Executive Summary

The Selection and Use of Essential Medicines 2019

Report of the 22nd WHO Expert Committee on the Selection and Use of Essential Medicines

WHO Headquarters, Geneva
1-5 April 2019

World Health Organization

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Executive summary

This Summary reports the recommendations made by the WHO Expert Committee on the Selection and Use of Essential Medicines for the 2019 Essential Medicines Lists update.

The 22nd meeting of the WHO Expert Committee on the Selection and Use of Essential Medicines took place in Geneva, Switzerland, from 1 to 5 April 2019. The aim of the meeting was to review and update the 20th WHO Model List of Essential Medicines (EML) and the 6th WHO Model List of Essential Medicines for Children (EMLc).

The Expert Committee considered **65 applications**, including proposals to add 53 new medicines and new formulations of 19 existing medicines, extend the indications for 34 listed medicines, and to remove 10 medicines or formulations from the lists. The Expert Committee also considered reports and recommendations from the EML Antibiotics and Cancer Medicines Working Groups. 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.

In summary, the Expert Committee:

- recommended the **addition of 28 new medicines to the EML** (12 to the core list and 16 to the complementary list);
- recommended the **addition of 23 new medicines to the EMLc** (6 to the core list and 17 to the complementary list);
- recommended the addition of **new formulations of 16 currently listed medicines**;
- recommended adding **additional indications for 26 currently listed medicines**;
- recommended the **deletion of 9 medicines** and of specific formulations of a further 4 medicines; and
- **rejected 21 applications** for inclusion, change or deletion of 31 medicines.

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

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

Section 6: Anti-infective medicines

Section 6.2 Antibacterials

AWaRe classification of antibiotics

The Expert Committee noted the adoption and utilization of the Access, Watch and Reserve (AWaRe) classification of antibiotics on the EML by several Member States including the endorsement of AWaRe by the G20 Health Ministers in Argentina in October 2018 [2]. Furthermore, a new target indicator based on AWaRe was adopted which specifies a country level target of at least 60% of antibiotic consumption being from the Access group. This indicator is intended to monitor access to essential medicines and progress

[1] http://www.who.int/selection_medicines/committees/subcommittee/2/eeb1098%5b1%5d.pdf
[2] http://www.g20.utoronto.ca/2018/2018-10-04-health.pdf

towards Universal Health Coverage under the WHO 13th General Program of Work[3]. The Committee recognized the emerging role of the AWaRe groups for stewardship and quality improvement programs.

The Expert Committee recommended that specific listing of antibiotics in the EML and the allocation of antibiotics to the different AWaRe groups should be distinguished from each other, recognizing their distinct albeit complementary purposes. The Committee acknowledged that EML-listed antibiotics represent a parsimonious, evidence-based selection of essential narrow spectrum antibiotics for first- and second-choice empiric treatment of most common bacterial infections and a tool for stewardship. However, the AWaRe classification should extend beyond the EML to all commonly used antibiotics globally. The Committee acknowledged the contributions of the EML Antibiotics Working Group and endorsed the Working Group's recommendations for AWaRe classification of 177 commonly used antibiotics, to better support antibiotic monitoring and stewardship activities. The Expert Committee recommended the development of an AWaRe classification database as a searchable resource for countries.

Antibiotics not classified as Access, Watch or Reserve

The Committee recommended, based on the advice of the EML Antibiotics Working Group, that WHO may wish to consider creating an additional group in the AWaRe classification database for antibiotics whose use is not evidence-based, nor recommended in high quality international guidelines, particularly fixed-dose combinations of multiple broad-spectrum antibiotics. Antibiotics in this group are not included on the Model Lists.

The AWaRe classification database will be published as an Online Appendix to the 2019 Model Lists and Technical Report of the meeting.

The Expert Committee recommended the re-structuring of Section 6.2 to better accommodate AWaRe classification, and that antibiotics on the EML be listed in revised sub-sections according to AWaRe groups, replacing the existing sub-sections based on chemical structure (e.g., beta-lactam and other antibacterials). The subsequent sub-sections within Section 6.2 are re-numbered accordingly:

- **6.2.1: Access group antibiotics**
- **6.2.2: Watch group antibiotics**
- **6.2.3: Reserve group antibiotics**
- **6.2.4: Antileprosy medicines**
- **6.2.5: Antituberculosis medicines**

Additions, changes and deletions

The Expert Committee recommended for inclusion three new recently registered antibiotics for treatment of multi-drug resistant infections caused by pathogens ranked as "Critical Priority" on the WHO Priority Pathogens List[4] and classified under AWaRe as Reserve antibiotics: ceftazidime + avibactam, meropenem + vaborbactam and plazomicin. Four recently registered antibiotics were not recommended for

[3] http://apps.who.int/gb/ebwha/pdf_files/EB144/B144_7-en.pdf
[4] The WHO PPL is tool to guide the research and development (R&D) of new antibiotics, ensuring that R&D responds to public health needs. The list is divided into three tiers – critical, high and medium risk pathogens. Gram negative bacteria are shown to be the most critical priority need (https://www.who.int/medicines/areas/rational_use/PPLreport_2017_09_19.pdf?ua=1).

EML inclusion, but were classified under AWaRE for monitoring purposes (ceftolozane + tazobactam, eravacycline and omadacycline as Reserve; delafloxacin as Watch).

The Committee recommended first- and second-choice empiric antibiotic treatment options for enteric fever, surgical prophylaxis and progressive apical dental abscess on the EML and EMLc, including the addition of cefuroxime (for surgical prophylaxis), classified under AWaRe as a Watch group antibiotic.

The Committee recommended the removal of aztreonam, fourth- and fifth-generation cephalosporins (as classes), tigecycline and daptomycin from the EML and EMLc as these antibiotics did not meet the revised criteria for inclusion on the Model Lists as individual Reserve group agents (see 6.2.3 RESERVE group antibiotics, below). Furthermore, the Committee agreed that fourth-generation cephalosporins should be re-classified as Watch group as they did not meet the revised criteria for classification as Reserve. The Committee also recommended the re-classification of faropenem from Watch to Reserve due to its high potential for inappropriate use. It is an orally available formulation with a broad spectrum activity whose inappropriate use may further the spread of carbapenemase-producing *Enterobacteriaceae*.

Section 6.2.1 Access group antibiotics

This category includes antibiotics that have activity against a wide range of commonly encountered susceptible pathogens while showing lower resistance potential than antibiotics in Watch and Reserve groups. The following 19 Access group antibiotics are recommended as first or second choice empiric treatment options for infectious syndromes reviewed by the Expert Committee and are listed as individual medicines on the Model Lists to promote optimal use and with the goal of improving global "access to Access" antibiotics.

Access group antibiotics included on the 2019 Model Lists			
Amikacin	Benzylpenicillin	Cloxacillin	Phenoxymethylpenicillin
Amoxicillin	Cefalexin	Doxycycline	Procaine benzylpenicillin
Amoxicillin + clavulanic acid	Cefazolin	Gentamicin	Spectinomycin
Ampicillin	Chloramphenicol	Metronidazole	Sulfamethoxazole + trimethoprim
Benzathine benzylpenicillin	Clindamycin	Nitrofurantoin	-

Section 6.2.2 Watch group antibiotics

The Watch group includes antibiotics that have higher resistance potential and includes most of the highest priority agents among the Critically Important Antimicrobials (CIA) for Human Medicine[5] and/or antibiotics that are at relatively high risk of selection of bacterial resistance. These medicines should be prioritized as key targets of national and local stewardship programs and monitoring. The following 11 Watch group antibiotics are recommended as essential first or second choice empiric treatment options for a limited number of specific infectious syndromes and are listed as individual medicines on the WHO Model Lists.

[5] The WHO CIA list is aimed at preserving medically important antimicrobials for human use by decreasing their use in the food chain (http://apps.who.int/iris/bitstream/10665/251715/1/9789241511469-eng.pdf?ua=1).

Watch group antibiotics included on the 2019 Model Lists	
Azithromycin	Ciprofloxacin
Cefixime	Clarithromycin
Cefotaxime	Meropenem
Ceftazidime	Piperacillin + tazobactam
Ceftriaxone	Vancomycin
Cefuroxime	

6.2.3 Reserve group antibiotics

The Reserve group includes antibiotics that should be reserved for treatment of confirmed or suspected infections due to multi-drug-resistant organisms. Reserve group antibiotics should be considered as "last resort" options. Seven selected Reserve group antibiotics are listed as individual medicines on the WHO Model Lists as they have a favourable benefit-risk profile and proven activity against "Critical Priority" or "High Priority" pathogens as identified by the WHO Priority Pathogens List, most notably carbapenem resistant *Enterobacteriaceae*. These antibiotics should be globally accessible, but their use should be tailored to highly specific patients and settings, when alternatives are not suitable or have failed. To preserve their effectiveness these Reserve group antibiotics should be prioritized as key targets of national and international stewardship programs including regular monitoring and reporting of their use.

Reserve group antibiotics included on the 2019 Model Lists	
Ceftazidime + avibactam	Meropenem + vaborbactam
Colistin	Plazomicin
Fosfomycin (intravenous)	Polymyxin B
Linezolid	

EML ANTIBIOTICS/AWaRe WORKING GROUP

The Expert Committee acknowledged that the existing EML listings and the classification of individual medicines to specific AWaRe groups may change slightly over time, due to the evolving epidemiology of infectious diseases and antimicrobial resistance, changes in the availability of antibiotics and emergence of new scientific evidence. The ongoing revision and consolidation of the antibiotics included on the EML and of AWaRe classification is a key activity of the Working Group, with the aim of balancing the objectives of preserving antibiotic effectiveness while guaranteeing necessary access. Therefore, the Committee recommended the continuation of the activities of the EML Antibiotics/AWaRe Working Group.

The Committee recommended that the Working Group should assess the adoption of AWaRe across countries and further explore how AWaRe can assist in activities to promote optimal antibiotic stewardship. Some areas needing more investigation are the incorporation of AWaRe in national essential medicines lists and clinical practice guidelines, and the adaptation of AWaRe for educational activities to improve antibiotic use. The Committee recommended the Working Group develop antibiotic stewardship algorithms for Reserve antibiotics to define how these medicines should be used and how their misuse can be prevented. This includes the identification of evidence gaps for the recommended uses in clinical practice. The Committee noted that the current regulatory approval process for new antibiotics, most of which qualify for the Reserve category due to their activity against priority multidrug-resistant pathogens (usually carbapenem resistant pathogens), does not result in adequate evidence to judge their role for their optimal

clinical use and guide appropriate policy interventions. The Working Group should identify and document these evidence gaps and propose research strategies for how to address them. In general, the AWaRe groups, WHO's Priority Pathogens List and the WHO list of critically important antimicrobials should become more closely aligned with regard to definitions and terminology to avoid confusion and the Working Group should support and expand this effort.

Additional proposed activities of the Working Group include the development of policy documents assessing optimal antibiotic dosage and treatment duration for common infectious syndromes in both adults and children. This information, together with the Model Lists and AWaRe should inform production of a WHO handbook outlining antibiotic treatment guidance for high-burden bacterial syndromes. This information should be made available also in an easily accessible electronic format, e.g. by incorporating this information in the electronic EML.

Section 6.2.4: Antituberculosis medicines

The Expert Committee recommended the inclusion of meropenem and of amoxicillin + clavulanic acid on the complementary list of the EML and EMLc for the new indication of treatment for MDR-TB. The Committee recommended that imipenem + cilastatin could be considered as an alternative to meropenem for use in adults. The Committee expressed concern in relation to increased use of carbapenem antibiotics (classified as Watch group) in the empiric treatment of MDR-TB and the development of carbapenem resistance and recommended that ongoing monitoring for the development of resistance be undertaken.

The Committee recommended the addition of several new formulations of currently listed medicines for use in children: cycloserine, ethambutol, ethionamide, isoniazid, levofloxacin, linezolid, and moxifloxacin. The addition of child-friendly formulations of antituberculosis medicines is fully in line with the latest WHO guideline recommendations on the management of MDR- and isoniazid-resistant TB.

The Committee recommended the deletion of capreomycin and kanamycin from the complementary list of the EML and EMLc, noting that their use is no longer recommended in WHO guidelines due to increased treatment failure and toxicity when compared to alternative oral therapeutic options. The Committee also recommended the deletion from the EML of fixed-dose combination of ethambutol + isoniazid, and specific formulations/strengths of fixed-dose combinations of isoniazid + pyrazinamide + rifampicin and isoniazid + rifampicin, no longer recommended in WHO guidelines due to their association with higher rates of treatment failure.

The Committee recommended the addition of bedaquiline to the complementary list of the EMLc the treatment of MDR-TB in children aged 6 years and older, as extrapolation of evidence from adult data suggests good efficacy and benefits outweigh risks. The Committee did not recommend a change to the age restriction (≥6 years) that applies to the listing of delamanid on the Model Lists, as the evidence used to support the lowering of the age limit in the WHO Guidelines used a formulation and strength of delamanid that is not currently commercially available, nor bioequivalent to the formulation and strength included in the EMLc.

The Committee did not recommend the addition of injectable formulations of ethambutol, isoniazid, p-aminosalicylic acid (PAS) and rifampicin: the Committee noted that WHO recommends oral treatment regimens, ideally administered in fixed-dose combinations. The Committee also noted that the availability of the proposed injectable agents was limited and recognized the potential for inappropriate use of prolonged

parenteral anti-TB medicines. The Committee did not recommend the addition of a new strength formulation of isoniazid oral liquid, giving preference to dispersible tablet formulations.

Section 6.4.2: Antiretrovirals

For the treatment of HIV infection, the Committee recommended the addition of the fixed-dose combination of dolutegravir + lamivudine + tenofovir disoproxil fumarate to the EML, and the addition of dolutegravir to the EMLc, in line with recommendations in WHO Guidelines. The Committee also recommended addition of new formulations of raltegravir, ritonavir, and lopinavir + ritonavir. Formulations of abacavir + lamivudine and zidovudine were recommended for deletion, while formulations of raltegravir and ritonavir proposed for deletion were recommended to be retained until the availability of newer, preferred formulations is assured.

Section 6.4.4.2: Medicines for hepatitis C

This section of the list has been amended to differentiate between pangenotypic and non-pangenotypic direct acting antivirals, and other antivirals for hepatitis C.

Section 6.4.4.2.1: Pangenotypic direct-acting antiviral combinations

The Expert Committee recommended the addition of the fixed dose combination of glecaprevir + pibrentasvir to the EML for the treatment of adult patients with chronic hepatitis C virus infection based on evidence of pan-genotypic effectiveness with acceptable safety, supported by current WHO guidelines. The Committee noted that the EML now contains multiple pangenotypic treatment options for hepatitis C (sofosbuvir + velpatasvir, sofosbuvir/daclatasvir, glecaprevir + pibrentasvir) and recommended that they be considered as therapeutically equivalent to facilitate selection and procurement at country level.

Section 6.4.4.2.2: Non-pangenotypic direct-acting antiviral combinations

The Committee also recommended the deletion from the EML of simeprevir, whose place in therapy has been superseded by the pangenotypic options. Other non-pangenotypic treatments could be considered for deletion in the future.

Section 6.5.3.2: (Antimalarial medicines) For prophylaxis

The Expert Committee recommended listing of fixed-dose combination formulations of sulfadoxine + pyrimethamine on the EML for the new indication of intermittent preventive treatment of malaria in pregnancy (IPTp), and on the EMLc for the new indication of intermittent preventive treatment of malaria in infancy (IPTi); and the addition of co-packaged formulations of amodiaquine and sulfadoxine + pyrimethamine dispersible tablets to the EMLc for seasonal malaria chemoprevention, in line with recommendations in WHO Guidelines for the treatment of malaria.

Section 6.5.5.1: African trypanosomiasis

The Expert Committee recommended the addition of fexinidazole to the EML and EMLc as an orally-administered treatment for treatment of 1st and 2nd stages of human African trypanosomiasis due to *Trypanosoma brucei gambiense* infection.

Section 6.6: (NEW) Medicines for ectoparasitic infections

The Expert Committee recommended listing of ivermectin on the EML and EMLc for the new indication of treatment of scabies, in a new sub-section of the list for ectoparasitic infections. The Committee noted the potential advantages of single-dose oral administration of ivermectin compared to topically administered alternatives in terms of improved compliance.

Section 7: Antimigraine medicines

The Expert Committee did not recommend the addition of sumatriptan to the EML for the treatment of adult patients with acute migraine. The Committee noted that available evidence supports the greater effectiveness of sumatriptan compared to placebo, but evidence comparing sumatriptan with analgesics currently included on the EML for treatment of migraine (aspirin and paracetamol) showed varying results, including no difference in effect. At its next meeting, the Committee would welcome a review of additional data of the role in therapy of sumatriptan in the context of other migraine therapies and current guideline recommendations.

Section 8: (RE-NAMED) Immunomodulators and antineoplastics

Section 8.1 (RE-NAMED) Immunomodulators for non-malignant disease

Anti-TNF biologics for chronic inflammatory conditions: The Expert Committee recommended the addition of adalimumab to the complementary list of the EML and EMLc for use in the treatment of chronic inflammatory autoimmune disorders – rheumatoid arthritis, ankylosing spondylitis, juvenile idiopathic arthritis and Crohn's disease based on a positive benefit-risk profile as second-line treatment (after methotrexate). Adalimumab is listed with a square box, representative of the class of tumour necrosis factor alpha (TNF-α) inhibitors, including biosimilars. Alternatives were limited to etanercept and infliximab on the EMLc and to etanercept, infliximab, certolizumab pegol and golimumab on the EML. The Committee recognized that these medicines are associated with a significant budget impact to health systems as they are used for long periods and often are highly priced. However, the availability of several therapeutically equivalent alternatives and increased availability of biosimilar products could lead to more market competition and reduced prices.

Medicines for multiple sclerosis: The Expert Committee recognized the public health need for effective and affordable treatments for multiple sclerosis (MS) but did not recommend the addition to the EML and EMLc of glatiramer acetate, fingolimod and ocrelizumab at this time. The Committee acknowledged the application's approach to increase access to MS treatments by prioritizing selected treatment options. However, the Committee noted that some relevant therapeutic options for MS were not included in the application (azathioprine and natalizumab) or were not given full consideration (rituximab). The superiority of presented medicines over other therapeutic options in the outcomes considered (benefits, harms, affordability) did not clearly emerge. The Committee would therefore welcome a revised application which comprehensively reviews the relative roles of relevant available medicines for MS.

Section 8.2: (RE-NAMED) Antineoplastic and supportive medicines

This section has been updated and amended to include sub-sections that better represent the pharmacologically diverse medicines currently listed:

- **8.2.1: Cytotoxic medicines**
- **8.2.2: Targeted therapies**
- **8.2.3: Immunomodulators**
- **8.2.4: Hormones and antihormones**
- **8.2.5: Supportive medicines**

Applications for new cancer medicines were the received from various sources, including a WHO Secretariat-led effort to engage with expert stakeholders through the Cancer Medicines Working Group to identify and prioritise the most effective cancer medicines for indications where they have clinically relevant benefits.

The Expert Committee recommended listing for a number of new high-priced cancer medicines for specific indications on the complementary list of the EML.

Melanoma: nivolumab (with a square box indicating pembrolizumab as a therapeutically equivalent alternative) for front-line monotherapy in patients with unresectable and metastatic melanoma. Both these medicines demonstrated highly relevant increases in overall survival and represent the first medicines on the EML for metastatic melanoma.

Multiple myeloma: bortezomib, lenalidomide, thalidomide and melphalan for the treatment of patients with newly-diagnosed multiple myeloma in both non-transplant and transplant eligible/available settings. These medicines demonstrated large improvements in survival with acceptable safety and represent the first medicines on the EML for multiple myeloma.

Lung cancer: erlotinib (with a square box indicating afatinib and gefitinib as therapeutically equivalent alternatives) for front-line treatment of EGFR mutation positive advanced non-small cell lung cancer. These medicines demonstrated relevant survival benefits (similar to that of cytotoxic chemotherapy) and offer better toxicity profiles and improved quality of life compared to chemotherapy.

Prostate cancer: abiraterone for the treatment of patients with metastatic castration-resistant prostate cancer. Abiraterone demonstrated relevant survival benefits for patients and an acceptable safety profile. It is associated with potential advantages in terms of emerging dosing strategies, lower pill burden and availability of generics which would be associated with cost-savings compared to similarly effective enzalutamide. Enzalutamide was not recommended for listing on the EML.

Leukaemias (EML and EMLc): arsenic (oral and IV formulations) for use in the treatment of patients with acute promyelocytic leukaemia. Arsenic-containing regimens were associated with less toxicity, high response rates and greater survival benefits compared to standard regimens. Pegaspargase was recommended for treatment of patients with acute lymphoblastic leukaemia as it is associated with less immunogenicity and antibody development compared to asparaginase.

The listings of some cancer medicines currently on the EML were recommended to be extended to include new indications of cervical cancer and multiple myeloma. Additionally, listing of 10 medicines currently included on the EML were recommended to be extended to the EMLc and additional indications were recommended for 11 cancer medicines currently included on the EMLc to improve access to these medicines for children. Refer to Table 1 for details.

Among the applications for cancer medicines that were not recommended for listing on the EML were:

- nivolumab, pembrolizumab and atezolizumab for the treatment of non-small cell lung cancer, as the Committee considered that their place in therapy for this condition is still evolving and that more data with longer follow-up are needed to better demonstrate estimates of their actual magnitude of benefit;
- pertuzumab for HER-2 positive breast cancer, as the evidence did not demonstrate a clinically meaningful survival benefit in early stage disease. A large overall survival benefit has been demonstrated in a single trial in metastatic disease, but similar results have not been seen in other trials. The Committee recommended further independent analysis of data from existing and ongoing trials be undertaken to inform future consideration for EML listing.
- Trastuzumab emtansine for HER-2 positive breast cancer, because while it demonstrates a relevant survival benefit, its use as second-line treatment of metastatic disease was considered not to be a priority in the context of treatment of breast cancer, and alternative EML-listed options are available.
- Subcutaneous formulations of rituximab and trastuzumab, as the Committee was concerned that listing of these formulations, for which biosimilars are not yet available, could limit competition and therefore limit access for patients.

EML CANCER MEDICINES WORKING GROUP

The Expert Committee acknowledged the work of the EML Cancer Medicines Working Group and endorsed the Working Group's recommendations that WHO adopt a threshold for benefit of at least 4-6 months survival gain to be considered as candidates for EML inclusion. The Committee acknowledged the role of the ESMO Magnitude of Clinical Benefit Scale[6] (ESMO–MCBS) as a screening tool to identify cancer treatments that have potential therapeutic value that warrants full evaluation for EML listing. Potential new EML cancer medicines, in general, should have a score on the ESMO-MCBS of A or B in the curative setting and of 4 or 5 in the non-curative setting. These scores would support a medicine being evaluated by the Expert Committee for inclusion in the EML through a full application.

The Committee recommended the continuation and further expansion of the activities of the Working Group. This should include the updated revision of treatment protocols for cancers previously considered by the Committee and identification of new cancer medicines that meet the above-mentioned criteria to be candidates for consideration of inclusion on the EML.

The Working Group should also review the issues being experienced at country level in relation to implementation of EML cancer medicine recommendations and access to cancer medicines. The Committee recommended the need for consolidation of cancer medicine recommendations and EML listings through

[6] https://www.esmo.org/score/cards

broader technical advisory group meeting, with country engagement to support implementation within a UHC perspective.

Section 10: Medicines affecting the blood

Section 10.2 Medicines affecting coagulation

The Expert Committee recommended the addition of dabigatran to the core list of the EML, with a square box (representative of the direct oral anticoagulants including apixaban, edoxaban and rivaroxaban) for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation, and for the treatment of venous thromboembolism. These medicines have a similar overall benefit-risk profile compared to warfarin, are associated with a lower risk of major bleeding, and may be particularly beneficial in settings where warfarin monitoring is not available.

Section 12: Cardiovascular medicines

Section 12.3 Antihypertensive medicines

The Expert Committee recommended the addition of four, two-drug fixed dose combination formulations to the core list of the EML for the treatment of hypertension: lisinopril + amlodipine, lisinopril + hydrochlorothiazide, telmisartan + amlodipine and telmisartan + hydrochlorothiazide. Each component is listed with a square box as representative of the relevant pharmacological classes. The Committee accepted that fixed-dose combinations may confer advantages for patients over single medicines given concomitantly in terms of better adherence and reduced pill burden. However, the Committee considered that the ongoing availability of single agent antihypertensive medicines remains critical to allow treatment modification where necessary.

Section 12.5.2 Thrombolytic medicines

The Expert Committee recommended the addition of alteplase to the complementary list of the EML for use in patients diagnosed with acute ischaemic stroke. The Committee noted that alteplase thrombolysis is associated with reductions in death and dependence when administered within 4.5 hours of the onset of stroke symptoms. Optimal use will require timely and highly organized care pathways, in facilities equipped and capable of managing stroke patients.

Section 17: Gastrointestinal medicines

Section 17.2 Antiemetic medicines

The Expert Committee recommended the addition of aprepitant to the complementary list of the EML and EMLc for management of chemotherapy-induced nausea and vomiting in patients undergoing moderately- to highly-emetogenic chemotherapy, as it has been shown to be more effective than standard antiemetics. The Expert Committee also recommended the addition of a square box to the current listings of ondansetron on the EML and EMLc, indicating therapeutic equivalence among 5HT3 receptor antagonists.

Section 17.5 Medicines used in diarrhoea

The Expert Committee recommended listing on the core list of the EMLc of a co-packaged presentation of oral rehydration salts and zinc sulfate tablets, noting the recommendations for co-administration of the two components in the management of diarrhoea in children. The co-packaged product was considered practical, and likely to support better adherence to treatment.

Section 18: (RE-NAMED) Medicines for endocrine disorders

This section has been updated and amended to include only medicines for endocrine disorders in revised sub-sections as follows:

- **18.1: Adrenal hormones and synthetic substitutes**
- **18.2: Androgens**
- **18.3: Estrogens**
- **18.4: Progestogens**
- **18.5: Medicines for diabetes**
- **18.6: Medicines for hypoglycaemia**
- **18.7 Thyroid hormones and antithyroid medicines**

Contraceptives and other medicines for reproductive health have been transferred to Section 22 (see below).

Section 18.5 Medicines for diabetes

The Expert Committee acknowledged that insulin is a life-saving essential medicine for which a compelling public health need exists. Yet, despite being available for almost 100 years, achieving reliable, equitable and affordable access to insulin remains a public health challenge in many countries. The Committee recognized the need for a wider understanding of the complexities of access to insulin and the current insulin market and recommended WHO prioritize the coordination of a series of actions to address the issues of insulin access and affordability.

This WHO coordinated approach should aim at tackling the different aspects of the current situation of suboptimal access to insulin in many countries. This includes:

- establishment of a WHO technical working group on access to insulin;
- consultation with Member States and other stakeholders to identify/clarify barriers to access at country level;
- strategies to address current regulatory barriers for biosimilar insulins, including the expansion of the WHO Prequalification Programme;
- development of a comprehensive approach to address insulin prices, including new mechanisms for pooled procurement through UN supply agencies (UNICEF and UNDP) and through providing support for countries;
- identification of evidence and research gaps regarding insulin use and supply, including setting-specific differences in clinical practice and health systems.

The Expert Committee did not recommend the addition of insulin analogues to the EML, reiterating the conclusion of the 2017 Expert Committee, that while long-acting insulin analogues are an effective treatment for type 1 diabetes, the available evidence shows efficacy and safety advantages of analogues compared to human insulin which are insufficiently large to justify the cost differential that continues to exist. In the absence of other coordinated actions, the Committee considered that the inclusion of insulin analogues for adults on the EML would be inadequate to address the underlying issues of poor access and affordability of insulins. The Expert Committee would therefore welcome a report that comprehensively

describes the actions that are undertaken over the next two years and an application that reviews more in depth current challenges for optimal global access and the role insulin analogues in children.

Section 18.6 Medicines for hypoglycaemia

The Expert Committee recommended addition of diazoxide on the complementary list of the EMLc for the management of hypoglycaemia secondary to prolonged hyperinsulinism based on a positive benefit to risk ratio and for its impact on reducing the serious neurological consequences of untreated hyperinsulinism in newborns.

Section 18.7 Thyroid hormones and antithyroid medicines

The Expert Committee recommended the addition of methimazole with a square box to the core list of the EML and to the complementary list of the EMLc for the treatment of primary hyperthyroidism. Carbimazole is a therapeutically equivalent alternative. The Committee also recommended that the square box be removed from the listing of propylthiouracil on the EML. Propylthiouracil remains the recommended first-line treatment for women in the first trimester of pregnancy, and in patients for whom first-line treatment with methimazole (or carbimazole) is not appropriate or available. Propylthiouracil remains listed on the complementary list of the EMLc for use in patients for whom alternative first-line treatment is not appropriate or available.

Section 19.3 Vaccines

This section was updated by the Secretariat for consistency and alignment with the most recent WHO immunization policy recommendations and vaccine position papers. Dengue vaccine was added to the EML and EMLc for use in some high-risk populations, in line with the September 2018 dengue vaccine WHO position paper[7].

Section 22: (RE-NAMED) Medicines for reproductive health and perinatal care

This section has been updated and amended to include contraceptives and other medicines for reproductive health, maternal and neonatal care (from Sections 18, 22 and 29).

Section 22.3 Uterotonics

The Expert Committee recommended the addition of heat-stable carbetocin injection to the core list of the EML for the prevention of postpartum haemorrhage based on similar effects compared to oxytocin for efficacy and safety outcomes. The Committee agreed that heat-stable carbetocin may offer advantages over oxytocin in some settings as it does not require cold-chain transport or refrigerated storage.

The Expert Committee did not recommend deletion of the indication of prevention of post-partum haemorrhage for misoprostol, noting that misoprostol is recommended in WHO guidelines as an alternative to oxytocin in settings where injectable uterotonics are not available or cannot be safely administered.

The Expert Committee recommended the transfer of mifepristone – misoprostol from the complementary to the core list of the EML, and removal of the note accompanying the listing stating, "Requires close medical supervision", based on the evidence presented that close medical supervision is not

[7] https://apps.who.int/iris/bitstream/handle/10665/274315/WER9336.pdf?ua=1

required for its safe and effective use. The Committee also recommended the addition of a co-packaged presentation of mifepristone and misoprostol to the core list of the EML.

Recalling that their role and responsibility is to provide WHO with technical guidance in relation to the selection and use of essential medicines, the Expert Committee noted that its mandate did not extend to providing advice regarding the statement "Where permitted under national law and where culturally appropriate". Subsequent to the Expert Committee meeting, the Director General, in consultation with the Department of Essential Medicines and Health Products, decided that no change to the statement be made.

Section 22.6 Other medicines administered to the mother

The Expert Committee recommended the addition of tranexamic acid to the core list of the EML for the new indication of treatment of post-partum haemorrhage, to be used as part of the standard PPH treatment package, including fluid replacement, uterotonics surgical and non-surgical interventions in accordance with WHO guidelines.

Section 24: Medicines for mental and behavioural disorders

The Expert Committee did not recommend inclusion of methylphenidate on the Model Lists for the treatment of attention-deficit hyperactivity disorder (ADHD) due to uncertainties in the estimates of benefit, and concerns regarding the quality and limitations of the available evidence for both benefit and harm.

Section 24.2.1 Medicines used in depressive disorders

The Expert Committee recommended the addition of a square box to the listing of fluoxetine on the core list of the EML for the treatment of depressive disorders. The Committee noted that medicines within the pharmacological class of selective serotonin reuptake inhibitors (SSRI) have demonstrated efficacy, but can differ in terms of pharmacokinetics, adverse events and drug-interaction profiles. The availability of different SSRIs as essential medicines may be beneficial at country level to expand therapeutic alternatives for patients and support better procurement. The Committee considered that it was not necessary to add escitalopram to the EML, as the addition of the square box to fluoxetine would allow the selection of escitalopram at national level.

Section 25: Medicines acting on the respiratory tract

The Expert Committee recommended the addition of tiotropium to the core list of the EML, with a square box as representative of the pharmacological class of long-acting muscarinic antagonists (LAMA) for the treatment of chronic obstructive pulmonary disease, based on evidence of effectiveness in controlling COPD symptoms and reducing exacerbations, and acceptable safety.

Section 27: Vitamins and minerals

The Expert Committee recommended a correction to the listed strength of iodine capsules to 190 mg, to accurately reflect the quantitative composition of this product.

The Expert Committee recommended the addition of multiple micronutrient powders to the core list of the EMLc for the prevention of anaemia in infants and children, noting that a standardized product monograph is to be included in the United States Pharmacopoeia.

Section 29: Medicines for diseases of joints

Formerly Section 30. Re-numbered following the transfer of medicines specific for neonatal care to Section 22. The former Section 30 has been deleted.

Follow up decisions from the 2017 Expert Committee meeting

Oseltamivir

The Expert Committee noted the advice from the WHO Secretariat that the WHO Guidelines for clinical management of influenza are in the process of being updated, but the recommendations of the guideline development group were not yet available. The Committee recommended that no change be made to the current listing for oseltamivir on the Model Lists until the updated guidelines and supporting evidence can be reviewed.

Ready to use therapeutic food (RUTF)

The Expert Committee did not recommend the addition of RUTF to the Model Lists for the treatment of severe acute malnutrition, but again acknowledged the effectiveness of this product for this condition. The Committee considered that the comprehensive report prepared by the WHO Department of Nutrition in response to the request of the previous Expert Committee, highlighted the divided opinions and ongoing uncertainty of the implications at country level of listing RUTF as a medicine on the Model List.

Working group on Transparency and access to clinical trial data

The Expert Committee reiterated its recommendation from 2017 to establish a Working Group on transparency and timely public disclosure of all clinical trial results and available data. The Working Group should identify strategic actions to address factors known to impact the availability of reliable data informing applications for the inclusion or removal of medicines on the Model Lists. Such factors include selective outcome reporting, publication bias and open access to clinical trial results. This Working Group could also action the recommendation made by the Expert Committee for further independent analysis of data for pertuzumab in breast cancer.

Improving access to and affordability of essential medicines

Throughout the meeting, the Expert Committee repeatedly noted and discussed the issue of improving access to high-priced essential medicines (e.g., insulin, immunomodulators and new cancer medicines) and the issue of affordability for health systems and patients.

The Committee acknowledged the limited role of WHO in price setting at country level, but identified several different actions that could contribute to making some of the recently listed essential medicines more affordable at country level:

1. A wider adoption of biosimilars
2. Expanding the remit of the medicines patent pool
3. The role of pooled procurement/tendering
4. Use of flexibilities enshrined in the WHO TRIPS agreement
5. Other existing instruments

1. Biosimilars

With the addition of new biological medicines to the Model Lists in 2019, the Expert Committee recognized that biologicals, including biosimilars, are associated with a significant budget impact to health systems. However, the availability of several therapeutically equivalent alternatives and the increasing availability of biosimilar products could lead to greater market competition, improved patient access and reduced costs. Access to biosimilars is critical for achieving affordable access to many biological medicines including new cancer treatments and immunomodulators for chronic inflammatory conditions such as rheumatoid arthritis. The Committee noted, with concern, the limited progress to date with access to biosimilars of some essential medicines (e.g. rituximab).

The Committee recommended that WHO expand its pre-qualification programme to include biosimilars of medicines listed on the EML, such that they are routinely evaluated along with the reference product, to ensure accessibility and affordability to quality-assured products.

The Expert Committee considered the issue of interchangeability of biosimilar products as a very important one for wider access and a crucial aspect to foster competition. The Committee recommended that EML Secretariat develops a concept note to summarise all the issues and barriers to full interchangeability for wider access to affordable biosimilars for consideration by the Expert Committee in 2021.

Finally, the Committee considered that where biosimilars of listed essential medicines exist, these are considered therapeutically equivalent also for procurement purposes.

2. The expanded role of MPP

The Medicines Patent Pool (MPP), a public health organization funded by Unitaid, has played a significant role in facilitating affordable access to essential medicines in the field of HIV and HCV through its public health oriented licences with originator companies. To date, the MPP has licences on 14 medicines on the WHO EML. Licensing through the MPP of patented essential medicines for the treatment of tuberculosis (e.g. bedaquiline) would also be a welcome contribution to improving access.

The recent expansion of the MPP to other patented essential medicines beyond HIV, hepatitis C and tuberculosis represents a real opportunity to facilitate affordable access to some of the new medicines that have been added to the list this year in low and middle-income countries. Licensing through the MPP could, for example, contribute to facilitating access to some of the cancer medicines, the novel oral anticoagulants, the new antibiotics and the heat-stable formulation of carbetocin. In the case of cancer, it would be important that the MPP also explore the application of its model to biotherapeutics so as to facilitate early entry of biosimilars through voluntary licensing agreements in low and middle-income countries.

3. The role of pooled procurement and tendering

The square box symbol (▪) is primarily intended to indicate similar clinical performance within a pharmacological class of medicines on the EML. The listed medicine should be the example of the class for which there is the best evidence for effectiveness and safety. In some cases, this may be the first medicine that is licensed for marketing; in other instances, subsequently licensed compounds may be safer or more effective. Where there is no difference in terms of efficacy and safety data, the listed medicine should be the one that is generally available at the lowest price, based on international drug price information sources. Examples of pharmacological classes with established therapeutic equivalence include proton pump inhibitors, ACE inhibitors and erythropoietins.

More recently, the square box has been selectively applied to some listings, indicating specific acceptable alternative options such as for morphine and enoxaparin. A square box was applied to three pangenotypic regimens for hepatitis C, to indicate similar clinical performance across the combination regimens.

When there are multiple options within the same pharmacological class or in the same therapeutic area there can be substantial market competition that can allow for price reductions. Large price reductions can be the result of tendering processes at country or local level. Applying the square box concept can improve outcomes in pooled procurement activities at national or sub-national levels, and has the advantage of improving transparent governance.

The Expert Committee recommended a comprehensive review of medicines listed with a square box on the Model Lists be undertaken for consideration at its next meeting. The review will provide greater clarity for countries regarding application of the square box concept for national essential medicines lists selection and procurement.

4. Use of TRIPS flexibilities in line with the Doha Declaration on TRIPS and Public Health

Application and management of intellectual property should contribute to innovation and promotion of public health, in line with WHO global strategy and plan of action on public health, innovation and intellectual property.

Member States have the possibility to make use of the provisions which provide public health flexibilities contained in the Agreement on Trade-Related Aspects of Intellectual Property Rights, including the public health flexibilities recognized by the Doha Ministerial Declaration on the TRIPS Agreement and Public Health in order to promote access to essential medicines.

5. Other existing instruments

Countries can define different pricing policies on how prices are set and negotiated at national level. However, medicines prices are the end result of a number of measures, actions and contextual factors (such as market size and cost structures) acting at country level. These can involve different stakeholders that include regulators, reimbursement systems/third-party payers, competition authorities.

Competition law and policies are also instruments available to governments in addressing public health concerns, competition policy has an important role to play in ensuring access to medical technology and fostering innovation in the pharmaceutical sector[8].

All applications and documents reviewed by the Expert Committee are available on the WHO website at: https://www.who.int/selection_medicines/committees/expert/22/en/

[8] http://www.who.int/iris/handle/10665/78069

Table 1: Recommended additions, changes and deletions on the 2019 EML and EMLc

EML – New medicines added		EMLc – New medicines added	
Medicine	**Indication**	**Medicine**	**Indication**
Abiraterone	Prostate cancer	□ Adalimumab	Chronic systemic inflammatory conditions
□ Adalimumab	Chronic systemic inflammatory conditions	All-trans retinoid acid (ATRA)	Acute promyelocytic leukaemia
Alteplase	Thrombolytic	Aprepitant	Nausea and vomiting
Aprepitant	Nausea and vomiting	Arsenic trioxide	Acute promyelocytic leukaemia
Arsenic trioxide	Acute promyelocytic leukaemia	Bedaquiline	Tuberculosis
Bortezomib	Multiple myeloma	Ceftazidime + avibactam	Reserve antibiotic
Carbetocin	Post-partum haemorrhage	Cefuroxime	Surgical prophylaxis
Ceftazidime + avibactam	Reserve antibiotic	Dasatinib	Imatinib-resistant chronic myeloid leukaemia (CML)
Cefuroxime	Surgical prophylaxis	Dengue vaccine	Vaccine
□ Dabigatran	Anticoagulant	Diazoxide	Hypoglycaemia
Dengue vaccine	Vaccine	Dolutegravir	HIV
Dolutegravir + lamivudine + tenofovir	HIV	Enoxaparin	Anticoagulant
□ Erlotinib	Lung cancer	Fexinidazole	Human African trypanosomiasis
Fexinidazole	Human African trypanosomiasis	Fluorouracil	Nasopharyngeal cancer, metastatic colorectal cancer, early colon cancer, early rectal cancer
Glecaprevir + pibrentasvir	Hepatitis C	Imatinib	Chronic myeloid leukaemia, gastrointestinal stromal tumour
Lenalidomide	Multiple myeloma	Irinotecan	Metastatic colorectal cancer
□ Lisinopril + □ amlodipine	Hypertension	□ Methimazole	Hyperthyroidism
□ Lisinopril + □ hydrochlorothiazide	Hypertension	Multiple micronutrient powders	Prevention of anaemia
Melphalan	Multiple myeloma	Nilotinib	Imatinib-resistant CML
Meropenem + vaborbactam	Reserve antibiotic	Oxaliplatin	Metastatic colorectal cancer, early colon cancer
□ Methimazole	Hyperthyroidism	Pegaspargase	Acute lymphoblastic leukaemia
□ Nivolumab	Metastatic melanoma	Procarbazine	Hodgkin lymphoma
Pegaspargase	Acute lymphoblastic leukaemia	RIF oral arsenic formulation	Acute promyelocytic leukaemia
Plazomicin	Reserve antibiotic	Rituximab	Diffuse large B-cell lymphoma
RIF oral arsenic formulation	Acute promyelocytic leukaemia		
□ Telmisartan + □ amlodipine	Hypertension		
□ Telmisartan + □ hydrochlorothiazide	Hypertension		
Thalidomide	Multiple myeloma		
□ Tiotropium	COPD		

EML - New / changed indications		**EMLc - New /changed indications**	
Amoxicillin	Dental abscess	Amoxicillin	Dental abscess
Amoxicillin + clavulanic acid	Surgical prophylaxis, MDR-TB	Amoxicillin + clavulanic acid	Surgical prophylaxis, MDR-TB
Azithromycin	Enteric fever	Azithromycin	Enteric fever
Carboplatin	Cervical cancer	Bleomycin	Kaposi sarcoma
Cefazolin	Surgical prophylaxis	Cefazolin	Surgical prophylaxis
Ceftriaxone	Enteric fever	Ceftriaxone	Enteric fever
Ciprofloxacin	Enteric fever	Ciprofloxacin	Enteric fever
Cisplatin	Cervical cancer	Cisplatin	Nasopharyngeal cancer
Cyclophosphamide	Multiple myeloma	Cyclophosphamide	Diffuse large B cell lymphoma
Dexamethasone	Multiple myeloma	Cytarabine	Acute myeloid leukaemia, acute promyelocytic leukaemia
Doxorubicin	Multiple myeloma	Daunorubicin	Acute promyelocytic leukaemia
Gentamicin	Surgical prophylaxis	Doxorubicin	Diffuse large B cell lymphoma, Kaposi sarcoma
Ivermectin	Scabies	Gentamicin	Surgical prophylaxis
Meropenem	MDR-TB	Hydroxycarbamide	Chronic myeloid leukaemia
Metronidazole	Surgical prophylaxis	Ivermectin	Scabies
Phenoxymethylpenicillin	Dental abscess	Mercaptopurine	Acute promyelocytic leukaemia
Prednisolone	Multiple myeloma, prostate cancer	Meropenem	MDR-TB
Sulfadoxine + pyrimethamine	Malaria - Intermittent preventive treatment in pregnancy	Methotrexate	Acute promyelocytic leukaemia
Tranexamic acid	Post-partum haemorrhage	Metronidazole	Surgical prophylaxis
		Phenoxymethylpenicillin	Dental abscess
		Prednisolone	Diffuse large B-cell lymphoma
		Sulfadoxine + pyrimethamine	Malaria – intermittent preventive treatment in infancy
		Vincristine	Diffuse large B-cell lymphoma, Kaposi sarcoma
EML – New formulation/strength		**EMLc – New formulation/strength**	
Calcium folinate	Tablet 5 mg and 25 mg	Amodiaquine with sulfadoxine + pyrimethamine	Co-package
Cyclophosphamide	Tablet 50 mg	Calcium folinate	Tablet 5 mg and 25 mg
Etoposide	Capsule 50 mg	Cyclophosphamide	Tablet 50 mg
Mifepristone-misoprostol	Co-package	Cycloserine	Solid oral dosage form 125 mg
Raltegravir	Granules 100 mg	Ethambutol	Dispersible tablet 100 mg
Ritonavir	Oral powder 100 mg	Ethionamide	Dispersible tablet 125 mg

		Etoposide	Capsule 50 mg
		Isoniazid	Dispersible tablet 100 mg
		Levofloxacin	Dispersible tablet 100 mg
		Linezolid	Dispersible tablet 150 mg
		Lopinavir + ritonavir	Granules 40 mg + 10 mg
		Moxifloxacin	Dispersible tablet 100 mg
		ORS + zinc sulfate	Co-package
		Raltegravir	Granules 100 mg
		Ritonavir	Oral powder 100 mg
EML – Medicines / formulations deleted		**EMLc – Medicines / formulations deleted**	
Abacavir + lamivudine	Dispersible tablet 60 mg + 30 mg	Abacavir + lamivudine	Dispersible tablet 60 mg + 30 mg
Aztreonam	Powder for injection 1 g; 2 g	Aztreonam	Powder for injection 1 g; 2 g
Capreomycin	Powder for injection 1 g	Capreomycin	Powder for injection 1 g
Daptomycin	Powder for injection 350 mg, 500 mg	Daptomycin	Powder for injection 350 mg, 500 mg
Ethambutol + isoniazid	Tablet 400 mg + 150 mg	Fifth-generation cephalosporins: e.g., ceftaroline	Powder for injection 400 mg; 600 mg
Fifth-generation cephalosporins: e.g., ceftaroline	Powder for injection 400 mg; 600 mg	Fourth-generation cephalosporins: e.g., cefepime	Powder for injection 500 mg; 1 g; 2 g
Fourth-generation cephalosporins: e.g., cefepime	Powder for injection 500 mg; 1 g; 2 g	Kanamycin	Powder for injection 1 g
Isoniazid + pyrazinamide + rifampicin	Tablet 150 mg + 500 mg + 150 mg	Tigecycline	Powder for injection 50 mg
Isoniazid + rifampicin	Tablet 60 mg + 60 mg; 150 mg + 150 mg	Zidovudine	Dispersible tablet 60 mg
Kanamycin	Powder for injection 1 g		
Simeprevir	Capsule 150 mg		
Tigecycline	Powder for injection 50 mg		
Zidovudine	Dispersible tablet 60 mg		
Other changes to listings			
Clofazimine	Replace ‘capsule’ with ‘solid oral dosage form’		EML and EMLc
Rifabutin	Replace ‘capsule’ with ‘solid oral dosage form’		EML
Propylthiouracil	Remove square box, add note “for use when alternative first-line treatment is not appropriate or available; and in patients during the first trimester of pregnancy”		EML
Propylthiouracil	Add note “for use when alternative first-line treatment is not appropriate or available”		EMLc
Fluoxetine	Add square box		EML
Iodine capsules	Amend strength from 200 mg to 190 mg		EML and EMLc
Ondansetron	Add square box		EML and EMLc
Mifepristone-misoprostol	Transfer from complementary to core list, remove note regarding requirement for close medical supervision		EML

Changes to terminology of indications		
	2017	**2019**
Infections	*Chlamydia trachomatis*	Sexually transmitted infection due to *Chlamydia trachomatis*
	Neisseria gonorrhoeae	Gonorrhoea
	Trichomonas vaginalis	Trichomoniasis
Cancers	Acute myelogenous leukaemia	Acute myeloid leukaemia
	Wilms tumour	Nephroblastoma (Wilms tumour)
Changes to sections and sub-sections of the Model Lists		
	2017	**2019**
Section 6.2: Antibacterials		
	6.2.1 Beta-lactam medicines	6.2.1 Access group antibiotics
	6.2.2 Other antibacterials	6.2.2 Watch group antibiotics
	6.2.3 Antileprosy medicines	6.2.3 Reserve group antibiotics
	6.2.4 Antituberculosis medicines	6.2.4 Antileprosy medicines
		6.2.5 Antituberculosis medicines
		6.6 Medicines for ectoparasitic infections
Section 6.4.4.2: Medicines for hepatitis C		
	6.4.4.2.1 Nucleotide polymerase inhibitors	6.4.4.2.1 □ Pangenotypic direct-acting antiviral combinations
	6.4.4.2.2 Protease inhibitors	6.4.4.2.2 Non-pangenotypic direct-acting antiviral combinations
	6.4.4.2.3 NS5A inhibitors	6.4.4.2.3 Other antivirals for hepatitis C
	6.4.4.2.4 Non-nucleoside polymerase inhibitors	**6.4.4.2.4 Deleted**
	6.4.4.2.5 Other antivirals	**6.4.4.2.5 Deleted**
Section 8: RENAMED - Immunomodulators and antineoplastics (was Antineoplastics and immunosuppressives)		
	8.1 Immunosuppressive medicines	8.1 Immunomodulators for non-malignant disease
	8.2 Cytotoxic and adjuvant medicines	8.2 Antineoplastics and supportive medicines
		8.2.1 Cytotoxic medicines
		8.2.2 Targeted therapies
		8.2.3 Immunomodulators
		8.2.4 Hormones and antihormones
		8.2.5 Supportive medicines
	8.3 Hormones and antihormones	**8.3 Deleted**
Section 18: RENAMED - Medicines for endocrine disorders (formerly Hormones, other endocrine medicines and contraceptives)		
	18.1 Adrenal hormones and synthetic substitutes	18.1 Adrenal hormones and synthetic substitutes
	18.2 Androgens	18.2 Androgens
	18.3 Contraceptives	18.3 Estrogens
	18.4 Estrogens	18.4 Progestogens
	18.5 Insulins and other medicines used for diabetes	18.5 Medicines for diabetes
	18.6 Ovulation inducers	18.6 Medicines for hypoglycaemia
	18.7 Progestogens	18.7 Thyroid hormones and antithyroid medicines

	18.8 Thyroid hormones and antithyroid medicines	**18.8 Deleted**
Section 22: RENAMED - Medicines for reproductive health and perinatal care (formerly Oxytocics and antioxytocics)		
	22.1 Oxytocics	22.1 Contraceptives
	22.2 Antioxytocics (tocolytics)	22.2 Ovulation inducers
		22.3 Uterotonics
		22.4 Antioxytocics (tocolytics)
		22.5 Other medicines administered to the mother
		22.6 Medicines administered to the neonate
Section 29: RENAMED – Medicines for diseases of joints (formerly Specific medicines for neonatal care)		
	29.1 Medicines administered to the neonate	29.1 Medicines used to treat gout
	29.2 Medicines administered to the mother	29.2 Disease modifying agents used in rheumatoid disorders (DMARDs)
		29.3 Juvenile joint diseases
Section 30: DELETED (formerly Medicines for diseases of joints)		
	30.1 Medicines used to treat gout	**30.1 Deleted**
	30.2 Disease-modifying agents used in rheumatoid disorders (DMARDs)	**30.2 Deleted**
	30.3 Juvenile joint diseases	**30.3 Deleted**

Table 2: Applications and medicines not recommended for 2019 EML and EMLc

ADDITIONAL MEDICINES	
Addition of anti-PD-1 immune checkpoint inhibitors for treatment of non-small cell lung cancer (**atezolizumab, nivolumab, pembrolizumab**)	EML
Addition of newly registered antibiotics for treatment of infections due to multi-drug resistant organisms (including AWaRe classification) (**ceftolozane + tazobactam, delafloxacin, eravacycline, omadacycline**)	EML
Addition of medicines for treatment of multiple sclerosis (**fingolimod, glatiramer acetate, ocrelizumab**)	EML & EMLc
Addition of long-acting insulin analogues for treatment of type 1 diabetes (**insulin detemir, insulin glargine, insulin degludec**)	EML
Addition of **enzalutamide** for treatment of metastatic castration-resistant prostate cancer	EML
Addition of **escitalopram** for treatment of major depressive disorder	EML
Addition of **methylphenidate** for treatment of attention-deficit hyperactivity disorder	EML & EMLc
Addition of **pertuzumab** for use in the treatment of breast cancer	EML
Addition of **sumatriptan** for treatment of migraine	EML
Addition of **trastuzumab emtansine** (TDM-1) for use in the treatment of breast cancer.	EML
ADDITIONAL FORMULATIONS / STRENGTHS	
New injectable formulation of **ethambutol** for treatment of drug-susceptible tuberculosis	EML & EMLc
New injectable formulation of **isoniazid** for treatment of drug-susceptible tuberculosis	EML & EMLc
New strength of **isoniazid** oral liquid for treatment of drug-susceptible tuberculosis	EMLc
New injectable formulation of **p-aminosalicylic** acid for treatment of drug-susceptible tuberculosis	EML & EMLc
New injectable formulation of **rifampicin** for treatment of drug-susceptible tuberculosis	EML & EMLc
New subcutaneous formulation of **rituximab** for use in the treatment of lymphoma and leukaemia	EML
New subcutaneous formulation of **trastuzumab** for use in the treatment of breast cancer.	EML
NEW INDICATIONS	
New indication for **5-fluorouracil** for treatment of cervical cancer in the curative setting.	EML
DELETIONS	
Deletion of **misoprostol** for the indication for prevention of postpartum haemorrhage	EML
Deletion of antiretroviral formulations for treatment of HIV infection (**raltegravir** 100 mg tablets, **ritonavir** 400 mg/5 mL oral liquid)	EML & EMLc
AGE RESTRICTIONS	
Change to age restriction for use of **delamanid** in children with multi-drug resistant tuberculosis	EMLc

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Declaration of Interests

Declarations of interests of Expert Committee Members and Temporary Advisers

Declaration of Interest, and management of any disclosures, is an important process governed by the WHO Guidelines for Declaration of Interests (WHO Experts). The WHO Essential Medicines Secretariat identified and screened a number of individuals, considered for participation at the 22nd Expert Committee on the Selection and Use of Essential Medicines, in different capacities – as Members and Temporary Advisors.

The screening process required close and detailed review of all the potential Members and Temporary Advisers and their disclosures prior to confirming participation. In this regarding, the WHO Essential Medicine Secretariat rigorously examined each potential participant. Guidance from the Office of Compliance, Risk Management and Ethics was additionally sought.

The declaration of interest process, resulted in the participation of Committee Members and Temporary Advisers as reported in the List of Participants (above)

Committee Members and Temporary Advisers who declared having no conflicts of interests were: Zeba AZIZ, Andrea BIONDI, Sumanth GANDRA, Armando GENAZZANI, Monica IMI, Maria AUXILIADORA OLIVEIRA; Gabriela PRUTSKY-LOPEZ, Nizal SARRAFZADEGAN, Fatima SULEMAN, Worasuda YOONGTHONG and Mei ZENG.

The following Committee Members declared interests that were determined not to represent a conflict of interest:

Dr Franco CAVALLI disclosed being a President of the World Oncology Forum, The World Oncology Forum is funded exclusively from independent, non-commercial sources. This is an unpaid activity.

Dr Graham COOKE disclosed having chaired the Lancet Gastroenterology & Hepatology Commission on Accelerating the elimination of viral hepatitis, for which he is unpaid. Dr Cooke also declared having received minimal honoraria for a speaking engagement in 2017 from Merck and Gilead Sciences Inc. respectively on subjects not related to the work of the Essential Medicine Secretariat. He has additionally received a minimal honoraria from Edixomed Ltd to provide advice on study designs to test nitric oxide, a treatment not related to any application under evaluation at this meeting. Conflicts of interests declared by Dr Cooke were considered minor and did not require further management.

Dr Gregory KEARNS disclosed a consultancy contract as a paediatric pharmacology adviser with Boehringer Ingelheim that will commence after the Expert Committee meeting. This is a paid activity at a level of remuneration below the threshold of US$5,000. This was considered not to represent a conflict.

Dr Mike SHARLAND disclosed being the chair of the Department of Health's Expert Advisory Committee on Antimicrobial Prescribing, Resistance and Healthcare Associated Infection (APRHAI); leading the NeoAMR Project, an initiative to address neonatal sepsis launched by the Global Antibiotic Research and Development Partnership (GARDP), a joint programme of WHO and the Drugs for Neglected Diseases initiative (DNDi) in support of the Global Action Plan for Antimicrobial Resistance. All positions are unpaid. Dr Sharland also declared that his institution, St George's University London, has received research funding from GARDP to support the development of academic activities, including observational cohort studies, on antibiotic use in children. GARDP is funded exclusively from independent, non-commercial sources. As a GARDP advisor, Dr Sharland was involved in discussion on several antibiotics, particularly fosfomycin and polymyxin B, antibiotics included in AWaRe and under discussion at this meeting. As the mandate of GARDP largely

coincides with WHO - to drive the global response to antimicrobial resistance and set health priorities – and all R&D activities are limited to neglected diseases to deliver not-for-profit, needs-driven R&D, Dr Sharland declaration was considered not to represent a conflict.

Professor Shalini SRI RANAGANATHAN declared that she has received research funding from the Colombo University, where she is employed, to conduct a survey on availability and affordability of essential medicines for children in Sri Lanka. This was determined not to represent a conflict.

Temporary Advisers

Dr Elisabeth de Vries participated as a Temporary Advisor and disclosed having served as an expert in Data Safety Monitoring Committee for trials promoted by no-profit research program (National Surgical Adjuvant Breast and Colon Project) and profit companies (Daiichi Sankyo, Merck, Synthon, Sanofi and Pfizer). The matters under consideration by the Data Safety Monitoring Committees are not related to medicines under evaluation or the work of the 22nd Expert Committee on the Selection and Use of Essential Medicines. Dr de Vries chairs the Magnitude of Clinical Benefit Scale Working Group of the European Society for Medical Oncology (ESMO-MCBS), the Cancer Medicines Working Group of ESMO, and the Response Evaluation Criteria in Solid Tumours (RECIST) Working Group. It is noted that ESMO is an NGO in official relations with WHO. All positions are unpaid. Through her involvement in the above mentioned ESMO and RECIST panels, Dr de Vries was involved in the evaluation of medicines to be considered by this Expert Committee (abiraterone, atezolizumab, enzalutamide, nivolumab, pembrolizumab, pertuzumab, trastuzumab emtansine).

Her institution (University of Groningen) is involved in early phase clinical trials to explore the therapeutic and diagnostic/prognostic roles of cancer medicines and biomarkers receiving institutional funding from Amgen, Astra Zeneca, Bayer, Chugai, CytomX, Genentech, G1 Therapeutics, Nordic Nanovector, Radius Health, Roche, Synthon. These trials are not directly related to medicines for which applications are to be evaluated at this meeting.

After reviewing Dr de Vries declarations, it was determined she could participate as a Temporary Advisor.

Dr Gilbert KOKWARO disclosed an appointment as Chair of the Universal Health Coverage Advisory Panel for Kenya. The Advisory Panel will develop a package of essential medicines that will form the benefits package to be provided under the UHC programme in Kenya. This was considered not to represent a conflict and it was determined that he could participate as a Temporary Advisor.

It is noted that the names and brief biographies of all the Committee Members and Temporary Advisers were made publicly available for comment ahead of the meeting.