Consideration of antibacterial medicines as part of the revisions to 2017 WHO Model List of Essential Medicines for adults (EML) and Model List of Essential Medicines for children (EMLc)

Section 6.2 Antibacterials

including Access, Watch and Reserve Lists of antibiotics

This summary has been prepared by the Health Technologies and Pharmaceuticals (HTP) programme at the WHO Regional Office for Europe.

It is intended to communicate changes to the 2017 WHO Model List of Essential Medicines for adults (EML) and Model List of Essential Medicines for children (EMLc) to national counterparts involved in the evidence-based selection of medicines for inclusion in national essential medicines lists (NEMLs), lists of medicines for inclusion in reimbursement programs, and medicine formularies for use in primary, secondary and tertiary care.

This document does not replace the full report of the WHO Expert Committee, 2017 and this summary should be read in conjunction with the full report (WHO Technical Report Series, No. 1006; http://apps.who.int/iris/bitstream/10665/259481/1/9789241210157-eng.pdf?ua=1).

The revised lists of essential medicines (in English) are available as follows:

2017 WHO Model List of Essential Medicines for adults (EML)
http://www.who.int/medicines/publications/essentialmedicines/20th_EML2017_FINAL_amendedAug2017.pdf?ua=1

2017 Model List of Essential Medicines for children (EMLc)
http://www.who.int/medicines/publications/essentialmedicines/6th_EMLc2017_FINAL_amendedAug2017.pdf?ua=1

Summary of changes to Section 6.2 Antibacterials:

Section 6 of the EML covers anti-infective medicines. Disease-specific subsections within Section 6, such as those covering medicines for tuberculosis, HIV, hepatitis and malaria, have been regularly reviewed and updated, taking into consideration relevant WHO treatment guidelines. However, antibacterial medicines in sections 6.2.1 (Beta-lactam medicines) and 6.2.2 (Other antibacterials) had not been similarly reviewed and updated and so were the focus of a comprehensive review in 2017. This review addresses Objective 4 of WHO's Global Action Plan on Antimicrobial Resistance,[1] which is to "optimize the use of antimicrobial medicines in human and animal health". Some antibacterials listed in sections 6.2.1 and 6.2.2 are also listed for the treatment of multidrug-resistant tuberculosis (MDR-TB). The impact of this review on antibacterials for treatment of tuberculosis was carefully considered, given the increasing problem represented by MDR-TB and the need to preserve effective treatments; however, the Committee made no changes to the antibiotics listed in section 6.4.2 Antituberculosis medicines as a result of the review.

After studying the proposals put forward for its consideration, the Expert Committee decided to consider only treatments for common infectious syndromes, excluding rare or hospital-acquired infections. The Committee then identified empirical treatment choices for common, community-acquired infections. These treatment choices are broadly applicable in most countries, using parsimony as a guiding principle. Alternatives for patients allergic to specific products were not considered. For each syndrome the Committee recommended first- and second-choice antibiotics, which are included on the Model Lists with the specific indication(s).

Taking account of the global recognition of the need for effective antimicrobial stewardship, as well as the need to ensure access to necessary antibiotics and appropriate prescribing, the Expert Committee also proposed that these antibiotics could be categorized in three groups – Access, Watch and Reserve. The Committee noted that the evidence base for assigning specific antibiotics and classes to the different groups was weak and the List will need further revision as new evidence accumulates. It was also clearly recognized that the general principles of Access/Watch/Reserve apply to many other antimicrobials, including antituberculosis medicines, antimalarials, antivirals and antifungals. The groups are described and defined in detail below.

- *Access*

  The Access group includes antibiotics that are recommended as empirical first- or second-choice treatment options for common infectious syndromes and are listed in the EML/EMLc with the syndromes for which they are recommended. They should be widely available, at an affordable price, in appropriate formulations and of assured quality. First choices are usually narrow-spectrum agents with positive risk–benefit ratios and low resistance potential; second choices are generally broader-spectrum antibiotics with higher resistance potential or less favourable risk–benefit ratios. Where antibiotics in the Access group are recommended only for a limited

[1] http://apps.who.int/iris/bitstream/10665/193736/1/9789241509763_eng.pdf?ua=1

number of indications and there are also concerns about existing or potential resistance, they may also be listed in the Watch group. Their use should be limited and monitored.

Access group antibiotics	
6.2.1 Beta-lactam medicines	**6.2.2 Other antibacterials**
amoxicillin	amikacin
amoxicillin + clavulanic acid	azithromycin*
ampicillin	chloramphenicol
benzathine benzylpenicillin	ciprofloxacin*
benzylpenicillin	clarithromycin*
cefalexin	clindamycin
cefazolin	doxycycline
cefixime*	gentamicin
cefotaxime*	metronidazole
ceftriaxone*	nitrofurantoin
cloxacillin	spectinomycin (EML only)
phenoxymethylpenicillin	sulfamethoxazole + trimethoprim
piperacillin + tazobactam*	vancomycin (oral)*
procaine benzyl penicillin	*vancomycin (parenteral)**
*meropenem**	

Italics = complementary list.
**Watch group antibiotics included in the EML/EMLc only for specific, limited indications.*

- *Watch*

  The Watch group includes antibiotic *classes* that are considered generally to have higher resistance potential and that are still recommended as first- or second-choice treatments but for a limited number of indications. These medicines should be prioritized as key targets of local and national stewardship programmes and monitoring. The group includes the highest priority agents on *the List of critically important antimicrobials for human medicine* (CIA).[2] The CIA list ranks antimicrobials according to their relative importance in human medicine and can be used in the development of risk management strategies for the use of antimicrobials in food-production animals. Seven pharmacological classes were identified for this group. As noted above, monitoring systems should be in place to ensure that their use is in line with recommended indications.

[2] http://apps.who.int/iris/bitstream/10665/251715/1/9789241511469-eng.pdf?ua=1

Watch group antibiotics
Quinolones and fluoroquinolones e.g. ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin
3rd-generation cephalosporins (with or without beta-lactamase inhibitor) e.g. cefixime, ceftriaxone, cefotaxime, ceftazidime
Macrolides e.g. azithromycin, clarithromycin, erythromycin
Glycopeptides e.g. teicoplanin, vancomycin
Antipseudomonal penicillins with beta-lactamase inhibitor e.g. piperacillin + tazobactam
Carbapenems e.g. meropenem, imipenem + cilastatin
Penems e.g. faropenem

- *Reserve*

  The Reserve group includes antibiotics that should be treated as "last-resort" options, or tailored to highly specific patients and settings, when other alternatives would be inadequate or had already failed (e.g. serious life-threatening infections due to multidrug-resistant bacteria). To preserve their effectiveness, these medicines could be protected and prioritized as key targets of high-intensity national and international stewardship programmes involving monitoring and utilization reporting. Eight antibiotics or antibiotic classes were identified for this group.

Reserve group ("last-resort") antibiotics
aztreonam
4th-generation cephalosporins, e.g. cefepime
5th-generation cephalosporins, e.g. ceftaroline
Polymyxins, e.g. polymyxin B, colistin
fosfomycin (IV)
Oxazolidinones, e.g. linezolid
tigecycline
daptomycin

The Expert Committee recommended the appointment of a standing EML working group to:

- consider reviewing additional clinical syndromes not included in the current update, e.g. medical and surgical prophylaxis, dental infections and acute undifferentiated fever;
- adapt the current clinical synopsis reviews with the aim of producing shorter structured documents;
- coordinate the development for the EML and EMLc of a guidance document on optimal dose and duration of antibiotic treatments to maximize clinical efficacy while minimizing the selection of resistance;
- review the differential effect of antibiotic classes on the selection of resistance;
- relate the work of the EML and EMLc to the future essential in vitro diagnostics list, which should include work on diagnostics related to antimicrobial resistance, as soon as feasible;
- propose improved methods for defining and communicating the key stewardship messages associated with the new categorization and develop more detailed guidance to assist with the implementation of recommendations in national programmes.

Comprehensive review of antibiotics for EML and EMLc

Overview

The comprehensive review of antibiotics in sections 6.2.1 and 6.2.2 of the EML and EMLc by the Expert Committee was informed by three applications.

- A review of antibiotics for 21 priority infectious syndromes in adults and children was conducted by the Department of Health Research Methods, Evidence and Impact, McMaster University, Canada (the McMaster Group):

  community-acquired pneumonia
  pharyngitis
  sinusitis
  otitis media
  hospital-acquired pneumonia
  ventilator-associated pneumonia
  sepsis in children
  urinary tract infection (UTI)
  catheter-associated UTI
  endocarditis
  meningitis
  central-line infections
  complicated intra-abdominal infections
  wound, skin and soft-tissue infections
  surgical site infections
  cellulitis
  acute infectious diarrhoea
  sexually transmitted infections
  exacerbations of chronic obstructive pulmonary disease
  bone and joint infections
  febrile neutropenia

- A review of antibiotics for five specific bacterial infections in children, based on a review of WHO guidelines, was conducted by the WHO Department of Maternal, Newborn, Child and Adolescent Health:

  community-acquired pneumonia
  sepsis
  dysentery
  cholera
  severe acute malnutrition

- A review of antibiotics for specific sexually transmitted infections, based on a review of updated WHO guidelines, was conducted by the WHO Department of Reproductive Health and Research:

  Neisseria gonorrhoeae
  Treponema pallidum (syphilis)
  Chlamydia trachomatis

The Expert Committee appreciated the comprehensive review submitted by the McMaster Group, which formed the basis for the selection of antibiotics for the updated EML and EMLc. It was noted, however, that the methodology – based on published systematic reviews and higher quality guidelines – provided limited information on antibiotic selection in the low- and middle-income country (LMIC) setting.

The Expert Committee included clinical infection syndromes requiring antibiotics that are commonly encountered globally. The main focus was on empirical treatment choices for important (mostly) community-acquired infections that are broadly applicable in most countries. Surgical prophylaxis was not considered as a part of this review because it is the subject of a WHO guideline being developed by the department of Service Delivery and Safety.

The recommendations for the Model Lists are not guidelines, and the recommended empirical treatment choices will be influenced by local/national specificities, such as the availability of antibiotics and local resistance patterns; they may also not apply to a specific patient and should not replace clinical judgment. As a general rule, alternatives for use in case of allergy were not considered by the Expert Committee when discussing first- and second-choice medicines for each syndrome.

Severity of infection was considered when relevant, to differentiate choices and help optimize antibiotic selection.

Guiding principles for antibiotic categorization

The Expert Committee noted that the prescription of any antibiotics must balance the benefits and risks to patients with the impact on public health.

The terms “core” and “targeted”, used in the application from the McMaster Group, were changed, because: “core” already has a definite meaning in the context of the EML/EMLc (core and complementary lists); and, in the context of infectious diseases, “targeted” means based on microbiology results.

Empirical therapy for each clinical infection syndrome includes first- and second-choice antibiotics. First-choice antibiotics are those generally recommended on the basis of available evidence and are usually narrow-spectrum agents with positive benefit–risk ratios and low resistance potential. Second-choice antibiotics are more broad-spectrum agents with a less favourable benefit–risk ratio and higher resistance potential.

First- and second-choice antibiotics were aligned to recent WHO guidelines on sexually transmitted infections (STIs; gonorrhoea, syphilis, chlamydia) and five paediatric syndrome reviews (community-acquired pneumonia, neonatal sepsis, cholera, dysentery and severe acute malnutrition). All first- and second-choice antibiotics are listed in the EML(c), each with the recommended indications.

To improve both access and clinical outcomes, the Expert Committee designated antibiotics that are first- or second-choice antibiotics in at least one syndrome as key "Access" antibiotics (Group 1, Table x), emphasizing their role as the antibiotics that should be widely available, affordable and quality-assured.

- *Access group antibiotics*

  In the lists that follow, antibiotics shown in italics appear on the complementary list; those marked with an asterisk are Watch group antibiotics, included in the EML/EMLc only for specific, limited indications.

6.2.1: Beta-lactam medicines

amoxicillin
amoxicillin + clavulanic acid
ampicillin
benzathine benzylpenicillin
benzylpenicillin
cefalexin
cefazolin
cefixime*
cefotaxime*
ceftriaxone*
clozacillin
phenozymethylpenicillin
piperacillin + tazobactam*
procaine benzylpenicillin
*meropenem**

6.2.2: Other antibacterials

amikacin
azithromycin*
chloramphenicol
ciprofloxacin*
clarithromycin*
clindamycin
doxycycline
gentamicin
metronidazole
nitrofurantoin
spectinomycin (EML only)
sulfamethoxazole + trimethoprim
vancomycin (oral)*
*vancomycin (parenteral)**

For clarity and cross-referencing purposes, the Expert Committee also wished to encourage the general principles of antibiotic stewardship in all sectors, building on and reflecting the important work done in designating the WHO *List of critically important antimicrobials for human medicine* (CIA List) (*1*), which aims at preserving medically important antimicrobials used in food animal production. The intent and purpose of the EML and EMLc include factors other than those considered by the CIA List: while the EML and EMLc take into account bacterial resistance, they also include issues of efficacy and access. The purpose of the CIA List was to assess the impact of resistance as well as the risk of transmission through the food chain. Thus, while there is relevant overlap between the EML Watch group and highest-priority agents on the CIA list (see below), there will also be inevitable differences, including the names of antibiotic groupings.

To assist in the development of tools for antibiotic stewardship at local, national and global levels, the Expert Committee developed two stewardship groups of antibiotics based on their probability of selecting resistance. The larger "Watch" group and a more focused "Reserve" group may be valuable for such activities as local, national and global monitoring of use, development of guidelines and educational activities.

- *Watch group antibiotics*

  The stewardship Watch group includes antibiotic classes that are generally considered to have higher resistance potential and that are still recommended as first- or second-choice treatments but for a limited number of indications. These medicines should be prioritized as key targets of local and national stewardship programmes and monitoring. The group includes the highest-priority agents on the CIA List (*1*) and/or antibiotics that are at relatively high risk of selection of bacterial resistance. The CIA List ranks antimicrobials according to their relative importance in human medicine and can be used in the development of risk management strategies for the use of antimicrobials in food production animals.

  Seven pharmacological classes were identified for this group. As noted above, monitoring systems should be in place to ensure that their use is in line with recommended indications.

  Quinolones and fluoroquinolones: e.g. ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin

  These antibiotics are considered highest-priority critically important antimicrobials on the CIA List and carry a high risk of selection of bacterial resistance (in particular methicillin-resistant *Staphylococcus aureus* (MRSA), extended spectrum beta-lactamases (ESBL), and resistance to fluoroquinolones).

  Ciprofloxacin is listed on the EML/EMLc as a first-choice option for acute invasive bacterial diarrhoea/dysentery, low-risk febrile neutropenia, pyelonephritis and prostatitis (mild to moderate), and as a second-choice option for cholera and complicated intraabdominal infections (mild to moderate).

  3rd-generation cephalosporins (with or without beta-lactamase inhibitor): e.g. cefixime, ceftriaxone, cefotaxime, ceftazidime

  These antibiotics are considered highest-priority critically important antimicrobials on the CIA List and carry a high risk of selection of bacterial resistance (in particular ESBL).

  Ceftriaxone is listed on the EML/EMLc as a first-choice option for acute bacterial meningitis, community-acquired pneumonia (severe), complicated intra-abdominal infections (mild, moderate and severe), hospital-acquired pneumonia, *Neisseria gonorrhoeae*, pyelonephritis and prostatitis (severe), and as a second-choice option for acute invasive bacterial diarrhoea/dysentery, bone and joint infections, pyelonephritis or prostatitis (mild to moderate), and sepsis in neonates and children.

Cefotaxime is listed on the EML/EMLc for the same indications as ceftriaxone with the exceptions of *Neisseria gonorrhoeae* and acute invasive bacterial diarrhoea/dysentery.

Cefixime is listed as a second-choice option for acute invasive bacterial diarrhoea/dysentery and *Neisseria gonorrhoeae*.

Macrolides: e.g. azithromycin, clarithromycin, erythromycin

These antibiotics are considered highest-priority critically important antimicrobials on the CIA List and carry a high risk of selection of bacterial resistance (particularly resistance to macrolides). With its remarkably long half-life, azithromycin carries the highest risk of resistance among the macrolides.

Azithromycin is listed on the EML/EMLc as a first-choice option for trachoma, yaws, *Chlamydia trachomatis*, cholera and *Neisseria gonorrhoeae*, and as a second-choice option for acute invasive bacterial diarrhoea/dysentery and *Neisseria gonorrhoeae*.

Clarithromycin is listed as a first-choice option for *Helicobacter pylori* and community-acquired pneumonia (severe), and as a second-choice option for pharyngitis.

Glycopeptides: e.g. teicoplanin, vancomycin

These antibiotics are considered highest-priority critically important antimicrobials on the CIA List and carry a high risk of selection of bacterial resistance (e.g. vancomycin-resistant enterococci (VRE)).

Vancomycin is listed on the EML/EMLc as a second-choice option for *Clostridium difficile* infections and high-risk febrile neutropenia.

Antipseudomonal penicillins with beta-lactamase inhibitor: e.g. piperacillin + tazobactam

These antibiotics have a broad spectrum of activity and carry a high risk of selection of bacterial resistance.

Piperacillin + tazobactam is listed on the EML/EMLc as a first-choice option for complicated intra-abdominal infections (severe), high-risk febrile neutropenia and hospital-acquired pneumonia.

Carbapenems: e.g. meropenem, imipenem + cilastin

Carbapenems have a broad spectrum of activity and their use should be limited to a small number of specific indications. Overuse of carbapenems has been associated with increasing prevalence of infections due to resistant organisms (e.g. MRSA, VRE).

Meropenem is listed on the EML and EMLc as second-choice treatment for acute bacterial meningitis in neonates, complicated severe intra-abdominal infections and high-risk febrile neutropenia. *Imipenem + cilastatin* is an alternative in some cases.

Penems: e.g. faropenem

No penems are included on the EML or EMLc.

- *Reserve group antibiotics*

The more focused stewardship "Reserve" group includes antibiotics and antibiotic classes on the basis of their "last resort" status (antibiotics or antibiotic classes to be used when other alternatives would be inadequate or have already failed, e.g. in serious life-threatening infections due to multidrug-resistant bacteria)). This group was identified to improve targeted access according to available recommendations and to reduce the risk of development of resistance to these agents. They could be protected and prioritized as key targets of high-intensity national and international stewardship programmes involving monitoring and utilization reporting, to preserve their effectiveness. Eight antibiotics or antibiotic classes were identified for this group:

aztreonam

4th-generation cephalosporins, e.g. cefepime

5th-generation cephalosporins, e.g. ceftaroline

polymyxins, e.g. poymyxin B, colistin

fosfomycin (IV)

oxazolidinones, e.g. linezolid

tigecycline

daptomycin

Other considerations

The Expert Committee noted that there remain many barriers to reducing broad-spectrum antibiotic use. For example, the Committee noted that allergy skin testing of all patients before penicillin use is required in some regions and recommended strongly against this as a routine practice. It is unnecessary and drives the use of broader-spectrum antibiotics such as cephalosporins and macrolides, leading to increased levels of bacterial resistance.

The Expert Committee noted that sustained availability of the key antibiotics in the Access group remains a major concern in countries of all income levels. Regular and prolonged shortages of antibiotics on the Access list are a threat to responsible antibiotic use, forcing clinicians to use broader-spectrum antibiotics that are sometimes less efficacious and more toxic for patients.

The Expert Committee noted that major concerns remain about substandard and counterfeit medicines within the key Access group of antibiotics.

The Expert Committee noted the development of the key principles of access and stewardship:

- Antibiotic stewardship is a strategy aimed at ensuring that antibiotics are used responsibly. Responsible use is a balance between best efficacy for the patient and minimization of the risk of adverse effects, both for the individual patient (classical adverse events, *C. difficile* infections, bacterial resistance) and for the population (bacterial resistance).

- Antibiotic stewardship is a behaviour change strategy and thus a complex and health system-wide intervention. Antibiotic stewardship programmes should use a combination of several interventions, in all settings (primary care, hospitals) and at all levels (local, national, international), adapted to the local context. A single intervention is not enough. These programmes can have a positive impact provided that sufficient resources are made available and are sustainable and that there is strong political and institutional support. However, disseminating recommendations at local or national level is not enough, and a detailed and long-term implementation plan must be rolled out in order to effect change. Long-term monitoring of indicators is critical to assess the impact of the stewardship programme and to adapt it when necessary.

- Antibiotic use is a complex interplay between patients, prescribers and non-prescriber health-care professionals, all influenced by their environment (system organization, culture, regulation). An antibiotic stewardship programme must target the general public, health-care professionals (whether they prescribe or not) and policy-makers. It must try to change behaviour – a notoriously difficult process – by acting at the level of both the individual and the system. The following are examples of the many behavioural interventions that can be used:

  - system change: having antimicrobial stewardship teams as a mandatory requirement in hospitals, or banning over-the-counter sale of antibiotics by law;
  - targeting the general public: awareness campaigns;
  - targeting prescribers: education, audits and feedback, promoting the use of guidelines (merely making guidelines available will not lead to a change in prescribing).

- The Expert Committee encouraged regular monitoring of the availability of the key Access antibiotics of the EML and EMLc. Monitoring systems will also be useful for the Watch group and applied more rigorously for the Reserve group, to capture data on actual versus optimal use.

- The Expert Committee noted the need for further work to develop and expand the key principles of access and stewardship; it recommended the appointment of a standing EML Antibiotics Working Group to:

- consider reviewing additional clinical syndromes not included in the current update, e.g. typhoid fever, medical and surgical prophylaxis, dental infections, acute undifferentiated fever;
- work on the current clinical synopsis reviews, adapting them into shorter structured documents;
- coordinate the development of a guidance document on optimal dose and duration of antibiotic treatments to maximize clinical efficacy while minimizing the selection of resistance;
- review the differential effect of antibiotic classes on the selection of resistance;
- relate the work of the EML and EMLc to the future essential in-vitro diagnostics list, which should include work on diagnostics related to antimicrobial resistance as soon as feasible;
- propose improved methods for defining and communicating the key stewardship messages associated with the new categorization and develop more detailed guidance to assist with the implementation of recommendations in national programmes.
- investigating, or making an inventory of, key older antibiotics that may be considered important to add to the Reserve group.

Reference

1. WHO Advisory Group on Integrated Surveillance of Antimicrogial Resistance (AGISAR). Critically important antimicrobials for human medicine, fourth revision 2013. Geneva: World Health Organization; 2016 (http://apps.who.int/iris/bitstream/10665/251715/1/9789241511469-eng.pdf?ua=1, accessed 21 March 2017).

Community-acquired pneumonia (CAP)

Community-acquired pneumonia (CAP) refers to pneumonia that is acquired in the community rather than within the health-care system. Patients of advanced age or with comorbid conditions or greater severity of illness are more likely to be hospitalized. Although there is consensus that *Streptococcus pneumoniae* is the most common bacterial cause of CAP, the need for so-called "atypical coverage" of pathogens such as *Chlamydia pneumoniae, Mycoplasma* or *Legionella* with antibiotics such as macrolides or fluoroquinolones has been controversial. The emergence of macrolide and fluoroquinolone resistance in the community has created concern, and the need for these medicines in addition to antibiotics with antipneumococcal coverage has been debated.

See TRS pages 69-74 for a summary that considers the CAP review conducted by the McMaster Group, and the review of CAP guidelines for paediatrics conducted by the WHO Department of Maternal, Newborn, Child and Adolescent Health.

Expert Committee recommendations

The Expert Committee endorsed the inclusion of amoxicillin and phenoxymethylpenicillin as first-choice therapy options and of amoxicillin + clavulanic acid or doxycycline as second-choice therapy in mild to moderate CAP.

For severe CAP in adults, the Expert Committee endorsed the inclusion of ceftriaxone or cefotaxime in combination with clarithromycin (EML) as first-choice and amoxicillin + clavulanic acid in combination with clarithromycin as second-choice therapy.

For severe CAP in children, the Expert Committee endorsed the inclusion of amoxicillin + clavulanic acid; ceftriaxone or cefotaxime (EMLc); and gentamicin in combination with benzylpenicillin, ampicillin or amoxicillin (EMLc).

These recommendations are summarised in the following table:

	First choice	*Second choice*
Endorsed existing EML medicines		
Mild to moderate CAP	amoxicillin phenoxymethylpenicillin	amoxicillin + clavulanic acid doxycycline
Severe CAP	ceftriaxone or cefotaxime in combination with clarithromycin	amoxicillin + clavulanic acid in combination with clarithromycin
Severe CAP in children	amoxicillin + clavulanic acid ceftriaxone or cefotaxime gentamicin in combination with benzylpenicillin, ampicillin or amoxicillin	

Pharyngitis

More than 85% of pharyngitis is viral in origin. Pharyngitis is distinct from laryngitis, or inflammation of the larynx, for which there was no evidence for antibiotic effectiveness when objective outcomes were assessed. The major cause of bacterial pharyngitis is Group A *Streptococcus* (GAS). It is notable that penicillin resistance has yet to be demonstrated by these bacteria, although resistance to macrolides has increased. The major reason for treating GAS, other than symptomatic relief, has been to reduce complications such as rheumatic fever and post-streptococcal glomerulonephritis.

See TRS pages 76-78 for a summary that considers the pharyngitis review conducted by the McMaster Group.

Expert Committee recommendations

The Expert Committee noted that, since the vast majority of pharyngitis cases are caused by viruses, routine practice in some countries is not to treat the infection with antibiotics, others use a delayed antibiotic prescription policy, and others rely on diagnostic tests to support an indication for antibiotic treatment. Indeed, antibiotics have limited benefit in streptococcal pharyngitis, unless rheumatic fever is still a problem in a particular setting.

The Committee also noted the absence of indication for routine skin testing for allergy before first treatment with penicillins.

The appropriate first-line treatment option for pharyngitis is watchful waiting, symptom relief and no antibiotic treatment.

For suspected or proved bacterial pharyngitis, the Committee endorsed the use of phenoxymethylpenicillin or amoxicillin as first-choice therapy and clarithromycin (EML) or cefalexin (EML/EMLc) as second-choice therapy.

The Committee recommended the addition of clarithromycin to the EMLc (with erythromycin as an alternative) as second-choice therapy for suspected or proven bacterial pharyngitis in children.

These recommendations are summarised in the following table:

	First choice	*Second choice*
Watchful waiting, symptom relief and no antibiotic treatment should be considered as the first-line treatment option		
Endorsed existing EML medicines	phenoxymethylpenicillin amoxicillin	clarithromycin cephalexin
Addition to EML		clarithromycin (EMLc) with erythromycin as an alternative

Sinusitis

Sinusitis is generally diagnosed and treated in an ambulatory setting and most clinical trials have been conducted in this setting. Patients are typically treated on a clinical basis with no attempt made to obtain cultures for etiological determination. Given that more than 90% of cases of rhinosinusitis are due to viral infections, many of the trials have been conducted to test whether antibiotics offer any benefit compared with placebo.

See TRS pages 79-81 for a summary that considers the sinusitis review conducted by the McMaster Group.

Sinusitis frequently does not require antibiotics, particularly when it is associated with the common cold when antibiotics offer limited benefit. Delayed prescribing is another strategy for reducing the use of antibiotics. Evidence from systematic reviews suggests a higher risk of failure with cephalosporins or macrolides compared with amoxicillin + clavulanic acid.

Given the principle of using narrower-spectrum agents, amoxicillin alone may be effective; either amoxicillin or amoxicillin + clavulanic acid was therefore proposed as the core choice. Ceftriaxone can be used for severe sinusitis. Fluoroquinolones (levofloxacin, moxifloxacin) should be used only if beta-lactams cannot be used.

Expert Committee recommendations

The Expert Committee noted that the appropriate first-line treatment option for sinusitis is watchful waiting, symptom relief and no antibiotic treatment.

The Committee endorsed the inclusion of amoxicillin and amoxicillin + clavulanic acid for suspected bacterial sinusitis as first-choice treatment on the EML and EMLc.

These recommendations are summarised in the following table:

	First choice	*Second choice*
Watchful waiting, symptom relief and no antibiotic treatment should be considered as the first-line treatment option		
Endorsed existing EML medicines	amoxicillin amoxicillin + clavulanic acid	

Otitis media

Acute otitis media is one of the most common infections in children. There has been controversy about the best approach, that is, whether otitis media should include early therapy or watchful waiting. On the one hand, avoidance of antibiotics could reduce resistance, adverse events and cost; on the other, concern has been raised about suppurative complications of otitis media if left untreated.

See TRS pages 82-84 for a summary that considers the review of otitis media conducted by the McMaster Group.

Expert Committee recommendations

The Expert Committee noted that the appropriate first-line treatment option for otitis media is watchful waiting, symptom relief and no antibiotic treatment, unless a child is under 2 years of age with bilateral otitis media.

The Committee endorsed the inclusion of amoxicillin as first-choice therapy and amoxicillin + clavulanic acid as second-choice therapy in suspected bacterial otitis media.

These recommendations are summarised in the following table:

	First choice	*Second choice*
Watchful waiting, symptom relief and no antibiotic treatment should be considered as the first-line treatment option, unless a child is under 2 years of age with bilateral otitis media.		
Endorsed existing EML medicines	amoxicillin	amoxicillin + clavulanic acid

Hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP)

Hospital-acquired pneumonia (HAP) is defined as pneumonia with onset starting more than 48 hours after admission to hospital. Patients are often exposed to different regimens of antibiotics and thus have an increased potential to acquire resistant bacteria, making antibiotic treatment more challenging.

Ventilator-associated pneumonia (VAP) is defined by the development of pneumonia while a patient is on a ventilator. Typically, the risk of infection with multidrug-resistant bacteria is high because of exposure to antimicrobials and the critical care setting. Various regimens have been assessed; a particular area of uncertainty is the need for double antipseudomonal coverage in severely ill patients.

The two syndromes were combined in the application because of the relative lack of data on HAP and because the guidelines consider these together.

See TRS pages 85-88 for a summary that considers the review of HAP and VAP conducted by the McMaster Group.

Expert Committee recommendations for HAP

The Expert Committee reviewed the evidence and limited its recommendation to hospital-acquired pneumonia (HAP). It did not include antibiotics for ventilator-associated pneumonia in this section because the condition is relatively rare and the choice of empirical antibiotic treatment in national guidelines is based on local epidemiology/microbiology.

The Expert Committee endorsed the inclusion on the EML and EMLc of amoxicillin + clavulanic acid, cefotaxime and ceftriaxone for first-choice therapy in hospital-acquired pneumonia.

The Committee recommended the addition of piperacillin + tazobactam to the EML and EMLc for use in hospital-acquired pneumonia as one of the first-choice therapies.

These recommendations for HAP are summarised in the following table:

	First choice	*Second choice*
Endorsed existing EML medicines	amoxicillin + clavulanic acid cefotaxime ceftriaxone	
Addition to EML	piperacillin + tazobactam	

Sepsis in children

Sepsis is a major global cause of morbidity and mortality in children. It is defined as "life-threatening organ dysfunction caused by a dysregulated host response to infection". It can be caused by a wide variety of pathogens, although bacteria are responsible for most cases. The purpose of this review is to focus on empirical therapy for young children (age ≤5 years) presenting with sepsis or septic shock (where profound circulatory, cellular and metabolic abnormalities exist and contribute to a higher risk of mortality).

See TRS pages 89-91 for a summary that considers the review of sepsis conducted by the McMaster Group, and the review of sepsis guidelines for children and neonates conducted by the WHO Department of Maternal, Newborn, Child and Adolescent Health.

The evidence from systematic reviews is extremely limited and essentially makes no contribution to the decision on which antibiotics should be on the EMLc. The guidelines suggest a penicillin (ampicillin, penicillin or IV benzylpenicillin) together with gentamicin to cover *Listeria* and Gram-negative organisms; these antibiotics were proposed as core agents for neonatal sepsis.

Expert Committee recommendations

The Expert Committee endorsed the inclusion on the EMLc of gentamicin, in combination with benzylpenicillin or ampicillin or amoxicillin, as the first-choice treatment for sepsis in neonates and children, and of ceftriaxone or cefotaxime as a second-choice treatment.

The Committee recommended the addition of amikacin in combination with cloxacillin as a second-choice option for use in sepsis in neonates and children.

These recommendations are summarised in the following table:

	First choice	*Second choice*
Endorsed existing EML medicines	gentamicin in combination with benzylpenicillin, ampicillin or amoxicillin	ceftriaxone or cefotaxime amikacin with cloxacillin
Addition to EML	n/a	amikacin

Urinary tract infections

Urinary tract infections (UTI) in the outpatient setting are a common reason for young women in particular to seek medical attention. Randomized controlled trials (RCTs) have addressed the type and duration of antibiotic treatments in this and other populations. Use of antibiotics for asymptomatic bacteriuria can drive antibiotic resistance and may also increase the risk for subsequent symptomatic UTI. While it is accepted practice that asymptomatic bacteriuria should be treated in pregnant women and in men about to undergo urological procedures, the benefits of therapy in other groups have been questioned and addressed in RCTs.

See TRS pages 92-95 for a summary that considers the review of urinary tract infections conducted by the McMaster Group.

Expert Committee recommendations

First-choice therapies on the EML and EMLc list:

- *lower UTI:* amoxicillin or amoxicillin + clavulanic acid or sulfamethoxazole + trimethoprim or nitrofurantoin
- *pyelonephritis or prostatitis, mild to moderate:* ciprofloxacin
- *pyelonephritis or prostatitis, severe:* ceftriaxone or cefotaxime.

Second-choice therapies on the EML and EMLc list:

- *pyelonephritis or prostatitis, mild to moderate:* ceftriaxone or cefotaxime.

The Committee recommended the addition of amikacin (in combination with ceftriaxone or cefotaxime) for severe pyelonephritis or prostatitis to the EML and EMLc for UTI therapy.

These recommendations are summarised in the following table:

	First choice	*Second choice*
Endorsed existing EML medicines		
Lower UTI	amoxicillin amoxicillin + clavulanic acid sulfamethoxazole + trimethoprim nitrofurantoin	
Pyelonephritis and prostatitis: mild to moderate	ciprofloxacin	ceftriaxone ceftriaxone
Pyelonephritis and prostatitis: severe	ceftriaxone or cefotaxime	
Addition to EML	amikacin (severe)	n/a

Meningitis

Acute bacterial meningitis is a medical emergency requiring prompt administration of antibiotics that penetrate well into inflamed meninges. Because of the severity of this infection, evidence from randomized controlled trials (RCTs) is limited; recommendations for antimicrobials are driven largely by susceptibility patterns of the most common pathogens together with experimental work in animal models.

See TRS pages 96-98 for a summary that considers the review of meningitis conducted by the McMaster Group.

Expert Committee recommendations

The Expert Committee endorsed the inclusion on the EML and EMLc of ceftriaxone or cefotaxime as first-choice option for use in suspected acute bacterial meningitis and of chloramphenicol, benzylpenicillin, ampicillin or amoxicillin as second-choice therapy, recognizing that the last three beta-lactams may be added as first-choice options in some countries for suspected acute bacterial meningitis in particular when *Listeria* is suspected.

The Committee recommended the addition of meropenem to the EMLc for use in neonates as a second-choice option to treat suspected acute bacterial meningitis where resistant Gram-negative organisms are the common causative agents.

These recommendations are summarised in the following table:

	First choice	*Second choice*
Endorsed existing EML medicines	ceftriaxone or cefotaxime	ampicillin or amoxicillin chloramphenicol benzylpenicillin
Addition to EML		meropenem (EMLc for neonatal meningitis)

Complicated intra-abdominal infections

Complicated intra-abdominal infections (cIAI) extend beyond the organ of origin into the peritoneal space and are associated with either peritonitis or abscess formation. They represent a diverse group of infections for which there are a broad spectrum of causative agents, although streptococci, Enterobacteriaceae and anaerobes predominate.

The application did not consider primary peritonitis from haematogenous dissemination (e.g. spontaneous bacterial peritonitis in the absence of an underlying infection of an organ), usually in the setting of an immunocompromised state, or dialysis-related infections.

See TRS pages 99-104 for a summary that considers the review of complicated intra-abdominal infections conducted by the McMaster Group.

Since the overview of systematic reviews yielded inconclusive findings, the proposals for the EML are based on clinical practice guidelines.

Expert Committee recommendations

The Expert Committee endorsed the inclusion of the following medicines on the EML and EMLc for complicated intra-abdominal infections (cIAI)

- *mild to moderate:* amoxicillin + clavulanic acid, or ceftriaxone or cefotaxime in combination with metronidazole as first-choice therapy, and ciprofloxacin in combination with metronidazole as second-choice therapy
- *severe:* ceftriaxone or cefotaxime in combination with metronidazole as first-choice therapy.

The Expert Committee recommended the addition of piperacillin + tazobactam as first-choice therapy and meropenem as second-choice therapy for severe complicated intra-abdominal infections.

These recommendations are summarised in the following table:

	First choice	*Second choice*
Endorsed existing EML medicines		
Mild to moderate	amoxicillin + clavulanic acid or ceftriaxone or cefotaxime in combination with metronidazole	ciprofloxacin in combination with metronidazole
Severe	ceftriaxone or cefotaxime in combination with metronidazole	
Addition to EML ***Severe***	piperacillin + tazobactam	meropenem

Skin and soft-tissue infections (including cellulitis and surgical site infections)

Uncomplicated skin and soft-tissue infections refer to infections in which the host is healthy, including cellulitis, erysipelas, human and animal bites, and carbuncles. Complicated skin and soft-tissue infections occur when there may be vascular insufficiency, diabetes, pre-existing non-healing wounds. These infections are frequently polymicrobial and may be have a greater chance for being caused by organisms that are multi-resistant to antibiotics. Surgical site infections are included here as a subgroup of skin and soft-tissue infections.

See TRS pages 105-111 for a summary that considers the review of skin and soft-tissue infections conducted by the McMaster Group.

For mild skin and soft-tissue infections, the following antibiotics were excluded: dicloxacillin (as cloxacillin was listed), cefuroxime, clindamycin, doxycycline, levofloxacin, ciprofloxacin, moxifloxacin and trimethoprim + sulfamethoxazole.

The antibiotics proposed in the application for severe skin and soft-tissue infections were excluded, since the Committee focused on the empirical treatment of common mild to moderate community-acquired infections.

Expert Committee recommendations

The Expert Committee endorsed the inclusion on the EML and EMLc of amoxicillin + clavulanic acid and cloxacillin (with a square box listing) as first-choice therapy and cefalexin as second-choice therapy for use in skin and soft-tissue infections.

These recommendations are summarised in the following table:

	First choice	*Second choice*
Endorsed existing EML medicines	amoxicillin + clavulanic acid cloxacillin *(square box)*	cefalexin

Acute infectious diarrhoea

Diarrhoea is an alteration in bowel movement characterized by an increase in the water content, volume and/or frequency of stools. Acute infectious diarrhoea can result from multiple causes depending on the setting and can include traveller's diarrhoea, for which therapy is typically empirical; it can also be cause-specific, e.g. cholera in epidemic settings. In this section, the focus is on empirical treatment in keeping with the other sections in which the major syndrome treated empirically is traveller's diarrhoea. However, because of the burden of infectious diarrhoea in low- and middle-income countries, the systematic review evidence for cause-specific diarrhoea is also assessed.

The potential benefits of antibiotics need to be weighed against increasing resistance rates, the risk of superinfection, and the harm caused by Shiga-toxin-producing organisms, which can be triggered by antibiotic exposure. Empirical treatment is usually considered in the case of febrile traveller's diarrhoea. In non-travel-related diarrhoea, empirical treatment should be considered only in the case of severe/invasive disease.

See TRS pages 112-117 for a summary that considers the review of acute infectious diarrhoea conducted by the McMaster group and the review of the cholera and dysentery (shigellosis) guidelines for paediatrics conducted by the WHO Department of Maternal, Newborn, Child and Adolescent Health.

Expert Committee recommendations

The Expert Committee noted that, in most circumstances of non-bloody and non-febrile diarrhoea, watchful waiting, symptom relief and no antibiotic treatment is the appropriate first-line treatment option. The Expert Committee endorsed the inclusion of the following medicines:

- Invasive bacterial diarrhoea/dysentery: ciprofloxacin as first-choice therapy and ceftriaxone or cefixime or azithromycin or sulfamethoxazole + trimethoprim as second-choice therapy (EML and EMLc)
- Cholera: azithromycin (EMLc) or doxycycline (EML) as first-choice therapy and ciprofloxacin or doxycycline (EMLc) as a second choice; doxycycline should be used only in severe/life-threatening cases
- *C. difficile* infection: metronidazole as first-choice therapy. The Expert Committee recommended the addition of vancomycin (oral) as second-choice therapy for *C. difficile* infection.

These recommendations are summarised in the following table:

	First choice	*Second choice*
Endorsed existing EML medicines		
Invasive bacterial diarrhoea/dysentery	ciprofloxacin	ceftriaxone cefixime azithromycin sulfamethoxazole + trimethoprim
Cholera	azithromycin (EMLc) doxycycline (EML)	ciprofloxacin doxycycline (EMLc)
C. difficile	metronidazole	
Addition to EML		vancomycin (oral) *C. difficile*

Sexually transmitted infections

Although there is a range of causative agents of urethritis, or inflammation of the urethra, the focus here is sexually transmitted infections (STIs). The McMaster application targeted comparative empirical therapy or comparative antimicrobials for *Gonococcus* and *Chlamydia trachomatis*, the two most common pathogens in infectious urethritis; syphilis was also included. The application from the WHO Department of Reproductive Health and Research was based on updated WHO treatment guidelines for gonorrhoea, syphilis and chlamydia.

STIs represent a major burden of disease worldwide and have significant negative effects on well-being. Gonorrhoea, syphilis and chlamydia often go undiagnosed and, if untreated, can result in serious complications such as pelvic inflammatory disease, infertility, ectopic pregnancy and miscarriage. Risk of infection with HIV is also increased in patients infected with gonorrhoea, syphilis or chlamydia.

Expert Committee recommendations

The Expert Committee endorsed the inclusion of the following medicines for use in sexually transmitted infections **(see TRS pages 118-125)**:

- *Neisseria gonorrhoeae*: first-choice therapy is ceftriaxone in combination with azithromycin and second-choice therapy is cefixime in combination with azithromycin, or gentamicin or spectinomycin.
- *Chlamydia trachomatis*: first-choice therapy is azithromycin or doxycycline.
- *Trichomonas vaginalis*: first-choice therapy is metronidazole.
- Syphilis: first-choice therapy is benzathine benzylpenicillin or procaine benzylpenicillin (EMLc) or benzylpenicillin, and second-choice therapy is procaine benzylpenicillin (EML).

The Expert Committee recommended the addition of erythromycin eye ointment to Section 21.1 of the EMLc for use in *Chlamydia trachomatis* and *Neisseria gonorrhoeae* as first-choice therapy in neonates for both infections. These recommendations are summarised in the following table:

	First choice	*Second choice*
Endorsed existing EML medicines		
Neisseria gonorrhoeae	ceftriaxone in combination with azithromycin (EML)	cefixime in combination with azithromycin (EML) gentamicin (EML) spectinomycin (EML)
Chlamydia trachomatis	azithromycin (EML) doxycycline (EML)	
Trichomonas vaginalis	metronidazole (EML)	
Syphilis	benzathine benzylpenicillin (EML) procaine benzylpenicillin (EMLc) benzylpenicillin	procaine benzylpenicillin (EML)
Addition to EML ***Severe***	erythromycin 0.5% eye ointment (EMLc for *Chlamydia trachomatis*	

and Neisseria gonorrhoeae)

Exacerbations of chronic obstructive pulmonary disease

Exacerbations of chronic obstructive pulmonary disease (COPD) are an important health-care burden. Although treatment can involve bronchodilators and anti-inflammatory agents, including steroids, antimicrobials are frequently used on the basis that a bacterial infection is suspected of acting as a trigger to the episode. However, antibiotics are indicated in only a minority of patients presenting with exacerbated COPD.

See TRS pages 126-129 for a summary that considers the review of COPD conducted by the McMaster Group.

COPD is a disease of the adult patient population and it was therefore not surprising that no systematic review data or guidelines were found for management in the paediatric population. No treatment recommendations were made for paediatric patients.

Expert Committee recommendations

The Expert Committee noted that antibiotics are not required in all patients presenting with COPD exacerbations.

The Committee endorsed the inclusion on the EML of amoxicillin and amoxicillin + clavulanic acid as first-choice therapy and of cefalexin and doxycycline as second-choice therapy for use in suspected bacterial exacerbations of COPD.

These recommendations are summarised in the following table:

	First choice	*Second choice*
Antibiotics are not needed in all patients presenting with exacerbations of COPD		
Endorsed existing EML medicines	amoxicillin amoxicillin + clavulanic acid	cefalexin doxycycline

Bone and joint infections

Bone and joint infections include infections of the native bone or joint, i.e. osteomyelitis and septic arthritis, as well as prosthetic joint infections (which are increasing in incidence as a result of the ever-greater number of joint replacements). Treatment is rarely empirical and targeted treatment based on microbiology is emphasized for this type of infection.

See TRS pages 130-133 for a summary that considers the review of bone and joint infections conducted by the McMaster Group.

Expert Committee recommendations

The Expert Committee endorsed the inclusion of cloxacillin (with a square box) as first-choice therapy for empirical treatment of bone and joint infections and of ceftriaxone, cefotaxime, cefazolin, clindamycin, and amoxicillin + clavulanic acid as second-choice therapy. All inclusions apply to both the EML and EMLc.

The Committee recommended inclusion of cloxacillin (with a square box), and considered that any IV antistaphylococcal penicillin would be appropriate. For oral administration, cloxacillin, dicloxacillin and flucloxacillin are preferred because of their better bioavailability.

These recommendations are summarised in the following table:

	First choice	*Second choice*
Endorsed existing EML medicines	cloxacillin (square box)	ceftriaxone or cefotaxime cefazolin clindamycin amoxicillin + clavulanic acid

Febrile neutropenia

Febrile neutropenia is a severe infectious syndrome needing empirical treatment in immunocompromised patients.

See TRS pages 134-138 for a summary that considers the review of febrile neutropenia conducted by the McMaster Group.

Expert Committee considerations

The Expert Committee made recommendations in line with Talcott criteria for risk classification (1).

The Expert Committee endorsed the inclusion of amoxicillin + clavulanic acid, with or without ciprofloxacin, as first-choice therapy in low-risk patients with febrile neutropenia.

The Committee endorsed the inclusion of IV vancomycin and the addition of meropenem (indicated in specific situations in combination with first-line regimens) as second-choice therapy in high-risk patients with febrile neutropenia.

The Committee recommended the addition of piperacillin + tazobactam and amikacin (indicated in specific situations in combination with a recommended beta-lactam agent) as first-choice therapy for high-risk patients with febrile neutropenia.

These recommendations are summarised in the following table:

	First choice	*Second choice*
Endorsed existing EML medicines		
Low risk	amoxicillin + clavulanic acid with or without ciprofloxacin	
High risk		vancomycin IV
Addition to EML ***High risk***	piperacillin + tazobactam amikacin	meropenem

Reference:

1. Talcott JA, Finberg R, Mayer RJ, Goldman L. The medical course of cancer patients with fever and neutropenia. Clinical identification of a low-risk subgroup at presentation. Arch Intern Med. 1988;148(12):2561–8.

Severe acute malnutrition

Severe acute malnutrition (SAM) affects nearly 20 million children under 5 years of age, causing up to 1 million deaths each year as a consequence of increasing susceptibility to death from severe infection. The most susceptible age for malnutrition is 6–18 months, but it is increasingly recognized that SAM may occur in younger infants. SAM is classified according to the absence or presence of medical complications:

- *Uncomplicated SAM:* children who are clinically well without signs of infection or other indication for hospital admission, with a retained appetite ("passed the appetite test"). Retained appetite is regarded as indicating the absence of severe metabolic disturbance. Patients are deemed to be most appropriately managed as outpatients, with ready-to-use therapeutic foods.
- *Complicated SAM:* children who have clinical features of infection, metabolic disturbance, severe oedema, hypothermia, vomiting, severe dehydration, severe anaemia or a lack of appetite, requiring inpatient treatment initially with low-protein milk-based feeds. Children are discharged to continue nutritional management as outpatients when complications have resolved.

See TRS pages 139-142 for a summary that considers the review of the available evidence for SAM conducted to inform the WHO Department of Maternal, Newborn, Child and Adolescent Health's review of its existing guidelines.

Expert Committee recommendations

The Expert Committee endorsed the inclusion on the EMLc of amoxicillin as a first-choice therapy for use in uncomplicated severe acute malnutrition, and of benzylpenicillin or ampicillin and gentamicin followed by amoxicillin as first-choice therapy in use in complicated severe acute malnutrition.

These recommendations are summarised in the following table:

	First choice	*Second choice*
Endorsed existing EML medicines		
Uncomplicated SAM	amoxicillin	
Complicated SAM	benzylpenicillin or ampicillin and gentamicin followed by amoxicillin	