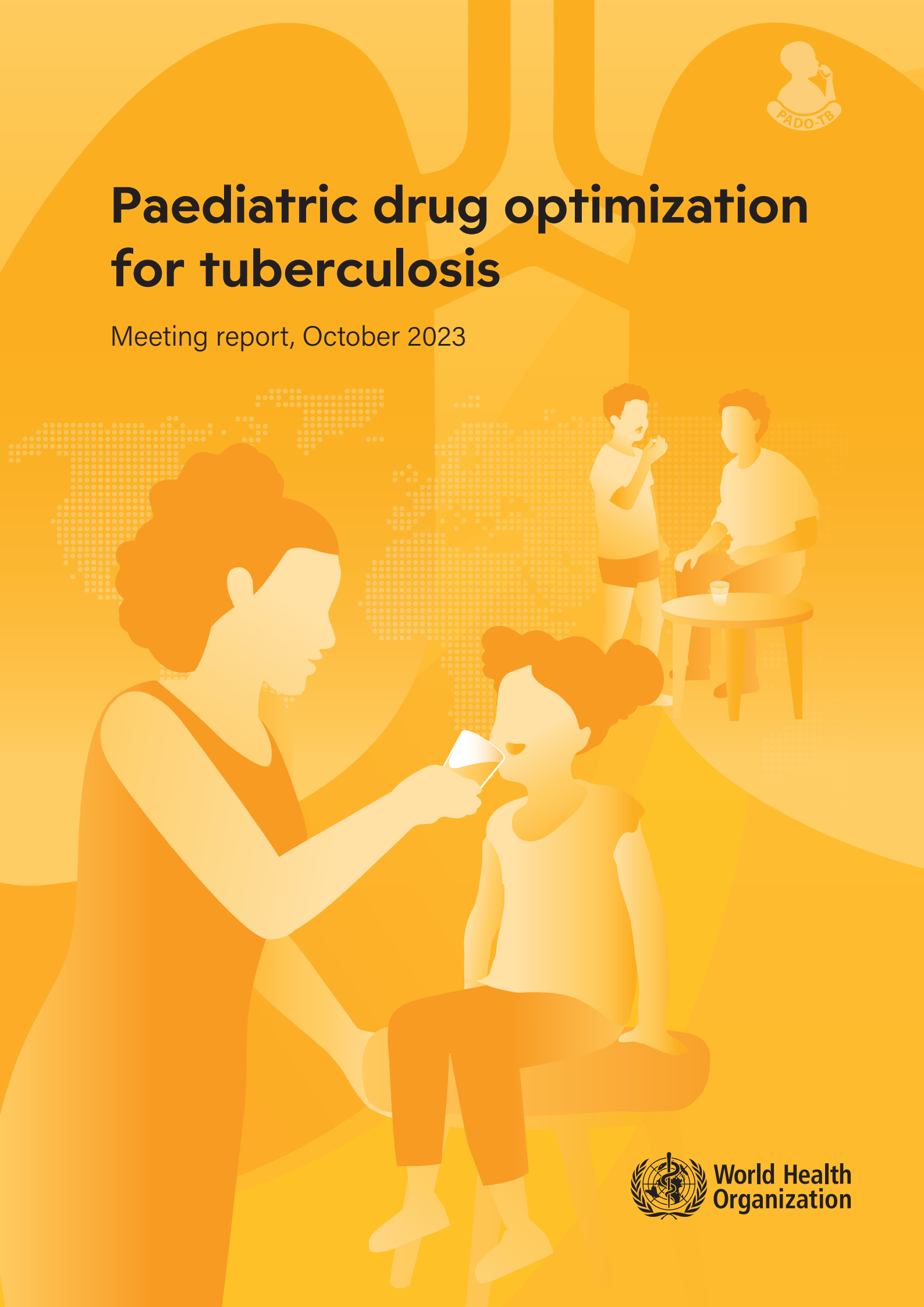
Paediatric drug optimization for tuberculosis

Meeting report, October 2023



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Contents

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Abbreviations

BPaLM/BPaL	6 months of bedaquiline, pretomanid, linezolid, with or without moxifloxacin
CHEETA	Chasing Expedited and Equitable Treatment Access for Children with TB
CPNP	1-cyclopentyl-4-nitrosopiperazine
CYP	cytochrome P450 enzymes
DR-TB	drug-resistant TB
DS-TB	drug-susceptible TB
FDC	fixed-dose combination
GDF	Stop TB Partnership Global Drug Facility
Global Fund	Global Fund to Fight AIDS, Tuberculosis and Malaria
HIV	human immunodeficiency virus
HP	isoniazid and rifapentine
1HP	1 month of daily isoniazid and rifapentine
3HP	3 months of weekly isoniazid and rifapentine
2HPMZ/2HPM	2 months of isoniazid, rifapentine, moxifloxacin and pyrazinamide, followed by 2 months of isoniazid, rifapentine and moxifloxacin
HR	isoniazid and rifampicin
3HR	3 months of daily rifampicin plus isoniazid
2HRZE/10HR	2 months of daily isoniazid, rifampicin, pyrazinamide and ethambutol followed by 10 months of daily isoniazid and rifampicin
6HRZEto	6 months of daily isoniazid, rifampicin, pyrazinamide and ethionamide
IPD	individual participant data
MDR/RR-TB	multidrug- or rifampicin-resistant TB
MDT-TB	multidrug-resistance TB
PADO	paediatric drug optimization
PADO-TB1	first PADO-TB meeting
PADO-TB2	second PADO-TB meeting
PK	pharmacokinetics
4R	4 months of daily rifampicin monotherapy
R&D	research and development
TB	tuberculosis
TBM	TB meningitis
TPT	TB preventive treatment
US FDA	United States Food and Drug Administration
WHO	World Health Organization

1. Background

1.1 Introduction and meeting objectives

Of the estimated 10.6 million people who became ill with tuberculosis (TB) in 2022, 1.25 million (12%) were children and young adolescents. Of these, 47% were aged under 5 years. Further, in 2022, 3900 children were diagnosed and treated for multidrug- and rifampicin-resistant TB (MDR/RR-TB), although this was far short of the estimated 25 000–32 000 children and young adolescents with MDR/RR-TB *(1, 2)*.

Despite recent advances in access to improved treatment regimens for children with TB, and formulations of TB medicines that are suitable for children, a number of barriers remain. Some features of TB medicines – such as palatability, frequency and complexity of administration, and the potential for administration to cause pain or discomfort – may be barriers to adherence in children and therefore affect treatment outcomes. In addition, paediatric investigation plans for new medicines are often delayed and initiated only after phase III trials in adults are either advanced or completed, resulting in delayed access to regimens that are already recommended for adults.

Optimization of paediatric TB medicines forms part of the key actions and milestones in the *Roadmap towards ending TB in children and adolescents, third edition (3)* and contributes to the achievement of the targets for ending TB in children and adolescents set out at the second United Nations High-level Meeting on the Fight Against TB in 2023 *(4)*.

Developing a prioritized portfolio of the most needed formulations for children is a necessary first step to identifying TB medicines and formulations to be prioritized for research and development (R&D) for children to enable alignment between researchers, funders, procurers, market coordination entities, innovators, generic manufacturers, product development partnerships and regulators, and ensure the unique needs of children are considered and effectively addressed upfront in the R&D process.

Paediatric drug optimization (PADO) exercises have been convened by the World Health Organization (WHO) for human immunodeficiency virus (HIV), hepatitis C, bacterial infections and neglected tropical diseases, demonstrating their potential and impact to accelerate access to optimal formulations in the context of fragmented small markets for medicines for children *(5)*.

The WHO Global Tuberculosis Programme has been convening PADO-TB meetings since February 2019 (PADO-TB1) *(6)*, followed by an interim review of the PADO-TB1 priorities in September 2020 *(7)*. The list of short- and long-term priorities agreed by the PADO-TB group during the interim review in 2020 is included in Annex 1.

Considering the latest WHO recommendations on drug-susceptible TB (DS-TB), drug-resistant TB (DR-TB) and TB preventive treatment (TPT), recent developments in new

TB medicines and formulations made available since February 2019, results of clinical trials, pharmacokinetics (PK) and pharmacodynamics studies, and advancements of key medicines in the TB R&D pipeline, WHO convened the second PADO-TB meeting (PADO-TB2) on 3–5 October 2023.

The objectives of this meeting were to:

- review available formulations of TB medicines and evaluate their age-appropriateness for children, given current WHO recommendations and available evidence from completed and ongoing studies;
- review TB medicines being studied in phase IIa and III trials (in adults), and assess whether some of them should be prioritized for paediatric development in the future;
- identify priority research gaps to be addressed on TB prevention and treatment of DS-TB and DR-TB in children, so that children with all forms of TB have prompt access to the best treatment options available.

1.2 Methods and meeting proceedings

PADO-TB2 was held as an online meeting on 3–5 October 2023, chaired by Tamara Kredo. The meeting was attended by over 75 participants (see Annex 2), including clinicians, researchers, representatives of national TB programmes from TB high burden countries, community representatives, financial and technical partners, representatives from regulatory agencies and market-shaping entities, members of product development partnerships and the Child and Adolescent TB Working Group, and representatives from various international agencies, including WHO.

Declarations of conflicts of interest were collected and reviewed for all participants before the meeting. Any participants with relevant conflicts were asked to participate as observers or resource people for the relevant sessions. Participants from funding agencies, regulatory agencies and product development partnerships were invited to participate as observers. All participants signed confidentiality undertaking forms before the meeting.

The meeting was divided into six sessions:

- Introductory session providing key updates from WHO.
- Session 1 outlining the meeting objectives and introducing the concept of acceptability of TB treatment for children.
- Session 2 on TPT and rifapentine.
- Session 3 on first-line TB medicines.
- Session 4 on second-line TB medicines.
- Session 5 on R&D and new technologies being explored for TB medicines.

Each session was composed of presentations from experts who provided an overview of the latest updates in the area, followed by questions and answers and a guided discussion moderated by the chair, using some structured questions to guide the discussion and facilitate the review of the PADO-TB list (see Annex 1). When deemed necessary, consensus on priority medicines to be investigated further or developed for infants, children and adolescents was reached through voting using preset polls. Consensus was defined as more than 70% of people eligible for voting. The outputs of PADO-TB2 were wrapped up and summarized in Session 6. The meeting agenda is available in Annex 3.

Current resources on TB treatment regimens, available formulations of quality-assured paediatric TB medicines, and other relevant information or meeting reports on paediatric TB studies were reviewed by WHO to inform the questions that were asked of the group during the meeting. An assessment of the status of current trials and studies on TB treatment and TPT in children was undertaken before the meeting.

1.3 PADO-TB outputs

This meeting report summarizes the discussions and main outputs of PADO-TB2:

- PADO-TB2 priority list, which contains priority formulations to be investigated and developed in the short term (3–5 years), and formulations that may be developed in the longer term but for which it is essential to flag importance;
- PADO-TB2 watch list, which contains promising candidates for investigation and development for children, within a time horizon of 5–10 years;
- list of priority research questions to address to promote future TB medicine optimization work for the paediatric population.

A more detailed description of general definitions and utility of the PADO-TB priority and watch lists, with specific examples related to TB, is included in Annex 4.

The outputs of PADO-TB are used by WHO and other stakeholders to provide clear messages aligned across stakeholders around priority paediatric formulations of TB medicines to be developed. The prioritization work is undertaken by WHO in conjunction with developing and updating normative guidance on the use of medicines for treating and preventing TB, and other relevant workstreams such as developing target product profiles.

2. Session 1: acceptability of TB treatment for children – beyond palatability

When referring to treatment, acceptability is defined as "the overall ability of the patient and caregiver (defined as 'user') to use a medicinal product as intended (or authorized)" *(8)*. Acceptability is an essential aspect to consider when implementing a health intervention and a key consideration for the development of WHO recommendations – but researchers, regulatory agencies and other entities have only recently started to consider it in research protocols and guidance documents.

During PADO-TB2, a conceptual framework of TB treatment acceptability in children was presented to inform the meeting discussions on priority formulations for development *(9)*. In this framework, three domains, each comprising several dimensions, are used to evaluate TB treatment acceptability:

- Usability involves the alignment between the requirements of treatment use and the ability of caregivers and children to integrate TB treatment into their everyday routines. Usability includes three dimensions: palatability (taste, smell), administration (how the administration process can be integrated into everyday routine and adhered to over time), and appeal (size and colour of the formulation, packaging and accompanying instructions). To determine treatment usability, quantitative (surveys as clinical report forms administered by a nurse or health-care worker to the child) and qualitative (activity-based semistructured interviews) measures can be used.
- Receptivity describes the end-user's perception and expectations of treatment and its actual use.
- Integration describes the relationship between available health services and the capacity of caregivers and children to make use of those services – that is, how easily a TB treatment can be taken up, considering contextual factors such as socioeconomic circumstances and health system delivery models (e.g. level of care offered, accessibility and availability of TB treatment-related services).

The PADO-TB2 group discussed the relevance of including acceptability as a key criterion to consider upfront in R&D projects. More specifically, the group discussed:

- the importance of carrying out acceptability studies with children, considering the feasibility of receiving meaningful input directly from children as young as 4–5 years;
- the importance of including families and caregivers in these studies, especially to understand the effect of socioeconomic issues on acceptability;

- the importance of taking into account child preferences with respect to TB medicines (e.g. research has shown that children prefer sweet flavours, with some specifically mentioning fruit-flavoured and coloured formulations, which were linked to health or healthiness) *(10)*;
- the relevance of the "integration" component of the acceptability framework, which should be inclusive of all service delivery models for children, including maternal and child health interventions and differentiated models of care.

3. Session 2: TPT and rifapentine

3.1 Introduction

Rifapentine is a key component of WHO-recommended regimens for TB prevention and the treatment of DS-TB. An overview of ongoing and completed studies that include rifapentine was presented during PADO-TB2 (Table 1). All new studies in the planning phase will use the newly developed child-friendly formulation of rifapentine that was prioritized by PADO-TB – a 150 mg scored dispersible tablet. Table 1 also includes completed or ongoing studies for the prevention of TB in children.

Table 1. Summary of ongoing and completed studies for the prevention of TB in children and other studies for treatment including rifapentine

Study	Description	Formulation(s) used	Status
TBTC S35 (NCT03730181)	Dose-finding and safety of rifapentine and isoniazid as part of the 12-week, once-weekly regimen of isoniazid and rifapentine (3HP) in HIV-infected and HIV-uninfected children aged 0–12 years with TB infection, including children on efavirenz and dolutegravir	A fixed-dose combination (FDC) of isoniazid and rifapentine 150/150 mg, unscored, dispersible tablet [a] Rifapentine 100 mg unscored, dispersible tablet for top-up [a]	Accrual to be completed in January 2024 Interim data on children aged under 2 years have been reviewed by the WHO technical advisory group on dosing in Q1 2024 [b]
DOLPHIN-Kids (NCT03435146)	Drug–drug interaction study that will assess pharmacokinetics (PK), safety and tolerability of 3HP among infants, children and adolescents aged under 18 years living with HIV and taking dolutegravir Dosing of 3HP in children aged under 2 years will be informed by the results of TBTC S35, showing how data-sharing across studies can streamline and accelerate evidence generation	Rifapentine 150 mg film-coated tablet (in children aged 2 years and over) Rifapentine 100 mg unscored dispersible tablet (in children aged under 2 years) [a] Isoniazid 100 mg uncoated tablet	Enrolment began in Q2 2023 Results expected in 2025

Study	Description	Formulation(s) used	Status
IMPAACT 2024 (DAIDS 38747)	PK and safety of 1 month of daily isoniazid and rifapentine (1HP) in children with and without HIV aged 2–12 years, including children on dolutegravir (plans to expand the study population to children aged under 2 years)	Rifapentine film-coated tablet (150 mg) and newly available rifapentine dispersible tablet (150 mg scored) [c] Isoniazid 100 mg uncoated tablet	Plans to open in Q2 2024 Dosing has been selected based on modelling
TB-CHAMP (ISRCTN92634082) V-QUIN (ACTRN12616000215426)	Phase III cluster randomized placebo-controlled trials to assess efficacy of levofloxacin-based TPT in child contacts aged under 5 years (TB-CHAMP) [d] and contacts aged 15 years and over (V-QUIN) of people with confirmed multidrug-resistant TB (MDR-TB)	Levofloxacin 250 mg tablets	Completed Data reviewed by a WHO-convened guideline development group in December 2023
PHOENIx MDR-TB (or ACTG A5300/ IMPAACT P2003) (NCT03568383)	Comparing efficacy and safety of 26 weeks of delamanid versus isoniazid to prevent TB among high-risk household contacts (all ages, including children) of an MDR-TB source case	Delamanid 25 mg dispersible tablets (in children aged under 6 years) and 50 mg tablets (in children aged 6 years and over)	Ongoing Expected completion date in 2026
Radiant Kids	Phase I/II multisite open-label single-arm PK dose finding and safety study over a 17-week treatment period of a regimen composed of isoniazid, rifapentine, moxifloxacin (and pyrazinamide) (2HPMZ/2HPM) in children aged under 14 years across the disease spectrum (severe and non-severe TB)	Standalone child-friendly formulations of all medicines, including the newly available child-friendly formulation of rifapentine (150 mg scored dispersible tablet) [c]	Protocol in development – expected to start late 2024
SMILE-TB	Open-label, randomized, controlled, treatment-shortening, non-inferiority trial in children aged under 10 years with presumed drug-susceptible pulmonary or lymph node TB. Children will be randomized to receive either the standard of care (a 4- or 6-month regimen of isoniazid, rifampicin, pyrazinamide (with or without ethambutol)) or the intervention (2-month regimen of isoniazid, rifapentine, moxifloxacin and pyrazinamide, 2HPMZ)	Standalone child-friendly formulations of all medicines, including the newly available child-friendly formulation of rifapentine (150 mg scored dispersible tablet)	Protocol in development – expected to start late 2024

[a] Will not be commercially developed (Source: presentation at PADO-TB2).

[b] Technical Advisory Group on dosing of TB medicines for adults and children. Geneva: World Health Organization (https://www.who.int/groups/technical-advisory-group-on-dosing-of-tb-medicines-for-adults-and-children, accessed 17 April 2024).

[c] This specific formulation of rifapentine was prioritized by PADO-TB in 2020 and became commercially available in Q4 2023.

[d] 10% of the sample population in TB-CHAMP included children and adolescents aged 5–17 years.

Although the PADO-TB prioritized formulation of rifapentine (150 mg scored dispersible tablet) became available in November 2023 (see below), it will take some time before this formulation is implemented by national TB programmes. This highlights the key role of bridging studies to understand the effect of manipulation of available adult formulations on bioavailability and acceptability, similar to the studies on bedaquiline and delamanid *(11, 12)*. The rifapentine crush study, which opened in September 2023, will be conducted in healthy adult volunteers to estimate the potential effects on exposures and acceptability *(13)*.

3.2 Status of development of the rifapentine 150 mg scored dispersible tablet

Box 1. Characteristics of the novel child-friendly rifapentine formulation

- Functionally scored, allowing for 75 mg dose increments.
- Disperses rapidly in about 10 mL of water.
- Taste-masked with raspberry or mint flavouring.
- Proposed packaging: Alu/Alu strips and Alu/Alu blisters.
- To be stored below 30 °C and protected from excessive heat and moisture.
- Shelf-life: 18 months (stability testing ongoing to expand to 24 months) *(14)*.

In 2020, after the 150 mg scored dispersible tablet formulation of rifapentine was prioritized for development by PADO-TB, WHO updated the WHO expression of interest for manufacturers to submit products for prequalification *(15)*. This formulation has since been developed by a generic manufacturer, which submitted for WHO prequalification in June 2023 (for characteristics of the formulation, see Box 1). It was approved in November 2023 by the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund) Expert Review Panel, making it the first child-friendly formulation of rifapentine available on the market. A collaboration between the manufacturer and the Clinton Health Access Initiative was established under the Unitaid-funded IMPAACT4TB project to provide financial incentives, development support, and support to guarantee initial procurement commitment to jumpstart launch. A second generic manufacturer is working on the development of this formulation.

N-nitrosamine impurities have been an ongoing issue for rifapentine-containing products. The United States Food and Drug Administration (US FDA) *(16)* and WHO Prequalification *(17)* have set temporary interim limits for the nitrosamine impurity found in rifapentine (1-cyclopentyl-4-nitrosopiperazine, CPNP) of not more than 20 ppm. The US FDA has issued an acceptable intake limit for CPNP of not more than 0.1 ppm. The US FDA has not issued the timing to implement the acceptable intake limit. Manufacturers of rifapentine-containing products, including the child-friendly rifapentine formulation, are required to meet the current interim limit for every batch released. Manufacturers are also required to conduct a risk assessment to identify causes for CPNP generation and to develop corrective and preventive actions to reduce CPNP levels in the rifapentine active pharmaceutical ingredient and finished pharmaceutical product; to develop and validate an analytical method to quantify CPNP levels; and to perform analytical testing on every finished pharmaceutical product batch to ensure levels comply with the interim limits.

At the current time and with the current interim limits set by the US FDA and WHO Prequalification, no concerns have been noted in terms of nitrosamine impurities for the child-friendly formulation of rifapentine.

The negotiated launch price for the child-friendly formulation of rifapentine will be lower than the price of the adult formulation, making the 3-month regimen of weekly isoniazid and rifapentine (3HP) cheaper than alternative TPT regimens available for children (US$ 6.53–15.80 per treatment course, depending on the weight of the child).[1] The formulation can be ordered from the Stop TB Partnership Global Drug Facility (GDF) or directly from the manufacturer *(18)*.

3.3 Summary of the discussion on rifapentine

Based on the evidence presented, the PADO-TB group agreed that the 150 mg scored dispersible tablet formulation of rifapentine remains the priority formulation for development in the short term, given that it provides higher dose flexibility across all indications and for all age groups. A rifapentine-containing fixed-dose combination (FDC) was not indicated as a priority formulation for development in the short term.

In early 2024, the WHO technical advisory group on dosing of TB medicines reviewed dosing for 3HP in children aged under 2 years (see Table 1). Based on information shared at the time of PADO-TB2 and previous modelling conducted to inform dosing of 3HP in children under 2 years as part of the TBTC S35 trial, the 150 mg scored dispersible tablet formulation of rifapentine is expected to be appropriate to provide the required dose flexibility, including for children aged under 2 years. Based on modelling studies, it is also expected to support dosing for the 1-month regimen of daily isoniazid and rifapentine (1HP) and shorter rifapentine-containing regimens for children with DS-TB that are being studied (see Table 1) *(19)*.

Although this formulation was approved by the Global Fund Expert Review Panel in November 2023, shortly after PADO-TB2, retaining it on the PADO priority list aims to ensure that suppliers continue to prioritize its development until a second quality-assured formulation is available.

Meeting participants noted that isoniazid 100 mg scored, dispersible tablets should be made available alongside the child-friendly formulation of rifapentine, in order to deliver 3HP for children. Some countries have reported stockouts of 100 mg scored, dispersible isoniazid. Ideally, having the same supplier providing both dispersible formulations and exploring co-packaging options would ensure the two supply chains move forward in parallel, and that both components of 3HP are available at any level of the health-care system. A difference in shelf-life of the two components (rifapentine – 18 months, with stability testing ongoing to expand to 24 months; isoniazid – 36–48 months, depending on the manufacturer) was not noted to be an issue. It was also noted that countries use other commodities with varying shelf-lives. Any co-packaging and label would need to include information on the shelf-lives of the two components. If rifapentine expires, isoniazid can still be used at the facility level for another purpose (e.g. for TPT regimens that use isoniazid only).

As an interim solution, the group agreed that exploring co-packaging options for rifapentine 150 mg scored dispersible tablets and isoniazid 100 mg scored, dispersible tablets could facilitate supply and logistics at the country level, and dispensing at the point of care, assuming that caregivers are trained on how to dispense or administer the tablets. This would not entail a complex weight-band-specific co-packaging, but more simply bulk co-packaging blister packs of rifapentine and isoniazid to ensure both formulations are

[1] A price comparison between several TPT regimens for a child weighing 15 kg can be found at https://impaact4tb.org/wp-content/uploads/2023/12/IMPAACT4TB-TPT-PEAD-PRODUCT-BRIEF-1.pdf.

available and can be used across all prevention and treatment regimens containing rifapentine and isoniazid. Leftover tablets could be used by health-care workers for other purposes (e.g. dispersible isoniazid could be used for administration of isoniazid-preventive therapy). GDF already supplies bulk packs of TB medicines, with health-care workers dispensing tablets to each patient based on their weight.

It was noted that co-packaging would help to address supply chain issues, but the pill burden for 3HP is still higher than for the 3-month regimen of daily rifampicin plus isoniazid (3HR) (e.g. five versus three tablets for a child weighing 15 kg). Considering that these tablets are dispersible, this should not be a major issue. The volume of water needed to dissolve a certain number of isoniazid and rifapentine tablets may affect acceptability, especially in children aged under 3 years. This specific aspect will be explored in the planned feasibility study. Palatability is not expected to be an issue, because the rifapentine dispersible tablet will be taste-masked with raspberry/mint flavouring, and the isoniazid dispersible tablet is strawberry-flavoured.

The group noted that conducting feasibility and acceptability studies with the new child-friendly formulation of rifapentine will be important. This is planned in the IMPAACT4TB study, to start in early 2024. This study plans to assess whether 3HP uptake will increase with the availability of this new formulation and will determine preferences of caregivers and children for 3HP over other TPT regimens. It also aims to assess barriers and facilitators for TPT implementation from a health system perspective, and to map logistics and supply chain issues related to country-level procurement, forecasting and distribution.

The group acknowledged that FDCs are preferred from a programme and supply perspective and that the availability of the isoniazid and rifapentine (HP) FDC was a gamechanger for the implementation of the 3HP regimen in adults. A paediatric FDC was not, however, considered as a priority product for development in the short term, due to the following considerations:

- The expected different ratio of the isoniazid : rifapentine components for 3HP (1 : 1 for children aged 2 years and over, as recommended by WHO) and 1HP (1 : 2 as implemented in the IMPAACT 2024 study for children weighing above 10 kg, based on preliminary modelling work conducted to inform the trial dosing strategy).
- As part of the 3HP regimen, the HP ratio is expected to differ for children aged under 2 years compared with that already used for children aged 2 years and over, with a higher dose of rifapentine needed for younger children (pending updated WHO dosing guidance in 2024). A 1 : 1 FDC would not meet dosing requirements for all ages and weight bands. Work is ongoing to explore whether a fixed HP ratio can be used across weight bands for 3HP to simplify administration.
- The potential need to develop another paediatric rifapentine-including FDC , if a regimen composed of isoniazid, rifapentine, moxifloxacin and pyrazinamide will be recommended by WHO for children with DS-TB (see Table 1).
- In general, 3HP and 1HP uptake has been lower among household contacts compared with people living with HIV, with 1HP uptake being much lower than 3HP uptake. Partners noted that 3HP volumes procured from GDF for adults have stagnated in recent years. This may change with the recently announced 30% price reduction for 3HP and new initiatives to support scaleup of 3HP in household contacts *(20)*. More specifically, rollout of 3HP in children remains limited (owing to the lack of data in younger children and lack of data on its use with dolutegravir), which makes it challenging to justify requesting the development of multiple formulations (e.g. a standalone formulation

and an FDC or two FDCs with different HP ratios). Additional considerations include logistic and supply challenges at the country level in case multiple rifapentine-including formulations would be developed, and the fact that the rifapentine active pharmaceutical ingredient is a red-coloured dye, needing dedicated manufacturing facilities for both active pharmaceutical ingredients and finished pharmaceutical products.

- Several TPT regimens with different age indications are being implemented, which may make it challenging for health-care workers and caregivers to implement TPT appropriately without appropriate capacity-building. Routine health management information system reporting tools do not routinely capture different regimens used in the field, with an impact on the quantification and therefore supply and logistics at the national level. Partners have reported that efforts by countries to streamline approaches across ages resulted in children receiving wrong TPT dosing (e.g. if the adult FDC was used, children would receive the wrong HP ratio). Completed and ongoing studies are addressing the remaining evidence gaps for TPT in children (see Table 1) and exploring programme preferences for TPT regimens.

Box 2. Experiences with 3HP implementation in children

Experience from the IMPAACT4TB project implementing 3HP in children aged 2–14 years (before the availability of the child-friendly rifapentine formulation) under programmatic conditions was shared during the meeting, demonstrating high completion rates in children across age groups. As part of the CHIP-TB pragmatic trial to assess home-based versus facility-based contact management when 3HP is administered in people aged 2–14 years, it was demonstrated that 3HP is safe and tolerable, with high completion rates in programmatic settings, despite the lack of a child-friendly formulation of rifapentine (at the time of the study). Early findings from post-trial qualitative work have shown that all stakeholder groups preferred 3HP over 3HR, despite the availability of a better-tasting dispersible isoniazid and rifampicin (HR) FDC. This was thought to be due to improved adherence with weekly dosing (with the possibility to administer HP at weekends to avoid dosing and potential side-effects on school days). Although 3HP and 3HR were tolerated well, challenges were noted with both regimens, including relatively long dissolution time for 3HR and a high pill burden for 3HP (managed by separating the dose for isoniazid and rifapentine).

These studies were conducted with the adult formulation of rifapentine, which may yield different findings to the feasibility and acceptability studies that are planned to be conducted with the child-friendly rifapentine formulation.

Box 2 highlights experiences with 3HP implementation presented during PADO-TB2.

Trials that are currently being conducted will provide additional comparative information between TPT regimens in terms of efficacy, feasibility and acceptability. The One-to-Three trial compares 1HP and 3HP among people living with HIV and household contacts aged 13 years and over (data expected in 2024). Ultracurto is a phase IV trial comparing 1HP and 3HP in adult and adolescent household contacts with TB infection in Brazil (data expected in late 2024). The TBTC Study 37 (ASTERoiD, NCT03474029) is a phase III multicountry trial in which people aged over 12 years with TB infection at high risk of progression to TB disease are randomized to receive either 6 weeks of single rifapentine or a 12- to 16-week rifamycin-based regimen (3HP, 3HR or the 4-month regimen of daily rifampicin monotherapy (4R)). An amendment to this study is planned to include children and other groups such as pregnant women (expected study completion in 2028).

If the scientific evidence generated from ongoing TPT trials will support the use of a specific TPT regimen over others, the group will reconsider the possibility of including an FDC as a priority product for development to promote the uptake of that regimen among children.

4. Session 3: first-line TB medicines

4.1 Introduction

As discussed during PADO-TB1 in September 2020 *(7)*, 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 of adults receiving the currently recommended WHO doses. Some studies have shown that rifampicin doses were below the target, especially in young children *(21)*, even though these studies have used a wide variety of formulations of rifampicin with different bioavailability. Rifampicin exposures at currently WHO-recommended doses have also been noted to be below the target in malnourished children *(22)*. A modelling study has shown that exposure target attainment can be improved with currently available FDCs, with stratified dosing methods *(22)*.

The main studies on first-line TB medicines were presented or summarized during PADO-TB2.

A systematic review and meta-analysis published in 2023 explored the relation between current dosing based on WHO guidance (and therefore PK exposures) and successful treatment outcomes. It 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 *(23)*. 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-resourced settings.

Two systematic reviews and individual participant data (IPD) meta-analyses confirmed that optimal dosing of first-line TB medicines cannot be achieved with current paediatric FDCs *(24, 25)*. Lower exposures to all first-line TB medicines were observed in both studies, 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 *(26)*. This could also be due to the lower bioavailability of certain formulations (isoniazid and rifampicin) in children aged under 2–3 years *(27)*. 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 *(24)*. One of the systematic reviews and IPD meta-analyses included studies using a wide variety of formulations of rifampicin, which may have an effect on rifampicin bioavailability. Non-quality-assured formulations of first-line medicines (based on international standards) were also used in some of the included studies *(25)*.

Therefore, there is some emerging evidence that optimal dosing of first-line TB medicines, especially in younger children, cannot be achieved with the current FDC.

In 2022, Denti and colleagues studied rifampicin, isoniazid and pyrazinamide exposures in children and young adolescents aged under 12 years when dosed according to WHO. They designed new FDCs to bring exposures in children in line with adult exposures *(27)*. In the IPD meta-analysis conducted by Miyakawa and colleagues, a model-informed dosing with the currently available FDCs topped up with a standalone formulation of rifampicin (100 mg scored dispersible) is proposed *(25)*.

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 *(28, 29)*.

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 (CYP) P450 enzymes. 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 *(30)*.

In the Opti-Rif study, a 65–70 mg/kg daily dose of rifampicin was needed in children to achieve the target exposures 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) *(31)*. 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 and completed in December 2023.

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 *(32)*. 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 *(33)*. In 2022, WHO recommended a 6-month regimen composed of isoniazid, rifampicin, pyrazinamide and ethionamide given daily throughout the course of treatment (6HRZEto) as an alternative option to the standard 12-month regimen composed of isoniazid, rifampicin, pyrazinamide and ethambutol daily for the first 2 months followed by isoniazid and rifampicin daily for an additional 10 months (2HRZE/10HR) for children and adolescents with bacteriologically confirmed or clinically diagnosed TBM, with higher isoniazid and rifampicin doses compared with the WHO recommended doses for pulmonary DS-TB *(34)*. 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 7–10 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 (R_{30}HRL) and a regimen of standard-dose rifampicin and ethambutol (R_{15}HRZE) for 8 weeks, followed by 10 months of standard treatment *(35)*.

The SURE-TBM trial (ISRCTN40829906; children and adolescents aged 28 days to 15 years with TBM), which is still enrolling and plans to recruit the last patient in Q3 2024, 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.

Importantly, 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 *(36)*. 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 *(36, 37)*. The RIFASHORT trial, however, did not demonstrate non-inferiority of a 4-month regimen of rifampicin at 1800 mg for DS-TB *(38)*. Other phase III trials (some of which are ongoing or being planned) are needed to establish whether high doses of rifampicin allow for better clinical outcomes and shorter treatment durations. These studies should be monitored closely to determine any impact on paediatric dosing.

WHO is planning to convene a technical advisory group meeting to review the latest evidence on first-line TB medicine dosing in children to potentially inform updated dosing guidance for children and adolescents with pulmonary DS-TB. Additional evidence on dosing of first-line TB medicines will be assessed at this meeting.

4.2 Discussion

Participants acknowledged that FDCs are generally preferred from a programmatic and patient perspective, because they improve adherence. During PADO-TB2 discussions, however, the group agreed that prioritizing a standalone formulation of rifampicin versus reformulating the FDCs is preferred in the short term. The group agreed that a 100 mg scored dispersible tablet formulation of rifampicin should be tentatively prioritized for development. A final decision would be taken if and when WHO dosing guidance for rifampicin (and other first-line TB medicines) is issued. Based on the evidence presented, this formulation provides enough dose flexibility for topping up rifampicin doses for children, if needed or recommended to reach target exposures. It was stressed that implementation of optimized dosing should be feasible under programmatic conditions with current or new formulations that are being proposed.

Additional considerations shared by PADO-TB2 participants on the potential availability of this top-up formulation of rifampicin, in particular from a programmatic perspective, included:

- the need to inform quantification with clear assumptions on the estimated number of children who would need this formulation (easier for countries implementing electronic-based rather than paper-based surveillance);
- the need to create demand at the country level and capacity-building for health-care workers to ensure correct guidance is given on how to use this formulation alongside existing formulations;
- the need to ensure treatment literacy for caregivers and communities;
- the importance of studying the feasibility and acceptability of this new formulation (procured or given alongside currently available FDCs), especially in countries that already face several challenges with currently available medicines.

The group acknowledged that although it is important to ensure optimal rifampicin doses for children with TB, the volumes of the currently available quality-assured FDCs procured by countries are decreasing (with countries moving to syrups, standalone tablets or FDCs of unknown quality from local or regional suppliers when procuring first-line medicines with domestic funding), signalling an urgent problem that should be addressed.

Participants noted that studies exploring optimized rifampicin doses in adults for improved outcomes are ongoing. If target exposures in adults change, this may correspond to different targets and dosing in children, leading to the need for different formulations. In the meantime, therefore, the development of a flexible standalone formulation of rifampicin is preferred over an FDC, where drug ratios are fixed. A flexible rifampicin formulation may also help optimize the dosing for malnourished or underweight children, who may require different top-up doses. The group noted that tailored approaches to dosing of TB medicines in subgroups of children should not compromise feasibility of administering TB treatment, especially considering the current move towards decentralization of paediatric TB care to primary health care. Aspects around feasibility should always be taken into account when developing optimized dosing strategies for children and specific subgroups.

From a supplier perspective, investing in a new formulation would require more certainty regarding the longevity of the product so that any investment from suppliers in development can be recouped. It was agreed that currently this cannot be guaranteed for a reformulated FDC. Another important consideration is the expected market size. Based on information shared during the meeting by the Stop TB Partnership Global Drug Facility, volumes of the currently available FDCs procured by countries are decreasing over time, due to transitions from donor funding to national budgets for the procurement of first-line medicines.

A summary of the pros and cons of prioritizing a standalone formulation of rifampicin versus reformulating the FDC, as discussed during the meeting, is provided in Table 2.

Table 2. Pros and cons of prioritizing a standalone formulation of rifampicin versus reformulating fixed-dose combinations

	Pros	Cons
Standalone rifampicin	Higher dose flexibility for rifampicin dose top-up for children across weight bands, including specific subgroups (e.g. malnourished) Use across indications (e.g. for isoniazid-resistant TPT) We can continue to use existing FDCs without disincentivizing manufacturers that invested in their development	Less preferred by programmes (more complex supply and logistics to deliver currently available FDCs and top-up at the point of care) Higher pill burden compared with an FDC
Reformulated FDC	Preferred by programmes (easier supply and logistics), children and caregivers (lower pill burden, increased adherence)	Need for more FDCs (with different drug ratios) depending on weight bands and subgroups Uncertainty over drug ratio in the long term, because studies are still ongoing and the drug ratio may change if studies in adults adapt the adult target exposure that paediatric dosing matches to Need to assess supplier engagement and interest to develop a new FDC and, in particular: ▪ need to provide a sound justification to suppliers for its development reflecting market considerations and durability of the formulation considering ongoing studies ▪ need to address suppliers' concerns about the market decrease over time observed for the currently available paediatric FDCs ▪ need to understand the development timeline for a new FDC versus a standalone tablet considering past experiences with developing the currently available FDCs, which took a long time and required a lot of donor support ▪ need to address potential concerns that this approach may disincentivize suppliers that invested in development of currently available FDC

5. Session 4: second-line TB medicines

5.1 Introduction

All 11 WHO-recommended DR-TB medicines are now available and accessible in child-friendly formulations. Table 3 summarizes the available dosage forms, strengths, number of suppliers and palatability of the currently available formulations, based on the presentations during PADO-TB2. All formulations are appropriate to reach target exposure across the paediatric age spectrum. Table 3 also indicates the formulations for which palatability needs improvement, in the context of dedicated studies that will deliver reformulated, taste-masked formulations in the near future.

Table 3. Child-friendly formulations of second-line TB medicines

	Dosage form and strength	Appropriate to reach target exposure across the paediatric age spectrum	Number of suppliers	Palatability
Moxifloxacin	100 mg scored dispersible tablet	Yes	2	Poorly palatable based on results from the ChildPref_ML study conducted by the BENEFIT Kids project *(39)* Improved taste-masked formulations (based on preferred novel blends in the ChildPref_ML study) are being developed, and updated dossiers are expected to be submitted to WHO Prequalification in Q4 2024
Levofloxacin	100 mg scored dispersible tablet	Yes	2	One formulation was assessed for palatability and found to be palatable (preferred over crushed adult tablets) Palatability of the second formulation was not assessed (but anecdotal information indicates it is not palatable)
Bedaquiline	20 mg scored dispersible tablet	Yes	1	No concern

	Dosage form and strength	Appropriate to reach target exposure across the paediatric age spectrum	Number of suppliers	Palatability
Linezolid	150 mg scored dispersible tablet	Yes	2	No concern based on results from the ChildPref_ML study by the BENEFIT Kids project *(39)*
Clofazimine	50 mg tablet [a]	Yes	1	Palatability studies in children have been carried out and data are being analysed (no expected issues with palatability are anticipated)
Delamanid	25 mg dispersible tablet	Yes	1	No concern
Pretomanid	50 mg dispersible tablet and 10 mg dispersible tablet (trial formulations)	n/a	n/a	n/a

n/a, not applicable.

[a] This formulation is formally not a dispersible tablet, but it disperses reasonably well in water.

For moxifloxacin, completed studies suggest that doses higher than 10–15 mg/kg may be required in younger children to match adult exposures *(40)*. These studies require further safety assessments, however, especially when moxifloxacin is co-administered with other QT-prolonging medicines. The CATALYST study is addressing gaps in PK, safety, tolerability and acceptability of moxifloxacin (as well as clofazimine) in children with the 100 mg dispersible tablet formulation, which is important because bioavailability across moxifloxacin formulations may differ (results expected in mid-2024). An additional IPD meta-analysis of moxifloxacin pharmacokinetics in children is being undertaken to investigate optimized moxifloxacin dose (A Garcia-Prats, personal communication, 2024).

Data from observational studies (MDRPK 1/2) using the crushed 250 mg tablet formulation of levofloxacin and the TB-CHAMP lead-in PK study, which used levofloxacin 100 mg dispersible tablets, demonstrated that levofloxacin exposures are low at the recommended doses in children. The PERFORM study found that levofloxacin dispersible tablets have increased bioavailability (approximately 20%) over crushed nondispersible tablets, but exposures remain below the adult targets for treatment of TB disease *(41)*. A PK IPD meta-analysis including children with MDR-TB on levofloxacin has been undertaken to confirm whether levofloxacin doses need to be adjusted to reach adult target exposures *(42)*.

Combined, these results could inform potential revisions of moxifloxacin and levofloxacin dosing in children and will be taken into account in the planned IMPAACT2020 and PRISM-TB trials, which are also looking at safety (see below).

The majority of adult studies with bedaquiline and delamanid are now using once-daily dosing. Daily dosing is expected to improve adherence and enables the development of potential future FDCs of medicines used in the same treatment regimen. Once-daily dosing for bedaquiline is already recommended by WHO as part of the 6-month regimen of bedaquiline, pretomanid, linezolid, with or without moxifloxacin (BPaLM/BPaL) for

MDR/RR-TB. Once-daily dosing for delamanid had been proposed by the developer *(43)*. Additional work has explored the effect on QT prolongation on daily dosing of bedaquiline and delamanid given together, indicating that the QT-prolonging effect is predicted to be within acceptable limits *(44)*. Results from an early bactericidal activity study *(45)*, derived exposure–response relations *(46, 47)* and pharmacological principles support the preference to retain the 2-week intensive loading dose for bedaquiline (versus an 8-week loading dose). A once-daily dosing scheme for bedaquiline and delamanid is also being implemented in ongoing or planned paediatric studies, including the IMPAACT2020 (SMaRT Kids), a phase II study of two 6-month all-oral regimens in children aged 0–15 years with probable or bacteriologically confirmed RR-TB (expected to open in 2024).

Daily dosing of bedaquiline and delamanid will also be implemented in the PRISM-TB Kids study, which will assess the safety, tolerability, acceptability, cost and access to a regimen composed of bedaquiline, delamanid, linezolid and levofloxacin (for fluoroquinolone-susceptible MDR-TB) or clofazimine instead of levofloxacin (for fluoroquinolone-resistant MDR-TB), including children and adolescents aged under 14 years (expected to open in 2024). The PHOENIx trial (NCT03568383), which includes children, is investigating once-daily delamanid versus isoniazid to prevent TB among high-risk household contacts of a source person with MDR-TB *(48)*.

For clofazimine, limited data exist on PK, dose, safety and acceptability in children, with dosing recommendations based on expert opinion by extrapolating doses (mg/kg) from adults. This gap is being addressed by several studies, including a clofazimine PK, dose and safety study with both the 50 mg soft gel capsule formulation (Clofazimine PK). Preliminary results indicate higher than expected exposures of clofazimine with the currently recommended doses, and an association between clofazimine exposure and QTcF prolongation *(49)*. The CATALYST trial (see above) is evaluating the PK, dose and safety of the 50 mg soft gel capsule formulation and the 50 mg tablet formulation, with results expected in mid-2024. The Clofazimine PK2 study will assess lower doses of clofazimine in children with MDR/RR-TB with the 50 mg tablet formulation, which are expected to approximate target exposures more closely. The study will also implement a once-daily dosing strategy for clofazimine (versus the intermittent dosing strategy of two or three times a week).

Evidence on PK, dose and safety from MDRPK 1/2 studies has informed WHO dosing guidance for linezolid across the age spectrum. The IMPAACT2020 study (SMaRT Kids) will explore the PK and dose of linezolid (given for 8 weeks) with the new 150 mg dispersible tablet formulation.

No data on PK, dose or safety of pretomanid in children are available. The IMPAACT 2034 study (NCT05586230) opened for enrolment in 2023 and will assess PK, dose and safety of single-dose pretomanid using 10 mg and 50 mg scored dispersible tablet formulations to accommodate dosing from 20 mg to 100 mg across weight bands *(50)*. IMPAACT 2034 will confirm the most appropriate pretomanid dose across the age spectrum, which will then be studied in a multiple-dose study of pretomanid (PAEDIATRIC-II study). The single-dose PK study IMPAACT 2034 is currently enrolling only female children because of the reduced fertility observed in male rats and mice treated with pretomanid. A meta-analysis of human male hormone data from pretomanid studies has already been published *(51, 52)*. Additional data are expected from a reproductive safety study focused on sperm count (PaSEM; NCT04179500). Results from these studies will be reviewed by the US FDA to determine whether the inclusion of male children in IMPAACT 2034 and other planned studies of pretomanid in children can proceed.

5.2 Discussion

The group agreed that ongoing studies are not expected to have an impact in terms of the need for new dosage forms or strengths of DR-TB medicines. In terms of the formulations to add, keep or remove from the PADO-TB priority list, the group agreed on the following:

- Moxifloxacin is to be kept in the PADO-TB priority list, acknowledging that palatability of currently available formulations is suboptimal, but that an improved taste-masked formulation is currently being developed (Table 3). The group agreed that when the taste-masked formulation becomes available, moxifloxacin can be removed from the PADO-TB priority list.
- Levofloxacin is not to be added to the PADO-TB priority list because the currently available formulation is appropriate to deliver the dose to reach the target exposure in children, and 100 mg dispersible tablets are available from two generic suppliers. One supplier's formulations was assessed as palatable *(53)*, but the second supplier's formulation was not assessed for palatability (although based on anecdotal information shared by meeting participants, it is less palatable) (Table 3). This uncertainty was not considered a sound enough rationale to add levofloxacin to the list. It was noted, however, that given the expected use of the paediatric levofloxacin formulation for DR-TB TPT, palatability is an essential aspect to consider for this medicine (see research questions).
- Bedaquiline and delamanid are to be removed from the PADO priority list because the currently available 20 mg scored dispersible tablet (bedaquiline) and 25 mg dispersible tablet (delamanid) formulations are flexible to administer required doses in children to reach target exposures, they do not have palatability issues, and the only current originator supplier is sufficient to cover countries' current demand, considering that volumes procured are low based on information shared from GDF, particularly for delamanid.
  - Many participants noted, however, that it is risky to rely on a single originator supplier for these medicines. Therefore, even if a decision was made to remove them from the PADO priority list, the group felt it was important to underline the need for the generic development of child-friendly formulations of originator medicines, because universal access to this medicine should be ensured.
  - The group indicated it will be important to carefully observe potential demand increases for bedaquiline and delamanid in the next few years (based on updated WHO recommendations or increased uptake) and re-evaluate the need for a second supplier (generic), if applicable. This will also be monitored by market-shaping entities and networks such as the TB Procurement and Market-Shaping Action Team (TPMAT). **Child-friendly formulations of bedaquiline and delamanid remain listed on the WHO Prequalification Expression of Interest.**
  - The group highlighted that bedaquiline and delamanid remain priority medicines for children, and that removal from the PADO-TB list is linked solely to the availability of appropriate formulations.
- Linezolid is to be removed from the PADO priority list, because the currently available 150 mg dispersible tablet formulation allows for the required dose flexibility, the formulation is expected to be palatable, and two generic suppliers have recently been prequalified by WHO.
- Clofazimine is to be removed from the PADO priority list because the currently available 50 mg tablet formulation is flexible (it disperses in water), it is not expected to have palatability issues, and one generic supplier was considered to be sufficient to guarantee

supply security. In addition, some countries procure adult tablets (100 mg) to cover dosing needs for older children and adolescents weighing 24 kg and over who require a minimum 100 mg dose.

- Pretomanid is to be kept on the PADO priority list to flag that despite the longer-term timeline for the completion of relevant studies (see Introduction), paediatric development of pretomanid remains a priority. Details on the specific dosage form and strength of the prioritized formulation of pretomanid will be added when more data from ongoing studies are available.

6. Session 5: medicines in the pipeline and new technologies

6.1 Introduction

A total of 22 new or repurposed compounds are currently in clinical development for TB, including many compounds from a new class or with a new mechanism of action, and compounds that are potentially advantageous alternatives to existing TB medicines *(54, 55)*. The presentation on the pipeline highlighted that there are several compounds progressing to phase II clinical testing in the past few years, including three DprE1 inhibitors (BTZ-043, TBA-7371, quabodepistat) and two oxazolidinones (delpazolid, sutezolid). The latter do not correspond to a new class of medicines, but they are linezolid analogues that are being developed to improve the safety profile of linezolid. An additional oxazolidinone (TBI-223) is about to progress to phase II. New diarylquinolines, which are the same class as bedaquiline, are being investigated in phase I trials (TBAJ-876, TBAJ-587), aiming to reduce the need for cardiac monitoring with bedaquiline. Ganfeborole is an oxaborole that targets Mtb LeuRS, a novel protein synthesis target for TB.

Some of these new medicines are already being explored and advanced as part of regimens investigated by consortia such as PanACEA, UNITE4TB and PAN-TB, across which coordination and information sharing are also happening, which should facilitate the path towards successful phase III trials.

Innovative delivery systems for paediatric medicines were presented. These are being designed to address the unique needs of children and for use in many settings, including in low- and middle-income countries *(56)*. An oral dispersible film of dolutegravir was tentatively approved by the US FDA in 2023, which is expected to bring a significant benefit in terms of adherence to paediatric HIV treatment *(57)*.

Long-acting technologies are being explored for TB medicines *(58)*. In general, long-acting technologies may help to overcome or manage nonadherence issues and simplify clinical management. These approaches offer several opportunities for treating TB in children or neonates, including issues related to bioavailability and the first-pass effect.[2] Generally, doses are lower for long-acting medicines than for oral medicines. Taste-masking challenges are overcome, and more efficient treatment support can be provided. Not all medicines are readily compatible with long-acting delivery, however, and some approaches necessitate complex manufacturing processes that are currently unfamiliar to generic manufacturers.

[2] The first-pass effect is a pharmacological phenomenon in which a medicine undergoes metabolism at a specific location in the body, leading to a reduction in the concentration of the active medicine before it reaches the site of action or systemic circulation.

Long-acting technologies are being explored for bedaquiline and rifabutin *(59, 60)*. As part of the LONGEVITY programme *(61)*, a long-acting injectable of rifapentine for TPT (as a single dose administered at the point of care) is being developed, with preclinical PK data consistent with those needed for TB prevention *(62)*. TPT regimens contain fewer medicines than treatment regimens for TB disease, which simplifies development of long-acting technologies in the shorter term. The development of a long-acting injectable formulation for isoniazid is also ongoing as a combination partner for rifapentine in TPT. The role of isoniazid in TPT will be elucidated further by the ASTERoiD phase III trial (NCT03474029), in which a rifapentine-only (oral) TPT regimen is currently under investigation.

The LONGEVITY rifapentine and isoniazid formulations are also being investigated for delivery via microarray patches *(63)*, which are anticipated to allow weekly administration for children. Microarray patches are an attractive technology, because they are minimally invasive, especially for the paediatric population, and they offer opportunities to control the release of medicines not compatible with other long-acting approaches. The patches are applied for a short period of time (hours) and the needles (composed of the long-acting formulation) biodegrade to release the medicine in the dermis, so there is no need for subsequent removal of the needles. Manufacturing complexity and lack of familiarity with the technology may be a barrier for production and implementation in the shorter term. More work needs to be done to assess whether microarray patches are cost-effective against higher production costs and preferences of patients and health-care providers for such long-acting technologies.

The Medicines Patent Pool secured its first licence on promising long-acting technologies for malaria, TB and hepatitis C in September 2021 *(64)*. The agreement allows sublicensees worldwide to develop finished products anywhere in the world, and to sell or distribute the resulting medicines for administration to people in all low- and middle-income countries, on a royalty-free basis.

Oral dispersible films/strips of standalone rifapentine and HP FDCs (with drug ratio to be defined) are also being planned for development. Product development plans are being drafted, and identification of potential manufacturing partners for production is ongoing. Oral films have the major advantage that they can be administered easily without the need for water and can be transported more easily than other dosage forms because they are lighter and less bulky. Flexibility of dosing can be achieved through the administration of different sizes of film. They usually require the inclusion of a flavour and/or sweetener to ensure palatability. In general, studies have found oral films to be more acceptable in the paediatric population over tablets *(47)*.

6.2 Discussion

The group agreed that all compounds currently being studied in, or shortly entering, phase II trials should be monitored closely. The group remarked that paediatric investigations for new compounds ideally should start as soon as enough evidence on efficacy and safety is available from adult trials, which corresponds to phase II of clinical development. The group felt that not enough information is available to prioritize some of the candidates over others for paediatric development. It also flagged that some compounds are more advanced (phase IIb/c) in their clinical development (delpazolid, sutezolid, GSK-656, quabodepistat, BTZ-043, TBI-223), and those should be monitored. No toxicity signals that are particularly relevant for the paediatric population – which may deprioritize them for paediatric development – were noted for any of these compounds.

An initiative called Chasing Expedited and Equitable Treatment Access for Children with TB (CHEETA) is engaged in several activities to accelerate paediatric evaluation of new compounds by setting up a platform trial and mapping and capacitating sites in high TB burden countries *(65)*. The CHEETA taskforce is also engaging key stakeholders, in particular innovators of new compounds in clinical development, to map where they are with paediatric investigation plans and product development plans and to offer technical support for paediatric studies.

The group agreed that long-acting technologies (long-acting injectables and microarray patches) may be attractive drug delivery models for children, as they are minimally invasive and may offer several advantages over standard drug delivery systems. A key research question to address for such new technologies relates to exploring users' acceptability and preferences for these technologies through specific user-engagement surveys to ensure such new technologies address the unique needs of children with TB. For example, it should be explored whether the red colour of the rifapentine active pharmaceutical ingredient may have an impact on user preferences for microarray patches and oral films. The group agreed that their development should be monitored in the future, and thus agreed to add them to the PADO-TB watch list.

7. Conclusions and next steps

The PADO-TB2 meeting brought together academic researchers, clinical experts, programme managers, regulators, funders, market-shaping entities and other key stakeholders involved in R&D to reach consensus on a revised PADO priority list (Table 4) and watch list (Table 5) for TB. The PADO-TB2 priority list was developed keeping in mind short-term needs but also longer-term considerations to ensure the unique needs of children with TB are addressed efficiently.

The PADO-TB2 watch list includes all compounds currently being studied in phase II clinical trials. It also includes a special flag for compounds that are more advanced in their clinical development, to signal that paediatric investigations should start without delay for these compounds. The group agreed that developments on new delivery technologies for TB medicines – long-acting formulations and oral dispersible films/strips – will be monitored carefully, because they hold promise to improve treatment delivery, especially in children, even if some aspects such as costs and acceptability should be looked at closely.

Table 4. PADO-TB2 priority list

Medicine	Remarks
Rifapentine, 150 mg scored dispersible tablet	This remains a priority formulation for development in the short term because it provides a higher dose flexibility across indications and age groups over rifapentine-containing FDCs. A first supplier was approved by the Global Fund Expert Review Panel in November 2023. The group agreed to keep the formulation on the PADO-TB priority list to ensure suppliers that are still working on its development continue to prioritize their development programmes. The group indicated that exploring potential co-packaging options with isoniazid 100 mg tablets (scored, dispersible) will facilitate supply, logistics and distribution of both medicines for 3HP at point of care. A rifapentine-containing FDC was not indicated as a priority formulation for development in the short term, especially given different HP dosing ratios expected for rifapentine-containing TPT regimens (3HP, 1HP) and different dosing ratio expected for younger and older children who are given the same regimen (3HP), and the potential need to develop another rifapentine-including FDC, if a regimen composed of isoniazid, rifapentine, moxifloxacin and pyrazinamide will be recommended by WHO for children with DS-TB.

Medicine	Remarks
Rifampicin 100 mg scored dispersible table *(tentative listing)*	Based on available evidence, this formulation provides the required dose flexibility to potentially top up rifampicin doses for children; this is pending updated WHO dosing guidance for first-line TB medicines, including rifampicin. Compared with a reformulated FDC, it could be used across indications and currently available FDCs can continue to be used. Reformulating an FDC was not considered a short-term priority. Reasons include the need for more FDCs (with different ratios) depending on weight bands and subgroups, and the durability of such formulations considering ongoing studies. The final prioritization of this formulation is pending a potential WHO dosing update for rifampicin.
Moxifloxacin 100 mg dispersible tablet (palatable)	The currently available formulation for children (100 mg dispersible tablet) is appropriate to deliver the required dose to reach adult target exposure, but currently available formulations are not palatable. A taste-masked formulations is being developed. When this formulation is available, moxifloxacin will be removed from the PADO-TB priority list.
Pretomanid	Despite the longer-term timeline for the completion of relevant paediatric studies, paediatric development of pretomanid remains a key priority. Details on the specific dosage form and strength of a prioritized formulation of pretomanid will be added when more data from ongoing and planned studies are available.

Table 5. PADO-TB2 watch list

Product	Remarks
All compounds in or shortly entering phase II, with special attention to compounds that are more advanced in development (phase IIb/c), including delpazolid, sutezolid, GSK-656, quabodepistat, BTZ-043 and TBI-223	Paediatric studies should start as soon as compounds enter phase II clinical development in adults. Not enough information is available to identify which compounds would be more promising than others – and thus, whether some compounds among those currently in phase II could be flagged for prioritization for paediatric development. Among compounds currently in or shortly entering phase II, none has concerns specific to paediatrics (e.g. toxicity).
Long-acting technologies (e.g. injectables, microarray patches) for TB medicines	Long-acting technologies that are minimally invasive have the potential to simplify treatment delivery for children with TB. Considerations around costs and end-users' preferences should be looked at closely during development.
Oral dispersible film/strips of rifapentine-including products	These can be administered easily without the need for water, which is a major advantage in low-resourced settings. Flexibility of dosing can be achieved through the administration of different sized films. Considerations around costs and end-users' preferences should be looked at closely during development.

Alongside key research priorities discussed during the PADO-TB2 meeting (Box 3), the group discussed overarching principles for R&D of TB medicines in children, including the need to account for acceptability (including palatability) of new paediatric formulations upfront in R&D programmes, and the need to carry out studies of acceptability (for children and caregivers) of new formulations in real-world settings. The group acknowledged the

need for close monitoring of the regimens being investigated for treatment and prevention, so that formulation development efforts are targeted at regimens (assuming they will be recommended by WHO) that will be preferred for implementation by programmes, caregivers and people with TB.

Box 3. Research priorities agreed by PADO-TB2

- Address remaining data gaps in the context of prevention of TB (see Table 1), especially in younger children.
- Conduct acceptability and feasibility studies with the newly available child-friendly formulation of rifapentine.
- Conduct modelling work to explore whether a fixed HP ratio for 3HP can be used across weight bands to facilitate administration.
- Fill current research gaps on second-line TB medicines, especially in paediatric populations. In particular:
  - Pretomanid – complete the single-dose PK study to confirm the most appropriate pretomanid dose to use in the follow-up multiple-dose study of pretomanid in children.
  - Clofazimine – PK, dose, safety and acceptability of clofazimine (50 mg tablets) in children to reach safe therapeutic exposure with once-daily dosing.
  - Linezolid – PK, dose and safety of the child-friendly formulation of linezolid as part of MDR/RR-TB regimens for children, exploring shorter linezolid duration.
- Study the palatability of the 100 mg dispersible tablet formulation of levofloxacin available from the second supplier.
- Study the feasibility and acceptability of the PADO-TB2 prioritized (tentatively) rifampicin 100 mg scored dispersible tablet formulation, and the best supply and procurement models to ensure the top-up formulation reaches the point of care alongside currently available FDCs. These studies should be carried out after a final decision on the prioritization of this formulation is undertaken, assuming WHO dosing guidance for rifampicin (and other first-line TB medicines) is issued.
- Accelerate paediatric evaluations of new compounds by supporting initiatives such as CHEETA.
- Assess cost-effectiveness of long-acting technologies, including microarray patches (against high production costs), and preferences of patients and health-care providers for long-acting technologies in the TB space.

The overall outcomes of the PADO-TB2 exercise will be disseminated widely via multiple opportunities for engagement with regulators, industry, funders, civil society and the general public. The WHO Global Tuberculosis Programme will ensure PADO-TB2 outcomes are considered carefully in the context of complementary discussions on dosing and other technical discussions in the areas given priority.

Any development related to PADO-TB2 priorities will be monitored closely and reviewed by the PADO-TB group in future.

References

1. Global tuberculosis report 2023. Geneva: World Health Organization; 2023 (https://www.who.int/teams/global-tuberculosis-programme/data, accessed 7 March 2024).
2. Verkuijl S, Bastard M, Brands A, Viney K, Masini T, Mavhunga F, et al. Global reporting on TB in children and adolescents: how far have we come and what remains to be done? Int J Tuberc Lung Dis Open. 2024;1:3–6.
3. Roadmap towards ending TB in children and adolescents, third edition. Geneva: World Health Organization; 2023 (https://iris.who.int/bitstream/handle/10665/373949/9789240084254-eng.pdf?sequence=1, accessed 4 March 2024).
4. Political Declaration on the High-level Meeting on the Fight against Tuberculosis: "Advancing science, finance and innovation, and their benefits, to urgently end the global tuberculosis epidemic, in particular by ensuring equitable access to prevention, testing, treatment and care". New York: United Nations; 2023 (https://www.un.org/pga/77/wp-content/uploads/sites/105/2023/09/TB-Final-Text.pdf, accessed 7 March 2024).
5. Paediatric drug optimization standard procedure. Geneva: World Health Organization; 2021 (https://iris.who.int/bitstream/handle/10665/349315/9789240039520-eng.pdf?sequence=1, accessed 7 March 2024).
6. Reaching UNGA HLM on TB targets for ending TB in children and adolescents: first Paediatric Antituberculosis Drug Optimization meeting (PADO-TB 1). Geneva: World Health Organization; 2019 (http://www.stoptb.org/wg/dots_expansion/childhoodtb/assets/documents/PADO-TB1_Meeting_Report_FINAL_v8March2019.pdf, accessed 4 March 2023).
7. Report of the meeting to review the paediatric antituberculosis drug optimization priority list. Geneva: World Health Organization; 2021 (https://iris.who.int/handle/10665/340316, accessed 4 March 2023).
8. Kozarewicz P. Regulatory perspectives on acceptability testing of dosage forms in children. Int J Pharm. 2014;469:245–248. doi:10.1016/j.ijpharm.2014.03.057.
9. Wademan DT, Palmer M, Purchase S, van der Zalm, MM, Osman M, Garcia-Prats AJ, et al. Toward a conceptual framework of the acceptability of tuberculosis treatment in children using a theory generative approach. PLoS Glob Public Health. 2022;2:e0001267. doi:10.1371/journal.pgph.0001267.
10. Wademan DT, Viljoen L, Jacobs S, Meyerson K, Nombewu Y, Busakwe L, et al. Children's priorities to improve the acceptability of MDR-TB treatment: qualitative data from South Africa. Int J Tuberc Lung Dis. 2023;27:543–550. doi:10.5588/ijtld.22.0573.
11. Svensson EM, du Bois J, Kitshoff R, de Jager VR, Wiesner L, Norman J, et al. Relative bioavailability of bedaquiline tablets suspended in water: implications for dosing in children. Br J Clin Pharmacol. 2018;84:2384–2392. doi:10.1111/bcp.13696.
12. Zou Y, de Jager V, Hesseling AC, Diacon AH, Wiesner L, Mostert J, et al. Relative bioavailability of delamanid 50 mg tablets dispersed in water in healthy adult volunteers. Br J Clin Pharmacol. 2023;24:10. doi:10.1111/bcp.15672.
13. Groundbreaking TB study investigates crushed tablets for TB prevention. Cape Town: TASK; 2023 (https://task.org.za/2023/10/12/groundbreaking-tb-study-investigates-crushed-tablets-for-tb-prevention/, accessed 7 March 2024).

14. Product brief: paediatric-friendly rifapentine and isoniazid for 3HP TB preventive treatment. Johannesburg: Aurum Institute (https://impaact4tb.org/wp-content/uploads/2023/12/IMPAACT4TB-PEDIATRIC-PRODUCT-BRIEF-3HP-DT.pdf, accessed 7 March 2024).

15. 22nd invitation to manufacturers of antituberculosis medicines to submit an expression of interest (EOI) for product evaluation to the WHO Prequalification Unit. Geneva: World Health Organization; 2024 (https://extranet.who.int/prequal/sites/default/files/document_files/EOI_TB_v21_29June2021_v1_2024Review_v7_final.pdf, accessed 3 May 2024).

16. FDA updates and press announcements on nitrosamines in rifampin and rifapentine. Silver Spring, MD: United States Food and Drug Administration (https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-nitrosamines-rifampin-and-rifapentine, accessed 7 March 2024).

17. Update on N-nitrosamine impurities. Geneva: World Health Organization; 2023 (https://extranet.who.int/prequal/news/update-n-nitrosamine-impurities, accessed 7 March 2024).

18. January 2024 medicines catalog. Geneva: Stop TB Partnership Global Drug Facility; 2024 (https://www.stoptb.org/sites/default/files/2024.01.18_gdf_medicines_catalog_jan_2024.pdf, accessed 7 March 2024).

19. Hibma JE, Radtke KK, Dorman SE, Jindani A, Dooley KE, Weiner M, et al. Rifapentine population pharmacokinetics and dosing recommendations for latent tuberculosis infection. Am J Respir Crit Care Med. 2020;202:866–877. doi:10.1164/rccm.201912–2489oc.

20. USAID launches new efforts in fight against tuberculosis, including additional $23 million in funding. Washington, DC: United States Agency for International Development; 2023 (https://www.usaid.gov/news-information/press-releases/sep-22–2023-usaid-launches-new-efforts-fight-against-tuberculosis-including-additional-23-million-funding, accessed 11 March 2024).

21. McIlleron HC, Hemanth Kumar A. Evidence-based dosing of first-line TB drugs in African and Indian children: the SHINE and DATIC studies. Presented at the 50th Union World Conference on Lung Health, 30 October–2 November 2019, Hyderabad, India.

22. Radtke KK, Dooley KE, Dodd PJ, Garcia-Prats AJ, McKenna L, Hesseling AC, et al. Alternative dosing guidelines to improve outcomes in childhood tuberculosis: a mathematical modelling study. Lancet Child Adolesc Health. 2019;3:636–645. doi:10.1016/S2352–4642(19)30196–8.

23. Solans BP, Béranger A, Radtke K, Mohamed A, Mirzayev F, Gegia M, et al. Effectiveness and pharmacokinetic exposures of first-Line drugs used to treat drug-susceptible tuberculosis in children: a systematic review and meta-Analysis. Clin Infect Dis. 2023;76:1668–1670. doi:10.1093/cid/ciac973.

24. Gafar F, Wasmann RE, McIlleron HM, Aarnoutse RE, Schaaf HS, Marais BJ, et al. Global estimates and determinants of antituberculosis drug pharmacokinetics in children and adolescents: a systematic review and individual patient data meta-analysis. Eur Respir J. 2023;61:2201596. doi:10.1183/13993003.01596–2022.

25. Miyakawa R, Solans BP, Floren S, Ruslami R, Mukherjee A, Denti P, et al. Rifampicin underexposure as a potential cause of unfavourable outcomes among children with tuberculosis: an individual participant meta-analysis and new dosing recommendations. Presented at the 54th Union World Conference on Lung Health, 15–18 November 2023, Paris (https://theunion.org/sites/default/files/2023–11/UNION2023_Abstracts-compressed.pdf, accessed 11 March 2024).

26. Denti P, Wasmann RE, Francis J, McIlleron H, Sugandhi N, Cressey TR, et al. One dose does not fit all: revising the WHO paediatric dosing tool to include the non-linear effect of body size and maturation. Lancet Child Adolesc Health. 2022;6:9–10. doi:10.1016/S2352–4642(21)00302–3.

27. Denti P, Wasmann RE, van Rie A, Winckler J, Bekker A, Rabie H, et al. Optimizing dosing and fixed-dose combinations of rifampicin, isoniazid, and pyrazinamide in pediatric patients with tuberculosis: a prospective population pharmacokinetic study. Clin Infect Dis. 2022;75:141–151. doi:10.1093/cid/ciab908.

28. Galileya LT, Wasmann RE, Chabala C, Rabie H, Lee J, Njahira Mukui I, et al. Evaluating pediatric tuberculosis dosing guidelines: a model-based individual data pooled analysis. PLoS Med. 2023;20:e1004303. doi:10.1371/journal.pmed.1004303.

29. Solans BP. Optimizing treatment of TB in children with severe acute malnutrition. Presented at the 54th Union World Conference on Lung Health, 15–18 November 2023, Paris (https://theunion.org/sites/default/files/2023–11/UNION2023_Abstracts-compressed.pdf, accessed 11 March 2024).

30. Stemkens R, de Jager V, Dawson R, Diacon AH, Narunsky K, Padayachee SD, et al. Drug interaction potential of high-dose rifampicin in patients with pulmonary tuberculosis. Antimicrob Agents Chemother. 2023;67:e0068323. doi:10.1128/aac.00683–23.

31. Garcia-Prats AJ, Svensson EM, Winckler J, Draper HR, Fairlie L, van der Laan LE, et al. Pharmacokinetics and safety of high-dose rifampicin in children with TB: the Opti-Rif trial. J Antimicrob Chemother. 2021;76:3237–3246. doi:10.1093/jac/dkab336.

32. Svensson EM, Dian S, Te Brake, L, Ganiem AR, Yunivita V, van Laarhoven A, et al. Model-based meta-analysis of rifampicin exposure and mortality in Indonesian tuberculous meningitis trials. Clin Infect Dis. 2020;71:1817–1823. doi:10.1093/cid/ciz1071.

33. Ruslami R, Gafar F, Yunivita V, Parwati I, Ganiem AR, Aarnoutse RE, et al. Pharmacokinetics and safety/tolerability of isoniazid, rifampicin and pyrazinamide in children and adolescents treated for tuberculous meningitis. Arch Dis Child. 2022;107:70–77. doi:10.1136/archdischild-2020–321426.

34. WHO operational handbook on tuberculosis: module 5 – management of tuberculosis in children and adolescents. Geneva: World Health Organization; 2022 (https://iris.who.int/handle/10665/352523, accessed 4 March 2024).

35. Paradkar MS, Devaleenal B, Mvalo T, Arenivas A, Thakur KT, Wolf L, et al. Randomized clinical trial of high-dose rifampicin with or without levofloxacin versus standard of care for pediatric tuberculous meningitis: the TBM-KIDS trial. Clin Infect Dis. 2022;75:1594–1601. doi:10.1093/cid/ciac208.

36. Te Brake LHM, de Jager V, Narunsky K, Vanker N, Svensson EM, Phillips PPJ, et al. Increased bactericidal activity but dose-limiting intolerability at 50 mg kg–1 rifampicin. Eur Respir J. 2021;58:2000955. doi:10.1183/13993003.00955–2020.

37. Boeree MJ, Diacon AH, Dawson R, Narunsky K, du Bois J, Venter A, et al. A dose-ranging trial to optimize the dose of rifampin in the treatment of tuberculosis. Am J Respir Crit Care Med. 2015;191:1058–1065. doi:10.1164/rccm.201407–1264OC.

38. Jindani A, Atwine D, Grint D, Bah B, Adams J, Ticona ER, et al. Four-month high-dose rifampicin regimens for pulmonary tuberculosis. N Engl J Med. 2023;2:EVIDoa2300054. doi:10.1056/EVIDoa2300054.

39. Hoddinott G, Vanqa N, Myeni S, Staples S, Draper H, Rafique M. Palatability preferences in children: the swish-and-spit taste panel approach for formulation development. Presented at the 54th Union World Conference on Lung Health, 15–18 November 2023, Paris (https://theunion.org/sites/default/files/2023–11/UNION2023_Abstracts-compressed.pdf, accessed 11 March 2024).

40. Radtke KK, Hesseling AC, Winckler JL, Draper HR, Solans BP, Thee S, et al. Moxifloxacin pharmacokinetics, cardiac safety, and dosing for the treatment of rifampicin-resistant tuberculosis in children. Clin Infect Dis. 2022;74:1372–1381. doi:10.1093/cid/ciab641.

41. Van der Laan LE, Hesseling AC, Schaaf HS, Palmer M, Draper HR, Wiesner L, et al. Pharmacokinetics and optimized dosing of dispersible and non-dispersible levofloxacin formulations in young children. J Antimicrob Chemother. 2023;78:2481–2488. doi:10.1093/jac/dkad257.

42. White YN, Solans BP, Denti P, van der Laan LE, Schaaf HS, Vonasek B, et al. Pharmacokinetics and optimal dosing of levofloxacin in children for drug-resistant tuberculosis: an individual patient data meta-analysis. Clin Infect Dis. 2024;ciae024. doi:10.1093/cid/ciae024.

43. Wang X, Mallikaarjun S, Gibiansky E. Population pharmacokinetic analysis of delamanid in patients with pulmonary multidrug-resistant tuberculosis. Antimicrob Agents Chemother. 2020;65:e01202–e01220. doi:10.1128/AAC.01202–20.

44. Tanneau L, Karlsson MO, Rosenkranz SL, Cramer YS, Shenje J, Caryn MU, et al. Assessing prolongation of the corrected QT interval with bedaquiline and delamanid coadministration to predict the cardiac safety of simplified dosing regimens. Clin Pharmacol Ther. 2022;112:873–881. doi:10.1002/cpt.2685.

45. Diacon AH, Dawson R, Von Groote-Bidlingmaier F, Symons G, Venter A, Donald PR, et al. Randomized dose-ranging study of the 14-day early bactericidal activity of bedaquiline (TMC207) in patients with sputum microscopy smear-positive pulmonary tuberculosis. Antimicrob Agents Chemother. 2013;57:2199–2203. doi:10.1128/AAC.02243–12.

46. Svensson EM, Karlsson MO. Modelling of mycobacterial load reveals bedaquiline's exposure–response relationship in patients with drug-resistant tuberculosis. J Antimicrob Chemother. 2017;72:3398–3405. doi:10.1093/jac/dkx317.

47. Tanneau L, Karlsson MO, Svensson EM. Understanding the drug exposure–response relationship of bedaquiline to predict efficacy for novel dosing regimens in the treatment of multidrug-resistant tuberculosis. Br J Clin Pharmacol. 2020;86:913–922. doi:10.1111/bcp.14199.

48. A5300B/I2003B: protecting households on exposure to newly diagnosed index multidrug-resistant tuberculosis patients (PHOENIx MDR-TB). ACTG (https://actgnetwork.org/clinical-trial/a5300b-i2003bprotecting-households-on-exposure-to-newly-diagnosed-index-multidrug-resistant-tuberculosis-participants-phoenix/, accessed 18 March 2024).

49. Hughes JA, Solans B, Garcia-Prats AJ, Nortier E, Draper H, Palmer M et al. Clofazimine pharmacokinetics and safety in children with rifampicin-resistant TB. Presented at the 54th Union World Conference on Lung Health, 15–18 November 2023, Paris (https://theunion.org/sites/default/files/2023–11/UNION2023_Abstracts-compressed.pdf, accessed 11 March 202448).

50. IMPAACT 2034: phase I study of the pharmacokinetics, safety, and acceptability of a single dose of pretomanid added to an optimized background regimen in children with rifampicin-resistant tuberculosis. Durham, NC: International Maternal Pediatric Adolescent AIDS Clinical Trials Network; 2022 (https://www.impaactnetwork.org/sites/default/files/2023–01/IMPAACT2034_Protocol_V1_15JUL22_withLOA1_22DEC22.pdf, accessed 14 March 2024).

51. Burke A, Alffenaar J, Denholm J. Evidence of safety for pretomanid and male reproductive health.50 Int J Tuberc Lung Dis. 2022;26:473–474. doi:10.5588/ijtld.22.0092.

52. Boekelheide K, Olugbosi M, Nedelman J, Everitt D, Smith E, Betteridge M, et al. Male reproductive hormones in patients treated with pretomanid. Int J Tuberc Lung Dis. 2022;26:558–565. doi:10.5588/ijtld.21.0654.

53. Wademan DT, Draper HR, Purchase SE, Palmer M, Hesseling AC, Van der Laan L, et al. Acceptability of levofloxacin dispersible and non-dispersible tablet formulations in children receiving TB preventive treatment. Int J Tuberc Lung Dis Open. 2024;1:69–75. doi:10.5588/ijtldopen.23.0462.

54. Clinical pipeline. Geneva: Stop TB Partnership Working Group on New TB Drugs; 2024 (https://www.newtbdrugs.org/pipeline/clinical, accessed 14 March 2024).

55. Pipeline report 2023: tuberculosis treatment. New York: Treatment Action Group; 2023 (https://www.treatmentactiongroup.org/wp-content/uploads/2024/03/pipeline_TB_Treatment_2023_final.pdf, accessed 14 March 2024).

56. Innovative delivery systems for paediatric medicines: technology landscape. Geneva: World Health Organization; 2020 (https://unitaid.org/assets/Innovative-delivery-systems-for-paediatric-medicines-technology-landscape.pdf, accessed 14 March 2024).

57. President's Emergency Plan for AIDS Relief (PEPFAR) database. Silver Spring, MD: United States Food and Drugs Administration (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=pepfar.page, accessed 14 March 2024).

58. Ammerman NC, Nuermberger EL, Owen A, Rannard SP, Freel Meyers C, Swindells S. Potential impact of long-acting products on the control of tuberculosis: preclinical advancements and translational tools in preventive treatment. Clin Infect Dis. 2022;75:S510–S516. doi:10.1093/cid/ciac672.

59. Kaushik A, Ammerman NC, Tyagi S, Saini V, Vervoot I, Lachau-Durand S, et al. Activity of a long-acting injectable bedaquiline formulation in a paucibacillary mouse model of latent tuberculosis infection. Antimicrob Agents Chemother. 2019;63:e00007–e000019. doi:10.1128/AAC.00007–19.

60. Kim M, Johnson CE, Schmalstig AA, Annis A, Wessel SE, Van Horn B, et al. A long-acting formulation of rifabutin is effective for prevention and treatment of *Mycobacterium tuberculosis*. Nat Commun. 2022;13:4455. doi:10.1038/s41467–022–32043–3.

61. Tuberculosis prevention in low- and middle-income countries. Liverpool: University of Liverpool (https://www.liverpool.ac.uk/centre-of-excellence-for-long-acting-therapeutics/longevity/tuberculosis/, accessed 14 March 2024)

62. Chang YS, Li S-Y, Pertinez H, Betoudji F, Lee J, Rannard SP, et al. Using dynamic oral dosing of rifapentine and rifabutin to simulate exposure profiles of long-acting formulations in a mouse model of tuberculosis preventive therapy. Antimicrob Agents Chemother. 2023;67:e00481–e00423. doi:10.1101/2023.04.12.536604.

63. Ismail A, Magni S, Katahoire A, Ayebare F, Siu G, Semitala F, et al. Exploring user and stakeholder perspectives from South Africa and Uganda to refine microarray patch development for HIV PrEP delivery and as a multipurpose prevention technology. PLoS One. 2023;18:e0290568. doi:10.1371/journal.pone.0290568.

64. Long-acting technologies for HCV, TB, and malaria treatment. Geneva: Medicines Patent Pool; 2021 (https://medicinespatentpool.org/licence-post/long-acting-technologies-for-hcv-tb-and-malaria-treatment, accessed 14 March 2024).

65. Howell P. Innovative approaches to expedite the evaluation of new TB drugs in children. Presented at the 54th Union World Conference on Lung Health, 15–18 November 2023, Paris (https://theunion.org/sites/default/files/2023–11/UNION2023_Abstracts-compressed.pdf, accessed 11 March 2024).

Annex 1: PADO-TB priorities defined by the interim review convened in 2020

Formulations: all scored and dispersible				
Short-term list				
	Drug-susceptible TB	**Drug-resistant TB**	**TB preventive treatment**	**Notes**
Rifapentine	✓		✓	150 mg scored dispersible tablet preferred formulation
Clofazimine		✓		
Delamanid		✓		PADO-TB2 to review results from studies investigating delamanid-containing regimens for TB preventive treatment, if available
Linezolid		✓		No paediatric formulation available
Bedaquiline [a]		✓		PADO-TB2 to review results from studies investigating bedaquiline-containing regimens for indications other than drug-resistant TB, if available
Pretomanid [b]		✓		PADO-TB2 to review results from studies investigating pretomanid-containing regimens for treatment of drug-susceptible TB, if available
Rifampicin [b]	✓		✓	
Watch list				
Moxifloxacin [c]	✓	✓ [d]	✓	Taste-masked formulation
All compounds currently in phase II clinical development				Paediatric investigations should start when trials involving adults show evidence of the efficacy and safety of the drug of interest (phase II)

[a] Flagged for potential deletion from the short-term list in 2020.

[b] Flagged for potential deprioritization to the watch list in 2020.

[c] Flagged for potential prioritization in 2020, based on the results of the TBTC Study 31.

[d] Including isoniazid-resistant TB.

Annex 2: PADO-TB2 participants

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All external participants acted in their personal capacity.

Annex 3: PADO-TB2 agenda

Day 1: Tuesday 3 October 2023

Session 1: introduction		
13.30–13.40	Welcome	Tereza Kasaeva
13.40–13.50	Introductions, relevant updates from WHO and meeting objectives	Kerri Viney
13.50–13.55	Conflict of interest declarations	Annemieke Brands
13.55–14.10	Overview of the PADO process and review of current PADO-TB priority list, watch list and research priorities	Tiziana Masini
14.10–14.20	Setting the stage – acceptability of TB treatment for children: beyond palatability	Dillon T Wademan
Session 2: TB preventive treatment and rifapentine		
14.20–14.25	Objectives of Session 2	Tiziana Masini
14.25–14.45	Overview of ongoing and planned studies on TB prevention and studies including rifapentine for other indications	Anneke Hesseling
14.45–14.55	Update on paediatric rifapentine development (PADO-TB priority)	Melynda Watkins
14.55–15.05	Break	
15.05–15.20	Experience from IMPAACT4TB	Makaita Gombe and Nicole Salazar Austin
15.20–15.30	Market perspective	Brian Kaiser
15.30–15.40	Questions and answers	Moderated by Tamara Kredo
15.40–16.25	Discussion around prioritization and research questions	Moderated by Tamara Kredo
16.25–16.30	Wrap-up and closing	Annemieke Brands

Day 2: Wednesday 4 October 2023

Session 3: first-line medicines		
13.30–13.35	Objectives of Session 3	Sabine Verkuijl
13.35–13.50	Global estimates and determinants of antituberculosis medicine pharmacokinetics in children and adolescents: systematic review and individual patient data meta-analysis	Jan-Willem Alffenaar and Fajri Gafar
13.50–14.05	Individual participant data meta-analysis of Rifampicin and other first-line medicines among children	Rada Savic
14.05–14.20	Overview of other studies on different or higher doses of first-line TB medicines	Anthony J Garcia-Prats
14.20–14.35	Use of first-line TB medicines in children with TBM	Kelly Dooley
14.35–14.50	Market perspective	Brian Kaiser

14.50–15.10	Questions and answers	Moderated by Tamara Kredo
15.10–15.20	Break	
15.20–16.15	Discussion around prioritization and research questions	Moderated by Tamara Kredo
16.15–16.30	Wrap-up and closing	Kerri Viney

Day 3: Thursday 5 October 2023

Session 4: second-line medicines		
13.30–13.35	Objectives of Session 4	Tiziana Masini
13.35–13.55	Overview of ongoing and planned studies	Anthony J Garcia-Prats and Elin Svensson
13.55–14.05	Questions and answers	Moderated by Tamara Kredo
14.05–14.35	Discussion around prioritization and research questions	Moderated by Tamara Kredo
14.35–14.45	Break	
Session 5: research and development pipeline		
14.45–15.05	Overview of TB medicine research and development	Kelly Dooley
15.05–15.15	Spotlight on long-acting formulations	Andrew Owen
15.15–16.05	Questions and answers and discussion	Moderated by Tamara Kredo
Session 6: wrap-up and new priority list		
16.05–16.15	Overview of PADO-TB2 priority list, watch list and research questions	Tiziana Masini
16.15–16.25	Next steps	Sabine Verkuijl
16.25–16.30	Closing	Kerri Viney

Annex 4: General definitions and utility of the PADO-TB priority and watch lists

Scope of PADO-TB

In 2021, the World Health Organization (WHO) published a paediatric drug optimization (PADO) standard procedure to provide guidance on how to undertake a paediatric drug optimization exercise and identify key priority products for research and development *(1)*. The guidance outlines the goals, methods and final products of a PADO process, and as anticipated use by all interested stakeholders. It also clearly indicates that each PADO process must be adapted to the specific needs of each therapeutic area, where it should be integrated and coordinated with other ongoing work in that area.

PADO exercises aim to develop a prioritized medicine portfolio of the most needed formulations for children to enable alignment between researchers, funders, procurers, market coordination entities, innovators, generic manufacturers, product development partnerships and regulators and ensure the unique needs of children are considered and effectively addressed upfront in the research and development (R&D) process.

PADO is not a platform in which dosing updates or sustainable and secured supply are discussed. In September 2023, the WHO Global Tuberculosis Programme established a technical advisory group on dosing of TB medicines for children and adults, which will provide formal advice to WHO on dosing guidance that is included in WHO operational handbooks on TB *(2)*. This group is composed of members with specific expertise in clinical pharmacology, pharmacometrics, clinical research, programmatic management of TB, and civil society and community perspectives *(3)*. Considerations on dosing may inform the priority formulations discussed and agreed upon during PADO-TB meetings, such that the two initiatives complement each other.

Although PADO-TB discussions on drug optimization include considerations on R&D with a market-shaping lens in mind, PADO-TB also complements the work carried out by other partners on aspects to ensure sustainable and secured supply for TB products.

PADO-TB outputs

PADO-TB priority list

This contains high-priority formulations to be investigated and developed in the short term (3–5 years) or formulations that may be developed in the longer term, but for which it is important to flag priority. The list may include the following:

- Formulations that are not available on the market yet and that should be developed based on information presented from completed studies, and forward-looking considerations for medicines included in ongoing studies (especially pharmacokinetic studies):

- Ideally, consensus should be reached on a specific formulation (dosage form, strength, scoring lines), in which case the formulation will be added by WHO to the list of products eligible for WHO prequalification (WHO prequalification expression of interest) *(4)*.

  An example is the rifapentine 150 mg scored dispersible tablet added to the WHO prequalification expression of interest following the virtual review of PADO-TB1 priorities in September 2020.

- If a new formulation is prioritized for development, most likely with certain characteristics, but if some information is still pending (e.g. on the recommended dosing of the medicine), the formulation can be included in the priority list, with the caveat that the characteristics are to be confirmed. It is acknowledged that manufacturers will require the specific characteristics of a prioritized products to be confirmed, but it is deemed important for them to understand in advance the rationale and consensus on priority formulations for certain diseases areas.

  An example is the inclusion of a rifampicin 100 mg scored dispersible tablet in the PADO-TB2 priority list. This will help WHO and all stakeholders to address requests from manufacturers about the addition of an FDC to the WHO prequalification expression of interest, and it can help to gauge the level of interest in a certain product.

- Formulations that are available but require improvement in terms of specific features, such as palatability or the addition of a scoring line to enhance dose flexibility or acceptability in children. If studies or prequalification by WHO are ongoing, this is flagged in the list. It is important to keep the formulation in the PADO priority list until the "improved formulation" is available. Keeping a formulation in the priority list can be used by researchers and developers to signal the relevance to prequalify this product when submitting to WHO Prequalification, or the relevance and need for continued research and development. When a quality-assured version of the formulation is available, it can be removed from the priority list.

  An example is the moxifloxacin 100 mg dispersible tablet, which is included in the PADO-TB2 priority list, and for which a taste-masked formulation is currently being developed.

- Formulations that may be generic versions of an innovator product to secure access in all settings. In the context of ensuring sustainable access to quality-assured, affordable medicines for all, the priority list can be used to flag whether a product that is available only as an innovator product should (also) be available as a generic product. This has a strong link to the WHO prequalification expression of interest, where these products are or will be added. If a product is available as a generic formulation, even if only from one supplier, it will be generally removed from the priority list, because it is not the mandate of PADO to discuss whether this one generic manufacturer is sufficient to ensure secured supply.

An example is the removal of clofazimine from the PADO-TB2 priority list because one generic supplier was considered to be enough to guarantee supply security, and also considering that some countries procure adult tablets (100 mg) to cover dosing needs for older children and adolescents weighing 24 kg and over who require a minimum 100 mg dose.

- Formulations that are not planned to be developed in the short term, but for which it is important to flag that they are a priority for development for TB treatment or TB prevention in children in the longer term.

An example is the inclusion of pretomanid on of PADO-TB2 priority list because it is included in the WHO recommended 6-month regimen composed of bedaquiline, pretomanid and linezolid, with or without moxifloxacin (BPaLM/BPaL) for adolescents and adults.

PADO-TB watch list

This contains promising candidates for investigation and development for children, within a time horizon of 5–10 years. These may include:

- Medicine candidates included in phase IIa/b clinical trials in adults that are expected to have good tolerability and toxicity profiles and without any major preclinical concerns noted for use among children.

Examples include compounds that are currently in phase IIa/b trials, which were added to the watch list during PADO-TB2. For medicines that are more advanced in terms of development, WHO and stakeholders can advocate for prompt initiation of paediatric studies.

- Formulations of existing medicines that are being investigated with innovative delivery approaches and new technologies.

Examples include long-acting formulations of rifapentine and isoniazid and a rifapentine oral film, which were included in the priority list in PADO-TB2. If new technologies are in the preclinical phase, they are included or remain on the watch list. They may be moved to the priority list when they are being investigated clinically.

Priority research agenda

This is to promote future TB medicine optimization work for paediatric populations. It may also relate to formulations that are no longer featured in the PADO-TB priority list.

An example is once-daily dosing of bedaquiline, delamanid and clofazimine, which was flagged as a priority research question, even though these medicines no longer appear on the PADO-TB2 list.

Utility of PADO-TB outputs for WHO and other stakeholders

The outputs of PADO-TB are used by WHO and other stakeholders to ensure priority formulations of TB medicines for children are developed and the messages provided around those are aligned across stakeholders. In particular:

- WHO technical departments use the outcome of the PADO process to update the WHO prequalification expression of interest, signalling to manufacturers the need to develop a certain formulation.
- WHO and stakeholders use the PADO priority list to respond to requests from manufacturers and developers about formulations to prioritize for development (and formulations not prioritized for development at a certain point in time, with a clear rationale agreed upon by the group). This ensures clear, aligned messages are given by all stakeholders.
- Stakeholders involved in the development or optimization of formulations or paediatric TB research projects can use the PADO-TB list and the list of research priorities to flag the relevance or importance of a work they are conducting to request for funding support for specific studies or follow-up studies in line with agreed needs.
- Stakeholders can use the PADO-TB watch list to advocate for prompt initiation of paediatric investigations for compounds that are in phase IIa/b for adults.

References

1. Paediatric drug optimization standard procedure. Geneva: World Health Organization; 2021 (https://iris.who.int/bitstream/handle/10665/349315/9789240039520-eng.pdf?sequence=1, accessed 7 March 2024).
2. WHO TB knowledge sharing platform. Geneva: World Health Organization (https://tbksp.org/en/implementation-books-solr, accessed 18 March 2024).
3. Technical Advisory Group on dosing of TB medicines for adults and children. Geneva: World Health Organization (https://www.who.int/groups/technical-advisory-group-on-dosing-of-tb-medicines-for-adults-and-children, accessed 17 April 2024).
4. 22nd invitation to manufacturers of antituberculosis medicines to submit an expression of interest (EOI) for product evaluation to the WHO Prequalification Unit. Geneva: World Health Organization; 2024 (https://extranet.who.int/prequal/sites/default/files/document_files/EOI_TB_v21_29June2021_v1_2024Review_v7_final.pdf, accessed 3 May 2024).

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