WHO MODEL LISTS OF ESSENTIAL MEDICINES

ANTIMICROBIAL WORKING GROUP

Advice for the Expert Committee on Selection and Use of Essential Medicines

INTRODUCTION:

The EML Antimicrobial Working Group has reviewed the applications received for antibiotics for the 2023 update of the Model Lists of Essential Medicines and Essential Medicines for Children. This document outlines the assessment by the Working Group of the antibiotic applications listed below. It provides a summary of the Working Group's considerations, and the consensus opinion of the Working Group members in relation to the potential listings for antibiotics. In case of diverging opinions among experts, these are explicitly mentioned in the statements.

APPLICATIONS REVIEWED:

- A.9 Ceftolozane + tazobactam - bacterial infections due to multidrug-resistant organisms - EML and EMLc
- A.17 Flomoxef sodium - intraabdominal and upper urinary tract infections - EML and EMLc
- A.20 Imipenem + cilastatin + relebactam - bacterial infections due to multidrug-resistant organisms - EML
- A.44 Tedizolid phosphate - acute bacterial skin and skin structure infections due to multidrug-resistant organisms - EML
- F.1 Amoxicillin + clavulanic acid - dispersible tablet 200 mg + 28.5 mg - EMLc

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ABBREVIATIONS USED IN THE DOCUMENT:

- ABSSSI: Acute bacterial skin and skin structure infection
- AWaRe: Access Watch Reserve
- CLSI: Clinical and Laboratory Standards Institute
- C/T: Ceftolozane-tazobactam
- cIAI: Complicated intraabdominal infection
- cUTI: Complicated urinary tract infection
- ESBL-E: Extended-spectrum β-lactamase-producing Enterobacterales
- EMA: European Medicines Agency
- EML: WHO Model List of Essential Medicines
- EMLc: WHO Model List of Essential Medicines for children
- EUCAST: European Committee for Antimicrobial Susceptibility Testing
- FDA: United States Food and Drug Administration
- GAP-f: Global Accelerator for Paediatric Formulations Network
- HAP: Hospital-acquired pneumonia
- IMR: Imipenem/cilastatin/relebactam
- KPC: *Klebsiella pneumoniae* carbapenemase
- LMIC: Low- and middle-income countries
- MBL: Metallo-beta-lactamases
- MRSA: Methicillin-resistant *Staphylococcus aureus*
- UNICEF: United Nations Children's Fund
- VAP: Ventilator-associated pneumonia
- WG: WHO Model List of Essential Medicines Antimicrobial Working Group

Application	Working Group conclusions / Advice for Expert Committee
General remarks	The Working Group (WG) supports the inclusion of ceftolozane + tazobactam and imipenem + cilastatin + relebactam as Reserve antibiotics for the treatment of infections caused by multidrug-resistant organisms. The WG also supports inclusion of tedizolid as Reserve antibiotic for the treatment of infections caused by multidrug-resistant organisms, albeit as a square box alternative to linezolid on the EML rather than as independent listing as requested in the application. Furthermore, the WG supports the inclusion of amoxicillin + clavulanic acid dispersible tablets at a 7:1 ratio (200 mg + 28.5 mg) on the EMLc. The WG does not support the inclusion of flomoxef sodium for the treatment of intraabdominal and upper urinary tract infections in adults and children at high risk of infection caused by extended-spectrum β-lactamase-producing Enterobacterales (ESBL-E) on the EML and EMLc at this time but considers that a re-evaluation of flomoxef once more data addressing the gaps outlined below are available may be worthwhile.
A.9 Ceftolozane + tazobactam - bacterial infections due to multidrug-resistant organisms - EML and EMLc	The WG supports the inclusion of ceftolozane + tazobactam (C/T) as Reserve antibiotic for the treatment of infections caused or suspected to be caused by carbapenem-resistant *Pseudomonas aeruginosa* on the EML and the EMLc. C/T combines a fifth-generation cephalosporin with a well-established beta-lactamase inhibitor. It has been licensed by the FDA and EMA for complicated urinary tract infections (cUTI) and complicated intra-abdominal infections (cIAI). The medicine has particularly high activity against the WHO Priority 1 Critical Pathogen carbapenem-resistant *Pseudomonas aeruginosa* which in some settings is a common cause of severe pneumonia in ventilated patients in intensive care (including those with COVID-19). Clinical trial and observational data suggest that it is equally effective in patients with nosocomial pneumonia as other commonly used “older” antibiotics. However, high levels of resistance to the most widely used antibiotics in high-risk settings are increasingly common and alternative antibiotics are needed to provide wider treatment options. C/T is generally well tolerated with no specific safety concerns. C/T has been licensed in around 80 countries globally. While the primary patent of ceftolozane is going to expire in 2023, secondary patents will be active up to 2032 - 2035. C/T has a notably higher price than other antibiotics for which generics are available. There is limited cost-effectiveness data in LMIC settings. Both the Phase 1 pharmacokinetics and Phase 2 safety study in children have been published (Pediatr Infect Dis J. 2018 Nov;37(11):1130-1136.Pediatr Infect Dis J. 2023 Apr 1;42(4):292-298). The suggestion of the Working Group is for C/T to be added to the Reserve group in the EML and EMLc with emphasis on associated stewardship interventions to ensure its appropriate use.
A.17 Flomoxef sodium - intraabdominal and upper urinary tract infections - EML and EMLc	The WG does not support the inclusion of flomoxef sodium for the treatment of intraabdominal and upper urinary tract infections in adults and children at high risk of infection caused by extended-spectrum β-lactamase-producing Enterobacterales (ESBL-E) on the EML and EMLc at this time. The WG acknowledged that flomoxef is associated with some positive characteristics such as activity against most strains of ESBL-E. It therefore could be used as an alternative to carbapenems for empiric or targeted use of infections suspected or known to be caused by these organisms in certain situations. The WG also noted that there was considerable real-life experience of effective and safe use of this antibiotic over several decades in millions of patients in some countries in Asia. The Working Group noted, however, that clinical data specifically for the efficacy of flomoxef for the treatment of infections by ESBL-E was limited (especially for severe infections where it would be most useful), that clinical trial data mostly predate the period when ESBL-E emerged as common pathogen, that clinical experience is mostly limited to a cluster of Asian countries where it is

	currently approved (e.g. Japan, China, South Korea), that validated clinical breakpoints for susceptibility testing are not available by the Clinical and Laboratory Standards Institute (CLSI) and the European Committee for Antimicrobial Susceptibility Testing (EUCAST) and that a trial funded by the applicant studying flomoxef in combination with another antibiotic for neonatal sepsis (an indication not requested in this application) is still ongoing, with active recruitment. Furthermore, it was mentioned that there were also other beta-lactam antibiotics that could be used as carbapenem-sparing options due to their activity against ESBL-E (e.g. temocillin, cefoxitin) that have not been evaluated for addition to the Model Lists. Based on these limitations the WG considered that inclusion on the Model Lists at this time may be premature but that a re-evaluation of flomoxef once more data are available may be worthwhile.
A.20 Imipenem + cilastatin + relebactam - bacterial infections due to multidrug-resistant organisms - EML	The WG supports the inclusion of imipenem + cilastatin + relebactam (IMR) as a Reserve antibiotic for the treatment of infections caused by multidrug-resistant organisms on the EML and the EMLc. IMR is a combination of a Group 2 carbapenem, a dehydropeptidase-1 inhibitor (preventing cleavage of imipenem in the renal tubule), and a serine beta-lactamase inhibitor. IMR has an FDA label for cUTI, cIAI and hospital-acquired and ventilator-associated pneumonia (HAP/VAP). IMR has broad activity against ESBL-E, some carbapenemase-producing Enterobacterales (mainly Class A carbapenemases - KPC and Class C – AmpC – but not Class B – metallo-beta-lactamases (MBLs) and Class D - OXA) and carbapenem-resistant *Pseudomonas aeruginosa*. Although NDM and OXA are globally the most common genotypes associated with carbapenem resistance in Enterobacterales, KPC remains an important cause in some LMICs, where treatment options are limited. Infections caused by carbapenem-resistant Enterobacterales and carbapenem-resistant *Pseudomonas aeruginosa* are a major public health concern and in many LMIC settings, antibiotic treatment options are now very limited. The only remaining treatment options may be older agents with important toxicity concerns (such as colistin). Limited clinical trial and observational data suggest that IMR has equal clinical efficacy in patients with infections caused by multi-drug resistant pathogens. Although the medicine has limited activity against some types of carbapenem resistance, it has good activity against other types seen in both HIC and LMIC settings. There is a clear public health need to increase the range of treatment options for carbapenem-resistant Enterobacterales and carbapenem-resistant *Pseudomonas aeruginosa*. IMR is well tolerated with no specific safety concerns. IMR is significantly more expensive than antibiotics for which generics are available. There is limited cost-effectiveness data in LMIC settings. The Phase 1 pharmacokinetic study in children has been published (Open Forum Infectious Diseases, Volume 8, Issue Supplement_1, November 2021, Page S671). The suggestion of the WG is for IMR to be added to the Reserve group in the EML with emphasis on associated stewardship interventions to ensure its appropriate use.
A.44 Tedizolid phosphate - acute bacterial skin and skin structure infections due to multidrug-resistant organisms - EML	The WG supports the inclusion of tedizolid as a Reserve antibiotic for the treatment of infections caused by multidrug-resistant organisms as a square box alternative to linezolid on the EML. The indications for use of tedizolid should be aligned with those for linezolid as detailed in the WHO AWaRe antibiotic book. Tedizolid is an oxazolidinone antibiotic in the same class as linezolid, which is already on the EML and EMLc for the treatment of infections caused by multidrug-resistant Gram-positive organisms (and for the treatment of multidrug-resistant tuberculosis). Tedizolid is active against Gram positive pathogens, mainly *Staphylococcus aureus* including methicillin-resistant *S. aureus* (MRSA). Tedizolid is licenced by the FDA and EMA for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults. MRSA remain a major global public health concern as cause of severe bacterial infections, with significant mortality associated with invasive disease noted in the recent GRAM study (Lancet. 2022 Feb 12;399(10325):629-655). Tedizolid is given only once daily for generally shorter treatment

	courses than linezolid which is given twice daily. Tedizolid has good bioavailability and has both an intravenous and oral preparation, encouraging oral treatment only or rapid switch from IV to oral treatment in stable patients. No dose adjustments need to be made in patients with hepatic or renal disease. Tedizolid's main advantage over linezolid is the significantly lower incidence of bone marrow suppression and gastro-intestinal toxicity. The medicine is more expensive than generic linezolid, although shorter treatment courses may impact on the relative costs. Based on current patent status, generic versions of tedizolid are unlikely to be widely available before the 2030s. There is limited cost-effectiveness data in LMIC settings. The Phase 1 pharmacokinetic study in children has been published (Pediatr Infect Dis J. 2021 Apr 1;40(4):317-323). The WG noted that the application requests addition to the EML specifically for "acute bacterial skin and skin structure infections". The indication for linezolid is broader and pathogen- rather than infection-based (including e.g. infections by vancomycin-resistant *Enterococcus faecium* or MRSA at sites other than ABSSSI). As outlined above the suggestion of the WG is for IMR to be added to the Reserve group as a square box alternative to linezolid in the EML with emphasis on associated stewardship interventions to ensure its appropriate use. Of note tedizolid is currently not considered an alternative to linezolid for the treatment of multidrug-resistant tuberculosis because of insufficient data for this indication.
F.1 Amoxicillin + clavulanic acid - dispersible tablet 200 mg + 28.5 mg - EMLc	The WG supports the inclusion of amoxicillin + clavulanic acid dispersible tablets at a 7:1 ratio (200 mg + 28.5 mg) on the EMLc. Orally administered amoxicillin + clavulanic acid is currently listed on the EMLc for a large variety of infections, such as acute otitis media, acute sinusitis, lower urinary tract infections, skin and soft tissue infections, intra-abdominal infections and bone and joint infections and listed as an option for these indications in the WHO AWaRe antibiotic book (if antibiotic treatment is indicated). The WG noted that the 7:1 dispersible tablets proposed in the application offer several advantages over currently listed pediatric formulations (125 mg + 31.25 mg powder for oral liquid; 250 mg + 62.5 mg powder for oral liquid) such as ease of administration and heat stability at a similar price. The oral liquid formulations currently listed on the Model Lists must be refrigerated after reconstitution which poses a challenge in many resource-limited settings. The WG acknowledged that amoxicillin + clavulanic acid was identified as one of the priority antibiotics during the WHO "Paediatric drug optimization for antibiotics" meeting in November-December 2022. While UNICEF currently procures amoxicillin + clavulanic acid dispersible tablets at a 4:1 ratio (250 mg + 62.5 mg), which is also being proposed for inclusion on the EMLc as part of the EMLc formulation review in the context of the GAP-f project, it was considered that the additional availability of a dispersible tablet at a 7:1 ratio may offer certain advantages, such as allowing higher doses of amoxicillin without dose-related side effects associated with a higher clavulanic acid dose (e.g. in settings where penicillin non-susceptible pneumococci are prevalent). The WG noted that the dispersible tablets proposed in this application did not receive regulatory approval from the EMA as they did not meet the EMA requirement of disintegration within 3 minutes, an issue which does not seem to impact hospital or community use or offset the key advantages. Given the public health need for this formulation, the WG did not consider this should preclude its addition to the EMLc.