Application for changes to section 6.2.5 Antituberculosis Medicines of the WHO Model Lists of Essential Medicines

WHO Global Tuberculosis Programme

CONSULTATION WITH WHO TECHNICAL DEPARTMENTS

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OTHER ORGANIZATION(S) CONSULTED AND/OR SUPPORTING THE SUBMISSION
The Tuberculosis Procurement and Market-Shaping Action Team (TPMAT) was consulted and is supporting the application.

SUMMARY OF THE PROPOSED CHANGES AND RATIONALE

The World Health Organization (WHO) Global Tuberculosis Programme (GTB) acknowledges the key role that the WHO Model List of Essential Medicines (EML) and the WHO Model List of Essential Medicines for Children (EMLc) play in guiding countries and regional authorities to prioritize medicines for procurement in accordance with local public health needs and treatment guidelines. As the WHO EML and EMLc influence the medicines that people have access to, the contents of these lists constitute important determinants of health worldwide. It is therefore of the utmost importance that medicines, and corresponding formulations included in the WHO EML and EMLc, as well as any information included in these documents, align with the most recent WHO recommendations and reflect the latest developments in the availability of quality-assured formulations, including those that may be more appropriate for specific populations (e.g., children).

WHO GTB carried out a review of the 2023 WHO EML and EMLc to examine the availability and appropriateness of the TB medicines and formulations included in both EMLs, in the context of the latest available WHO recommendations on TB and also procurement patterns.

Based on this review, WHO GTB would like to propose the following modifications:

1. Removal of the footnote regarding the indication for use of rifabutin

rifabutin	Solid oral dosage form: 150 mg.* ~~***For use only in patients with HIV receiving protease inhibitors.**~~

The interactions of rifampicin (the mainstay of TB treatment) with antiretroviral therapy (ART) are of concern in HIV-associated TB *(1)*. When the 6-month rifampicin-containing regimen is used, these drug interactions may result in decreased concentrations of antiretroviral drugs. Standard, rifampicin-containing anti-TB treatment was recommended in combination with efavirenz-based ART and now with dolutegravir-based ART. Conversely, key contraindicated drug combinations were rifampicin with nevirapine and protease inhibitors. Rifabutin is a less potent inducer of the cytochrome P450 system, which may be considered in people on some ART regimens that include nevirapine or a protease inhibitor, with close monitoring for safety and tolerability *(2)*. However, rifabutin is also the preferred rifamycin to be administered alongside opioid agonist maintenance therapy (OAMT) *(3)*.

Given that the indication for use listed on the WHO EML does not cover all possible uses of rifabutin (ie, the use alongside OAMT is not included), and considering that WHO TB guidelines and operational handbook are the reference documents that include up to date information on the clinical use of TB medicines, we propose to remove the footnote from the WHO EML listing.

2. Group all TB medicines under the WHO EML (and EMLc) Core List in alphabetical order
The Complementary List of section 6.2.5 Antituberculosis medicines of the WHO EMLs has historically included TB medicines used for multidrug-resistant tuberculosis (MDR-TB). The complementary list is

published alongside a note specifying that "*Medicines for the treatment of multidrug-resistant tuberculosis (MDR-TB) should be used in specialized centres adhering to WHO standards for TB control.*" This is in line with the more general definition of "Complementary List" for WHO EMLs.

In the past, MDR-TB care used to be mostly centralised and managed by specialized centres located in larger cities, posing logistical and financial challenges to people who had limited access to specialized facilities. In 2017, WHO published a recommendation indicating that decentralized model of care is recommended over a centralized model for patients on MDR-TB treatment *(conditional recommendation, very low certainty of evidence) (4, 5)*. Decentralized care means care that is provided in smaller, ambulatory, non-specialized health-care centres closer to where a person with TB lives, often by community health workers or nurses, non-specialized doctors, community volunteers or TB treatment supporters. Care could occur at local centres (e.g. community health centres), or at the person's home or workplace. Having treatment and care provided in decentralized health-care centres helps improve access to treatment and increase the number of people with TB who receive regular, community-based treatment and support. Decentralized care is often less disruptive to persons' lives, allowing them to access treatment, care and counselling more easily and with less cost. It may also allow them to continue to work (therefore lessening the financial burden of TB disease) and to remain with their families.

Moreover, some TB medicines are now used as both first- and second-line agents and, as such, were listed in both the Core List and in the Complementary List of the TB section. These include moxifloxacin, which is a core component of key MDR-TB regimens including the 6-month BPaLM regimen alongside bedaquiline, pretomanid and linezolid *(6)*, as well as the 4-month regimen for drug-susceptible TB composed of isoniazid, rifapentine, moxifloxacin and pyrazinamide (2HPMZ/2HPM) *(7)*; ethionamide is also listed in both lists, as it is used both for MDR-TB treatment as well as the treatment of drug-susceptible TB meningitis for children and adolescents as part of the intensive 6-month regimen alongside daily isoniazid, rifampicin and pyrazinamide throughout *(8)*.

Acknowledging that WHO promotes decentralized ambulatory care (over hospital-based care) for MDR-TB and that many TB medicines are currently being investigated for both drug-susceptible and drug-resistant TB, we propose to list all TB medicines in alphabetical order in section 6.2.5 of the WHO EMLs. Detailed information about the clinical use of the listed medicines will be found in relevant WHO guidelines and operational handbooks.

In addition to the changes requested above, a separate application is being submitted by WHO GTB for the addition of a child-friendly formulation of rifapentine (150 mg scored, dispersible tablet) to the WHO EML and WHO EMLc.

We thank you in advance for requesting that these changes be made to the WHO EML and the EMLc.

References

1. WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities, second edition. Geneva: World Health Organization; 2024 (https://iris.who.int/bitstream/handle/10665/376549/9789240091290-eng.pdf?sequence=1).
2. WHO operational handbook on tuberculosis Module 4: Treatment – drug-susceptible tuberculosis treatment. Geneva: World Health Organization; 2022 (https://iris.who.int/bitstream/handle/10665/354548/9789240050761-eng.pdf?sequence=1).
3. Integrating collaborative TB and HIV services within a comprehensive package of care for people who inject drugs: consolidated guidelines. Geneva: World Health Organization; 2016 (https://iris.who.int/handle/10665/204484).
4. WHO consolidated guidelines on tuberculosis. Module 4: treatment. Tuberculosis care and support. Geneva: World Health Organization; 2022 (https://iris.who.int/bitstream/handle/10665/353399/9789240047716-eng.pdf?sequence=1).
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6. WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment, 2022 update. Geneva: World Health Organization; 2022 (https://iris.who.int/bitstream/handle/10665/365308/9789240063129-eng.pdf?sequence=1).
7. WHO consolidated guidelines on tuberculosis. Module 4: Treatment - drug-susceptible tuberculosis treatment. Geneva: World Health Organization; 2022 (https://iris.who.int/bitstream/handle/10665/353829/9789240048126-eng.pdf?sequence=1).
8. World Health Organization. WHO consolidated guidelines on tuberculosis: Module 5: Management of tuberculosis in children and adolescents. Geneva: World Health Organization; 2022 (https://apps.who.int/iris/rest/bitstreams/1414329/retrieve).