Wider access to quality-assured rifapentine-based regimens is needed to accelerate tuberculosis prevention and care globally

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To the Editor:

In their correspondence, Guglielmetti *et al.* [1] emphasise the importance of improved access to rifapentine globally, both for the treatment of tuberculosis (TB) disease and as part of TB preventive treatment (TPT) regimens. They also highlight some of the major problems with access to this medicine, especially in the European Union (EU), foremost amongst which being the absence of market authorisation of rifapentine in the EU. In this letter we highlight key actions taken by the World Health Organization (WHO) to address important barriers to the implementation of recommendations on rifapentine.

Over the past years, as data on the efficacy and safety of rifapentine have become available, WHO has reviewed the most recent evidence in a timely manner and updated its recommendations, *de facto* expanding the market for rifapentine. In 2018, a 3-month TPT regimen of weekly isoniazid (H) and rifapentine (P) (3HP) was recommended. In 2020, WHO further updated its prevention guidelines and recommended an even shorter TPT regimen of 1-month daily isoniazid plus rifapentine (1HP) [2]. In May 2022, WHO released updated, consolidated guidelines on the treatment of drug-susceptible (DS) TB and recommended for the first time a 4-month regimen including daily rifapentine for treatment of TB in people aged 12 years and above [3]. To facilitate dissemination and uptake of the latest WHO guidelines, including on these rifapentine-containing shorter regimens, WHO also launched a one-stop TB Knowledge Sharing Platform [4].

As a complement to its guidance, WHO also updated its Model Lists of Essential Medicines (EML) to encourage countries to include rifapentine-based products in their national EMLs, so as to streamline procurement and, ultimately, facilitate access [5]. In 2021, two rifapentine-based products were added to the WHO EML, including a 300 mg standalone formulation which meets the dosing requirements for both TPT regimens and treatment of DS-TB, and a fixed-dose combination (FDC) with isoniazid (300/300 mg) that helps to reduce pill burden for TPT. In parallel, in view of the forthcoming new recommendation on the use of rifapentine to treat DS-TB, WHO removed the restriction of rifapentine for TPT on the EML.

Until a few months ago, there was only one source of quality-assured rifapentine tablets (a 150 mg tablet) for global supply. Since 2018, WHO has issued expressions of interest (EOIs) inviting pharmaceutical manufacturers to submit applications to the WHO Prequalification of Medicines Programme (PQM) for two rifapentine preparations best aligned to recommended dosing. The EOIs foster the manufacturing of selected, quality-assured TB medicines [6]. In May 2022, the first HP FDC (300/300 mg) was prequalified by WHO. In addition, another HP FDC (300/300 mg) and two standalone rifapentine formulations (300 mg) are currently being reviewed by the WHO PQM [7]. As a general principle, WHO supports reliance mechanisms for regulators to benefit from work done by PQM and by Stringent Regulatory Authorities to make the best use of available resources and expertise [8]. For example, to incentivise in-country registration of WHO prequalified medicines, WHO promotes reliance practices through the WHO Collaborative Registration Procedure [9]. The same mechanism can be used to streamline registration of products approved by Stringent Regulatory Authorities.

In 2021, a child-friendly formulation of rifapentine was also added to the WHO PQM EOI (150 mg scored, dispersible tablets), following consensus reached through the Paediatric Drug Optimization for TB

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medicines group convened by WHO [10]. This formulation will be particularly important to dose young children, who are at higher risk of progression from TB infection to TB disease.

Rifapentine products are also included in the Global Fund Expert Review Panel EOI, a list that includes a subgroup of medicines included in the WHO PQM EOI and that functions as an interim mechanism to enable access to quality-assured, priority medicines ahead of WHO prequalification [11]. An HP FDC (300/300 mg) was approved from the Global Fund Expert Review Panel at the end of 2019 and has been available from the Stop TB Partnership Global Drug Facility (GDF) since early 2020 [12]. In May 2022, two additional rifapentine formulations received approval from the Global Fund Expert Review Panel, namely a 300 mg rifapentine formulation, which will be soon included in the GDF catalogue, and an additional HP FDC (300/300 mg).

In recent years, the high price of rifapentine has been one of the main barriers to the scale up of TPT globally. In 2019, WHO, as well as other partners, advocated for lower rifapentine price for low-resource settings. This resulted in a 66% price drop negotiated between UNITAID, the Global Fund and the manufacturer of the only rifapentine formulation available at that time (*i.e.* 150 mg tablets) [13]. The lowered price was eventually also applied to generic rifapentine products developed subsequently.

Concerns around nitrosamine impurities in rifamycin-including medicines have also been addressed by Stringent Regulatory Authorities and WHO. Based on the level of nitrosamines reported in these medicines, they advised against the interruption of treatment with rifamycins, given that the benefits would outweigh any potential risk [14].

WHO calls for a rapid uptake of its latest recommendations on treatment of TB infection and disease to accelerate the progress in reaching the global targets in ending TB globally. Global access to rifapentine is essential to achieve this. Dialogue with manufacturers to deliver quality drug preparations, attracting more generic production, negotiating price reductions and strengthening regulatory reliance practices – especially in the EU, where the absence of market authorisation is blocking access to rifapentine – are some of the measures that can be used more extensively to increase access to rifapentine worldwide.

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