# Executive summary
# The Selection and Use of Essential Medicines 2021

Report of the 23rd WHO Expert Committee on the Selection and Use of Essential Medicines

Virtual meeting, 21 June–2 July 2021

World Health Organization

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# Contents



# Annexes

# Executive summary

The meeting of the 23rd WHO Expert Committee on the Selection and Use of Essential Medicines took place virtually and was hosted in Geneva, Switzerland, from 21 June to 2 July 2021. The aim of the meeting was to review and update the 21st WHO Model List of Essential Medicines (EML) and the 7th WHO Model List of Essential Medicines for Children (EMLc), the "Model Lists".

The Expert Committee considered a total of 88 applications, including 40 proposals for the addition of 38 new medicines or medicine classes, 16 proposals for new indications for 32 currently listed medicines, 13 proposals for the addition of new formulations of 19 currently listed medicines, and 3 proposals for the removal of 19 medicines or formulations on the Model Lists. In accordance with applicable procedures[1], the Expert Committee evaluated the scientific evidence for the comparative effectiveness, safety and cost-effectiveness of the medicines in question. The Committee also considered a review of the therapeutic alternatives for medicines on the Model Lists ("square box" listings), an update to the AWaRe (Access, Watch and Reserve) classification of antibiotics to support stewardship activities, a review of the available evidence for CAR-T cell therapies for B-cell lymphoma, and reports on insulin pricing and access, and switching between originator and similar biotherapeutic products ("biosimilars").

The Expert Committee did not consider any applications for the inclusion of medicines for the treatment or prevention of COVID-19. The COVID-19 pandemic has seen the quick evolution of knowledge on a previously unknown disease, rapidly evolving clinical hypotheses and proposals of potential treatments. As knowledge accumulates within an emergency framework for a pathogen that is rapidly evolving, the quality of the evidence necessarily also changes over short timeframes. This scenario does not fit within the intended aim of the EML, which has a longer-term scope and gives much weight to the certainty of the value of selected medicines. In the emergency context WHO recommendations on best available treatments are presented as part of WHO guidelines. However, this scenario might evolve and therapeutic options for COVID-19 may be considered for inclusion in Model Lists in the future.

In summary, the Expert Committee:

- recommended the addition of 20 new medicines to the EML (13 to the core list and 7 to the complementary list);
- recommended the addition of 17 new medicines to the EMLc (12 to the core list and 5 to the complementary list);
- recommended adding additional indications for 28 currently listed medicines;
- recommended the addition of new formulations of 23 currently listed medicines;
- recommended the deletion of 2 medicines and of specific formulations of a further 13 medicines;
- updated 72 square box listings, removed the square box from 7 listings, and recommended a review of a further 23 square box listings; and
- did not recommend 25 proposals for inclusion, change or deletion for 28 medicines, medicine classes or formulations.

The recommended changes bring the total number of medicines (including fixed-dose combinations) on the EML to 479 (from 460 in 2019), including 350 on the EMLc (from 336 in 2019). The total number of listed

[1] http://www.who.int/selection_medicines/committees/subcommittee/2/eeb1098%5b1%5d.pdf

medicines takes into account the additions and deletions, as well as changes made as a result of the revision of therapeutic equivalent alternatives.

The recommendations are briefly described below in order of their appearance on the Model Lists.

A full summary of changes to the Model Lists is shown in Table 1. Applications not recommended are shown in Table 2.

## *Section 4: Antidotes and other substances used in poisonings*

**Section 4.2 Specific**

The Expert Committee did not recommend listing for N-acetylcysteine for the new indication of non-paracetamol induced acute liver failure based on very low certainty of the available evidence and heterogeneity in the results, making confidence in the estimates of benefit in this indication limited.

## *Section 5: Anticonvulsants/antiepileptics*

The Expert Committee recommended the inclusion of a cautionary note with the listings for valproic acid (sodium valproate) on the EML and EMLc, to avoid use in pregnancy and in females of child-bearing potential, unless alternative treatments are ineffective or not tolerated, due to the high risk of birth defects and developmental disorders in children exposed to valproate in the womb. The Committee did not recommend transferring the listings of valproic acid from the core to the complementary list due to concerns that doing so may reduce access and undermine the important role of this medicine in the management of epilepsy and bipolar disorder. This recommendation also applies to the listing on the EML for valproic acid in Section 24.2.2 Medicines used in bipolar disorders.

## *Section 6: Anti-infective medicines*

**Section 6.1.4 (NEW) Cysticidal medicines**

The Expert Committee recommended inclusion of albendazole, mebendazole and praziquantel on the complementary list of the EML and EMLc for the new indication of treatment of diseases caused by taeniid cestode infections. Albendazole and mebendazole are recommended for treatment of cystic echinococcosis and alveolar echinococcosis; albendazole and praziquantel are recommended for treatment of neurocysticercosis. The Committee noted that these medicines are considered treatments of choice for these neglected tropical diseases and are recommended in current WHO guidelines.

**Section 6.2.1 Access group antibiotics**

**Section 6.2.2 Watch group antibiotics**

**Section 6.2.3 Reserve group antibiotics**

The Expert Committee recommended the inclusion of cefiderocol on the EML for treatment of adults with multi-drug resistant infections due to carbapenem-resistant Enterobacterales and carbapenem-resistant *Pseudomonas aeruginosa* and endorsed cefiderocol as a Reserve antibiotic in the AWaRe classification. The Committee noted that cefiderocol is one of the few medicines that has activity against carbapenem-resistant Enterobacterales, *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, which are ranked as "Critical Priority" on the WHO Priority Pathogens List. Cefiderocol was shown to be non-inferior to carbapenems with

regard to microbiologic/clinical response and mortality (with the possible exception of infections due to carbapenem-resistant *Acinetobacter* spp., where higher mortality has been observed in patients receiving cefiderocol) in settings where there are few alternatives for multidrug-resistant Gram-negative organisms producing metallo-betalactamases. The Committee highlighted the importance of antibiotic stewardship activities to assure appropriate use, while preserving access for patients in need of this medicine.

The Committee did not recommend empiric use of any antibiotics for the treatment of bronchitis and bronchiolitis, noting that these infections are usually caused by respiratory viruses and the available evidence does not suggest benefit of antibiotic use compared with placebo and symptomatic treatment.

The Committee recommended empiric antibiotic treatment options for endophthalmitis (ceftazidime, ceftriaxone and vancomycin), necrotizing fasciitis (ceftriaxone, clindamycin, metronidazole, piperacillin + tazobactam and vancomycin), neonatal meningitis (gentamicin), and intraabdominal infections in children (ampicillin and gentamicin); revised the existing treatment recommendations for lower urinary tract infections (removing amoxicillin as a recommended treatment) and skin and soft tissue infections (recommending cefalexin as a first-choice treatment option), and recommended the addition of new strength formulations for a number of currently listed antibiotics. The Committee also endorsed the current listings on the EML and EMLc for systemic and topical antibiotic treatment of trachoma, and topical antibiotic treatment of bacterial blepharitis, conjunctivitis and keratitis.

**Section 6.2.5 Antituberculosis medicines**

The Expert Committee recommended the inclusion of new strength, child-friendly formulations of bedaquiline and delamanid on the EMLc for the treatment of multi-drug resistant tuberculosis in children.

The Committee recommended inclusion of a new strength formulation of rifapentine and a fixed-dose combination formulation of rifapentine + isoniazid on the EML and EMLc for TB preventive treatment (TPT, previously known as treatment for latent tuberculosis infection (LTBI)), to reduce pill burden and improve treatment adherence to WHO-recommended TPT regimens.

The Committee recommended inclusion of rifapentine and moxifloxacin on the core list of the EML for the new indication of treatment of drug-susceptible tuberculosis, in line with updated WHO recommendations for a 4-month treatment regimen comprising rifapentine, isoniazid, pyrazinamide and moxifloxacin as alternative to the standard 6-month regimen with rifampicin, isoniazid, pyrazinamide and ethambutol. The Committee also recommended inclusion of a new strength formulation of pyrazinamide on the EML and EMLc for use in treatment regimens for drug-susceptible tuberculosis, which will offer a reduced pill burden for patients.

The Committee did not recommend the addition of injectable formulations of ethambutol, isoniazid and rifampicin to the EML and EMLc for the treatment of tuberculosis in specific patient populations, notably patients with severe forms of tuberculosis associated with poor outcomes, patients with acute or chronic gastrointestinal disease or malabsorption disorders, patients with severe comorbidities and patients unable or unwilling to take oral dosage forms. The Committee judged as insufficient the evidence presented in the applications on differences in terms of important benefits (e.g. mortality) between oral and injectable formulations by severity of illness. Important factors influencing this decision included the consistent preference for oral treatment for tuberculosis instead of intravenous administration in WHO guideline recommendations, the limited availability of these formulations in most countries, and the potential for

unnecessary use of intravenous formulations, and related hospitalization, in patients otherwise able to take oral therapy.

The Committee recommended deletion from the EML and EMLc of various formulations and strengths of amikacin, amoxicillin + clavulanic acid, isoniazid, isoniazid + pyrazinamide + rifampicin, linezolid, p-aminosalicylic acid and pyrazinamide, noting that they are not optimal formulations and strengths for tuberculosis treatment, in line with recommendations in current WHO treatment guidelines. The Committee recommended the addition of new injection solution formulations for amikacin, that have the advantage over powder for injection formulations of not requiring reconstitution for administration. The Committee did not recommend deletion of the oral liquid formulations of ethambutol, isoniazid and pyrazinamide, nor a 125 mg tablet formulation of ethionamide at this time, due to concerns about limited uptake and availability of preferred dispersible tablet formulations in some countries.

**Section 6.3 Antifungal medicines**

The Expert Committee recommended the inclusion of the echinocandin antifungal micafungin (with a square box indicating caspofungin and anidulafungin as therapeutic alternatives) on the complementary list of the EML and EMLc for the empiric treatment of suspected or proven invasive *Candida* infections in adults and children. The evidence presented suggested that echinocandins were associated with greater treatment success when compared with amphotericin B or triazole antifungals and supported the use of echinocandins in the empiric treatment of suspected or proven invasive *Candida* infections in critically ill patients, especially where there is a high probability of azole resistance. Furthermore, echinocandin antifungals were associated with a more favourable tolerability profile compared to non-echinocandin antifungals (e.g. amphotericin B). The Committee did not support listing for indications of prophylaxis of invasive *Candida* infections, nor treatment of invasive *Aspergillus* infections due to more limited evidence, and the availability of effective alternatives already included on the Model Lists.

**Section 6.4.2 Antiretrovirals**

The Expert Committee recommended the inclusion of a new strength, child-friendly formulation of dolutegravir on the EMLc for the treatment of HIV infection in children. The Committee also recommended the deletion of various formulations and strengths of abacavir, atazanavir, efavirenz, lamivudine, lamivudine + nevirapine + zidovudine, lopinavir + ritonavir, raltegravir and ritonavir from the EML and/or EMLc, in line with recommendations in WHO HIV treatment guidelines and the updated Optimal Formulary and Limited-Use list for Antiretroviral Drugs for Children. The Committee did not recommend listing for the fixed-dose combination formulation of abacavir + lamivudine + lopinavir/ritonavir, noting that this formulation did not demonstrate bioequivalence with the reference product and does not yet have regulatory approval.

**Section 6.4.3 Other antivirals**

The Committee recommended deletion of oseltamivir oral powder formulation from the complementary list of the EML and EMLc, noting that this formulation is no longer manufactured or marketed.

**Section 6.4.4.2 Medicines for hepatitis C**

The Expert Committee recommended the inclusion of fixed-dose combinations of daclatasvir + sofosbuvir, glecaprevir + pibrentasvir and sofosbuvir + velpatasvir, as well as single agent daclatasvir and single agent sofosbuvir to the core list of the EMLc for the treatment of children with chronic hepatitis C virus infection, based on evidence of pan-genotypic effectiveness and acceptable safety. The Committee also recommended the inclusion of the fixed-dose combination of daclatasvir + sofosbuvir on the core list of the EML.

## *Section 7: Antimigraine medicines*

**Section 7.1 For treatment of acute attack**

The Expert Committee recommended inclusion of sumatriptan on the core list of the EML for the treatment of adult patients with acute migraine. Sumatriptan is associated with improvements in clinically meaningful outcomes such as pain freedom, headache relief, and reduction of rescue medication use. Compared to acetylsalicylic acid and paracetamol, the analgesics currently included in the Model Lists for acute migraine treatment, sumatriptan has a different toxicity profile, and may offer long-term safety advantages particularly in patients who experience frequent migraine attacks. The Committee considered that overall, the available evidence indicated a positive benefit to risk profile for sumatriptan and that listing would provide an additional treatment option for patients who cannot tolerate or do not respond adequately to alternative analgesics already listed.

## *Section 8: Immunomodulators and antineoplastics*

**Section 8.1 Immunomodulators for non-malignant disease**

The Expert Committee recommended the inclusion of tacrolimus on the complementary list of the EML and EMLc for use as maintenance immunosuppression following organ transplantation, based on evidence of a favourable benefit to harm ratio. Tacrolimus significantly reduces acute rejection and graft loss when compared to ciclosporin, an alternative listed in the EML, and it has a different toxicity profile. The Committee recognized the public health importance of survival of transplanted organs and transplant recipients, given the shortage of donor organs and the significant investment of resources associated with organ transplantation.

**Section 8.2 Antineoplastic and supportive medicines**

A total of 23 applications for cancer medicines were received from various sources. Several applications were the product of efforts of the EML Cancer Medicines Working Group to engage with expert stakeholders to