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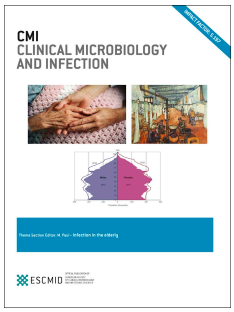

WHO's essential medicines and AWaRe: recommendations on first- and second-choice antibiotics for empiric treatment of clinical infections

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WHO's Essential Medicines and AWaRe: recommendations on first- and second-choice antibiotics for empiric treatment of clinical infections

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ABSTRACT

The WHO Model List of Essential Medicines (EML) prioritizes medicines that have significant global public health value. The EML can also deliver important messages on appropriate medicine use. Since 2017, in response to the growing challenge of antimicrobial resistance, antibiotics on the EML were reviewed and categorized into three groups: Access, Watch and Reserve, leading to a new categorization called AWaRe. These categories were developed taking into account the impact of different antibiotics and classes on antimicrobial resistance, and the implications for their appropriate use. The 2023 AWaRe classification provides empiric guidance on 41 essential antibiotics for over 30 clinical infections targeting both the primary health care and hospital facility setting. A further 257 antibiotics not included on the EML have been allocated an AWaRe group for stewardship and monitoring purposes.

This article describes the development of AWaRe focussing on the clinical evidence base that guided the selection of Access, Watch or Reserve antibiotics as first and second choices for each infection. The overarching objective was to offer a tool for optimising the quality of global antibiotic prescribing and reduce inappropriate use by encouraging the use of Access antibiotics (or no antibiotics) where appropriate. This clinical evidence evaluation and subsequent EML recommendations are the basis for the AWaRe antibiotic book and related smartphone applications. By providing guidance on antibiotic prioritization, AWaRe aims to facilitate the revision of national lists of essential medicines, update of national prescribing guidelines and surveillance of antibiotic use. Adherence to AWaRe would extend the effectiveness of current antibiotics while helping countries to expand access to these life-saving medicines for the benefit of current and future patients, health professionals, and the environment.

Introduction

In 2019 antimicrobial resistance (AMR) was estimated to be responsible for the death of about 1.3 million people worldwide and impacted the quality of life of millions more.[1] Reliable, comprehensive surveillance data on antimicrobial resistance in human pathogens are mostly generated in high income countries.[2, 3] However, available data for low- and middle-income countries (LMICs), particularly for community-acquired infections, clearly suggest that AMR is a worldwide problem with low-income countries likely to suffer the greatest burden.[4-6] AMR has many causes but the inappropriate use of antibiotics in humans is well established as a key driver.[7] Inappropriate use of antibiotics such as using them when none are needed or use of the wrong antibiotic at the wrong dose, for the wrong duration and by the wrong route is a common problem concerning between 30-50% of all antibiotic prescriptions.[8, 9] The COVID-19 pandemic has aggravated the widespread and inappropriate use of antibiotics even though SARS-CoV-2 is a virus and infrequently complicated by bacterial superinfections. In 2020 most patients hospitalized with COVID-19 received an antibiotic.[10-12] Most antibiotic prescriptions for adults were for azithromycin and ceftriaxone, with increase in prescribing corresponding to peaks in cases of COVID-19.[11] This is likely to have further exacerbated the selection of multidrug-resistant strains, both among healthy adults in the community and hospitalized patients.[13, 14]

In 2019 the World Health Organization (WHO) has declared that AMR is one of the top 10 global public health threats facing humanity.[15] Previously in 2015, WHO Member States endorsed a Global Action Plan on AMR committing countries to develop national action plans and actions to tackle AMR and reduce inappropriate use of antimicrobials.[16] A core part of the plan was to update the antibiotics included in the WHO Model List of Essential Medicines (EML). The EML,

first published in 1977 and updated every two years since then, is a list of the safest and most effective medicines that can meet the most important health needs of people and health systems worldwide. The EML is a guide for countries to help them develop their own national lists of essential medicines to ensure affordable access to quality-assured essential medicines for all who need them.[17, 18] Changes to the EML are made on the basis of applications from external organizations, including academic centres, the pharmaceutical industry and public or private institutions, or WHO departments. An expert committee consisting of 10-20 experts from all WHO regions is appointed by the WHO Director-General and meets every 2 years to review the applications and decide which modifications to recommend. In 2002 the procedure for selecting essential medicines was revised and a more standardized and rigorous approach for their evaluation was adopted.[19] The deliberations of the Expert Committee are submitted to the Director General for approval and also presented to the WHO Executive Board. Countries are informed about the implications of the revisions to the list and any follow-up actions that may need to be taken. The Committees' reports are published in the WHO Technical Report Series.

Most of the antibiotics on the Model List were included decades ago (with already 16 antibiotics on the first EML) without comprehensive review and update since then. In response to an urgent call for action from the 2015 World Health Assembly and other partners, WHO was charged with reviewing the evidence on antibacterial medicines for their inclusion in the Model List (section 6.2 of the list) and recommending any necessary changes.[16, 20] In this paper, we describe the process that led to the update of the EML including antibiotic recommendations on empiric treatment for common clinical infections (hereafter, called the "recommendations"). We had three main aims:

- first, to describe the available scientific evidence and expert consensus that informed the review of antibiotics eligible as essential medicines;
- second, to describe the guiding principles used to select antibiotics, providing an opportunity to link the prioritization of antibiotics to measures that could best prevent inappropriate use of these medicines; and
- third, to develop a system for categorizing antibiotics – Access, Watch and Reserve – in which categories have clear implications in terms of stewardship, monitoring and assessment of antibiotic use.

The recommendations originated through this revision address the empiric treatment (that is, treatment on the basis of a presumptive rather than "targeted" treatment based on a laboratory-confirmed diagnosis) of common community-acquired and hospital infections. These recommendations also address objective 4 of WHO's 2015 global action plan on antimicrobial resistance - to "optimize the use of antimicrobial medicines in human and animal health".[21]

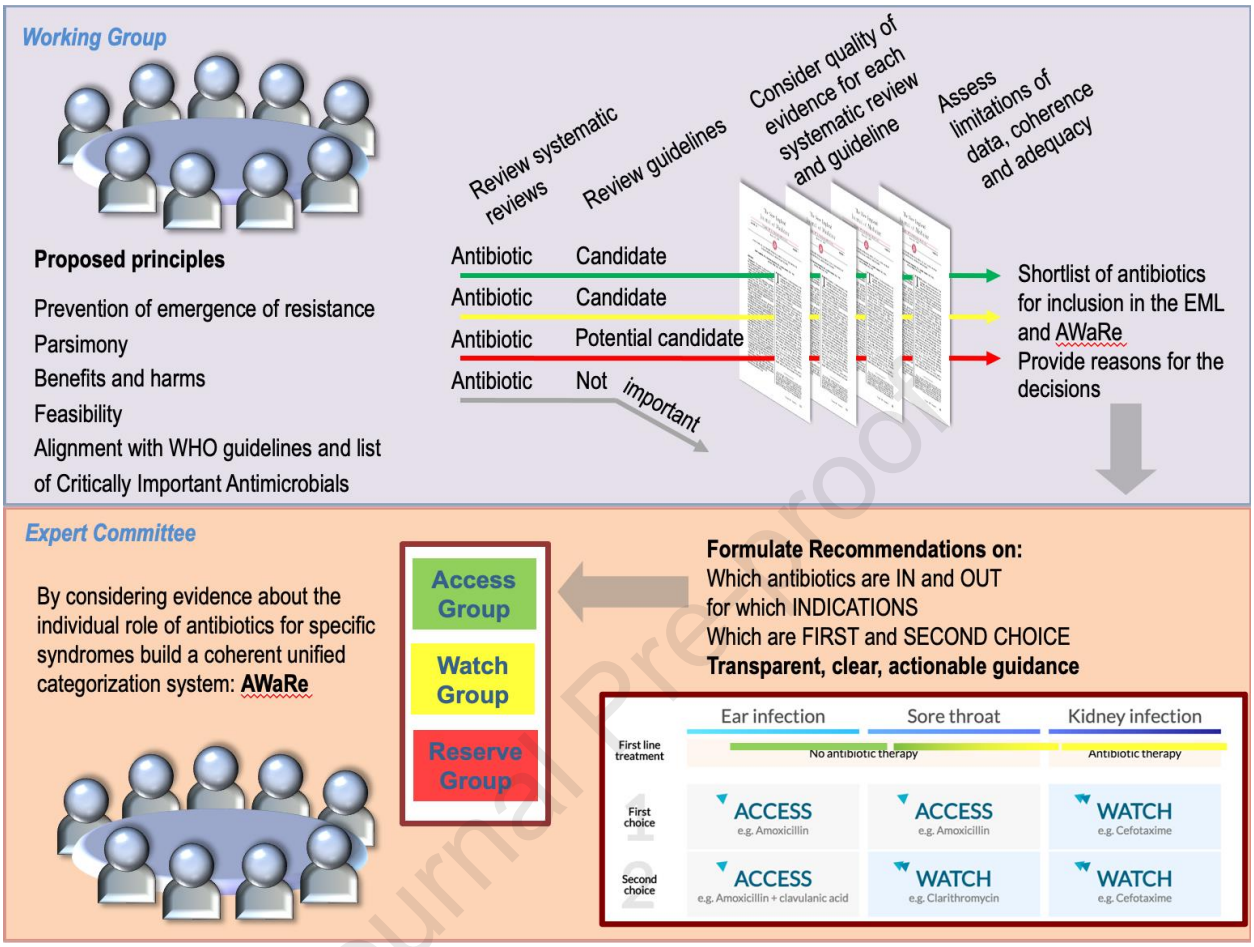
These recommendations are intended for all health care professionals directly involved in antibiotic prescribing and/or dispensing (e.g. physicians, nurses, pharmacists), for infection prevention and control professionals, professionals responsible for surveillance of antimicrobial resistance and surveillance of antibiotic use, and policy-makers making decisions on antimicrobial use and stewardship policies.

Methods

Overview of the process and timeline

The Secretariat for the WHO Model List of Essential Medicines decided to implement a two-step process to finalize the selection of antibiotics, using two expert groups (Fig. 1). The first group was a formally constituted global expert panel of specialists in clinical infectious diseases and microbiology (called here the Working Group), whose task was to finalize the applications (i.e. review of the evidence and proposal of the optimal antibiotic options) to include specific antibiotics in the Model List. The second group was the Expert Committee on the Selection and Use of Essential Medicines (called here the Expert Committee), a multidisciplinary international panel in which several clinal and non-clinical (e.g. medicines procurement, pharmacy) specialties are represented. The Expert Committee meets every two years and is responsible for independently reviewing the antibiotic choices proposed by the Working Group and for making the final recommendations on which antibiotics should be included in the WHO Model List of Essential Medicines (EML). Antibiotics have been an important component of the EML (accounting for around 8% of all listed medicines) since the first list was published in 1977. Minor additions and occasional deletions of antibiotics have occurred over time, but this was the first complete review of the whole class of antibiotics on the EML.

Fig. 1. Roles and tasks of the Working Group and the Expert Committee, and their relationship



Working Group

Goals of the Working Group

The Working Group was established in 2016 and, since has continued its activities to build the evidence base of the AWaRe framework and related guidance (e.g. AWaRe antibiotic book) on optimal use of antibiotics. Its main tasks were to suggest guiding principles to be considered for the selection of antibiotics to include in the Model List and for reviewing and summarizing the evidence on the efficacy and safety of the selected antibiotics.

Methods of the Working Group

In March 2016, at the first preparatory meeting, the Working Group proposed that applications for revision of antibiotics should not be by medicine, as was done before, but rather by clinical infection. In a first step the most important common infections globally requiring antibiotic treatment were identified. The second step was to review the evidence to select the essential antibiotics required to treat those infections. This infection-based approach was similar to the approach used in 2015 to update the Model List for cancer medicines.[22] The list of priority infections is presented in Box 1. Inclusion of the infections was based on their incidence, clinical relevance, impact of antibiotic treatment and overall contribution to the global use of antibiotics, including excessive use. Community-acquired infections were privileged over hospital-acquired infections. The following examples illustrate the principles used:

- Meningitis is an example of a disease with a relatively low incidence but a high clinical relevance in terms of morbidity and mortality and high potential impact of optimal antibiotic treatment.[23]

- Otitis media, conversely, is a disease with a high incidence, low mortality, and limited impact of antibiotics on the evolution of the disease. Antibiotics are therefore not indicated in most cases of otitis media. Inappropriate use of antibiotics for self-limiting infections, such as otitis media, is very common and a major contributor to AMR. So, otitis media is included on the basis of disease burden and high potential for inappropriate antibiotic use.

Infections that were excluded from the analysis were based on low incidence, more regional relevance, the lack of substantial impact of antibiotic therapies, or all the above. A number of important infection-based recommendations already exist within WHO guidelines (e.g sexually transmitted diseases, cholera). These infections were equally prioritized and counted as separate

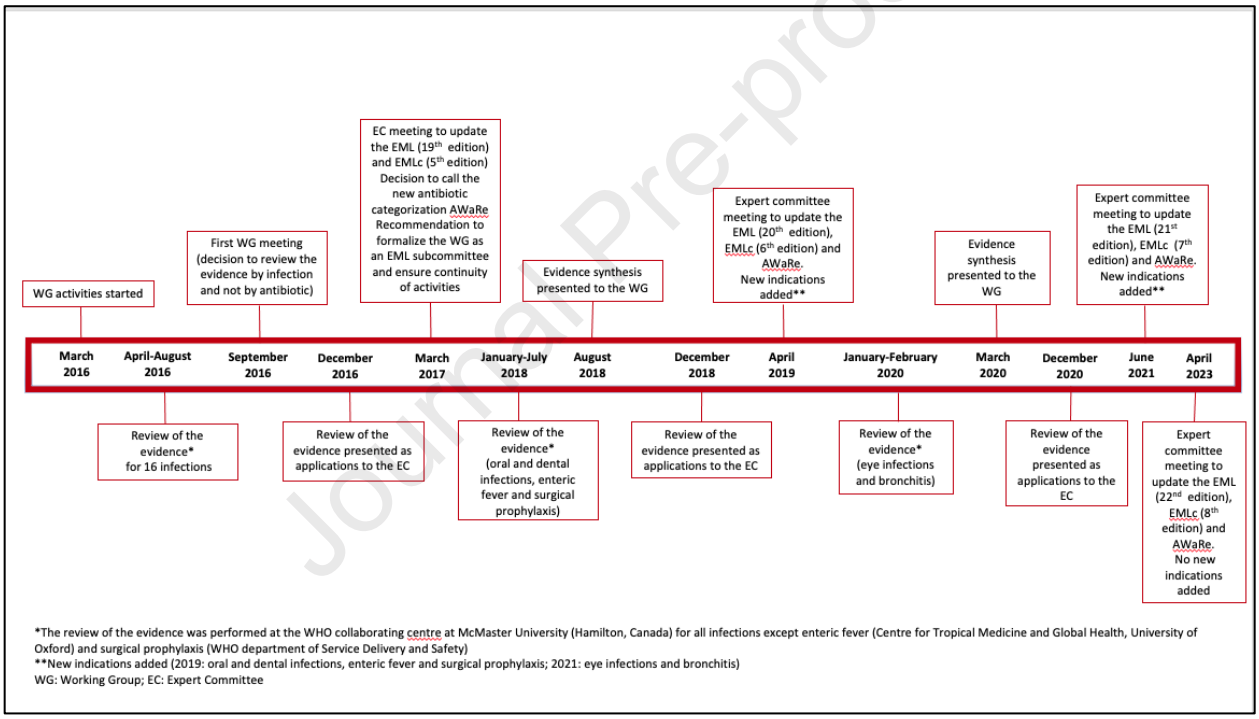
infections in addition to the others. The list was updated in 2019 and 2021 to include additional infections (Box 1); in 2023 no new infections were added. This can be interpreted as a sign of maturity of the tool. The chronology of events is presented in Figure 2.

Box 1. Infections considered in the selection and use of essential medicines[a]	
Bacterial diarrhoea (acute infectious)	Oral and dental infections (added in 2019)
Bronchitis and bronchiolitis (added in 2021)	Otitis media (acute)
Bone and joint infections	Pharyngitis
Community-acquired pneumonia	Sinusitis (acute)
Complicated intra-abdominal infections	Sexually transmitted infections: • Chlamydial urogenital infection • Gonococcal infection • Syphilis • Trichomoniasis
Exacerbations of chronic obstructive pulmonary diseases	Skin and soft tissue infections (including impetigo, erysipelas, cellulitis and necrotising fasciitis)
Eye infections (added in 2021)	Surgical prophylaxis (added in 2019)
Febrile neutropenia	Typhoid and paratyphoid (enteric) fever (added in 2019)
Hospital-acquired pneumonia	Urinary tract infections (lower and upper)
Meningitis (bacterial)	Children • Cholera • Community-acquired pneumonia

	• Sepsis • Severe acute malnutrition • Dysentery (shigellosis)

[a]Infections presented in alphabetical order except for paediatric infections, which are presented at the end (these infections are presented separately because the supporting evidence to make antibiotics treatment recommendations mostly relied on existing WHO guidelines as detailed in the Methods' section "Guiding principles for selecting antibiotics").

Fig. 2. Chronology of events (2016-2023)



Review of systematic reviews and meta-analyses, and guidelines

It was recognised that it was not feasible to conduct comprehensive systematic reviews of all potential antibiotic treatments for each infection in the limited time available. A more pragmatic approach was agreed on by the Working Group to only evaluate the evidence from published systematic reviews and meta-analyses of randomized controlled trials and high-quality clinical

practice guidelines. The Working Group delegated this task to the WHO Collaborating Centre for Infectious Diseases, Research Methods and Recommendations of McMaster University in Hamilton, Canada.[24] The initial work was carried out between March and September 2016. It was then replicated for the following EML updates (i.e. 2019 and 2021) although in slightly different periods of the year preceding the Expert Committee meeting. In 2023 only minor changes were made (e.g. formulations) so there was no need to conduct any new review of the evidence.

A comprehensive search for systematic reviews and meta-analyses of randomized controlled trials on antibiotic treatment for the list of clinical infections selected by the Working Group (Box 1) was performed. For each infection, MEDLINE (through PubMed), Embase, and the Cochrane Database for Systematic Reviews were searched to identify relevant articles. No language restrictions were applied while searching for articles. However, eligibility was restricted to English-language articles. Other inclusion criteria for systematic reviews and meta-analyses were: publication year between 1996 and June 2016 for the 2017 EML update, December 2018 and 2020 for the 2019 and 2021 EML updates, respectively, and studies focused on comparing treatment with different antibiotics or antibiotic classes and/or comparing antibiotic treatment with no treatment or with placebo. Antitubercular, antiviral, antifungal, and antiparasitic agents were not considered. The reference lists of eligible reviews were checked to identify randomized controlled trials not included in the analyses of secondary literature and included in narrative synthesis of evidence eventually. For clinical practice guidelines, MEDLINE (through PubMed) and relevant websites, including the Infectious Diseases Society of America,[25] European Society of Clinical Microbiology and Infectious Diseases,[26] and the National Institute for Health and Care Excellence, were searched.[27] All search strategies are available on request.

Systematic reviews and guidelines used to support the decision making are presented in tables along the text. Entries are presented in chronological date order, followed by alphabetical order by first author's family name.

Quality and relevance of systematic reviews and meta-analyses

The quality of evidence for each systematic review and meta-analysis was then evaluated based on five factors: conclusions of the original authors (e.g. including overall quality of the evidence according to GRADE assessment[28]), sample size of the studies, number of events, number of studies per outcome, and publication year. A rating of high, moderate, low, or very low quality was assigned for each of these five factors (high = score 1.0, moderate = 0.75, low = 0.5, and very low = 0.25). The mean score for each systematic review was calculated and multiplied by 100 to obtain a percentage, summarising the compliance of the document with pre-planned desirable criteria.

Only information about outcomes that were considered of particular relevance to the patient was extracted; for example, more weight was assigned to death and serious adverse events, followed by clinical cure, use of biomarkers and imaging. No difference between antibiotic comparisons was considered to be relevant when the 95% confidence intervals (CI) were within 5% of no effect for mortality, and within 10% for other important patient outcomes. Scoring was implemented independently by pairs of reviewers. Conflicts were resolved by discussion between the two reviewers.

Clinical practice guidelines

Guidelines were considered as potentially relevant if they had an explicit methodology section, which provided sufficient detail of how they were developed, such as an explicit search strategy,

assessment of the quality of the evidence, and methods used to make recommendations. Guidelines were ranked using 11 relevant items (Box 2) of the 23 items in the Appraisal of Guidelines for Research and Evaluation II (AGREE II) Instrument.[29] The mean score for each guideline was calculated and multiplied by 100 to obtain a percentage, summarising the compliance of the document with pre-planned desirable AGREE II criteria. Scoring was implemented independently by pairs of reviewers. Conflicts were resolved by discussion between the two reviewers.

Box 2. Domain items/questions used to rank Clinical Practice Guidelines (rating on a 1-7 point scale, 1=strongly disagree and 7=strongly agree)
1. The overall objective(s) of the guideline is (are) specifically described.
2. The health question(s) covered by the guideline is (are) specifically described.
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.
4. The guideline development group includes individuals from all the relevant professional groups.
5. Systematic methods were used to search for evidence.
6. The criteria for selecting the evidence are clearly described.
7. The strengths and limitations of the body of evidence are clearly described.
8. The methods for formulating the recommendations are clearly described.
9. The health benefits, side effects, and risks have been considered in formulating the recommendations.
10. There is an explicit link between the recommendations and the supporting evidence.
11. The guideline has been externally reviewed by experts prior to its publication.

Discussion of the evidence

The Working Group met in September 2016 for the first time and the evidence was summarized and discussed within the group. The Working Group agreed on a set of principles to guide their selection of antibiotics for the EML based on the evidence from the literature review. The Working Group recognised the need to develop a new method to categorize the hundreds of antibiotics being used globally to support the implementation of antimicrobial stewardship activities and to guide monitoring of antibiotic use. The new method of grouping antibiotics was also aimed at simplifying guidance, improving access to the essential antibiotics, improving clinical outcomes, while reducing inappropriate prescribing and the subsequent risk of antimicrobial resistance. Another central element of the proposed framework was preserving the effectiveness of the last-resort Reserve antibiotics. The principles of new AWaRe categorization were used to guide EML 2019 and 2021 updates regarding to antibiotic selection and classification.

In 2017 the documents resulting from the work of the Working Group, detailing first and second choice antibiotic proposals and a potential antibiotic classification system were made publicly available on WHO website for comment before the Expert Committee met to review the Working Group's proposals. For each iteration comments on the applications were received from Médicines Sans Frontières (MSF), the Global Antibiotic Research and Development Partnership (GARDP) and the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA). These third parties were supportive of the WHO initiative to develop a new classification system of antibiotics to better support stewardship activities. At the same time all parties commented on the need for a new classification to not restrict access to antibiotics. Working Group proposals and related comments were considered by the EML Expert Committees during the 2017 meeting (Geneva, Switzerland, from 27th to 31st March). The same dual approach (Working Group detailing

the proposals, EML Expert Committees approving and making final recommendations) was also followed in 2019 (Geneva, Switzerland, from 1st to 5th April), 2021 (Geneva, Switzerland, from June 21st to 2nd July) and 2023 (Geneva, Switzerland, from 24th to 28th of April) meetings. All documents are summarized and referred in the Committee's meeting reports.[30-33]

Guiding principles for selecting antibiotics

The Working Group decided on the following guiding principles for the selection of antibiotics to be included in the updated WHO EML:

- **Prevention of the emergence and spread of antibiotic resistance.** The Working Group considered the implications of antibiotic use on potential resistance to refine the list of possible antibiotics for the EML generated from the systematic reviews and guidelines. Given the lack of an accepted method for determining the risk of the development and spread of antibiotic resistance and the limited empiric evidence available, the Working Group considered that deliberations on antibiotic resistance could be based on opinions of experts participating in the Working Group meetings, complemented whenever possible by data from the Global Antimicrobial Resistance and Use Surveillance System (GLASS) [34]. It was decided to privilege antibiotics with a narrower spectrum of activity and to use a strategy of fluoroquinolone- and carbapenem-sparing therapies where appropriate. Therefore, alternative choices were listed unless there was evidence for the superiority of fluoroquinolones and carbapenems over other alternatives in a given infection.

- **Parsimony.** The Working Group considered the availability of specific antibiotics and their formulations across countries and took a parsimonious approach. When several potentially effective antibiotic alternatives were identified, a limited number of key narrow

spectrum antibiotics were prioritised. If several comparable options were listed for a specific infection, antibiotics that were most frequently listed across all the infections were chosen. This approach is consistent with the selective nature of the EML, which aims to provide prescribers, policymakers and health care providers with a limited number of agents to facilitate procurement and enhance access to the key antibiotics required to treat most common infections.

- **Benefits and harms.** For benefits, the Working Group considered different aspects of clinical efficacy including, for example, time to resolution of symptoms and impact on the risk of complications, including mortality when relevant. Harms, included specific drug toxicity such as short- and long-term side-effects including the development of antimicrobial resistance, were also considered. The Group placed a relatively low value on prevention of allergic reactions, as true and severe allergic reactions (e.g. anaphylaxis) are rare.

- **Feasibility.** The Working Group particularly considered the availability of appropriate oral formulations (particularly when evaluating options for children) and options that facilitate the transition of treatment from hospital to primary care (i.e. changing from intravenous to oral treatment). Antibiotics that could be prescribed for a short duration of treatment were given preference provided they fulfilled all other guiding principles.

- **Alignment with the WHO List of Critically Important Antimicrobials for Human Medicine.** The One Health approach to antimicrobial resistance and the principle of promoting antibiotic stewardship across all sectors (human, animal, and environment) was considered by the Working Group.[35] Therefore, whenever possible, the antibiotic

selection was aligned with the WHO List of Critically Important Antimicrobials for Human Medicine (WHO CIA List).[36, 37] This is a list aimed at preserving medically important antimicrobials for human use by decreasing their use in the food chain.[38] However, as the EML takes into account factors other than those considered by the List of Critically Important Antimicrobials (e.g. issues of efficacy and access), the Working Group acknowledged that some differences between the EML and the List of Critically Important Antimicrobials, including the categorization of antibiotic groupings, would be unavoidable.

- **Alignment with WHO guidelines**. In some therapeutic areas – sexually transmitted infections, surgical prophylaxis and some diseases in children – specific WHO guidelines are regularly updated based on a stringent guideline development process based on the GRADE approach.[39] These updates inform decisions on antibiotics that are candidates for inclusion in the EML.[40] For consistency and cross-referencing purposes, close alignment was sought with available WHO clinical practice guidelines, specifically on sexually transmitted infections [41-43], surgical prophylaxis [44], and paediatric infections [45-49] (community-acquired pneumonia, neonatal sepsis, cholera, severe acute malnutrition, and dysentery (shigellosis)). The recommendations on empiric antibiotic treatment of infections in children, surgical prophylaxis and sexually transmitted infections were developed and published independently from the Expert Committee meeting. The guideline development panels might have privileged selection criteria other than those considered in AWaRe. Furthermore, evidence from WHO guidelines was complemented by evidence from the systematic reviews and other clinical practice guidelines, mimicking the process of other infections.

Expert Committee

The Expert Committee met in March 2017 for the first time to review the antibiotics proposed by the Working Group for the various paediatric and adult clinical infections. They endorsed the guiding principles for the selection of antibiotics proposed by the Working Group and reviewed, refined and approved the new AWaRe groups of antibiotics. To make the final list of recommendations for each infection, the Expert Committee built on the Working Group's reviews of infections by accepting or rejecting the Working Group's suggestions. The same approach was followed in 2019 and 2021. In 2023 the Working Group did not propose any major change to antibiotics proposed in the previous years. The Expert Committee adhered to the following principles to guide their decisions on the selection of antibiotics for the EML:

- Integrating the evidence from the published literature with expert opinion when the evidence on a specific topic was limited
- Prioritising parsimony and prevention of the development and spread of antibiotic resistance, often reducing the number of options suggested by the Working Group for certain infections and across infections
- Developing a risk-stratified approach for specific antibiotic options in certain groups of patients (e.g. limiting the options for patients with mild or moderate infections but not for those with severe infections)
- Commitment to update the recommended antibiotics and continuously monitor bibliographic and other databases (e.g. GLASS) to identify new research that can lead to a major update.

Guiding principles set to develop AWaRe were confirmed by the Expert Committee in 2019, 2021 and 2023.

Results

The antibiotic categorization is presented first (including the initial categorization proposed by the Working Group) followed by the antibiotic recommendations for each infection. For each infection, a summary of the evidence from the systematic reviews and the recommendations of the relevant clinical practice guidelines is presented. The selection process is also outlined. The final recommendations of the Expert Committee are reported at the end of each infection. The reasons for any deviations from the Working Group's recommendations by the Expert Committee are explained. For each infection, a table summarizes the antibiotics proposed by the Expert Committee, grouping them as first- or second-choice options. Infections are presented in alphabetical order except for paediatric infections, which are presented at the end.

AWaRe and the antibiotic groups

The groups of antibiotics initially proposed by the Working Group (Box 3) in 2017 were further revised by the Expert Committee.

Box 3. Antibiotic initially proposed by the Working Group
1. CORE antibiotics (or unrestricted antibiotics) that should be available in all settings and are considered first-line antibiotics
2. TARGETED antibiotics that should be used in specific cases, depending on circumstances, such as antibiotic sensitivity profile of an isolated bacterial pathogen, or for the empiric treatment of a

bacterial infection in settings where antimicrobial resistance to the most likely pathogens is likely to be high
3. PRESERVED antibiotics that should only be used if no other options exist in order to prevent the emergence of resistance to this group of antibiotics

While adopting the same concept hierarchy and similar category definitions, the Expert Committee refined this initial semantic over a 5-day meeting, preferring terms that were less ambiguous and more coherent as part of a simple framework. The final result is the AWaRe framework, which allocated antibiotics to the following three groups: Access, Watch and Reserve (i.e. AWaRe) (Box 4). These groups were confirmed during later committee meetings (2019 – 2023).

Access antibiotics are those that have good clinical activity against common susceptible bacteria and show lower resistance potential than antibiotics in other groups and should be widely available in all health care facilities. Watch antibiotics have a relatively higher risk of selection of antibiotic-resistant bacteria and should be targets of antimicrobial monitoring and stewardship programmes. They are generally associated with more adverse events and toxicities, and often come at a higher price. Reserve antibiotics are the last-resort options that should only be used for the treatment of confirmed or suspected infections due to multidrug-resistant bacteria and a major target for antimicrobial stewardship programmes.[50]

The Expert Committee decided to use first- and second-choice antibiotic options instead of core and targeted categories. First-choice antibiotics are usually narrow-spectrum agents with favourable risk–benefit ratios (i.e. benefits outweigh risks) and for which relatively low levels of resistance have been reported. Second-choice antibiotics are generally broader-spectrum agents

for which higher rates of resistance have been reported or that have less favourable risk–benefit ratios. It should be noted that the two categorizations – first and second choice, and AWaRe – are independent of each other. Particularly, the first and second choice level is not appropriate for all infections as this additional dimension is primarily needed to signal to health professionals a preferred order among agents for a specific indication. For other infections all recommended antibiotics might have the same priority. Instead, the AWaRe framework is used consistently across all infections and can be considered an overarching grouping of antibiotics. It primarily serves policymakers by highlighting which antibiotics should be monitored and targeted for antibiotic stewardship activities.

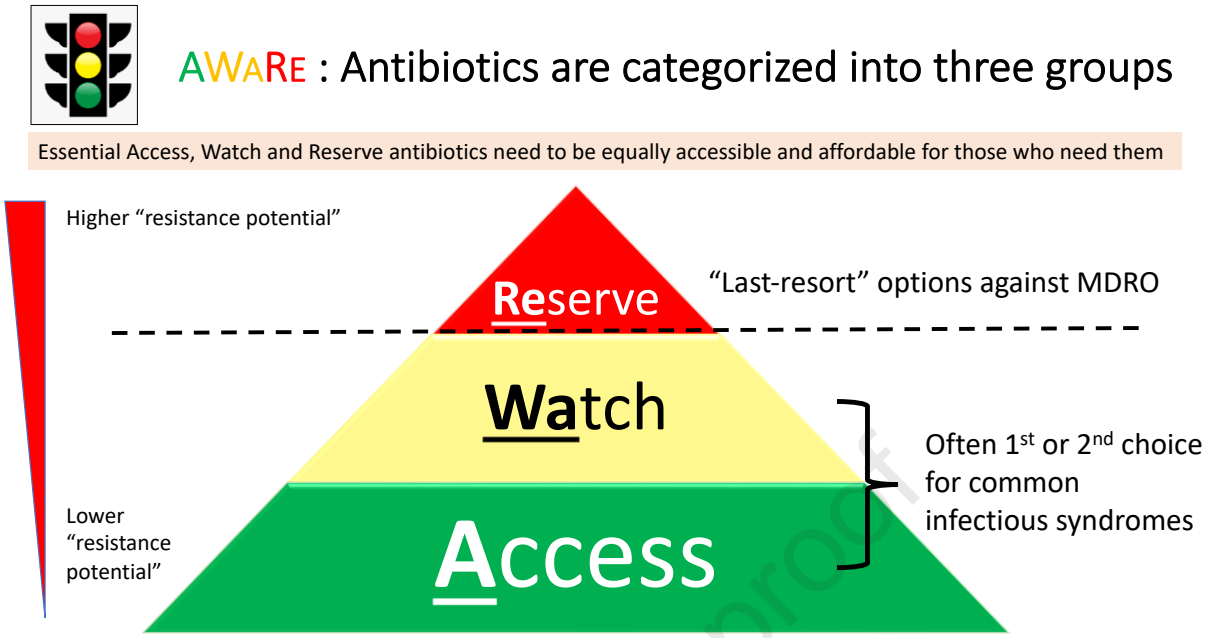
Box 4. The AWaRe framework and three antibiotic groups - Access, Watch and Reserve (i.e. AWaRe).

1. AWaRe – Access. This group includes antibiotics that are recommended as empiric, first- or second-choice treatment options for common clinical infections. These antibiotics should be widely available, affordable, in appropriate formulations, and of assured quality.
2. AWaRe – Watch. This group includes antibiotic classes that are considered to have greater concerns about toxicity or the potential for the development of antimicrobial resistance but they are still recommended as first- or second-choice options for some indications. These antibiotics should be key targets of local and national antibiotic stewardship and monitoring programmes. This group includes the highest priority agents on the List of Critically Important Antimicrobials for human medicine, such as fluoroquinolones and carbapenems. It should be noted that antibiotics may be listed as first choice for some indications and second choice for other indications, depending on the availability of other "better" options. The Access and Watch groups are not mutually exclusive: access to both groups is vital, but antibiotics in the Watch group should be used only for specific indications or pathogens.

3. AWaRe – Reserve. This group includes antibiotics that should be treated as last-resort options or used only for highly specific patient populations and settings when other alternatives would be inadequate or have already failed (e.g. severe or life-threatening infections due to multidrug-resistant bacteria). In the context of the AWaRe categorization, last-resort antibiotics are those that show consistent activity against organisms resistant to many or all of the first- or second-choice antibiotic options. To preserve their effectiveness, these medicines should be protected and prioritized in national and international antibiotic stewardship programmes that monitor and report on their use and, ideally, also on resistance to these classes. Eight antibiotics were identified for this group.

The AWaRe categorization is represented as a traffic-light approach (Fig. 3), a simple model used to facilitate behavioral change, help mitigating risks associated with inappropriate antibiotic prescribing and to structure it in such a way that it can be easily incorporated in clinical practice.[51, 52] It focuses on three levels of alertness: Access = green, Watch = orange and Reserve = red. Simple graphics using the traffic light approach can be used to show the proportions of Access and Watch antibiotics used in settings such as a community clinic or pharmacy or as part of central monitoring of antibiotic consumption.[53, 54] To date, the Expert Committee has classified 257 antibiotics used globally into Aware groups.[55] Among the 257 antibiotics, 41 are listed as essential medicines in the 2023 EML.[56, 57]

Fig. 3. The traffic light WHO AWaRe categorization approach



Clinical infections

Bacterial diarrhoea (Acute infectious e.g. traveller's diarrhoea) in adults

Summary of systematic reviews: We retrieved five reviews with quality scores ranging from 55% to 73%.[58-62] One of the reviews was excluded as it focused on the efficacy of antibiotics in children with chronic rather than acute diarrhoea.[58] Table 1 gives a summary of the findings of the systematic reviews included.

Table 1. Acute infectious bacterial diarrhoea (including traveller's diarrhoea) in adults: summary of findings from systematic reviews

First author (year)	Aim of the study	Findings

Leibovici-Weissman Y (2014) [59]	Compared antibiotics with placebo or no treatment for cholera and assessed differences between classes of antibiotics	• Shorter duration of diarrhoea by about 1.5 days and reduced stool volume of about 50% with antibiotics than placebo or no treatment • No conclusions on efficacy of specific antibiotic classes as many antibiotics were considered • Reduced diarrhoea duration by more than a day (MD 32.4 hours, 95% CI 1.95–62.9) and lower risk of clinical failure (RR 0.32, 95% CI 0.23–0.44) with azithromycin (single dose) than ciprofloxacin • Lower risk of clinical failure with tetracycline than sulfamethoxazole–trimethoprim (RR 0.56, 95% CI 0.34 to 0.92)
Onwuezobe IA (2012) [60]	To compare antibiotics with placebo/no treatment for non-typhoidal salmonella diarrhoea	• Lower risk of microbiological failure in the first week of treatment with fluoroquinolones than placebo (RR 0.33, 95% CI 0.20–0.56) • No difference in clinical failure between antibiotics and placebo
Christopher PR (2010) [61]	Compared different antibiotics for the treatment of dysentery caused by *Shigella* spp.	• Where 90% of participants had confirmed *Shigella* spp. infection, fewer patients had still diarrhoea on follow-up with beta-lactams than fluoroquinolones (RR 4.68, 95% CI 1.74–12.59)
De Bruyn G (2000) [62]	Compared antibiotics with placebo for traveller's diarrhoea	• Greater cure by 72 hours (OR 5.90, 95% CI 4.06–8.57) but more side-effects (OR 2.37, 95% CI 1.50–3.75) with antibiotics than placebo

OR: odds ratio; CI: confidence intervals; MD: mean difference; RR: risk ratio/relative risk.

Summary of guidelines: Six guidelines were considered [63-68], three of which we included (quality scores ranging from 65.3% to 68.5%).[65, 66] Clinical practice guidelines include antibiotics for traveller's diarrhoea or for laboratory-confirmed infection. Table 2 gives a summary of recommendations of the guidelines included.

Table 2. Acute infectious bacterial diarrhoea (including traveller's diarrhoea): summary of guideline recommendations

Guideline	Acute infectious bacterial diarrhoea: type	Recommendation
American College of Gastroenterology (2016) [67]	Traveller's diarrhoea	• Fluoroquinolone, azithromycin or rifaximin – only if likelihood of bacterial pathogens is high enough to justify the potential adverse effects of antibiotics
Society for Healthcare Epidemiology of America (2010) [63]	*Clostridium difficile* infections	• Metronidazole, oral vancomycin
Infectious Diseases Society of America (2001) [68]	Traveller's diarrhoea	• Fluoroquinolones; the guideline warns about the increase in fluoroquinolone-resistant *Campylobacter* spp. • No antibiotics for patients with enterohaemorrhagic *Escherichia coli* infections because of higher risk of haemolytic uraemic syndrome
	Cholera	• Doxycycline or tetracycline, or a single dose of a fluoroquinolone

	Non-typhi *Salmonella* species	• Antibiotics not recommended routinely • Sulfamethoxazole–trimethoprim (if susceptible), or a fluoroquinolone, or ceftriaxone and azithromycin for severe infection, or patient < 6 months or > 50 years, or patient with prostheses, valvular heart disease, severe atherosclerosis, malignancy or uraemia
	Shigella spp. infections	• Sulfamethoxazole–trimethoprim, a fluoroquinolone, nalidixic acid, ceftriaxone, or azithromycin

Working Group considerations: The Working Group acknowledged that evidence was limited to either empiric therapy for traveller's diarrhoea or for laboratory-confirmed infections. However, if treatment is considered necessary, then sulfamethoxazole–trimethoprim is recommended as an Access antibiotic. Azithromycin, clarithromycin and fluoroquinolones, although listed as alternatives in clinical practice guidelines, should only be used if no other more appropriate options are available because of concerns of resistance as well as potential harm – the United States Food and Drug Administration (FDA) has issued Drug Safety Communications and strengthened warnings on the product labels of these antibiotics [69-71]. For confirmed *Shigella* spp. infections, beta-lactams appear to be more effective than fluoroquinolones. Therefore, the Working Group included ceftriaxone as an Access antibiotic for treatment of confirmed *Shigella* spp. infections. This proposal was modified by the Expert Committee (i.e. ceftriaxone categorized as a Watch antibiotic). For cholera, azithromycin appears to be more effective than fluoroquinolones. In addition, sulfamethoxazole–trimethoprim should be avoided as it was less effective than doxycycline. Therefore, the Working Group proposed azithromycin as the first-choice treatment for cholera, with doxycycline as an alternative second-choice. As regards other antibiotics

commonly used to treat cholera in clinical practice, the Working Group decided not to recommend ciprofloxacin based on data from systematic reviews and clinical experience for those antibiotics that lacked direct evidence (i.e. erythromycin).

The Working Group did not include ofloxacin, norfloxacin or nalidixic acid for acute infectious bacterial diarrhoea, because of redundancy with other fluoroquinolones (e.g. ciprofloxacin) that were listed as options for other infections. Rifaximin was also not included for the same reason.

For *Clostridioides difficile* infections, the Working Group included metronidazole (oral) and vancomycin (oral) as an Access antibiotic, a proposal in part modified by the Expert Committee (vancomycin categorized as a Watch antibiotic).

For enteric fever, chloramphenicol was included as a last-resort option when no other antibiotics are available. This decision was based on suggestions from experts from low- and middle-income countries during the Working Group's panel meeting.

Expert Committee recommendations: The main focus was on community-based infections in adults. The Committee noted that in most cases, if a patient presents with non-bloody and non-febrile diarrhoea, a watchful waiting approach with relief of symptoms and no antibiotic treatment is the appropriate first-choice treatment option. For invasive bacterial diarrhoea, in contrast to the Working Group's recommendation, the Committee selected ciprofloxacin as the first-choice option because of concerns about resistance to sulfamethoxazole–trimethoprim (Table 3).

Azithromycin, cefixime, ceftriaxone, and sulfamethoxazole–trimethoprim were recommended as second-choice options. For cholera, the Committee followed the Working Group's recommendations for first-choice options (i.e. azithromycin and doxycycline). However, it included ciprofloxacin as second-choice treatment.

For *Clostridioides difficile*, metronidazole was selected as the first choice with oral vancomycin as the second choice.

Table 3. Recommendations of the Expert Committee for antibiotics to treat acute infectious diarrhoea in adults

Acute infectious bacterial diarrhoea	
First choice	**Second choice**
Invasive bacterial diarrhoea/dysentery	
Ciprofloxacin[a] (W)	Azithromycin[b] (W)
	Cefixime[b] (W)
	Ceftriaxone (W)
	Sulfamethoxazole–trimethoprim (A)
Cholera	
Azithromycin (W)	Ciprofloxacin (W)
Doxycycline (A)	
Clostridium difficile	
Metronidazole[c] (A)	Vancomycin (oral) (W)
Antibiotics proposed by the Working Group but not recommended by the Expert Committee	
Chloramphenicol for enteric fever[d]	

A: Access, W: Watch

[a]The Working Group had initially suggested sulfamethoxazole–trimethoprim as the first-choice option for traveller's diarrhoea and ceftriaxone for dysentery. However, despite resistance concerns and potential harm, the Expert Committee considered that ciprofloxacin should be the first choice for this indication because of concerns about resistance to sulfamethoxazole–trimethoprim. However, local risk of fluoroquinolone resistance should also be considered and second-choice options are preferred when resistance to quinolones is high. According to the last

GLASS report the median percentage of *Shigella* isolates resistant to ciprofloxacin was close to (but lower than) 20% (based on data from 15 countries).

[b]Cefixime was suggested as second-choice option after a request from the WHO department for maternal, newborn, child and adolescent health.

[c]Both oral and intravenous formulations are recommended (but oral formulations are preferred).

[d]The Expert Committee decided not to make recommendations for enteric fever because the topic would require an in-depth assessment. A separate EML application that takes into account the different therapeutic options was then presented in 2021 (see section enteric fever).

Bone and joint infections

Summary of systematic reviews: We identified eight systematic reviews [72-79] and two were included (quality scores were 55% and 65%) [73, 75]. Table 4 gives a summary of the findings of the systematic reviews included.

Table 4. Bone and joint infections: summary of findings of systematic reviews

First author (year)	Aim of the study	Findings
Conterno LO (2013) [73]	Compared different systemic antibiotic regimens for chronic osteomyelitis	• No difference between treatments, but the included studies lacked power
Karamanis EM (2008)[75]	Compared fluoroquinolones with beta-lactam-based regimens for osteomyelitis	• No difference between antibiotics, but wide confidence intervals

Summary of guidelines: Two guidelines [80, 81] developed by the Infectious Diseases Society of America were assessed. Two other documents that were retrieved were opinion pieces and not clinical practice guidelines [82, 83]. The clinical practice guidelines were similar in quality (quality scores 79.9% and 82.2%). Table 5 gives a summary of the recommendations of the guidelines.

Table 5. Bone and joint infections: summary of recommendations of guidelines

Guideline (year)	Bone and joint infection: type	Recommendation
Infectious Diseases Society of America (2015) [80] – native vertebral osteomyelitis	Native vertebral osteomyelitis	• Pathogen-targeted treatment. If required, vancomycin and a third- or fourth-generation cephalosporin for empiric use • First-line antibiotics the same as those recommended for prosthetic joint infections for the different pathogens • Ciprofloxacin for *Salmonella* spp.
Infectious Diseases Society of America (2013) [81] – prosthetic joint infections	Methicillin-susceptible *Staphylococcus aureus*	• Pathogen-specific therapy (nafcillin, cefazolin or ceftriaxone) in combination with rifampicin • After intravenous treatment, an oral antibiotic (ciprofloxacin or levofloxacin), or sulfamethoxazole–trimethoprim, minocycline, doxycycline or oral first-generation cephalosporins (e.g. cefalexin), or

		antistaphylococcal penicillins plus rifampicin for methicillin-susceptible *Staphylococcus aureus* infections
	Methicillin-resistant *Staphylococcus aureus*	• Vancomycin plus rifampicin
	Enterococcus spp. susceptible to penicillin	• Penicillin or ampicillin
	Enterococcus spp. resistant to penicillin	• Vancomycin
	Pseudomonas aeruginosa	• Cefepime or meropenem
	Enterobacter spp.	• Cefepime or ertapenem
	Enterobacterales	• Intravenous beta-lactam based on susceptibility or ciprofloxacin
	Beta-haemolytic *Streptococcus* spp. and *Propionibacterium acnes*	• Penicillin or ceftriaxone

Working Group considerations: Of the antibiotics proposed in the guidelines, cefepime was not included in the Working Group list because of safety concerns in a setting where an alternative antibiotic is available (meropenem); however, the group considered cefepime an antibiotic for the treatment of pathogens resistant to other beta-lactams and could be a carbapenem-sparing option which should not be prioritized for empiric use. As with other infections, ertapenem was also proposed as an antibiotic to be used when activity against Gram-negative organisms is needed (excluding coverage for *Pseudomonas aeruginosa*) and not for empiric use. Doxycycline (but not minocycline) was proposed in the interest of parsimony since doxycycline is also recommended for other infections. Similarly, dicloxacillin, rather than nafcillin, was proposed as an anti-staphylococcal penicillin, as it is listed for several other infections. Finally, rifampicin was listed

as a preserved antibiotic for prosthetic joint infection and only to be used for treatment of rifampicin-susceptible *Staphylococcus* spp.

Expert Committee recommendations: Based on the epidemiology of the pathogens typically found in this type of infection, the Expert Committee recommended antibiotics only for possible empiric treatment (Table 6). The Committee selected cloxacillin as the first choice and amoxicillin–clavulanic acid, cefazolin, cefotaxime or ceftriaxone, and clindamycin as second-choice options.

Antibiotics that would be used for targeted treatment (i.e. laboratory-confirmed pathogens) were excluded, including ampicillin, benzylpenicillin, ciprofloxacin, doxycycline, levofloxacin, rifampicin, and sulfamethoxazole–trimethoprim. Cefalexin was not included because of redundancy, and vancomycin was excluded because methicillin-resistant *Staphylococcus aureus* (MRSA) is a rare cause of community-acquired invasive infections in many countries and the Expert Committee focused on options for empiric treatment. The Committee noted that an update of the evidence for vancomycin should be provided for consideration to one of the next Committee meetings, to review available data on MRSA trends and potential implication about the role of vancomycin, particularly for severe infections.

Table 6. Recommendations of the Expert Committee for antibiotics to treat bone and joint infections

Bone and joint infections	
First choice	**Second choice**
Cloxacillin (A)	Amoxicillin–clavulanic acid (A)

	Cefazolin (A)
	Cefotaxime or ceftriaxone (W)
	Clindamycin (A)
Antibiotics proposed by the Working Group but not recommended by the Expert Committee	
Ampicillin[a], benzylpenicillin[a], ciprofloxacin[a], dicloxacillin[b], doxycycline[a], ertapenem[c] levofloxacin[a], rifampicin[a], sulfamethoxazole-trimethoprim[a], vancomycin[d]	

A: Access, W: Watch

[a]The Expert Committee did not recommend these antibiotics because they are suitable options for targeted treatment but not for empiric treatment.

[b]The Expert Committee decided to exclude dicloxacillin in the interest of parsimony because cloxacillin (listed as first choice) offers the same antibacterial spectrum of action.

[c]The Expert Committee decided to exclude ertapenem because of redundancy with other beta-lactam options suitable for empiric treatment.

[d]The Expert Committee decided to exclude vancomycin as community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) infections causing invasive diseases are rare.

Bronchitis

Summary of systematic reviews: Two systematic reviews were identified and reviewed in detail. Nine other reviews were excluded as they focussed on exacerbations of chronic obstructive pulmonary diseases, asthma or bronchiectasis. Table 7 gives a summary of the findings of the included systematic reviews. Quality scores ranged from 50% to 72.5%.

Table 7. Bronchitis: summary of findings from systematic reviews

First author (year)	Aim of the study	Findings

Smith (2017) [84]	Assessed the effects of antibiotics in people with acute bronchitis	• No difference in clinical improvement between antibiotics and placebo groups (RR 1.07, 95%CI 0.99-1.15) • Adverse events increased with antibiotics compared to placebo (RR 1.20, 95%CI 1.05-1.36)
Linder (2002)[85]	Assessed the efficacy of antibiotics in smokers with acute bronchitis	• No overall benefit of antibiotics in 5 of 9 of the RCTs. • Adverse events were more frequent with antibiotics compared to placebo (16% vs 11%)

Summary of guidelines: Nine documents were identified but only two met the criteria for clinical practice guidelines and were included. Table 8 gives a summary of recommendations of the guidelines included. Quality scores ranged between 62.5% and 68.5%.

Table 8. Bronchitis: summary of recommendations of guidelines

Guideline (year)	Bronchitis: type	Recommendation
UK National Institute for Health and Care Excellence (NICE). Cough (acute): antimicrobial prescribing.(2019) [86]	Acute cough associated with an upper respiratory tract infection or bronchitis in adults, young people and children	• Antibiotics not recommended in patients with bronchitis who are not systemically unwell or at high risk for complications

American College of Physicians and the Centers for Disease Control and Prevention (2016)[87]	Acute respiratory tract infection in adults	• Antibiotics not recommended in patients with bronchitis unless pneumonia is suspected

Working Group considerations: The Working Group decided that based on the evidence from systematic reviews and statements in guidelines, antibiotics should not be recommended for acute bronchitis in otherwise healthy people.

Expert Committee recommendations: The Committee followed the Working Group's recommendations and confirmed that antibiotics are not needed and should not be routinely prescribed for the treatment of acute bronchitis.

Bronchiolitis

Summary of systematic reviews: Two systematic reviews focussing on bronchiolitis were included and reviewed in detail. Table 9 gives a summary of the findings of the systematic reviews included. Quality scores ranged from 60 and 62.5%.

Table 9. Bronchiolitis: summary of findings from systematic reviews

First author (year)	Aim	Findings
McCallum (2017) [88]	Compared the effectiveness of antibiotics versus placebo (or no treatment) in the post-acute phase of acute bronchiolitis in children <2 years	• No difference at 6 months for wheeze (OR 0.47, 95% CI 0.06-3.95) and readmission for respiratory illness (OR 0.54, 95% CI 0.05-6.21), no difference for persistent symptoms at follow up (OR 0.69, 95% CI 0.37-1.28)
Farley (2014) [89]	Assessed the effectiveness of antibiotics for acute	• No difference for length of hospital stay (MD -0.58 days; 95% CI -1.18-0.02 days), duration

	bronchiolitis in children < 2 years compared to placebo or other interventions	of oxygen requirement (MD -0.20 days; 95% CI -0.72-0.33 days)

MD: mean difference.

Summary of guidelines: Three guidelines were included. Table 10 gives a summary of recommendations of the guidelines included. Quality scores ranged between 68.8% and 71.4%.

Table 10. Bronchiolitis: summary of recommendations of guidelines

Guideline (year)	Bronchiolitis: type	Recommendation
American Academy of Pediatrics (2014) [90]	Acute bronchiolitis	No antibiotics unless concomitant bacterial infection or a strong suspicion of concomitant infection
Canadian Pediatric Society (2014) [91]	Acute bronchiolitis	No antibiotics unless strong suspicion of concomitant bacterial infection
Italian Inter-Society consensus (2014) [92]	Acute bronchiolitis	No routine use of antibiotics

Working Group considerations: The Working Group decided that based on the evidence from systematic reviews and statements in guidelines, antibiotics should not be recommended for bronchiolitis in young children.

Expert Committee recommendations: The Committee followed the Working Group's recommendations and confirmed that antibiotics are not needed and should not be prescribed for the treatment of bronchiolitis unless there is clear evidence for or a strong suspicion of a secondary bacterial infection.

Community-acquired pneumonia

Summary of systematic reviews: For adults, one randomized controlled trial [93] and 21 systematic reviews were reviewed.[94-114] Five systematic reviews and the RCT were included with quality scores of 60–90%.[93-98] Table 11 gives a summary of the findings of systematic reviews included.

Table 11. Community-acquired pneumonia: summary of findings of reviews

First author (year)	Aim of the study	Findings
Postma DF (2015)[93]	Compared empirical treatment with beta-lactam monotherapy, beta-lactam–macrolide combination therapy, or fluoroquinolone monotherapy for community-acquired pneumonia[a]	• No difference in 90-day mortality between the three treatments
Pakhale S (2014)[94]	Compared different antibiotics for community-acquired pneumonia	• No difference in effectiveness between the classes of antibiotics, wide confidence intervals[b] • Fewer adverse events with clarithromycin than with erythromycin (OR 0.30, 95% CI 0.20–0.46) • More adverse events with azithromycin than with levofloxacin (OR 1.78, 95% CI 1.04–3.03)

Skalsky K (2013) [95]	Compared macrolides with quinolones for community-acquired pneumonia	• No difference in mortality between macrolides and fluoroquinolones (RR 1.03, 95% CI 0.63–1.68) • More adverse gastrointestinal events with macrolides than with quinolones, wide confidence intervals

CI: confidence intervals; OR: odds ratio; RR: risk ratio.

[a]Cluster-randomized, crossover trial.

[b]Similar findings reported in other reviews. [96-98]

Summary of guidelines: For adults, eight potentially relevant clinical practice guidelines were identified and these ranged in quality from 62% to 90%.[115-122] Only two met the eligibility criteria;[115, 119] one from the United Kingdom of Great Britain and Northern Ireland and the other from the United States of America. Table 12 gives a summary of recommendations of the guidelines.

Table 12. Community-acquired pneumonia: summary of recommendations of guidelines

Guideline (year)	Community-acquired pneumonia: type	Recommendation
British Thoracic Society (2009) [115] & National Institute for Health and Care Excellence (2014)	Treatment based on severity of illness	• Low severity: single antibiotic as initial empiric therapy • Moderate severity: combination of amoxicillin and a macrolide • High severity: combination of a beta-lactam with a beta-lactamase inhibitor and a macrolide
Infectious Diseases Society of America & American Thoracic Society (2007) [119]	Treatment based on severity of illness in adult patients	• No comorbidities: macrolide or doxycycline • Presence of comorbidities: respiratory fluoroquinolone (levofloxacin, moxifloxacin, or gemifloxacin) or combination of a beta-lactam and a macrolide (or doxycycline) • Intensive care treatment: combination of a beta-lactam (ceftriaxone, cefotaxime, or ampicillin–sulbactam) and a macrolide or a respiratory fluoroquinolone
	Suspected or confirmed *Pseudomonas aeruginosa*	• Piperacillin–tazobactam or carbapenem in combination with ciprofloxacin (or levofloxacin) or beta-lactam with an aminoglycoside and azithromycin
	Suspected or confirmed Methicillin-resistant *Staphylococcus aureus*	• Vancomycin or linezolid

Working Group considerations: Amoxicillin (or phenoxymethylpenicillin) was selected as the first choice for mild to moderate community-acquired pneumonia based on the non-inferiority of beta-lactams in a randomized controlled trial, the absence of statistically significant differences in

effectiveness of one class over the others in the systematic reviews, the relatively low potential for resistance compared with macrolides and fluoroquinolones, and the selection of amoxicillin as the first choice in some guidelines. Amoxicillin–clavulanic acid and doxycycline were selected as the second choices based on their inclusion in clinical practice guidelines and low potential for resistance. Cefotaxime or ceftriaxone in combination with clarithromycin was the first choice for severe community-acquired pneumonia for similar reasons, and amoxicillin–clavulanic acid and clarithromycin were selected as the second choice.

As erythromycin was found to have more adverse events than clarithromycin, the Working Group did not recommend it for the list. Azithromycin was also not proposed for listing because of the increased risk of cardiovascular events [70]. Despite the fact that all fluoroquinolones are associated with potentially relevant adverse events involving tendons, muscles, joints, nerves and the central nervous system, levofloxacin was proposed for targeted treatment only, as were piperacillin–tazobactam and ceftazidime. Their use should be limited to severe pneumonia, or for patients at high risk of infection by resistant pathogens, such as *Pseudomonas aeruginosa*. The use of ceftazidime can be considered in settings where melioidosis is endemic. Vancomycin is a treatment option for MRSA pneumonia: although the Working Group found no evidence on vancomycin in the systematic reviews, the group considered it reasonable to include vancomycin for empiric therapy in cases of suspected MRSA infection, as suggested in clinical practice guidelines. The use of vancomycin for pneumonia should be monitored, as should be the use of the other antibiotics in the Watch group.

Expert Committee recommendations: The Expert Committee based their selection of antibiotics for treatment of community-acquired pneumonia privileging the principle of parsimony, in

continuity also with evidence to treat pneumonia in children (see section *Community-acquired pneumonia in children*).

The Expert Committee recommended amoxicillin and phenoxymethylpenicillin as first-choice antibiotics for mild to moderate community-acquired pneumonia, and amoxicillin–clavulanic acid, or doxycycline as second-choice agents (Table 13). For severe community-acquired pneumonia in adults, the Expert Committee recommended clarithromycin in combination with ceftriaxone or cefotaxime as the first-choice options, and amoxicillin–clavulanic acid in combination with clarithromycin as second-choice treatment.

Table 13. Recommendations of the Expert Committee for antibiotics to treat community-acquired pneumonia

Community-acquired pneumonia	
First choice	**Second choice**
Mild to moderate community-acquired pneumonia	
Amoxicillin (A)	Amoxicillin–clavulanic acid (A)
Phenoxymethylpenicillin (A)	Doxycycline (A)
Severe community-acquired pneumonia	
Cefotaxime or ceftriaxone (W) + clarithromycin (W)	Amoxicillin–clavulanic acid (A) + clarithromycin (W)
Antibiotics proposed by the Working Group but not selected by the Committee	
Ceftazidime[a], gentamicin (children)[b], levofloxacin[a], piperacillin-tazobactam[a], vancomycin[c]	

A: Access, W: Watch

[a]The Expert Committee decided to exclude piperacillin–tazobactam, ceftazidime and levofloxacin because they considered these suitable options for targeted treatment but not for empiric treatment. With regard to levofloxacin, there were also concerns about resistance and potential harmful side-effects.

[b]The Expert Committee decided to exclude gentamicin based on parsimony to align antibiotic options with those recommended for adults.

[c]The Expert Committee decided to exclude vancomycin because they considered it a suitable option for targeted treatment of infections caused by methicillin-resistant *Staphylococcus aureus* but not routinely needed for empiric treatment.

Complicated intra-abdominal infections

Summary of systematic reviews: We identified 27 systematic reviews with quality scores ranging from 50% to 72%. Only six were included, which focused on complicated intra-abdominal infection with secondary peritonitis.[114, 123-127] Table 14 gives a summary of the findings of the systematic reviews included.

Table 14. Intra-abdominal infections: summary of findings of systematic reviews

First author (year)	Aim of the study	Findings
Shen F (2015) [114]	Compared tigecycline with other antibiotics for severe infectious diseases, including complicated intra-abdominal infections	• Tigecycline was not as effective as the other antibiotics for clinical cure and tigecycline was associated with more adverse events (OR: 1.49, 95% CI: 1.23-

		1.80) and higher mortality rate OR: 1.33, 95% CI: 1.03-1.72)
Bai N (2014) [123]	Compared ertapenem with ceftriaxone for complicated infections including complicated intra-abdominal infections	• Similar clinical cure, wide CI (OR 1.46, 95% CI 0.77–2.78)
Mu YP (2012) [125]	Compared moxifloxacin monotherapy with other antibiotics for complicated intra-abdominal infections	• More overall adverse events with moxifloxacin than other antibiotics (OR 1.33, 95% CI 1.07–1.63) however the incidence of drug-related events or serious adverse events was similar between the treatment groups compared
An MM (2009) [124]	Compared ertapenem with piperacillin–tazobactam for complicated infections including complicated intra-abdominal infections	• Similar clinical success, wide CI (OR 1.11, 95% CI 0.76–1.61)
Matthaiou DK (2006) [126]	Compared ciprofloxacin plus metronidazole with a beta-lactam for intra-abdominal infections	• Better clinical cure with ciprofloxacin plus metronidazole than a beta-lactam (OR 1.69, 95% CI 1.20–2.30)[1]
Wong PF (2005) [127]	Compared different antibiotics for secondary peritonitis of gastrointestinal origin	• No difference in mortality between antibiotics and combinations, wide CI • Poorer clinical success with aminoglycosides than all comparators (OR 0.65, 95% CI 0.46–0.92)

		• Better clinical cure with cephalosporins and beta-lactams (OR 3.21, 95% CI 1.49–6.92) and with fluoroquinolones combined with an anti-anaerobic agent (OR 1.74, 95% CI 1.11–2.73) than all other comparators

CI: confidence intervals; OR: odds ratio.

Summary of guidelines: Eight guidelines were considered.[128-135] Only two met the eligibility criteria (quality scores of 83.4% and 70.5%): the Surgical Infection Society and the Infectious Diseases Society of America [128], and the World Society of Emergency Surgery [129]. These guidelines base their recommendations on site of acquisition (e.g. community- versus hospital-acquired), anatomic site (biliary versus non-biliary), risk of extended spectrum beta-lactamases, and severity of illness. Table 15 gives a summary of recommendations of the guidelines.

Table 15. Intra-abdominal infections: summary of recommendations of guidelines

Guideline (year)	Intra-abdominal infections: type	Recommendation
World Society of Emergency Surgery (2011) [129]	Extra-biliary or biliary acute infection in patients who are not critically ill and who have no risk factors for extended-spectrum beta-lactamases	• Amoxicillin–clavulanic acid, or ciprofloxacin and metronidazole

	Hospital-acquired infection without critical illness but a risk of a multidrug-resistant organisms	• Piperacillin and tigecycline
	Hospital-acquired infection in critically ill patients	• Piperacillin, tigecycline or a carbapenem (meropenem, imipenem, or doripenem), teicoplanin plus an antifungal agent
Surgical Infection Society and the Infectious Diseases Society of America (2010) [128]	Mild to moderately severe infection in adults	• Single agent empiric therapy: cefoxitin, ertapenem, moxifloxacin, tigecycline, and ticarcillin–clavulanic acid • Combination therapy: a cephalosporin (cefazolin, cefuroxime, ceftriaxone, cefotaxime, ciprofloxacin, or levofloxacin) in combination with metronidazole
	High-risk or severely ill adults	• Imipenem, meropenem, doripenem, and piperacillin–tazobactam
	Community-acquired infection in children	• Aminoglycosides (ampicillin and gentamicin, or tobramycin in combination with metronidazole or clindamycin); or • Carbapenem (ertapenem, meropenem, or imipenem);or • Beta-lactam/beta-lactamase inhibitor combination (piperacillin–tazobactam, ticarcillin–clavulanic acid); or • Advanced-generation cephalosporins (cefotaxime, ceftriaxone, ceftazidime, or cefepime) together with metronidazole • For children with severe beta-lactam allergies, either an aminoglycoside or ciprofloxacin plus metronidazole

Working Group considerations: The Group noted that the clinical trial evidence was limited as confidence intervals for non-inferiority comparisons were wide. For non-severe infections amoxicillin-clavulanic acid or a cephalosporin (cefotaxime and ceftriaxone) with metronidazole fulfil the curative as well the preservative intent. Fluroquinolones (levofloxacin or ciprofloxacin) were considered as second options due to resistance and harm concerns. For severe cases the same cephalosporins with metronidazole, fluoroquinolones and piperacillin-tazobactam, were prioritized. Ampicillin was added to offer additional enterococcal coverage if the used regimen (e.g. ceftriaxone-metronidazole) would otherwise not covering enterococcus. Cefazolin, cefoxitin and cefuroxime were considered redundant because ceftriaxone is a better candidate that also offers broader Gram-negative coverage. Ceftazidime, meropenem and aminoglycosides (gentamicin or tobramycin) were proposed as alternatives to be used based on local resistance patterns. For carbapenems, only meropenem was proposed as it is the most frequently recommended carbapenem for all infections. Vancomycin was proposed for patients with concerns about methicillin-resistant *Staphylococcus aureus* infection. Ticarcillin–clavulanic acid and piperacillin were excluded as piperacillin–tazobactam is considered more appropriate and is listed for several infections. Cefepime was not included because it was considered redundant to the antibiotics already listed above, and because of concerns about increased mortality. However, the Working Group proposed to add this antibiotic to the Watch list. The Group also did not include ampicillin–sulbactam, cefotetan, and clindamycin as their use is discouraged in the Infectious Diseases Society of America guideline because of concerns about resistance. Tigecycline was not considered due to the boxed warning approved by the FDA related to potential higher mortality rate [136].

Expert Committee Recommendations: The Expert Committee focused on community-acquired intra-abdominal infections and revised the Working Group's selection of antibiotics (Table 16). Antibiotics were selected based on parsimony from the broader list of potential antibiotic choices listed in the clinical practice guidelines and prioritized by the Working Group. For non-severe infections, the Expert Committed recommended amoxicillin–clavulanic acid as the first-choice option while ciprofloxacin in combination with metronidazole was recommended as second-choice. Ciprofloxacin was preferred over levofloxacin (for parsimony and to preserve levofloxacin as a treatment for multidrug-resistant tuberculosis). Ceftazidime, tobramycin and vancomycin were not recommended as they have limited indications in community-acquired complicated intra-abdominal infections and are not an ideal option for empiric treatment. In 2017 ampicillin and gentamicin were not recommended, ampicillin because it has limited indications in community-acquired complicated intra-abdominal infections and aminoglycosides because they were considered suitable options for targeted treatment but not for empiric treatment. Both ampicillin and gentamicin were recommended in 2021, aligning AWaRe recommendations with other WHO recommendations (e.g. Pocket book of hospital care for children [137]). For severe and hospital-acquired infections, the first-choice antibiotics are the third-generation cephalosporins cefotaxime or ceftriaxone in combination with metronidazole. For severely ill patients, piperacillin–tazobactam is the first-choice antibiotic and meropenem the second choice.

Table 16. Recommendations of the Expert Committee for antibiotics to treat intra-abdominal infections

Intra-abdominal infections	

First choice	Second choice
Mild to moderate infection	
Amoxicillin–clavulanic acid (A)	Ciprofloxacin (W) + metronidazole (A)
Ampicillin (A) + gentamicin (A) + metronidazole[a, b] (A)	
Severe infection	
Cefotaxime or ceftriaxone (W) + metronidazole (A)	
Piperacillin–tazobactam (W)	Meropenem (W)
Antibiotics proposed by the Working Group but not selected by the Expert Committee	
Ampicillin, ceftazidime[c], tobramycin[c], vancomycin[d]	

A: Access, W: Watch

[a]Added in 2021.

[b]Only in children.

[c]The Expert Committee decided to exclude ceftazidime and aminoglycosides because they considered these suitable options for targeted treatment but not for empiric treatment.

[d]The Expert Committee decided to exclude vancomycin because, while they considered it a suitable option for targeted treatment of methicillin-resistant *Staphylococcus aureus* infections, it was not an ideal option for empiric treatment.

Exacerbations of chronic obstructive pulmonary disease

Summary of systematic reviews: We identified 11 systematic reviews on exacerbations of chronic obstructive pulmonary disease (COPD);[138-148] one had been withdrawn [140] and two were excluded.[142, 147] Quality scores of the eight reviews included ranged from 65% to 78%. Table 17 gives a summary of the findings of the systematic reviews included.

Table 17. Exacerbations of COPD: summary of findings of systematic reviews

First author (year)	Aim of the study	Findings
Vollenweider DJ (2012) [138]	Compared antibiotics with placebo	• No difference in outcomes in outpatients between antibiotics and placebo, wide CI • Reduced risk of treatment failure with antibiotics for inpatients (RR 0.77, 95% CI 0.65 to 0.91)
Korbila IP (2009) [148]	Compared penicillins with trimethoprim-based treatments for bacterial exacerbations of chronic bronchitis	• No difference in treatment success, number of adverse events and side-effects between the antibiotics, wide CI
El Moussaoui R (2008) [144]	Compared short course antibiotic treatment (≤ 5 days) with longer (> 5 days) treatment	• No difference in clinical cure between short and longer treatment[a]
Quon BS (2008) [145]	Compared antibiotics with placebo	• Reduced risk of treatment failure with antibiotics in inpatients (RR 0.34, 95% CI 0.20–0.56) but not in outpatients • Reduced risk of in-hospital death with antibiotics (RR 0.22, 95% CI 0.08–0.62)
Dimopoulos G (2007) [146]	Compared first-line[b] with second-line[c] antibiotics for acute exacerbations of chronic bronchitis	• Lower treatment success with first-line antibiotics (OR 0.51, 95% CI 0.34–0.75)
Ram FS (2006) [141]	Compared antibiotics with placebo	• Antibiotic therapy, regardless of choice, significantly decreases short-term mortality, treatment failure and sputum purulence. Analysis restricted to

		community-based studies did not find differences between antibiotic and placebo.
Saint S (1995) [139]	Compared antibiotics with placebo	• Reduced mortality with antibiotic treatment (effect size 0.22%, 95% CI 0.10–0.34%)

CI: confidence intervals; RR: risk ratio; OR: odds ratio.

[a]Similar findings reported in another review [143].

[b]Amoxicillin, ampicillin, pivampicillin, sulfamethoxazole–trimethoprim, and doxycycline.

[c]Amoxicillin–clavulanic acid, macrolides, second- or third-generation cephalosporins, and quinolones.

Summary of guidelines: We identified four clinical practice guidelines.[149-152] One of the documents did not meet the definition of a clinical practice guideline and was excluded.[149] Quality scores ranged between 51.9% and 66.6%. Table 18 gives a summary of the recommendations in the guidelines.

Table 18. Exacerbations of COPD: summary of recommendations of guidelines

Guideline (year)	Exacerbations of COPD: type	Recommendation
National Institute for Health and Care Excellence (2010) [150]	Patients > 16 years of age	• Antibiotics only if there is purulent sputum or clinical or radiographic evidence of pneumonia: aminopenicillin, macrolide, or tetracycline taking into account local prevalence of antimicrobial resistance
American Thoracic Society	Outpatients	• Start antibiotics if sputum characteristics change (amoxicillin or ampicillin, doxycycline, azithromycin,

& European Respiratory Society (2004) [152]		clarithromycin, dirithromycin, roxithromycin, levofloxacin, moxifloxacin depending on local prevalence of antimicrobial resistance)
	Inpatients	• Amoxicillin–clavulanic acid or respiratory fluoroquinolones (levofloxacin and moxifloxacin) based on local prevalence of antimicrobial resistance. Combination treatment in cases of suspected *Pseudomonas* spp. and other Gram-negative bacterial infections
Canadian Thoracic Society & Canadian Infectious Disease Society (2003) [151]	Tracheobronchitis	• No antibiotics
	Chronic bronchitis without risk factors	• Macrolides, second- or third-generation cephalosporins, amoxicillin, doxycycline or sulfamethoxazole–trimethoprim
	Complicated bronchitis with risk factors	• Fluoroquinolones, beta-lactam with a beta-lactamase inhibitor
	Chronic suppurative bronchitis	• Targeted treatment of the identified pathogen

In 2016, the FDA published a boxed warning against the use of fluoroquinolones for acute bacterial exacerbation of chronic bronchitis because of potential side-effects associated with antibiotics of this class.[71]The main concerns were related to disabling and potentially permanent side-effects affecting tendons, muscles, and joints, and also to peripheral neuropathy and central nervous system effects reported in otherwise healthy patients. The FDA continues to recommend the use

of fluoroquinolones in life-threatening infections where the potential benefit outweighs the potential risk.

Working Group considerations: The Working Group acknowledged that the evidence from randomized controlled trials was insufficient for recommending one antibiotic or class of antibiotics over another. Therefore, clinical practice guidelines informed the choice of antibiotics. Amoxicillin with or without clavulanic acid was selected as the first choice while cefalexin and doxycycline were chosen as second-choice options. Dirithromycin and roxithromycin were not proposed as there is no benefit compared with clarithromycin, which is also recommended for other infections. Sulfamethoxazole–trimethoprim was also not proposed as it was only listed in one clinical practice guideline and is not frequently used for COPD. Due to the side-effects of fluoroquinolones and the emergence of resistance, levofloxacin and moxifloxacin were not listed. The Working Group considered that levofloxacin could be considered only when first- and second-choice options are unavailable (moxifloxacin is not more effective than levofloxacin).

Expert Committee recommendations: The Committee noted that few options were available and that antibiotics were only needed for a subgroup of patients who had exacerbations of COPD. Amoxicillin or amoxicillin-clavulanic acid were recommended as the first-choice antibiotics and cefalexin and doxycycline as the second choice (Table 19).

Table 19. Recommendations of the Expert Committee for antibiotics to treat exacerbations of COPD

Exacerbations of COPD	
First choice	**Second choice**

Amoxicillin (A)	Cefalexin (A)
Amoxicillin–clavulanic acid (A)	Doxycycline (A)
Antibiotics proposed by the Working Group but not recommended by the Committee[a]	
Azithromycin[a], clarithromycin[a], levofloxacin[a]	

A: Access, W: Watch

[a]Given resistance and safety concerns.

Eye infections, including conjunctivitis, keratitis, and endophthalmitis

Infections of the skin and soft tissue surrounding the eye (periorbital cellulitis) and disseminated gonococcal infection with eye involvement were not included in the evidence review.

Summary of systematic reviews: Six systematic reviews focussing on conjunctivitis were included of which two were specifically focussed on conjunctivitis caused by *Chlamydia trachomatis* (trachoma). Concerning other eye infections, two systematic reviews were included for keratitis, and none could be found for endophthalmitis. Table 20 gives a summary of the findings of the systematic reviews by type of eye infection. Of note, neither of the four systematic reviews identified for conjunctivitis included head-to-head antibiotic comparisons, therefore there was no data to guide the choice of topical antibiotics. Quality scores ranged from 45.0% to 72.5%.

Table 20. Eye infections: summary of findings from systematic reviews

Eye infection	First author (year)	Aim of the study	Findings

Conjunctivitis	Zikic (2018) [153]	Evaluated the effects of macrolides or trimethoprim in neonates with chlamydial conjunctivitis	• Erythromycin associated with high clinical (96%, 95% CI 94%–100%) and microbiological cure rates (97%, 95% CI, 95%–99%) • Azithromycin (single dose) associated with lower cure rates than erythromycin (60%, 95% CI 27%–93%) but not when given for 3 days (86%, 95% CI 61%–100%) • No study assessed the effects of trimethoprim
	Azari (2013) [154]	Examined the role of different antibiotics in infectious conjunctivitis	• No antibiotic treatment necessary in uncomplicated cases but topical treatment decreases duration of symptoms. • Topical and systemic broad-spectrum antibiotics recommended for gonorrhea or chlamydia and for purulent conjunctivitis and in contact lens wearers
	Sheikh (2012)[155]	Assessed benefits and harms of antibiotics for acute bacterial conjunctivitis	• Topical antibiotics associated with higher remission rates in days 2-5 (RR for clinical remission 1.36, 95% CI 1.15-1.61; RR for microbiological remission 1.55, 95% CI 1.37-1.76)

			• Topical antibiotics associated with modest benefits in days 6-10 (RR for clinical remission 1.21, 95% CI 1.10–1.33; RR for microbiological cure 1.37, 95% CI 1.24–1.52) • In the placebo group 41% of patients were cured by day 6 to 10 • No serious adverse events in either study arms
	Jefferis (2011) [156]	Determined benefits of antibiotics for acute infective conjunctivitis	• Topical antibiotics associated with relevant benefit at day 7 (RD 0.08, 95% CI 0.01–0.14) • Benefit was consistent in case of purulent discharge (RD 0.09, 95% CI 0.01–0.17) or in case of mild eye redness (RD 0.10, 95% CI 0.02–0.18)
Bacterial keratitis	McDonald (2014) [157]	Evaluated the effectiveness of topical antibiotics in the management of bacterial keratitis	• No differences in treatment success (moxifloxacin versus tobramycin–cefazolin RR 1.02; 95% CI 0.91–1.14; ciprofloxacin versus gentamicin–cefazolin RR 1.11; 95% CI 0.84–1.45; fluoroquinolones versus aminoglycoside–cephalosporin RR 1.01; 95% CI 0.94–1.08), time to cure, or serious

			complications (including corneal perforation) between groups • Fluoroquinolones associated with reduced eye discomfort compared to aminoglycoside-cephalosporin combinations (RR 0.32, 95% CI 0.22–0.47)
	Hanet (2012) [158]	Reviewed the evidence of fluoroquinolones compared to fortified antibiotics[a] for bacterial keratitis	• No difference in healing (OR 1.05, 95% CI 0.64–1.73) when only RCTs were included
Trachoma	Evans (2019) [159]	Assessed the effects of antibiotics on active trachoma in the context of the WHO SAFE strategy	• Antibiotics associated with a reduction in active trachoma at 3 months (RR 0.78, 95% CI 0.69–0.89) but not at 12 months (RR 0.74, 95% CI 0.55–1.00) • No difference between systemic and topical antibiotics at 3 months (RR 0.97, 95% CI 0.81–1.16) and 12 months (RR 0.93, 95% CI 0.75–1.15) but single dose oral azithromycin was associated with a better outcome compared to topical tetracycline at 12 months (RR 0.76, 95% CI 0.59–0.99)

	Bhosai (2016) [160]	Reviewed evidence for the treatment of trachoma	• Azithromycin single oral dose

CI: confidence interval; OR: odds ratio; RCT: randomized controlled trials; RD: risk difference; RR: risk ratio; SR: systematic review.

[a]Antibiotics (typically aminoglycoside plus cephalosporin) used in highly concentrated solutions to achieve high local concentrations.

Summary of guidelines: Five guidelines were included for conjunctivitis and trachoma, two for keratitis and one for endophthalmitis. Table 21 gives a summary of recommendations of the guidelines included by type of eye infection. Quality scores (all eye infections) ranged from 61.1% to 96.1%.

Table 21. Eye infections: summary of recommendations of guidelines

Guideline (year)	Eye infection: type	Recommendation
Médecins Sans Frontières (2022) [161]	Conjunctivitis	• 1% tetracycline eye ointment twice daily for 7 days plus eye cleaning 4X/day
American Academy of Ophthalmology (2019) [162]	Conjunctivitis	• Topical antibiotics to be considered for mild cases. Testing for MRSA and targeted treatment for severe cases.
World Health Organization (2016) [41]	Ophthalmia neonatorum	• Azithromycin single dose for 3 days
UK College of Optometrists (2022) [163]	Keratitis	• Topical levofloxacin or moxifloxacin, plus systemic antibiotics if the lesion is close to the limbus

Royal Victorian Eye and Ear Hospital in Australia (2022) [164]	Keratitis	• Topical fluoroquinolones at least for the first 48 hours
American College of optometrists[a] (2016)[165]	Endophthalmitis	• No specific antibiotic recommended, only general recommendations for management with topical and systemic antibiotics
American Academy of Ophtalmology (2019)[162]	Trachoma	• Azithromycin single dose, or doxycycline for 7 days
Australian guideline by the Communicable Diseases Network Australia (2014)[166]	Trachoma	• Azithromycin single dose

[a]This guideline specifically addressed post-surgical endophthalmitis.

Working Group considerations: The Working Group decided that based on the evidence from systematic reviews and clinical practice guidelines, for the treatment of conjunctivitis, topical antibiotics should be considered for infections with moderate or severe presentations but also for mild cases as they reduce the duration of symptoms. The available evidence did not make it possible to identify specific, preferred antibiotics for this indication. For trachoma the WG recommended single dose oral azithromycin or a week of oral tetracycline as an alternative for adults.

For bacterial keratitis, the WG recommended the use of topical fluoroquinolones with the choice of the agents based on local availability and for lesions close to the limbus, they suggested considering the additional use of systemic antibiotics.

For endophthalmitis, no recommendation could be made because of no evidence from systematic reviews and the identified guideline, however the WG proposed intravitreal treatment (ceftazidime plus vancomycin) and systemic treatment (ceftriaxone plus vancomycin) because these options target the most common causative pathogens.

Expert Committee recommendations: The Committee acknowledged the lack of evidence on preferred antibiotic options for conjunctivitis and endorsed the current EML listing of topical gentamicin and tetracycline and the addition of topical ofloxacin for this indication. For trachoma, a single dose of oral azithromycin (or topical azithromycin or tetracycline) was recommended by the Committee based on the evidence presented by the WG.

For bacterial keratitis and endophthalmitis, the Committee agreed with all suggestions made by the WG however for keratitis no recommendation could be made on the type of systemic antibiotic in cases with lesions close to the limbus. First and second choice options selected by the Committee are indicated in Table 22.

Table 22 Recommendations of the Expert Committee for antibiotics to treat eye infections

Eye infections: Conjunctivitis	
First choice	**Second choice**
Gentamicin (eye drops) (A), Ofloxacin (eye drops) (W), Tetracycline (eye ointment) (A)	

Eye infections: Trachoma	
First choice	**Second choice**
Azithromycin (oral) (W) Azithromycin (eye drops) (W) or tetracycline (eye ointment)(A)	
Eye infections: Keratitis	
First choice	**Second choice**
Ofloxacin (eye drops) (W) plus consider adding a systemic antibiotic if lesions close to the limbus	
Eye infections: Endophthalmitis	
First choice	**Second choice**
• Intravitreal treatment: ceftazidime (W) plus vancomycin (W) • Systemic treatment: ceftriaxone (W) plus vancomycin (W)	

A: Access, W: Watch

Febrile neutropenia

Summary of systematic reviews: We retrieved 13 systematic reviews [167-179] and excluded two.[167, 169] Quality scores of the reviews included ranged from 63% to 83%. A meta-analysis of increased mortality with cefepime use was also included [180]. Table 23 gives a summary of the findings of the systematic reviews included.

Table 23. Febrile neutropenia: summary of findings of systematic reviews

First author (year)	Aim of the study	Findings
Paul M (2014) [175]	Compared one antibiotic regimen with the same regimen with the addition of an anti-Gram-positive antibiotic treatment	• No difference in mortality between treatments, wide CI
Paul M (2013) [172]	Compared beta-lactam with or without an aminoglycoside[a]	• No statistically significant difference in all-cause mortality (RR 0.87, 95% CI 0.75–1.02) • Lower infection-related mortality with monotherapy (RR 0.80, 95% CI 0.64–0.99) • Fewer adverse events with monotherapy (RR 0.87, 95% CI 0.81–0.94)
Vidal L (2013) [168]	Compared oral versus intravenous antibiotics	• No difference in mortality (RR 0.95, 95% CI 0.54–1.68) or treatment failure (RR 0.96, 95% CI 0.86–1.06)[b] at 30-day follow-up
Sung L (2012) [179]	Compared different fluoroquinolones	• No difference in treatment failure between the different fluoroquinolones, wide CI
Kim PW (2010) [180]	Compared cefepime with other beta-lactams	• No statistically significant increase in mortality with cefepime (adjusted RD/1000 population 9.67, 95% CI –2.87 to 22.21)
Paul M (2010) [171]	Compared different beta-lactams for empiric therapy	• Highest mortality with cefepime (RR 1.39, 95% CI 1.04–1.86) • Lowest mortality with piperacillin–tazobactam (RR 0.56, 95% CI 0.34–0.92)

Paul M (2006) [170]	Compared different beta-lactams for empiric therapy	• Higher mortality with cefepime than other beta-lactams (RR 1.44, 95% CI 1.06–1.94) • More frequent pseudomembranous colitis with carbapenems (RR 1.94, 95% CI 1.24–3.04) • Lowest rate of adverse events with piperacillin–tazobactam (RR 0.25, 95% CI 0.12–0.53)
Bliziotis IA (2005) [176]	Compared ciprofloxacin plus beta-lactam with aminoglycoside plus beta-lactam	• No difference in mortality between the treatments, wide CI • Better clinical cure with ciprofloxacin plus beta-lactam (OR 1.32, 95% CI 1.0–1.74)
Vardakas KZ (2005) [177]	Compared beta-lactam with or without an aminoglycoside	• Better treatment success with aminoglycoside (OR 1.63, 95% CI 1.17–2.28) • No difference in mortality (OR 0.67, 95% CI 0.42–1.05) • More adverse events with aminoglycoside (OR 4.98, 95% CI 2.91–8.55)
Furno P (2000) [178]	Compared combinations including ceftriaxone with combinations including an antipseudomonal beta-lactam	• No differences in treatment failures between ceftriaxone-containing combinations (32.7%) and antipseudomonal beta-lactam regimens (32.1%), OR 1.04 95% CI 0.84 to 1.29) • No difference for bacteraemic episodes, OR 0.93 (95% CI 0.58 to1.49) • No difference in overall mortality, OR 0.84 (95% CI 0.57 to 1.24)

RR: risk ratio/relative risk; CI: confidence intervals; RD: risk difference; OR: odds ratio.

[a]Similar findings reported in two other reviews[173, 174].

[b]Exceeded our definition of non-inferiority.

Summary of guidelines: Three clinical practice guidelines with similar quality scores (71–73%) were reviewed [181-183]. Table 24 gives a summary of recommendations of the guidelines.

Table 24. Febrile neutropenia: summary of recommendations of guidelines

Guideline	Febrile neutropenia: type	Recommendation
International Pediatric Fever and Neutropenia Guideline (2012) [182]	Children with cancer and/or undergoing hematopoietic stem-cell transplantation	• Monotherapy with an antipseudomonal beta-lactam, or carbapenem in high-risk patients • Add a second Gram-negative agent or glycopeptide for clinically unstable patients, or when a resistant infection is suspected, or for patients in centres with a high rate of resistant pathogens
National Institute for Health and Care Excellence (2012) [183]	Suspected neutropenic sepsis	• Monotherapy with intravenous piperacillin–tazobactam • Avoid aminoglycosides
	Patients at low risk of developing septic complications	• Consider outpatient treatment • If hospitalized, switch to oral regimen after 48 hours of treatment if risk of septic complications has been assessed as low
Infectious Diseases Society of America (2011) [181]	Low-risk patients	• Combination therapy with ciprofloxacin combined with amoxicillin–clavulanic acid
	High-risk patients	• Monotherapy with an antipseudomonal beta-lactam agent: cefepime, ceftazidime, a carbapenem (meropenem or imipenem–cilastatin), or piperacillin–tazobactam
	High-risk patients with complications	• Add aminoglycosides, fluoroquinolones, and/or vancomycin for complications, if antimicrobial resistance is suspected, or if patients are allergic to beta-

		lactam antibiotics (aztreonam is also an alternative in patients with beta-lactam allergies)
	Patients with continuing fever after 4–7 days of broad-spectrum antibiotics and no identified fever source	• Add empiric antifungals, e.g. echinocandins, voriconazole, or amphotericin B

Working Group considerations: The Group selected amoxicillin–clavulanic acid combined with ciprofloxacin as the first choice for treatment for ambulatory low-risk patients presenting with febrile neutropenia. For all other patients, piperacillin–tazobactam, which is supported by all clinical practice guidelines for adults as well as for children, was selected as a first-choice option. Cefepime was not added to the list as it was considered redundant given the antibiotics already listed above and because of concerns about the potential higher risk of mortality. However, it has a possible role as a carbapenem-sparing antibiotic for other indications; therefore, it was included in the preserved list. Colistin, aztreonam, daptomycin, linezolid, and tigecycline are also included in the preserved list as alternative agents for febrile neutropenia and other indications if none of the antibiotics proposed here are considered appropriate because of resistance or other concerns. Ceftazidime was considered redundant because of the inclusion of piperacillin–tazobactam, and because other alternatives with indications for more infections have also been listed for treatment of febrile neutropenia (e.g. meropenem, fluoroquinolones, and aminoglycosides). The carbapenem imipenem–cilastatin was considered redundant because meropenem was included and because meropenem is recommended for many other infections. Meropenem, aminoglycosides (amikacin and gentamicin), and vancomycin are only to be used if needed in addition to or instead of the

first-line regimen (piperacillin–tazobactam) based on local epidemiology and presentation of the patient, e.g. in cases where there is a high suspicion of a central line infection, in patients presenting with septic shock or in settings with high prevalence of extended-spectrum beta-lactamases producing Enterobacterales.

Expert Committee recommendations: The Committee agreed with the Working Group's recommendations (Table 25). The Committee selected amoxicillin–clavulanic acid and ciprofloxacin for low-risk patients and piperacillin–tazobactam and amikacin for high-risk patients. Second-choice antibiotics included vancomycin and meropenem. Amikacin or vancomycin should be added to either piperacillin–tazobactam or meropenem.

Table 25. Recommendations of the Expert Committee for antibiotics to treat febrile neutropenia

Febrile neutropenia	
First choice	**Second choice**
Low-risk patients	
Amoxicillin–clavulanic acid (A) + ciprofloxacin (W)	
High-risk patients	
Piperacillin–tazobactam (W)	Meropenem (W)
Piperacillin–tazobactam (W) + amikacin (A)	Meropenem (W) + vancomycin, intravenous (W)

A: Access, W: Watch

Hospital-acquired pneumonia, including ventilator-associated pneumonia

Summary of systematic reviews: We evaluated 14 systematic reviews for hospital-acquired pneumonia and/or ventilator-associated pneumonia.[184-197] Of these reviews, four were included with scores ranging from 55% to 77%.[184, 185, 191, 195] Table 26 gives a summary of the findings of the systematic reviews included.

Table 26. Hospital-acquired pneumonia including ventilator-associated pneumonia (VAP): summary of findings of systematic reviews

First author (year)	Aim of the study	Findings
Pugh R (2015) [184]	Compared short (7–8 days) course of antibiotics with long (10–15-days) course	• Significantly more patients with 28 antibiotic-free days in the short-course group (MD 4.02 days, 95% CI 2.26–5.78) • Reduced recurrence of VAP due to multidrug-resistant organisms in the short-course group (OR 0.44, 95% CI 0.21–0.95) • Greater recurrence of VAP due to non-fermenting Gram-negative bacilli in the short-course group (OR 2.18, 95% CI 1.14–4.16)
Kalil AC (2013) [185]	Compared linezolid with vancomycin or teicoplanin	• No difference in 28-day all-cause mortality (RD 0.01%, 95% CI –2.1% to 2.1%, and clinical response (RD 0.9%, 95% CI –1.2% to 3.1%) between the antibiotics

		• More gastrointestinal side-effects with linezolid than vancomycin (RD 0.01, 95% CI 0.00–0.02)
Dimopoulos G (2013) [191]	Compared short (7–8 days) course of antibiotics with long (10–15-days) course	• No difference in 28-day mortality between the short and long courses (OR 1.20, 95% CI 0.84–1.72) • Significantly more antibiotic-free days in the short-course group (MD 3.40 days, 95% CI 1.43-5.37) • No difference in relapses of VAP, although a strong trend to fewer relapses in the long-course group (OR 1.67, 95% CI 0.99–2.83)
Aarts MA (2008) [195]	Compared various antimicrobial regimens for suspected VAP	• No difference in 28- or 30-day all-cause mortality between any of the regimens compared • Lower risk of treatment failure with meropenem than with combination of ceftazidime and aminoglycoside (RR 0.70, 95% CI 0.53–0.93) • No difference in 28- or 30-day all-cause mortality and treatment failure between monotherapy and combined therapy (RR for mortality with monotherapy 0.94, 95% CI 0.76–1.16; RR for treatment failure with monotherapy 0.88, 95% CI 0.72–1.07)

MD: mean difference; CI: confidence intervals; OR: odds ratio; RD: risk difference; RR: relative risk.

Summary of guidelines: We retrieved six clinical practice guidelines for hospital-acquired pneumonia and ventilator-associated pneumonia [116, 117, 198-201] and included three, with

scores ranging from 72% to 83%.[116, 198, 200]. Table 27 gives a summary of recommendations of the guidelines.

Table 27. Hospital-acquired pneumonia: summary of recommendations of guidelines

Guideline (year)	Hospital-acquired pneumonia: type	Recommendation
Infectious Diseases Society of America & American Thoracic Society (2016) [200]	Low risk of mortality and no risk factors for methicillin-resistant *Staphylococcus aureus* (MRSA)	• Piperacillin–tazobactam, cefepime, levofloxacin, or a carbapenem
	Low risk of mortality but risk factors for MRSA	• Add vancomycin or linezolid
	High risk of mortality or received intravenous antibiotics in the previous 90 days	• Empiric double coverage using antibiotics from two different classes with activity against *Pseudomonas. aeruginosa* (piperacillin–tazobactam, cefepime or ceftazidime, meropenem or imipenem, aztreonam, ciprofloxacin or levofloxacin or an aminoglycoside) • Guidelines recommend not using an aminoglycoside as the only antipseudomonal agent • Coverage for MRSA (vancomycin or linezolid)
National Institute for Health and Care	Hospital-acquired pneumonia	• Select antibiotics according to hospital policy

Excellence (2014) [116]		
British Society for Antimicrobial Chemotherapy (2008) [198]	Hospital-acquired pneumonia occurring < 5 days after hospital admission in low-risk patients (no recent exposure to antibiotics and no risk factors for multidrug-resistant pathogens)	• Amoxicillin–clavulanic acid or cefuroxime
	Hospital-acquired pneumonia occurring < 5 days after hospital admission in patients who have recently received antibiotics and/or who have other risk factors	• Third-generation cephalosporin (cefotaxime or ceftriaxone), a fluoroquinolone, or piperacillin–tazobactam
	Hospital-acquired pneumonia with suspected *Pseudomonas aeruginosa* infection	• Ceftazidime, ciprofloxacin, meropenem, or piperacillin–tazobactam

Working Group considerations: The Working Group proposed amoxicillin–clavulanic acid as an Access antibiotic on the basis that it has a reasonably broad spectrum of activity and low potential for resistance, and it is recommended in guidelines when multidrug resistance is not suspected. Third-generation cephalosporins (cefotaxime and ceftriaxone) and piperacillin–tazobactam were also listed as an Access antibiotics. This proposal was in part modified by the Expert Committee (cefotaxime and ceftriaxone categorized as Watch antibiotics). Other antibiotics were listed as targeted antibiotics that are appropriate in specific circumstances only, such as the use of empiric vancomycin with suspicion of MRSA. Given the concern about carbapenem resistance, these agents should only be used when there are no other alternatives. Similarly,

fluoroquinolones and aztreonam should be used only when needed, for example, in the case of a serious allergy.

Expert Committee recommendations: The Committee decided to focus their recommendations primarily on hospital-acquired pneumonia. The Committee a priori reasoned that where mechanical ventilators are available, local microbiology and epidemiological data should also be available, switching the antibiotic selection from empiric to targeted. The Committee recommended that Access antibiotics include amoxicillin–clavulanic acid and Watch antibiotics include cefotaxime, ceftriaxone, or piperacillin–tazobactam (Table 28).

Table 28. Recommendations of the Expert Committee for antibiotics to treat hospital-acquired pneumonia

Hospital-acquired pneumonia	
First choice	**Second choice**
Amoxicillin–clavulanic acid (A)	
Cefotaxime (W)	
Ceftriaxone (W)	
Piperacillin–tazobactam (W)	
Antibiotics proposed by the Working Group but not recommended by the Committee	
Aminoglycosides[a], aztreonam[a], levofloxacin[a], meropenem[a], vancomycin[b] (for suspected methicillin-resistant *Staphylococcus aureus*)	

A: Access, W: Watch

[a]The Expert Committee decided to exclude aminoglycosides, aztreonam, meropenem and levofloxacin because they focused on empiric treatment of patients at low risk of short-term mortality and with no risk factors for MRSA or multidrug-resistant Gram-negative infections.

[b]Expert Committee decided to exclude vancomycin because they considered it a suitable option for targeted treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infections but not an ideal option for empiric treatment.

Meningitis (Bacterial)

Summary of systematic reviews: We evaluated eight reviews [202-209] and retained three,[202, 205, 206] with quality scores ranging from 63% to 70%. Table 29 gives a summary of the findings of the systematic reviews included.

Table 29. Bacterial meningitis: summary of findings of systematic reviews

First author (year)	Aim of the study	Findings
Eliakim-Raz N (2015) [206]	Compared chloramphenicol with other antibiotics	• Higher mortality at end of follow-up with chloramphenicol (RR 1.27, 95% CI 1.00–1.60)
Karageorgopoulos DE (2009) [205]	Compared short (4–7 days) course antibiotic therapy with long (7–14 days) course in children	• No difference in clinical success, long-term neurological complications, or long-term hearing impairment, wide CI
Prasad K (2007) [202]	Compared third-generation cephalosporins with penicillin and ampicillin–chloramphenicol	• No difference in mortality in follow-up (RD 0% 95% CI –3% to 2%), deafness (RD –4%, 95% CI –9% to 1%), or treatment failure (RD –1%, 95% CI –4% to 2%) between the antibiotics • Reduced risk of culture positivity of cerebrospinal fluid after 10–48 hours (RD –6%,

		95% CI –11% to 0%) and increased risk of diarrhoea with cephalosporins (RD 8%, 95% CI 3%–13%)

RR: risk ratio; CI: confidence intervals; RD: risk difference.

Summary of guidelines: We evaluated two guidelines with quality scores of 67% and 68%; the guidelines of the National Institute for Health and Care Excellence [210] and those of the Infectious Diseases Society of America [211]. Table 30 gives a summary of recommendations of the guidelines.

Table 30. Bacterial meningitis: summary of recommendations of the guidelines

Guideline (year)	Meningitis: type	Recommendation
National Institute for Health and Care Excellence (2010) [210]	Patients < 3 months	• Intravenous cefotaxime, and amoxicillin or ampicillin
	Patients ≥ 3 months	• Ceftriaxone
	Patients with prolonged or multiple exposure to antibiotics in the previous 3 months and those who have been outside the United Kingdom	• Add vancomycin
Infectious Diseases Society of America (2004) [211]	Infants < 1 month	• Ampicillin and cefotaxime, or an aminoglycoside
	Patients 1 month to 50 years	• Vancomycin and ceftriaxone, or cefotaxime
	Patients > 50 years	• Add ampicillin to cover *Listeria monocytogenes*

	Patients with penetrating trauma, who are post-neurosurgery, or who have a cerebrospinal shunt	• Vancomycin plus cefepime, ceftazidime, or meropenem

Working Group considerations: Evidence from systematic reviews suggests that chloramphenicol is associated with higher mortality than other antibiotics; as such, it was not proposed as an Access antibiotic. Ampicillin, ceftriaxone, and cefotaxime were proposed for multiple indications and were proposed as Access antibiotics. Aminoglycosides and vancomycin were included for more specific indications (e.g. by age or indication) and were therefore categorized as Watch antibiotics, as were ceftazidime and meropenem. These proposals were in part modified by the Expert Committee (cefotaxime and ceftriaxone categorized as Watch antibiotics and aminoglycosides as Access).

Expert Committee recommendations: In 2017 the Committee agreed with the Working Group's recommendations (Table 31). However, despite the fact that the evidence suggests poorer outcomes with chloramphenicol, the Committee kept this antibiotic on the list as a second choice because of its wide availability for use when it is the only choice available. The first-choice antibiotics were cefotaxime and ceftriaxone, and the second choice were ampicillin, amoxicillin, benzylpenicillin, chloramphenicol (for children > 2 years and adults), and meropenem (for neonates).

In 2021 an application proposed to add gentamicin as an alternative to treat acute bacterial meningitis in neonates. The application emphasized how in neonates, the clinical presentation of meningitis is less typical than in adults or in older children and symptoms (fever, poor feeding, lethargy and/or reduced interaction with caregivers, vomiting, irritability, seizures and rash) are

usually non-specific. These non-specific symptoms overlap with those of neonatal sepsis and meningitis should always be suspected in case of signs of serious bacterial infection. In agreement with WHO guidelines, the Committee added gentamicin in combination with ampicillin, or ceftriaxone or cefotaxime for meningitis in neonates when referral is not feasible.[212, 213]

Table 31. Recommendations of the Expert Committee for antibiotics to treat bacterial meningitis

Meningitis	
Adults and children	
First choice	**Second choice**
Cefotaxime (W)	Amoxicillin (A)
Ceftriaxone (W)	Ampicillin (A)
	Benzylpenicillin (A)
	Chloramphenicol (> 2 years and adults)[a] (A)
Neonates, <1 month	
First choice	**Second choice**
Ampicillin (A) + gentamicin (A)	Meropenem (W)
Cefotaxime (W) + gentamicin (A)	
Ceftriaxone (W) + gentamicin (A)	
Antibiotics proposed by the Working Group but not recommended by the Committee	
Amikacin[b], ceftazidime[c], vancomycin[d]	

A: Access, W: Watch

[a]The Expert Committee recommended chloramphenicol as a second choice for this infection because it is widely available but recommended its use when it is the only available option because of toxicity.

[b]The Expert Committee decided to exclude amikacin for this infection because they considered this a suitable option for targeted treatment but not an ideal option for empiric treatment.

[c]The Expert Committee decided to exclude ceftazidime for this infection because they considered it a suitable option for targeted treatment in certain cases (e.g. penetrating trauma, post-neurosurgery) but not an ideal option for empiric treatment of community-acquired meningitis.

[d]The Expert Committee decided to exclude vancomycin for this infection because the risk of penicillin resistance in *Streptococcus pneumoniae* isolates is low in many settings.

Oral and Dental infections

Summary of systematic reviews: We included 19 systematic reviews covering chronic and apical periodontitis, acute apical abscesses and irreversible pulpitis with quality scores ranging from 40% to 75%. Tables 32 to 34 give a summary of the findings of the systematic reviews included by type of condition.

Table 32. Chronic periodontitis in adults: summary of the findings of systematic reviews

First author (year)	Aim of the study	Findings
McGowan K (2018) [214]	Determined the optimum dose and duration of amoxicillin/metronidazole prescribed as an adjunct to non-surgical treatment of periodontitis	• No clinically meaningful difference between different doses or duration of amoxicillin–metronidazole at 3 months post-treatment • No clinically important difference between amoxicillin–metronidazole compared to no antibiotics as an adjunct to non-surgical treatment of periodontitis

Assem NZ (2017) [215]	Examined the effect of systemic antibiotics in the periodontal treatment of smokers compared to SRP alone	• Statistically significant reduction of probing depth and clinical attachment level gain but with limited clinical relevance
Grellmann AP (2016) [216]	Examined the effect of systemic antibiotics in the periodontal treatment of diabetic patients compared to SRP alone	• Significant difference in reduction of probing depth with antibiotics compared to SRP alone, but no significant difference for other outcomes (clinical attachment level gain, bleeding on probing, plaque index)
Renatus A (2016) [217]	Verified a possible benefit of azithromycin (as an alternative adjuvant antibiotic in combination with SRP)	• Significant beneficial effects of azithromycin for outcomes of probing depth, clinical attachment level and bleeding on probing
Rovai ES (2016) [218]	Examined the effect of local antibiotics in the periodontal treatment of diabetic patients compared to SRP alone	• Significant reduction of probing depth and gain in clinical attachment level with antibiotics compared to SRP alone •
Santos RS (2016) [219]	Assessed the effect of adjunctive antibiotics (in associaiton with mechanical debridement) for the treatment of refractory periodontitis	• Greater reduction in probing depth and in loss of clinical attachment level with antibiotics compared to debridement alone
Chambrone L (2016) [220]	Evaluated whether use of local or systemic antibiotics improves clinical results of non-surgical periodontal therapy for smokers with chronic periodontitis	• Significant reduction of probing depth (0.81 mm) and clinical attachment level gain (0.91 mm) at sites with baseline probing depth ≥5 mm • Meta-analysis failed to detect significant differences in mean changes from baseline

Zandbergen D (2016) [221]	Compared the efficacy of amoxicillin / metronidazole adjunctive to SRP compared to SRP alone	• Greater reduction in probing depth (0.86 mm, 95% CI 0.65–1.07 mm) and clinical attachment level gain (0.75 mm, 95% CI 0.40–1.09) in patients taking amoxicillin–metronidazole (adjunctive to SRP) compared to SRP alone
Zhang Z (2016) [222]	Verified a possible benefit of azithromycin (as an alternative adjuvant antibiotic in combination with SRP)	• Significant reduction of probing depth by 0.99 mm (95% CI 0.42–1.57) and increased attachment level by 1.12 mm (95% CI 0.31–1.92) with locally delivered azithromycin • Significant reduction of probing depth by 0.21 mm (95% CI 0.12–0.29), bleeding on probing by 4.50% (95% CI 1.45–7.56) and increased attachment level by 0.23 mm (95% CI 0.07–0.39) with systemic azithromycin
Fritoli A (2015) [223]	Assessed the effect of systemic antibiotics for non-surgical periodontal therapy	• Greater reduction in probing depth (0.9 mm) and clinical attachment level gain (0.7 mm) in patients taking metronidazole–amoxicillin at the initial phase of treatment compared to patients taking antibiotic after healing
Keestra JA (2015) [224]	Compared systemic antibiotics in combination with SRP compared to SRP alone	• Systemic antibiotics significantly improved pocket depth reduction and clinical attachment level gain. Results suggested that metronidazole–amoxicillin was the most potent combination
Rabelo CC (2015) [225]	Assessed the effect of specific antibiotics in combination with scaling	• Greater clinical attachment level gain and reduction in probing depth with metronidazole

	and root planning (SRP) compared to SRP alone in patients with chronic periodontitis	(attachment gain 1.08 mm, reduction in probing depth 1.05 mm) or metronidazole/amoxicillin (attachment gain 0.45 mm, reduction in probing depth 0.53 mm) compared to SRP alone
Sgolastra F (2014) [226]	Compared the efficacy of metronidazole adjunctive to SRP compared to SRP alone	• Greater reduction in probing depth (0.18 mm, 95%CI 0.09–0.28) and clinical attachment level gain (0.10 mm, 95%CI 0.08–0.12) with metronidazole adjunctive to SRP compared to SRP alone
Sgolastra F (2012) [227]	Compared the efficacy of amoxicillin–metronidazole adjunctive to SRP compared to SRP alone	• Greater reduction in probing depth (0.58 mm, 95% CI 0.39–0.77) and clinical attachment level gain (0.42 mm, 95% CI 0.23–0.61) in patients taking amoxicillin–metronidazole (adjunctive to SRP) compared to SRP alone
Sgolastra F (2011) [228]	Assessed the actual evidence of the effectiveness of SRP in combination with subantimicrobial-dose doxycycline (SDD) compared to SRP and placebo in the treatment of chronic periodontitis	• Significant differences were observed for all investigated clinical outcomes in favour of the SRP–SDD combination: significant reduction of probing depth (0.9 mm, 95%CI 0.43–1.37), clinical attachment level gain (0.88 mm, 95%CI 0.08–1.67), changes in plaque index, gingival index and gingival crevicular fluid at the nine-months stage (SDD= systemic use of low-dose doxycycline 20 mg every 12 hours for 3 months)

Angaji M (2010) [229]	Evaluated the efficacy of adjunctive antibiotic therapy to periodontal therapy in smokers with periodontitis	• Insufficient and inconclusive evidence of a benefit of adjunctive antibiotic therapy in smokers with chronic periodontitis

SRP: scaling and root planning

Table 33. Apical periodontitis and acute apical abscess in adults: summary of findings from the systematic reviews

First author (year)	Aim of the study	Findings
Cope AL (2018) [230]	Compared the effects of penicillin versus placebo (both with surgical intervention and analgesics)	• No statistically significant differences in participant-reported measures of pain or swelling at any of the time points assessed
Matthews DC (2003) [231]	Compared antibiotics to placebo or no pharmacotherapy for acute apical abscesses in patients who had received incision and drainage, endodontic therapy or extraction	• No statistically significant difference for the outcomes "absence of infection" and "absence of pain" • In one study azithromycin better than amoxicillin–clavulanic acid for reduction of pain but not for absence of infection

Table 34. Pulpitis in adults: summary of findings from the systematic reviews

First author (year)	Aim of the study	Findings
Agnihotry A (2016) [232]	Assessed the effects of systemic antibiotics for irreversible pulpitis	• No statistically significant difference in outcomes between groups (penicillin versus placebo)

Summary of guidelines: Eleven guidelines were reviewed, 5 of which were included (quality scores ranging from 63.0% to 71.4%). Table 35 gives a summary of recommendations of the guidelines included.

Table 35. Oral and dental infections: summary of guideline recommendations

Guideline (year)	Oral and dental infections: type	Recommendation
Médecins sans frontières – Dental infections (2019) [233]	Acute dental and dento-alveolar abscess, infections extending into cervico-facial tissues	• For acute dental abscess, the treatment is only surgical (root canal therapy or extraction of the tooth) • For acute dento-alveolar abscesses, incision and drainage then amoxicillin for 5 days • For infections extending to underlying soft tissues, tooth extraction and treat as necrotizing fasciitis
European Society of Endodontology (2018) [234]	Apical periodontitis, acute apical abscess, irreversible pulpitis	• Do not use antibiotics in patients with acute apical periodontitis and acute apical abscess. Surgical drainage is key • Adjunctive antibiotics recommended in specific patients' groups: medically compromised patients, patients with systemic involvement, and patients with progressive infections where referral to oral surgeons may be necessary (first choice: phenoxymethylpenicillin) • Do not e use of antibiotics for the treatment of irreversible pulpitis

American Dental Association (2015) [235]	Chronic periodontitis	• Use of systemic sub-antimicrobial dose doxycycline (20 mg twice daily for three to nine months) as an adjunct to SRP
Scottish Dental Clinical Effectiveness Programme (2014) [236]	Chronic periodontitis	• Do not use antimicrobials for chronic periodontitis or peri-implantitis
Canadian Collaboration on Clinical Practice Guidelines in Dentistry (2004) [237][a]	Acute apical abscess	• Do not use of antibiotics for acute apical periodontitis and acute apical abscess as no benefit had been shown over drainage alone • Antibiotics may be helpful in case of systemic complications (fever, lymphadenopathy, cellulitis), diffuse swelling or in patients with medical indications • No antibiotic can be recommended over another

[a]Recommendations aligned with 2019 guidelines by the American Dental Association[238]

Working Group considerations: The Working Group acknowledged that the evidence from systematic reviews and guidelines was not supporting routine antibiotic treatment for conditions such as apical periodontitis and acute apical abscess while source control and drainage are key. However for the treatment of these conditions, antibiotic use might be considered on a case-by-case basis in patients at risk of complicated and severe infections where drainage alone may not be sufficient. First choice options (phenoxymethylpenicillin or amoxicillin with the addition of metronidazole in case of treatment failure) were chosen in alignment with those indicated by European guidelines. The Working Group did not recommended antibiotic treatment in case of irreversible pulpitis.

Expert Committee recommendations: The Committee aligned with Working Group proposals, noting that in most cases of oral and dental infections (including acute or chronic periodontitis and irreversible pulpitis) antibiotics are not needed. The Committee endorsed listing of amoxicillin and phenoxymethypenicillin as first choice options for the treatment of systemically complicated progressive apical dental abscesses or apical abscesses in medically compromised patients.

Table 36. Recommendations of the Expert Committee for antibiotics to treat oral and dental infections

Oral and dental infections[a]	
First choice	**Second choice**
Amoxicillin (A)	
Phenoxymethylpenicillin (A)	

A: Access

[a]The Expert Committee recommendations aligned with Working Group proposals.

Otitis media (Acute)

Summary of systematic reviews: We retrieved nine reviews [239-247] and included two [246, 247] (scores 90% and 83%). Table 37 gives a summary of the findings of the systematic reviews included.

Table 37. Acute otitis media: summary of findings of systematic reviews

First author (year)	Aim of the study	Findings

Venekamp RP (2016) [246]	Compared oral antibiotics with placebo, no treatment or therapy of unproven effectiveness	• Reduced residual pain at 2–3 days with antibiotics (RR 0.70, 95% CI 0.57–0.86) • Fewer children with tympanic membrane perforations with antibiotics (RR 0.37, 95% CI 0.18–0.76) • No difference in abnormal tympanometry at 3 months or late acute otitis media recurrence, wide CI • More frequent adverse events with antibiotics (RR 1.38, 95% CI 1.19–1.59)
Thanaviratananich S (2013) [247]	Compared 1 or 2 daily doses with 3 or 4 daily doses of amoxicillin, with or without clavulanic acid	• No difference in clinical cure at follow-up between the two groups (RR 1.02, 95% CI 0.95 to 1.09)

RR: risk ratio; CI: confidence intervals.

Summary of guidelines: We identified two guidelines; one from the American Academy of Pediatrics with a score of 71% [248], and one from the Canadian Pediatric Society with a score of 49%. [249] Table 38 gives a summary of recommendations of the guidelines.

Table 38. Acute otitis media: summary of recommendations of the guidelines

Guideline (year)	Otitis media: type	Recommendation
Canadian Paediatric Society (2016) [249]	Children ≥ 6 months	• Amoxicillin if antibiotics needed
	Children 6 months–12 years	• Amoxicillin

American Academy of Pediatrics (2013) [248]	Previous exposure to amoxicillin	• Amoxicillin–clavulanic acid
	Allergy to penicillin	• Cephalosporins

Working Group considerations: The Working Group considered that antibiotics are usually not needed in most cases of otitis media and a strategy of watchful waiting could reduce unnecessary antibiotic use. Unless a child is younger than 2 years with bilateral otitis media, [248] giving no antibiotics is a reasonable first-line option. Amoxicillin or amoxicillin–clavulanic acid were proposed and categorized as Access antibiotics on the basis of trial evidence and existing guidelines. Cefuroxime axetil and ceftriaxone were proposed for severe cases and categorized as Watch antibiotics.

Expert Committee recommendations: Antibiotics recommended for first and second choice were amoxicillin and amoxicillin–clavulanic acid, respectively (Table 39).

Table 39. Recommendations of the Expert Committee for antibiotics to treat acute otitis media

Otitis media	
First choice	**Second choice**
Amoxicillin (A)	Amoxicillin–clavulanic acid (A)
Antibiotics proposed by the Working Group but not recommended by the Committee[a]	
Ceftriaxone, cefuroxime	

A: Access, W: Watch

[a]The Expert Committee decided to exclude cefuroxime and ceftriaxone for severe otitis media to put less emphasis on the need to routinely provide empiric treatment for penicillin-resistant *Streptococcus pneumoniae* and also to favour oral options over intravenous and intramuscular treatments.

Pharyngitis

Summary of systematic reviews: We retrieved eight systematic reviews [250-257] of which three met our eligibility criteria with scores from 85% to 90% [255-257] Table 40 gives a summary of the findings of the systematic reviews included.

Table 40. Pharyngitis: summary of findings of systematic reviews

First author (year)	Aim of the study	Findings
Spinks A (2013) [257]	Compared antibiotics with placebo for sore throat	• Lower risk of rheumatic fever with antibiotics (RR 0.27, 95% CI 0.12–0.60) • Lower incidence of acute otitis media within 14 days (RR 0.30; 95% CI 0.15–0.58), acute sinusitis within 14 days (RR 0.48, 95% CI 0.08–2.76), and peritonsillar abscess within 2 months (RR 0.15, 95% CI 0.05–0.47) with antibiotics
van Driel ML (2013) [255]	Compared different antibiotic treatments for group A streptococcal pharyngitis	• No difference between macrolides and penicillin (OR 1.11, 95% CI 0.92–1.35) for symptom resolution and clinical relapse • Lower rate of clinical relapse with cephalosporins compared with penicillin (OR 0.55, 95% CI 0.31–0.99), but no difference in symptom resolution

Altamimi S (2012) [256]	Compared 2–6 days of newer oral antibiotics with 10 days of oral penicillin for streptococcal pharyngitis	• Lower risk of early clinical failure (OR 0.80, 95% CI 0.67–0.94) with short course of newer macrolides (including azithromycin and clarithromycin) than 10-day penicillin course • No differences in early bacteriological cure (OR 1.08, 95% CI 0.97–1.20) or late clinical recurrence (OR 0.95, 95% CI 0.83–1.08) • Greater risk of late bacteriological recurrence with short-course macrolide treatment (OR 1.31, 95% CI 1.16–1.48)

OR: odds ratio; CI: confidence intervals; RR: risk ratio.

Summary of guidelines: Only one guideline was retrieved and considered (quality score 81%).[258] Table 41 gives a summary of recommendations of the guideline.

Table 41. Pharyngitis: summary of recommendations of guidelines

Guideline (year)	Pharyngitis: type	Recommendation
Infectious Diseases Society of America (2012) [258]	Group A streptococcal infection	• Penicillin or amoxicillin
	Serious penicillin allergy	• Macrolides, azithromycin, or clarithromycin

Working Group considerations: The Working Group considered that pharyngitis has predominantly a viral origin and treatment ranges from no antibiotic treatment, delayed antibiotic treatment, or treatment based on microbiological testing results. Treatment for group A

streptococcal pharyngitis with penicillin and amoxicillin compared with other or no antibiotics reduced rheumatic fever and suppurative complications with similar overall outcomes. Cephalexin was selected as a second-line antibiotic based on the lower rate of relapse, good tolerability, and narrow spectrum. Clarithromycin, which was categorized by the Working Group as Watch, was proposed for use in pharyngitis where there is a severe allergy to penicillin.

Expert Committee recommendations: The Committee endorsed a strategy of watchful waiting, symptom relief, and no antibiotic treatment as the first-choice approach. The use of amoxicillin or phenoxymethylpenicillin was recommended as the first-choice antibiotics for suspected or proven bacterial pharyngitis, and cefalexin or clarithromycin as second-choice therapy (Table 42). The Committee noted that routine skin testing for allergy before first exposure to penicillins, as is current practice in some regions, is not necessary. For patients with a known severe penicillin allergy who live in regions with high rates of macrolide resistance, cefalexin is the preferred option.

Table 42. Recommendations of the Expert Committee for antibiotics to treat pharyngitis

Pharyngitis[a]	
First choice	**Second choice**
Amoxicillin (A)	Cephalexin (A)
Phenoxymethylpenicillin (A)	Clarithromycin (W)

A: Access, W: Watch

[a]The Expert Committee recommendations aligned with Working Group proposals.

Sinusitis (Acute)

Summary of systematic reviews: We retrieved 12 systematic reviews [259-270] and included four,[259-262] with quality scores ranging from 80% to 90%. Table 43 gives a summary of the findings of the systematic reviews included.

Table 43. Acute sinusitis: summary of findings of systematic reviews

First author (year)	Aim of the study	Findings
Burgstaller JM (2016) [261]	Compared antibiotics with placebo	• Greater improvement in symptoms after 3 days (OR 2.78, 95% CI 1.39–5.58) and 7 days (OR 2.29, 95% CI 1.19–4.41) with antibiotics • No difference in improvement after 10 days, wide CI
Ahovuo-Saloranta A (2014) [262]	Compared different antibiotics and placebo	• Lower risk of clinical failure with amoxicillin or penicillin than placebo for maxillary sinusitis (RR 0.66, 95% CI 0.47–0.94) • Higher risk of clinical failure with cephalosporins or macrolides than amoxicillin–clavulanic acid (RR 1.37, 95% CI 1.04–1.80) • High cure and improvement rates with both placebo (86%) and antibiotics (91%) • More adverse effects with antibiotics than placebo (median of difference between groups 10.5%, range 2–23%).
Kenealy T (2013) [260]	Compared antibiotics with placebo	• No difference in cure or symptom persistence for purulent sinusitis • Increased risk of adverse effects with antibiotics (RR 1.8, 95% CI 1.01–3.21)

Lemiengre MB (2012) [259]	Compared antibiotics with placebo	• Faster resolution of purulent secretions with antibiotics (OR 1.58, 95% CI 1.13–2.22) • More adverse events with antibiotics (OR 2.10, 95% CI 1.60–2.77)

OR: odds ratio; CI: confidence intervals; RR: risk ratio.

Summary of guidelines: We identified and reviewed three guidelines with quality scores between 83% and 85%.[271-273] Table 44 gives a summary of recommendations of the guidelines.

Table 44. Acute sinusitis: summary of recommendations of guidelines

Guideline (year)	Sinusitis: type	Recommendation
American Academy of Otolaryngology--Head and Neck Surgery Foundation (2015) [272]	Adult sinusitis	• Amoxicillin with or without clavulanic acid
American Academy of Pediatrics (2013) [273]	Acute bacterial sinusitis in children 1–18 years	• Amoxicillin with or without clavulanic acid. Ceftriaxone for children who cannot be treated with oral antibiotics
Infectious Diseases Society of America (2012) [271]	Acute bacterial sinusitis in children and adults	• Amoxicillin–clavulanic acid as first-line treatment because of concern about beta-lactamase-producing *Haemophilus influenzae*
	Allergy to beta-lactams	• Respiratory fluoroquinolone (levofloxacin or moxifloxacin), or doxycycline (for adults)

Working Group considerations: The Working Group considered that sinusitis did not require antibiotics in most instances, particularly when it is associated with the common cold with symptoms not lasting for a prolonged period of time. Delayed prescribing is a strategy that could minimize the use of antibiotics. Evidence suggests a higher risk of failure with cephalosporins or macrolides compared with amoxicillin–clavulanic acid. Given the principle of use of narrower-spectrum agents, amoxicillin alone or amoxicillin–clavulanic acid were proposed as Access antibiotics, and ceftriaxone (Watch antibiotic) was proposed for severe sinusitis (Table 45). Levofloxacin was included if beta-lactams cannot be used and categorized by the Working Group as a Watch antibiotic.

Expert Committee recommendations: Based on the principle of parsimony, only amoxicillin and amoxicillin–clavulanic acid were recommended.

Table 45. Recommendations of the Expert Committee for antibiotics to treat acute sinusitis

Sinusitis	
First choice	**Second choice**
Amoxicillin (A)	
Amoxicillin–clavulanic acid (A)	
Antibiotics proposed by the Working Group but not recommended by the Committee	
Ceftriaxone[a], levofloxacin[b]	

A: Access, W: Watch

[a]The Expert Committee decided to exclude ceftriaxone for this infection based on the principle of parsimony because they elected to focus on the empiric treatment of mild cases since such cases are more frequent.

[b]The Expert Committee decided to exclude levofloxacin for sinusitis because they considered it a suitable option for targeted treatment but not an ideal option for empiric treatment.

Sexually transmitted infections

Summary of systematic reviews: We found eight systematic reviews[274-281] and excluded two [275, 276]. Scores ranged from poor quality (i.e. impossible to assess) to 63%. We also included a randomized controlled trial [282]. Table 46 gives a summary of the findings of the systematic reviews and trial included.

Table 46. Sexually transmitted infections: summary of findings of systematic reviews

First author (year)	Aim	Findings
Geisler WM (2015) [282]	Compared azithromycin with doxycycline for genital chlamydia[a]	• Efficacy of azithromycin was 97% and doxycycline was 100%. However, non-inferiority of azithromycin was not established
Lau A (2015) [274]	Compared azithromycin for genital *Mycoplasma genitalium* over time	• Microbial cure (at last follow-up after treatment) with azithromycin fell from 85.3% (95% CI 82.3–88.3%) before 2009 to 67.0% (57.0–76.9%) since 2009
Kong FY (2014) [277]	Compared azithromycin with doxycycline for genital chlamydia	• No difference between azithromycin and doxycycline for urethritis caused by *Chlamydia trachomatis*[a]
Bai ZG (2012) [280] Bai ZG (2008) [281]	Compared azithromycin with benzathine benzylpenicillin for early syphilis	• Better cure rate with azithromycin (OR 1.37, 95% CI 1.05–1.77) and no statistically significant difference in adverse events [281]

		• No statistically significant difference between the two groups for clinical cure (OR 1.04, 95% CI 0.69 to 1.56) [280]
Pitsouni E (2007) [279]	Compared single-dose azithromycin with erythromycin or amoxicillin for chlamydia	• Fewer adverse events with azithromycin (OR 0.11, 95% CI 0.07–0.18)

CI: confidence intervals; OR: odds ratio.

[a]Similar findings reported in another systematic review [278].

[b]Randomized controlled trial.

Summary of guidelines: We identified 17 guidelines, [41-43, 283-296] nine of which were included [41-43, 283, 286, 289, 294, 296, 297]. Their quality scores ranged from 55.5% to 77.3%. The highest ranked guideline for urethritis was that of the European Association of Urology [297]. The highest ranked guideline on syphilis, chlamydia and gonococcal infections were published by WHO [41-43]. Table 47 gives a summary of recommendations of the guidelines.

Table 47. Sexually transmitted infections: summary of recommendations of guidelines

Guideline (year)	Sexually transmitted infections: type	Recommendation
World health Organization (2021) [296]	Trichomonas vaginalis	• Metronidazole
European guideline on the	Non-gonococcal urethritis	• Doxycycline. Lymecycline, tetracycline, or azithromycin as alternatives

management of non-gonococcal urethritis (2016) [286]	*Mycoplasma genitalium* infection	• Azithromycin, but not routinely because of concern of macrolide resistance with *Mycoplasma genitalium*
	Persistent or recurrent non-gonococcal urethritis	• If doxycycline was used as the first-line treatment, then use azithromycin and metronidazole, if *Trichomonas vaginalis* is prevalent in the local population. • If azithromycin was used as the first-line treatment, then use moxifloxacin and metronidazole
United Kingdom national guideline (2016) [283]	Non-gonococcal urethritis in men	• Doxycycline or azithromycin. Ofloxacin as an alternative
World Health Organization (2016) [43]	Syphilis	• Primary, secondary and early latent syphilis: benzathine penicillin G • Late latent syphilis: benzathine penicillin G
	Congenital syphilis	• Aqueous benzylpenicillin. Procaine benzylpenicillin as an alternative
World health Organization (2016) [42]	Genital and anorectal gonococcal infections	• Dual therapy: ceftriaxone + azithromycin or cefixime + azithromycin • Single therapy: ceftriaxone, cefixime, or spectinomycin
	Oropharyngeal gonococcal infections	• Dual therapy: ceftriaxone + azithromycin or cefixime + azithromycin • Single therapy: ceftriaxone

	Gonococcal ophthalmia neonatorum (conjunctivitis)	• Ceftriaxone, or kanamycin, or spectinomycin
World health Organization (2016) [41]	Uncomplicated genital chlamydia	• Azithromycin or doxycycline. Tetracycline, erythromycin or ofloxacin as alternatives
	Anorectal chlamydia infection	• Doxycycline
	Genital chlamydial infection in pregnant women	• Azithromycin
	Lymphogranuloma venereum	• Doxycycline
	Chlamydial ophthalmia neonatorum (conjunctivitis)	• Azithromycin
European Association of Urology (2015) [297]	Urethritis	• Ceftriaxone or cefixime in combination with azithromycin
	Chlamydia and mycoplasma infection	• Azithromycin
	Ureaplasma urealyticum	• Doxycycline
Centers for Disease Control and Prevention (2015) [289]	Non-gonococcal urethritis	• Azithromycin or doxycycline. Erythromycin, levofloxacin, or ofloxacin as alternatives
	Syphilis	• Primary and secondary syphilis: benzathine penicillin G • Early latent and late latent syphilis: benzathine penicillin G • Tertiary syphilis: benzathine penicillin G
	Neurosyphilis	• Aqueous crystalline penicillin G

	Congenital syphilis	• Aqueous crystalline benzylpenicillin. Procaine benzylpenicillin as an alternative
United Kingdom national guidelines (2015) [294]	Syphilis	• Primary, secondary and early latent syphilis: benzathine penicillin G • Late latent syphilis: benzathine penicillin G • Neurosyphilis: procaine penicillin with probenecid, benzylpenicillin
	Neurosyphilis	• Procaine benzylpenicillin with concomitant probenecid
	Congenital syphilis	• Benzylpenicillin and procaine benzylpenicillin

Working Group considerations: For gonococcal urethritis, ceftriaxone (intravenous or intramuscular) and cefixime (oral) were proposed. Doxycycline (categorized by the Working Group as Access) was proposed for the treatment of chlamydial and non-gonococcal urethritis, with azithromycin as an alternative option, as suggested by most of the clinical practice guidelines. Furthermore, based on the evidence from systematic reviews that the efficacy of azithromycin has decreased in recent years, and the warnings of the FDA about the safety of this antibiotic, [70] azithromycin should only be used if doxycycline has failed or is contraindicated, or if there are major concerns about patient adherence to a longer regimen of doxycycline. For syphilis, benzylpenicillin in various formulations was proposed, depending on the stage of syphilis to be treated. Moxifloxacin, levofloxacin and ofloxacin were not included as treatments based on the principle of parsimony (i.e. to limit the number of alternative options). Tetracycline and lymecycline were also not listed due to redundancy with doxycycline, which is already proposed for several other infections. Other than congenital syphilis, sexually-transmitted infections

are – with a few exceptions – limited to the adult population, thus, the reviews and clinical practice guidelines identified did not cover management in children.

Expert Committee recommendations: The Committee aligned their recommendations with the WHO 2016 guidelines on sexually transmitted infections for combination therapy [41-43]. Access antibiotics include azithromycin, ceftriaxone, cefixime, benzathine benzylpenicillin, benzylpenicillin, procaine benzylpenicillin, doxycycline, metronidazole, as well as additional second-choice medicines, i.e. gentamicin and spectinomycin (Table 48).

Table 48. Recommendations of the Expert Committee for antibiotics to treat sexually transmitted infections

Sexually transmitted infections[a]	
First choice	**Second choice**
Chlamydia trachomatis	
Azithromycin (W)	
Doxycycline (A)	
Erythromicin[b] (W)	
Neisseria gonorrhoeae	
Ceftriaxone (W) in combination with azithromycin[b] (W)	Cefixime (W) in combination with azythromicin (W)
Erythromicin[b] (W)	Gentamicin[c] (A)
	Spectinomycin[d] (A)
Syphilis	
Benzathine benzylpenicillin (A)	Procaine benzylpenicillin (A)
Procaine benzylpenicillin[e] (A)	

Benzylpenicillin (A)	
Trichomonas vaginalis	
Metronidazole (A)	

A: Access, W: Watch

[a]Recommendations aligned with the 2016 WHO guidelines for sexually transmitted infections.[41-43]

[b]Eye ointment (0.5%) for the prevention of gonococcal and chlamydial ophthalmia neonatorum.

[c]The Expert Committee decided to include gentamicin as a second choice for *Neisseria gonorrhoeae* because it is included as an option in the 2016 WHO guidelines for the treatment of *Neisseria gonorrhoeae* in cases of treatment failure (in combination with azithromycin).

[d]The Expert Committee decided to include spectinomycin because it is included as an option in the 2016 WHO guidelines for the treatment of *Neisseria gonorrhoeae* in cases of susceptible isolates (as monotherapy) or in combination with azithromycin in cases of treatment failure or for the treatment of neonatal gonococcal conjunctivitis (as monotherapy).

[e]Procaine benzylpenicillin is recommended in infants with congenital syphilis (another option is aqueous benzylpenicillin) or as a second choice in cases of neurosyphilis as recommended by WHO guidelines.

Skin and soft tissue infections

Summary of systematic reviews: Of 23 systematic reviews identified, 12 met the eligibility criteria, with quality scores ranging from 55% to 75%.[298-309] Several reviews compared linezolid with vancomycin and other antibiotics.[299, 301, 303, 307-309]. Table 49 gives a summary of the findings of the systematic reviews included.

Table 49. Skin and soft tissue infections: summary of findings of systematic reviews

First author (year)	Aim of the study	Findings

Ferreira A (2016) [304]	Compared beta-lactams to macrolides or lincosamides for cellulitis or erysipelas	• No difference in clinical cure between the groups, small sample size
Yue J (2016) [299]	Compared linezolid with vancomycin	• Better clinical cure with linezolid (RR 1.09, 95% CI 1.03–1.16) • More thrombocytopenia (RR 13.06, 95% CI 1.72–99.22) and nausea (RR 2.45, 95% CI 1.52–3.94) reported with linezolid
Selva Olid A (2015) [300]	Compared different antibiotics for diabetic foot infections, and antibiotics with topical foot care or placebo	• No antibiotic was superior to another in terms of clinical resolution of infection, time to resolution, complications and adverse events
Wang SZ (2014) [298]	Compared daptomycin with other antibiotics	• No difference in clinical success between daptomycin and other antibiotics, wide CI[a]
Gurusamy KS (2013) [308]	Compared different antibiotics for methicillin-resistant *Staphylococcus aureus* (MRSA) infection in non-surgical wounds	• No significant difference in the proportion of people in whom MRSA was eradicated between any of the antibiotics compared
Koning S (2012) [306]	Compared treatments for impetigo, including non-pharmacological interventions and no intervention	• Better cure rates with topical antibiotic treatment than placebo (RR 2.24, 95% CI 1.61–3.13) • No clear evidence that mupirocin was more effective than fusidic acid (RR 1.03, 95% CI 0.95–1.11) • Topical mupirocin was slightly more effective than oral erythromycin (RR 1.07, 95% CI 1.01–1.13)

		• No significant differences in cure rates between topical and oral antibiotics • Better cure with oral erythromycin than penicillin (RR 1.29, 95% CI 1.07–1.56) • Better cure with cloxacillin than penicillin (RR 1.59, 95% CI 1.21–2.08)
Beibei L (2010) [307]	Compared linezolid with vancomycin for Gram-positive infections	• Better treatment success with linezolid in patients with skin and soft tissue infections (OR 1.40, 95% CI 1.01–1.95) • No difference in treatment success in patients with bacteraemia (OR 0.88, 95% CI 0.49–1.58) or pneumonia (OR 1.16, 95% CI 0.85–1.57) • No difference in total adverse events (OR 1.14, 95% CI 0.82–1.59)
Bounthavong M (2010) [301]	Compared linezolid with vancomycin for methicillin-resistant *Staphylococcus aureus* infection	• Better clinical cure with linezolid (OR 1.41, 95% CI 1.03–1.95)
Kilburn SA (2010) [305]	Compared different interventions for cellulitis	• Better cure with macrolides and streptogramins than penicillin (RR 0.84, 95% CI 0.73–0.97) • No difference in treatment effect between penicillins and cephalosporins (RR 0.99, 95% CI 0.68–1.43) • No difference in treatment effect between different generations of cephalosporins (RR 1.00, 95% CI 0.94–1.06)

Dodds TJ (2009) [309]	Compared linezolid with vancomycin for methicillin-resistant *Staphylococcus aureus* infection	• No difference in clinical cure, wide CI
Falagas ME (2008) [303]	Compared linezolid with glycopeptide or beta-lactam for Gram-positive infections	• Greater clinical success with linezolid than beta-lactams (OR 1.67, 95% CI 1.31–2.12), although beta-lactams are less potent which limits inferences

CI: confidence intervals; OR: odds ratio; RR: risk ratio.

[a]Similar findings (no significant difference in clinical success between daptomycin and comparators) were reported in a previous systematic review on the same topic [302]

Summary of guidelines: Six guidelines with quality scores ranging from 58% to 81% were analyzed.[310-315] Only two of the guidelines met the criteria of relevance.[310, 311] Both were guidelines of the Infectious Disease Society of America and covered a broad spectrum of infections, including impetigo, cellulitis, necrotizing infections, incisional surgical site infections, and diabetic foot infections. The 2014 Infectious Diseases Society of America guidelines on skin and soft tissue infections [310] cover paediatric and adult patients. Table 50 gives a summary of the recommendations of the guidelines.

Table 50. Skin and soft tissue infections: summary of recommendations of guidelines

Guideline (year)	Skin and soft tissue infections: type	Recommendation
Infectious Diseases Society	Impetigo (paediatric and adult patients)	• Oral dicloxacillin, cefalexin, erythromycin, clindamycin, and amoxicillin–clavulanic acid

of America[a] (2014) [310]	Purulent skin and soft tissue infections (most likely due to *Staphylococcus aureus*)	• (Dicl)oxacillin, cefazolin, clindamycin, cefalexin, doxycycline, and sulfamethoxazole–trimethoprim
	Methicillin-resistant *Staphylococcus aureus* infections, or if this is highly suspected	• Vancomycin, linezolid, clindamycin, daptomycin, ceftaroline, doxycycline, and sulfamethoxazole–trimethoprim
	Non-purulent skin and soft tissue infections	• Benzylpenicillin or phenoxymethylpenicillin, clindamycin, nafcillin, cefazolin, or cefalexin
	Necrotizing fasciitis	• Vancomycin or linezolid plus piperacillin–tazobactam or a carbapenem, or ceftriaxone and metronidazole
	Specific pathogens, e.g. *Streptococcus* spp., *Staphylococcus aureus*, *Clostridium* spp., *Aeromonas hydrophila* and *Vibrio* spp. infections	• *Streptococcus*: penicillin plus clindamycin • *Staphylococcus aureus*: nafcillin, oxacillin, cefazolin, vancomycin, clindamycin • *Clostridium* spp.: clindamycin plus penicillin • *Aeromonas hydrophila*: doxycycline plus ciprofloxacin or ceftriaxone • *Vibrio vulnificus*: doxycycline plus ceftriaxone or cefotaxime
	Animal bites	• Oral treatment: amoxicillin–clavulanic acid • Intravenous treatment: ampicillin–sulbactam, piperacillin–tazobactam, second- and third-generation cephalosporins (cefuroxime, cefoxitin, ceftriaxone, and cefotaxime), carbapenems, doxycycline, sulfamethoxazole–trimethoprim, and fluoroquinolones (ciprofloxacin, levofloxacin, and moxifloxacin)

		• Anaerobic coverage: metronidazole and clindamycin
	Human bites	• Amoxicillin–clavulanic acid and ampicillin–sulbactam. Carbapenems and doxycycline as alternatives. Vancomycin, daptomycin, linezolid, and colistin for selective multidrug-resistant bacteria
	Incisional surgical site infections of the intestinal or genitourinary tract	• Single-drug regimens: ticarcillin–clavulanic acid, piperacillin–tazobactam, carbapenems (imipenem, meropenem, and ertapenem). Combinations regimens: ceftriaxone and metronidazole, a fluoroquinolone (ciprofloxacin or levofloxacin) and metronidazole, and ampicillin–sulbactam together with gentamicin or tobramycin
	After surgery of the trunk or an extremity away from axilla or perineum	• Oxacillin or nafcillin, cefazolin, cefalexin, sulfamethoxazole–trimethoprim, and vancomycin
	Surgery of the axilla or perineum	• Ceftriaxone or a fluoroquinolone (ciprofloxacin or levofloxacin) in combination with metronidazole
Infectious Diseases Society of America (2012) [311]	Diabetic wound infections	• Clinically uninfected wounds: no antibiotics. Infected wound: antibiotic treatment supported by debridement as needed and wound care
	Diabetic wound, mild infections	• Dicloxacillin, clindamycin, cefalexin, levofloxacin, amoxicillin–clavulanic acid, and doxycycline. Potential or confirmed methicillin-resistant *Staphylococcus aureus* infection: sulfamethoxazole–trimethoprim
	Diabetic wound, moderate to severe infections	• Levofloxacin, cefoxitin, ceftriaxone, ampicillin–sulbactam, moxifloxacin, ertapenem, tigecycline,

		ciprofloxacin together with clindamycin, and imipenem–cilastatin. Suspected or confirmed methicillin-resistant *Staphylococcus aureus* infection: linezolid, daptomycin, or vancomycin
	For (potential) *Pseudomonas. aeruginosa* infection	• Piperacillin–tazobactam, ceftazidime, cefepime, aztreonam, and carbapenems

[a]Other than the usual recommendation not to use certain antibiotics in young children if it can be avoided (fluoroquinolones and doxycycline), the recommendations did not vary by age of the patients.

Working Group considerations: Amoxicillin–clavulanic acid, dicloxacillin, cefuroxime, and cefalexin are recommended in the guidelines and all provide appropriate Gram-positive coverage as needed for treatment of mild skin and soft tissue infections and bites. For moderate to severe infections, the Working Group also included intravenous antibiotics that provide appropriate Gram-positive coverage (e.g. vancomycin or cloxacillin), and, if needed, additional Gram-negative coverage (e.g. ceftriaxone or fluoroquinolones) and both Gram-negative and anaerobic coverage (e.g. piperacillin–tazobactam or meropenem). Metronidazole was also proposed if combined with another antibiotic for complex infections that could include anaerobes (e.g. abdominal abscesses). The Working Group also included clindamycin as an option for necrotizing fasciitis.

Expert Committee recommendations: In 2017 the Expert Committee focused only on empiric therapy of mild to moderate community-acquired infections. Severe infections were not considered because it was decided to focus on the treatment of pathogens commonly encountered in the most skin and soft tissue infections (usually *Streptococcus* spp., and methicillin-susceptible *Staphylococcus aureus*) and not to extend the recommendations to severe infections (which are more rare) because they would require treatment with broader-spectrum antibiotics (mostly against

Gram-negative bacteria) and their choice would be largely influenced by the local epidemiology (e.g. risk of multidrug-resistant Gram-negative bacteria in cases of surgical site infections). The Committee also decided to postpone decisions on surgical site infections. Therefore, much of the information from the clinical practice guidelines was not applicable. Given the focus on mild infection, only a few antibiotics were selected. Amoxicillin–clavulanic acid and cloxacillin were selected as first-choice antibiotics because they have good activity against methicillin-susceptible staphylococci, and amoxicillin–clavulanic also provides coverage for bites (Table 51). Cefalexin was selected as a second-choice antibiotic because it has good activity against methicillin-susceptible *Staphylococcus aureus* and is well tolerated.

In 2021 the Expert Committee considered adding necrotizing fasciitis to mild to moderate infections. The Infectious Diseases Society of America guidelines were used to support recommendations for necrotizing fasciitis. The Committee included antibiotics that would be effective in most cases of skin and soft tissue infections encountered in clinical practice (i.e. antibiotics with activity against the most frequent Gram-positive bacteria), offering a broader coverage against Gram-negative bacteria (e.g. ceftriaxone), Gram-positive bacteria (e.g. vancomycin) and anaerobes (metronidazole).

Table 51. Recommendations of the Expert Committee for antibiotics to treat skin and soft tissue infections (including impetigo, erysipelas, cellulitis and necrotizing fasciitis)

Skin and soft tissue infections	
First choice	**Second choice**
Amoxicillin–clavulanic acid (A)	

Cloxacillin[a] (A)	
Cefalexin[b] (A)	
Antibiotics proposed by the Working Group but not selected by the Committee	
Mild infections[c]: Cefuroxime, dicloxacillin	
Necrotizing fasciitis	
First choice	**Second choice**
clindamycin (A) + piperacillin-tazobactam (W) (with or without vancomycin (W)), ceftriaxone (W) + metronidazole (A) (with or without vancomycin (W))	
Antibiotics proposed by the Working Group but not selected by the Committee	
Severe infections[d]: fluoroquinolones, meropenem	

A: Access, W: Watch

[a]Square box listing in the WHO EML (i.e. the Expert Committee listed cloxacillin but noted that any intravenous staphylococcal penicillin would be appropriate; for oral administration, dicloxacillin and flucloxacillin are preferred because of better oral bioavailability among options within the class).

[b]In 2021 the Expert Committee change to the listing for cefalexin on the EML and EMLc from second choice to first choice for skin and soft tissue infections.

[c]The Expert Committee decided to exclude cefuroxime and dicloxacillin for mild cases based on the principle of parsimony.

[d]The Expert Committee decided to exclude meropenem and fluoroquinolones for necrotizing fasciitis based on the principle of parsimony.

Surgical antibiotic prophylaxis

Summary of systematic reviews: We retrieved 17 systematic reviews covering surgical prophylaxis. Reviews that focussed on subclasses of surgical procedures that presented limited external validity (e.g. bariatric surgery, face-lifting procedures or colorectal surgery in children

only) were excluded. Table 52 gives a summary of the findings of the 10 systematic reviews included, with quality scores ranging from 40% to 95%.

Table 52. Surgical antibiotic prophylaxis: summary of findings from systematic reviews

First author (year)	Aim of the study	Findings
Liu, 2013 [316]	Compared the effect of third-generation cephalosporins to other antibiotic regimen on surgical site infections (SSI) incidence in neurosurgery	• No significant difference between third-generation cephalosporins and alternative regimen for SSIs prophylaxis (OR 0.94, 95% CI 0.59–1.52)
Abraham, 2017 [317]	Compared the effect of various antibiotic regimens on SSI incidence in neurosurgery	• Better coverage against SSI with lincosamides, glycopeptides, third generation cephalosporins, other combinations of antibiotics, or penicillin-family antibiotics alone than with first generation cephalosporin
Garnier, 2013 [318]	Evaluated the indications for antibiotic prophylaxis and choice of antibiotics in head and neck cancer surgery	• Surgical prophylaxis needed for certain head and neck cancer surgical procedures • Best antibiotic options are amoxicillin+clavulanic acid and clindamycin+gentamicin
Lador, 2012 [319]	Compared the effect of various antibiotic regimens on deep sternal wound infections in cardiac surgery	• No significant differences of various antibiotic regimens in preventing deep sternal wound infections or other SSI • Lower rate of post-operative pneumonia (RR 0.68, 95% CI 0.51–0.90) and all-cause mortality (RR 0.66, 95% CI 0.47–0.92) with β-lactams also active against Gram-

		negative bacteria than with antibiotics with anti- Gram-positive activity only
Vos, 2018 [320]	Evaluated interventions to prevent deep sternal wound infections in cardiac surgery (only results about antibiotic prophylaxis reported)	• First-generation cephalosporin for at least 24 h recommended to prevent SSI
Nelson, 2009 [321]	Evaluated whether any antibiotic is clearly more effective than the currently recommended gold standard in preventing surgical wound infection in colorectal surgery	• Lower risk of post-operative wound infection with prophylaxis compared to no prophylaxis (risk ratio 0.34, 95% CI 0.28–0.41) • Lower risk of post-operative wound infection with antibiotics with aerobic (RR 0.44, 95% CI 0.29–0.68) and additional anaerobic coverage (RR 0.47, 95% CI 0.31–0.71) • Lower risk of post-operative wound infection with combined oral and intravenous (IV) antibiotic prophylaxis compared to IV alone (RR 0.56, 95% CI 0.43–0.74), or oral alone (RR 0.56, 95% CI 0.40–0.76) • No significant differences of various antibiotic regimens compared to what is recommended by major guidelines
Dahlke, 2013 [322]	Evaluated the appropriate practices to prevent surgical site infections after caesarean delivery	• No better outcomes with different antibiotic combinations (e.g. ampicillin+sulbactam, ampicillin in combination with gentamicin and metronidazole, penicillin and cefalotin) than with cefazolin

		• Ampicillin or first-generation cephalosporins (cefazolin) recommended in all women undergoing C-section
Saleh, 2015 [323]	Compared the efficacy of glycopeptides and β-lactams in preventing SSI in cardiac, vascular, and orthopedic surgery	• No difference in rates of overall SSI between glycopeptides or β-lactams • However, lower rates of resistant staphylococcal (RR 0.52, 95% CI 0.29–0.93) and enterococcal SSI (RR 0.36, 95% CI 0.16-0.80) with glycopeptides • Higher rates of respiratory tract infections (RR 1.54, 95% CI 1.19–2.01) with glycopeptides
Chambers, 2010 [324]	Evaluated whether there is a threshold of MRSA prevalence at which switching from non-glycopeptide to glycopeptide antibiotic prophylaxis is justified in terms of clinical efficacy	• No evidence to support the use of glycopeptides in preference to other antibiotics for the prevention of MRSA infections and SSI • No threshold identified at which switching from non-glycopeptide to glycopeptide prophylaxis would be recommended
Luo, 2015 [325]	Compared the efficacy of gentamicin/flucloxacillin versus cefuroxime in preventing post-operative wound infections	• Similar efficacy in preventing wound infections • Lower risk of *C. difficile* infection with gentamicin/flucloxacillin

Summary of guidelines: Thirty guidelines were identified, 9 of which were assessed in terms of quality (scores ranging from 52.0% to 87.7%). Guidelines that provided general guidance on

antibiotic use without prioritizing individual antibiotics over others were excluded. Table 53 gives a summary of recommendations of the 9 guidelines recommending appropriate antibiotics.

Table 53. Surgical antibiotic prophylaxis: summary of recommendations of guidelines

Guideline (year)	Surgical antibiotic prophylaxis: type of procedure	Recommendation
European association of urology (2020) [284]	Urological procedures	• Radical prostatectomy: prophylaxis should be used, but not enough evidence to recommend specific antibiotics • Prostate biopsy: ciprofloxacin
Australian Therapeutic guidelines (2019) [326]	All types	• Prophylaxis should be directed against the pathogens that more often cause postoperative infections • Cefazolin is preferable for most procedures when prophylaxis is needed • First choice options for the most common procedures: o GI surgery: cefazolin (+ metronidazole for colorectal surgery including appendicectomy, or in alternative cefoxitin single therapy) o Cardiac surgery: cefazolin o Gynaecological surgery: cefazolin+metronidazole (e.g. for hysterectomy)

		○ Obstetric surgery: amoxicillin+clavulanic acid (vaginal delivery), cefazolin (C-section) ○ Orthopedic surgery: cefazolin ○ Urological procedures: gentamicin or cefazolin
French Society of Anesthesia and Intensive Care Medicine (SFAR) (2018)[327]	All types	• Prophylaxis recommended for all clean-contaminated and for some clean procedures • Prophylaxis should target those pathogens that more often cause SSI based on the type of procedure • Procedure-specific recommendations reported in the document: cefazolin recommended for most cases where prophylaxis is indicated. • First-choice options by type of surgery: ○ Neurosurgery: cefazolin ○ Cardiac and vascular surgery: cefazolin or cefamandole or cefuroxime (except for limb amputation where an aminopenicillin+beta-lactamase inhibitor is recommended) ○ Orthopedic surgery: cefazolin or cefamandole or cefuroxime (except for certain types of open fractures where an aminopenicillin+beta-lactamase inhibitor is recommended) ○ Thoracic surgery: cefamandole, cefuroxime, cefazolin or

		aminopenicillin+beta-lactamase inhibitor (only for lung resection) o ORL: cefazolin or aminopenicillin+beta-lactamase inhibitor o GI surgery: cefazolin, cefuroxime or cefamandole. Cefoxitine+ metronidazole for colorectal surgery. Aminopenicillin+beta-lactamase inhibitor for rectal prolapse o Urological procedures: cefazolin, cefamandole or cefuroxime. Ofloxacin for prostate biopsy. No prophylaxis for total prostatectomy o OB/Gyn: cefazolin, cefamandole or cefuroxime. • Plastic surgery: cefazolin
UK National Institute for Health and Care Excellence (2019)[328]	Clean, clean-contaminated and contaminated surgery	• Using the local antibiotic formulary taking into account potential adverse effects • No antibiotic-specific recommendation, only recommendations to give prophylaxis before clean-contaminated and contaminated surgery and before clean surgery involving the placement of a prosthesis or implant
American society for gastrointestinal endoscopy (2015)[329]	Gastrointestinal endoscopy	• Prophylaxis recommended before ERCP when incomplete drainage is anticipated or before percutaneous endoscopic feeding tube placement (PEG/PEJ), or in patients undergoing continuous

		peritoneal dialysis or before EUS-FNA of pancreatic/peripancreatic cysts • Cefazolin recommended before PEG/PEJ tube placement • Ceftriaxone recommended for all cirrhotic patients presenting with GI bleeding
Canadian urological association (2015)[330]	Urological procedures	• Prophylaxis recommended before transrectal prostate biopsy, usually with a fluoroquinolone (single dose or short course) and before TURP with an antibiotic chosen based on local epidemiology among uropathogens • Prophylaxis could be considered in patients undergoing extracorporeal shock wave lithotripsy (when risk of infectious complications is high) or other stone manipulation or endoscopic procedures. The choice of antibiotic should be based on local epidemiology among uropathogens
American society of health-systems pharmacists, Infectious diseases society of America, Surgical infection society, Society for healthcare epidemiology of America (2013)[331]	All types	• For most procedures, cefazolin is the antibiotic of choice for prophylaxis • For colorectal procedures, metronidazole should be added to cefazolin • Routine use of vancomycin is not recommended for any procedure but may be considered in specific situations (e.g. known MRSA colonization)
North American spine society (2013)[332]	Spine surgery	• Prophylaxis recommended but no evidence of proven superiority of one antibiotic over the others

Society of obstetricians and gynecologists of Canada (2010)[333]	Obstetrical procedures	• Single dose first generation cephalosporin for all women undergoing Caesarean section • Prophylaxis to be considered for 3rd and 4th degree perineal injury repair • No prophylaxis solely to prevent endocarditis for any obstetrical procedure

ERCP: Endoscopic retrograde cholangiopancreatography, EUS-FNA: Endoscopic ultrasound fine-needle aspiration, GI: gastrointestinal, PEG: percutaneous endoscopic gastrostomy, PEJ: percutaneous endoscopic jejunostomy, TURP: transurethral resection of the prostate.

Working Group considerations: The WG considered that key factors for appropriate surgical prophylaxis include selecting the right antibiotic taking into account the type of surgical procedure and probable causative pathogens and their resistance patterns. The WG noted that ceftriaxone is often inappropriately used as first-line option in many LMICs and did not prioritize it. The WG acknowledged that based on the evidence retrieved, the first-choice antibiotics recommended for most procedures were cefazolin (with or without metronidazole) and cefuroxime. Second-line proposed antibiotics were gentamicin and amoxicillin + clavulanic acid. Alternative antibiotics were proposed for cases of known or highly suspected allergies (e.g. vancomycin, clindamycin) or the combination of an aminoglycoside (gentamicin) plus clindamycin in settings where the prevalence of resistance to quinolones is high. Quinolones were mentioned for special circumstances where no other options are available but were not formally proposed.

Expert Committee recommendations: The application included procedure-specific recommendations while the Expert Committee decided to give standard recommendations valid

across surgical procedures. Based on the principle of parsimony, only cefazolin was recommended as first line, alone or in in combination with metronidazole. Amoxicillin + clavulanic acid and gentamicin were recommended as second-choice options along with cefuroxime recommended as an alternative where cefazolin is not available. Antibiotics recommended by the Expert Committee are presented in Table 54.

Table 54 Recommendations of the Expert Committee for antibiotics to use for surgical prophylaxis

Surgical prophylaxis	
First choice	**Second choice**
Cefazolin (A) (alone or in combination with metronidazole (A))	Amoxicillin+clavulanic acid (A) Gentamicin (A) Cefuroxime[a] (W)
Antibiotics proposed by the Working Group but not recommended by the Committee[b]	
Cefuroxime first choice, vancomycin when allergic to first-line options, clindamycin	

A: Access, W: Watch

[a]Cefuroxime was added by the Expert Committee as an alternative to cefazolin

[b]The application included procedure-specific recommendations while the Expert Committee decided to provide recommendations valid across surgical procedures.

Typhoid and paratyphoid (enteric) fever

Summary of systematic reviews: We retrieved 2 systematic reviews covering treatment of enteric fever in children and adults with quality scores ranging from 65% to 90%. Table 55 gives a summary of the findings of the systematic reviews included.

Table 55. Enteric fever: summary of findings from systematic reviews

First author (year)	Aim of the study	Findings
Effa EE (2011) [334]	Evaluated fluoroquinolone antibiotics for treating children and adults with enteric fever	• Higher risk of clinical failure with older antibiotics (chloramphenicol, sulfamethoxazole–trimethoprim, amoxicillin and ampicillin) than with fluoroquinolones. • Conflicting results with fluoroquinolones versus current second-line options (ceftriaxone, cefalexin, and azithromycin) • Studies were old and resistant patterns have changed over time
Effa EE (2008) [335]	Compared azithromycin with other antibiotics for treating uncomplicated enteric fever in children and adults	• Lower risk of clinical failure (OR 0.48, 95% CI 0.26–0.89) and shorter hospital stay (-1.04 days, 95% CI -1.73 – -0.34 days) with azithromycin than with fluoroquinolones • Lower risk of relapse (OR 0.09, 95% CI 0.01–0.70) with azithromycin than with ceftriaxone
Koirala S (2013) [336]	Compared gatifloxacin versus ofloxacin for uncomplicated enteric fever in Nepal (adults and children)[a]	• No statistically significant difference in treatment failure (HR 0.81, 95% CI 0.25-2.65) between ofloxacin and gatifloxacin • More rapid fever clearance with gatifloxacin (HR 1.59, 95% CI 1.16- 2.18) in a setting with

		high proportion of nalidixic acid- resistant isolates (170 out of 218 patients with culture confirmed infection)
Arjyal A (2016)[337]	Compared gatifloxaicn versus ceftriaxone for uncomplicated fever in Nepal (adults and children)[a, b]	• No statistically significant difference in treatment failure in the mITT population between gatifloxacin and ceftriaxone (HR 1.04, 95% CI 0.55-1.98) • In the culture-confirmed population, ceftriaxone was associated with lower risk of failure (HR 0.24, 95% CI 0.08-0.73)

HR: hazard ratio; mITT: modified intention to treat.

[a]Randomised clinical trial.

[b]The trial was stopped early by the data safety and monitoring board because of the emergence of S Typhi exhibiting high-level resistance to ciprofloxacin and gatifloxacin.

Summary of guidelines: Two WHO guidelines were included (quality scores ranging from 51.3% to 94.8%). Table 56 gives a summary of recommendations of the guidelines included.

Table 56. Enteric fever: summary of guideline recommendations

Guideline (year)	Enteric fever	Recommendation
World Health Organization (2012) [338]	Treatment of typhoid fever in children	• First line: fluoroquinolone (i.e. ciprofloxacin, gatifloxacin, ofloxacin and perfloxacin). Second line (poor response to first line): third-generation cephalosporin (e.g. ceftriaxone) or azithromycin

World Health Organization (2003) [339]	Diagnosis, treatment and prevention of typhoid fever	• Fully sensitive *Salmonella* Typhi: fluoroquinolone (ofloxacin or ciprofloxacin). Alternative (if fluoroquinolones are not available or where the bacterium is still sensitive): chloramphenicol, amoxicillin or sulfamethoxazole + trimethoprim • Multidrug resistant strains: fluoroquinolone or cefixime. Alternative: azithromycin or cefixime • Quinolone resistant: azithromycin or ceftriaxone. Alternative: cefixime

Working Group considerations: The Working group acknowledged the lack of evidence from systematic reviews to recommend older antibiotics (ampicillin / amoxicillin and trimethoprim + sulfamethoxazole, chloramphenicol) and cefixime for the treatment of enteric fever even though these options were recommended by WHO in 2003. Chloramphenicol was not proposed due to the risk of important adverse events, need to monitor the blood count during treatment and the availability of alternatives. The Working group recommended ciprofloxacin (ofloxacin was not recommended for parsimony given it has a similar clinical performance), ceftriaxone and azithromycin supported by the evidence from systematic reviews and guidelines.

Expert Committee recommendations: The Committee acknowledged the importance of considering local resistance patterns for *Salmonella* Typhi and Paratyphi in making specific recommendations for empiric treatment of enteric fever due to increasing levels of fluoroquinolone-resistance in some settings. First and second choice options selected by the Committee are reported in Table 57.

Table 57. Recommendations of the Expert Committee for antibiotics to treat enteric fever

Enteric fever[a]	
First choice	**Second choice**
Ciprofloxacin (W) (except where high prevalence of fluoroquinolone resistance exists) [b]	
Ceftriaxone (W)	
Azithromycin (W)	

W: Watch

[a]The application proposed the inclusion of ofloxacin, ciprofloxacin, ceftriaxone and azithromycin on the EML and EMLc. Ofloxacin was rejected for the principle of parsimony.

[b]This is the first time the Expert Committee has considered resistance patterns in making specific recommendations for empiric treatment.

Urinary tract infections (Lower and upper)

Summary of systematic reviews: We evaluated 12 systematic reviews [340-351]. However, only three were retained for further evaluation, with scores ranging from 78% to 80% [340-342]. We also identified four systematic reviews on catheter-associated urinary tract infections [352-355] but none focused on therapy. Table 58 gives a summary of the findings of the systematic reviews included.

Table 58. Urinary tract infections: summary of findings of systematic reviews

First author (year)	Aim of the study	Findings
Zalmanovici Trestioreanu A (2015) [340]	Assessed the effectiveness and safety of antibiotic treatment for asymptomatic bacteriuria in adults	• No difference between the different antibiotics and antibiotics and placebo in cure for symptomatic urinary tract infection (RR 1.11, 95% CI 0.51–2.43), complications (RR 0.78, 95% CI 0.35–1.74) and death (RR 0.99, 95% CI 0.70–1.41) • Antibiotics were more effective for bacteriological cure (RR 2.67, 95% CI 1.85–3.85) but also more adverse events developed in the antibiotic group (RR 3.77, 95% CI 1.40–10.15)
Strohmeier Y (2014) [342]	Compared antibiotics for treatment of acute pyelonephritis in children	• No difference in duration of fever, persistent infection at 72 hours, or persistent kidney damage at 6–12 months between oral antibiotic therapy (10–14 days) and intravenous therapy (3 days) followed by oral therapy (10 days), wide CI • No difference in persistent bacteriuria or kidney damage between short- and long-term therapy, wide CI
Zalmanovici Trestioreanu (2010) [341]	Compared different antibiotics for acute uncomplicated lower urinary tract infection in women	• No difference between sulfamethoxazole–trimethoprim and fluoroquinolones for short-term (RR 1.00, 95% CI 0.97–1.03) and long-term (RR 0.99, 95% CI 0.94–1.05) symptomatic cure • No difference between beta-lactams and sulfamethoxazole–trimethoprim for short-term (RR 0.95, 95% CI 0.81–1.12) and long-term (RR 1.06, 95% CI 0.93–1.21) symptomatic cure but our criteria for equivalence were not met

		• No difference between nitrofurantoin and sulfamethoxazole–trimethoprim for short-term (RR 0.99, 95% CI 0.95–1.04) and long-term (RR 1.01, 95% CI 0.94–1.09) symptomatic cure

RR: risk ratio; CI: confidence intervals.

Summary of guidelines: We evaluated eight guidelines,[356-363] and retained four with scores ranging from 70% to 89%.[356-359] We found two guidelines on catheter-associated urinary tract infection[364, 365], but no specific recommendations on the choice of antibiotics for empiric treatment are provided. Table 59 gives a summary of recommendations of the included guidelines.

Table 59. Urinary tract infections: summary of recommendations of guidelines

Guideline (year)	Urinary tract infections: type	Recommendation
European Association of Urology & European Society for Paediatric Urology[b] (2015) [356]	Urinary tract infections in children	• Antimicrobial choice based on local resistance patterns
	Urinary tract infections in newborns and infants	• Parenteral ampicillin and an aminoglycoside or a third-generation cephalosporin
	Pyelonephritis in children ≤ 6 months	• Ceftazidime and ampicillin, or an aminoglycoside and ampicillin
	Uncomplicated pyelonephritis in children > 6 months	• Third-generation cephalosporin
	Complicated pyelonephritis (all ages)	• Ceftazidime and ampicillin, or an aminoglycoside and ampicillin

American Academy of Pediatrics (2011)[357]	Children 2–24 months, empiric treatment	• Amoxicillin–clavulanic acid and sulfamethoxazole–trimethoprim
Infectious Diseases Society of America & European Society for Microbiology and Infectious Diseases[a] (2011) [359]	Uncomplicated cystitis in women	• Nitrofurantoin and sulfamethoxazole–trimethoprim. Amoxicillin–clavulanic acid as an alternative
	Acute pyelonephritis (adults)	• Fosfomycin where available, and ceftriaxone and ciprofloxacin

[a]The guideline recommends that local resistance rates for empirically selected antibiotics should be < 10% for pyelonephritis and < 20% for treatment of lower urinary tract infection, a threshold no longer met by fluoroquinolone in many countries.

[b]Italian recommendations are similar to the guidelines of the European Association of Urology & European Society for Paediatric Urology.[358]

Working Group considerations: The evidence from the systematic reviews showed that sulfamethoxazole–trimethoprim was equivalent (based on our definition) to fluoroquinolones for uncomplicated urinary tract infections, and that nitrofurantoin was equivalent to sulfamethoxazole–trimethoprim. Therefore, sulfamethoxazole–trimethoprim and nitrofurantoin were proposed (they were categorized as Access antibiotics). Fosfomycin was also proposed and categorized as Access by the Working Group because of minimal resistance to this antibiotic and its good safety profile. The proposal was in part rejected by the Expert Committee (fosfomycin was in fact not recommended for this indication). Amoxicillin–clavulanic acid was added to the list for young children and ampicillin and gentamicin were added for children with severe illness. Fluoroquinolones were not listed because of the emergence of resistance and because a sufficient number of alternatives to treat urinary tract infections was available.

Expert Committee recommendations: The Committee chose amoxicillin–clavulanic acid, nitrofurantoin and sulfamethoxazole–trimethoprim as the first-choice options for the treatment of lower urinary tract infections. In this case, parsimony (i.e. recommending a very limited number of antibiotic options) was given less importance than feasibility (i.e. giving several alternatives in view of differences in availability). Amoxicillin was recommended as a first-choice treatment option for empiric treatment in 2017. The Expert Committee initially decided to include amoxicillin for the treatment of lower urinary tract infections because it is widely available and cheap. It was considered an acceptable option for the treatment of cystitis in young non-pregnant women. The rationale was to put more emphasis on the risk of favouring resistance with antibiotics with a broader spectrum of activity compared with amoxicillin rather than on the possible risk of treatment failure (but only for selected patients at low risk of adverse outcomes). However, in 2021 the Committee took into consideration data from the 2020 report by the Global Antimicrobial Resistance Surveillance System (GLASS) on global antimicrobial resistance.[366] These data (from 22 countries) showed that a median of 75% (range 45-100%) of *Escherichia coli* urinary isolates were resistant to amoxicillin. These resistance patterns discouraged multiple guidelines to recommend the empiric use of amoxicillin for treatment of lower urinary tract infections.[284, 359, 367] In 2021 the Expert Committee aligned AWaRe guidance on lower urinary tract infections removing amoxicillin from the recommended options. In 2021 GLASS data were not available for amoxicillin + clavulanic acid or nitrofurantoin. The Expert Committee noted that the susceptibility of *Escherichia coli* to amoxicillin + clavulanic acid or nitrofurantoin in urinary isolates remains generally high, in both adults and children.[368-370]

Ciprofloxacin was recommended as the first-choice option for empiric treatment of mild-to-moderate pyelonephritis and prostatitis if local/national data on antimicrobial resistance patterns

(of the most frequent causative pathogens of urinary tract infections) allow its use (Table 60). Of note, since 2016 the FDA has warned of serious safety issues of fluoroquinolones that can affect tendons, muscles, joints, nerves and the central nervous system. The FDA continues to recommend their use for serious infections where the benefits outweigh the risks.[71] For severe cases, amikacin was preferred to gentamicin because it is usually more frequently active on Enterobacterales. Ceftriaxone and cefotaxime were also listed for severe infections.

Table 60. Recommendations of the Expert Committee for antibiotics to treat lower and upper urinary tract infections

Urinary tract infections	
First choice	**Second choice**
Lower urinary tract infection	
Amoxicillin–clavulanic acid (A)	
Nitrofurantoin (A)	
Sulfamethoxazole–trimethoprim (A)	
Pyelonephritis and prostatitis: mild to moderate	
Ciprofloxacin (W)	Ceftriaxone or cefotaxime (W)
Pyelonephritis and prostatitis: severe	
Ceftriaxone or cefotaxime (W)	
Amikacin[a] (A)	
Antibiotics proposed by the Working Group but not selected by the Committee	
Lower urinary tract infection: fosfomycin[b]	
Upper urinary tract infection: ampicillin in combination with gentamicin[c] (for children with severe illness)	

A: Access, W: Watch

[a]The Expert Committee decided to include amikacin instead of gentamicin because amikacin is considered to have a better resistance profile, is still effective against isolates producing extended-spectrum beta-lactamases (ESBL) and is considered an appropriate carbapenem-sparing option in settings where ESBL-producing isolates are very prevalent.

[b]The Expert Committee decided to exclude fosfomycin for the treatment of lower UTIs based on the results of the randomized controlled trials comparing 5 days of nitrofurantoin to a single dose of fosfomycin that showed a significantly greater likelihood of clinical and microbiologic resolution at 28 days after treatment with nitrofurantoin among women with uncomplicated urinary tract infections [371]. Cost was also considered: fosfomycin is more expensive than nitrofurantoin.

[c]The Expert Committee decided to exclude ampicillin in combination with gentamicin for severe upper urinary tract infections in children based on the principle of parsimony (in this case by giving the same option for children and for adults).

Cholera in children

Summary of systematic reviews: We retrieved three studies of moderate quality of which two were systematic reviews (quality scores 60% and 35%) and one a randomized controlled trial.[59, 372, 373] Table 61 gives a summary of the findings of the articles included.

Table 61. Cholera in children: summary of findings of systematic reviews

First author (year)	Aim of the study	Findings
Leibovici Weissman Y (2014) [59]	Compared different classes of antimicrobials and dosing schedules in adults and children	• Shorter duration of diarrhoea by over 1 day with single-dose azithromycin compared with ciprofloxacin (MD –32.4 hours, 95% CI –62.9 to –1.95 hours) and by half a day compared with erythromycin (MD –12.1, 95% CI –22.0 to –2.08) • Both children and adults were included; authors reported that there were not

		statistically subgroup differences between the two age groups
Das JK (2013) [372]	Compared antibiotics for treatment of acute cholera in children	• Antibiotics were more effective for clinical failure (RR 0.37, 95% CI: 0.19 to 0.71) and bacteriological failure (RR 0.25, 95% CI: 0.12, 0.53)
Kaushik JS (2010) [373]	Compared single-dose azithromycin with ciprofloxacin in children[a]	• Greater clinical success with azithromycin (RR 1.34 95% CI 1.16–1.54)

MD: mean difference; CI: confidence intervals; RR: risk ratio.

[a]Randomized controlled trial.

Summary of guidelines: Seven guidelines were assessed.[68, 374-379] Most of the guidelines recommend antimicrobial therapy for children who are moderately to severely ill. Almost all the guidelines (particularly those most recently updated) recommend azithromycin as the preferred first-line therapy for children, largely because of the reduced effectiveness of tetracycline and fluoroquinolones in treating cholera. Table 62 gives a summary of recommendations of the guidelines.

Table 62. Cholera in children: summary of recommendations of guidelines

Guideline (year)	Cholera in children: type	Recommendation
BMJ Best Practice (2018) [378]	Severely ill children	• Azithromycin single dose

American Academy of Paediatrics (2015) [379]	Severely ill children	• Azithromycin or erythromycin or tetracycline
Centers for Disease Control and Prevention (2015) [377]	Severely ill children	• Azithromycin as first-line treatment for children with moderate dehydration, not just severe dehydration
Therapeutic Guidelines (Australia) (2015) [376]	Severely ill children	• Azithromycin single dose, or ciprofloxacin single dose
World Gastroenterology Organisation (2013) [374]		• Routine treatment with azithromycin single dose for clinically recognizable cholera infection (not limited by hydration status)
Infectious Diseases Society of America (2001) [68]		• Doxycycline or tetracycline or trimethoprim-sulfamethoxazole[a]
International Centre for Diarrhoeal Disease Research (1997) [375]	Clinically diagnosable cholera	• Antibiotics for all with clinically diagnosable cholera (not restricted by severity): tetracycline as the first-line therapy[a]

[a]These guidelines are more than 2 decades old.

Working group considerations: The latest WHO guideline in 2005 recommended a 3-day course of tetracycline for children with severe dehydration and no antibiotics for children with less severe dehydration.[380] The Working Group concluded that there was still no reason to question the key role of fluid resuscitation and that antibiotics should only be given to patients with severe dehydration. Instead of tetracycline for antimicrobial therapy, the Working Group suggested doxycycline because it is easier to administer and already available on the EML. As alternatives, the Group suggested ciprofloxacin, erythromycin, or azithromycin. There was a concern about the

long half-life of azithromycin and therefore it was recommended only in epidemic situations where single-dose treatment is especially useful.

Expert Committee Recommendations: The Expert Group recommended azithromycin as the first choice (for children), and doxycycline or ciprofloxacin as the second choice (Table 63).

Table 63. Recommendations of the Expert Committee for antibiotics to treat cholera in children

Cholera in children	
First choice	**Second choice**
Azithromycin (W)	Ciprofloxacin (W), doxycycline[a] (A)
Antibiotics proposed by the Working Group but not recommended by the Committee	
Erythromycin[b]	

A: Access, W: Watch

[a]The Expert Committee recommended doxycycline as a second choice for children because many authorities consider it safe only for children over 12 years of age. It should only be used in severe or life-threatening cases.

[b]The Expert Committee decided to exclude erythromycin based on the principle of parsimony.

Community-acquired pneumonia in children

Summary of systematic reviews: Of the nine systematic reviews included with quality scores of 60–90%,[93-101] three were specific to children [99-101]. Table 64 gives a summary of the findings of these three reviews.

Table 64. Community-acquired pneumonia in children: summary of findings of systematic reviews

First author (year)	Aim of the study	Findings
Lassi ZS (2014) [100]	Compared different antibiotics for pneumonia in children 2–59 months	• Higher failure rates with sulfamethoxazole–trimethoprim than amoxicillin (RR 1.79, 95% CI 1.13–2.84). • Very severe pneumonia: no significant difference in death rates between ampicillin and gentamicin versus chloramphenicol (RR 0.71, 95% CI 0.51–1.00) but lower failure rate with ampicillin and gentamicin than chloramphenicol (RR 0.79, 95% CI 0.66–0.94)
Lodha R (2013) [99]	Compared antibiotics for CAP of varying severity in children	• Non-severe CAP: amoxicillin compared with sulfamethoxazole–trimethoprim had similar failure rates (OR 1.18, 95% CI 0.91–1.51) and cure rates (OR 1.03, 95% CI 0.56–1.89) • Severe CAP: oral antibiotics (amoxicillin or sulfamethoxazole-trimethoprim) compared with injectable penicillin had similar failure rates (OR 0.84, 95% CI 0.56–1.24), hospitalization rates (OR 1.13, 95% CI 0.38–3.34) and relapse rates (OR 1.28, 95% CI 0.34–4.82) • Very severe CAP: higher death rates (OR 1.25, 95% CI 0.76–2.07) and higher failure rates on day 5 (OR 1.51, 95% CI 1.04–2.19), on day 10 (OR 1.46, 95% CI 1.04–2.06) and on day 21 (OR 1.43, 95% CI 1.03–

		1.98) with chloramphenicol compared with penicillin or ampicillin plus gentamicin
Haider BA (2008) [101]	Compared short-course (3 days) and long-course (5 days) antibiotic therapy for non-severe pneumonia in children aged 2–59 months	• No significant difference between short and long antibiotic courses in rates of clinical cure at the end of treatment (RR 0.99, 95% CI 0.97–1.01), treatment failure at the end of treatment (RR 1.07, 95% CI 0.92–1.25) and relapse rate after 7 days of clinical cure (RR 1.09, 95% CI 0.83–1.42)

OR: odds ratio; CI: confidence intervals; RR: risk ratio.

Summary of guidelines: For children, recently published British, European, Canadian and American guidelines were reviewed.[381-385] Taken together, paediatric antibiotic guidelines recommend oral amoxicillin for uncomplicated community-acquired pneumonia in children, often with macrolides as an alternative. However, the guidelines differ in the recommended duration of treatment and age banding. British and European guidelines recommend oral amoxicillin as the first choice and a macrolide (clarithromycin) in case of treatment failure, an atypical pathogen, or penicillin allergy. Canadian and American guidelines recommended azithromycin as the macrolide of choice with doxycycline as an alternative for older children. For inpatient therapy, intravenous antibiotics recommended by all the guidelines included are beta-lactams and second- and third-generation cephalosporins. Vancomycin is recommended if MRSA is suspected. Table 65 gives a summary of recommendations of the guidelines.

Table 65. Community-acquired pneumonia (CAP) in children: summary of recommendations of guidelines

Guideline (year)	CAP in children: type	Recommendation
British National Formulary (2016) [384]	Uncomplicated CAP in children 1 month to 18 years	• Oral amoxicillin. Clarithromycin if treatment failure or penicillin allergy
	Suspected staphylococcal pneumonia	• Oral amoxicillin and flucloxacillin, or amoxicillin–clavulanic acid alone
	Complicated CAP	• Intravenous amoxicillin, amoxicillin–clavulanic acid, cefuroxime, or cefotaxime (or ceftriaxone)
RCPCH & ESPID (2016) [385]	Uncomplicated CAP in children < 5 years	• Oral amoxicillin for 5 days as the first-line antibiotic
	Suspected *Mycoplasma pneumoniae* or *Chlamydia pneumoniae*	• Macrolides
	Severe CAP	• Intravenous antibiotics (penicillin or amoxicillin, amoxicillin–clavulanic acid, cefuroxime, or cefotaxime or ceftriaxone)
Canadian Paediatric Society (2015) [383]	Uncomplicated CAP	• Oral amoxicillin
	Inpatient CAP	• Intravenous ampicillin
	Mycoplasma pneumoniae or *Chlamydia pneumoniae* infection	• Azithromycin for 5 days, or doxycycline for children 8 years and older
	Severe CAP	• Third-generation cephalosporins
	Highly penicillin-resistant pneumococcus	• Ceftriaxone or cefotaxime
	Staphylococcal empyema	• Vancomycin
British Thoracic Society (2011) [382]	Uncomplicated CAP	• Oral amoxicillin as the first choice. Amoxicillin–clavulanic acid, cefaclor, erythromycin, azithromycin and clarithromycin as alternatives. If

		no response to first-line empirical therapy, add macrolides
	Suspected *Mycoplasma pneumoniae* or *Chlamydia pneumoniae* infection or very severe disease	• Macrolide antibiotics
	Pneumonia associated with influenza	• Amoxicillin–clavulanic acid
PIDS & IDSA (2011) [381]	Mild to moderate CAP in fully immunized infants and pre-school children with presumed bacterial pneumonia	• Amoxicillin
	Mild to moderate CAP in fully immunized school-aged children	• Amoxicillin
	Presumed atypical pneumonia (in school-aged children and adolescents)	• Macrolides (azithromycin, clarithromycin, or erythromycin)
	Inpatient CAP	• Ampicillin or benzylpenicillin (in fully immunized infants and children), or ceftriaxone or cefotaxime (infants or children not fully immunized), or a combination of a macrolide and a beta-lactam for all ages (if atypical pathogens are suspected)

RCPCH: Royal College of Paediatrics and Child Health; ESPID: European Society for Paediatric Infectious Diseases; PIDS: Pediatric Infectious Diseases Society; IDSA: Infectious Diseases Society of America.

Working Group considerations: In 2014, WHO recommended for children a 5-day course of oral amoxicillin for uncomplicated pneumonia and intravenous ampicillin or penicillin combined with gentamicin for severe conditions.[386] The Working Group agreed that the reviews did not

provide new data to justify a change in the WHO recommended empirical therapy. For example, higher failure rates with chloramphenicol compared with ampicillin and gentamicin supported the inclusion of ampicillin and gentamicin. The better cure rate with amoxicillin than cefpodoxime supported the inclusion of amoxicillin and exclusion of oral third-generation cephalosporins.

Expert Committee recommendations: The Committee selected amoxicillin and phenoxymethylpenicillin as first-choice options, and amoxicillin–clavulanic acid and doxycycline as second-choice options for mild-to-moderate community-acquired pneumonia in children (Table 66). For severe community-acquired pneumonia in children, they selected amoxicillin–clavulanic acid, cefotaxime or ceftriaxone, and gentamicin in combination with ampicillin, amoxicillin or benzylpenicillin as first-choice options.

Lately the choice of recommending amoxicillin–clavulanic acid has been debated. A draft of the WHO AWaRe Book was published online for public consultation In November 2021. The British Society for Antimicrobial Chemotherapy requested removing amoxicillin–clavulanic acid as this recommendation is likely to reinforce extensive consumption, when the majority of these infections could be handled with amoxicillin alone.[387] The other disadvantages of adding clavulanic acid are the potential selection pressure for resistant Gram-negative organisms (e.g. extended-spectrum beta-lactamases producing organisms) in the intestinal flora and the increased association with diarrhoea, that can be detrimental in children.[388] The Working Group removed amoxicillin–clavulanic acid from recommended options in the WHO AWaRe Book, and flagged amoxicillin–clavulanic acid to be considered for deletion from the EML for community-acquired pneumonia in children through the standard submission process in 2023 unless new evidence is received in support of its retention.

Table 66. Recommendations of the Expert Committee for antibiotics to treat community acquired pneumonia in children

Community-acquired pneumonia in children	
First choice	**Second choice**
Mild to moderate	
Amoxicillin (A)	Amoxicillin–clavulanic acid[a] (A)
Phenoxymethylpenicillin (A)	Doxycycline (A) (in children > 8 years)
Severe	
Amoxicillin–clavulanic acid[a] (A)	
Cefotaxime[b] (W)	
Ceftriaxone[b] (W)	
Gentamicin (A) in combination with ampicillin (A), amoxicillin (A) or benzylpenicillin (A)	

A: Access, W: Watch

[a]Amoxicillin-clavulanic acid has been flagged for deletion from the EML in 2023 unless new evidence is received in support of its retention.

[b]The Expert Committee decided to include cefotaxime or ceftriaxone in alignment with WHO guidelines.

Sepsis in children

Summary of systematic reviews: We identified 11 reviews [389-399], two of which were included.[389, 390] No suitable new reviews were found since the previously published WHO guidelines.[137, 213] Table 67 gives a summary of the findings of the systematic reviews included. Additional evidence was sought from five more recent randomized controlled trials on suspected

outpatient neonatal sepsis which compared antibiotic treatments in a low-risk community setting in neonates and young infants (0–59 days) in low- and middle-income countries.[400-404] These trials considered possible simplification of the current WHO treatment for infants for whom admission to inpatient care was not acceptable or possible. In this group of infants, evidence suggests that treatment regimens could be simplified by using intramuscular gentamicin for 2 days and oral amoxicillin for 7 days.

Table 67. Sepsis in children: summary of findings of systematic reviews

First author (year)	Aim of the study	Findings
Gordon A (2005) [390]	Compared beta-lactams with beta-lactams plus aminoglycosides for late-onset neonatal sepsis	• No significant difference in mortality (RR 0.17, 95% CI 0.01–3.23) or treatment failure (RR 0.17, 95% CI 0.01–3.23) but the study did not meet the criteria for good methodological quality specified by the authors of the systematic review
Mtitimila EI (2004) [389]	Compared single to combination antibiotic regimens for early-onset neonatal sepsis	• Inconclusive results on mortality within 28 days (RR 0.75, 95% CI 0.19–2.9) because of inadequate sample size

RR: risk ratio; CI: confidence intervals.

Summary of guidelines: We identified six clinical practice guidelines or guidance documents.[379, 405-411] Table 68 gives a summary of recommendations of the guidelines. The recommended empirical treatment for late-onset neonatal sepsis varied more between the

guidelines likely reflecting the different patterns of antibiotic resistance and pathogens reported globally.

Table 68. Sepsis in children: summary of recommendations of guidelines

Guideline (year)	Sepsis in children: type	Recommendation
BMJ Best practice (2016) [405]	Suspected or proven sepsis	Early onset (first 72 hours of life): benzylpenicillin plus gentamicin or ampicillin plus gentamicin (but insufficient evidence to support any antibiotic regimen being superior to another) Late onset (>72 hours to 1 month of life) – In developed countries, coagulase-negative staphylococci is the leading cause followed by GBS and gram-negative bacteria. - Coagulase-negative staphylococci: vancomycin - GBS, *Escherichia coli*, enterococci: cefotaxime or piperacillin+tazobactam
UK National Institute for Health and Care Excellence (NICE)- NICE guideline 51 (2016) [410]	Suspected sepsis	• Ceftriaxone (plus ampicillin or amoxicillin in neonates up to 3 months of age) • Benzylpenicillin and gentamicin in neonates with early-onset sepsis (first 72 hours of life)
BNF for children, blood infection	Blood infection	*Intravenous first line*:

antibacterial therapy (2015) [407]		• Benzylpenicillin with gentamicin (unless microbiological surveillance data shows local bacterial resistance patterns). • If Gram-negative bacterial sepsis suspected, add an antibacterial active against Gram-negative bacteria (e.g. cefotaxime); if Gram-negative infection confirmed, stop benzylpenicilin.
Polin RA – Clinical report by the Committee on fetus and newborn (COFN) of the American Academy of Pediatrics (2012) [411]	Suspected or proven early-onset bacterial sepsis	Ampicillin and an aminoglycoside (usually gentamicin). Third-generation cephalosporins (eg, cefotaxime) represent a reasonable alternative to an aminoglycoside. Recommendations for the secondary prevention of GBS: - All asymptomatic infants born to women with suspected chorioamnionitis should receive broad-spectrum antibiotics - All premature infants (<37 weeks) should be treated with broad spectrum antibiotics if either history of chorioamnionitis OR PROM ≥ 18 hours OR inadequate GBS intrapartum antimicrobial prophylaxis
Surviving sepsis campaign (formed by the Society of Critical Care Medicine, the *European*	Severe sepsis	The empiric drug choice should be changed as epidemic and endemic ecologies dictate

Society of Intensive Care Medicine and the International Sepsis Forum) – 3rd edition (section on pediatrics) (2012) [409]		
UK National Institute for Health and Care Excellence (NICE) (2012) [408]	Early-onset neonatal infection	• Intravenous benzylpenicillin combined with gentamicin as first-line empirical treatment unless local bacterial resistance patterns suggest using a different antibiotic. • If evidence of Gram-negative bacterial sepsis cefotaxime should be added (or another antibiotic active against Gram-negative bacteria)

GBS: group B *Streptococcus.*

Working Group considerations: The Working Group considered that the systematic reviews did not contribute any new information and therefore used the WHO Pocket book of hospital care for children and WHO guidelines.[137, 213] Selection of first-line antibiotics was based on the most common pathogens encountered in sepsis: therefore, antibiotics such as amoxicillin, ampicillin and benzylpenicillin were chosen because of their activity against for example group B streptococcus, and aminoglycosides (i.e. gentamicin and amikacin) for their activity against Gram-negative bacteria (e.g. Enterobacterales). Procaine benzylpenicillin was not proposed as a first-line

treatment for neonatal sepsis except when given by trained health care workers in settings with high neonatal mortality in cases where hospital care is not possible.

Expert Committee recommendations: The Committee selected the antibiotics proposed by the Working Group. Access antibiotics recommended included gentamicin, to be used in combination with ampicillin, amoxicillin, or benzylpenicillin, as first choices. Amikacin to be used in combination with cloxacillin, cefotaxime, and ceftriaxone were recommended as second choices (Table 69). Cefotaxime and ceftriaxone were selected as second choice to be used in certain cases.

Table 69. Recommendations of the Expert Committee for antibiotics to treat sepsis in children

Sepsis[a]	
First choice	**Second choice**
Amoxicillin (A) + gentamicin (A)	Amikacin (A) + cloxacillin (A)
Ampicillin (A) + gentamicin (A)	Cefotaxime (W)
Benzylpenicillin (A) + gentamicin (A)	Ceftriaxone (W)

A: Access, W: Watch

[a]Recommendations aligned with WHO guidelines for antibiotic use for sepsis in neonates and children [137, 213] as proposed by the Working Group.

Severe acute malnutrition in children

Summary of systematic reviews: For uncomplicated severe acute malnutrition evidence from one systematic review [412] and one meta-analysis [413] was considered, complemented by findings

from four randomized controlled trials.[414-417] Table 70 gives a summary of the findings of the articles included.

Table 70. Severe acute malnutrition in children: summary of findings of reviews

First author (year)	Aim of the study	Findings
Million M (2017) [413]	Assessed efficacy of amoxicillin for uncomplicated severe acute malnutrition	• Better nutritional recovery from kwashiorkor, marasmic kwashiorkor and marasmus with amoxicillin (RR 1.03, 95% CI 1.00–1.06) compared with placebo • Better nutritional recovery from marasmus with amoxicillin (RR 1.05, 95% CI 1.00–1.11) compared with placebo
Isanaka S (2016) [415]	Compared amoxicillin with placebo for uncomplicated severe acute malnutrition[a]	• No difference in nutritional recovery between amoxicillin and placebo (RR 1.05, 95% CI 0.99–1.12) • Accelerated early growth with amoxicillin but had no significant effect by week 4 • Lower risk of transfer to inpatient care with amoxicillin (RR 0.86, 95% CI 0.76–0.98)
Trehan I (2013) [417]	Compared amoxicillin, cefdinir, or placebo as part of the management of severe acute malnutrition[a]	• Higher mortality rate with placebo than either amoxicillin (RR 1.55, 95% CI 1.07–2.24) or cefdinir (RR 1.80, 95% CI 1.22–2.64) • Less frequent recovery with placebo than either amoxicillin (3.6 percentage points

		lower, 95% CI 0.6–6.7) or cefdinir (5.8 percentage points lower, 95% CI 2.8–8.7)
Lazzerini M (2011) [412]	Reviewed the evidence in support of WHO guidelines recommending broad-spectrum antibiotics for children with severe acute malnutrition	• No significant difference in any of the efficacy outcomes between oral amoxicillin for 5 days and intramuscular ceftriaxone for 2 days • No benefit of amoxicillin over placebo for uncomplicated cases • Significant reduction in mortality in hospitalized children treated with ampicillin and gentamicin (OR 4.0, 95% CI 1.7–9.8) • No significant difference in treatment failure between oral chloramphenicol and sulfamethoxazole–trimethoprim in children with pneumonia
Trehan I (2010) [416]	Compared oral amoxicillin to no antibiotic in treatment of children aged 6–59 months with uncomplicated severe acute malnutrition[a]	• Poorer recovery in children given amoxicillin at 4 weeks (OR 0.22, 95% CI 0.17–0.28), but similar rate of recovery at 12 weeks (OR 0.90, 95% CI 0.65–1.25)
Dubray C (2008) [414]	Compared intramuscular ceftriaxone for 2 days with oral amoxicillin 5 days in children aged 6-59 months with severe acute malnutrition[a]	• No significant differences in mortality and weight gain between oral amoxicillin and intramuscular ceftriaxone

RR: risk ratio; CI: confidence intervals.

[a]Randomized controlled trial

[b]Undiagnosed HIV was a potential selection bias, as was failure to include children with oedema or recurrent malnutrition.

Additional evidence was obtained from studies evaluating pharmacokinetic data.[412, 418-420] The findings available do not permit firm conclusions to be drawn on the magnitude of the association between bioavailability of antibiotics and nutritional status. In malnourished children, several medicines do not seem to have reduced protein binding; however, clearance is lower for medicines metabolized in the liver, which is of potential concern because of toxicity. A pharmacokinetic study of gentamicin reported that an intravenous dose of 7.5-15 mg/kg once daily in children with severe acute malnutrition and normal renal function is likely to reach high enough serum levels for clinical effect to occur (i.e. the minimum inhibitory concentration for common infecting organisms), with a low risk of nephrotoxicity.[418] Clearance appears largely unchanged for medicines metabolized in the kidneys.[419] A pharmacokinetic study of ciprofloxacin suggested absorption was unaffected by the simultaneous administration of feeds.[420] Pharmacokinetic studies do not suggest doses, and intervals of oral penicillins and parenteral penicillins and gentamicin should be modified in children with severe acute malnutrition; the same doses used for adequately nourished children should be administered unless severe diarrhoea, renal failure or shock are present.

Summary of guidelines: The most recent (2013) WHO recommendations for treatment of severe acute malnutrition [421] and four other guidance documents on this infection were evaluated, with score ranging from 22.3% to 80.3% [422-424] [49]. Table 71 gives a summary of recommendations of the guidelines.

Table 71. Severe acute malnutrition in children: summary of recommendations of guidelines

Guideline (year)	Severe acute malnutrition in children: type	Recommendation
Williams PCM (2018) [49] systematic review of guidelines	Complicated severe acute malnutrition	• Inconsistent recommendations on first-line treatment which include ampicillin, amoxicillin, or gentamicin. Alternative treatments include third-generation cephalosporins, ciprofloxacin, amoxicillin–clavulanic acid, metronidazole, and amikacin. Dosages also differ, for example for gentamicin, although beta-lactam dosages are consistent throughout
World Health Organization (2013) [421]	Severe acute malnutrition in children: uncomplicated and complicated	• Empirical oral amoxicillin, if no complications. Parenteral benzylpenicillin and gentamicin, if complications
Action against Hunger (2011) [422], Médecins sans Frontières (2016) [423], and National Interim Guidelines, Cambodia (2011) [424][a]	Uncomplicated severe acute malnutrition	• Amoxicillin: dosages vary (from 50 mg/kg a day to 100 mg/kg a day) as does the duration of therapy (5 to 7 days)

[a]These were considered relevant information documents although they cannot be considered proper clinical practice guidelines.

Working Group considerations: Based on the recent review of guidelines,[49] the Group found little new evidence to warrant a change in WHO treatment guidance.

Expert Committee recommendations: The selected antibiotics matched the treatment/antibiotics proposed by the Working Group (Table 72).

Table 72. Recommendations of the Expert Committee for antibiotics to treat severe acute malnutrition in children

Severe acute malnutrition in children[a]	
First choice	**Second choice**
Uncomplicated severe acute malnutrition	
Amoxicillin (A)	
Complicated severe acute malnutrition	
Amoxicillin (A)	
Ampicillin (A)	
Benzylpenicillin (A)	
Gentamicin (A)	

A: Access, W: Watch

[a]Recommendations aligned with the 2017 WHO guideline for antibiotic use for severe acute malnutrition in children as proposed by the Working Group based on the recent review of guidelines.[49]

Dysentery in children (shigellosis)

Summary of systematic reviews: Nine studies met our inclusion criteria, of which six were systematic reviews and three primary studies with different designs. Four papers were classified as high-quality evidence [372, 425-427] three as moderate-quality [428-430] and two as low-quality evidence.[61, 431] Table 73 gives a summary of the findings of the systematic reviews and primary studies included.

Table 73. Dysentery (shigellosis) in children: summary of the findings of systematic reviews

First author (year)	Aim of the study	Findings
Thompson CN (2016) [431]	Assessed clinical outcomes and resistance of Shigella in children treated with fluoroquinolones in Vietnam[a]	• Shigella flexneri patients treated with gatifloxacin had longer fever clearance time than those treated with ciprofloxacin
Gu (2015) [427]	Assessed resistance of Shigella to third generation cephalosporins worldwide from 1998 to 2012	• Resistance rates to ceftriaxone were 2·5% (95% CI 1.9–3.2) in Asia-Africa versus 0·4% (95% CI 0.2–0.6) in Europe-America • After 2007, in Asia- Africa resistance rates reached 14·2% (95% CI 3·9–29·4)
Das JK (2013) [372]	Assessed effectiveness of antibiotics for treatment of cholera, shigellosis and cryptosporidiosis in children < 16 years	• Current recommendations of the WHO for the treatment of shigellosis (with either ciprofloxacin, pivmecillinam, or ceftriaxone) reduced clinical failure rates by 82% (95% CI 67%–99%)[b]
Gu (2013) [426]	Assessed resistance of Shigella to aminoglycoside worldwide from 1999 to 2010	• Resistance rates to gentamicin, kanamycin and amikacin were 10.81% (95% CI 8.34–13.52), 19.63% (95% CI 11.85–28.80) and 8.90% (95% CI 6.00–12.34%) versus 0.68 (95% CI 0.39–1.05), 0.60% (95% CI 0.37–0.88) and 0.16% (95% CI 0.03–0.40) • Lower rates were observed for studies from Europe-America compared to studies from Asia-Africa
Gu B (2012) [425]	Assessed resistance of Shigella to quinolone in	• Resistance rates to nalidixic acid and ciprofloxacin were 33.6% (95% CI 21.8–46.6) and 5.0% (95%

	Europe–America and Asia–Africa from 1998 to 2009	CI 2.8–7.8) in Asia-Africa versus 3.2% (95% CI 1.2–6.2) and 0.3% (95% CI 0.1–0.6) in Europe-America • Resistance to nalidixic acid and ciprofloxacin in Asia–Africa progressively increased each year • Resistance rates to quinolones were greater in children than in adults
Vinh H (2011) [430]	Compared gatifloxacin with ciprofloxacin for uncomplicated shigellosis[c]	• No difference in treatment failure between gatifloxacin and ciprofloxacin (ARR 1.00, 95% CI -4.7–6.7) • No difference in fever clearance time, diarrhea clearance time, or failure on follow up
Christopher PR (2010) [61]	Compared different antibiotics for the treatment of dysentery caused by *Shigella* spp.	• Where 90% of participants had confirmed *Shigella* spp. infection, fewer patients had still diarrhoea on follow-up with beta-lactams than fluoroquinolones (RR 4.68, 95% CI 1.74–12.59)
Von Seidlen (2006) [429]	Assessed resistance of Shigella to ampicillin, cotrimoxazole, nalidixic acid and ciprofloxacin[d]	• A high percentage of Shigella strains were resistant to ampicillin and cotrimoxazole, while resistance to nalidixic acid was variable and resistance to ciprofloxacin was more limited

CI: confidence intervals.

[a]Secondary data analysis from a randomized clinical trial.

[b]Another review also concluded that the current antimicrobials recommended by WHO were clinically and microbiologically effective [428].

[c]Randomized controlled trial.

[d]Population-based surveillance study.

Summary of guidelines: Four evidence-based international guidelines were reviewed; Infectious Diseases Society of America, American Academy of Pediatrics, Therapeutic Guidelines (Australia) and BMJ Clinical Evidence.[68, 379, 432, 433] Table 74 gives a summary of recommendations of the guidelines.

Table 74. Dysentery (shigellosis) in children: summary of recommendations of guidelines

Guideline (year)	Dysentery (shigellosis) in children: type	Recommendation
Therapeutic Guidelines (Australia) (2018) [432], BMJ Clinical Evidence (2016) [433], American Academy of Pediatrics (2015) [379] and Infectious Diseases Society of America (2001) [68]	Dysentery	• Fluoroquinolones as first-line therapy, although recommended dosage of ciprofloxacin varied (from 12.5 mg/kg to 20 mg/kg)

Working Group considerations: Overall, the available evidence does not seem to support a major change from the 2005 WHO guidelines [434]. These guidelines recommend the fluoroquinolone ciprofloxacin as the first-line antibiotic for shigellosis in children, and beta-lactams (pivmecillinam) and cephalosporins (parenteral ceftriaxone) as second-line antibiotics when local strains are known to be resistant to ciprofloxacin. Despite ciprofloxacin being associated with potentially relevant adverse events in children (e.g. arthropathy), the Working Group considered that shigellosis is one of the few indications where this antibiotic is highly effective and appropriately used in this age group.

The Working Group excluded pivmecillinam from the list of recommended medicines because of its cost, complicated dosing and limited availability. As alternative oral choices, the Working Group recommended azithromycin and cefixime, which have been shown to be effective against shigellosis in adult and paediatric patients.[435-437] Both were considered appropriate, especially in regions where the rate of non-susceptibility to ciprofloxacin is known to be high, although there was also a concern about an increase in antimicrobial resistance with the use of these broad-spectrum antibiotics. WHO guidelines currently give 15 mg/kg of ciprofloxacin as the recommended dosage and there is no compelling evidence to support changing this dose.

Expert Committee recommendations: The antibiotics selected by the Committee matched the antibiotics proposed by the Working Groups (Table 75). Given widespread resistance, sulfamethoxazole–trimethoprim was recommended only in communities where strains are known to be susceptible, and risk of therapy failure is low.

Table 75. Recommendations of the Expert Committee for antibiotics to treat dysentery (shigellosis) in children

Dysentry (shigellosis) in children[a]	
First choice	**Second choice**
Invasive bacterial diarrhoea/dysentery	
Ciprofloxacin (W)	Azithromycin (W)
	Cefixime (W)
	Ceftriaxone (W)
	Sulfamethoxazole–trimethoprim (A)

A: Access, W: Watch

[a]Recommendations are aligned with the 2005 WHO guideline for antibiotic use in dysentery in children, as proposed by the Working Group.[434]

Discussion

Providing sustainable access to safe and effective antibiotics is a prerequisite for limiting the global morbidity and mortality associated with common infectious diseases across all ages, a risk particularly high for dysentery or pneumonia in children.[438] While critically low thirty years ago in some parts of the world, overall antibiotic use in many low- and middle-income countries has increased to levels comparable to those observed in high-income countries.[439] Today's global abundance of antibiotics is, however, not without contradictions. Many essential antibiotics, including key Access antibiotics such as amoxicillin, are unavailable in a considerable proportion of public health-care facilities in low-income countries.[440] However, the problem of medicine shortages is not limited to low-income countries: recent shortages of paediatric formulations of amoxicillin have been signalled in several high-income countries. These shortages are often explained by both supply (e.g. manufacturing issues or logistics of distribution) and demand side issues. [441] Additionally, and often for different reasons (costs), Reserve antibiotics for drug-resistant bacterial infections are also unavailable in many settings with more limited financial resources. [442] Irrespective of the AWaRe category they are in, there is a clear need for strong global initiatives to improve the availability of antibiotics worldwide.[443] Strengthening fragile supply chains around AWaRe can improve access to essential medicines and contribute to better health outcomes. The selection of first and second choice antibiotics on the WHO EML and AWaRe categories have been designed to emphasize universal access to essential quality assured

antibiotics across all three AWaRe categories. Increased access to antibiotics has however been accompanied by increased inappropriate use, contributing to the global problem of antimicrobial resistance.[444]

The comprehensive review of the antibiotic section of the EML is a strategy to help assure access to safe and effective antibiotics for those who need them while at the same time minimizing their inappropriate use to tackle the emergence and spread of antimicrobial resistance. To reach this aim two complementary approaches were followed. The first was an evaluation of the evidence to support specific antibiotics for the empiric treatment of common mild and severe clinical infections. The second was the development of the AWaRe framework for classification of the antibiotics included in the EML into three categories (Access, Watch and Reserve) based on the need for access, their potential to contribute to resistance, and the need to preserve their use as a last resort for multidrug-resistant infections.

The systematic review of evidence for optimal empiric treatment highlighted important gaps such as data to inform the balance between benefits and harms, or data on the impact on AMR. Unfortunately, the evidence is heavily skewed toward high-income countries, with little research conducted in LMICs.[445] International clinical practice guidelines, which incorporate expert opinion, also informed the selection process. Guideline prescribing recommendations varied in quality and often recommended a multitude of different antibiotics for the same infections.[446] Using a parsimonious approach by prioritizing antibiotics that could be used for multiple infections limited the number of different options. This should facilitate procurement and access (by limiting the number of essential antibiotics that should be available for the most common infections) and also clinical decision-making (by limiting the number of alternative options for each infection which can be confusing for prescribers). This approach differs from that of guideline panels that

list many alternatives for the same infections and may explain why EML antibiotic recommendations do not always align with those of infectious disease or other society practice guidelines.[447] Such an approach provides an opportunity to reinvigorate local antibiotic guidance aligning it to global and national targets (e.g. WHO endorsed a target that, by 2023, 60% of all antibiotics consumed on a national level must come from the Access group - the group of antibiotics at lowest risk of resistance).

A meta-analysis of 349 studies that assessed the impact of antibiotic exposure to antibiotics from each AWaRe category on risk of colonization or infection with multidrug-resistant organisms supports the AWaRe framework which classifies antibiotics according to their risk of resistance.[448] When compared to Access, the use of Watch antibiotics was associated with a doubling risk of colonization with a multidrug-resistant organism. While there was variation in the magnitude of the association, the results clearly document that exposure to any antibiotic is associated with an increased risk of colonization or infection with any multidrug-resistant organism. This highlights the need to avoid unnecessary antibiotic use and provides evidence that this risk is higher with the use of Watch and Reserve than with Access antibiotics. It is important to note that the AWaRe framework is dynamic and adapts based on the experience with its use in different settings. For instance, while AWaRe was initially only applied to antibiotics on the EML, later it has been expanded to include the majority of marketed antibiotics. Furthermore, discussions are ongoing to refine the definitions of the different categories.

Limitations

Despite the efforts to conduct a very comprehensive review of the published evidence to inform antibiotic decisions for the included infections, we acknowledge methodological limitations in our

approach. Only studies published in English were searched. Feasibility and resource constraints (time and funding) were the main reasons: all evidence had to be first presented to the Working Group and then at the Expert Committee meeting that takes place every two years for the update of the EML, giving only few months to finalize the evidence review. Another limitation is that for the first (and largest) review of the evidence (carried out in 2016 for the 2017 EML update) a timeframe of 20 years (1996 to 2016) was chosen. This timeline is arbitrary. We might have missed important evidence originated before 1996 or we might have diluted "new" evidence generated over the last 5 years with "old" evidence (e.g. guidelines published in the late '90s or early 2000s'). We believe that the choice of limiting the search to a defined timeframe was justified both for feasibility reasons and because we do not know what the exact "survival of truth" of medical conclusions is (and by which factors is affected).[449, 450] Out choice – a time window of 20 years – minimizes the risk of selection bias, as we were almost invariably able to consider multiple sources as a base for our recommendations. Where newer evidence superseded older evidence, because for instance of changes in the epidemiology of antibiotic-resistant pathogens, both the Working Group and the Expert Committee gave more value to newer evidence.

While several recommendations presented are based on evidence that may be considered "old", we are not aware of a situation where key recommendations would need to be changed or adjusted based on newer evidence. Nevertheless, we clearly acknowledge that this possibility reflects the lack of "new" high-quality clinical studies on older antibiotics and that the evolving epidemiology is an issue that needs to be considered.

How to keep the tool updated

The WHO EMLs, AWaRe and the AWaRe antibiotic book are not static. They are intended as tools that adapt to the changing needs of countries, changes in the epidemiology of diseases and availability of new evidence. The AWaRe framework is still in its early stages and may need adjustments to optimize its usefulness for global antibiotic stewardship activities. WHO is committed to ensure that these tools continue to provide trustworthy and evidence-based recommendations on ensuring access to and appropriate use of antibiotics.

The AWaRe antibiotic book and implications for antimicrobial stewardship

By providing a standardized approach, the AWaRe framework allows for a coordinated stewardship approach worldwide for antibiotics. As comprehensive antibiotic guidance is a crucial component of any antimicrobial resistance stewardship programme, WHO developed the AWaRe antibiotic book which incorporates information from the EMLs and other relevant WHO guidelines to guide the optimal management of over 30 infections in both primary care and healthcare facility settings.[451] The AWaRe book was produced for ease of implementation in LMICs and it is available in multiple formats (downloadable print version, summary infographics targeting infections of children and adults, and an AWaRe book smartphone application), to allow for ease of dissemination and increase in uptake. [54, 56] The AWaRe book is intended to complement the WHO practical toolkit developed in 2019 to provide practical guidance on how to start and implement an antimicrobial stewardship programme in LMIC health-care facilities.[452] It is encouraging that several countries (e.g. Indonesia, Italy, Jordan, Malaysia, Mexico, UK) already have adopted the AWaRe framework and some have translated the AWaRe antibiotic book in local languages (Indonesia, Italy), endorsing responsible and appropriate use of antimicrobials.

Implications of AWaRe for monitoring and surveillance of antibiotic use

Targeting areas where stewardship is needed with the aim to meet global and national targets is an important public health priority. To achieve this, systematic monitoring of antibiotic use and surveillance of key indicators are critical. AWaRe provides a pragmatic way to monitor patterns of antibiotic use, particularly with respect to Watch antibiotics. Surveillance should include trends in the development of resistance to selected antibiotics and proportions of patients without access to essential antibiotics. To facilitate comparisons, WHO has developed a standardized methodology for global surveillance where antibiotic consumption is regularly reported.[453] At the end of 2021, only 25% of countries were actively providing information on annual antibiotic consumption data to GLASS, illustrating the gap between the request to assess antibiotic consumption and actual uptake.[366] There is however reason for optimism given that AWaRe has been successfully used for comparing patterns of antibiotic consumption grouped by the AWaRe categorization.[440, 454-458] Furthermore, countries have begun to use the AWaRe classification to estimate their relative use of narrow-spectrum and broad-spectrum antibiotics, as well as to complement their existing antibiotic stewardship efforts.[459, 460]

It should be noted that national lists of essential medicines include, on average, only 66% of the antibiotics from the EML. It follows that many LMICs do not include antibiotics such as carbapenems (Watch and Reserve), glycopeptides (Watch), and polymyxins (Reserve).[445] This raises concern about access. Despite the fact that these antibiotics should be reserved for only a very few selected patients and settings, they nonetheless should be accessible when needed.

Implications of AWaRe for the development and management of antibiotics for resistant infections

Even though the number of antibiotic-resistant pathogens keeps rising, only a limited number of new antibiotics (mostly from already existing classes) are in active development.[461] The 2015 Global Action Plan on Antimicrobial Resistance specifies the urgent need to increase investment in new medicines, diagnostic tools and vaccines as a strategic objective. The commitment to address this problem was taken at the highest levels in recent years (G7, G20, UN General Assembly and World Health Assembly). WHO publishes a biennial update of an analysis that identifies which antibacterials are in clinical development for priority pathogens and highlights current gaps for global health needs. [462, 463] In addition, WHO has drawn up a list of priority pathogens for which antibiotic research and development should be prioritized.[464]

Alternative and complementary models to tackle AMR

AWaRe is one of a number of policies developed to mitigate AMR worldwide. The UN Interagency Coordination Group on AMR proposed a structured roadmap centered on the One Health approach to curb AMR at the interface between humans, animals and the environment, which AWaRe complies with. [465-467] Antibiotics used in animals that are critical for human medicine have been classified by WHO, the Food and Agriculture Organization of the United Nations (FAO) and the World Organisation for Animal Health (WOAH) in the List of Critically Important Antimicrobials (CIA) since 2005. The list of antimicrobial agents of veterinary importance is another list of critically important antibiotics.[468] Lists such as AWaRe, CIA, and the list by the WOAH should ideally be integrated. Innovative policies using financial strategies [469, 470] and the use of classification schemes for resistant organisms in order to prioritize threats to public health [471], provide important and complementary models to combat AMR. Despite such efforts, gaps including pragmatic strategies in national action plans for AMR remain. [472]

Conclusions

The WHO EMLs, the AWaRe framework and the WHO AWaRe antibiotic book provide a blueprint on which national and local stakeholders can base their own recommendations and policies on appropriate antibiotic use and antimicrobial stewardship efforts. All three tools can help prescribers and policy makers make informed choices about which antibiotics to prioritize for access and how to assure the appropriate use of these life-saving medicines. We hope these tools are received as a call to action for all stakeholders involved in the control of AMR, facilitating communication across different settings and leading to effective evidence-based interventions to preserve the effectiveness of essential antibiotics for future generations.

Acronyms

AMR: Antimicrobial resistance

AWaRe: Access, Watch and Reserve

CAP: Community-acquired pneumonia

CIA: Critically Important Antimicrobials

EC: Expert Committee

EML: Model Lists of Essential Medicines

EMLc: Model Lists of Essential Medicines for children

FAO: Food and Agriculture Organization of the United Nations

GARDP: Global Antibiotic Research and Development Partnership

GLASS: Global Antimicrobial Resistance and Use Surveillance System

HAP: Hospital-acquired pneumonia

IFPMA: International Federation of Pharmaceutical Manufacturers & Associations

LMIC: Low and middle-income countries

MSF: Médicines Sans Frontières

WHO: World Health Organization

WG: Working Group

WOAH: World Organisation for Animal Health (formerly OIE: Office International des Epizooties)

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Mike Sharland is the chair of the WHO EML Antibiotic Working Group. Graham Cooke served as the co-chair of the EML Expert Committee in the period 2017 – 2021.

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