1. Historical Background

Rifampicin (R), isoniazid (H), pyrazinamide (Z) and ethambutol (E) are essential tuberculosis (TB) drugs in the standard first-line treatment of drug-susceptible TB, where they are used in combination (i.e. two months of HRZE followed by four months of HR for most people with drug-susceptible TB OR two months of HRZ(E) followed by 2 HR for children and young adolescents with non-severe presumed drug-susceptible TB). All four TB medicines are included in the WHO Model Lists of Essential Medicines (EML) for adults and children (1) both as part of adult or paediatric fixed-dose combinations or as oral single-dose formulations.

The recommended dose of rifampicin traditionally used for the treatment of drug-susceptible TB in adults, 10 mg/kg (8-12 mg/kg) once daily with a maximum daily dose capped at 600 mg and 15 mg/kg (10-20 mg/kg) in children, also with a maximum daily dose at 600 mg, was introduced in 1971, when rifampicin was approved by the United States Food and Drug Administration (US FDA), based on pharmacokinetic (PK) and toxicity evidence, as well as cost considerations. This development followed several clinical trials where regimens containing rifampicin were shown to be effective and when combined with pyrazinamide allowed a reduction of treatment duration for drug-susceptible TB to 6 months. Most of these trials used rifampicin at a single daily dose of 600 mg, without providing detailed reasoning for the selection of this dose. In 2017, WHO removed the cap on the maximum daily dose of rifampicin to allow the target dose of rifampicin to be achieved in all patients with drug-susceptible TB, especially those in the higher body-weight bands (2).

Recently, concentrations of rifampicin in adults, achieved at the site of pulmonary infection have been described as very low when 10mg/kg dosing is used. In vitro, animal, and early bactericidal activity studies suggest that the 600 mg once daily dose is at the lower end of the dose-response curve, therefore delivering suboptimal concentrations for patients above 50 kg (3). Both toxicity studies and clinical experience using rifampicin for the treatment of other diseases showed no increased toxicity or tolerability problems when daily doses used were two or three times higher than currently recommended (4-7).

The standard dose of isoniazid traditionally used for the treatment of drug-susceptible TB in adults is between 4-6mg/kg/day while “high” dose (most commonly 10-15mg/kg/day) is used for treatment of people with a form of isoniazid-resistant TB associated with the inhA mutation, usually as part of a regimen for the treatment of multi-drug or rifampicin-resistant TB (MDR/RR-TB). In the host, isoniazid is metabolized by N-terminal acetyltransferase 2 (NAT2), and a mutation in the NAT2 genotype leads to substantial differences in isoniazid metabolism, and individuals are classified as either “slow” or “fast” acetylators. In the presence of the inhA mutation, the same dose may suffice in slow acetylators but fast
Acetylators may require a higher dose (e.g. 15mg/kg/day) to reach the threshold. In children, the currently recommended daily dose of isoniazid is 7-15 mg/kg/day, with the lower range expected to provide adequate levels in the majority of children, except in children below two years of age and fast acetylators to whom the higher range applies (8).

The current recommended dose of pyrazinamide is 20-30 mg/kg/day. Preclinical and clinical evidence suggest that the current dose of pyrazinamide is not optimal (9-12). For children, pyrazinamide dosing has been determined at 35 mg/kg/day (30-40 mg/kg range) in WHO guidance since 2010 (13).

The currently recommended dose of ethambutol is 15-25mg/kg/day for both adults and children.

Some studies have shown that increasing the dose of pyrazinamide or ethambutol could probably improve effectiveness in certain people with TB, but would be expected to increase toxicity to unacceptable levels if this was applied to all (14).

For the treatment of drug-susceptible TB meningitis (TBM) in adults and children, the composition of the regimen is the same as for pulmonary TB, with an extended continuation phase of 7-10 months instead of four months. For children and adolescents, a short intensive treatment regimen, consisting of rifampicin, isoniazid, pyrazinamide and ethionamide instead of ethambutol (6HRZE/to) is conditionally recommended as an alternative to the standard 12-month regimen (2HRZE/10HR) (15). In the short intensive regimen for TBM slightly higher doses of rifampicin (22.5-30 mg/kg/day) and isoniazid (15-20 mg/kg/day) are used given the need to reach the site of disease. The dosing of pyrazinamide in this regimen is 35-45 mg/kg/day.

2. Recent evidence on dosing of first-line TB medicines
Emerging evidence has indicated that some first-line TB medicines may be underdosed and or target exposures may not be reached, including for certain populations such as young children and or those with comorbidities such as HIV or undernutrition. WHO has started to assess this evidence to determine if updates to dosing of first-line TB medicines are required.

2.1 Adults
In 2020 WHO commissioned four systematic reviews (one for each of the first-line TB drugs) which were conducted according to a single master protocol to assess the efficacy and safety of doses of first-line TB drugs higher than those currently recommended by WHO when used as part of a combination regimen for treating or re-treating adults with presumed drug-susceptible TB (16).

For rifampicin (13 trials), the review did not find evidence of higher rates of treatment success at rifampicin doses of 15, 20 or 35 mg/kg, while it found slightly reduced treatment failure, risk of relapse and all-cause mortality at doses between 15 and 20 mg/kg. Higher doses may increase the risk of serious adverse events, but the evidence is very uncertain. For isoniazid (4 trials, all published before 1969) the review found some evidence of increasing numbers of adverse events with higher doses. For pyrazinamide (1 trial from 1959) the evidence was very uncertain and largely inconclusive. No trials met the inclusion criteria for ethambutol. In addition to the absence of studies on pyrazinamide and
ethambutol, the reviewers concluded that there were significant concerns about the risk of bias in many of the included studies and they were unable to analyze indirect comparisons or formal dose-response relations due to the limitations in the data.

A study by Boeree et al suggested that increased doses of rifampicin, as part of the first-line TB regimens or in combination with other drugs, may contribute to potential shortening of the regimen duration in adults. (17).

Several studies have explored and are still evaluating rifampicin target exposures for adults, investigating the effect of doses higher than 10 mg/kg on clinical outcomes and corresponding safety and tolerability of such higher doses. Studies suggest that the maximal tolerated dose in adults is 40 mg/kg once daily, with an increased frequency of adverse events observed above this dose (18). From an efficacy perspective, increasing bactericidal activity and time of sputum culture conversion from positive to negative has been observed with increasing doses and exposures of rifampicin (6, 18). The RIFASHORT trial, however, did not demonstrate non-inferiority of a 4-month regimen of rifampicin at 1800 mg for DS-TB when compared to the current standard of care (19).

In terms of the impact of higher rifampicin dosing on drug–drug interactions, the PHENORIF study showed that high-dose rifampicin resulted in no or mild additional effect on cytochrome P450 enzymes (CYP). In particular, there was no effect on CYP1A2 and only mild additional induction of CYP2C9, CYP2C19, CYP2D6 and CYP3A, indicating that existing recommendations on managing drug-drug interactions with rifampicin can remain unchanged for the majority of co-administered medicines when using high-dose rifampicin (20).

A model-based meta-analysis of rifampicin exposure and mortality in TB meningitis (TBM) trials in adults has shown that higher rifampicin exposures (corresponding to a dose of 1350 or 1800 mg) substantially decreased the risk of death (21).

2.2 Children

There is a growing body of scientific evidence showing that higher doses of first-line TB medicines may be needed to reach target exposures in children to match exposures in adults receiving the currently recommended WHO doses. Some studies have shown that rifampicin doses were below the target, especially in very young children (22), although these studies used a wide variety of formulations of rifampicin, with different bioavailability. Rifampicin exposures at current WHO-recommended doses have also been noted to be below the target in malnourished children. A modelling study has shown that exposure target attainment can be improved with currently available FDCs, with stratified dosing methods (23). Modelling studies have suggested poor outcomes in these paediatric populations (22-25).

A systematic review and meta-analysis commissioned by WHO explored the relation between current dosing of rifampicin, isoniazid, pyrazinamide and ethambutol and PK exposures based on WHO guidance and successful treatment outcomes in children and adolescents aged below 18 years. The impact of doses higher than those currently recommended by WHO on efficacy could not be established. The review concluded that at WHO-recommended doses, clinical outcomes in children treated for DS-TB are variable, with an average of 82% achieving a favourable outcome (26, 27). However, the study
confirmed that exposures of rifampicin, pyrazinamide and ethambutol are routinely lower in children than in adults, constituting a risk factor for unfavourable outcomes.

In general, isoniazid appears within the exposure target, but fast acetylators have significantly lower exposure than slow acetylators, meaning that isoniazid dosing could only be adjusted based on genotypic testing, which is not widely available in low-resource settings. This applies to all ages.

Two subsequent systematic reviews and individual participant data (IPD) meta-analyses confirmed that optimal dosing of first-line TB medicines in children cannot be achieved with current paediatric fixed-dose combinations (28, 29). When compared to the target exposure in adults, lower exposures to all first-line TB medicines were observed in both reviews, particularly in children aged under 2 years, in which the nonlinear effect of weight on clearance due to allometric scaling leads to low exposures when these children are dosed at the same mg/kg as older children and adolescents (30). This could also be due to the lower bioavailability of certain medicine formulations (isoniazid and rifampicin) in children aged under 2–3 years (31). A subgroup analysis in one study demonstrated that children and adolescents weighing 25 kg and over who received adult WHO-recommended doses had lower isoniazid and rifampicin exposures than those on WHO-recommended paediatric doses (28).

Optimizing dosing and weight bands in children weighing 25 kg and over may be needed to ensure adequate exposure to first-line TB medicines. Acknowledging that rifampicin exposure is affected by several factors, including age, weight, the specific formulation used, nutritional status and HIV status, the optimization of rifampicin dosing for malnourished children and children living with HIV, who are particularly vulnerable, has been explored further (32, 33).

In the Opti-Rif study, a 65–70 mg/kg daily dose of rifampicin was needed in children to achieve the target exposures observed in adults receiving 35 mg/kg. Safety was assessed over only 2 weeks, however, and some concerns over tolerability were noted, which may be associated with the formulation used in the trial (rifampicin capsules opened and administered as a nonpalatable suspension) (34). A few trials with high-dose rifampicin in children are ongoing or planned, including the HighRif-C study (NCT04437836), a phase I and II PK, safety and tolerability study of higher doses of rifampicin (30 mg/kg and 40 mg/kg) conducted in children and adolescents aged 1–14 years in the United Republic of Tanzania which was completed in December 2023 (results pending).

As children have a higher risk of disseminated or severe TB, such as TBM, optimization of dosing for paediatric TBM is essential, considering penetration of the blood–brain barrier and resulting cerebrospinal fluid concentrations. Some studies point to the need for higher rifampicin doses in treatment of children and adolescents with TBM (35). The currently enrolling HARVEST trial (comparing two regimens composed of isoniazid, pyrazinamide, ethambutol and rifampicin given at either 35 mg/kg or 10 mg/kg for 8 weeks, followed by a continuation phase of treatment for 7 to 10 months according to national guidelines at standard doses) will provide evidence on the effect of high-dose rifampicin on TB treatment outcomes in adults with TBM.

The completed TBM-KIDS trial (NCT02958709; children aged 6 months to 12 years with TBM) did not meet enrolment targets, but it showed statistically significantly better fine motor, expressive and receptive language neurocognitive outcomes in the intervention arm composed of isoniazid, pyrazinamide, ethambutol and rifampicin given at a dose of 30 mg/kg (R_{30}HZE) compared with a regimen
of high-dose rifampicin (30 mg/kg) and levofloxacin (R30HRL) and a regimen of standard-dose rifampicin and ethambutol (R15HRZE) for 8 weeks, followed by 10 months of standard treatment (36).

The SURE-TBM trial (ISRCTN40829906; children and adolescents aged 28 days to 15 years with TBM) is investigating a 6-month regimen composed of rifampicin (30 mg/kg), isoniazid (20 mg/kg), pyrazinamide (40 mg/kg) and levofloxacin (20 mg/kg) dosed once daily versus the 12-month WHO-recommended regimen (2HRZE/10HR) with standard doses of corresponding medicines. It is expected to provide evidence on the comparative efficacy and safety of higher rifampicin doses in TBM.

2.3 Harmonized weight bands
Simplifying drug-dosing strategies to achieve target drug exposure is of critical importance in successfully administering drugs to children and adolescents. The same frontline healthcare worker is often in charge of providing treatment or prevention for several diseases at the same time. Aligning weight bands within a therapeutic area and cross-therapeutic areas has the potential to simplify paediatric drug dosing for the end user and to create uniformity in disease guidelines across diseases, ideally without causing concerns for toxicity and efficacy. WHO commissioned work to investigate the impact of applying proposed harmonized weight bands across therapeutic disease areas, including TB. Expert panels observed minimal impact on drug exposures and no expected reduced drug efficacy or safety for children when dosed in harmonized weight bands. It was therefore suggested that harmonized weight bands be investigated when dosing in children is determined and in future dosing recommendations in children, across disease areas. The TB expert panel suggested that exceptions for specific drugs and unique circumstances (e.g., dosing based on genotype) should be retained in the dosing recommendations to provide flexibility in individualized dosing, as is currently recommended (37).

4. WHO’s Technical Advisory Group (TAG) on dosing
WHO's Global Tuberculosis Programme develops evidence-informed policy on all aspects of TB care as new evidence becomes available. As many of the new policy recommendations on treatment and prevention are at the cutting edge of science, important practical questions remain related to implementation. These include aspects to optimize TB medicine dosing strategies and drug delivery approaches among children and adults, for which several studies have been conducted or are ongoing. However, these are beyond the scope of the WHO guideline development process and require additional evidence and critical evaluation from technical experts.

The Technical Advisory Group (TAG) on dosing of TB medicines for adults and children has been established to provide an independent evaluation and advice to WHO on dosing issues related to TB medicines for all ages and all indications, aligned to WHO recommendations1. The Advisory Group is composed of 20 members who have a range of technical knowledge, skills and experience in clinical pharmacology, pharmacokinetics/pharmacodynamics, pharmacometrics, clinical research and clinical

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medicine, including paediatricians with experience in tuberculosis. The group also includes experts from national TB programmes and civil society and community representatives.

As an advisory body to WHO, the Advisory Group has the following functions:

- to provide an independent evaluation and advice to WHO on scientific and technical aspects of dosing of anti-tuberculosis medicines for children and adults with all forms of TB, aligned to WHO recommendations and based on the latest available scientific evidence with the aim to optimize the dosing of TB medicines and the operational guidance on their use by country programmes; and
- to advise WHO on the new developments in the dosing and drug delivery approaches of medicines used in TB care.

WHO will be convening a TAG meeting on dosing to review the latest evidence on first-line TB medicine dosing to inform updated dosing guidance for children, adolescents and adults with drug-susceptible TB.

5. Objectives

This concept note serves to outline the proposed steps to develop updated dosing guidance for first-line medicines for the treatment of drug-susceptible TB in children and adults (covering all weight bands from 3kg body weight) based on the latest studies and analyses, and available or prioritized formulations of TB medicines. Developing proposed dosing strategies will require development and testing of pharmacometrics models to characterize the pharmacokinetics of rifampicin, isoniazid, pyrazinamide and ethambutol as well as investigate the association of human immunodeficiency virus (HIV), antiretroviral therapy (ART), malnutrition, drug formulation, age, and body size with their pharmacokinetics.

The dosing strategy needs to be aligned with the approach to utilize harmonized weight bands across therapeutic areas and age groups. The proposed harmonized weight bands were developed based on the WHO AWaRe (Access, Watch, Reserve) antibiotic book\(^2\) and WHO Pocket Book of Hospital Care for Children, 2013\(^3\) (3-<6 kg, 6-<10kg and every 5 kg thereafter up to 45 kg for children) to streamline alignment of WBs across diseases that may be treated in the same facilities in low-resource settings.

The objectives of this work therefore are as follows:

- Development and testing of pharmacometrics models to characterize the pharmacokinetics of the first-line medicines including the association with various variables related to specific sub-populations and comorbidities
- Development of pragmatic dosing guidance for children, adolescents and adults for first-line medicines for the treatment of drug-susceptible TB, aligned with the proposed harmonized weight bands

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\(^2\) https://www.who.int/publications/i/item/9789240062382
\(^3\) https://iris.who.int/bitstream/handle/10665/81170/9789241548373_eng.pdf?sequence=1
6. Approach to developing dosing guidance for first-line medicines

The following steps are envisaged for dosing guidance for the treatment of drug-susceptible TB in children, adolescents and adults to be developed:

a) Develop terms of reference (TORs) for the work to develop updated dosing guidance
b) Seek input on the TORs from external experts
c) Discuss and agree the TORs with the TAG on dosing
d) Develop and publish a request for proposals
e) Select an appropriate expert or expert group to conduct the modelling and simulation work and develop pragmatic dosing strategies in the harmonised weight bands
f) The selected review group or individual develops the proposal for the modelling work, including a detailed protocol in consultation with the WHO team and with input from selected experts in the TAG on dosing
g) The individual or group proceeds with the modelling work based on the approved protocol
h) The WHO team reviews the results and dosing strategies proposed
i) The group presents the results of the modelling work and the dosing strategies to the TAG on dosing
j) The TAG on dosing advises WHO on the most optimal dosing strategy based on the presented results
k) WHO publishes updated dosing guidance as part of updates to the relevant operational handbook on tuberculosis and the WHO TB Knowledge Sharing Platform.
References


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