longer period of time (ThemenCheck details, Chapter A11 of the full report). At the same time, one patient said that he had been very irritated by the short prescription period of an antibiotic (not investigated here) and had therefore made several enquiries to different doctors and pharmacists (ThemenCheck details Chapter A11 of the full report, [194]). Easily accessible information with counselling options for the treating staff and the patients and participatory decision-making can help to increase acceptance [6,123,194,195]. Furthermore, the development of strategies for identifying and dealing with reservations on the part of the treating staff and the patients regarding shorter-duration antibiotic therapy can help to increase acceptance [193,194].

In addition, the monitoring of resistance [196], the strengthening of prevention and hygiene [196] and the strengthening of evidence-based health care in general [193-195] have a positive influence on the successful implementation of appropriate antibiotic prescribing.

6.5 Results on environmental and climate aspects

The analysis of environmental and climate aspects is based on the aspects of greenhouse gas emissions, the release of toxic substances, waste management and other aspects (see Table 62 of the full report).

A total of 16 publications were included for the content analysis of the environmental and climate aspects in this ThemenCheck report. These were publications on the environmental and climate aspects of antibiotic therapy in general, which make it possible to assess the consequences of shorter-duration antibiotic therapy. In addition, the results of the patient survey and the "reflective thoughts" of the report authors [63] were integrated into the analysis.

Greenhouse gas emissions

In 2014, emissions caused by the health care system in Germany accounted for 6.7% of the total greenhouse gas emissions, totalling 55.1 megatons of CO_2 [197]. Around a third of emissions from the health care sector are attributable to drugs and medical devices [198]. Longer-duration therapies require larger quantities of drugs to be produced and transported, which increases energy consumption and CO_2emissions. Shorter treatment times reduce the need for drugs and thus also the environmental impact of their production. Therefore, careful and efficient use of drugs could help reduce unnecessary emissions [199].

Information on the CO_2 emissions of penicillin (6.0 g CO_2/g [200]), vancomycin (57.2 g CO_2/g [201]) and amoxicillin (14.3 g CO_2/g [198]) is found in the HealthcareLCA database [202]. The treatment of adults with amoxicillin (dosage: 3 g/day [33]) thus causes 42.9 g CO_2 emissions, and treatment of a child weighing 19 kg (at 55 mg/kg BW) generates 14.9 g CO_2 emissions per day of treatment [198]. In adults, this leads to cumulative amoxicillin-related CO_2 emissions of 128.7 g for a 3-day treatment, 214.5 g for a 5-day treatment, 300.3 g for a 7-day treatment and 429.0 g for a 10-day treatment [198]. For a child weighing 19 kg (mean weight of a 5-year-old child [111]), the cumulative CO_2 emissions from amoxicillin are 44.8 g (3 days), 74.7 g (5 days), 104.6 g (7 days) or 149.4 g (10 days).

However, there are differences in the form of administration. In relation to the amount of active substance, CO<3723>2</3723> emissions increase 1.5-fold for low-dose tablets and 5-fold for suspensions [203]. It can also be determined that all pharmaceutical products have a CO_2 footprint, regardless of whether they are actually used [199]. This is particularly relevant with regard to the wastage involved in unsuitable pack sizes (see Section 5.1). In addition to CO_2, antibiotics have also been shown to influence methane formation in freshwater systems [204].

Toxic substances

The Stockholm International Water Institute (SIWI) draws attention to the inadequate environmental standards in the production of antibiotics, which entail major ecological risks [205]. In particular, the contamination of water bodies by chemical substances and antibiotic residues is criticized, which in turn can promote the development and spread of antibiotic resistance [205,206].

Waste management

Longer-duration antibiotic therapy increases the amount of excreted drugs that can enter the wastewater system via human metabolism and ultimately end up in natural waters [207]. In addition, the improper disposal of unused drugs in particular poses a challenge [208]. Longer-duration antibiotic therapy can lead to an increased amount of medical waste. This also includes unused drugs and contaminated packaging, which can accumulate to varying degrees

depending on pack size, dosage, duration of and adherence to therapy. This waste must be disposed of safely to prevent antibiotics from being released into the environment and to reduce the need for new raw materials through recycling, thereby reducing the environmental impact of raw material extraction and processing [209]. In the context of outpatient therapy, however, most people state that they dispose of the drug containers in the household waste or the toilet [208]. However, wastewater treatment plants are often not designed to completely remove pharmaceutical substances, which leads to contamination of the wastewater and can impair the efficiency of the wastewater treatment processes. In addition, wastewater treatment plants can even favour the spread of antibiotic-resistant bacteria [210].

Further aspects

Careful use of antibiotics is relevant from both an individual and a global perspective. Longer-duration antibiotic therapy leads to an increased excretion of antibiotics and their metabolites into the environment - in the production process, through use and through improper disposal. These substances enter rivers, lakes and oceans via wastewater, which leads to chronic pollution of aquatic ecosystems and promotes the formation of resistance [205-207]. It has even been postulated that a specific "antibiotic footprint" analogous to the CO_2 footprint should be established [211]. The persons surveyed within the framework of patient interviews were also aware that a shorter-duration antibiotic therapy could conserve resources. However, it was pointed out that insufficient healing or recurrence could have the opposite effect due to the need for repeat treatment (ThemenCheck details, Chapter A11 of the full report). Inadequate healing or recurrence often requires (repeat) prescription of antibiotics, partially with a broader spectrum of activity [24,33,34,102]. Environmental pollution and emissions can therefore only be reduced if shorter-duration antibiotic therapy is sufficiently effective.

7 Synthesis of results across domains

As part of this project, an initial logic model based on INTEGRATE-HTA [212] was created as an integrated method for the assessment of complex health technologies. This was revised and expanded during the course of the project in line with the results. The aim was to graphically summarize the relevant aspects for the assessment of the health technology. It includes epidemiological, political, legal (details in Section 6.3), socio-cultural (details in Section 6.2), ethical (details in Section 6.1), geographical/environmental/climate (details in Section 6.5) and socio-economic contextual factors. Furthermore, criteria for study participants and the tested intervention with intervention theory and expectations as well as the comparator intervention are presented (details in Chapter 3). Finally, patient-relevant outcomes (details in Chapter 4) and other (health economic and ecological) outcomes (details in Chapter 5 and Section 6.5) are summarized in an overview and factors for successful implementation (see Section 6.4) are defined.

Figure 1 summarizes the results of this ThemenCheck report as a logic model based on INTEGRATE-HTA [212].

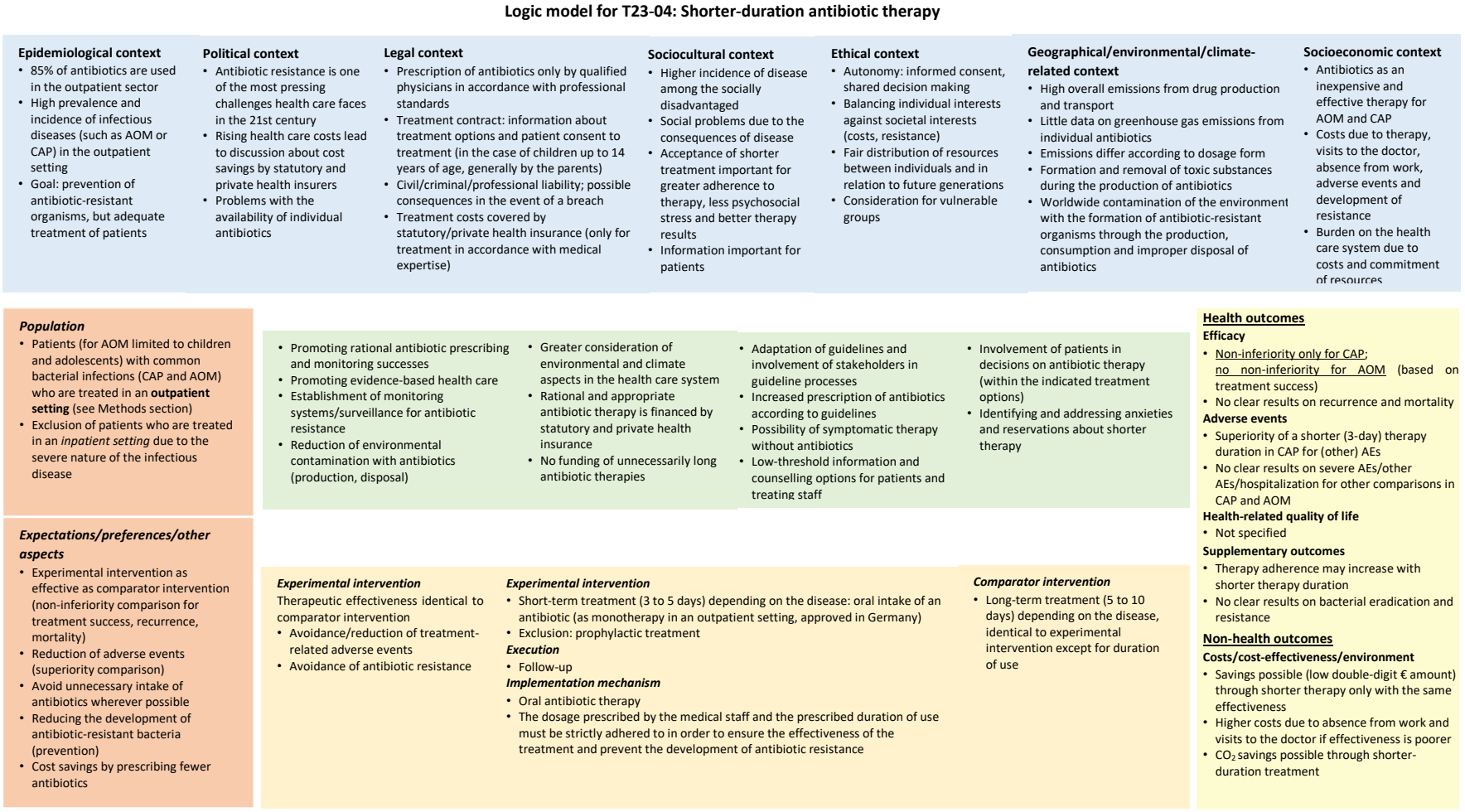

Figure 1: Logic model for T23-04: Shorter-duration antibiotic therapy

8 Discussion

AOM and CAP are common clinical pictures in primary care and paediatric primary care [19,20,36,38,47]. Effective and inexpensive antibiotic therapies are available for both diseases. The choice of the antibiotic used depends on the severity of the disease and the expected pathogen spectrum as well as patient-related factors [24,33,34,102]. For AOM and CAP in children and adults, amoxicillin is the first-choice antibiotic in uncomplicated cases and in the absence of contraindications [24,33,34,102]. If there is insufficient improvement, contraindications or risk factors, other antibiotics are also available. However, discussions are ongoing as to how long initial antibiotic therapy should last. The guidelines specify a treatment duration of 7 to 10 days for AOM and 5 days for CAP [24,33,34].

Shorter-duration antibiotic therapy would be desirable in principle since every administration of antibiotics can potentially trigger side effects in the treated persons or resistance in bacteria [7], which also play an increasing role in society as a whole [164], 2021 #3889}. In addition, shorter-duration treatment can also reduce the psychosocial effects of the disease [6,125]. It may also be possible to reduce treatment costs (see Section 5.1, [168]), to increase treatment adherence (see Section 4.5.6; [123,124]) and to avoid CO<5144>2 </5144> emissions and environmental pollution during the production, packaging and disposal of antibiotics (see Section 6.5). The (improper) discharge of antibiotic-contaminated substances into the environment during production as well as improper disposal also stimulate the formation of resistance in bacterial strains [205-208,210].

On the other hand, patients desire a fast recovery and symptom relief and hope to avoid recurrences, which may not only be stressful for the individual, but can also be important against the background of possible social obligations. For children in particular, absence from school has a negative impact on education and opportunities for social advancement - especially in view of the fact that children from socially disadvantaged families may be more commonly affected by the diseases [144,151,152,169]. AOM can also affect hearing, which in turn can have long-term social consequences [141-149]. However, the effects of the disease on hearing were considered (without statistically significant difference) in only one of the identified studies [71] and consequential long-term effects were not reported in any study.

Also, treatment costs can only be reduced by shorter-duration antibiotic therapy if the savings in the prescription of antibiotics are not exceeded by frequent visits to the doctor, treatment of complications or longer absences (of parents) from work [113]. The same applies to the prevention of resistance or environmental impact: If antibiotic therapy is not sufficiently effective, subsequent treatments with a new prescription of antibiotics (possibly with a broader spectrum) are necessary [24,33,34,102].

Accordingly, the benefit assessment and here, in particular, the outcome treatment success (and recurrence of infection) are of the utmost importance. This also became clear in the patient interviews (ThemenCheck details, Chapter A11 of the full report). AEs, mortality and health-related quality of life are also important factors for patients. Sustainable advantages in terms of costs/cost-effectiveness, environmental pollution, microbiological resistance or treatment adherence can only be expected if the medical benefits are roughly equivalent.

With equivalent effectiveness, organizational and legal issues would have to be addressed, taking ethical and social aspects into account. Shorter-duration treatment could be adopted in the guidelines as a professional standard, with the involvement of stakeholders and taking into account other factors such as clinical expertise or patient needs [178,193]. Without anchoring in professional standards, liability issues in the event of shorter-duration antibiotic therapy would be unclear (see Section 6.3). To efficiently reduce costs and conserve resources, manufacturers could also adjust pack sizes in some constellations (see Section 5.1 and Section A4.1 of the full report).

When a disease is treated by qualified physicians (only these physicians are authorized to prescribe antibiotics), a treatment contract is made which obliges the practitioner to provide information about the advantages and disadvantages of the treatment options and to document them (see Section 6.3 and Section A5.3 of the full report in the ThemenCheck details of the full report). For children up to the age of 14, information is always provided to the parents [179]. In the spirit of shared decision-making between the practitioner and the patient, information should be provided about the effect and potential side effects as well as treatment alternatives before any therapy so that the patient and the practitioner can make the best possible informed decision [128,129]. However, the treatment must be based on professional standards and therefore the patient's choice only applies to medically indicated treatment options [180,213].

Providing patients with reliable information can also increase treatment adherence [123]. However, social consequences, such as the increased risk of developing resistance, should also be considered in the decision [125,129,130]. In justified cases, however, it may be possible to deviate from the guidelines and administer a longer-duration antibiotic therapy [179]. In the case of medically necessary measures, the treatment costs are generally covered by statutory and private health insurance, but not in the case of unnecessary prescriptions of antibiotics (see Section 6.3 and Section A5.3 in the ThemenCheck details of the full report).

It should also be noted that, under certain circumstances, treatment for both AOM and CAP can be purely symptomatic without antibiotics [24,34,102]. Avoiding antibiotics in these cases could also have a positive impact on side effects, psychosocial burden, costs, environmental factors and the development of resistance.

The targeted provision of information to patients and treating staff also plays an important role in the general quality of treatment, as in many cases treatment is not uniformly based on the guidelines [174]. Obstacles and reservations on the part of the practitioners and the patients should be identified and addressed [193,194]. Regulations based on antibiotic stewardship can also reduce unnecessary prescriptions of antibiotics and thus prevent the development of resistance [132,178,193,195]. A system for monitoring the development of resistance in bacteria could also be helpful in making antibiotic therapy even more targeted [196].

8.1 ThemenCheck report compared with other publications

There are a large number of systematic reviews comparing shorter-duration with longer-duration antibiotic therapy for AOM or CAP in children or adults. For many of these systematic reviews it was decided to summarize different classes of antibiotics in meta-analyses [214-220]. However, in view of the different points of attack and modes of action of the antibiotic classes and the therefore limited informative value of an overall result, the antibiotic classes were considered individually in this ThemenCheck report.

8.1.1 AOM

A Cochrane review by Kozyrskyj (2010) [214] and a systematic review by the WHO (2009) [220] included studies comparing different antibiotics as well as drugs without marketing authorization in Germany in addition to the studies investigated in this ThemenCheck report. The WHO report found no statistically significant difference between a shorter (≤ 3 days) and a longer-duration treatment in terms of treatment success [220], while Kozyrskyj (2010) determined that a shorter-duration treatment was statistically significantly less effective in many comparisons of treatment success [214]. When analysing individual antibiotic classes, both publications agree on results that, similar to the results of this ThemenCheck report, suggest a possibly lesser efficacy of shorter-duration treatment with various beta-lactam antibiotics, such as amoxicillin(-clavulanic acid) [214,220].

A systematic review with network meta-analysis by Kim (2024) [221] including drugs without marketing authorization in Germany and comparisons of different antibiotics also concludes that a 5-day treatment duration shows worse treatment results for some antibiotics than a 10-day treatment duration. However, non-inferiority of 7-day versus 10-day antibiotic therapy with amoxicillin and amoxicillin-clavulanic acid was concluded on the basis of indirect comparisons. The non-inferiority boundary used was not reported. However, neither the systematic review by Kim (2024) nor this ThemenCheck report identified any RCTs with a direct comparison of these treatment durations for the comparison of 7 vs. 10 days of treatment.

8.1.2 CAP

Regarding CAP, a Cochrane Review by Haider (2008) [216] and a systematic review by Li (2022) [217] came to the same conclusion regarding treatment success as this ThemenCheck report, i.e. that 3-day therapy with amoxicillin is not inferior to 5-day amoxicillin therapy in the treatment of CAP in children. Two included studies on co-trimoxazole did not fulfil the inclusion criteria of this ThemenCheck report, as no full publications were available [103,104].

A systematic review by Kuitunen (2023) [222] included studies comparing 3 to 5 days of treatment with 7 to 10 days of treatment in children > 6 months of age. Here, 4 studies were included and a non-inferiority of the shorter-duration treatment in terms of treatment success was shown, but without going into the comparison of 3 vs. 5 days of amoxicillin. Similar results were also shown for 5 vs. 10 days of amoxicillin therapy in the systematic review by Marques (2022) [223], which included 3 studies. All studies included in these reviews were also part of this ThemenCheck report.

This ThemenCheck report could not identify any relevant studies on the duration of antibiotic therapy for outpatient treatment of CAP in adults. Other systematic reviews, such as the Cochrane review by López-Alcalde (2018) [224], also failed to identify any relevant studies.

Other systematic reviews, for example by Furukawa (2023) [215], Tansarli (2018) [219] or Royer (2018) [218], included studies with hospitalized patients as well as studies with drugs not approved in Germany or studies with different antibiotics and dosages used between the intervention and comparator group. In most cases, shorter-duration antibiotic therapies yielded a comparable effect.

8.2 ThemenCheck report compared with guidelines

8.2.1 AOM

The latest available guidelines describing the treatment (duration) of AOM are the S2k guideline on antibiotic therapy for ENT infections from the German Society of Oto-Rhino-Laryngology, Head and Neck Surgery (Deutschen Gesellschaft für Hals-Nasen-Ohren-Heilkunde, Kopf- und Hals-Chirurgie e.V., DGHNO-KHC) from 2019, and an S2k guideline on earache from the German Society of General Practice and Family Medicine (Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin e.V., DEGAM) from 2014 [24,102]. Both guidelines are currently being updated, with the finalization being planned for mid-2025 [225] and mid-2026 (the latter as an S3 guideline) [226].

The available guidelines explain in detail the possibility of purely symptomatic therapy. Not all children in all studies included in this ThemenCheck report met the current requirements for the indication of antibiotic therapy (see Table 14 in the ThemenCheck details in Section

A3.2.1.1 of the full report). For example, Hendrickse (1988) included children up to 12 years of age with AOM without the need for other factors to justify antibiotic therapy.

If antibiotics are required, amoxicillin 50 mg/kg BW/day (2-3 single doses) over 7 days is recommended as the first choice [24,102]. Under certain circumstances, however, the dose can be increased and a beta-lactamase inhibitor can be added (amoxicillin-clavulanic acid). Alternatives include second-generation (e.g. cefuroxime) or third-generation cephalosporins (cefpodoxime) and macrolides (e.g. erythromycin) [24,102]. Studies on amoxicillin, amoxicillin-clavulanic acid, cefuroxime and cefpodoxime were identified in this ThemenCheck report, although the only study on cefuroxime could not be included in the benefit assessment for important outcomes due to high rates of study discontinuation. The results of this report were unable to show non-inferiority of shorter-duration therapy (2/3/5 days) compared with longer-duration therapy (7/10 days) for any of the antibiotics under investigation. Some of the results of the individual studies even showed statistically significantly lower rates of treatment success with 5-day therapy compared to 10-day therapy.

Various studies have shown that the probability of treatment success after antibiotic therapy increases with the children's age [73,81,227]. Many professional associations therefore recommend an antibiotic therapy duration for AOM that is adapted to the child's age. The German Society for Pediatric Infectious Diseases (Deutsche Gesellschaft für Pädiatrische Infektiologie, DGPI), the German Society of Pediatrics and Adolescent Medicine (Deutsche Gesellschaft für Kinder- und Jugendheilkunde, DGKJ), the German Academy for Paediatric and Adolescent Medicine (Deutsche Akademie für Kinder- und Jugendmedizin, DAKJ) and the German Professional Association of Paediatricians (Berufsverband der Kinder- und Jugendärzte, BVKJ) jointly recommend 10 days of antibiotic therapy for children < 2 years of age, 7 days for children ≥ 2 years and 5 to 7 days for children ≥ 6 years [228], as does the American Academy of Pediatrics [27]. The British NICE guidelines generally recommend antibiotic therapy for 5 to 7 days, referring to the present but, in the committee's view, tolerable difference between shorter and longer-duration treatment [229], which was demonstrated in the systematic review by Kozyrskyj (2010) [214].

8.2.2 CAP

The current S2k guideline of the German Society for Paediatric Pneumology (Gesellschaft für Pädiatrische Pneumologie, GPP) and the German Society for Paediatric Infectiology (Deutsche Gesellschaft für Pädiatrische Infektiologie, DGPI) on CAP in children was published in 2024 and recommends oral amoxicillin at a dosage of 50 mg/kg BW/day over 5 days as first-line treatment for non-severe pneumonia [34]. The British NICE guidelines also make similar recommendations [44]. With regard to the duration of antibiotic therapy, this ThemenCheck report was also able to determine the non-inferiority of a 5-day therapy compared to a 10-day therapy.

At the same time, the guidelines emphasize the lack of need for antibiotic therapy in infants and young children with signs of viral genesis. However, some of the studies analysed in this ThemenCheck report included children with signs of viral origin. This is referred to in the German guidelines when discussing 3-day amoxicillin therapy – with regard to the studies by MASCOT (2002) [82], ISCAP (2004) [83] and Ginsburg (2020) [84], which are also included in this ThemenCheck report. These were conducted in Pakistan, India and Malawi. As in Germany, the diagnosis was based on the clinical condition without the need for an X-ray examination. Airway obstruction in the form of wheezing as an adventitious breath sound occurred as a symptom of viral disease in 22.3% [82], 13.1% [83] and 1.6% [84] of the study population, respectively. In ISCAP (2004), the outcome of treatment success is also stated separately for children with and without wheezing, without relevant differences [83]. RSV smears also only provided positive detection in a minority of around 20% and this does not rule out co-infection with bacteria [34]. In addition, pyrexia as a common indication for antibiotic therapy in Germany [34] was present in the medical history of many participants in the studies (see Table 19 in the ThemenCheck details in Section A3.2.1.2 of the full report). The underweight status of some sick children and breastfeeding in children > 12 months, as well as the relatively lower rate of children with complete vaccination against pneumococci additionally increases the probability of bacterial pneumonia [230-232]. The chest wall retractions of the children included in the study by Ginsburg (2020) also point to pronounced symptoms, which are also a decisive factor for antibiotic therapy in Germany [34]. In order for a statistical non-inferiority to be no longer present in these studies, the results of > 40% of the patients included would have to be unusable. This percentage of patients included would therefore not have to receive an indication for antibiotic therapy under German standards. This seems unlikely given the characteristics of the study populations for the studies by ISCAP (2004) and Ginsburg (2020). The transferability only remained unclear in the study by MASCOT (2002), as only a small proportion of the children showed signs of pneumonia in radiological examinations. Sensitivity analyses were conducted without this study, but these did not significantly change the overall result.

In addition, the multicentre study by Bielicki (2021) [87], also mentioned above, with 824 children included, is also a study from high middle-income countries that excluded children with signs of non-bacterial pneumonia and showed non-inferiority of a 3-day therapy. The study by Greenberg (2014) [90], which is also cited in the DGPI guidelines, but which showed a poorer efficacy of a 3-day therapy, was also included in this ThemenCheck report and had a high risk of bias and only 18 analysed participants (in this study phase), and therefore had little influence on the overall result.

However, it should be noted that all included studies only included children aged 2 months to just under 5 years or up to a weight of 24 kg.

Based on the summarized review of the studies, an initial 3-day treatment duration with amoxicillin in younger children under 5 years of age without clinically significant underlying disease with non-severe CAP appears to be justifiable if (as recommended for non-severe cases) the diagnosis is made purely clinically on the basis of symptoms and clinical examination. However, if there are additional radiological or laboratory findings, a different approach may be more suitable. The reference in the guidelines to a Cochrane review by Lassi (2015) [233], which refers to a lack of evidence for a 2 to 3-day therapy duration, is not relevant with regard to this ThemenCheck report, as the Cochrane review only addresses intravenous therapy.

The current S3 guideline on CAP in adults from the German Respiratory Society German Society for Pneumology and Respiratory Medicine (Deutschen Gesellschaft für Pneumologie und Beatmungsmedizin, DGP) (together with other professional societies), which was published in an updated version in 2021, recommends a treatment duration of 5 days for non-severely ill patients if clinical stabilization has been achieved for at least 2 days [33]. Amoxicillin is recommended as the drug of first choice for patients without relevant comorbidity. The reviews already discussed in Section 8.1.2, which also include hospitalized patients and drugs without marketing authorization in Germany as well as comparisons of different drugs or dosages, were used to prove this [219,234].

Shorter treatment durations are also proposed as a treatment option for some antibiotics - azithromycin for 3 days and amoxicillin for 3 days [33]. The underlying studies also include hospitalized patients or compare treatment regimens with different antibiotics. In this ThemenCheck report, no conclusion could be drawn about shorter-duration antibiotic therapy in adults with CAP, as no studies could be identified that met the inclusion criteria.

8.3 Limitations and critical reflection on the approach

Inclusion criteria

This ThemenCheck report only included outpatients with AOM or CAP. In the study by Bielicki (2021), it is pointed out that, especially in children with the same severity of CAP, outpatients and inpatients can be expected to achieve similar results; therefore, the primary analysis no longer distinguished between outpatients and inpatients [87]. Other reviews also included studies with inpatients or on the comparison of different antibiotics and antibiotic doses [215,218,219]. Such an approach would have allowed more studies to be identified and included, particularly with regard to CAP in adults, where no studies could be identified that met the inclusion criteria of this ThemenCheck report. However, due to other patient characteristics, greater disease severity, the antibiotics used and the intravenous administration that may have been applied, the results would have been transferable to the outpatient health care context only to a limited extent.

As IQWiG's ThemenCheck reports generally do not investigate drugs without a valid marketing authorization in Germany, 3 studies on AOM in children (on cefprozil [97] and ceftibuten [98,99]) and 2 studies on CAP in adults (on gemifloxacin [101] and telithromycin [100]) were excluded. Although cefprozil has no marketing authorization in Germany, it is approved in other European countries and in the USA [235,236]. The marketing authorization for ceftibuten in Germany expired in 2017 after the product was no longer marketed by the manufacturer for economic reasons [237,238]. The marketing authorization for telithromycin in Germany also expired in 2019, after its use had already been restricted due to severe side effects in some cases [238,239]. An application for marketing authorization of gemifloxacin in Europe to the EMA Committee for Medicinal Products for Human Use (CHMP) was withdrawn by the manufacturer in 2009 [240]. Although the drugs themselves do not have marketing authorization, there are drugs in the same antibiotic class of second/third generation cephalosporins, fluoroquinolones or macrolides that do have marketing authorization and are used for the treatment of these clinical pictures [24,33,34,102].

In the study on cefprozil, not difference was found between 5 and 10 days of treatment for the outcome treatment success in AOM (RR [95% CI]: 0.98 [0.94; 1.02]; p=0.273) [97]. In one study, when administered for 5 days compared to 10 days, the efficacy of ceftibuten was statistically significantly weaker in terms of treatment success in AOM (RR [95% CI]: 0.80 [0.71; 0.89]; p<0.001) [98]. One other study on ceftibuten did not provide any results on treatment success in AOM, but recurrence occurred statistically significantly more often in the 5-day treatment group compared to the 10-day treatment group (RR [95% CI]: 4.75 [1.68; 13.40]; p=0.003) [99].

The excluded study by Tellier (2004) [100] investigated 5 vs. 7 days of telithromycin for the treatment of CAP in adults and showed comparable rates of treatment success between the groups (RR [95% CI]: 1.00 [0.91; 1.10]; p=0.969). This study also provided health economic data, which were published in Niederman (2004), but could not be included in this report due to the lack of marketing authorization of the antibiotic in Germany [241]. The excluded study by File (2007) [101] investigated 5 vs. 7 days of gemifloxacin for the treatment of CAP in adults and also showed comparable rates of treatment success between the groups (Days 7 to 9: RR [95% CI]: 1.02 [0.97; 1.07]; p=0.474; day 24 to 30: RR [95% CI]: 1.06 [1.00; 1.13]; p=0.039).

Study characteristics

The included studies are of different ages (published between 1982 and 2022) and therefore differ in terms of methods, the drugs analysed and the treatment durations investigated. Not all comparisons are relevant in today's context. For example, the antibiotics penicillin V and cefixime investigated in the studies included here are not recommended in the guidelines as the treatment of choice for the outpatient treatment of AOM [24,102]. Therefore, only investigated and recommended drugs for the treatment of AOM or CAP were analysed as

examples for the health economic intervention costs. With 10 vs. 20 days of amoxicillin, Mandel (1995) [72] also investigated an irrelevantly long period of antibiotic use; therefore, the relevance of the study is limited for the German context, where 5 to 10 days are recommended depending on the recommending professional society and the age of the child [24,102,228]. Pathogen spectrum and resistance situation also differ in the temporal and geographical context [242-245].

The diagnosis of infectious diseases in the studies was based on different symptoms and examinations. For example, in the studies by Pernica (2021) [92] and Greenberg (2014) [90] CAP required an X-ray with typical findings, whereas MASCOT (2002) [82], ISCAP (2004) [83], Ginsburg (2020) [84] and Bielicki (2021) [87] did not. In AOM, the required symptoms or the required otoscopy findings differed. The age and exclusion criteria were also not consistent between the individual studies and not consistent with current indications for antibiotic therapy. This may result in limitations to the transferability of studies to the current German health care context, as discussed for the studies by MASCOT (2002) [82], ISCAP (2004) [83] and Ginsburg (2020) [84] in Section 8.2.2. Based on the characteristics of the study population, transferability of the results could be attested at least for the studies by ISCAP (2004) and Ginsburg (2020), and sensitivity analyses were conducted for MASCOT (2002). The inclusion and exclusion criteria are shown in Table 14 and Table 18 and the study populations are characterized in Table 15 and Table 19 in the ThemenCheck details in Section A3.2.1 of the full report.

The definition of the composite outcome treatment success also differed between the studies. This often consisted of symptom relief and possibly also improvement of the clinical findings. In many studies, recurrence was included in this outcome. The time point of recording also did not always follow the recommendations of the EMA (AOM: 1 to 2 days after the end of treatment and possibly approx. 14 to 21 days after the start of treatment; CAP: 5 to 10 days after the end of treatment) [57]. As different outcome definitions and data recording times can jeopardize the comparability of the studies and influence the interpretation of the results, Table 13 and Table 17 in the ThemenCheck details in Section A3.2.1 of the full report present the individual definitions of the studies for the outcome treatment success with data recording times in detail. Subgroup analyses did not prove useful due to the data situation.

Overall, only a few deaths were reported in the studies. These were also not recorded in a structured manner in the studies on AOM. However, given the extremely low mortality from AOM in Europe of < 5 cases per 10 million people [15], the recording of deaths would have been difficult in studies anyway and in very few cases would have been causally attributable to the course of disease.

With regard to the recording of treatment adherence, studies with different analysis dates and non-placebo-controlled studies are of particular interest, as the duration of

administration is different only in these studies. However, the lack of blinding involves higher risks of bias of the results.

Non-inferiority research question

The choice of non-inferiority boundaries of the RR (0.9 and 1.1) for AOM and CAP was based on EMA recommendations [57,58]. The use of relative values results in different absolute differences due to the different occurrences of the events investigated. Relative deviations of 10% concur with an absolute difference of 9 percentage points (number needed to harm (NNH) of 11) at a treatment success rate of the control group of approx. 90%. With a recurrence rate of the infection of approx. 5%, a relative deviation of 10% concurs with an absolute difference of only 0.5 percentage points (NNH of 200). Accordingly, the outcome treatment success is the most important item in the overall assessment, as it affects most of the patients and the largest absolute changes occur for this outcome. The outcomes recurrence and mortality, on the other hand, affect only a few people due to the low incidence rate; therefore, changes here have only very minor absolute effects and are thus of secondary importance for individual patients.

In principle, the ITT analysis, which takes into account all randomized study participants, is preferred in ThemenCheck reports [246]. However, for non-inferiority research questions, this can contribute to alterations in the results [247]. The use of ITT analyses nevertheless appears to lead to more conservative estimates in the context of non-inferiority research questions on antibiotic therapy [248]. The ITT analyses were therefore used in this ThemenCheck report, but the PP analyses (if available) were also considered (see footnotes in the tables in Section A3.3 in the ThemenCheck details of the full report). However, these always delivered comparable results.

In the case of non-inferiority research questions, there is also a risk in serial testing that acceptable differences (within the non-inferiority boundaries) accumulate and ultimately lead to significant differences (unacceptable differences beyond the non-inferiority boundaries), which are not detected by the serial comparisons [249-252]. This phenomenon, also known as bio-creep, might also have an influence in the study situation of this ThemenCheck report on CAP with studies comparing 5 vs. 10 days of amoxicillin therapy and other studies comparing 3 vs. 5 days of amoxicillin therapy. However, due to a more recent study on bio-creep in antibiotic therapy [252], the clarity of the non-inferiority and the study situation with further included studies (3 vs. 7 days, 3 vs. 10 days), a relevant influence on the result seems unlikely.

9 Conclusion

This ThemenCheck report included a total of 19 randomized studies with 22 publications, which investigated shorter with longer-duration antibiotic therapy in children treated as outpatients - 12 studies (with 12 publications) on AOM and 7 studies (with 10 publications) on CPA. Studies on the duration of antibiotic therapy for CAP in adults that met the inclusion criteria of this report were not identified.

AOM

12 studies on AOM with 3409 randomized children investigated the antibiotics penicillin V (n=2), amoxicillin (n=2), amoxicillin-clavulanic acid (n=3), a first-generation cephalosporin (cefaclor, n=2), a second-generation cephalosporin (cefuroxime, n=1) and third-generation cephalosporins (cefixime and cefpodoxime, n=2). The compared treatment durations were 5 vs. 10 days (n=8), 2 vs. 7 days (n=1), 3 vs. 7 days (n=1), 3 vs. 10 days (n=1) and 10 vs. 20 days (n=1). The age of the included children ranged from 1 month to 14 years and varied between the studies. One study had a low risk of bias and the other 11 studies had a high risk of bias across outcomes.

Nine studies investigating children with AOM provided data on the outcome treatment success. A hint of non-inferiority of the shorter treatment duration could not be found for any of the comparisons. Many individual studies even reported statistically significantly poorer rates of treatment success with shorter therapy.

Ten studies also reported the outcome recurrence, 8 studies reported AEs and data on mortality could be derived from 2 studies. No data were available on any of these outcomes that could justify a hint of non-inferiority of the shorter-duration treatment. However, a lacking hint of non-inferiority cannot generally be used to conclude an inferiority of the shorter-duration antibiotic therapy. Data on health-related quality of life were not reported.

Overall, based on the current data situation, it cannot be assumed that shorter-duration treatment (of 2/3/5 days) provides equivalent therapy results compared to longer-duration treatment (of 7/10 days). However, there is a lack of analyses on age-stratified approaches and studies on adolescents. Reliable data on other outcomes, such as health-related quality of life, are also missing. In addition, there is a lack of reliable studies on further comparisons of antibiotic therapy durations (such as 7 vs. 10 days) and on various antibiotics used in Germany, above all amoxicillin, which is mentioned in the guidelines as the first choice in the antibiotic therapy of AOM.

CAP

All 7 studies on CAP with 8590 randomized children investigated amoxicillin as an antibiotic. The compared treatment durations were 3 vs. 5 days (n=3), 3 vs. 7 days (n=1), 3 vs. 10 days

(n=1), 5 vs. 10 days (n=3) (one study investigated both 3 vs. 10 days and 5 vs. 10 days). The age of the included children ranged from 2 months to 10 years. Six studies had a low risk of bias and 1 study had a high risk of bias across outcomes.

All 7 studies delivered data on the outcome treatment success. With regard to treatment success, proof could be derived that 5-day treatment with amoxicillin is not inferior to 10-day treatment for the outpatient treatment of CAP. Moreover, this proved that even 3-day treatment with amoxicillin is not inferior to longer-duration treatment (of 5/7/10 days) in terms of treatment success. For other AEs, there was not only proof of non-inferiority, but even proof of superiority of shorter-duration treatment of 3 days versus a longer-duration treatment of 5 days. However, no hint of non-inferiority could be derived from the comparison of AEs of 5-day versus 10-day treatment. Nor could a hint of non-inferiority of the shorter treatment durations be derived for the outcomes recurrence (reported in 5 studies) and mortality (reported in 7 studies). However, the absence of a hint of non-inferiority cannot generally be used to conclude an inferiority of the shorter-duration antibiotic therapy. Data on health-related quality of life were not reported.

A summary of the outcomes thus showed that 3-day antibiotic therapy with amoxicillin is not inferior to longer therapy in the treatment of clinically diagnosed non-severe CAP in children, even if the study situation permitted a derivation of superiority (in terms of other AEs) of shorter-duration antibiotic therapy only for the comparison of 3 versus 5 days of therapy. The effects of an even shorter duration of antibiotic remain unclear. In this context, reference should be made to an ongoing study from Australia, which compares a treatment duration of 2, 3, 4 and 5 days of amoxicillin in 4 study arms. Furthermore, studies on the duration of antibiotic therapy for other common antibiotics such as amoxicillin-clavulanic acid, clarithromycin or doxycycline are missing. There is also a lack of studies on the duration of antibiotic therapy in older children and adolescents.

No relevant studies on the outpatient treatment of CAP in adults could be identified. Here, too, there are no studies on the duration of treatment with the drugs recommended in Germany, i.e. amoxicillin, amoxicillin-clavulanic acid and doxycycline, as well as with fluoroquinolones and macrolides approved in Germany.

General results on shorter-duration antibiotic therapy

For the supplementary outcome treatment adherence, 8 studies reported data (4 studies each on AOM and CAP). This may increase with shorter treatment duration: 2 studies showed better treatment adherence with shorter-duration treatment (1 study on AOM comparing 5 vs. 10 days and 1 study on CAP comparing 3 vs. 5 days). The other studies investigated only one point in time and were placebo-controlled, so that both groups had to take drugs for the same period of time.

Five studies reported data for the supplementary microbiological outcomes (4 studies on AOM and 1 study on CAP). These did not reveal any clear differences between shorter and longer-duration treatment in terms of eradication and resistance development.

The costs of the indicated antibiotic therapy are covered by statutory or private health insurance funds with co-payments by the patient if applicable. In example calculations, the therapy costs for SHI funds can be reduced by up to approx. 35 € for an infant weighing 5 kg, a child weighing 19 kg or an adult by shortening the treatment duration with various antibiotics used. The therapy costs were significantly lower when tablets were administered instead of solutions. In some calculations, the treatment costs remained unchanged due to the available pack sizes for different treatment durations. Adjusting the pack size could therefore reduce wastage and achieve a further reduction in antibiotic costs.

Two studies with health economic evaluations (1 modelling study on AOM and 1 RCT on CAP) were identified. The study on AOM showed that the shorter treatment duration (5 days) is less efficient, but entails lower drug costs compared to a longer treatment duration (7 to 10 days). Overall, however, shorter-duration treatment caused higher costs due to visits to the doctor and absence from work. Overall, the reduction in the treatment duration from 5 days to 3 days resulted in cost savings, with equivalent efficacy as shown in the study on CAP. However, it must be noted that these studies were conducted in the context of other health care systems (USA and India) and the calculations of the studies are therefore only transferable to the German context to a limited extent.

Drug production and transport is one of the main sources of CO_2 emissions in the health care sector. Furthermore, antibiotics and metabolites are released into the environment as a result of discharge during production, excessive use and improper disposal, where they result in increased resistance formation. Shorter treatment durations reduce the amount of drugs required if pack sizes adapted to the shorter-duration treatment are available. Shorter-duration antibiotic therapy can thus help to reduce CO_2 emissions and environmental pollution, provided that it is also sufficiently effective without the need for consecutive administration of antibiotics.

In ethical terms, it is especially the autonomy of patients (and especially of vulnerable groups) that plays a major role. This can be strengthened through comprehensive (age-appropriate) information and participatory decision-making in the sense of shared decision making, which leads to better treatment adherence and better treatment outcomes. However, in certain constellations, individual patient autonomy can be in conflict with societal interests (avoiding unnecessary prescriptions of antibiotics and resistance development), so that careful balancing should be carried out, tailored to the individual cases - taking into account fairness in the distribution of resources and towards future generations.

Important social aspects are the unequal distribution of the likelihood of falling ill and unequal treatment measures as well as the consequences of illness, such as hearing damage in children with otitis media, missed school and work days or mortality (especially in older people with pneumonia). In addition, the acceptance of shorter-duration antibiotic therapy is important, which can be achieved primarily through good treatment results in terms of symptoms and relapse, but also through comprehensive information. For the latter, the range of information available to the treating staff and the patients could be expanded.

Legally, only physicians are authorized to prescribe prescription medicines (which include antibiotics). Treatment should be based on professional standards, otherwise civil and criminal law consequences with liability may follow. In the event of deviations from the standards, as is currently the case with shorter-duration antibiotic therapy, for example, individual factors must therefore be balanced in detail and carefully explained. In principle, the treatment contract involves obligations to provide information about the advantages and disadvantages of indicated treatment options, with the patient being able to choose between the indicated therapies. In the case of minors who are incapable of giving consent, this primarily concerns the guardians.

In organizational terms, the adaptation of professional standards to findings on the duration of antibiotic therapy is of central importance, also in view of the results of this ThemenCheck report and taking into account other factors important for the development of guidelines, such as the clinical expertise of the treating staff or the needs of patients. In view of the great variability in treatment in Germany, measures that facilitate the uniform, appropriate prescription of antibiotics in accordance with professional standards in practice and that increase acceptance are particularly important. Practical education with low-threshold counselling options for those providing treatment and for patients as well as the involvement of patients in decision-making processes play a major role here.

Overall, shorter-duration antibiotic therapy appears to be easy to carry out, cost-effective, environmentally and resource-friendly, ethically and socially acceptable and can be implemented without considerable legal hurdles, provided that the therapy can be considered equivalent in terms of the medical treatment result. While in clinically diagnosed CAP in children, shortening the treatment duration to 3 days (with amoxicillin) was non-inferior to longer-duration treatment, non-inferiority could not be determined for AOM in children; in otitis media, a shorter treatment duration rather led to poorer treatment results. A superiority of shorter-duration treatment in terms of (non-severe) AEs was shown for the comparison of 3 days versus 5 days of treatment with amoxicillin in CAP. In both clinical pictures, treatment adherence may also increase with shorter treatment duration. However, the effects of a shorter-duration antibiotic therapy for other commonly used antibiotics and for different age groups remain unclear. The optimal duration of outpatient treatment for CAP in adults also

remains unclear due to a lack of relevant studies. In principle, the adaptation of medical standards to new findings on the duration of therapy as well as the education and involvement of patients and those treating them are central to successful implementation.

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Please see full HTA report for the full reference list.

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The full HTA report (German version) is published under https://www.iqwig.de/sich-einbringen/themencheck-medizin/berichte/t23-04.html

Appendix A – Topics of the EUnetHTA Core Model

The European Network for Health Technology Assessment (EUnetHTA) is a network of European HTA agencies. EUnetHTA promotes the exchange of HTA information between its members and developed the core model [253] for this purpose. IQWiG is also a member of the network.

In order to make it easier for readers of this HTA report to find information on the superordinate domains of the EUnetHTA Core Model, Table indicates where the relevant information can be found. The original names of the domains of the core model are used to describe the topics.

Table 9: Domains of the EUnetHTA Core Model

EUnetHTA domain	**Information in chapters and sections of the HTA report**
Health problem and current use of the technology (CUR)	**Background** Chapter 1
Description and technical characteristics of technology (TEC)	
Safety (SAF)	**Benefit assessment** Section 3.1; Chapter 4
Clinical effectiveness (EFF)	
Costs and economic evaluation (ECO)	**Health economic evaluation** Section 3.2; Chapter 5
Ethical analysis (ETH)	**Ethical aspects** Section 3.3; Section 6.1
Patients and social aspects (SOC)	**Social aspects** Section 3.4; Section 6.2
Legal aspects (LEG)	**Legal aspects** Section 3.4; Section 6.3
Organizational aspects (ORG)	**Organizational aspects** Section 3.4; Section 6.4

Appendix B – Search strategies

B.1 – Search strategies for the benefit assessment

B.1.1 – Searches in bibliographic databases

Search for systematic overview

1. MEDLINE

Search interface*: Ovid*

- Ovid MEDLINE(R) ALL 1946 to October 20, 2023

The following filter was adopted:

- Systematic review: Wong [254] – High specificity strategy

#	Searches
1	exp anti-bacterial agents/
2	(antibiotic* or anti-biotic* or antibacterial* or anti-bacterial* or antimicrobial* or anti-microbial* or antiinfective* or anti-infective*).ti,ab.
3	or/1-2
4	exp Time Factors/
5	exp duration of therapy/
6	exp Drug Administration Schedule/
7	((short* or long* or standard* or prolong* or treatment or therap* or regime*) adj3 (term* or course* or duration or length or day*)).ti,ab.
8	or/4-7
9	exp Pneumonia/
10	(pneumon* or pleuropneumon* or bronchopneumon*).ti,ab.
11	or/9-10
12	exp Otitis Media/
13	(acute adj3 (OM or otitis media or ear)).ti,ab.
14	or/12-13
15	or/11,14
16	and/3,8,15
17	Cochrane database of systematic reviews.jn.
18	(search or MEDLINE or systematic review).tw.
19	meta analysis.pt.
20	or/17-19
21	and/16,20
22	21 and (english or german or multilingual or undetermined).lg.
23	..l/ 22 yr=2010-Current

2. International HTA Database

Search interface: INAHTA

#	Searches
1	"anti-infective agents"[mh]
2	"anti-bacterial agents"[mh]
3	(antibiotic* or anti-biotic* or antibacterial* or anti-bacterial* or antimicrobial* or anti-microbial* or antiinfective* or anti-infective*)[Title] OR (antibiotic* or anti-biotic* or antibacterial* or anti-bacterial* or antimicrobial* or anti-microbial* or antiinfective* or anti-infective*)[abs]
4	#3 OR #2 OR #1
5	"Pneumonia"[mh]
6	pneumon*[Title] OR pneumon*[abs]
7	#6 OR #5
8	"Otitis Media"[mh]
9	"otitis media"[Title] OR "otitis media"[abs]
10	#9 OR #8
11	#10 OR #7
12	#11 AND #4
13	(*) FROM 2010 TO 2023
14	#13 AND #12

Search for primary studies

2. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) ALL 1946 to February 05, 2024

The following filter was adopted:

- RCT: Lefebvre [255] – Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision), InterTASC Information Specialists SubGroup [256]

#	Searches
1	exp Anti-Bacterial Agents/
2	exp Carbapenems/
3	exp Cephalosporins/
4	exp Fluoroquinolones/
5	exp Lincosamides/
6	exp Macrolides/
7	exp Penicillins/

#	Searches
8	exp Tetracyclines/
9	antibiotic*.ti,ab.
10	penicillin*.mp.
11	amox?cillin*.mp.
12	ampicillin*.mp.
13	azit?romycin*.mp.
14	(cefaclor* or cephaclor*).mp.
15	(cefalexin* or cephalexin*).mp.
16	cefdinir*.mp.
17	cefotaxim*.mp.
18	cefpodoxim*.mp.
19	cefprozil*.mp.
20	ceftizox*.mp.
21	ceftriaxon*.mp.
22	cefuroxim*.mp.
23	clarit?romycin*.mp.
24	clindamycin*.mp.
25	doxycyclin*.mp.
26	ertapenem*.mp.
27	erythromycin*.mp.
28	imipenem*.mp.
29	levofloxacin*.mp.
30	meropenem*.mp.
31	moxifloxacin*.mp.
32	trimet?oprim*.mp.
33	or/1-32
34	exp Drug Administration Schedule/
35	((short* or day or days) adj5 (course or therapy or treatment* or regimen*)).ti,ab.
36	((((one or "1" or two or "2" or three or "3" or four or "4" or five or "5" or six or "6" or seven or "7" or eight or "8" or nine or "9" or ten or "10") adj1 (day or days)) or (single adj2 dose)) adj5 (therapy or treatment* or regimen*)).ti,ab.
37	(((single adj2 dose) or ((one or "1" or two or "2" or three or "3" or four or "4" or five or "5") adj1 (day or days))) and ((six or "6" or seven or "7" or eight or "8" or nine or "9" or ten or "10") adj1 (day or days))).ti,ab.
38	or/34-37
39	exp Pneumonia/
40	pneumonia?.ti,ab.
41	or/39-40
42	exp Otitis Media/
43	(otitis adj1 media).ti,ab.

#	Searches
44	or/42-43
45	exp randomized controlled trial/
46	controlled clinical trial.pt.
47	(randomized or placebo or randomly).ab.
48	clinical trials as topic.sh.
49	trial.ti.
50	or/45-49
51	50 not (exp animals/ not humans.sh.)
52	33 and 38 and (41 or 44) and 51
53	(animals/ not humans/) or comment/ or editorial/ or exp review/ or meta analysis/ or consensus/ or exp guideline/
54	hi.fs. or case report.mp.
55	or/53-54
56	52 not 55
57	56 and (english or german or multilingual or undetermined).lg.

2. Embase

Search interface: Ovid

- Embase 1974 to 2024 February 05

The following filter was adopted:

- RCT: Wong [254] – Strategy minimizing difference between sensitivity and specificity

#	Searches
1	antibiotic therapy/
2	carbapenem derivative/
3	exp cephalosporin derivative/
4	exp quinolone derivative/
5	lincosamides/
6	exp macrolides/
7	exp penicillin derivative/
8	tetracycline/
9	antibiotic*.ti,ab.
10	penicillin*.mp.
11	amox?cillin*.mp.
12	ampicillin*.mp.
13	azit?romycin*.mp.
14	(cefaclor* or cephaclor*).mp.

#	Searches
15	(cefalexin* or cephalexin*).mp.
16	cefdinir*.mp.
17	cefotaxim*.mp.
18	cefpodoxim*.mp.
19	cefprozil*.mp.
20	ceftizox*.mp.
21	ceftriaxon*.mp.
22	cefuroxim*.mp.
23	clarit?romycin*.mp.
24	clindamycin*.mp.
25	doxycyclin*.mp.
26	ertapenem*.mp.
27	erythromycin*.mp.
28	imipenem*.mp.
29	levofloxacin*.mp.
30	meropenem*.mp.
31	moxifloxacin*.mp.
32	trimet?oprim*.mp.
33	or/1-32
34	treatment duration/
35	((short* or day or days) adj5 (course or therapy or treatment* or regimen*)).ti,ab.
36	((((one or "1" or two or "2" or three or "3" or four or "4" or five or "5" or six or "6" or seven or "7" or eight or "8" or nine or "9" or ten or "10") adj1 (day or days)) or (single adj2 dose)) adj5 (therapy or treatment* or regimen*)).ti,ab.
37	(((single adj2 dose) or ((one or "1" or two or "2" or three or "3" or four or "4" or five or "5") adj1 (day or days))) and ((six or "6" or seven or "7" or eight or "8" or nine or "9" or ten or "10") adj1 (day or days))).ti,ab.
38	or/34-37
39	exp Pneumonia/ or Streptococcus pneumoniae/ or community acquired pneumonia/
40	pneumonia?.ti,ab.
41	or/39-40
42	exp "Otitis Media"/
43	(otitis adj1 media).ti,ab.
44	or/42-43
45	(random* or double-blind*).tw.
46	placebo*.mp.
47	or/45-46
48	33 and 38 and (41 or 44) and 47
49	48 not medline.cr.
50	49 not (exp animal/ not exp human/)

#	Searches
51	50 not (Conference Abstract or Conference Review or Editorial).pt.
52	51 not ((afrikaans or albanian or arabic or armenian or azerbaijani or basque or belorussian or bosnian or bulgarian or catalan or chinese or croatian or czech or danish or dutch or english or esperanto or estonian or finnish or french or gallegan or georgian or german or greek or hebrew or hindi or hungarian or icelandic or indonesian or irish gaelic or italian or japanese or korean or latvian or lithuanian or macedonian or malay or norwegian or persian or polish or polyglot or portuguese or pushto or romanian or russian or scottish gaelic or serbian or slovak or slovene or spanish or swedish or thai or turkish or ukrainian or urdu or uzbek or vietnamese) not (english or german)).lg.

3. The Cochrane Library

Search interface: Wiley

- Cochrane Central Register of Controlled Trials: Issue 02 of 12, February 2024

#	Searches
#1	[mh "Anti-Bacterial Agents"]
#2	[mh Carbapenems]
#3	[mh Cephalosporins]
#4	[mh Fluoroquinolones]
#5	[mh Lincosamides]
#6	[mh Macrolides]
#7	[mh Penicillins]
#8	[mh Tetracyclines]
#9	antibiotic*:ti,ab
#10	penicillin*:ti,ab,kw
#11	amox?cillin*:ti,ab,kw
#12	ampicillin*:ti,ab,kw
#13	azit?romycin*:ti,ab,kw
#14	(cefaclor* OR cephaclor*):ti,ab,kw
#15	(cefalexin* OR cephalexin*):ti,ab,kw
#16	cefdinir*:ti,ab,kw
#17	cefotaxim*:ti,ab,kw
#18	cefpodoxim*:ti,ab,kw
#19	cefprozil*:ti,ab,kw
#20	ceftizox*:ti,ab,kw
#21	ceftriaxon*:ti,ab,kw
#22	cefuroxim*:ti,ab,kw
#23	clarit?romycin*:ti,ab,kw
#24	clindamycin*:ti,ab,kw
#25	doxycyclin*:ti,ab,kw

#	Searches
#26	ertapenem*:ti,ab,kw
#27	erythromycin*:ti,ab,kw
#28	imipenem*:ti,ab,kw
#29	levofloxacin*:ti,ab,kw
#30	meropenem*:ti,ab,kw
#31	moxifloxacin*:ti,ab,kw
#32	trimet?oprim*:ti,ab,kw
#33	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32
#34	[mh "Drug Administration Schedule"]
#35	((short* or day or days) NEAR/5 (course or therapy or treatment* or regimen*)):ti,ab
#36	((((one or "1" or two or "2" or three or "3" or four or "4" or five or "5" or six or "6" or seven or "7" or eight or "8" or nine or "9" or ten or "10") NEAR/1 (day or days)) or (single NEAR/1 dose)) NEAR/5 (therapy or treatment* or regimen*)):ti,ab
#37	(((single NEAR/2 dose) or ((one or "1" or two or "2" or three or "3" or four or "4" or five or "5") NEAR/1 (day or days))) and ((six or "6" or seven or "7" or eight or "8" or nine or "9" or ten or "10") NEAR/1 (day or days))):ti,ab
#38	#35 OR #36 OR #37
#39	[mh Pneumonia]
#40	pneumonia?:ti,ab
#41	#39 OR #40
#42	[mh "Otitis Media"]
#43	(otitis NEAR/1 media):ti,ab
#44	#42 OR #43
#45	#33 AND #38 AND (#41 OR #44)
#46	#45 not (*clinicaltrial*gov* or *trialsearch*who* or *clinicaltrialsregister*eu* or *anzctr*org*au* or *trialregister*nl* or *irct*ir* or *isrctn* or *controlled*trials*com* or *drks*de*):so
#47	#46 not ((language next (afr or ara or aze or bos or bul or car or cat or chi or cze or dan or dut or es or est or fin or fre or gre or heb or hrv or hun or ice or ira or ita or jpn or ko or kor or lit or nor or peo or per or pol or por or pt or rom or rum or rus or slo or slv or spa or srp or swe or tha or tur or ukr or urd or uzb)) not (language near/2 (en or eng or english or ger or german or mul or unknown)))
#48	#47 in Trials

B.1.2 – Searches in study registries

1. ClinicalTrials.gov

Provider: U.S. National Institutes of Health

- URL: http://www.clinicaltrials.gov
- Type of search: Basic Search

Search strategy
(pneumonia OR pneumoniae OR otitis OR "lung infection") [Condition/disease] ("antibiotic treatment" OR "antibiotic therapy" OR penicillins OR amoxycillin OR amoxicillin OR BRL-2333 OR ampicillin OR azithromycin OR CP-62993 OR cefaclor OR cephaclor OR S-6472 OR cefalexin OR cephalexin OR cefdinir OR CI-983 OR FK-482 OR PD-134393 OR cefotaxime OR HR-756 OR Ru-24756 OR cefpodoxime OR R-3746 OR RU-51746 OR cefprozil OR BMY-28100 OR ceftizoxime OR FK-749 OR FR-13749 OR ceftriaxone OR Ro-13-9904 OR cefuroxime OR clarithromycin OR A-56268 OR TE-031 OR clindamycin OR doxycycline OR BMY-28689 OR BU-3839T OR ert*apenem OR erythromycin OR imipenem OR MK-0787 OR levofloxacin OR meropenem OR SM-7338 OR moxifloxacin OR BAY-128039 OR trimethoprim) AND (short OR reduction OR day OR course OR (single AND dose)) [Intervention/treatment] Filter Study Phase: Phase 2, Phase 3, Phase 4, Not applicable

2. International Clinical Trials Registry Platform Search Portal

Provider: World Health Organization

- URL: https://trialsearch.who.int
- Type of search: Standard Search

Search strategy
(pneumonia* OR otitis* OR "lung infection") AND (antibiotic* OR antimicrobial* OR penicillin* OR amoxycillin* OR amoxicillin* OR BRL-2333 OR BRL2333 OR BRL 2333 OR ampicillin* OR azithromycin* OR CP-62993 OR CP62993 OR CP 62993 OR cefaclor* OR cephaclor* OR S-6472 OR S6472 OR S 6472 OR cefalexin* OR cephalexin* OR cefdinir* OR CI-983 OR CI983 OR CI 983 OR FK-482 OR FK482 OR FK 482 OR PD-134393 OR PD134393 OR PD 134393 OR cefotaxim* OR HR-756 OR HR756 OR HR 756 OR Ru-24756 OR Ru24756 OR Ru 24756 OR cefpodoxim* OR R-3746 OR R3746 OR R 3746 OR RU-51746 OR RU51746 OR RU 51746 OR cefprozil* OR BMY-28100 OR BMY28100 OR BMY 28100 OR ceftizox* OR FK-749 OR FK749 OR FK 749 OR FR-13749 OR FR13749 OR FR 13749 OR ceftriaxon* OR Ro-13-9904 OR Ro139904 OR Ro 13 9904 OR cefuroxim* OR clarithromycin* OR A-56268 OR A56268 OR A 56268 OR TE-031 OR TE031 OR TE 031 OR clindamycin* OR doxycyclin* OR BMY-28689 OR BMY28689 OR BMY 28689 OR BU-3839T OR BU3839T OR BU 3839T OR ertapenem* OR erythromycin* OR imipenem* OR MK-0787 OR MK0787 OR MK 0787 OR levofloxacin* OR meropenem* OR SM-7338 OR SM7338 OR SM 7338 OR moxifloxacin* OR BAY-128039 OR BAY128039 OR BAY 128039 OR trimethoprim*) AND (short* OR reduc* OR day* OR course OR (single AND dose))

3. EU Clinical Trials Register

Provider: European Medicines Agency

- URL: https://www.clinicaltrialsregister.eu/ctr-search/search
- Type of search: Basic Search

Search strategy
(pneumonia* OR otitis* OR "lung infection") AND (antibiotic* OR antimicrobial* OR penicillin* OR amoxycillin* OR amoxicillin* OR BRL-2333 OR BRL2333 OR (BRL 2333) OR ampicillin* OR azithromycin* OR CP-62993 OR CP62993 OR (CP 62993) OR cefaclor* OR cephaclor* OR S-6472 OR S6472 OR (S 6472) OR cefalexin* OR cephalexin* OR cefdinir* OR CI-983 OR CI983 OR (CI 983) OR FK-482 OR FK482 OR (FK 482) OR PD-134393 OR PD134393 OR (PD 134393) OR cefotaxim* OR HR-756 OR HR756 OR (HR 756) OR Ru-24756 OR Ru24756 OR (Ru 24756) OR cefpodoxim* OR R-3746 OR R3746 OR (R 3746) OR RU-51746 OR RU51746 OR (RU 51746) OR cefprozil* OR BMY-28100 OR BMY28100 OR (BMY 28100) OR ceftizox* OR FK-749 OR FK749 OR (FK 749) OR FR-13749 OR FR13749 OR (FR 13749) OR ceftriaxon* OR Ro-13-9904 OR Ro139904 OR (Ro 13 9904) OR cefuroxim* OR clarithromycin* OR A-56268 OR A56268 OR (A 56268) OR TE-031 OR TE031 OR (TE 031) OR clindamycin* OR doxycyclin* OR BMY-28689 OR BMY28689 OR (BMY 28689) OR BU-3839T OR BU3839T OR (BU 3839T) OR ertapenem* OR erythromycin* OR imipenem* OR MK-0787 OR MK0787 OR (MK 0787) OR levofloxacin* OR meropenem* OR SM-7338 OR SM7338 OR (SM 7338) OR moxifloxacin* OR BAY-128039 OR BAY128039 OR (BAY 128039) OR trimethoprim*) AND (short* OR reduc* OR day* OR course OR (single AND dose))

4. Clinical Trials Information System

Provider: European Medicines Agency

- URL: https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en
- Type of search: Basic Search

Search strategy
antibiotic, antibiotics, antimicrobial, antimicrobials, penicillin, penicillins, amoxycillin, amoxicillin, BRL-2333, BRL2333, BRL 2333, ampicillin, azithromycin, CP-62993, CP62993, CP 62993, cefaclor, cephaclor, S-6472, S6472, S 6472, cefalexin, cephalexin, cefdinir, CI-983, CI983, CI 983, FK-482, FK482, FK 482, PD-134393, PD134393, PD 134393, cefotaxime, HR-756, HR756, HR 756, Ru-24756, Ru24756, Ru 24756, cefpodoxime, R-3746, R3746, R 3746, RU-51746, RU51746, RU 51746, cefprozil, BMY-28100, BMY28100, BMY 28100, ceftizoxime, FK-749, FK749, FK 749, FR-13749, FR13749, FR 13749, ceftriaxon, ceftriaxone, Ro-13-9904, Ro139904, Ro 13 9904, cefuroxime, clarithromycin, A-56268, A56268, A 56268, TE-031, TE031, TE 031, clindamycin, doxycycline, BMY-28689, BMY28689, BMY 28689, BU-3839T, BU3839T, BU 3839T, ertapenem, erythromycin, imipenem, MK-0787, MK0787, MK 0787, levofloxacin, meropenem, SM-7338, SM7338, SM 7338, moxifloxacin, BAY-128039, BAY128039, BAY 128039, trimethoprim

B.2 – Search strategies for the health economic evaluation

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) ALL 1946 to February 13, 2024

The following filter was adopted:

- Health economy study: Glanville, Fleetwood [257]

#	Searches
1	exp Anti-Bacterial Agents/
2	exp Carbapenems/
3	exp Cephalosporins/
4	exp Fluoroquinolones/
5	exp Lincosamides/
6	exp Macrolides/
7	exp Penicillins/
8	exp Tetracyclines/
9	antibiotic*.ti,ab.
10	penicillin*.mp.
11	amox?cillin*.mp.
12	ampicillin*.mp.
13	azit?romycin*.mp.
14	(cefaclor* or cephaclor*).mp.
15	(cefalexin* or cephalexin*).mp.
16	cefdinir*.mp.
17	cefotaxim*.mp.
18	cefpodoxim*.mp.
19	cefprozil*.mp.
20	ceftizox*.mp.
21	ceftriaxon*.mp.
22	cefuroxim*.mp.
23	clarit?romycin*.mp.
24	clindamycin*.mp.
25	doxycyclin*.mp.
26	ertapenem*.mp.
27	erythromycin*.mp.
28	imipenem*.mp.
29	levofloxacin*.mp.
30	meropenem*.mp.

#	Searches
31	moxifloxacin*.mp.
32	trimet?oprim*.mp.
33	or/1-32
34	exp Drug Administration Schedule/
35	((short* or day or days) adj5 (course or therapy or treatment* or regimen*)).ti,ab.
36	((((one or "1" or two or "2" or three or "3" or four or "4" or five or "5" or six or "6" or seven or "7" or eight or "8" or nine or "9" or ten or "10") adj1 (day or days)) or (single adj2 dose)) adj5 (therapy or treatment* or regimen*)).ti,ab.
37	(((single adj2 dose) or ((one or "1" or two or "2" or three or "3" or four or "4" or five or "5") adj1 (day or days))) and ((six or "6" or seven or "7" or eight or "8" or nine or "9" or ten or "10") adj1 (day or days))).ti,ab.
38	or/34-37
39	exp Pneumonia/
40	pneumonia?.ti,ab.
41	or/39-40
42	exp Otitis Media/
43	(otitis adj1 media).ti,ab.
44	or/42-43
45	(economic$ or cost$).ti.
46	cost benefit analysis/
47	treatment outcome/ and ec.fs.
48	or/45-47
49	48 not ((animals/ not humans/) or letter.pt.)
50	33 and 38 and (41 or 44) and 49
51	50 not (comment or editorial).pt.
52	51 and (english or german or multilingual or undetermined).lg.

2. Embase

Search interface: Ovid

- Embase 1974 to 2024 February 13

The following filter was adopted:

- Health economy study: Glanville, Fleetwood [257]

#	Searches
1	antibiotic therapy/
2	carbapenem derivative/
3	exp cephalosporin derivative/

#	Searches
4	exp quinolone derivative/
5	lincosamides/
6	exp macrolides/
7	exp penicillin derivative/
8	tetracycline/
9	antibiotic*.ti,ab.
10	penicillin*.mp.
11	amox?cillin*.mp.
12	ampicillin*.mp.
13	azit?romycin*.mp.
14	(cefaclor* or cephaclor*).mp.
15	(cefalexin* or cephalexin*).mp.
16	cefdinir*.mp.
17	cefotaxim*.mp.
18	cefpodoxim*.mp.
19	cefprozil*.mp.
20	ceftizox*.mp.
21	ceftriaxon*.mp.
22	cefuroxim*.mp.
23	clarit?romycin*.mp.
24	clindamycin*.mp.
25	doxycyclin*.mp.
26	ertapenem*.mp.
27	erythromycin*.mp.
28	imipenem*.mp.
29	levofloxacin*.mp.
30	meropenem*.mp.
31	moxifloxacin*.mp.
32	trimet?oprim*.mp.
33	or/1-32
34	treatment duration/
35	((short* or day or days) adj5 (course or therapy or treatment* or regimen*)).ti,ab.
36	((((one or "1" or two or "2" or three or "3" or four or "4" or five or "5" or six or "6" or seven or "7" or eight or "8" or nine or "9" or ten or "10") adj1 (day or days)) or (single adj2 dose)) adj5 (therapy or treatment* or regimen*)).ti,ab.
37	(((single adj2 dose) or ((one or "1" or two or "2" or three or "3" or four or "4" or five or "5") adj1 (day or days))) and ((six or "6" or seven or "7" or eight or "8" or nine or "9" or ten or "10") adj1 (day or days))).ti,ab.
38	or/34-37
39	exp Pneumonia/ or Streptococcus pneumoniae/ or community acquired pneumonia/

#	Searches
40	pneumonia?.ti,ab.
41	or/39-40
42	exp "Otitis Media"/
43	(otitis adj1 media).ti,ab.
44	or/42-43
45	(Cost adj effectiveness).ab.
46	(Cost adj effectiveness).ti.
47	(Life adj years).ab.
48	(Life adj year).ab.
49	Qaly.ab.
50	(Cost or costs).ab. and Controlled Study/
51	(Cost and costs).ab.
52	or/45-51
53	33 and 38 and (41 or 44) and 52
54	53 not medline.cr.
55	54 not (exp animal/ not exp human/)
56	55 not (Conference Abstract or Conference Review or Editorial).pt.
57	56 and (english or german).lg.

3. International HTA Database

Search interface: INAHTA

#	Searches
#1	"Anti-Bacterial Agents"[mhe]
#2	Carbapenems[mhe]
#3	Cephalosporins[mhe]
#4	Fluoroquinolones[mhe]
#5	Lincosamides[mhe]
#6	Macrolides[mhe]
#7	Penicillins[mhe]
#8	Tetracyclines[mhe]
#9	(antibiotic* OR penicillin* OR amoxycillin* OR amoxicillin* OR ampicillin* OR azithromycin* OR cefaclor* OR cephaclor* OR cefalexin* OR cephalexin* OR cefdinir* OR cefotaxim* OR cefpodoxim* OR cefprozil* OR ceftizox* OR ceftriaxon* OR cefuroxim* OR clarithromycin* OR clindamycin* OR doxycyclin* OR ertapenem* OR erythromycin* OR imipenem* OR levofloxacin* OR meropenem* OR moxifloxacin* OR trimethoprim*)[title] OR (antibiotic* OR penicillin* OR amoxycillin* OR amoxicillin* OR ampicillin* OR azithromycin* OR cefaclor* OR cephaclor* OR cefalexin* OR cephalexin* OR cefdinir* OR cefotaxim* OR cefpodoxim* OR cefprozil* OR ceftizox* OR ceftriaxon* OR cefuroxim* OR clarithromycin* OR clindamycin* OR doxycyclin* OR ertapenem* OR erythromycin* OR imipenem* OR levofloxacin* OR meropenem* OR moxifloxacin* OR trimethoprim*)[abs]
#10	#9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1

#	Searches
#11	Pneumonia[mhe]
#12	pneumonia*[title] OR pneumonia*[abs]
#13	#12 OR #11
#14	"Otitis Media"[mhe]
#15	"otitis media"[title] OR "otitis media"[abs]
#16	#15 OR #14
#17	#16 OR #13
#18	#17 AND #10