Proposal for the addition of new antibiotic formulations to the WHO Model List of Essential Medicines

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Summary statement of the proposal for inclusion, change or deletion.

This application concerns the updating of the forthcoming WHO Model List of Essential Medicines (EML) to add new strength oral and intravenous formulations of antibiotics already listed in the last version of the EML (21st edition, 2019).

These new strength formulations should enable prescribers to more effectively treat common bacterial infections and favour patient compliance (e.g. new oral formulations are higher strength and allow for a lower total number of daily pills).

The new formulations are higher strength dosage forms and are mostly aligned with the dosing needs of adults. All of these formulations are approved by several regulatory agencies, including the FDA, and are available in most countries around the world and listed in multiple pharmacopoeias including the United States Pharmacopeia and European Pharmacopoeia.

For each antibiotic, the proposed new formulations and the indications for which they are proposed are presented in the table below. The indication for the use of the new formulation is aligned with recommendations in the current EML. However, only those infections for which the proposed new formulation would be preferable compared to the currently listed formulation(s) are described.

Antibiotic	Formulation and strength	Indication for the proposed new formulation
Amoxicillin	Solid oral dosage form: 1 g	*- community acquired pneumonia (mild to moderate)* *- sinusitis*
Cefalexin	Solid oral dosage form: 500 mg	*- exacerbations of COPD* *- pharyngitis* *- skin and soft tissue infections*
Ceftriaxone	Powder for injection: 2 g	*- acute bacterial meningitis* *-community acquired pneumonia (severe)* *- complicated intraabdominal infections (mild to moderate)* *- complicated intrabdominal infections (severe)* *- hospital acquired pneumonia* *- enteric fever*
Ciprofloxacin	Tablet: 500 mg	*- acute invasive bacterial diarrhoea / dysentery* *- low-risk febrile neutropenia* *- pyelonephritis or prostatitis (mild to moderate)* *- enteric fever* *- cholera* *- complicated intraabdominal infections (mild to moderate)*
Clindamycin	Injection: 600 mg, 900 mg	*- bone and joint infections*
Phenoxymethylpenicillin	Tablet: 500 mg	*- community acquired pneumonia (mild to moderate)* *- pharyngitis* *- progressive apical dental abscess*
Vancomycin	Powder for injection: 500 mg, 1 g	*- high-risk febrile neutropenia*

Amoxicillin 1 g oral formulation:

Target population(s)
Adult and adolescent patients diagnosed with mild community-acquired pneumonia or acute sinusitis. Other formulations (e.g. liquid formulations) are more appropriate for children and are recommended in the EMLc.

Likely impact of treatment on the disease
The new proposed formulation of 1 g would allow for a reduced number of daily pills to complete the course of treatment compared to the currently listed 500 mg formulation. This should facilitate adherence to treatment.

- **Mild community-acquired pneumonia (CAP)**

Community-acquired pneumonia is common worldwide and is a leading cause of morbidity and mortality, with an especially high burden in low-income countries (1). The primary goal of empiric antibiotic treatment in CAP is to provide effective and timely treatment for *Streptococcus pneumoniae* infection because this is the predominant bacterial pathogen and untreated pneumococcal pneumonia is associated with high mortality. The great majority of episodes of CAP in the primary care setting are caused by pneumococcal isolates that clinically respond to oral penicillins. Most people who develop CAP can therefore be successfully treated with a 5-day antibiotic regimen of amoxicillin (1 g every 8 hours).

- **Sinusitis**

Acute sinusitis is usually caused by respiratory viruses (e.g. rhinovirus, coronavirus and respiratory syncytial virus); only a small percentage (usually less than 2%) of cases are complicated by bacterial infection (usually *Streptococcus pneumoniae*). Therefore antibiotic treatment is not required in the great majority of cases and a watchful waiting approach with symptom relief and no antibiotic treatment is usually adequate. However, in particular situations antibiotic treatment could be considered. In particular in case of severe onset of symptoms (fever ≥ 39.0 °C and purulent nasal discharge for at least 3–4 consecutive days), in patients with underlying comorbid diseases (e.g. chronic malignancies and immunodeficiency) or in those at increased risk of complications. When antibiotic treatment is considered, amoxicillin is a first-choice option because it still has good clinical activity against most isolates of *Streptococcus pneumoniae*. Most people can therefore be successfully treated with a 5-day antibiotic regimen of amoxicillin (1 g every 8 hours).

Cefalexin 500 mg oral formulation

Target population(s)
Adult patients diagnosed with exacerbations of chronic obstructive pulmonary disease (COPD), and adult and adolescent patients diagnosed with pharyngitis or mild skin and soft tissue infections. For pharyngitis and skin and soft tissue infections, other formulations (e.g. liquid formulations) are more appropriate for children and are recommended in the EMLc.

Likely impact of treatment on the disease
The new proposed formulation of 500 mg would allow for a reduced number of daily pills to complete the course of treatment compared to the currently listed 250 mg formulation. This should facilitate adherence to treatment.

- **COPD exacerbation**

According to the global burden of diseases study, in 2017, there were 299 million prevalent cases of COPD and 3.19 million deaths caused by COPD (2, 3). In 2014, more than 90% of deaths occurred in low to middle-income countries (4). Most exacerbations of COPD are not triggered by bacterial infections but rather by respiratory viruses, therefore only certain cases will benefit from antibiotic treatment. Antibiotic treatment could be considered in severe exacerbations of COPD, especially if an increased volume and purulence of sputum is present, because these cases are more likely to be caused by a bacterial infection. Severe exacerbations benefit more from antibiotic treatment. Current evidence suggests that the benefit in terms of reduced short-term mortality and reduced treatment failure is limited to hospitalized patients in intensive care units (5). Cefalexin could be considered in patients at low-risk of multidrug-resistant infections (i.e. in patients that have not received multiple courses of antibiotic treatment during

the year for frequent episodes of COPD exacerbations). When antibiotic treatment is considered, cefalexin is an adequate second-choice option because it still has good clinical activity against most isolates of *Haemophilus influenzae*, *Moraxella catarrhalis* and *Streptococcus pneumoniae* and can be used in patients allergic to first-choice options (amoxicillin and amoxicillin-clavulanic acid) that can tolerate cephalosporins. Most people can therefore be successfully treated with a 5-day antibiotic regimen of cefalexin (500 mg every 12 hours).

- **Pharyngitis**

Most (> 80%) cases of pharyngitis are caused by a viral infection and only a minority of cases are caused by bacteria, mainly *S. pyogenes* (group A streptococci). When bacterial pharyngitis is suspected or proven, the decision to give antibiotic treatment is usually based on the likelihood of *S. pyogenes* infection and on the local prevalence or patient history of rheumatic fever. *S. pyogenes* is still universally susceptible to penicillin (resistance to penicillin has never been reported, including no evidence of increasing minimal inhibitory concentrations) and amoxicillin/penicillin are the recommended first line treatment. However, in patients allergic to penicillins that can tolerate cephalosporins, cefalexin (500 mg every 8 hours) can be used as a second-choice option for 5 days.

- **Mild skin and soft tissue infections (impetigo, erysipelas and cellulitis)**

Bacterial skin infections occur worldwide and can affect all age groups; erysipelas is more frequent in children and elderly patients. Damage of the skin predisposes to infections of the deeper layers beneath the epidermis. When such damage occurs, both endogenous (*i.e.* pathogens that naturally reside in the body) and exogenous (i.e. pathogens that enter the body from the environment) pathogens can penetrate the epidermis and spread to deeper structures through the lymphatic system. Depending on the depth of the infection, different clinical diseases can occur: impetigo and erysipelas (infections of the upper layer of the skin) and cellulitis (infection of the deep dermis and subcutaneous tissue). Empiric antibiotic options need to have good activity against the most likely pathogens (*Staphylococcus* aureus and *Streptococcus* spp.). Empiric treatment against community-acquired methicillin-resistant *Staphylococcus* aureus (MRSA) is not routinely needed but may be considered in certain cases based on individual risk factors (e.g. known MRSA colonization) and on the local prevalence of community-acquired MRSA. In mild cases, when MRSA is not of concern, cefalexin (500 mg every 8 hours) can be used for 5 days.

Ceftriaxone 2 g powder for injection

Target population(s)

Adult and adolescent patients diagnosed with acute bacterial meningitis, severe community-acquired pneumonia, hospital-acquired pneumonia, complicated intra-abdominal infections, and enteric fever. Other formulations (e.g. 250 mg, 1 g) are more appropriate for children and are recommended in the EMLc.

Likely impact of treatment on the disease

The new proposed formulation of 2 g is preferable for the treatment of certain infections because it maximizes the chances of bacterial eradication in order to achieve clinical success (e.g. in case of acute bacterial meningitis 2 g every 12 hours of ceftriaxone is needed to achieve adequate concentrations in the central nervous system).

- **Acute bacterial meningitis**

The burden of bacterial meningitis is still high, especially in low-income countries despite an increase in immunization programmes (6). According to data from the Global Burden of Disease study, in 2017, there were around 5 million new cases of meningitis (considering all ages and both sexes combined) (2). Almost half of the cases were of viral origin (2.4 million cases). In the same year, the number of new cases of acute pneumococcal (about 440 000) and meningococcal (about 400 000) meningitis were similar, while *Haemophilus influenza*e accounted for an estimated 262 000 new cases (2). The most frequently implicated bacteria (beyond neonatal age) are *Streptococcus pneumoniae, Neisseria meningitidis* and *Haemophilus influenzae* serotype b. Currently, because of the risk of penicillin-resistance in *Streptococcus pneumoniae* isolates and because meningitis is a very serious and potentially fatal disease, a third-generation cephalosporin is recommended for empiric treatment. Isolates with intermediate or complete resistance to ceftriaxone have rarely been described. The suggested dose is 2 g every 12 hours for 10 days when no pathogen is identified.

- **Severe community-acquired pneumonia (CAP)**

The primary goal of empiric antibiotic treatment in CAP is to provide effective and timely treatment for *Streptococcus pneumoniae* infection because this is the predominant bacterial pathogen and untreated pneumococcal pneumonia is associated with high mortality.

Most people who develop CAP and require hospitalization (not in the ICU -intensive care unit) can be successfully treated with a 5-day antibiotic regimen of ceftriaxone (1 g/day) in combination with clarithromycin (for coverage of atypical bacteria).

- **Hospital-acquired pneumonia (HAP)**

HAP may be caused by the same pathogens found in community-acquired pneumonia or by multidrug-resistant pathogens. In general resistance is higher in hospital-acquired strains but the frequency of multidrug-resistant pathogens varies among hospitals and between different patient populations. In patients with no risk factors for multidrug-resistant infections, ceftriaxone (2 g/day for 7 days) is a recommended option.

- **Complicated intra-abdominal infections**

In patients with peritonitis or when an abscess is present, intra-abdominal infections are defined as complicated. The most common pathogens involved in intra-abdominal infections are Gram-negative bacilli and anaerobic bacteria from the intestinal microbiota.

In complicated intra-abdominal infections, eliminating the source of infection (e.g. abscess, perforated appendix) and the ongoing contamination of the peritoneal cavity (e.g. in cases of perforation) are the foundation of treatment. In general, empiric antibiotic treatment should be chosen based on the severity of symptoms (mild or severe), taking into account local rates of resistance, particularly rates of isolates producing extended-spectrum beta-lactamases (ESBL), as these can vary in different settings. Ceftriaxone (2 g for 5 days if adequate source control is achieved) in combination with metronidazole (for the anaerobic coverage) is a recommended option when ESBL strains are not suspected.

- **Enteric fever**

Most cases of enteric fever are caused by *Salmonella* Typhi (70–80% of cases) and the disease is still endemic, mostly in sub-Saharan Africa and in South Asia (7). In 2017, about 14.3 million cases of enteric fever occurred worldwide (7). In endemic countries, children are affected the most with almost 60% of cases occurring in children under 15 years of age.

In cases of enteric fever, antibiotic treatment should be started promptly because delays are associated with higher risk of complications and severe disease. Severe cases should be treated as inpatients with systemic intravenous treatment. Ciprofloxacin remains the first-choice option to treat enteric fever however when choosing empiric treatment, the local prevalence of fluoroquinolone resistance should be considered because of the increasing number of fluroquinolone-resistant isolates, mostly in Asia (8). In these settings, a third-generation cephalosporin is appropriate options because resistance to these antibiotics is still low in most settings (< 5% for ceftriaxone).

If ceftriaxone is used, 2 g/day for 10 days should be used to treat severe cases.

Ciprofloxacin 500 mg oral formulation

Target population(s)

Adult and adolescent patients diagnosed with acute invasive bacterial diarrhoea, low-risk febrile neutropenia, mild upper urinary tract infection, enteric fever, cholera and mild complicated intra-abdominal infections. Other formulations (e.g. liquid formulations) are more appropriate for children and are recommended in the EMLc.

Likely impact of treatment on the disease

The new proposed formulation of 500 mg would allow for a reduced number of daily pills to complete the course of treatment compared to the currently listed 250 mg formulation. This should facilitate adherence to treatment.

- **Acute invasive bacterial diarrhoea**

Most cases of acute diarrhoeal disease do not need antibiotic treatment because they are of viral origin and the illness is usually self-limiting regardless of the causative pathogen. Rehydration is the main treatment for acute diarrhoeal disease (9). Even in cases with severe dehydration, antibiotic treatment is not routinely needed. However, in certain cases, such as patients with significant bloody diarrhoea and in severely immunosuppressed patients, antibiotics may be given. Empiric treatment should be chosen considering the risk of fluoroquinolone-resistant infection. When the risk is considered to be low, ciprofloxacin can be used (500 mg every 12 hours for 3 days).

- **Cholera**

Antibiotic treatment for cholera should only be considered in the context of an outbreak and not based on the degree of dehydration. The rationale of giving an antibiotic during outbreaks is to reduce transmission but the cornerstone of treatment remains rehydration. Ciprofloxacin 1 g (single dose) is considered an adequate second-choice option. In this case the advantage of using the 500 mg oral formulation of ciprofloxacin is the lower number of pills compared to the 250 mg formulation.

- **Low-risk febrile neutropenia**

In neutropenic patients, the risk of developing severe infection depends on the duration and severity of neutropenia; therefore, initial risk assessment is an important step to identify patients at low or high risk of developing serious complications (e.g. complications requiring hospitalization or prolonging hospitalization). Low-risk patients can be managed in an outpatient setting if adequate monitoring and follow-up is available and if they are able to tolerate oral treatment. The choice of empiric treatment should always consider a combination of factors, including the most likely site of primary infection and the infecting pathogens (including risk of viral and invasive fungal infections) and the local pattern of antimicrobial resistance. Other factors, such as known colonization or previous infection with multidrug-resistant organisms and recent antibiotic exposure (including antibiotic prophylaxis) are also important factors to consider. In general, in low-risk patients, ciprofloxacin (500 mg every 12 hours) in combination with amoxicillin-clavulanic acid for 7 days is considered adequate.

- **Mild upper urinary tract infection (UTIs)**

Most UTIs are caused by enteric Gram-negative bacteria, most frequently *Escherichia coli*, which is responsible for about 80% of cases in children and adults. The choice of empiric treatment should be based on the severity of symptoms (mild to moderate versus severe). Mild/moderate cases of upper UTI are defined as patients who are not critically ill and there is no suspicion of sepsis or septic shock. In these cases, oral treatment with ciprofloxacin (500 mg every 12 hours) for 7 days is considered adequate.

- **Enteric fever**

In cases of enteric fever, antibiotic treatment should be started promptly because delays are associated with higher risk of complications and severe disease. Severe cases should be treated as inpatients with systemic intravenous treatment. Ciprofloxacin remains the first-choice option to treat enteric fever however when choosing empiric treatment, the local prevalence of fluoroquinolone resistance should be considered because of the increasing number of fluroquinolone-resistant isolates, mostly in Asia (8). In low-risk settings, mild cases can be treated with oral ciprofloxacin (500 mg every 12 hours) for 7 days.

- **Mild complicated intra-abdominal infections**

Complicated intra-abdominal infections are defined as cases where peritonitis or an abscess is present. Mild cases are defined as patients who are not critically ill, with no suspicion of sepsis or septic shock. In these cases, eliminating the source of infection (e.g. abscess, perforated appendix) and the ongoing contamination of the peritoneal cavity (e.g. in cases of perforation) are the foundation of treatment. Empiric antibiotic treatment should be chosen based on the severity of symptoms (mild or severe), taking into account local rates of resistance, particularly rates of isolates producing extended-spectrum beta-lactamases, as these can vary in different settings. Individual risk factors for resistant pathogens (e.g. recent antibiotic treatment, colonization with resistant pathogens) should also be considered**.** If multidrug-resistant infection is not suspected, ciprofloxacin (500 mg every 12 hours) in combination with metronidazole for 5 days (if source control is achieved) is considered adequate in most cases.

Clindamycin 600 mg, 900 mg injection

Target population(s)
Adult and adolescent patients diagnosed with bone and joint infections. Other strength formulations (e.g. 150 mg) are more appropriate for children and are recommended in the EMLc.

Likely impact of treatment on the disease
The new proposed formulation of 600 mg or 900 mg is preferable for the treatment of certain infections because it maximizes the chances of bacterial eradication in order to achieve clinical success.

- **Bone and joint infections**

In adults with osteomyelitis, targeted antibiotic treatment based on microbiology is always preferred because there are many potential causative pathogens and high levels of resistance (e.g. methicillin-resistant *Staphylococcus aureus*) making it difficult to specify appropriate empiric treatment. In children there is usually less variability in the most likely causative pathogens (in children the disease is mostly caused by spread of *Staphylococcus* spp. and *Streptococcus* spp. through the bloodstream) and therefore empiric treatment is common practice.
Clindamycin is still an acceptable option when community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) is suspected or detected if antimicrobial susceptibility tests show that MRSA is sensitive to clindamycin or in settings where MRSA maintains high levels of susceptibility to clindamycin. Clindamycin can also be used in patients allergic to penicillin. In these cases, intravenous clindamycin at the dose of 600 mg every 8 hours for 4-6 weeks is considered adequate in most cases. Longer treatments may be required if implants or foreign material are present or in case of inadequate control at the source of infection (e.g. where there is an abscess that has not been adequately drained).

Phenoxymethylpenicillin 500 mg oral formulation

Target population(s)
Adult and adolescent patients diagnosed with mild community acquired pneumonia, pharyngitis or dental infection. Other formulations (e.g. liquid formulations) are more appropriate for children and are recommended in the EMLc.

Likely impact of treatment on the disease
The new proposed formulation of 500 mg would allow for a reduced number of daily pills to complete the course of treatment compared to the currently listed 250 mg formulation. This should facilitate adherence to treatment.

- **Mild community acquired pneumonia**

Community-acquired pneumonia is common worldwide and is a leading cause of morbidity and mortality, with an especially high burden in low-income countries (1). The primary goal of empiric antibiotic treatment in CAP is to provide effective and timely treatment for *Streptococcus pneumoniae* infection because this is the predominant bacterial pathogen and untreated pneumococcal pneumonia is associated with high mortality. The great majority of episodes of CAP in the primary care setting are caused by pneumococcal isolates that clinically respond to oral penicillins. Most people who develop CAP can therefore be successfully treated with a 5-day antibiotic regimen of phenoxymethylpenicillin (500 mg every 6 hours).

- **Pharyngitis**

Most (> 80%) cases of pharyngitis are caused by a viral infection and only a minority of cases are caused by bacteria, mainly *S. pyogenes* (group A streptococci). When bacterial pharyngitis is suspected or proven, the decision to give antibiotic treatment is usually based on the likelihood of *S. pyogenes* infection and on the local prevalence or patient history of rheumatic fever.

S. pyogenes is still universally susceptible to penicillin (resistance to penicillin has never been reported, including no evidence of increasing minimal inhibitory concentrations) and amoxicillin/penicillin are the recommended first line

treatment. When antibiotic treatment is indicated, phenoxymethylpenicillin 500 mg every 6 hours is considered an adequate option. Treatment duration (5 or 10 days) should be chosen based on the local prevalence or previous history of rheumatic fever.

Vancomycin powder for injection 500 mg, 1 g

Target population(s)
Adult and adolescent patients with high-risk febrile neutropenia when MRSA infection is suspected based on the local prevalence of MRSA and on individual patient risk factors (e.g. known colonization with MRSA). Other formulations (e.g. 250 mg) are more appropriate for children and are recommended in the EMLc.

Likely impact of treatment on the disease
Vancomycin is dosed based on patient weight (15-20 mg/kg every 12 hours) therefore the proposed higher strength formulations of 500 mg or 1 g (compared to the currently listed 250 mg) would allow for the correct treatment dose in adult patients to be achieved with fewer vials (usually the dose in an average adult patient ranges from 1 to 2 g every 12 hours).

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