Pragmatic global dosing recommendations for the 3-month, once-weekly rifapentine and isoniazid preventive TB regimen in children

To the Editor:

The End TB Strategy, proposed by the World Health Organization (WHO) in 2014, calls for a 90% reduction in tuberculosis (TB)-related deaths and an 80% reduction in TB incidence by 2030 [1]. TB remains a leading cause of death in children under 5 years of age [2], and interventions to eliminate preventable child deaths from TB are urgently needed. Additional and effective TB prevention measures are crucial for the End TB Strategy goals to be met [3].

Children have a high risk of progressing to TB disease following *Mycobacterium tuberculosis* infection, especially if young (<5 years of age) or HIV-infected [4]. Since 2014, the WHO has placed an increased emphasis on TB prevention with multiple guidelines promoting household contact investigation and management to identify children at the greatest risk of TB disease [5, 6]. The updated 2019 WHO guidelines for latent TB infection recommend TB preventive therapy in at-risk children, including all children living with HIV and children under 5 years of age with a household TB source case [6].

A 3-month regimen of once-weekly rifapentine and isoniazid (3HP) has demonstrated efficacy and improved safety and tolerability in preventing TB disease in adults and children (2 years and older) [7, 8]. However, these drugs are not co-formulated, and rifapentine is not available in a child-friendly formulation. Based on existing paediatric pharmacokinetic data, rifapentine dosing follows a weight band algorithm [6, 9]. In contrast, isoniazid is dosed in $mg \cdot kg^{-1}$, which differs in young children *versus* adolescents and adults [6]. This requires healthcare workers to calculate and round isoniazid doses to determine the appropriate tablet count for children. Dosing complexity is a major barrier to children receiving this effective, short-course preventive regimen in the field.

To address these shortcomings, we performed pharmacokinetic modelling and simulations to devise a synchronised, simple and pragmatic dosing strategy for 3HP in children that utilises currently available formulations based on request from the WHO PK-PD Task Force. This work will provide interim guidance on the optimal dosing with existing formulations (rifapentine 150 mg; isoniazid 100 mg), while informing the development of child-friendly rifapentine formulations for young children.

We performed dosing simulations with paediatric population pharmacokinetic models for isoniazid [10] and rifapentine [9] to predict concentrations using the current once-weekly 3HP dosing recommendations and adult formulations: rifapentine 300 mg (10–14 kg), 450 mg (14.1–25 kg), 600 mg (25.1–32 kg), or 750 mg (32.1–50 kg) and isoniazid 25 $mg \cdot kg^{-1}$ (age 2–11 years) or 15 $mg \cdot kg^{-1}$ (age ⩾12 years) [6]. With predicted drug exposures, unified weight band doses were determined for each drug and aligned with WHO pre-specified weight bands for TB treatment in children and current formulations. Dosing simulations were performed for adults using drug-specific population pharmacokinetic models and recommended dosing: 900 mg rifapentine and 600 mg (<50 kg) or 900 mg (50+ kg) isoniazid [11, 12].

Demographic data (*i.e.* gender, weight, age) representative of actual paediatric global populations acquired from national surveys (*e.g.* Demographic and Health Surveys Program) were used in simulations of

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This study proposes a revised synchronised and pragmatic dosing table for the 3HP regimen in children that utilises available formulations. The revised doses are predicted to deliver adequate rifapentine and isoniazid exposure in children. https://bit.ly/3eUHm86

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children 2–4 years [13]. Child demographics from the randomised controlled trial on 3HP (PREVENT-TB) were used for children 5–14 years [9]. Children <10 kg were excluded due to the lack of rifapentine pharmacokinetic data in this group.

The revised weight bands matched WHO pre-specified weight bands for anti-TB drug dosing in children (table 1). These weight band break-points differ from those currently in the rifapentine product label by 1–2 kg. Isoniazid doses for each weight band in the revised recommendations are clearly defined and match available formulations (table 1). Under this revised dosing method, median (interquartile range) rifapentine exposures were 725 (549–952) $mg{\cdot}h{\cdot}L^{-1}$ in children 10–15 kg, 888 (670–1177) $mg{\cdot}h{\cdot}L^{-1}$ in children 16–23 kg, 955 (724–1272) $mg{\cdot}h{\cdot}L^{-1}$ in children 24–30 g, and 909 (679–1189) $mg{\cdot}h{\cdot}L^{-1}$ in children >30 kg, compared to 660 (509–839) $mg{\cdot}h{\cdot}L^{-1}$ in adults. Median (interquartile range) isoniazid exposures were 66 (38–113) $mg{\cdot}h{\cdot}L^{-1}$ in children 10–15 kg, 84 (47–148) $mg{\cdot}h{\cdot}L^{-1}$ in children 16–23 kg, 64 (37–115) $mg{\cdot}h{\cdot}L^{-1}$ in children 24–30 kg, and 52 (30–90) $mg{\cdot}h{\cdot}L^{-1}$ in children >30 kg compared to 55 (41–90) $mg{\cdot}h{\cdot}L^{-1}$ in adults, assuming 1:1 ratio of slow:fast acetylator.

We propose a revised pragmatic dosing table for the 3HP regimen that 1) simplifies isoniazid dosing into weight bands, 2) aligns with pre-specified WHO weight bands for paediatric TB dosing, and 3) utilises the available and registered formulations in the field. We demonstrate adequate rifapentine and isoniazid exposure in children 2–14 years with these revised doses, and therefore expect equal efficacy to current dosing practices.

Our field-friendly dosing table is readily accessible to healthcare workers in TB services and clearly defines rifapentine and isoniazid doses by weight band. This new dosing strategy is a substantial improvement to current guidelines that require calculations and rounding for isoniazid that may potentiate dosing errors and add complexity to regimen implementation, especially in high TB burden regions where human resources for TB services are typically limited. Aligning weight bands with other TB drugs simplifies paediatric dose determination across TB disease states and is an important next step towards co-formulation of this important TB prevention regimen.

These dosing recommendations are based on data from normal weight children and cannot be confidently applied to overweight or obese children as no pharmacokinetic data currently exist in this population. Given the growing global issue of childhood obesity, pharmacokinetic studies are urgently needed in obese children to establish optimal dosing approaches and avoid sub- or supra-therapeutic exposures.

Despite US Food and Drug Administration approval of rifapentine for paediatric use in 2014, no child-friendly rifapentine formulation is licensed or routinely available; such formulations are currently limited to paediatric phase I/II trials. A novel child-friendly rifapentine formulation is urgently needed to support safe and effective 3HP dosing in all children, including those <2 years of age who have the highest risk of TB disease progression and disseminated TB. A dose-finding and safety study of rifapentine in these young children is ongoing (study 35: clinicaltrials.gov NCT03730181). Our work demonstrates adequate rifapentine exposure with a 150 mg tablet, supporting development of a dispersible formulation at this strength. The dispersible tablet should be scored to allow for accurate dosing in small children and be palatable. This will allow for evaluation and potential programmatic use in novel ultrashort regimens (*e.g.* 28 days of daily rifapentine/isoniazid) and potentially TB disease as data emerge (study 31; clinicaltrials.gov NCT02410772). The time between drug approval and paediatric dosing and formulation

TABLE 1 Revised dosing recommendations for 3-month, once-weekly rifapentine and isoniazid (3HP) preventive treatment regimen

Weight band	Rifapentine		Isoniazid	
	Dose	Tablets	Dose	Tablets
Children[#]				
10–15 kg	300 mg	2	300 mg	3
16–23 kg	450 mg	3	500 mg	5
24–30 kg	600 mg	4	600 mg	6
⩾31 kg	750 mg	5	600 mg	6
Adults[¶]				
<50 kg	900 mg	6	600 mg	2
⩾50 kg	900 mg	6	900 mg	3

[#]: child tablet sizes are 150 mg (rifapentine) and 100 mg (isoniazid); [¶]: adult tablet sizes are 150 mg (rifapentine) and 300 mg (isoniazid).

development has historically been long in TB. The WHO has established the Global Accelerator for Paediatric Formulations (GAP-f), which will hopefully accelerate child formulation development and uptake across diseases.

It is clear that implementing safe and effective shorter TB prevention therapy in children needs to be scaled up worldwide, especially in the context of HIV and novel pandemics like SARS-CoV-2, given the dramatic impact such diseases may have on TB burden. It is essential that TB services, including testing, prevention and treatment, are maintained, as a small decline in TB services may dramatically increase TB incidence and mortality [14]. Simple, pragmatic dosing and short-course TB prevention therapy will aid efforts to significantly prevent morbidity and death due to TB in children.

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