Report of the meeting to review the Paediatric Antituberculosis Drug Optimization priority list
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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>1HP</td>
<td>1 month of daily isoniazid plus rifapentine</td>
</tr>
<tr>
<td>3HP</td>
<td>3 months of weekly isoniazid plus rifapentine</td>
</tr>
<tr>
<td>3HR</td>
<td>3 months of daily isoniazid plus rifampicin</td>
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<tr>
<td>4R</td>
<td>4 months of daily rifampicin monotherapy</td>
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<tr>
<td>6/9H</td>
<td>6–9 months of daily isoniazid monotherapy</td>
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<tr>
<td>Bdq</td>
<td>bedaquiline</td>
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<td>Cfz</td>
<td>clofazimine</td>
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<td>Dlm</td>
<td>delamanid</td>
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<td>DR-TB</td>
<td>drug-resistant tuberculosis</td>
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<tr>
<td>DS-TB</td>
<td>drug-susceptible tuberculosis</td>
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<tr>
<td>DT</td>
<td>dispersible tablet</td>
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<tr>
<td>DTG</td>
<td>dolutegravir</td>
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<tr>
<td>E, EMB</td>
<td>ethambutol</td>
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<tr>
<td>EFV</td>
<td>efavirenz</td>
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<tr>
<td>EML</td>
<td>Essential Medicines List</td>
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<tr>
<td>EOI</td>
<td>expression of interest</td>
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<tr>
<td>FDC</td>
<td>fixed-dose combination (medicines)</td>
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<tr>
<td>FQ</td>
<td>fluoroquinolone</td>
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<tr>
<td>GAP-f</td>
<td>Global Accelerator for Paediatric formulations</td>
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<td>GDF</td>
<td>Stop TB Partnership's Global Drug Facility</td>
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<td>Global Fund to Fight AIDS, Tuberculosis and Malaria</td>
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<td>Global TB Programme</td>
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<tr>
<td>H, INH</td>
<td>isoniazid</td>
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<td>HIV</td>
<td>human immunodeficiency virus</td>
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<td>Lzd</td>
<td>linezolid</td>
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<td>M, Mfx</td>
<td>moxifloxacin</td>
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<tr>
<td>MDR-TB</td>
<td>multidrug-resistant tuberculosis</td>
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<tr>
<td>PADO</td>
<td>Paediatric Antituberculosis Drug Optimization</td>
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<tr>
<td>Pa</td>
<td>pretomanid</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<td>--------------</td>
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<tr>
<td>PD</td>
<td>pharmacodynamics</td>
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<tr>
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<td>pharmacokinetics</td>
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<td>prequalification (of medicines)</td>
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<td>rifampicin</td>
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<td>R, RPT</td>
<td>rifapentine</td>
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<tr>
<td>RR-TB</td>
<td>rifampicin-resistant tuberculosis</td>
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<tr>
<td>TB</td>
<td>tuberculosis</td>
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<tr>
<td>TPMAT</td>
<td>Tuberculosis Procurement and Market Shaping Action Team</td>
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<tr>
<td>TPT</td>
<td>tuberculosis preventive treatment</td>
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<tr>
<td>US FDA</td>
<td>United States Food and Drug Administration</td>
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<tr>
<td>WAZ</td>
<td>weight-for-age z-scores</td>
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<td>WHO</td>
<td>World Health Organization</td>
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GLOSSARY

ESSENTIAL MEDICINES LIST
The Essential Medicines List (EML) is a list of the minimum medicine needs for a basic health care system. It includes the most effective, safe and cost-effective medicines for priority conditions. The World Health Organization (WHO) updates its EMLs (for adults and children) every 2 years. The WHO EML (also called the Model List) serves as a model for national EMLs.

Relevant links:
https://essentialmeds.org/

EXPERT REVIEW PANEL
The Expert Review Panel (ERP) is an independent advisory body of technical experts coordinated by WHO. It assesses the potential risks and benefits associated with the use of antiretroviral, antituberculosis (anti-TB) and antimalarial products that are not yet WHO-prequalified or authorized by a stringent regulatory authority. The ERP makes recommendations to procurement agencies that procure or fund procurement (or both), such as the Global Fund to Fight AIDS, Tuberculosis and Malaria (the Global Fund) and the Global Drug Facility, on whether procurement of such products can be authorized. The recommendation is valid for a period of no more than 12 months or until the product is either WHO-prequalified or authorized by stringent regulatory authorities.

Relevant links:
The Expert Review Panel: https://extranet.who.int/pqweb/medicines/expert-review-panel

EXPRESSION OF INTEREST FOR PRODUCT EVALUATION BY THE WHO PREQUALIFICATION UNIT
The first step in the WHO prequalification process of a finished pharmaceutical product or an active pharmaceutical ingredient is its inclusion in an invitation to manufacturers to submit an expression of interest (EOI) for product evaluation. EOIs are issued by WHO, by therapeutic area, following consultation with WHO disease programmes and/or clinical specialists. EOIs for product evaluation by the WHO Prequalification (PQ) Unit, including those related to finished pharmaceutical products for treating TB, are updated on an ad hoc basis (e.g. when WHO recommendations are issued, or when new drugs or formulations become available).

Relevant links:
20th Invitation to manufacturers of antituberculosis medicines to submit an expression of interest (EOI) for product evaluation to the WHO Prequalification Unit:

GLOBAL FUND ERP EOI
Similar to the WHO PQ EOI, the purpose of the Global Fund ERP EOI is to invite submissions of product dossiers for review by the ERP. The EOI covers products for which there could be supply bottlenecks (including the cases where there are two or fewer quality-assured products of the same formulation available in the global market), or some formulations even where there are more than two eligible products in the market, where it has been determined that such products are eligible for distribution to a
restricted number of countries only, or when it has been identified that the available production capacity of the qualified products cannot cover the demand.

Relevant links:
List of tuberculosis pharmaceutical products classified according to the Global Fund quality assurance policy:
https://www.theglobalfund.org/media/4757/psm_productstb_list_en.pdf?u=637319006341100000

WHO PREQUALIFICATION (PQ) PROGRAMME
The WHO PQ Programme was set up in 2001. It ensures the availability of active pharmaceutical ingredients and finished pharmaceutical products of key medicines (including TB medicines) that are safe and appropriate, and meet stringent quality standards.

Relevant links:
WHO - Prequalification of Medical Products (IVDs, Medicines, Vaccines and Immunization Devices, Vector Control): https://extranet.who.int/pqweb/medicines
Database of WHO prequalified medicines: https://extranet.who.int/pqweb/medicines/prequalified-lists/finished-pharmaceutical-products
EXEcutive summary

The Paediatric Antituberculosis Drug Optimization (PADO-TB) meetings provide a forum for clinicians, researchers, financial and technical partners and other relevant key stakeholders to work together, to ensure that priority optimal paediatric formulations of TB medicines are investigated, developed and made available to children in a timely manner.

After the first meeting (PADO-TB1) in February 2019,¹ the World Health Organization (WHO) hosted an interim review of the PADO-TB1 priorities. The review considered the latest WHO recommendations and other relevant development since February 2019, such as results of clinical trials, results of pharmacokinetics (PK) and pharmacodynamics (PD) studies, and advancements of key drugs in the TB research and development (R&D) pipeline.

The 4.5-hour virtual review was attended by more than 50 experts including clinicians, researchers, representatives of national TB programmes (NTPs) from high TB burden countries, community representatives, financial and technical partners, members of the Child and Adolescent TB Working Group and representatives from various international agencies, including WHO (see Annex 3 for the list of participants).

A guidance document on PADO processes will be developed and published by WHO in the first quarter of 2021, and will inform discussions during PADO-TB2. The remainder of this summary highlights the main developments presented for various TB medicines and decisions taken with regard to the PADO-TB priority list.

rifapentine (P, RPT)

- Ideally, we should aim for an RPT formulation that is durable and can serve multiple indications. It is therefore important to consider immediate needs, medium- and long-term needs, and related data gaps:
  - Short-term needs: 3HP dosing and safety in children across ages
    Data gaps in these areas are being addressed by several studies, such as TBTC Study 35 (NCT03730181) and DOLPHIN-Kids (NCT03435146),² which aim to generate evidence for the use of 3HP (3 months of weekly isoniazid [H, INH] plus RPT) in children across the age spectrum, including those aged under 2 years (HIV coinfected and uninfected).
  - Medium-term needs: a) 1HP dosing across ages, and b) treatment of drug-susceptible TB (DS-TB)
    a) 1HP (1 month of daily INH plus RPT) has only been recommended in adolescents and adults aged 13 years or more (regardless of HIV status), given the lack of data on dosing and safety of daily RPT in children aged under 13 years.³ A study to determine the safety and optimal dosing of 1HP for the prevention of TB among children with and without HIV, including children on dolutegravir (DTG) or efavirenz (EFV), is planned (IMPAACT P2024).

b) An RPT-containing regimen (2HPZM/2HPM) was recently shown to successfully reduce the duration of DS-TB disease treatment in adults and adolescents aged 12 years or more (HIV coinfected and uninfected) from 6 to 4 months (TBTC Study 31/A5349; NCT02410772). However, PK and safety data for once-daily dosing of RPT in children are currently lacking for the recommended dose used in this study.

- A nitrosamine impurity identified in the active pharmaceutical ingredient of RPT is delaying many of these ongoing studies.
- Given different dosing requirements for RPT within different regimens as well as across indications, a standalone RPT formulation that is scored and dispersible will offer the best flexibility for RPT use in children.

**SECOND-LINE DRUGS**

- Bedaquiline (Bdq): a child-friendly Bdq formulation (20 mg functionally scored tablets) that can be dispersed in water was approved by the United States Food and Drug Administration (US FDA) in May 2020 and is now available from the Stop TB Partnership’s Global Drug Facility (GDF). Although a 20 mg scored tablet allows for flexibility when dosing small children, it has yet to be determined whether it corresponds with the best strength to optimally dose children across ages.
- Delamanid (Dlm): Dlm 25 mg dispersible tablets (DTs) are currently only available through compassionate use. Otsuka is expecting approval from the European Medicines Agency (EMA) in late 2021. Major data gaps (PK and optimal dose and safety in children aged <3 years) are being addressed by IMPAACT 2005 (NCT03141060), which is enrolling HIV uninfected and infected children with multidrug-resistant TB (MDR-TB) aged under 18 years.
- Clofazimine (Cfz): a 50 mg unscored tablet is available from the GDF that is not dispersible but is easier to manipulate than soft-gel capsules. Major research gaps include PK, optimal dose, safety, palatability and acceptability in children; these gaps are being investigated in the Clofazimine PK Study and in the Clofazimine and moxifloxacin PK, safety and AccepTAbiLitY trial for paediatric TB treatment STudy (CATALYST).
- Linezolid (Lzd): no child-friendly dispersible formulation is available. The Unitaid-funded BENEFIT Kids project and others are working to identify appropriate manufacturing partners for a 150 mg scored, DT

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4 Dorman SE. The design and primary efficacy results of Study 31/A5349: SP-10 High-dose rifapentine with or without moxifloxacin for shortening treatment of TB (NCT02410772). 51st Union World Conference. 2020.


9 Destito, Marc (Otsuka, Geneva). Personal communication with Tiziana Masini, WHO GTB (December 2020).

formulation of Lzd. Data from an observational PK study implemented in Cape Town, South Africa, have informed dosing of Lzd in children to match 600 mg daily adult dosing. However, alternative dosing strategies in adults are still under evaluation (e.g. the ZeNix trial [NCT03086486], results expected in 2021).

- Pretomanid (Pa): paediatric trial formulations of Pa (50 mg and 10 mg DT) have been developed and tested in healthy adult volunteers, but have not been studied in children and are not yet commercially available. A male fertility study and a single dose paediatric study must be completed before a multiple dose paediatric study can begin.

- Moxifloxacin (M, Mfx): quality-assured 100 mg DTs of Mfx are currently available from two suppliers through the GDF. BENEFIT Kids is exploring an innovative taste-masking strategy to improve acceptability of this formulation. Data from the observational study MDRPK212 and the CATALYST trial will help to address gaps in PK data, safety, tolerability and acceptability of Mfx in young children, and will inform more optimal Mfx dosing across age groups.

RIFAMPICIN (R, RIF)

- WHO is in the process of commissioning a systematic review of current evidence on the most effective dosing of Rif, INH, pyrazinamide (Z, PZA) and ethambutol (E, EMB). For some specific subgroups (e.g. children), additional PK data may be used when available; an additional individual patient data meta-analysis may be needed following these reviews.

- PK/PD evidence shows that higher Rif doses are needed, especially in high-risk groups (e.g. malnourished and TB/HIV coinfected children), even to match exposures of adults receiving the standard currently recommended 10 mg/kg Rif dose (SHINE [ISRCTN63579542] and DATIC [NCT01637558] studies).14

- New data available from OptiRif Kids show good safety of Rif doses up to 60–75 mg/kg with short-term dosing (15 days). Longer term dosing data in children, which are particularly relevant for safety evaluations, are currently lacking. TBM-KIDS is evaluating increased Rif doses (30 mg/kg) in children with TB meningitis.

- The currently available Rif formulations do not support optimal Rif dosing; however, optimized dosing algorithms can improve exposure in high-risk groups such as malnourished children, even with the currently available FDC.15

THE CURRENT TB DRUG DEVELOPMENT PIPELINE AND EMERGING RESEARCH PRIORITIES FOR CHILDREN


o Among the drugs that are still in clinical development\textsuperscript{16,17} and have not yet been approved for any indication, two classes of compounds are of particular interest; namely, oxazolidinones (sutezolid, delpazolid, contezolid, TBI-223) – which are the same chemical class as Lzd, with chemical modifications aimed at improving the safety profile while retaining the anti-TB activity of Lzd; and DprE1 inhibitors (OPC-167832, BTZ043, macozinone, TBA-7371) – a completely new drug class, with OPC-167832 having been tested at different doses and in combination with Dlm.

o Additional interesting drug candidates include telacebec (recent results\textsuperscript{18} showing the dose effect on bactericidal activity are promising); new diarylquinolines such as TBAJ876, which is in the same chemical class as Bdq and was developed to have drugs maintaining Bdq sterilizing activity against \textit{Mycobacterium tuberculosis} but with a lower QT prolonging effect; GSK 286, which has a new mechanism of action; and SPR-720.

o At this point we do not know which of these drugs will go beyond their current clinical stage.

**OUTCOMES OF THE DISCUSSION: UPDATED PADO-TB LIST**

- The group agreed to prioritize a standalone RPT formulation (150 mg scored DT) that allows for better dosing across indications (3HP in the short term, 1HP and DS-TB treatment in the medium term) and age groups, over a 1:1 fixed-dose combination (FDC). An FDC is preferred for programmatic implementation and may be prioritized in the future once the exact dosing needs for all age groups have been determined.

- Given the availability of the 20 mg scored DT approved by the US FDA, Bdq was proposed for deletion from the PADO-TB short-term list. However, although this formulation gives flexibility in terms of dosing in small children, it has not been established whether this is the best (and whether it is the only) formulation for appropriate dosing of young children across different ages. Once data from ongoing studies (e.g. P1108 and C211) become available, they will guide discussions and decisions on the optimal dose form or forms of paediatric Bdq.

- Lzd, Cfz and Dlm remain short-term priorities. The group highlighted the need to push for commercialization of Dlm 25 mg DT, because delaying this until doses are known across all age groups will be detrimental for the majority of children, for whom dosing schedules are already known.

- Pa was proposed for deprioritization from the short-term list to the watch list for drug-resistant TB (DR-TB), given that paediatric investigations have not yet begun, and it might be some time before multidose studies to inform dosing are undertaken.

- Given the emerging role of Mfx, especially in light of the results of TBTC Study 31, discussions on whether to include Mfx (and, specifically, a child-friendly taste-masked Mfx formulation) in the PADO-TB short-term list will be discussed during PADO-TB2. However, it was proposed to flag Mfx for DS-TB treatment in the updated PADO-TB list.

- Rif was flagged for potential deprioritization from the short term list to the watch list. During PADO-TB2, the group will decide on the inclusion of Rif in the PADO-TB list, taking into account the positive results of the SHINE trial and TBTC Study 31.\textsuperscript{19}


\textsuperscript{19} The results of these trials were available after the virtual review of the PADO-TB priorities, being announced at the 50th Union World Conference on Lung Health. Hyderabad, India. 2019.
- As an interim solution, while awaiting alignment with the recommendations included in the WHO guidance document for PADO processes, telacebec, sutezolid, delpazolid and OPC-167832 were removed from the watch list and replaced with the text “All compounds currently in Phase II clinical development”.

1. BACKGROUND

In May 2016, the 69th World Health Assembly adopted a resolution (WHA69.20) on promoting innovation in and access to quality, safe, efficacious and affordable medicines for children (1). Optimization of paediatric tuberculosis (TB) drugs forms part of the key actions and milestones in the 2018 Roadmap towards ending TB in children and adolescents (2). The availability of child-friendly formulations of TB drugs is essential to facilitate the implementation of World Health Organization (WHO) recommendations for prevention and treatment of TB in younger children; it will also help in reaching the targets for ending TB in children and adolescents set at the United Nations high-level meeting (UNHLM) on the fight against TB (3). Certain features of drugs (e.g. palatability, dose volume and frequency, complexity of administration, and the potential for administration to cause pain or discomfort) can have a huge impact on adherence in children and can ultimately affect outcomes. Despite recent advances, there are still major barriers to timely access for children to improved TB treatments. Reaching consensus among stakeholders on priority paediatric TB formulations is key to ensuring that researchers, research funders, donors and manufacturers focus on the timely development of those formulations.

In February 2019, the WHO Global Tuberculosis Programme (GTB) held the first Paediatric Antituberculosis Drug Optimization (PADO) TB meeting (PADO-TB1) (4). PADO-TB1 brought together relevant stakeholders, including representatives of national TB programmes (NTPs), community representatives, members of the Child and Adolescent TB Working Group, clinicians, researchers, and financial and technical partners (some of whom have years of experience with drug optimization). Taking into consideration WHO guidelines, the participants identified current and potential future gaps in availability of paediatric formulations, discussed ongoing paediatric studies and emerging results, and jointly reached consensus on a list of priorities (short to medium term, and long term) for paediatric TB medicines (for DS-TB, DR-TB and TPT) for which accelerated development and marketing were considered urgently needed (see Annex 1).

Since February 2019, priorities identified by the PADO group have been discussed and reviewed by the Global Accelerator for Paediatric formulations (GAP-f) (5), a WHO network established under the WHO Science Division. GAP-f aims to accelerate and enhance the impact of ongoing initiatives for optimizing medicine formulations for children across multiple disease areas. Priorities identified by PADO-TB1 have also contributed to key processes such as the update of the invitation to manufacturers of anti-TB medicines to submit an expression of interest (EOI) for product evaluation to the WHO Prequalification (PQ) Unit (6), and the work done by the TB Procurement and Market Shaping Action Team (TPMAT) to submit recommendations to the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund) on that organization’s invitation to manufacturers to submit an EOI for product evaluation by the Global Fund Expert Review Panel (ERP) (7).

Following PADO-TB1, WHO conducted an interim review of the PADO-TB1 priorities, considering the latest WHO recommendations on DR-TB and TPT, recent developments in new TB drugs and formulations made available since February 2019, results of clinical trials, and pharmacokinetics (PK) and pharmacodynamics (PD) studies, as well as advancements of key drugs in the TB research and development (R&D) pipeline. The current meeting focused on short- to medium-term priorities but also touched on long-term ones (i.e. the watch list) to identify whether there is a need to urgently shift priorities at this point. The full agenda of the meeting is included in Annex 2, the list of participants is available in Annex 3.

2. SUMMARY OF THE PRESENTATIONS

Results of two trials – the Shorter Treatment for Minimal Tuberculosis in Children (SHINE) trial and the Tuberculosis Trials Consortium (TBTC) Study 31 – were not available and thus were not discussed during the meeting. However, because those trials were announced shortly after the meeting and their results are relevant to the topics discussed in this meeting report, WHO decided to include the results here. This report also includes discussion of some of the commitments agreed upon during the high-level dialogue on
paediatric HIV and TB in children living with HIV (8) that are relevant for the topics discussed here, even though those commitments had not been made at the time of the meeting.

2.1. OPENING SESSION

Tereza Kasaeva (Director, WHO GTB) opened the meeting by remarking that, despite the ongoing COVID-19 pandemic, we should continue working together to ensure that all children with TB have access to affordable, safe and suitable TB medicines. Targets for ending TB in children and adolescents, set at the UNHLM on the fight against TB, are very ambitious, and access to shorter and safer child-friendly regimens for prevention and treatment of DS-TB and DR-TB is key to reaching these targets (3). TB treatments for children are still unsatisfactory, despite major advances in this area, including child-friendly first-line fixed-dose combinations (FDCs) that became available in 2016, child-friendly formulations of many second-line drugs that became available in 2018, and child-friendly bedaquiline (Bdq) tablets that became available in June 2020 from the Stop TB Partnership’s Global Drug Facility (GDF), after being approved by the United States Food and Drug Administration (US FDA) (9). Access to better medications for children has been limited by a small and fragile market for these medicines, lack of availability of child-friendly options and limited data on new treatments, including for TPT and multidrug-resistant TB (MDR-TB) in children. It is therefore vital that all of us – clinicians, researchers, programme managers, technical partners, civil society and representatives of people affected by TB – collaborate, taking advantage of platforms such as PADO-TB to agree on priorities, and provide clear and strong signals to developers to optimize their investments in drugs and formulations that serve critical unmet needs.

Annemieke Brands (WHO GTB) remarked that this meeting is subject to WHO declaration of interest (DOI) and confidentiality undertaking (CU) procedures. All participants were asked to submit a DOI and CU. Among the 10 participants that declared interests, only one submission was potentially significant, mandating partial exclusion. Following WHO internal discussions, that participant was invited to join the meeting as an observer. All DOIs were made publicly available to all participants.

Sabine Verkuil (WHO GTB) discussed developments and achievements since PADO-TB1, including relevant guideline updates:

- Release of updated WHO guidelines for TPT (10) and an operational handbook (released in March 2020) (11). These guidelines have strong recommendations on the use of the following regimens: 6/9H, which is 6–9 months of daily isoniazid (H, INH) monotherapy; 3HP, which is 3 months of weekly INH plus rifapentine (P, RPT), for those aged 2 years or more; and 3HR, which is 3 months of daily INH plus rifampicin (R, Rif). In addition, the guidelines have conditional recommendations on 4R, which is 4 months of daily Rif monotherapy; and 1HP, which is 1 month of daily INH plus RPT, for adolescents and adults aged 13 years or more. While waiting for a suitable paediatric formulation for RPT (to allow administration of 1HP and 3HP), the preferred regimen for most children is 3RH (the HR FDC is now available in more than 90 countries worldwide). For children living with HIV, 6H – administered preferably using INH dispersible tablets (DTs) – is still the most suitable regimen considering the drug–drug interactions with most antiretroviral drugs, except in children who are on efavirenz (EFV)-based antiretroviral therapy.

- Launch of the target product profile (TPP) for TPT (August 2020) (12). The TPP aim to identify the product attributes to be considered in developing the best and most suitable TPT regimens. This document does not specifically target the paediatric population.

- Release of updated WHO guidelines for DR-TB along with an operational handbook (released in June 2020) (13, 14). These guidelines recommend a shorter, all-oral Bdq-containing regimen that is also suitable for children aged 6 years or more. For children aged under 6 years, Bdq is not yet recommended because of the lack of safety data and data on use as part of the shorter all-oral
regimens. Longer individualized regimens are recommended for those not eligible for the shorter regimen, including children aged under 6 years and those with extrapulmonary TB other than TB lymphadenitis. Delamanid (Dlm) is recommended in children aged 3 years or more. The BPaL treatment regimen – which is composed of Bdq, pretomanid (Pa) and linezolid (Lzd) and lasts 6–9 months, may be used under operational research conditions in MDR-TB patients aged 14 years or more who have TB that is resistant to fluoroquinolones (FQs), and who have either had no previous exposure to Bdq and Lzd or have been exposed to those drugs for no more than 2 weeks.

- Dose optimization of first-line drugs – see Section 2.4

While going through the PADO-TB prioritization exercise, it is important to have a clear overview of initiatives and mechanisms that are strongly linked to this work, which include:

- the WHO invitation to manufacturers to submit an EOI for product evaluation to the WHO PQ Unit (6);
- the WHO PQ mechanism (15);
- the Global Fund ERP and corresponding EOI (7); and
- the WHO model list of essential medicines for children (16).

The TB medicines dashboard (17) – developed and regularly updated by the GDF, in close collaboration with WHO and others – includes comprehensive information on TB medicines. The dashboard helps to track progress on development and quality assurance of new medicines and formulations, and to identify areas of divergence across contributing institutions to guide actions towards improved alignment and efficiency.

Sabine Verkuijl then summarized the objectives of the meeting and the expected outcomes.

Objectives of the meeting:

- Review developments relevant for the PADO-TB priorities identified in February 2019 during PADO-TB1.
- Reflect on ongoing paediatric drug developments in DS-TB, DR-TB and TPT.
- Discuss shifts in priorities and research gaps, and reach consensus on the PADO-TB priorities, including short- to medium-term and long-term priorities (i.e. watch list).

Expected outcomes of the meeting:

- Reach consensus on an updated version of the PADO-TB1 priority list with a focus on the short to medium term, to guide development of appropriate paediatric formulations.
- Coordination with existing initiatives and partner organizations that can take the PADO-TB priorities forward, such as TPMAT and GAP-f.
- Expected immediate outcomes:
  - Dissemination of agreed PADO-TB priorities (through a meeting report, and possibly through a publication in an open access, peer-reviewed journal).
  - Inform updates to the WHO PQ EOI and other relevant processes.

Based on the results of a randomized controlled trial conducted by the manufacturer, the US FDA has extended approval for the use of Bdq for children aged 5 years or more (9). However, these data have not yet been assessed by WHO.
Brian Kaiser (Stop TB Partnership’s GDF) presented an overview of multipartner approaches to address harmonization and formulation priorities, which have resulted in multiple formulations becoming quality assured and available on the market.

- TPMAT was established in early 2017, in collaboration with key partners including the Treatment Action Group and Médecins Sans Frontières. Opportunities for changes, improvements and consolidations identified within TPMAT have been implemented and communicated in collaboration with partners (e.g. WHO GTB and the WHO Department of Health Product Policy and Standards), through applications or letters of support for changes to the WHO Essential Medicines Lists (EMLs) for both adults and children \((16, 18)\), inputs to the WHO PQ EOI \((6)\) update and review of the Global Fund ERP EOI \((7)\). The GDF also has regular communication with all the quality-assured suppliers (including on their development plans), and a supplier meeting at which more strategic topics are discussed is organized on an annual basis.

- In terms of child-friendly formulations available for DS-TB, DR-TB and TPT from quality-assured suppliers, progress has been made recently, with many drugs having two quality-assured suppliers. A major gap persists for Lzd, for which a quality-assured 150 mg DT formulation is not yet available.

- The GDF launchpad approach was developed in collaboration with partners, to speed up the steps from pre-development through to launch and scale-up. Once a product is available, initial global demand is estimated and used for negotiations on factors such as price, terms and batches. An implementation roadmap is developed by working with clinicians, country representatives and partners on aspects such as registration requirements and phase-in/phase-out plans, after which grants are secured to support initial procurement of new tools (e.g. the funding from the Government of Japan for the procurement of child-friendly second-line TB medicines). The launchpad approach also includes monitoring of initial feedback on quality and acceptability, and support for national programmes to plan for scale-up, budgeting, quantification, forecasting and order management. Successful implementation of this approach has so far resulted in more than 60 countries procuring the paediatric DR-TB formulations using various funding sources, and the inclusion of Bdq 20 mg in the GDF catalogue at a price proportional to the adult treatment course price, with 25 countries having already placed orders with GDF.

- Remaining gaps include:
  - Lzd – a 150 mg DT is urgently needed;
  - RPT – the market cannot support multiple FDCs and standalone formulations of RPT for each specific use; harmonization and consolidation are needed; and
  - Rif – do we want to focus on a “top-up” approach to the current FDCs, on new FDCs or on 4R for TPT?

### 2.2. SESSION 1 – RIFAPENTINE

Anneke Hesselink (Stellenbosch University) provided an overview of data and developments on RPT, summarized below.

Younger children, especially those aged under 2 years, are at high risk of progression from TB infection to disease, making provision of TPT to this age group particularly important. WHO currently recommends several TPT regimens, some of which are conditional recommendations (shown in italics): 6/9H, 3HP \((\geq 2\) years of age), 3HR, 1HP \((\geq 13\) years of age) and 4R \((10)\). The only RPT-containing TPT currently recommended by WHO for use in children is 3HP. However, the lack of data (e.g. on PK and safety) means that it is not currently possible to recommend this regimen in children aged under 2 years; also, there is no child-friendly formulation of RPT that would allow for effective dosing in young children. Ideally, we should aim to have an RPT formulation that is durable and that could serve multiple indications. It is therefore important to consider immediate needs, but also medium- and long-term needs, and data gaps that must
be closed to address those needs:

- **First indication, immediate need: 3HP dosing and safety in children across ages**
  
  There is a lack of data for dosing children aged under 2 years. The current WHO dosing recommendations for 3HP provide different dosing requirements for RPT and INH in children aged 2–14 years (i.e. not necessarily 1:1). Data gaps are being addressed in two studies: TBTC Study 35 and DOLPHIN-Kids (19):
  
  - TBTC Study 35 (NCT03730181) is looking at dosing of RPT and INH in HIV-infected and HIV-uninfected children (aged 0–12 years) with TB infection. The study includes HIV-infected kids on EFV and dolutegravir (DTG), although data on patients on DTG will be limited given the limited roll-out of DTG so far. The primary objective of the study is to establish, through population PK modelling, the dose of RPT that will achieve the target adult exposures from TBTC Study 26. The trial is using a water-dispersible (unscored) FDC, namely, RPT/INH 150/150 mg. The initial RPT dose will be at least 20–25 mg/kg, and INH will be dosed up to a maximum of 25 mg/kg once weekly. However, the RPT dose may be adjusted based on the interim analysis if target exposures are not achieved. Two standalone trial formulations of RPT (100 mg and 20 mg DTs) may be used to adjust RPT doses, if necessary, and for dosing children in the youngest cohorts (<2 years of age) where more precise dosing may be needed.
  
  - DOLPHIN-Kids (NCT03435146) is a complementary study run by the IMPAACT 4TB consortium that aims to assess the safety, tolerability, and PK of 3HP among infants, children and adolescents living with HIV and taking DTG. This study will provide complementary data to TBTC Study 35. However, the timeline of this study has been affected by the presence of a nitrosamine impurity in the active pharmaceutical ingredient of RPT.

- **Second indication, medium-term needs: 1HP dosing across ages and treatment of DS-TB**
  
  The BRIEF-TB/A5279 study (NCT01404312) has already informed WHO guidelines, and 1HP is now recommended to adolescents aged 13 years or more, regardless of HIV status (20). 1HP has not yet been recommended for use in younger children, given the lack of data on dosing and safety of daily RPT in children aged under 13 years, and the potential for drug–drug interactions between antiretroviral therapy and 1HP.

  In general, the remaining data gaps for 1HP will be addressed by the following: bridging studies to compare the safety, tolerability and effectiveness of 1HP and 3HP in adults and adolescents, including in those who are living with HIV; preferences for TPT; and, as data emerge, a specific paediatric study to compare 1HP and 3HP in the field.

  Assuming that the efficacy of 1HP can be extrapolated from adults to children (which is reasonable), the current priority for children is to collect data on PK and the safety of 1HP. This will be done by the IMPAACT P2024 study, which will enrol HIV-infected and uninfected children aged under 15 years, including HIV-infected children on DTG or EFV. This trial will also be affected by the impurity issue with RPT, and investigators are considering opening the trial with the adult, non-dispersible formulation and including a dispersible formulation as it becomes available.

  The objective of TBTC Study 31/A5349 (NCT02410772) was to determine whether the substitution of Rif with RPT and of ethambutol (E, EMB) with moxifloxacin (M, Mfx) – in addition to the substitution with RPT – makes it possible to reduce DS-TB treatment duration from 6 to 4 months; that is, first arm: 2HRPZE/2HP for 17 weeks; second arm: 2HPZM/2HPM for 17 weeks; control: 2RHZE/4RH for 26 weeks. This study was a Phase III open-label trial that included adults and adolescents aged 12 years or more, and also included HIV-infected individuals. The results of the trial were announced at the 51st Union World Conference on Lung Health (October 2020) (21), after the virtual review of the PADO-TB1 priorities. The 4-month regimen including a combination of high-dose RPT, INH, pyrazinamide (Z, PZA) and Mfx (2HPZM/2HPM) was shown to be non-inferior in terms of efficacy to the currently recommended 6-month regimen (2RHZE/4RH). In addition, this 4-month regimen was safe and was well-tolerated by patients (21). Once the final data become available, WHO intends to
initiate a process to refine its current policy recommendations on the treatment of DS-TB.

The flat (daily) dose of RPT in this study (i.e. 1200 mg) is higher than RPT weekly dose in 3HP and RPT daily dose in 1HP in adults. The frequency of dosing might affect the PK targets that need to be achieved in children. Further research is needed to understand how to dose children aged under 12 years who will be initiated on this 4-month regimen (including those living with HIV), and to identify suitable formulations to do so.

Results of the SHINE (ISRCTN63579542) study were also presented at the 51st Union World Conference on Lung Health (October 2020) (22), after the virtual review of the PADO-TB1 priorities. The SHINE trial is a Phase III randomized open-label trial comparing 4 versus 6 months of treatment with Rif, INH and PZA, with or without EMB, in children with smear-negative, non-severe TB. It was conducted at five sites in four countries: India, South Africa, Uganda and Zambia. A total of 1204 children aged under 16 years participated in the trial, including 127 children living with HIV infection. The key finding was that 4 months of treatment was not inferior to the standard 6-month treatment. There was no statistically significant difference when comparing the cohorts of patients on the 6-month or 4-month regimens in terms of the proportion with an unfavourable outcome (treatment failure, TB recurrence, death of any cause and loss to follow-up). Side-effects related to treatment were few and were similar across both groups. It is expected that the trial findings will be considered during the forthcoming update to the WHO guidelines on the management of TB in children and adolescents.

The nitrosamine impurity detected in the active pharmaceutical ingredient of RPT and Rif will delay most of the trials mentioned above, and might cause global shortages of rifamycin-containing products, especially for RPT (there are fewer manufacturers of RPT than of Rif) (23, 24). If the US FDA agrees, trials will be able to move forward, potentially using either adult or trial formulations to generate the data, if the impurity is at an acceptable interim level. The child-friendly trial formulation RPT/INH 150/150 mg DT FDC is currently being analysed. Sanofi has halted work on development of the paediatric formulation until the impurity issue is resolved. Promisingly, several manufacturers have shown interest in pursuing an RPT product that has clear target compound characteristics and can support multiple doses and indications once the impurity issue has been resolved.

Given the current lack of trial data in children aged under 2 years, the University of California San Francisco (UCSF) undertook modelling work to predict weight-band dosing requirements for children (using robust, well-established PK models) and to understand the benefit of a scored 150 mg RPT tablet to inform an update of the WHO PQ EOI (25) (Annex 4).

For both 1HP and 3HP, the modelling shows that, in the two lower weight bands (3–4 kg and 5–6 kg), RPT exposure is much closer to the adult target when using a scored 150 mg RPT tablet, because the scoring makes it possible to provide a child with half a tablet. In contrast, there may be overexposure to RPT when using an un-scored 150 mg RPT tablet, because doses far exceed the currently recommended 25 mg/kg, especially in very young children.

A 1:1 HP FDC would allow appropriate dosing of the 3HP regimen (at least in children aged 2–15 years), based on the currently similar milligram per kilogram dose ranges of INH and RPT in these age groups. However, the same formulation would not deliver the appropriate dosing schedule in any age group (or weight band) in regimens that include daily dosing of RPT (1HP or DS-TB treatment in the medium term). For 1HP, current dosing recommendations for adolescents and adults aged 13 years or more are much higher for RPT (30 mg/kg per day) than for INH (10 mg/kg per day). Thus, RPT doses required to achieve target exposures with a 1:1 FDC would overexpose children to INH, which would be particularly concerning for children with slow acetylation status.

Given different dosing requirements for RPT within different regimens and across indications, a standalone RPT formulation that is scored and dispersible will offer the best flexibility for RPT use in children. This is especially important as newer regimens may become available for children in the medium term (e.g. 1HP and RPT-containing DS-TB regimens).
RPT formulation landscape – summary

- Commercial product – 150 mg unscored tablet, non-dispersible; crushing is challenging and alters bioavailability; licensed down to 2 years for 3HP.
- Trial formulations – water-dispersible FDC tablets of RPT/INH 150/150 mg (not scored); two additional standalone trial formulations (100 mg and 20 mg tablets) that may be needed to adjust RPT doses throughout the study, if needed.
- RPT 150 mg DT is currently listed in the WHO PQ EOI, but there has been little interest by generic manufacturers. This could be due to confusion caused by multiple regimens, multiple dosing requirements and multiple indications, which could result in fragmentation of an already fragile market.
- Priority agreed by the RPT working group – a flexible standalone RPT formulation, namely 150 mg dispersible, scored tables (ideally, functionally scored) that can support multiple indications.

Highlights from the discussion

- Role of INH in rifamycin-containing regimens – there are good data on 4R, and the efficacy of TPT regimens combining rifamycins and INH seems to be mainly driven by rifamycins. Ongoing studies on RPT only for TPT in adults and adolescents (e.g. TBTC Study 37) may provide further insights on this.
- Standalone RPT versus an FDC – caregivers and national programmes seem to prefer FDCs; however, there is a need for one product that can be used across weight bands and that serves multiple indications without risks such as high H exposures in young children, which can potentially lead to hepatotoxicity. An FDC may be the product to pursue in the future, to accommodate programmatic aspects once dosing schedules are clear for all age groups.

2.3. SESSION 2 – SECOND-LINE MEDICINES

Anthony Garcia-Prats (Wisconsin University) provided an overview of data and developments on second-line medicines, summarized below.

- Bedaquiline

  Major advancement: a child-friendly Bdq formulation (20 mg functionally scored tablets) that can be dispersed in water was approved by the US FDA in May 2020, and is now available from the GDF (9). Major research gap: PK, optimal dose and safety in children aged under 5–6 years, which are currently being evaluated in studies C211 (NCT02354014; sponsor: Janssen; HIV uninfected children and adolescents aged up to 18 years) (26) and P1108 (NCT02906007; sponsor: National Institutes of Health; data from cohort 1, aged 6–17 years, have already been shared with WHO; study includes HIV-infected and uninfected children with MDR-TB).

  Other relevant paediatric Bdq studies include:
  - Bdq Crush study – this study showed that the bioavailability of the 100 mg tablet used for adults is the same whether the tablet is whole or is crushed or suspended in water (this approach was intended to be used as a bridging strategy until a paediatric-specific formulation was available) (27).
  - IMPAACT 2020 (SMaRT Kids) – this is a Phase II study of two 6-month all-oral regimens in children aged 0 up to 15 years with probable or confirmed rifampicin-resistant TB (RR-TB). The opening has been delayed to early 2021.
• **Delamanid**

Trial formulations include 5 mg and 25 mg DTs. Currently, the 25 mg DT formulation is available through compassionate use (28). In September 2020, the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) issued a positive opinion for the use of Dlm to treat pulmonary MDR-TB in adolescents and children weighing at least 30 kg (29). Otsuka is expecting a CHMP opinion for children weighing less than 30 kg in the coming months, and approval of its dispersible Dlm formulation in late 2021.

**Major research gap:** understanding of the PK and optimal dose, and of safety in children aged under 3 years. IMPAACT 2005 (NCT03141060), enrolling HIV uninfected and infected children aged under 18 years, aims to address this gap (30). Otsuka trials 232 (NCT01856634) and 233 (NCT01859923) were completed and data were shared with WHO. Exposure of doses evaluated in older children were within the adult target ranges; in younger children, the exposures were within target ranges (except for some of the youngest children, who did not reach the targets, so dosing remains unknown for children weighing <16 kg). However, these studies were implemented using the DT trial formulation, which complicated the recommendation because that specific formulation is not available except via CU. Also, when the adult tablet (50 mg) is broken, the contents are bitter and unpleasant, and the impact of crushing could appreciably alter (most likely reduce) the bioavailability of Dlm.

Other relevant paediatric Dlm studies include:

- PHOENIx MDR-TB/ A5300B/I2003B (NCT03568383) – Dlm versus INH to prevent TB among high-risk household contacts of an MDR-TB source case; this study includes children;
- Dlm Crush (part of BENEFIT Kids) – relative bioavailability of different doses of Dlm in healthy adult volunteers, using adult tablets dispersed in water versus swallowed whole (as a bridging strategy until a paediatric Dlm formulation is available in the field); and
- IMPAACT 2020 (SMART Kids) – both of the 6-month all-oral regimens investigated include once-daily Dlm.

• **Clofazidine**

Formulation: a 50 mg solid tablet of Clofazidine (Cfz) is available from GDF. This is not a truly dispersible formulation, but it is easier to manipulate than the soft-gel capsules (Novartis), which cannot be split or otherwise manipulated.

**Major research gaps:** PK, optimal dose, safety and acceptability in children, which are to be studied in two trials:

- Clofazidine Kids Study – with Cfz 50 mg gel caps; opened in the third quarter of 2020 in South Africa; enrolling children and adolescents aged <18 years; and the Clofazidine and moxifloxacin PK, safety and Acceptability in Paediatric TB treatment (Catalyst) trial – with Cfz 50 mg solid tabs; to open in the first quarter of 2021 in India, the Philippines and South Africa; enrolling children and adolescents aged under 15 years. These two studies will generate much needed information on PK and the optimal dose of Cfz in children.
- IMPAACT 2020 (SMArt Kids) – arm 2 includes children with RR-TB and with resistance to FQs who will receive Cz as part of the regimen.

Bdq, Dlm and Cfz are also included in the BEAT-TB (NCT04062201) trial, a Phase III, open-label, multicentre, randomized controlled trial that aims to compare the efficacy and safety of a study strategy comprising 6 months of Bdq, Dlm, Lzd and Cfz, with or without Lfx (depending on resistance to FQs), in adolescents and adults aged 12 years or more with the current South African standard of care (9 months).
for the treatment of RR-TB.

- **Linezolid**

  *Major gap in the field:* unavailability of a child-friendly, dispersible formulation. Output 3 of the BENEFIT Kids project looks at targeted formulation development, which is specifically relevant because it aims to identify appropriate manufacturing partners to develop a new formulation of Lzd (150 mg scored DT) (31). A request for proposals was launched, and generic suppliers were invited to respond. The proposals are currently being reviewed.

  As part of the action plan agreed upon by participants of the high-level dialogue on paediatric HIV and TB in children living with HIV, held in November 2020 (8), after the virtual review of the PADO-TB1 priorities meeting, Micro Labs committed to finalizing the development of child-friendly Lzd for the treatment of DR-TB, with the aim of submitting a dossier to WHO PQ and the Global Fund ERP by the third quarter of 2021 (8).

  *Major research gaps:*
  
  - Data from an observational PK study implemented in Cape Town have informed dosing of Lzd in children (to match 600 mg daily adult dosing) (31). However, it may be interesting to look at alternative Lzd dosing strategies, such as those being evaluated in the ZeNix trial (NCT03086486; results expected in 2021), where lower doses and shorter durations of Lzd are being evaluated within a 6-month all-oral regimen that combines Bdq, Pa and Lzd for treating FQ-resistant MDR-TB (NiX-TB follow-on trial). No paediatric-specific studies are being conducted.
  
  - Impact on PK and bioavailability of manipulating the 600 mg tablet, which is currently the only option available for children, should also be investigated.

- **Pretomanid**

  Paediatric trial formulations of Pa (10 mg, 50 mg DTs) have been developed and tested in healthy adult volunteers. These formulations are not yet commercially available.

  *Major research gaps:*
  
  - There have been limitations in initiating paediatric Pa studies, mainly due to preclinical data that signalled reproductive toxicities in animals. A male fertility study and a single dose paediatric study (to define the dose for the multiple dose study) must be completed before a multiple dose paediatric study can commence. The study to evaluate the male reproductive safety of Pa in healthy volunteers is expected to start in May 2021 (PaSEM; NCT04179500). Also being planned is IMPAACT CAP 556, which aims to evaluate the PKs and safety of a single dose of Pa in children receiving treatment for DR-TB.

- **Moxifloxacin**

  Quality-assured 100 mg DT formulations of Mfx have been developed by two manufacturers and are now available through GDF.

  BENEFIT Kids is also working with manufacturers to develop an improved Mfx DT formulation. Mfx is very bitter and not palatable; hence, the project aims to improve acceptability using an innovative taste-masking strategy. There was consensus that palatability and acceptability of formulations are a high priority.
It is expected that data will soon be published from the observational study MDRPK2 (32) on PK and safety of model-optimized doses of key second-line anti-TB drugs, including Mfx, in HIV-infected and non-infected children aged 0–17 years; these data will help to address some of the knowledge gaps we still have in terms of PK data in children aged under 7 years. This will help in optimizing doses across all ages.

The CATALYST trial (see above) will evaluate PK, safety, tolerability and acceptability of the newly available generic child-friendly formulation of Mfx (100 mg DT) in children treated for DR-TB.

Highlights from the discussion:

- It would be interesting to study Bdq as part of preventive treatment regimens for DS-TB and DR-TB. However, such studies (e.g. PHOENIx) are expensive to implement, limiting their current feasibility.
- Different age groups should be enrolled in parallel (except for very young children, who could be enrolled in a staggered manner). The US FDA recently released guidance on the evaluation of anti-infectives in children, in which they clearly indicate that it is acceptable not to undertake age de-escalation studies (33). This is something that GAP-f has also been highlighting, as a strategy to accelerate the development of paediatric products.
- Personalized medicine approaches to dosing would also be of interest, but experts in the field have concerns about the feasibility of this approach. It could be worth exploring this approach for Lzd, where toxicity may be of concern (in the absence of the results of the ZeNix trial).
- Much more needs to be done to improve case finding of children with DR-TB (an estimated 25 000–30 000 per year) to ensure they receive timely and appropriate treatment. Indeed, children with DR-TB generally respond well to treatment. It is also important to explore ways to sustain the market of child-friendly TB medicines.

2.4. SESSION 3 – FIRST-LINE MEDICINES

Linh Nguyen (WHO GTB) presented on the planned systematic review on dose optimization of the first-line TB medicines:

- Preclinical, clinical and PK/PD evidence suggests that the current standard dose of first-line drugs has not been optimized for adults or children. There are concerns about low exposure to first-line drugs with recommended dosages, including in children. A WHO PK/PD consultation in 2017 concluded that a full review of evidence on the optimal dose of first-line drugs is required once new data become available (34).
- To address these issues, WHO is in the process of commissioning a systematic review on the landscape of current evidence on the most effective dosing of Rif, INH, PZA and EMB (35). The primary focus of the review is on the relation of different dosing and outcomes of treatment for adults and children; additional PK data for some specific subgroups (e.g. children) may be used when available. In particular, the research question is: In patients on combination regimens for DS-TB, does a higher dose of first-line drugs than the currently recommended doses safely increase the likelihood of treatment success and reduce the unfavourable treatment outcomes?
- If the review indicates that the current evidence is sufficient to make changes to recommended dosing, a broader expert group will be convened to discuss the next steps on dosage revision.
- PK data linked to treatment outcomes in the paediatric population are expected to be limited; therefore,
an additional individual patient data meta-analysis may be needed following these reviews.

- This review is planned for early 2021, with results expected in the second quarter of 2021.

**Rada Savic (University of California San Francisco)** provided an overview of data and developments on Rif, summarized below.

- Appropriateness of dosing algorithms in children is always done by comparing plasma PK exposures in children and adults. For Rif, current dosing strategies for children aim to match exposures of adults receiving the standard 10 mg/kg dose.

- The FDC formulations that are currently used in the field for the treatment of DS-TB in children are RHZ 75/50/150 (for the intensive phase of treatment) and RH 75/50 (for the continuation phase). Other formulations that have been used in ongoing studies include a 150 mg Rif capsule in OptiRif and a 20 mg/mL Rif suspension for top-up in the TBM-KIDS study (both formulations are quality-assured, marketed formulations rather than trial formulations). Studies showed that Rif suspensions have poor bioavailability (36, 37).

- Studies evaluating either PK and safety with high-dose Rif or PK levels in children at different ages and weights following standard WHO doses include OptiRif Kids (South African trial identifier 27-0117-5411; study completed), SHINE (results presented at the Union Conference 2020) (20), TBM-KIDS (NCT 02958709; children aged 6 months to 12 years with TB meningitis, interim complete), DATiC (NCT01637558; final PK results completed), and SURE-TBM (ISRCTN40829906; children and adolescents with TB meningitis, aged 28 days to 15 years).

- A substudy of the SHINE trial conducted in South Africa and Zambia included 76 children with non-severe forms of TB treated with the recommended FDC. The study found low Rif exposures, especially in small children (4–8 kg) and children weighing more than 25 kg compared with the adult exposures when receiving the standard 10 mg/kg WHO-recommended dose (38).

- The DATiC study in 179 children in South Africa and Malawi had similar findings; that is, low exposure to Rif, especially in small children (4–8 kg). Paediatric single drug suspensions were used in DATiC, and these have low bioavailability for Rif. Simulations show that, with the currently available FDC, exposures to Rif are under the target for most weight bands, whereas INH exposures are above the target and PZA delivers target adult exposures. These results led researchers to recommend new FDC ratios (RHZ, 120/30/135) to address this problem.

- Current WHO dosing guidelines are based on weight, and they may leave young and malnourished children vulnerable to underdosing. Indeed, Rif target exposure outcomes are poor for all children, but are worse for malnourished children. Modelling work has shown that target attainment can be improved even with currently available FDCs, with stratified dosing methods replacing current WHO weight-based dosing (39). In particular, dosing stratified by nutritional status – using weight-for-age z-scores (WAZ) – is easy to implement in resource-limited clinical settings because it requires only the measurement of weight, the recording of age and gender, and the estimation of nutritional status. Modelling work also showed that current dosing algorithms using uniform milligram per kilogram dosing cannot lead to a higher probability of TB-unfavourable outcomes, especially in high-risk children (e.g. those living with HIV and malnourished); in contrast, the probability of TB-unfavourable outcomes decreases, especially in malnourished children, when using dosing stratified by WAZ.

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21 The weight-for-age Z score indicates a child’s body weight for their age and sex relative to the reference population. It is an important indicator of a child’s nutritional status, such as underweight or overweight in young children aged under 2 years.
• Extensive published data on children’s exposure to Rif show that the probability of TB-unfavourable outcomes in children decreases with increased exposure to Rif. Based on efficacy data from children, the optimal target exposure for children would correspond to 185 μg·h/mL; however, it reaches less than 40 μg·h/mL with the current WHO dosing.

• OptiRif Kids (South African trial identifier 27-0117-5411, study completed), which included three cohorts of HIV-negative infants and children aged 0–12 years, dosed up to 60–75 mg/kg over 15 days, showed that by increasing the doses of Rif, exposure also increased. In terms of safety, no serious adverse events were observed when dosed over 15 days. Data are lacking on the longer term safety and tolerability of a higher Rif dose in children.

• TBM-KIDS is evaluating high-dose of Rif (30 mg/kg) in 120 children with TB meningitis. Preliminary results of this study were presented during the meeting but are confidential.

• While waiting for new evidence and the outcome of the systematic review to inform higher Rif dosing, it was proposed that new ways be used to construct dosing charts that are not limited to weight-band dosing; such charts could make it easier to use the currently available formulation more efficiently.

• It remains to be determined what an optimal Rif formulation would look like. The systematic review that WHO is planning and the individual patient data meta-analysis will inform formulation development.

• In summary, there is now sufficient evidence that, with current FDCs and recommended doses, Rif exposures are frequently below target, particularly in younger children, underweight patients, patients with TB meningitis and immunocompromised HIV-infected TB patients. There is a need to synthesize all existing PK data (paediatric and adult) on Rif, to inform how the existing FDCs could be used more optimally, and whether a standalone Rif formulation would be needed for top up. The strength and dosing of such a formulation should also be defined, and any incremental benefit on outcomes from improved Rif dosing using this formulation should be determined.

2.5. SESSION 4 – THE CURRENT TB DRUG DEVELOPMENT PIPELINE AND EMERGING RESEARCH PRIORITIES FOR CHILDREN

Kelly Dooley (Johns Hopkins University School of Medicine) provided an overview of drugs that are currently in the TB clinical pipeline and are showing promising activity.

Bdq, Dlm and Pa were defined as "second wave" drugs; that is, drugs that are already approved for a certain indication. Studies on these drugs for indications other than those for which the drugs are currently licensed are summarized below.

• Bdq is being evaluated for short-course MDR-TB regimens and in the context of 4-month and 2-month DS-TB regimens (SimpliciTB: BPaMZ regimen; TRUNCATE-TB, arm: 2HZE-Lzd-Bdq. This means that the market for Bdq could increase dramatically in the future, depending on the results of these studies.

• Dlm is being assessed by PHOENIx MDR-TB for MDR prophylaxis. Dlm is also part of several trials that are assessing short-course MDR-TB regimens.

• Pa is being evaluated in trials studying shorter durations of DS-TB regimens (<4 months).

The endTB trial enrolled more than 450 patients as of June 202022 (of the 750 patients accrued). The trial is looking at regimens including new and repurposed medicines for the treatment of FQ-susceptible MDR-

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22 As of 21 October 2020, 500 patients were enrolled.
TB. Final results are expected in 2022.

The Pragmatic Clinical Trial for a More Effective Concise and Less Toxic MDR-TB Treatment Regimen(s) (TB-PRACTECAL) is currently enrolling and the cohort includes adults and adolescents aged 15 years and above. Investigators have submitted the interim analysis. The second part of the study may not continue with all three arms of the trial.

“Third wave” drugs were defined as drugs that have not been approved for any indication but are still in the clinical pipeline (40, 41). The two most important classes of “third wave” drugs are described below.

- **Oxazolidinones** include sutezolid, delpazolid, contezolid and TBI-223. This is the same chemical class as Lzd, which is a potent anti-TB drug, but given its toxicity it requires significant monitoring when used in patients for a long period, and often requires reductions in dose or even discontinuation. Sutezolid will be tested in the PanACEA Sutezolid Dose-finding and Combination Evaluation (SUDOCU), where a combination of Bdq, Dlm, Mfx and several dose ranges of sutezolid are being studied to gain a sense of sutezolid’s contribution to efficacy and safety. TBI-223 is a new drug developed by the TB Alliance; it has a lot of preclinical supportive data and will soon be advanced to Phase I trials.

- **DprE1 inhibitors** are a completely new class of drugs and they include OPC-167832, BTZ043 macozinone and TBA-7371. All these drugs are in Phase II trials. The compound OPC-167832, developed by Otsuka, has already been tested at different doses (once-daily oral doses of 3, 10, 30 and 90 mg). There are also arms in the trial in which the compound is tested at low and high doses with Dlm at 300 mg, but no results of those studies have been published. BTZ043 is being developed by the University of Munich, in a dose escalation trial (250–2000 mg). TBA-7371 is being studied by the Gates Medical Research Institute, which was granted a non-exclusive license to develop the drug. The trial is now enrolling, and several doses and dose frequencies are being studied.

- **Additional “third wave” drug candidates include the following:**
  - Telacebec – this is an energy suppressing drug; it is similar to Bdq but has a different mechanism of action. Data from the 2A EBA study were published recently (42), where the dose effect in terms of early bactericidal activity was shown, in comparison to RHZE given for 14 days.
  - New diarylquinolines such as TBAJ876 (Phase I testing, enrolling), which are in the same class as Bdq, are being developed with the idea of maintaining sterilizing activity against *Mycobacterium tuberculosis* but having a lower QT prolonging effect.
  - GSK 286 is a cholesterol-dependent *M. tuberculosis* inhibitor that has a new mechanism of action. It has not yet been registered in clinicaltrials.gov; human studies are expected to start in the fourth quarter of 2020.
  - SPR-720 is a gyrase B inhibitor. Phase I trials are complete and Phase II trials have been conducted in patients with nontuberculous mycobacterial pulmonary disease due to *M. avium* complex (results pending).

*Highlights from the discussion*

- By the end of 2020 or early 2021, data are expected on which combination therapies are proposed to go forward in larger combination trials.

- Among the "third wave" drugs, data for OPC-167832 may soon be available, and TBA737 and BTZ043 trials are enrolling.
3. UPDATED PADO-TB PRIORITY LIST

Based on discussions during the meeting, the PADO-TB list was updated, as shown in Table 3.1 and as summarized below:

- **RPT was kept in the short-term list**, with a focus on a flexible, standalone RPT formulation that can serve multiple indications, including 3HP (short-term need), 1HP and DS-TB treatment shortening (in the medium term). A 150 mg scored DT was identified as the formulation to pursue.

- **Lzd, Ctz and Dlm were kept as short-term priorities for DR-TB**. PADO-TB2 will review results from studies investigating these drugs for indications other than DR-TB, which may lead to additional changes to the list.

- **Bdq was flagged for potential deletion from the short-term list**, given the availability of 20 mg scored tablets. A final decision will be taken during PADO-TB2, when additional information may be available to help in establishing whether this is the best (and whether it is the only) formulation for appropriate dosing of young children across ages. PADO-TB2 will also review results from studies investigating Bdq-containing regimens for indications other than DR-TB, if available, and will adapt the list where necessary.

- **Pa was flagged for potential deprioritization from the short-term list to the watch list for DR-TB**, given that paediatric investigations have not yet begun. A final decision will be taken during PADO-TB2. Meanwhile, Pa was removed from the watch list for TPT, because it is not under investigation for this indication.

- **Rif was flagged for potential deprioritization from the short-term list to the watch list**. This was proposed because there is sufficient evidence showing that Rif exposures are frequently below targets with the current FDCs and recommended doses, but highlighting the need to synthesize all existing paediatric and adult PK data on Rif, to inform optimal Rif dosing in children and the corresponding formulations needed for appropriate dosing. A final decision on Rif will be taken during PADO-TB2.

- **RHZE and RHZLfx were removed from the watch list**, because there are no data to support the need for these kinds of FDCs. In particular, for RHZE, studies showed that EMB is extremely underdosed in children, meaning that we do not have evidence of its contribution in treatment regimens. In addition, there would be safety concerns for children if the dose were to be increased to adult levels.

- **Telacebec (Q203), sutezolid (PNU-100480), delpazolid (LCB01-0371) and OPC-167832 were proposed for removal from the watch list**, because there is no evidence that these drugs are the most promising among those that are currently being evaluated in clinical studies. As an alternative, the group proposed that the watch list include all drugs that are currently in Phase II clinical development, to provide a clear signal that paediatric investigations should start once trials involving adults show evidence of the efficacy of safety of the drug of interest (Phase II). As an interim solution while waiting to align with the recommendations included in the upcoming WHO guidance document for PADO processes, telacebec (Q203), sutezolid (PNU-100480), delpazolid (LCB01-0371) and OPC-167832 were removed from the watch list, and were replaced with the text “All compounds currently in Phase II clinical development”.

- **Mfx (in particular, a taste-masked paediatric formulation) was flagged for potential prioritization** given its emerging role, based on the results of TBTC Study 31. This specific indication was added to the updated PADO-TB priority list (Table 3.1), but a final decision on whether to include Mfx in the list of short-term priorities will be taken during PADO-TB2.

An additional proposal discussed during the meeting includes the development of two distinct watch lists, namely:
• a watch list for drugs that are already being used for TB patients (existing drugs); and
• a watch list for experimental drugs, including those that are still in the clinical pipeline (at least in Phase II) and have not yet been approved for any indication.

This proposal was not implemented in the updated PADO-TB priority list (Table 3.1); however, it will be reviewed again during PADO-TB2, which will also consider the PADO guidance document that WHO plans to publish in the first quarter of 2021, to inform and harmonize PADO processes across WHO.

Table 3.1. Updated PADO-TB priority list

<table>
<thead>
<tr>
<th>Formulations: all scored and dispersible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short term list</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>DS-TB</th>
<th>DR-TB</th>
<th>TPT</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifapentine (RPT)</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>150 mg scored DT preferred formulation</td>
</tr>
<tr>
<td>Clofazimine (Cfz)</td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Delamanid (Dlm)</td>
<td></td>
<td>✓</td>
<td></td>
<td>PADO-TB2 to review results from studies investigating Dlm-containing regimens for TPT, if available</td>
</tr>
<tr>
<td>Linezolid (Lzd)</td>
<td></td>
<td>✓</td>
<td></td>
<td>No paediatric formulation available</td>
</tr>
<tr>
<td>Bedaquiline (Bdq)</td>
<td>✓</td>
<td></td>
<td></td>
<td>PADO-TB2 to review results from studies investigating Bdq-containing regimens for indications other than DR-TB, if available</td>
</tr>
<tr>
<td>Pretomanid (Pa)</td>
<td></td>
<td>✓</td>
<td></td>
<td>PADO-TB2 to review results from studies investigating Pa-containing regimens for the treatment of DS-TB, if available</td>
</tr>
<tr>
<td>Rifampicin (Rif)</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>

| Watch list             |

<table>
<thead>
<tr>
<th></th>
<th>DS-TB</th>
<th>DR-TB</th>
<th>TPT</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moxifloxacin (Mfx)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>Taste-masked formulation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>* Including INH-mono-resistant TB</td>
</tr>
<tr>
<td>All compounds currently in Phase II clinical development</td>
<td></td>
<td></td>
<td></td>
<td>Paediatric investigations should start once trials involving adults show evidence of the efficacy and safety of the drug of interest (Phase II)</td>
</tr>
</tbody>
</table>


a Flagged for potential deletion from the short term list. A final decision will be taken during PADO-TB2.

b Flagged for potential deprioritization to the watch list. A final decision will be taken during PADO-TB2

c Flagged for potential prioritization, based on the results of TBTC Study 31.

d See (40) for an up-to-date status of the TB clinical pipeline.
4. NEXT STEPS

Following the virtual review of the PADO-TB priority list, WHO will:

• finalize the meeting report, share it with participants and other relevant stakeholders, and publish it on the WHO website;

• debrief with relevant stakeholders, including TPMAT, Unitaid, the Global Fund and research networks (TB and TB/HIV paediatric networks) on the outcome of the PADO-TB virtual review and next steps;

• prepare relevant WHO internal documentation that is needed to support updating of the WHO PQ EOI; that is, proposing the addition of “scored” to RPT 150 mg DT and the removal of the paediatric FDC (RPT/INH 150/150 mg), as agreed during the PADO-TB virtual review;

• consult internally and with relevant partners, to agree on the best ways to widely disseminate the outcomes of the virtual meeting;

• develop a WHO guidance document for PADO processes, in collaboration with other WHO departments;

• consider establishing a Rif subgroup when results of the systematic review on the optimization of dosing of the first-line anti-TB medicines (planned by WHO) become available and can better inform the deliberations of such a subgroup;

• identify priority topics for discussion at PADO-TB2; and

• aim to organize PADO-TB2 in 2022.
## ANNEX 1. PRIORITIES AGREED BY PADO-TB1 (FEBRUARY 2019)

### Formulations: all scored and dispersible

<table>
<thead>
<tr>
<th></th>
<th>DS-TB</th>
<th>DR-TB</th>
<th>TPT</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampicin (Rif)</td>
<td>√</td>
<td></td>
<td>√</td>
<td>4R was not a preferred TPT regimen for children at the time</td>
</tr>
<tr>
<td>Rifapentine (RPT)</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bedaquiline (Bdq)</td>
<td></td>
<td>√</td>
<td></td>
<td>Watch-list TPT and DS-TB</td>
</tr>
<tr>
<td>Clofazimine (Cfz)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delamanid (Dlm)</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linezolid (Lzd)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pretomanid (Pa)</td>
<td>√</td>
<td></td>
<td></td>
<td>Watch-list TPT and DS-TB</td>
</tr>
</tbody>
</table>

### Watch list

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>RHZLfx FDC</td>
<td>√</td>
<td></td>
<td></td>
<td>If SHINE is not successful and if studies with short FQ-based regimens are successful</td>
</tr>
<tr>
<td>RHZE FDC</td>
<td>√</td>
<td></td>
<td></td>
<td>To address barriers to use of ethambutol</td>
</tr>
<tr>
<td>Telacebec (Q203)</td>
<td>√</td>
<td></td>
<td></td>
<td>Currently Phase IIa</td>
</tr>
<tr>
<td>Sutezolid (PNU-100480)</td>
<td>√</td>
<td></td>
<td></td>
<td>Currently Phase IIa</td>
</tr>
<tr>
<td>Delpazolid (LCB01–0371)</td>
<td>√</td>
<td></td>
<td></td>
<td>Currently Phase IIa</td>
</tr>
<tr>
<td>OPC-167832</td>
<td>√</td>
<td></td>
<td></td>
<td>Currently Phase IIa/IIb</td>
</tr>
<tr>
<td>Moxifloxacin (Mfx)</td>
<td>√*</td>
<td></td>
<td>√</td>
<td>Taste-masked formulation</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>* Including INH-mono-resistant TB</td>
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</tbody>
</table>

## ANNEX 2. AGENDA OF THE VIRTUAL REVIEW OF PADO-TB1 PRIORITIES

Virtual review of the PADO-TB1 priority list, Tuesday, 22 September 2020, 13:00–17:30 CET

<table>
<thead>
<tr>
<th>Time</th>
<th>Session/Session 1: Rifapentine</th>
<th>Session 2: Second-line medicines</th>
<th>Session 3: First-line medicines</th>
<th>Session 4: The current TB drug development pipeline and emerging research priorities for children</th>
<th>Session 5: Discussion &amp; wrap up</th>
</tr>
</thead>
<tbody>
<tr>
<td>13:00–13:10</td>
<td>Welcome &amp; opening remarks</td>
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<tr>
<td></td>
<td>Tereza Kasaeva (WHO GTB Director)</td>
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<tr>
<td>13:10–13:15</td>
<td>Assessment of interests declared</td>
<td></td>
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<tr>
<td></td>
<td>Annemiek Brands (WHO GTB)</td>
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<tr>
<td>13:15–13:30</td>
<td>Developments and achievements since PADO-TB1</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Sabine Verkuijl (WHO GTB)</td>
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<tr>
<td>13:30–13:45</td>
<td>StopTB/GDF-led prioritization, harmonization and the launchpad approach: successes and opportunities</td>
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<td></td>
<td>Brian Kaiser (Stop TB Partnership’s Global Drug Facility – GDF)</td>
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<tr>
<td>13:45–14:15</td>
<td>Session 1: Rifapentine</td>
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<tr>
<td></td>
<td>Rifapentine: summary of data and developments</td>
<td>Anneke Hesseling (Stellenbosch University)</td>
<td></td>
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<tr>
<td>14:15–14:45</td>
<td>Discussion on rifapentine as part of the PADO-TB priorities</td>
<td>All</td>
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<tr>
<td>14:45–15:15</td>
<td>Second-line medicines</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Second-line medicines: summary of data and developments</td>
<td>Anthony Garcia-Prats (Wisconsin University)</td>
<td></td>
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</tr>
<tr>
<td>15:15–15:30</td>
<td>Discussion on second-line medicines as part of the PADO-TB priorities</td>
<td>All</td>
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<tr>
<td>15:30–15:40</td>
<td>BREAK</td>
<td></td>
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<tr>
<td>15:40–15:50</td>
<td>Planned systematic review on dose optimization of the first-line TB medicines</td>
<td>Linh Nguyen (WHO GTB)</td>
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<tr>
<td>15:50–16:05</td>
<td>Rifampicin: summary of data and developments</td>
<td>Rada Savic (University of California San Francisco, UCSF)</td>
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<tr>
<td>16:05–16:20</td>
<td>Discussion on first-line medicines as part of the PADO-TB priorities</td>
<td>All</td>
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<tr>
<td>16:20–16:35</td>
<td>Watch the space: State of the art of the clinical pipeline for TB drugs</td>
<td>Kelly Dooley (JHUSOM)</td>
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<tr>
<td>16:35–16:45</td>
<td>Discussion</td>
<td>All</td>
<td></td>
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<tr>
<td>16:45–17:20</td>
<td>Reaching consensus on updated priorities Evidence gaps/ high-priority research questions</td>
<td>All</td>
<td></td>
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<tr>
<td>Time</td>
<td>Event</td>
<td>Speaker(s)</td>
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<td>----------------------------------------------------------------------------</td>
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<td></td>
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<tr>
<td>17:20–17:30</td>
<td>Wrap up and closing remarks</td>
<td>Farhana Amanullah, Chair of the Child and Adolescents Working Group, and Tereza Kasaeva, WHO GTB Director</td>
<td></td>
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<tr>
<td></td>
<td>Next steps: communication of identified priorities to manufacturers and other relevant partners</td>
<td></td>
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<tr>
<td></td>
<td>Seeking inputs for PADO-TB2</td>
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</tbody>
</table>
### ANNEX 3. LIST OF PARTICIPANTS

<table>
<thead>
<tr>
<th></th>
<th>Name</th>
<th>Position/Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Farhana Amanullah</td>
<td>Senior Consultant&lt;br&gt;The Indus Hospital&lt;br&gt;Karachi, Pakistan</td>
</tr>
<tr>
<td>2.</td>
<td>Draurio Barreira</td>
<td>TB Senior Advisor&lt;br&gt;Unitaid&lt;br&gt;Geneva, Switzerland</td>
</tr>
<tr>
<td>3.</td>
<td>Grania Brigden</td>
<td>Director, TB Department&lt;br&gt;The International Union Against TB and Lung Disease (The Union)&lt;br&gt;Geneva, Switzerland</td>
</tr>
<tr>
<td>4.</td>
<td>Michael Campbell</td>
<td>Senior Director, Tuberculosis&lt;br&gt;Clinton Health Access Initiative (CHAI)&lt;br&gt;Bethesda, United States of America (USA)</td>
</tr>
<tr>
<td>5.</td>
<td>Martina Casenghi</td>
<td>Technical Director CaP TB Project&lt;br&gt;Elizabeth Glaser Pediatric AIDS Foundation (EGPAF)&lt;br&gt;Geneva, Switzerland</td>
</tr>
<tr>
<td>6.</td>
<td>Chishala Chabala</td>
<td>Paediatrician/Lecturer&lt;br&gt;University of Zambia, School of Medicine&lt;br&gt;Lusaka, Zambia</td>
</tr>
<tr>
<td>7.</td>
<td>Thomas Chiang</td>
<td>Senior TB Technical &amp; Drug Management Advisor&lt;br&gt;USAID&lt;br&gt;Washington, DC, USA</td>
</tr>
<tr>
<td>8.</td>
<td>Gavin Churchyard</td>
<td>Group Chief Executive Officer&lt;br&gt;The AURUM Institute&lt;br&gt;Johannesburg, South Africa</td>
</tr>
<tr>
<td>9.</td>
<td>Charlotte Colvin</td>
<td>Senior TB Technical Advisor&lt;br&gt;USAID&lt;br&gt;Washington, DC, USA</td>
</tr>
<tr>
<td>10.</td>
<td>Sarah Cook-Scalise</td>
<td>Program Manager, Pediatrics</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Global Alliance for TB Drug Development&lt;br&gt;New York, USA</td>
</tr>
<tr>
<td>11.</td>
<td>Kelly Dooley</td>
<td>Associate Professor&lt;br&gt;Johns Hopkins University School of Medicine&lt;br&gt;Baltimore, USA</td>
</tr>
<tr>
<td>12.</td>
<td>Jennifer Furin</td>
<td>Director of Capacity Building&lt;br&gt;The Sentinel Project on Pediatric Drug Resistant TB&lt;br&gt;Boston, USA</td>
</tr>
<tr>
<td>13.</td>
<td>Anthony Garcia-Prats</td>
<td>University of Wisconsin School of Medicine and Public Health&lt;br&gt;Madison, USA</td>
</tr>
<tr>
<td>14.</td>
<td>Steve Graham</td>
<td>Professor of International Child Health&lt;br&gt;University of Melbourne&lt;br&gt;Northcote, Australia</td>
</tr>
<tr>
<td>15.</td>
<td>Katy Hayward</td>
<td>Senior Clinical Advisor TB&lt;br&gt;Clinton Health Access Initiative&lt;br&gt;USA</td>
</tr>
<tr>
<td>16.</td>
<td>Anneke Hesseling</td>
<td>Professor in Paediatric and Child Health&lt;br&gt;Director, Desmond Tutu TB Centre&lt;br&gt;Stellenbosch University&lt;br&gt;Cape Town, South Africa</td>
</tr>
<tr>
<td>17.</td>
<td>Catherine Hewison</td>
<td>TB Advisor&lt;br&gt;Médecins Sans Frontières&lt;br&gt;Paris, France</td>
</tr>
<tr>
<td>18.</td>
<td>Jeremy Hill</td>
<td>TB Consultant&lt;br&gt;KNCV&lt;br&gt;Den Haag, The Netherlands</td>
</tr>
<tr>
<td>19.</td>
<td>Fabienne Jouberton</td>
<td>Médecins Sans Frontières&lt;br&gt;Geneva, Switzerland</td>
</tr>
</tbody>
</table>
20. Brian Kaiser  
Technical Officer, Global Drug Facility,  
Stop TB Partnership  
Geneva, Switzerland  

21. Alexander Kay  
Baylor College of Medicine  
Mbabane, Eswatini  
Pediatrics, Baylor College of Medicine,  
Houston, USA  

22. Alexei Vladimirovich Kazakov  
Senior Scientist  
National Medical Research Center of  
Phthisiology and Pulmonology and Infectious  
Diseases  
Ministry of Health  
Moscow, Russian Federation  

23. Muhammad Amir Khan  
Chief Coordinating Professional  
Association for Social Development  
Islamabad, Pakistan  

24. Kobto Koura  
Programme Coordinator – Africa  
The International Union Against TB and  
Lung Disease (The Union)  
Paris, France  

25. Linda Lewis  
Director  
Clinical and Regulatory Affairs  
CHAI  
Bethesda, USA  

26. Christian Lienhardt  
Research Director  
Institut de Recherche pour le  
développement  
Montpellier, France  

27. Nicola Loffredi  
Business Development Manager  
Medicines Patent Pool  
Geneva, Switzerland  

28. Susan Maloney  
Chief, Global TB Branch  
United States Centers for Disease Control  
and Prevention (US CDC)  

29. Ben Marais  
University of Sydney  
Sydney, Australia  

30. Helen McIlleron  
Director PK Research in Clinical  
Pharmacology  
University of Cape Town  
Cape Town, South Africa  

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TB Project Co-Director  
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Rifapentine (RPT) is given with isoniazid (H, INH) for tuberculosis (TB) prevention (3HP, 1HP) and potentially for treatment (study TBTC Study 31, 2HPZM/2HPM for 17 weeks). However, the dosing requirements for RPT differ from those for INH. Furthermore, the RPT pharmacokinetics (PK) targets are different for 1HP and 3HP; they also differ for the 4-month RPT-including regimen for treatment of drug-susceptible TB (DS-TB). Therefore, RPT dosing strategies may vary considerably for these regimens. Further data are needed to determine the appropriate RPT doses for these different regimens.

**RPT formulation requirements**

The current commercially available RPT formulation is a 150 mg tablet that is unscored and is not dispersible. Crushing is challenging and alters bioavailability.

In general, fixed-dose combination (FDC) strategies are preferred to support practical and reliable dosing of TB medicines in children. However, given the different dosing requirements for RPT and INH, a one-size-fits-all approach using RPT in an FDC strategy will not support the appropriate and safe dosing of both RPT and INH for the multiple regimens that may be recommended moving forward.

For 3HP, an FDC of RPT/INH 150/150 mg would only allow appropriate dosing in some weight bands, given current similar milligram per kilogram dose ranges of INH and RPT in most weight bands.

A 1:1 FDC would also not deliver an appropriate dosing schedule in regimens including daily RPT dosing (1HP in the medium term or DS-TB treatment in the long term). For 1HP, current dosing recommendations for adolescents and adults aged 13 years and older are much higher for RPT than for INH (10 mg/kg per day for INH versus 30 mg/kg per day for RPT). Thus, a 1:1 FDC would overexpose children to INH, which is particularly concerning for children with slow acetylation status.

A standalone RPT formulation would support the immediate needs of 3HP dosing in children across the age spectrum, while also supporting the use of RPT in 1HP and the DS-TB treatment regimen studied in TBTC Study 31.

**Methods for RPT PK modelling work to determine appropriate doses of RPT for 3HP and 1HP regimens**

Radtke and Savic, from the University of California San Francisco (UCSF), undertook population PK modelling work to predict weight-band dosing requirements for children, for both 1HP and 3HP. For children in the lowest weight band (3–6 kg), the results show that RPT exposure is considerably closer to the adult target with a scored 150 mg RPT tablet, because the scoring makes it possible to provide children with half a tablet. In contrast, when using an unscored 150 mg RPT tablet there may be considerable overexposure to RPT – the adult target is the predicted area under the curve (AUC) with the 900 mg dose from the adult PK model (25) with an adult AUC of 689 mg*h/L (Table A4.1, Fig. A4.1). For 1HP, the RPT exposure using a scored 150 mg RPT tablet would also be considerably closer to the adult target exposure (adult target is predicted AUC with 600 mg dose from the adult PK model (25) using an adult AUC of 486 mg*h/L) (Table A4.2, Fig. A4.2).

Paediatric RPT doses were based on predicted oral clearance (CL/F) from established population PK models. In children aged 2–14 years, the established CL/F function has been described using data collected from TBTC Study 26 (43).

There are currently no RPT PK data for children aged under 2 years. In these youngest children, the typical CL/F in adults was allometrically scaled – that is, [weight/70]^{0.75} – (25), and an age maturation function with parameter values equal to those of rifampicin (Rif) was added (44). This assumed function
for CL/F in children aged under 2 years aligned well with the function for children aged 2–14 years.

Dosing simulations were performed in the statistical computing software R (v 4.0) to predict the optimal weight band doses to reach the adult exposure targets for 1HP and 3HP. Simulations were performed in a demographically representative population of children aged 0–14 years (45). The AUC target was set to 689 mg*h/L for 3HP and 486 mg*h/L for 1HP, based on the median adult AUC from the adult PK model (25).

Table A4.1. Dosing predictions for 3HPa by weight band

<table>
<thead>
<tr>
<th>Weight band</th>
<th>Rifapentine Unscored 150 mg</th>
<th>Rifapentine Scored 150 mg</th>
<th>Isoniazid Scored 100 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-4 kg</td>
<td>1 150 (37-50)</td>
<td>0.5 75 (18-25)</td>
<td>1 100 (25-33)</td>
</tr>
<tr>
<td>5-6 kg</td>
<td>1 150 (25-30)</td>
<td>0.5 75 (12-15)</td>
<td>1.5 150 (25-30)</td>
</tr>
<tr>
<td>7-9 kg</td>
<td>1 150 (17-21)</td>
<td>1 150 (17-21)</td>
<td>2 200 (22-28)</td>
</tr>
<tr>
<td>10-15 kg</td>
<td>2 300 (20-30)</td>
<td>2 300 (20-30)</td>
<td>3 300 (20-30)</td>
</tr>
<tr>
<td>16-23 kg</td>
<td>3 450 (19-28)</td>
<td>3 450 (19-28)</td>
<td>5 500 (21-32)</td>
</tr>
<tr>
<td>24-30 kg</td>
<td>4 600 (20-25)</td>
<td>4 600 (20-25)</td>
<td>6 600 (20-25)</td>
</tr>
<tr>
<td>&gt;=31 kg</td>
<td>5 750 (17-24)</td>
<td>5 750 (17-24)</td>
<td>6 600 (13-19)</td>
</tr>
</tbody>
</table>

a 3HP: 3 months of weekly isoniazid plus rifapentine.

Fig. A4.1. 3HPa AUCb prediction with proposed weight-band dosing

a 3HP: 3 months of weekly isoniazid plus rifapentine; b AUC: area under the curve
Table A4.2. Dosing predictions for 1HP\(^a\) by weight band

<table>
<thead>
<tr>
<th>Weight band</th>
<th>Rifapentine Unscored 150 mg</th>
<th>Rifapentine Scored 150 mg</th>
<th>Isoniazid Scored 100 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tabs</td>
<td>Dose in mg (mg/kg)</td>
<td>Tabs</td>
</tr>
<tr>
<td>3-4 kg</td>
<td>1</td>
<td>150 (37-50)</td>
<td>0.5</td>
</tr>
<tr>
<td>5-6 kg</td>
<td>1</td>
<td>150 (25-30)</td>
<td>0.5</td>
</tr>
<tr>
<td>7-9 kg</td>
<td>1</td>
<td>150 (17-21)</td>
<td>1</td>
</tr>
<tr>
<td>10-15 kg</td>
<td>2</td>
<td>300 (20-30)</td>
<td>1.5</td>
</tr>
<tr>
<td>16-23 kg</td>
<td>2</td>
<td>300 (30-19)</td>
<td>1.5</td>
</tr>
<tr>
<td>24-30 kg</td>
<td>2</td>
<td>300 (10-13)</td>
<td>2</td>
</tr>
<tr>
<td>&gt;=31 kg</td>
<td>3</td>
<td>450 (10-15)</td>
<td>3</td>
</tr>
</tbody>
</table>

\(^a\) 1HP: 1 month of weekly isoniazid plus rifapentine.

Fig. A4.2. 1HP\(^a\) AUC\(^b\) prediction with proposed weight-band dosing

\(^a\) 1HP: 1 month of weekly isoniazid plus rifapentine; \(^b\) AUC: area under the curve.


5. Accelerating the development and uptake of the most needed drug formulations for children. GAP-f. 2020 (https://gap-f.org/).


21 Dorman SE. The design and primary efficacy results of Study 31/A5349: SP-10 High-dose rifapentine with or without moxifloxacin for shortening treatment of TB (NCT02410772). 51st Union World Conference. 2020.


