

F.3	New antibiotic formulations
<p>Does the application adequately address the issue of the public health need for the medicine?</p>	<p><input checked="" type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input type="checkbox"/> Not applicable</p> <p>Comments:</p> <p>Appropriate use of antibiotics is of utmost importance both at the individual and societal level (Amabile-Cuevas 2016) as antibiotic use, both appropriate and not, can promote the emergence of resistance in bacteria.</p> <p>A wide range of determinants can influence the rational use of antibiotics, including clear recommendations, knowledge and awareness of health professionals, patient preferences and perceived needs, incentives and resources, and social, political and legal factors.</p> <p>Treatment complexity has already been described as a barrier to adherence in other studies, especially for chronic treatments. The prescription of simpler regimens instead of regimens with a higher number of daily doses or a longer duration of treatment is reported as a possible 'facilitator' of antibiotic adherence (Zanichelli 2019).</p>
<p>Briefly summarize the role of the proposed medicine(s) relative to other therapeutic agents currently included in the Model List, or available in the market.</p>	<p>The Application concerns the inclusion of new formulations of common antibiotics in the WHO Model List of Essential Medicines. The scope is to add higher strength of oral and intravenous formulations to better align with the dosing needs of adults.</p> <p>All the antibiotics included in this Application are already listed in the Model List and the indications for the use of the new formulations match the recommendations in the current list.</p> <p>A brief description of the indications mentioned in the Application is reported below (Main source: CDC website https://www.cdc.gov/)</p> <p>Community acquired pneumonia (CAP) is one of the most common acute infections, affecting people of all ages. Its symptoms result from the reduced oxygen-absorbing areas in lungs which are filled with fluid. This inhibits the lung function, causing chest pain, cough, dyspnea, fever and sometimes requires hospital admission. Antibiotic recommendations for the empiric treatment of CAP are based on selecting agents effective against the major treatable bacterial causing CAP (<i>Streptococcus pneumoniae</i>, <i>Haemophilus influenza</i>, <i>Mycoplasma pneumoniae</i>, <i>Staphylococcus aureus</i>, <i>Legionella</i> species, <i>Chlamydia pneumoniae</i>, <i>Moraxella catarrhalis</i>).</p> <p>In contrast, hospital-acquired pneumonia (HAP) is seen in patients who have recently visited a hospital or who live in long-term care facilities and so it is caused by pathogens that are present in the hospital settings. The time of onset of HAP also affects the possible aetiology, empirical antimicrobial treatment and outcomes. Empiric therapy for HAP should include agents with activity against <i>Staphylococcus aureus</i>, <i>Pseudomonas aeruginosa</i> and other gram-negative bacilli. The choice of a specific regimen for empiric therapy should be based upon knowledge of prevailing pathogens and susceptibility patterns within the healthcare setting as well as the individual patient's risk factors for multi-drug resistance.</p> <p>Bacterial meningitis is a severe infectious disease of the membranes lining the brain resulting in high mortality and morbidity throughout the world. Most people recover from meningitis; however, permanent disabilities (brain damage, hearing loss and learning disabilities) can result from the infection. Several types of bacteria can cause meningitis: <i>Streptococcus pneumoniae</i>, group B <i>Streptococcus</i>, <i>Neisseria meningitidis</i>, <i>Haemophilus influenza</i>, <i>Listeria monocytogenes</i>.</p>

Sinus infections happen when fluids build up in the air-filled pockets in the sinuses, which allow germs to grow. Viruses cause most of sinusitis, but bacteria can cause some sinusitis too. Indeed, antibiotics are not needed for many sinusitis, because most sinus infections get better on their own without antibiotics.

Pharyngitis is the inflammation of the mucous membranes of the oropharynx. In most cases, the cause is an infection, either bacterial or viral. *Streptococcus pyogenes*, which are also called group A *Streptococcus*, cause acute pharyngitis known as strep throat.

Chronic obstructive pulmonary disease (COPD) is a chronic condition that affects the passage of air into and out the lungs. As a consequence, patients experience shortness of breath and coughing. Acute exacerbations of COPD are important cause of morbidity, mortality, hospital admission, impaired health status and increased costs. Half of the exacerbations of COPD are bacterial in origin (*Haemophilus influenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*), so that broad-spectrum antibiotics are widely prescribed (Vollenweider 2018).

Intra-abdominal infections (IAIs) are common surgical emergencies and have been reported as major contributors to non-trauma deaths in the emergency department worldwide. The cornerstones of effective treatment of IAIs are early recognition, adequate source of control, and appropriate antimicrobial therapy. IAIs include several different pathological conditions and are usually classified into uncomplicated and complicated. In uncomplicated IAIs the infectious process only involves a single organ and does not proceed to the peritoneum; in complicated IAIs the infectious process extends beyond the organ and causes either localized peritonitis or diffuse peritonitis. The major pathogens involved are usual gastrointestinal flora, including Enterobacteriaceae, streptococci, and certain anaerobes (*Bacteroides fragilis*). Narrower spectrum antimicrobial agents are appropriate for these patients.

Enteric fever (or typhoid fever) is a bacteremic illness that has an insidious onset characterized by fever, headache, constipation or diarrhea, malaise, chills and myalgia, with few clinical features that reliably distinguish them from a variety of other infectious diseases. Enteric fever is treated with antibiotics that should be started promptly. To note, antimicrobial resistance in enteric fever has been increasing.

Most persons infected with the cholera bacterium have mild diarrhea or no symptoms at all. Although small proportion (10%) of persons infected may have illness requiring treatment, cholera outbreaks can spread rapidly, cause many deaths and quickly become a serious issue. In this scenario, the aim of giving antibiotics is to reduce the transmission. In acute invasive diarrhea, the pathogen penetrates the epithelial cells of the intestinal mucosa. Symptoms are produced by enterotoxins, increased synthesis of prostaglandins, and impaired reabsorption of fluids and electrolytes. The invasive process often results in dysentery, which is characterized by watery stools containing blood and mucus, accompanied by cramps, rectal burning, fever. Although often unnecessary in simple cases of invasive diarrhea, antimicrobials are useful when risk factors related to age, clinical condition, malnourishment, dehydration, or underlying disease are present.

Urinary tract infections (UTIs) are common infections that happen when bacteria, often from the skin or rectum, enter the urethra, and infect the urinary tract. The infections can affect several parts of the urinary tract, but upper UTIs are not as common as lower UTIs. Upper UTIs mainly refers to the kidneys and the ureters. *E. coli* causes about 90% of cases of upper UTIs.

Bacterial skin infections may occur more frequently after bites, minor scratches, or abrasions, particularly when maintaining good hygiene is difficult. Common organisms responsible are *Staphylococcus aureus* or *Streptococcus pyogenes*. Resulting infections are collectively called pyodermas and can present as impetigo, folliculitis,

	<p>ecthyma, boils, cellulitis and erysipelas, lymphagitis or ulceration. Empiric treatment against community-acquired methicillin-resistant <i>Staphylococcus aureus</i> (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.</p> <p>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., those requiring or prolonging hospitalization).</p> <p>Osteomyelitis often occurs when an infection elsewhere in the body, such as a urinary tract infection or pneumonia, spreads through the blood to the bones; an open wound or a recent surgery can also lead to osteomyelitis. Without prompt treatment, bone and joint infections can become long-term conditions. Many types of bacteria can cause bone and joint infections, including <i>Staphylococcus aureus</i>, <i>Enterobacter</i> and <i>Streptococcus</i>. Despite multiple courses of antibiotics, the condition may return if the bacteria causing the infection becomes resistant to antibiotics.</p>
<p>Have all important studies and all relevant evidence been included in the application?</p>	<p><input type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input checked="" type="checkbox"/> Not applicable</p> <p>If no, please provide brief comments on any relevant studies or evidence that have not been included:</p> <p>The Application regards the inclusion of new formulations of well-established antibiotics treatment (amoxicillin, cefalexin, ceftriaxone, ciprofloxacin, clindamycin, phenoxymethylpenicillin, vancomycin) for a wide range of infection.</p> <p>Comparative evidence assessing the proposed and existing formulations are not considered necessary in this context.</p>
<p>Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed indication?</p>	<p><input type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input checked="" type="checkbox"/> Not applicable</p> <p>Briefly summarize the reported benefits (e.g. hard clinical versus surrogate outcomes) and comment, where possible on the actual magnitude and clinical relevance of benefit associated with use of the medicine(s).</p> <p>The new proposed formulations allow either a reduced number of daily pills to complete the course of treatment (oral treatments) or the optimization of the intravenous regimes to achieve clinical success.</p> <p>Though not empirically demonstrated, these benefits appear plausible and obvious especially in the case of oral therapies.</p> <p>The inclusion of new formulations does not change the standard schedule proposed for each antibiotic-indication dyad. These standard schedules are in line with the main clinical guidelines with the possible exception of:</p> <p>- Cefalexin for COPD exacerbation, ("Management of COPD exacerbations: a European Respiratory Society and American Thoracic society guidelines" and the "Global strategy for prevention, diagnosis and management of COPD"). However, it should be noted that the Expert Committee endorsed the inclusion in 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.</p>

	<p>Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)?</p> <p>No specific data were included in the Application. However, it is reasonable that easier schedules can improve adherence to treatments and may have a greater impact in disadvantaged settings.</p>
Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	<p><input type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input checked="" type="checkbox"/> Not applicable</p> <p>Comments:</p> <p>The inclusion of new formulations is not affecting the standard schedule proposed for each antibiotic-indication dyad. Thus, no specific safety issue arises from this Application.</p>
Are there any adverse effects of concern, or that may require special monitoring?	<p><input type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input checked="" type="checkbox"/> Not applicable</p> <p>Comments:</p>
Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	It is not possible to formally assess the benefit-harm ratio of the inclusion of these new formulations.
Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	Not applicable
Are there any special requirements for the safe, effective and appropriate use of the medicine(s)? (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	<p><input type="checkbox"/> Yes</p> <p><input checked="" type="checkbox"/> No</p> <p><input type="checkbox"/> Not applicable</p> <p>Comments:</p>
Are you aware of any issues regarding the registration of the medicine by national regulatory authorities? (e.g. accelerated approval, lack of regulatory approval, off-label indication)	<p><input type="checkbox"/> Yes</p> <p><input checked="" type="checkbox"/> No</p> <p><input type="checkbox"/> Not applicable</p> <p>Comments:</p>

2021 Expert Committee on Selection and Use of Essential Medicines
Application review

<p>Is the proposed medicine recommended for use in a current WHO Guideline approved by the Guidelines Review Committee? (refer to: https://www.who.int/publications/who-guidelines)</p>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable</p> <p>Comments: 2019 WHO AWaRe Classification Database developed on the recommendation of the WHO Expert Committee on Selection and Use of Essential Medicines. https://adoptaware.org/</p>
<p>Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.</p>	<p>The Application does not report on costs of the new formulations. Costs is unlikely to be an issue for these well-established antibiotics and formulations. However, the inclusion of the proposed new formulations must also be cost-effective. It is necessary to ensure that the costs of the proposed new formulations are not higher than the old ones.</p>
<p>Any additional comments</p>	
<p>Based on your assessment of the application, and any additional evidence / relevant information identified during the review process, briefly summarize your proposed recommendation to the Expert Committee, including the supporting rationale for your conclusions, and any doubts/concerns in relation to the listing proposal.</p>	<p>This Reviewer is of the opinion that the proposed new formulations can represent a logistic improvement and their inclusion in the Model List can facilitate treatment feasibility and patients' compliance.</p>
<p>References (if required)</p>	<p>Amabile-Cuevas C. Society must seize control of the antibiotics crisis. Nature 2016;533:439.</p> <p>Bonkat G, Bartoletti R, Bruyère F, et al. EAU Guidelines on Urological Infections. 2020. Available at: https://uroweb.org/guideline/urological-infections/?type=panel.</p> <p>GOLD Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (2021 report). Available at: https://goldcopd.org/2021-gold-reports/.</p> <p>Ingersoll KS, Cohen J. The impact of medication regimen factors on adherence to chronic treatment: a review of literature. J Behav Med 2008;31:213e24.</p> <p>Jin J, Sklar GE, Min Sen Oh V, Chuen Li S. Factors affecting therapeutic compliance: a review from the patient's perspective. Ther Clin Risk Manag 2008;4:269e86.</p> <p>Klompas M, File TM, Jr, Bond S. Treatment of hospital-acquired and ventilator-associated pneumonia in adults. Nov 03, 2020. Available at: https://www.uptodate.com/contents/treatment-of-hospital-acquired-and-ventilator-associated-pneumonia-in-adults.</p> <p>Sethi S, Murphy T. F, Sexton DJ, Bond S, Hollingsworth H. Evaluation for infection in exacerbation of chronic obstructive pulmonary disease. UpToDate Dec 05, 2019. Available at: https://www.uptodate.com/contents/evaluation-for-infection-in-exacerbations-of-chronic-obstructive-pulmonary-disease.</p>

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