

**Reaching UNGA HLM on TB targets for ending TB in children and adolescents:
First Paediatric Antituberculosis Drug Optimization Meeting (PADO-TB 1)
Date: 14-15 February 2019**

**Meeting room CDS65, fourth floor of the WHO D-building/UNAIDS building,
Geneva, Switzerland**



Executive summary

To reach the UN General Assembly High Level Meeting on TB targets for treatment and prevention in children, timely access to the most effective and safest medications in affordable, child-friendly formulations is critical. Building on the experience in the WHO HIV programme, the first paediatric antituberculosis drug optimization (PADO TB 1) meeting aimed to establish a formal transparent process to reach evidence-based consensus among a variety of stakeholders regarding priority antituberculosis drugs and formulations for children.

The meeting was attended by 45 participants with six additional attendees participating remotely and included representatives from NTPs from TB high burden and priority countries, clinicians, scientists, funding organizations, international organizations and technical partners.

The meeting objectives were to:

1. Discuss the PADO for TB platform and modus operandi.
2. Develop a list of short/medium- and long-term priorities for paediatric TB drug optimization.
3. Agree on a way forward to accelerate development and uptake of the priority medicine formulations.

During the first day, presentations covered the size and specifics of the paediatric anti-TB drug market, the concept of paediatric antituberculosis drug optimization, experiences with antituberculosis drug development and market-shaping and the current adult and paediatric TB research and clinical trial landscape, priorities and overview of drug development. Participants engaged in discussions on the PADO for TB mechanism and modus operandi in the context of complementary efforts in paediatric drug optimization as well as the process to reach consensus on short/medium and long-term priorities for the development of paediatric antituberculosis drugs and formulations.

On the second day, after providing additional background information on the PADO for HIV priority list, participants broke up into three groups to discuss short/medium and long term priorities for a) treatment of drug-susceptible TB; b) treatment of drug-resistant TB; and c) treatment of latent TB infection (LTBI – both drug-susceptible [DS-TB] and drug-resistant TB [DR-TB]). A summary of the agreed priorities can be found in the table below. The meeting also discussed how to best take these priorities forward, taking advantage of existing structures.

Summary of agreed priorities:

Formulations: All scored dispersible				
Short-term list	DS-TB	DR-TB	LTBI	Remarks
Rifampicin (RIF)	√		√	Currently 4R is not a preferred LTBI regimen for children
Rifapentine (RPT)	√		√	
Bedaquiline (BDQ)	(√)	√	(√)	Watch-list LTBI and DS-TB

Clofazimine (CFZ)		√		
Delamanid (DLM)		√	√	
Linezolid (LZD)		√		
Pretonamid (Pa)	(√)	√	(√)	Watch-list LTBI and DS-TB
Watch list				
Bedaquiline (BDQ)	√	(√)	√	Short-term list for DR-TB
Pretonamid (Pa)	√	(√)	√	Short-term list for DR-TB
RHZZ FDC	√			If SHINE not successful and if studies with short FQN based regimens are successful.
RHZE FDC	√			To address barriers to use of ethambutol
Telacebec (Q203)		√		Currently phase IIa
Sutezolid (PNU-100480)		√		Currently phase IIa
Delpazolid (LCB01-0371)		√		Currently phase IIa
OPC-167832		√		Currently phase IIa/IIb
Moxifloxacin (MFX)	(√)	√		Taste-masked

Next steps:

- Meeting report with wide dissemination
- Suggest establishment of sub-group of PADO TB and report to the Strategic and Technical Advisory Group for Tuberculosis (STAG-TB)
 - Show need for prioritization
 - Learn more from PADO HIV experiences
 - Make use of advantage of having GDF and UNITAID funding
 - Work closely with WHO HIV and WHO MVP, in particular PQ
- In future, involve more representatives from TB high burden countries as well as communities affected by TB in PADO TB
- Share outcome of PADO TB with the core team of the Child and Adolescent TB Working Group
- Participate in IAS webinar 27 February 14:00 CET (15:00 SAST; 8:00 ET)

Day 1, Thursday 14 February 2019

Opening address – Tereza Kasaeva

TB has a visible and important place on the WHO agenda (GPW13). After UNGA HLM, the time for action is now. Targets regarding treatment and prevention are ambitious, in line with End TB Strategy and its milestones. We need to increase our prevention efforts at least 30 times to reach the target.

Overview of meeting objectives – Annemieke Brands

An overview of the meeting objectives and the agenda was provided. Participants were reminded regarding the need to complete declarations of interest, and declare any conflicts of interests.

Pdf versions of the presentations given on day 1 have been uploaded in a Dropbox folder:
<https://www.dropbox.com/sh/b9ut6x94fxkrmgw/AAA5c5EkewQvl-AB7RuJ-PtKa?dl=0>

Session 1 - An introduction to the size and specifics of the paediatric anti-TB drug market and to the concept of paediatric antituberculosis drug optimization

The concept of drug optimization and the Global Accelerator for Paediatric Formulations (GAP-f) framework: learning from experiences of the HIV programme - Martina Penazzato, WHO HIV

- To reach SDG 3 (Ensuring healthy lives and promote wellbeing for all at all ages), drug optimization is needed, as the best drugs or dosage formulations are not available to treat children: Clinical evidence is lacking to define appropriate paediatric doses, paediatric formulations do not exist for most drugs and time to market lags adult products by over a decade.
- Key challenges that hamper the rapid development and introduction of optimal paediatric formulations include: Market fragmentation, lack of child-friendly formulations, complexity and cost of the projects, internal prioritization within companies, lack of market incentives/small markets, and difficult and slow market uptake.
- Developing medicines for children requires addressing unavoidable complexities (e.g. natural history, growth and puberty, drug metabolism, co-morbidities, palatability and ease of administration) while promoting simplification and harmonization across the age spectrum.
- In May 2016, the World Health Assembly called on WHO to take all necessary measures to support access to quality, safe, efficacious and affordable medicines for children; encourage research and development on appropriate medicines for diseases that affect children and ensure that high-quality clinical trials are undertaken; and, strengthen national regulatory systems including pharmacovigilance and post-market surveillance (Resolution WHA69.20)
- HIV PADO has identified key priority products since 2013 to ensure a consistent clear message to manufacturers regarding needs through collaborative and coordinated action: key formulations are prioritised in the context of a public health approach; technical/research work is undertaken to support development of the priority formulations; priority formulations are included in

optimal formulary for selection; priority formulations are procured via a pooled mechanism; and, priority formulations are reliably supplied to countries.

- Linkages between PADO and guidelines development process: Guideline Development Group (GDG) develops evidence-based recommendations accounting for product development; PADO prioritizes based on existing and expected WHO guidelines but also provide a vision for policy change; these groups provide guidance on product development to industry.
- The Global Accelerator for Paediatric formulations (GAP-f) is a collaboration platform that promotes a faster, more efficient and more focused approach to paediatric clinical and formulation development and introduction leveraging both public and private investments.

***The burden of paediatric TB (infection and disease), targets and recent policy developments -
Malgosia Grzemska, WHO GTB***

- Malgosia Grzemska gave an overview of childhood TB epidemiology, the updated Roadmap towards ending TB in children and adolescents, developments in child-friendly formulations and updated policy recommendations for the treatment of TB infection and DR-TB. Despite the fact that TB is preventable and treatable, 1 million children (0-14 years) develop TB every year, representing 10% of the total TB burden.
- Children who receive treatment for TB have excellent outcomes, but 233,000 children (0-14 years) have died of TB in 2017, including 39,000 children who were living with HIV. An estimated 96% of deaths from childhood TB globally are among children not receiving TB treatment.
- An estimated 67 million children are infected with drug-susceptible TB strains and 2 million with multidrug-resistant strains. These children can potentially benefit from preventive treatment. However, in 2017, out of the 1.3 million eligible household contacts under 5 years of age, over 75% did not access preventive treatment.
- An estimated 25,000 children <15 years, fell ill with MDR-TB in 2014. Less than 10% of them were diagnosed and had access to treatment (Dodd et al, 2016; Jenkins et al, 2014).
- In September 2018, the UNGA High Level Meeting on TB has set ambitious targets for care and prevention of TB in children: **3.5 million children with DS-TB and 115,000 children with MDR-TB to be reach with TB care in the period 2018-2023; and, at least 4 million children under 5 years of age to be reached with TB prevention services in the same period.**
- On 24 September 2018, the Roadmap towards ending TB in children, adolescents and families was launched. The ten key actions highlighted in the Roadmap are: 1) Strengthen advocacy at all levels; 2) Foster national leadership and accountability; 3) Foster functional partnerships for change; 4) Increase funding for child and adolescent TB programmes; 5) Bridge the policy-practice gap; 6) Implement and expand interventions for prevention; 7) **Scale up child and adolescent TB case-finding and treatment** (in both the public and private health sectors, ensure availability of child-friendly formulations of TB medicines for all children with TB and of preventive treatment regimens for children at risk, including uninterrupted quality-assured supply with functional quantification and forecasting systems); 8) Implement integrated family- and community-centred strategies; 8) Improve data collection, reporting and use; and 10)

Encourage child and adolescent TB research (*Developing shorter, safer and more child-friendly regimens for TB prevention and treatment of both drug-susceptible and drug-resistant TB*).

- The roadmap contains the following milestones for 2020: Shorter and safer child-friendly regimens for prevention of drug-susceptible and drug-resistant TB; Expanded availability and access to child-friendly TB formulations including for prevention; and, funded research agenda on new diagnostics, drugs and vaccines as well as implementation models.
- In terms of treatment, the launch of the child-friendly (water-dispersible and fruit-flavoured) TB Fixed Dose Combinations (FDCs) in December 2015 (TB Alliance and WHO funded by Unitaid and USAID) in line with the WHO recommendations has been a major step forward.
- In terms of prevention, the 2018 WHO LTBI guidance provides options: Isoniazid monotherapy for 6 months for adults and children in countries with high and low TB incidence; Rifampicin plus Isoniazid daily for 3 months for children and adolescents aged <15 years in countries with a high TB incidence; Rifapentine and Isoniazid weekly for 3 months for both adults and children in countries with a high TB incidence; and, in low incidence countries: 9 months isoniazid, 3 months weekly rifapentine plus isoniazid, 3-4 months rifampicin plus isoniazid, 3-4 months rifampicin alone.
- 3RH is available in a child-friendly formulation (same FDC as for continuation phase treatment – RH 75/50mg) and is suitable for younger children (up to 25 kg). For older children adult FDCs can be used. A shorter regimen is likely to improve adherence and cost are relatively low. But 3RH should not be given to patients on protease inhibitors or nevirapine-based ART.
- 3HP is a very promising future regimen. The 1-month daily option is being evaluated. The shorter regimen is likely to improve adherence. However, there is no child-friendly formulation available yet and there is no evidence for use in children under 2 years of age. It is safe to use in PLHIV on efavirenz and raltegravir. Ongoing studies with dolutegravir (so far no interactions noticed). High cost.
- 6H: low adherence/completion rates with longer regimen however still the regimen of choice for CLHIV on ART. Lowest cost (film-coated tab), but high cost for the dispersible tab.
- In selected high-risk household, preventive treatment for contacts of patients with MDR-TB may be considered based on an individualised risk assessment and sound clinical justification. Drug choice would be later generation fluoroquinolones (e.g. LFX, MFX) unless the source case is resistant to these drugs.
- The WHO treatment guidelines for MDR-TB and RR-TB (December 2018) regroups the key medicines into three categories ranked on the latest evidence about the balance of effectiveness to safety. These groups form the overall approach to design longer MDR-TB regimens for children and adolescents.
- Since May 2018, the Global Drug Facility offers child-friendly medicines for both drug-sensitive and drug-resistant TB and has supported the introduction of pediatric formulations of second-line TB medicines in 17 countries.
- The Sentinel Project has just launched their updated field guidance in line with the WHO treatment guidelines for MDR-TB and RR-TB: http://sentinel-project.org/wp-content/uploads/2019/02/Updated_DRTB-Field-Guide-2019-V3.pdf

Paediatric TB medicines market overview and coordination - Brenda Waning, GDF

- GDF: The largest global supplier of quality-assured TB medicines and diagnostics; GDF is a team of the Stop TB Partnership since 2001, hosted by UNOPS, largely funded by USAID.
- GDF is much more than a procurement mechanism: GDF shapes markets and coordinates partners; strengthens country procurement & global supply systems; and facilitates uptake of new TB tools.
- Second-line drug (SLD) market gains: Increase in the number GDF Suppliers (5-fold) and products (10-fold in ten years), decrease in GDF Prices (44% between 2012 and 2016) as well as a reduction in SLD lead time from 6 to 3 months.
- GDF medicines catalogue includes: Drug Sensitive TB (DS-TB) and related products, required for the treatment of drug-susceptible TB; Drug Resistant TB (DR-TB) and related products required for the treatment of all forms of drug-resistant TB; and Latent TB Infection (LTBI) and related products required for the treatment of Latent TB infection for both adults and children.
- Paediatric first line FDCs: 88 countries ordered, 95% of procurement through GDF
- The TB Procurement and Market-shaping Action Team (TPMAT), co-chaired by GDF and TAG maximizes efficiency of TB market to ensure timely, consistent and affordable access to quality assured TB products in order to sustain and scale up TB prevention, diagnosis and treatment.
- Through close collaboration between GDF, WHO EMP, WHO GTB, GF and others, a TB medicines dashboard (<http://www.stoptb.org/gdf/medicinesdashboard/>) was launched in January 2019 including information on DR-TB, DS-TB, LTBI, paediatric TB medicines from 15 different data sources (WHO guidelines, EML, WHO PQ EOI/approved, GF ERP EOI/approved, GDF catalogue) – an interactive content with built-in links to relevant documents. Soon a list of health products funded through the Global Fund will be added. The dashboard will help to identify areas of divergence, expedite new product introduction and scale-up; send clear, consistent signals to suppliers on gaps in medicines and formulations, support market consolidation, facilitate benchmarking and revision of national tools, and, support national procurement of WHO-recommended, affordable, quality-assured medicines.
- GDF removed medicines from the GDF catalogue no longer recommended by WHO.
- Jointly with WHO GTB, WHO EMP, TAG and other CSOs, GDF submitted 28 modifications (additions, deletions and new indicators) for inclusion in the 2019 EML.
- In addition, priority medicines have been added to the GF expert review panel (ERP) expression of interest (Eoi) for expedited review: Paediatric Fixed-Dose Combination Medicines for DS-TB (RH, RHZ): Rifampicin/Isoniazid 75mg/50mg dispersible approved Jul-2018 (Lupin); Clofazimine 50mg and Clofazimine 100mg: Clofazimine 50mg & 100mg approved Aug-2018 (Macleods); 2-year shelf life approved Jan-2019; Clofazimine 100mg approved Jan-2019 (Dong-A); 2-year shelf life; ERP EOI Round 20 (to be released soon): Linezolid 150mg DT; Rifapentine/Isoniazid 300mg/300mg, rifapentine 300mg tablet

Ensuring children benefit scientific progress – Lindsay McKenna, TAG

- The right to benefit from scientific progress is a fundamental human right, but the right to science is less explored and defined than the right to health.
- Obligations of governments: development (Invest in research and channel resources to support a “purposive development” of science and technology to meet the needs of marginalized and disadvantaged groups), diffusion (Connect people to the benefits of science (tangible and intangible) in a way that ensures non-discrimination and enables participation) and conservation (Establishing and maintaining a stable market for quality-assured paediatric formulations; and ensuring countries can continue to access this market, even without donor support) of science and culture.
- Application to children with TB:
 - Development: Paediatric pharmacokinetic (PK) & safety studies; Paediatric efficacy studies; and Formulation development and acceptability work;
 - Diffusion: Paediatric treatment policies & dosing guidelines; and Awareness about & access to paediatric formulations and regimens;
 - Conservation: Establishing and maintaining a stable market for quality-assured paediatric formulations; and, ensuring countries can continue to access this market, even without donor support.
- How are we doing?
 - Development: Great strides have been made, but there is a lot of work to be done which spans the cascade of care (HIV TB HCV Pipeline Report 2018 <http://www.pipelinereport.org/2018/toc>).
 - Diffusion: There are a number of rate limiting steps: The initiation of paediatric investigations; The translation of research findings into policy; and the translation of policy into practice, which includes access to diagnosis and treatment with paediatric formulations; Expert consensus says that paediatric PK and safety studies should begin once an efficacious and safe adult dose has been established (phase IIB) and that preparation for paediatric investigations should begin when a drug shows promising efficacy and safety in adults (phase IIA).
 - Conservation: Currently, many countries are cut out of access to the paediatric formulations, including the U.S., the EU, and countries in Latin America and Central Asia. In the U.S. and Europe, it is because the products aren’t registered (for various reasons). In other countries, those that have or are in the process of graduating from GF funding and so are co-financing or domestically financing procurement, national laws and regulations block access to the global market, and few of these countries have the volumes necessary to attract manufacturers to register these products and bid for tenders, or to meet batch minimums. Without action by donors and countries, this problem is going to get worse as more countries increase domestic financing for TB.
- What do we need to do? Reduce research delays and eliminate research and knowledge gaps between adults and children; When research results in a new standard of care that redefines the “highest attainable” standard of health, it needs to be implemented, for everybody, including

children; Understand who is excluded from research and why; Recognize that the way research is conducted determines who is excluded and sets limits on diffusion; Market-driven approaches to R&D are inconsistent with the obligation to support purposive (or needs-driven) development; Maximalist approaches to intellectual property (IP) mean some people will be excluded from enjoying the benefits of science; Premature withdrawal of donor support may jeopardize conservation if mechanisms for disseminating scientific benefits are weakened (e.g., the threat domestic financing poses to sustainable and stable access to quality-assured medicines); Explore and try different approaches to support the development, diffusion, and conservation of science for people with or at risk of TB; Innovative models for financing R&D (e.g. de-linkage), including for children; Approaches to aid that see solidarity as a lasting, evolving relationship, not as a contingent arrangement or eligibility to “graduate” from.

Session 2: Experiences with antituberculosis drug development and market-shaping

Dr. Soumya Swaminathan (WHO DDG), previously an active member of the core team of the Child and Adolescent TB Working Group, joined the meeting after the break. Dr Swaminathan welcomed the initiative to convene a meeting on paediatric TB drug optimization. She referred to the child-friendly TB FDCs which are a major step forward. More research is needed with respect to adequate dosing of Rifampicin, in particular for the youngest children. With respect to DR-TB, Dr Swaminathan applauded the recommended injectable free regimens. More evidence is needed with respect to the use of the new drugs, delamanid and bedaquiline in young children; Dr. Swaminathan highlighted the important role partners and funders of research must play in developing the science.

Development of child-friendly TB Fixed-Dose Combinations: lessons learned - Shelly Malhotra, TB Alliance (presenting remotely via Webex)

- The STEP-TB initiative aimed to increase access to correctly dosed, properly formulated, affordable, high quality paediatric TB medicines by bringing to market affordable, appropriately dosed, first-line TB medicines for children; improving understanding of the paediatric TB market; building momentum and increasing access to treatments; and accelerating pathways for new paediatric TB drugs.
- Historical challenges in the first-line paediatric TB market included: Limited commercial interest; Lack of market optimization; Limited prioritization of childhood TB; Access hurdles hindered market potential; and Low uptake of existing medicines.
- Results: More than 950,000 treatments sold in first 3 years (since December 2015); Almost ninety countries accessing treatment; Registration in 15 countries (with files pending in several others); Transition to optimized paediatric formulations among large HBCs previously not in the market (India, Philippines).
- Lessons learned:
 - Key Challenge #1: Limited commercial interest: Articulating broader market potential; De-risking commercial investment through technical contributions;

- Key Challenge #2: Lack of market optimization: Strong WHO policy guidance and stakeholder advocacy critical in driving alignment around optimized paediatric formulations;
- Key Challenge #3: De-prioritization of paediatric TB: Positioning paediatric TB within broader child health & TB/HIV agendas important in building awareness, mobilizing complementary resources, & garnering political will; Highlighting leadership among trailblazer countries raised awareness and catalysed broader adoption;
- Key Challenge #4: Access hurdles can hinder market potential: Negotiation of access-friendly terms helped mitigate access barriers; GDF platform important in consolidating demand and affording rapid access; Bringing highest burden middle income countries into the market essential for market stability and impact; strategies to de-risk and facilitate broad registration critical for small volume products;
- Key Challenge #5: Low uptake: Partnerships essential in generating demand and supporting transition; Strengthened linkages with child health sector critical in expanding uptake; Deployment of complementary resources from national programs, GF and USAID critical to success; Private sector strategies needed to link additional missing cases with optimal treatments.
- Implications for second-line paediatric TB market: tapping into broader market potential can help incentivize & expand commercial investment (demonstrating long-term viability of medicines & potential for broader, non-TB indications); regimen optimization can help attract commercial investment (consolidation around optimized novel regimens, couples with appropriate DST can support volumes); product development partnerships can help de-risk commercial entry & scale up (sharing know-how, cost and capacity related to development, formulation and commercialization); leveraging collective capacity essential in order to realize market potential (support to diagnosing, linking to treatment, pooling procurement, forecasting, garnering demand, transition planning and policy guidance); and, strategies to overcome access hurdles in middle income HBCs where the majority of paediatric MDR-TB cases are living.

Dr Soumya Swaminathan thanked Shelly Malhotra, TB Alliance for the update and asked about the Paediatric Investigation Plan (PIP) for Pretomanid (Pa). Shelly responded that the EMA has approved the PIP. A first step will be to do the PK studies in adults but PK work across ages and weight bands is supposed to start soon after. The TB Alliance and the IMPAACT network will collaborate to accelerate the evaluation in children. The protocol is in development funded by NIH. Sites have been identified in South Africa and possibly in other countries. The focus will be on short-term dosing and safety.

Development and introduction of TB medicines: the case of paediatrics - Brian Kaiser, GDF

- Currently available DR-TB products for children: Dispersible tablets for levofloxacin (LFX), moxifloxacin (MXF), ethambutol (E), pyrazinamide (Z) and ethionamide (ETO)
 - All of the products are WHO prequalified already. There is also an isoniazid (H) 100mg dispersible tablet that is Global Fund ERP approved (more applicable to LTBI than DR-TB)

- A mini capsule of cycloserine (125 mg) is available
- Technically, there is a suspension for linezolid but it is only stable for 10 days at room temperature once it is mixed and it is very expensive.
- A 50mg tablet of clofazimine has been ERP approved and is in theory easier to administer than a capsule but it has not yet been fully tested in the paediatric population.
- The Stop TB/GDF Paediatric Drug-Resistant Tuberculosis Initiative:
 - 3-prong approach to introduce SLD products: (1) Providing initial procurement support: GDF funding initial quantities for project countries; (2) Matching supply with demand: GDF working with suppliers to decrease batch sizes, lower prices; and, GDF pooling procurement to meet minimum order quantities; (3) Identifying early adopters and build demand: GDF provided a small contract to the Sentinel Project on Paediatric Drug-Resistant TB to help; GDF staff doing quantification and forecasting.
- Implementing challenge – Quantifying and Forecasting
 - To date, children have been treated with adult formulations and in such small numbers that there has not been a need to quantify and forecast separately from adults
 - Challenges: Lack of disaggregation by age in country reporting to WHO nor in WHO burden estimates for DR-TB; and, regimen options (Short-regimen, individualized longer regimen, injectable-free 12-month regimen for non-severe disease, new DR-TB guidance in 2018)
- Implementing Challenge – Matching Demand and Supply:
 - Minimum order quantity (MOQ), the minimum amount needed to produce a batch of medicines): this will lead to waste, longer lead-times, supply insecurity and high prices, especially for countries ordering small amounts
 - GDF is placing orders together in order to shorten lead-times, increase global supply security, lower prices available to all countries regardless of their purchase capacity
- Implementing Challenge– Importation
 - StopTB/GDF can get a registration waiver to allow importation of products – in cases where registration is mandatory, GDF can usually work with the supplier and regulatory agency to facilitate registration quickly. However, as countries move to more domestic procurement and the market fragments, there are maintenance fees for suppliers to stay in the quality assured (QA) market (WHO PQ – fees waived, for now), fees for registration in many countries, and possibly increased costs for local packaging, labelling in local languages – limiting or prohibiting product to be supplied to multiple buyers.
 - The question is how do (or don't) small volume products fit in this type of system?
- Lessons from paediatric first line FDC introduction:
 - It took 5 years from the WHO recommendation until a new quality-assured appropriate product
 - The market went from a potential 3 suppliers to 1
 - Unitaid funded procurement was more than 525,000 treatment courses with the GDF grant (2006) but zero with the STEP-TB grant (2013)

- GDF intervened to facilitate the new FDCs introduction by: narrowing the product selection to one flavour per product and negotiating a lower price, refusing the MOQ; Working with WHO for a statement on preference to use the child-friendly FDCs; Quantifying waste and transitions plans to get Global Fund endorsement to write off old products; Working with TPMAT partners to set an end date for procurement of old FDCs; and; Providing grants (e.g., procurement support) directly to programmes to buy the products (Global Affairs Canada).
- Balancing formulations and the supply chain – examples of formulations included in the GDF catalogue however in varying stages of approval/availability:
 - Ethambutol: 8 different formulations; Isoniazid: 7 different formulations (oral liquid, dispersible tablets, [scored] tablet/capsule, vials)
 - Rifapentine: 7 different formulations (dispersible tablet, scored tablet, normal tablet, FDCs)
- Balancing research, implementation and the supply chain
 - TPMAT is using the dashboard to ensure each organization is sending clear messaging to suppliers on what products need to be developed and watching the research pipeline carefully to see what possible effects it may have on the supply chain
 - DS-TB: Multiple trials on-going or being prepared for dose optimization of rifampicin
 - DR-TB: On-going trial of dose optimization for SLDs in children: Multiple formulations of ethambutol and isoniazid in the PQ pipeline (splitting an already small market)
 - LTBI: WHO guidance recommends 3-4RH – product is available and quality-assured; PEPFAR COPs recommends 4R – child-friendly formulation not quality-assured; Research is focused on 3HP in kids (TBTC35) – Multiple different formulations requested in WHO PQ Expression of interest for suppliers to make; 1HP and 3 HP have a different ratio rifapentine:isoniazid
- Take home messages:
 - Collecting and reporting disaggregated data on age/weight for DR-TB would be helpful for programmes (and probably others);
 - The market for DR-TB products is small, minimum order quantities are high, shelf-life is short, and national registration unlikely in most countries– a pooled procurement mechanism is probably necessary to balance supply and demand;
 - Changing doses of products has implications on product availability and there can be significant time delays in product development, implementation and scale-up;
 - TPMAT, via the medicines dashboard, is working to provide clarity to suppliers on what formulations are needed for development; and,
 - There needs to be a balance between the research, the optimal formulation for every clinical scenario and what the supply chain can handle.

Role of the WHO Access to Medicines, Vaccines and Health Products (MVP) cluster in improving access to and use of appropriate TB medicines for children - Samvel Azatyan, WHO MVP

- The structure of MVP cluster will change at the end of February 2019, but currently includes 4 units under Regulation of Medicines and other Health Technologies (RHT): Technologies Standards and Norms (TSN), Regulatory Systems Strengthening (RSS), Prequalification Programme (PQT) and Safety and Vigilance (SAV).
- Strengthening regulatory capacity to ensure quality, safety and efficacy of medicines and health technologies aims at: reducing regulatory burden, time and cost for regulation, increasing capacity in LMIC, and ultimately reducing mortality and morbidity.
- RHT work is guided by the decisions of WHO Governing Bodies: WHA Resolution 60.20 (2007) – Better Medicines for Children; and WHA Resolution 69.20 (2016) – Promoting Innovation and access to quality, safe, efficacious and affordable medicines for children; To take all necessary measures to support access to quality, safe, effective and affordable medicines for children; To strengthen research and development on appropriate medicines for diseases that affect children and ensure that high-quality clinical trials are undertaken; To strengthen national regulatory systems including pharmacovigilance and post-market surveillance. After WHA resolution 60.20 (2007), a paediatric regulators network was established.
- Prequalification steps to facilitate access to novel quality assured paediatric formulations: RHT has taken a new approach: A bioequivalence (BE) study with a new FDC against a combination of the single ingredient originators was deemed acceptable provided the efficacy/safety documentation for the combination of the individuals was sufficient. This approach was not common at the time due to the fact that many of the individual ARVs were under patent. Traditional Biopharmaceutics Classification System (BCS) biowaivers require equivalent strength products to be compared. Following discussion with the scientific community, PQ has also applied BCS biowaivers principles and criteria designed to address differences between the adult and paediatric populations (e.g., solubility requirements for the active product ingredient(s) (API) in 50 mL aqueous buffers as opposed to the 250 mL volume normally employed), in order to apply biowaivers to paediatric products for which there is not an equivalent paediatric reference product. PQ seeks to collect solubility and absorption/permeability data on the APIs invited to the programme for the purpose of identifying APIs eligible for a BCS based biowaiver.
- One of the bigger challenges in the development of paediatric forms of generic products is that pharmaceutically equivalent comparator products are not available. Paediatric products available on stringent regulatory authorities (SRA) markets are often liquids (e.g. oral solutions and syrups). Although useful, products that are better suited to difficult shipping and storage situations are often preferred. Therefore, flexibility in the design of BE studies is necessary to obtain data to establish the safety and efficacy of the proposed paediatric products. PQ has been at the forefront of this work. The variations in design may be as simple as comparison of multiple units of a paediatric strength to a single unit of an adult strength of the same dosage form. This practice is now well established. However, further changes may be necessary as the proposed paediatric product's method of preparation and administration may vary from the methods used for the administration of the adult product with proven safety and efficacy. PQ

advises manufacturers on how to develop BE study designs that will provide sufficient information on safety and efficacy of paediatric products. Since 2009, ERP has assisted GF and other stakeholders in making important paediatric products available to patients while these products progress towards prequalification or approval by SRAs. Recent examples include, the new paediatric TB products (TB302 and TB309, now both prequalified), artesunate rectal capsules (now prequalified MA124), all made available months ahead of prequalification of the products, as well as SP based dispersible tablets (soon to be prequalified).

- Supporting availability of paediatric medicines:
 - Through new regulatory pathways (e.g. WHO PQ Collaborative registration procedure; Facilitated registration procedure of SRA [Stringent Regulatory Authority] approved medicines (SRA pilot); EU Article 58 procedure; US PEPFAR, etc.
 - Prequalification assessment followed by collaborative registration procedure: Assessment by one of the SRA followed by collaborative registration procedure for SRA products; Use of the regulatory networks and regional harmonization initiatives for raising awareness and facilitating joint assessments of clinical trials and medical products (AVAREF, AMRH, etc.).
- Collaborative registration procedures (CRP): Two procedures: (1) Following WHO Prequalification or SRA approval; or (2) Based on abridged review processes (reliance)
 - Impact on access: Faster start of procurement and wider availability; Quality control by same methods and specifications; Assurance about product quality, safety and efficacy; “90 days” CRP median time to registration instead of >2 years);
- Pilot projects: etravirine 25 mg tablets, darunavir 400mg tablets & 100mg/ml oral suspension, bedaquiline 100 mg tablets
- WHO is currently reactivating the Paediatric Medicines Regulatory Network with the establishment of an online resource to collect all guidance and information on paediatric medicines platform technologies to address technical challenges of developing paediatric friendly dosage forms; strategic guidance for selecting paediatric dosage forms and identifying target product profiles; appropriate clinical trial guidance; and, approaches to market shaping for essential paediatric medicines.

Discussions:

- How to overcome in-country BE requirements (like in South Africa)? Regional harmonization mechanisms could be applied.

SRAs versus WHO PQ – Will the EMA accept the dossier submitted for WHO PQ? So far, the EMA has not expressed such an interest. And the FDA will not share information unless a number of agreements are being signed.

Session 3: Current adult and paediatric TB research and clinical trial landscape, priorities and overview of drug development

An overview of the adult TB trial landscape and implications for paediatric TB drug optimization - Kelly Dooley, Johns Hopkins University (remotely)

- The global scientific agenda: Drug-sensitive TB: treatment shortening to < 3 months; more options for patients; MDR-TB: treatment shortening to < 6 months; reduced toxicity; TB prophylaxis: highly-safe, ultra-short course treatments for (drug-sensitive); LTBI: effective, well-tolerated therapy for MDR-TB contacts; HIV-TB co-treatment: regimens that can be used together, avoiding or mitigating drug interactions; Special unmet medical need: extrapulmonary TB, specifically regimens for TBM that reduce mortality; Clinical pharmacology: optimizing use of the drugs we have.
- Adult trials for DS-TB:

Key studies in Adults	Phase	Status
• HIGHRIF1: Rifampin max tolerated dose (max 40 mg/kg)	II	Completed
• HIRIF: Higher-dose rifampicin (max 1200)	II	Completed
• RIFASHORT: Higher-dose rifampicin (to 1800), 4 months	III	Enrolling
• MAMS-TB-01: High-dose rifampicin +/- moxifloxacin	II	Complete
• TBTC 31/A5349: High-dose RPT +/- moxifloxacin	III	Fully enrolled
• SUDOCU (PanACEA): BDM+STZ vs. R _{high} HZ _{high} E vs. R _{high} HZE vs. SOC	IIC	Planning
• SimpliciTB: BDQ+Pretomanid+MFX+PZA, 4 months	III	Enrolling
• APT: pretomanid+INH+PZA+RBT or RIF, 12 weeks	II	Enrolling
• TRUNCATE-TB: multiple 2 month regimens	III	Enrolling
• Clo-FAST (ACTG A5362): Clofazimine + RPT+ HZE, 13-17 weeks	IIC	Planning
• CRUSH-TB (TBTC): BDQ+MFX+PZA+ RBT or DLM, 4 months	IIC	Planning

Studies optimizing rifamycins in red; Regimens involving new drugs in blue; Both in purple

- Will these work? – some results:
 - MAMS: R₃₅HZE and R₂₀MHZ higher % conversion than control (R₁₀HZE) , regimens RQHZ lower conversion rates
 - Rifapentine for treatment-shortening (TBTC 29X RPT 10-20 mg/kg versus RIF 10 mg/kg daily (8 week study)): Significantly higher culture conversion with RPT 10, 15 and 20 mg/kg (solid culture medium)
 - NC-005 trial: 96% culture conversion BPazM (MDR) Z sensitive
- Themes around DS-TB:
 - High-dose rifamycins (rifampicin, rifapentine) are in Phase 3 testing for treatment shortening for patients with drug-sensitive pulmonary TB (including hardest-to-treat patients). Are we ready for: Stand-alone rifampicin in paediatric formulation (to get to equivalent of 1800mg or 35 mg/kg in adults); and for Rifapentine dose confirmation, equivalent to 1200mg in adults?

- Other treatment shortening regimens for DS-TB under evaluation mostly include bedaquiline or pretomanid. Are we ready for pretomanid, paediatric plan; and bedaquiline dosing, to youngest children?

- Adult trials for DR-TB:

Key studies in Adults	Phase	Status
• A5312: INH dose-finding EBA	II	Enrolling
• LIN-CL001: Linezolid EBA/safety, dose-finding (DS-TB)	II	In f/u
• OptiQ: Levofloxacin dose-finding	II	Enrolling
• Trial 213: Delamanid + OBR vs. placebo + OBR x 6 months	III	Completed
• STREAM Stage 1: 4MCEZHKPro/5MCZE (9 months) vs. SOC	III	Completed
• STREAM Stage 2: SOC vs. MCEZHKPro (9 mo) vs. BLCEZHPro (9 months, all-oral) v. BLCZHK (6 months, incl injectable)	III	Enrolling
• NC-005: B-Pa-M-Z	II	Completed
• SimpliTB: B-Pa-M-Z	III	Enrolling
• NIX-TB: B-Pa-LZD x 6 months (XDR-TB)	III	In f/u
• ZeNIX-TB: B-Pa-LZD (LZD dose/duration finding)	III	Enrolling
• A5343: bedaquiline + delamanid added to OBR x 6 months	II	In f/u
• A5356: D+LZD+OBR (all-oral) vs. D+OBR	II	Planning
• NEX-5001: LzBLvZ(H or Eth or Ter) vs. SOC	II/III	Enrolling
• MDR-END: D+Lv+Lzd+Z vs. SOC	II	Enrolling
• TB-PRACTECAL: BPaMLz v BPaLzC v BPaLz vs. SOC	II/III	Enrolling
• endTB: 9BLzMZ v 9BLzCLvZ v 9BLzDLvZ v 9DCMZ v SOC	III	Enrolling

Role/optimization of single agents; Whole new combination regimens

Key: Lz=linezolid; Lf=levofloxacin; D=delamanid; B=bedaquiline; Pa=pretomanid; C=clofazimine; Z=pyrazinamide

- Themes around DR-TB:

- We are learning about ‘optimized’ doses of individual drugs for treatment of MDR-TB in adults. Are we ready for: use of high (and potentially variable) doses of isoniazid for children; levofloxacin, at doses that achieve adult-equivalent exposures; linezolid dosing that gives best efficacy while minimizing toxicity?
- Treatments are being tested as full regimens, with multiple component ‘new’ drugs. Are we ready for combinations that include clofazimine, bedaquiline, delamanid, and/or pretomanid for children of all ages?

- Adults trials for HIV-TB co-treatment:

Antiretroviral medication§	Rifamycin*	Trial name/sponsor	Dose adjustments in adults
Efavirenz	High-dose rifampicin	RIFAVIRENZ/ANRS	Probably none
Raltegravir	Rifampicin	REFLATE/ANRS	Increase raltegravir to 800 mg bd
Dolutegravir	Rifampicin	INSPIRING/ViiV	Increase dolutegravir 50 mg bd
Ritonavir-boosted lopinavir	Rifabutin	ACTG A5290	Decrease rifabutin to 150 mg od
Tenofovir alafenamide (TAF)	Rifampicin	Gilead Sciences	Likely not necessary

- Themes around HIV-TB co-treatment:
 - Integrase inhibitors are being increasingly used globally, now we know how to use dolutegravir (DTG) and raltegravir (RAL) in HIV-associated TB in adults. Are we ready for DTG dosing in children taking rifampicin-containing TB treatment; RAL dosing in children taking rifampicin-containing TB treatment (IMPAACT P1101, age >2 years)?
 - Rifabutin (RBT) can be used with boosted PI in adults. Are we ready for formulation of RBT for children, confirmation of safety (Rawizza et al, Clinical Pharmacology Antiretroviral Drugs, 2018)?
 - Efavirenz can be used in adults taking rifampicin (high or standard doses) without dose adjustment. Are we ready for efavirenz dosing in < 3 years, when the child is taking rifampicin?
- Adult trials: TB prophylaxis (LTBI treatment):
 - CDC recommendations: Updated recommendations for 3HP for the treatment of latent tuberculosis infection. LTBI: CDC continues to recommend use of 3HP for treatment of LTBI in adults. With regard to age limits, HIV infection, and administration of the treatment, CDC now also recommends the following: use of 3HP in persons aged 2–17 years; use of 3HP in persons with LTBI who are living with HIV infection, including AIDS and taking antiretroviral medications (efavirenz or raltegravir) with acceptable drug-drug interactions with rifapentine.
 - Newer and shorter: 1HP- Daily rifapentine + INH for 4 weeks (ACTG A5279, the BRIEF TB trial):
 - Multicenter, randomized, open-label, phase III clinical trial, comparing Rifapentine 600 mg + Isoniazid 300 mg DAILY x 28 days (vs. 9H); Sample size: 3000 participants; Population: HIV-infected individuals ≥ 13 years old and no evidence of active TB; Stratification: 1) CD4+ cell count at entry (<100, 100-250, and >250 cells/mm³); 2) ART use at entry (Yes/No – 50% on ART at entry); ART: Efavirenz or nevirapine based ART permitted while on RPT/INH; Duration: 3 years (156 weeks) after the last participant is enrolled
 - So far: very similar survival
- Themes around LTBI treatment:
 - 3HP is effective, increasingly being rolled out. Are we ready for dosing in under two-year olds?
 - 1HP with efficacy shown in adult trial in PLWHIV. Are we ready for Rifapentine daily dosing in children?
- Adult trials: severe or extra-pulmonary TB:
 - Optimizing rifampicin for TBM - Survival in adults with TBM dramatically increased as oral dose goes from 10 mg/kg (450 mg) to 30 mg/kg (1350 mg); To achieve the target exposure associated with reduced mortality in adults (C_{max} of about 22), children would need at least 30 mg/kg of oral rifampicin daily

- Adults with Grade 2 or 3 TBM: HRZE with vs. without LZD: better GCS recovery with LZD; Children without improvement in fever or neurologic symptoms after two weeks: HRZ(E) with vs. without linezolid: improved outcomes with LZD, similar adverse events
- Themes around EPTB:
 - High-dose rifampicin (if the dose is sufficiently high) reduces mortality in adults. Does it do the same in children? At what dose? Might we see improvements in neurocognitive development with higher doses in children?
 - Linezolid and other drugs with better CSF and CNS penetration may be a better bet for TBM than simply giving drugs optimized for pulmonary TB for longer duration.
- Summary: There are many trials in adults that are transforming TB treatment: High-dose rifamycins or new drug combinations for DS-TB; Totally new combinations for DR-TB, or better-optimized dosing of existing drugs; Shortened, simplified treatment for LTBI; More options for HIV-TB co-treatment; TBM regimens that reduce mortality.
- Significant gaps remain for children, mainly around formulations, adult-equivalent dosing, safety, outcomes unique to children.

Discussion:

- What happens in the adult space (in particular Phase II trials) is extremely important for paediatrics. Close follow up is needed. It is important that early data are being shared with WHO. The smallest weight bands are the most challenging.
- We have to advocate that adolescents and children are included in adult trials at a much earlier stage involving relevant stakeholders. Sub-studies can be included in trials right from the beginning looking at drug-drug interactions and making dose adjustments as needed. For example, we need to study if shorter regimens are effective in PLHIV. Not just older adolescents. In some trials adolescents are eligible but only a handful participate/are enrolled. Often it is not ethical committees blocking enrolment of adolescents. Education needed to this extent.
- There has been advocacy to address TB in HIV trials. Is this done vice versa?
- Also efforts needed to include pregnant women in trials.

An overview of the paediatric TB (infection and disease) trial landscape - Anneke Hesselings/Tony Garcia-Prats, Desmond Tutu TB Centre

- Overview of paediatric DR-TB studies currently ongoing:

Planned or ongoing Phase 2 or 3 trials of MDR-TB treatment or preventive therapy

MDR-TB Treatment trials		MDR-TB Preventive therapy trials	
Trial	Components of intervention arm	Trial	Components of intervention arm
NC005	PZA, BDQ, PTA	VQUIN	LFX
Opti-Q	LFX + standard of care	TB-CHAMP	LFX
STREAM	hdMFX, PZA, EMB, KAN, INH, CFZ	PHOENIX	DLM
STREAM	BDQ, CFZ, EMB, PZA, LFX, INH, PTO		
NIX-TB	LZD, BDQ, PTA		
STAND	PZA, MFX, PTA		
NEXT-TB	PZA, LFX, ETO/hdINH, LZD, BDQ		
C208	BDQ + standard of care		
Trial 213	DLM + standard of care		
TB-PRACTECAL	BDQ, PTA, MFX, LZD, CFZ		
MDR-END	DLM, LFX, LZD, PZA		
endTB	LFX, MFX, BDQ, DLM, LZD, CFZ		
A5356	DLM, LZD, DBR		

PZA-pyrazinamide; BDQ-bedaquiline; PTA-pretomanid; LFX-levofloxacin; EMB-ethambutol; MFX-moxifloxacin; PTO-prothionamide; CFZ-clofazimine; hdINH-high dose isoniazid; LZD-linezolid; ETO-ethionamide; DLM-delamanid

- Phase I/II BDQ paediatric trials: C211: BDQ PK and safety in HIV-uninfected children (n=60); P1108: PK, safety and tolerability of BDQ with optimized background regimen (OBR) in HIV-infected and uninfected children with MDR-TB (n=54-72)
- BDQ CRUSH study: Difference in bioavailability dissolved versus whole tablets not statistically significant: bioequivalence criteria fulfilled
- DLM trials: Otsuka trials 232 (Phase 1 - 10d DLM) and 233 (Phase 2 - 6m DLM)
 - DLM dosing: lots of caveats in children in 16-24 kg weight band: 25mg twice daily (dispersible tablet not bioequivalent compared to adult tabs; No evidence on crushing or suspending adult tabs; Manipulation may reduce bioavailability; Unscored tablets: Can be used, but must be aware of uncertainty, and balance risks/benefits)
 - IMPAACT 2005: Phase I/II: PK and safety of DLM in HIV-infected and uninfected children (0-<18y) with DR-TB (n=36 evaluable), to provide additional information on PK and safety in children; Include HIV-infected children to evaluate drug-drug interactions with EFV, LPV/r
- Other novel and repurposed medications: studies ongoing with respect to levofloxacin, moxifloxacin, linezolid, PAS, ETO, TZD/CS, high dose INH. But so far no studies of clofazimine, pretomanid and newer compounds such as sutezolid.
- MDRPK1,2: LZD dosing, simulated AUCs
- IMPAACT 2020 (SMaRT Kids): Design: Phase 2 multi-centre trial in children 0 to <15 years of age; with probable or confirmed pulmonary or extrapulmonary MDR/RMR-TB/Rif-R, and MDR-TB with FQN resistance, HIV-infected and uninfected. Assignment to 1 of 2 arms based on FQN-susceptibility:
 - Arm 1 – FQN-Susceptible – 26 weeks BDQ-DLM-LFX, 8 weeks LZD
 - Arm 2 – FQN-Resistant – 26 weeks BDQ-DLM-CFZ, 8 weeks LZD
 - Objectives: primary - Safety; secondary - outcomes, PK, others (N=148)

- Paediatric trials on DR-TB prevention:
 - VQUIN: 6m LFX versus placebo; Phase 3; All ages, children not treated, TST+; N=2785 contacts; Vietnam (currently open)
 - TB-CHAMP: 6m LFX versus placebo; Phase 3; 0-<5y, HIV-positive and negative; N=1556 contacts; 3 sites in SA (currently open n,>200)
 - A5300/I2003: 26 weeks DLM versus INH; Phase 3; All <5y, >5y if HIV+, TST/IGRA+; N=3452 contacts; Multicentre (to open in 2019)
- Transitions in tuberculosis: from susceptibility to cure: Once infected with *Mycobacterium tuberculosis*, the risk of disease progression is much higher in children, especially those < 5 years of age. Adolescents also have a high risk of TB after infection and therefore have specific needs. Once diagnosed and treated, outcomes are generally very good in children.
- Paediatric trials on prevention:
 - There are more options for shorter treatment – but how should these be implemented?
 - Gap between recommendations and what is available – for example major challenges in HP formulation
 - TBTC Study 26: efficacy of 12 weeks weekly RPT/INH 900/900mg (3HP): lower rates of TB after 33 months in adults
 - Brief Rifapentine-Isoniazid Efficacy for TB Prevention (BRIEF-TB A5279) (1HP): conducted in HIV+ adults and adolescents only
 - 4R: new evidence on efficacy (Menzies NEJM 2018) – but there is currently no standalone paediatric formulation
 - Evidence gaps on shorter preventive treatment regimens:
 - 3HR: Rigorous implementation science needed to guide optimal and cost-effective implementation of 3HR. FDCs to support preventive treatment already WHO prequalified (pending registration in South Africa)
 - 3HP: PK and safety data on rifapentine and INH (12 doses over 12 weeks in total) in children < 3 years pending (TBTC Study 35 opened in South Africa in Q 2018): RPT standalone versus FDC. Trial formulations, possibly future Sanofi product
 - 1 HP in children: Paediatric PK and safety data needed: IMPAACT CS 5109: Phase I/II PK and safety trial in HIV-infected and uninfected children (planned). Sanofi product
 - 1HP versus 3HP in pregnant women (HIV+/-): IMPAACT CS 5021: adult generic RPT in development (IMPAACT4TB: Unitaid)
 - TBTC Study 35 (3HP): Building on Study 26: HIV-infected and HIV-uninfected children aged 0-12 years of age; To establish, through population PK modelling, the dose(s) of RPT that will achieve the target adult exposures [median area under the curve₂₄ (AUC₂₄) no more than 25% lower than, and no more than 50% higher than, the target AUC of 522 mcg*h/L] from TBTC Study 26, when RPT was given once-weekly in combination with INH for 12 weeks; Due to open in Cape Town and Johannesburg: Q2 2019 with 18 months' enrolment period; FDA IND (approved December 2018); Will use new RPT and INH FDC and RPT standalone formulations (trial formulations only); Sanofi plans on

completing registration of paediatric formulations. Will support EMA submission;
Opening Q2 2019:

- Child-friendly RPT formulations: Water-dispersible FDC tablet: 150 mg RPT/150 mg INH; Water-dispersible RPT-only 100-mg tablet; Sanofi is also developing 50mg and 20mg RPT-only tablets to increase dosing options. Trial opening not dependent on additional RPT formulation strengths.
 - MDR-TB prevention: TB-CHAMP, V-Quin (no children treated), PHOENix
 - LFX levels with dispersible tablet much higher than standard adult tablet
 - 81% of caregivers rated taste of new formulation (much) better than previous one
 - Market considerations: Multiple indications: treatment disease (DS and DR-TB), prevention; Rifamycins: RPT, RH; Levofloxacin; Formulations: keep it simple – need for flexible, dispersible, scored, no FDC; Standalone formulation more useful in some cases.
- Summary of ongoing and planned studies:

PK STUDIES: DS TB	ONGOING/PLANNED PAEDIATRIC PREGNANCY STUDIES
<p>Phase I/II: PK/safety studies <i>Standard first- and second-line drugs-Establishing doses that achieve adult-equivalent exposure</i></p>	<ul style="list-style-type: none"> • DATiC: PK/safety first-line TB drugs (enrolment completed 2016): completed • STEP-TB: New pediatric dispersible formulations of first-line drugs (TBA, Unitaid) completed • Infant PK study: (TBA/Unitaid): Hesselning/Bekker: completed • Rifabutin in children, NIRT (terminated; NICHHD • OptiRIF Kids: high-dose rifampicin PK safety: TB Alliance/Unitaid): Hesselning: ongoing • P1026S: including new TB drug arms (pregnancy): ongoing
<p>Efficacy trials</p> <ul style="list-style-type: none"> • TBM: Reduce mortality, improve neurocognitive dysfunction • Non-severe DS-TB Reduce treatment duration 	<ul style="list-style-type: none"> • TBM-KIDS: High-dose RIF +/- Levo for children with TBM (Dooley): ongoing • SURE Kids: Gibb (planned) • SHINE: 4 vs. 6 months standard TB Rx (new FDCs, nested PK): open label (MRC CTU; Gibb) N=1200 accrual completed: non-severe PTB • DS TB Rx shortening kids needed (formulation needs). Clinicians can identify non-severe disease but how to write up a definition of “non-severe”?
<p>HIV/TB DDI studies</p>	<ul style="list-style-type: none"> • DNDi: Ritonavir boosting of LPV/r in TB/HIV: completed • NICHHD PK: first-line TB drugs with ART: completed • P1101: RAL-based ART with standard TB drugs: ongoing • CS 5019: RFPT and DTG for TB prevention and treatment: development
<p>TB prevention <i>Phase I, II, II (DS AND DR-TB)</i></p>	<ul style="list-style-type: none"> • A5300 PHOENIX: delamanid vs. INH for MDR-TB prevention: 2018 • TB-CHAMP: LFX vs placebo for MDR-TB prevention: 2016 • VQUIN: LFX vs. placebo for MDR-TB prevention: open • ACTG5279: 1HP daily for DS-TB prevention • Study 35: 3RH in HIV+/-children < 12 years of age: TBTC 2019 • P4v9 Trial: 4 months RIF vs 9 months INH for DS-TB prevention • TBTC 37: RPT 6 weeks vs. local SOC (4R or 3HP) • P1078: IPT in HIV-infected pregnant women • P2001: safety and PK of rifapentine in HIV+ pregnant women • 1 HP in children: CS 5109 (HIV+/-): planned

- | | |
|--|---|
| | <ul style="list-style-type: none"> • 1 HIV vs. 3 HP in pregnant women: CS 5021 (HIV+/-): planned |
|--|---|

- DS-TB treatment considerations: >75% pulmonary /intrathoracic TB; Wide spectrum of disease; Paucibacillary disease; Severe and disseminated TB (TBM and miliary TB) especially in young children; Treatment outcome in children generally good provided initiated early (paucibacillary); All treatment data extrapolated from adult studies: what is the PK at site of disease?;
 - Formulations needed to support appropriate dosing
- Gaps for DS-TB treatment: Optimize rifamycin exposure; Optimize FQN; Shorten treatment; Include spectrum of disease beyond SHINE; Treatment shortening: build on adult phase IIb/III trials (TBTC Study 31, TB Alliance): FQN, rifamycins, PZA = BDQ/DLM; Innovative design and outcome assessment; Informed by drug optimization studies and site of disease PK; Consider HIV co-infected children and DDI;
 - Formulations needed: rifampicin, rifapentine, rifabutine?
- Formative research about the acceptability – including palatability – of the FDC of first-line anti-TB drug formulation used in the SHINE trial:
 - In general, the FDC was adequately palatable although there was some variability in responses to administration challenges, as well as the innovative strategies to overcome these:
 - Caregivers often set aside 15-30 minutes to administer treatment.
 - To comply with the recommended morning administration, a mother described waking up at 04:00, undressing herself and her daughter, and then spending 30-45 minutes coaxing her daughter to take the treatment before washing up and going to work.
 - Caregivers also cited their child’s physical and emotional state, the caregiver’s psychosocial factors, stigma, and lack of knowledge/education or misperceptions about adverse-effects, affected treatment administration and adherence as hindering or helping administration.

TB/HIV-coinfection, ARVs and implications for paediatric TB drug development/Identifying synergies and alignment between TB and HIV - Helena Rabie, Stellenbosch University (remotely)

- HIV and TB have a lot in common: they are both a tale of 2 worlds; both are still in need of an appropriate vaccine; are neglected in the young; are difficult to diagnose in the young; need appropriate dosing and formulations; the principles of therapy are similar - combination therapy, fixed dose combination, weight band dosing; they also both need a programmatic approach to therapy in low resource settings.
- HIV in childhood: 76% of pregnant woman receive ART; there were 160 000 new infections in 2016; there are 2.1 million HIV+ children (95% in sub-Saharan Africa), of whom 43% are on ART.
- Challenges around HIV in children include: identification and diagnosis and linking to care; insufficient formulations (especially for the neonatal period); planning second and third line regimens; factoring in rising ARV resistance for treatment and prevention; adherence and

maintaining virological suppression; toxicity; virological failure; treatment fatigue exacerbated by drug intolerance; dealing with behavioural choices; adolescents and TB.

- Dosing and formulations are needed for all ages.
- Traditional study progress: paediatric study development – weight band dosing – FDC development – study the FDC – Bring FDC to the market; However, in practice some of these steps may not be taken, leading to further delays in getting products to the market.
- Integrase strand inhibitors: Dolutegravir studied (P1093 and ODYSSEY); Available formulations: up to 14kg dispersible tablets, 14-25kg scored adults tablets, >25kg adult formulation.
- Protease inhibitors: Solid formulations of Lopinavir/ritonavir 4:1: slow progress; Single ritonavir: 100mg Sachets, 25mg / 50 mg tablets
- Children with HIV or ongoing exposure: will always need ART/PEP; may/will need TB prevention; may need TB therapy; rifamycins drug-drug interactions (rifampicin = rifapentine < rifabutin)
- Gaps related to TB management in HIV-infected children: ART approaches (raltegravir, dolutegravir, other approaches to LPV/r: Double dosing of solid LPV/r formulations, more frequent dosing); prevention (new regimens, e.g. INH/RPT, DR-TB prevention); higher rifampicin dosing regimens; new approaches; DR-TB.
- Studies in TB/HIV co-infected children:
 - ODYSSEY: Once daily Dolutegravir (DTG)-based ART in young people versus standard therapy with a PK sub-study for children developing TB on study DTG 2X daily
 - IMPAACT 1110: Phase I/II dose-finding, safety, tolerance and PK study of a raltegravir (RAL)-containing ART regimen in HIV-infected and TB co-infected infants and children (double dose: adequate levels and safe)
 - Using a protease inhibitor (PI) with rifampicin: Super-boosting lopinavir/ritonavir with added ritonavir is safe and effective (no excess failure and no PI resistance in children failing treatment); Using a PI with rifampicin: 3 times a day is “Better” than double dosing, although still not achieving target PK effectively - Higher doses need to be studied
- Prevention: combination with INH – how do we use this with ART?
- Taking these issues further:
 - Children can be small adults (as long as they weigh more than 25kg)
 - Develop FDC for children with more complex TB (this will benefit children with TB and those with HIV)
 - PADO for TB: Let’s talk about it e.g. is it really necessary to use different weight bands in TB and HIV?
 - Let us not exclude children from research (TB studies – include children with HIV and be flexible; HIV studies – include children with TB and be flexible)
 - Using modeling to estimate dosing of new ART/TB – rapid extrapolation
 - Robust assessment of tolerability / palatability

Discussion:

- The UCL has done a PK study with adult dose DTG in children. Results will be shared at CROI.

- Ritonavir mini pills are available but issue with taste so only a small step forward for children living with HIV
- Discussion took place on the importance of aligning HIV and TB weight bands.
- When adjusting weight bands and dosing, we need to keep in mind what will be most practical (look at what would benefit the majority of children and do not focus on exceptions).

An overview of the current TB drug development pipeline and remaining research priorities - Lindsay McKenna, TAG

Regimens/ medicines recommended by WHO:

Regimen/ medicine	Knowledge gaps	Pediatric formulations available	Status
IPT 3HR 4R 3HP	PK + safety in children < 2 years old	100 mg DT 50/75 mg DT NA (75 mg DT) NA (HP:150/150 mg DT; P:100 mg DT)	GF ERP WHO PQ ??? in clinical trial
HRZ HR E Z		50/75/150 mg DT 50/75 mg DT 100 mg DT 150 mg DT	WHO PQ WHO PQ WHO PQ WHO PQ
M Lx Lz B Cz Cys D E Z Eto PAS	PK + safety in children < 6 years old PK + safety in children < 3 years old	100 mg DT 100 mg DT NA (150 mg DT) NA (20 mg DT) 50 mg capsule; 50 mg DT 125 mg capsule NA (25, 10, 5 mg DTs) 100 mg DT 150 mg DT 125 mg DT granules; powder oral sol.	WHO PQ WHO PQ DT in development in clinical trial GF ERP; DT in development WHO PQ in clinical trial WHO PQ WHO PQ WHO PQ WHO PQ

Black: formulations that are already available on the global market; Blue: formulations that are in development or could be in development with what we know now; Red: formulations for which PK and safety studies are ongoing; for these we may want to wait to see how dosing looks in younger cohorts before deciding what optimal formulation(s) is

TB prevention:

Study	Results expected	Regimen(s)	Data to be collected (gaps in red)
ACTG A5279 (BRIEF TB)	2018	1HP (P:600mg; H:300mg QD)	Efficacy + safety in HIV-positive adults PK + safety of HP dosed daily in children Efficacy in HIV-negative adults
V-QUIN and	2020	6m Lx	Efficacy + safety in adults

TB CHAMP		(Lx: 250–750mg in adults, 15–20 mg/kg in children)	Efficacy + safety in children
TBTC S37 (ASTERoid)	2020	6wP (P:600mg QD)	Efficacy + safety in adults PK + safety of P dosed daily in children
TBTC S35	2022	3HP (P:900mg; H:900mg 1xW)	PK + safety of HP dosed once-weekly in children (H:25 mg/kg; P:25 mg/kg)
ACTG 5300/ IMPAACT 2003	2024	6m D (D:200mg)	Efficacy + safety in adults Efficacy + safety in children (1.5–3.8 mg/kg)

Blue: data being collected; Red: data gaps

TB treatment (drug sensitive)

Study	Results expected	Regimen(s)	Data to be collected (gaps in red)
TBTC S31/ ACTG A5349	2020	4m HPZM 4m HPZE (P: 1200 mg; M: 400 mg)	PK + safety of P at higher doses in children
RIFASHORT	2020	4m HRZE (R: 1200mg v. 1800mg)	PK + safety of R at higher doses in children
NC-008 (SimpliciTB)	2022	4–6m BPamZ (B: 8w200 mg,100 mg; Pa: 200 mg; M: 400 mg)	PK + safety of Pa in children PK + safety of B in children
TRUNCATE-TB	2022	2–3m RHZELz 2–3m RHZECz 2–3m PHZLzLx 2–3m HZELzB (R:35mg/kg; P:1200mg; B:2w400mg QD, 200mg 3xW)	PK + safety of R at higher doses in children PK + safety of B in children PK + safety of P at higher doses in children
ACTG A5362 (CLO-FAST)	--	4m HRZECz (C: 50mg v. 100mg)	

Blue: data being collected; Red: data gaps

TB treatment (drug-resistant)

Study	Results expected	Regimen(s)	Data to be collected (gaps in red)
STREAM II	2020	9m BCzLxEZHPTo (B:2w400mg QD, 200mg 3xW; H: 300–600mg; Mx: 400–800mg)	PK + safety of B in children PK + safety of Mx at higher doses in children?
NEXT	2020	6-9m BLzLxEto/H/Cys (B: 2w400mg QD, 200mg 3xW; H: 500–1000mg)	PK + safety of B in children PK + safety of H at higher doses in children?

endTB/ endTB-Q	2021	9m BLzMZ 9m BLzLxZCz 9m BLzLxZD 9m DLzLvZCz 9m DMZC 6-9m BDCzLz (B: 2w400mg QD, 200mg 3xW; D:200mg; Cz: 8w200mg, 100mg)	PK + safety of B in children PK + safety of D in children PK + safety of Cz loading dose in children?
MDR-END	2021	9-12m DLzLxZ (D: 200mg)	PK + safety of D in children
ZeNix	2022	6-9m BPaLz (B: 8w200mg, 100mg; Pa: 200mg; Lz: 6m v. 2m, 1200 v. 600mg)	PK + safety of Pa in children PK + safety of B in children PK + safety of Lz at higher doses in children
TB- PRACTECAL	2022	BPaLzM BPaLzCz BPaL (B:2w400mg QD, 200mg 3xW; Pa: 200mg)	PK + safety of B in children PK + safety of P in children
BEAT TB	--	6m BLzDCzLx (B:2w400mg QD, 200mg 3xW; D:200mg)	PK + safety of B in children PK + safety of D in children

Dose optimization work

Study	Regimen(s)	Data to be collected (gaps in red)
HR1 Extension	R: 10, 20, 25, 30, 35, 40, 45, 50, 55 mg/kg (currently dosed at 10 mg/kg)	PK + safety of R at higher doses in children (currently recommended range: 10–20 mg/kg)
OptiRif Kids	R: up to 35–40 mg/kg (currently dosed at 10–20 mg/kg)	PK + safety of R at higher doses in children (currently recommended range: 10–20 mg/kg)
TBTC S32 (Opti-Q)	Lx: 11, 14, 17, 20 mg/kg (currently dosed at 11–14 mg/kg)	PK + safety of Lx at higher doses in children (currently recommended range: 15–20 mg/kg)
ACTG A5312	H: 5, 10, 15 mg/kg (currently dosed at 5 mg/kg, hd:10- 15mg/kg)	PK + safety of H at higher doses in children? (currently recommended range: 7-15, hd:15-20 mg/kg)
CRUSH TB	R: 35mg/kg (currently dosed at 10 mg/kg) Z: 25, 40 mg/kg (currently dosed at 20–30 mg/kg)	PK + safety of Z at higher doses in children? (currently recommended range: 30–40 mg/kg)

New compounds (phase I)

Drug Name	Drug Class	Target/ MoA	Phase	Sponsor	Comment
TBI-223	oxazolidinone (linezolid)	protein synthesis inhibitor	phase Ia SAD: 50– 1400mg	TB Alliance/ Institute of Materia Medica	improved toxicity profile

contezolid (MRX-1/MRX-4)	oxazolidinone (linezolid)	protein synthesis inhibitor	phase Ib SAD/MAD: 150–1800mg	MicRx Pharmaceuticals	IV and oral dosing
TBI-166	riminophenazine (clofazimine)	binds to DNA and disrupts cell cycle	phase Ia	Institute of Materia Medica/ CAMS & PUMC	more soluble; will prevent skin discoloration
TBI-7371	Azaindole	DprE1 (cell wall synthesis inhibitor)	phase Ib SAD/MAD: 100–1500 mg	TB Alliance	
BTZ-043	benzothiazinone	DprE1 (cell wall synthesis inhibitor)	phase Ia MAD planned 2019	DZIF/ PanACEA	very potent with low toxicologic potential
macozinone (PBTZ-169)	benzothiazinone	DprE1 (cell wall synthesis inhibitor)	Phase Ia SAD: 10–320mg MAD planned 2019	iM4TB	optimized from lead BTZ-043; lower cost of goods and better pharmacodynamics supported by BMGF
GSK 656	oxaborole	LeuRS (protein synthesis inhibitor)	phase Ib SAD/MAD: 5–1500mg	GlaxoSmithKline	

CAMS: Chinese Academy of Medical Sciences; PUMC: Peking Union Medical College; DZIF: University of Munich Hans-Knöll Institute, Jena German Center for Infection Research; iM4TB: Innovative Medicines for Tuberculosis

- 8 compounds, 4 from new classes, and 3 that may prove to be safer/ more acceptable alternatives to existing medicines

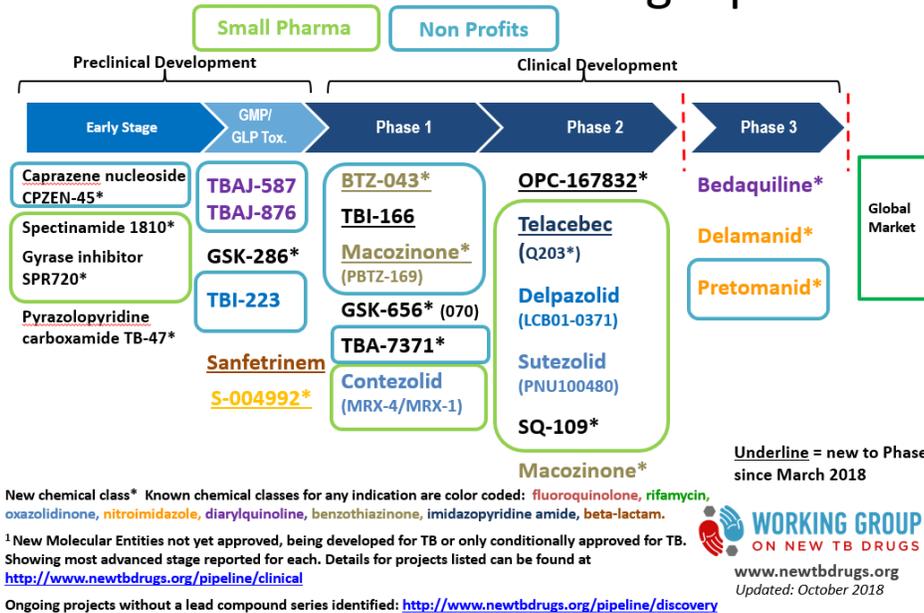
New compounds (phase II)

Drug Name	Drug Class	Target/ MoA	Phase	Sponsor	Comments
telacebec (Q203)	imidazopyridine amide (IPA)	Cyt- $bc_1:aa_3$ respiration inhibitor	phase IIa	Qurient/ Infectex/ PanACEA	bacteriostatic; does not kill persisters
macozinone (PBTZ-169)	benzothiazinone	DprE1 (cell wall synthesis inhibitor)	phase IIa (Russia)	Nearmedic Plus	iM4TB developing PBTZ-169 in Europe
sutezolid (PNU-100480)	oxazolidinone (linezolid)	protein synthesis inhibitor	phase IIa	Sequella/ TB Alliance	safety signal in rats; PanACEA dose ranging study under

					development
delpazolid (LCB01-0371)	oxazolidinone (linezolid)	protein synthesis inhibitor	phase IIa EBA: 800mg QD; 400mg BID; 800 mg BID	LegoChem Biosciences	
SQ109	Ethylenediamine	MmpL3 (cell wall synthesis inhibitor)	phase IIb MAMS 300mg + HRZ (R:10 or 20 mg/kg)	Sequella/Infectex	No EBA in phase IIa; in phase IIb, SQ109-containing arms discontinued at interim analysis
OPC-167832	carbostyryl derivative	DprE1 (cell wall synthesis inhibitor)	phase Ib/IIa MAD/EBA: 10–270mg +/- 200mg delamanid	Otsuka	being developed in combination with delamanid; supported by BMGF

- 6 compounds, 3 from new classes, and 2 candidates that might be safer alternatives to linezolid
- Expert consensus is that you need to see some proof of efficacy in adults (phase IIb) to begin paediatric PK and safety studies; For kids, phase IIb is when we really start paying attention.
- Only 1 compound (SQ109) completed phase IIb so far and efficacy remains unclear; game of wait and see/ anticipate where you can.
- Compounds to watch as phase IIb trials are proposed or underway are sutezolid, Q203, delpazolid, and OPC-167832.

2018 Global New TB Drug Pipeline ¹



- These are exciting times: The TB drug pipeline is fuller than it's ever been.

- We need to keep watching to see which compounds move forward and to continue advocating for the resources and coordination necessary to do so in a timely way.
- In the meantime, there is a lot of important work still to be done to ensure that children are able to benefit from scientific advancements, including new regimens and optimized dosing schemes, as shown by the following summary of paediatric research priorities.

Summary of paediatric research priorities:

Drug	Dosing used in adults (target exposures [to be] investigated for children)	Pediatric investigation underway or planned	Dosing under investigation in adults (paediatric research gaps?)
bedaquiline	2w400mg QD, 200mg 3xW	Y P1108; C211	8w200 mg QD, 100 mg QD
delamanid	200mg QD	Y C212/213; P2005	200mg QD
clofazimine	100mg QD	Y MDR PK; P2020	8w200mg QD, 100mg QD
Isoniazid	300–600mg QD (5mg/kg, hd:10–15mg/kg)	Y MDR PK	500–1000mg QD
linezolid	300–600mg QD	Y MDR PK; P2020	600–1200mg QD
moxifloxacin	400mg QD	Y MDR PK	400–800mg QD
pretomanid	200mg QD	planned TB Alliance and IMPAACT	200mg QD
rifampicin	600 mg QD (10mg/kg)	Y OptiRif Kids	35mg/kg QD
rifapentine	P:900mg/H:900mg 1xW	Y TBTC S35; CAP543	P:900mg/H:900mg 1xW P:600mg/H:300mg QD P:600mg QD P:1200mg QD

In the column on the right (dosing under investigation in adults) is **highlighted in red** where no paediatric studies are being planned. Here we can make a big push!

Discussions

- Weight bands for HIV and first-line TB treatment are different, although DR-TB dosing tables use similar weight bands as HIV. Malnourished children may be under-dosed if dosed according to their actual weight.
- Spectrum of disease from mild through to severe disease: children with mild disease have better outcomes, but it can be hard to define what constitutes non-severe disease. The vast majority of

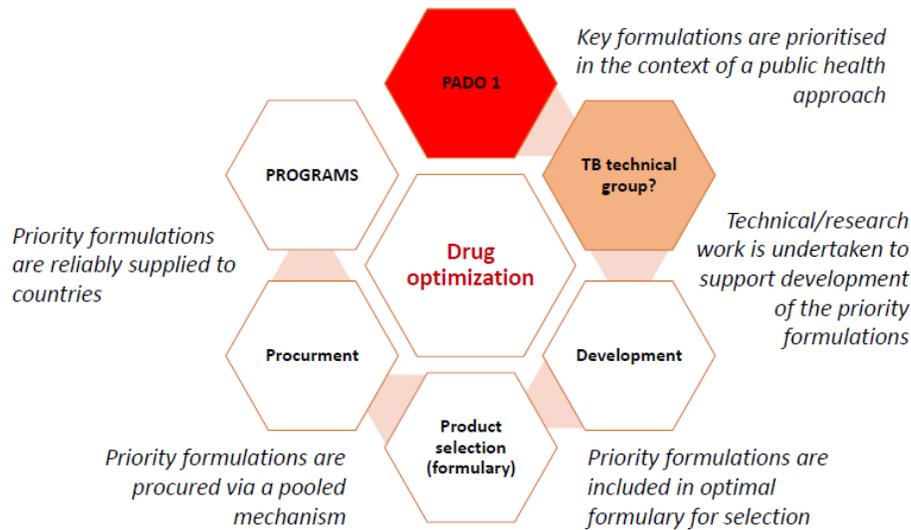
children get more treatment than they need. But a pragmatic approach is needed. The exception is young children with smear positive disease.

- The 2016 WHO guidelines already recommended an oral regimen for children with non-severe DR-TB. It might take years to agree on an exact definition of “non-severe” disease. The 2019 Sentinel Field Guide already recommends that the duration of the regimen be based on disease severity taking into account underlying co-morbidities, CD4 count, malnutrition and severe forms of EPTB. The guide provides some practical guidance to this extent.

Session 4: PADO for TB

Discussions on the PADO for TB mechanism and modus operandi in the context of complementary efforts in paediatric drug optimization and to reach consensus on priorities for the development of paediatric antituberculosis drugs and formulations - Facilitated by WHO (Martina Penazzato and Martin Van Den Boom)

- Introduction: Going back to the concepts that were discussed today:
 - Do we understand why we are here?
 - How do we place ourselves in the broader picture?
 - How do we feel about the PADO mechanism we are proposing?
- Developing and delivering paediatric formulations through collaborative and coordinated action:



- Partners:
 - GDF: has procurement side well covered
 - TPMAT: harmonizes signals sent to suppliers using existing pathways and mechanisms, including expressions of interests invited by the WHO Pre-Qualification Program (WHO PQP) and the Global Fund Expert Review Panel (ERP)
- Prioritization:

- The remaining upstream work: PADO to develop a list of priorities. A subset of this needs clinical and pharmacological expertise – strategizing on how best to use this expertise is needed.
- What seems to be missing is the link between scientific thinking and the formulations that need to be made. Manufacturers need to be aware of scientific developments. We need greater clarity on priorities and flexibility. It can be really demotivating if things change along the line. What is a priority right now may not be a priority in a few years from now. Therefore the time factor and the guidance factor are important.
- The right product needs to be available at the right time. We could detail the right formulation now, and what we think will be right in several years, and plan to transition to future needs. The number one formulation needs to be defined, e.g. a dispersible scored tablet.
- We need a good sense of new regimens and dosing required in 2-3 years' time (using existing drugs). Based on preliminary results of ongoing trials, we can anticipate. The risk will be to get the dose wrong. What can be done within available formulations, e.g. re-adjust ratios in FDCs?
- More time is needed to identify the vision, and how to inform dosing (e.g. ideally the drug and dosing ranges should be defined first, and the formulation developed based on this, rather than the other way around)
- Prioritization process:
 - What is already available?
 - What is needed in terms of existing and future needs?
 - Steps: Identification of needs – prioritization – development – preparation for procurement – access
- Two overlapping processes:
 - Optimal formulary to deliver on current guidance
 - Clarity on needs (clinical, programmatic, procurement) for the medium/long term (to communicate with researchers, funders etc.) to be able to deliver on future guidance
- Normative component:
 - Strong link needed between PADO and norms/standards, but this is a separate process led by WHO
 - Hand over to the right people (e.g. GDF) afterwards
 - A connection is needed between:
 - The drug optimization agenda and the scientific portfolio (the prioritization exercise to be done on day 2 of this meeting)
 - PADO and global guidelines: to define the optimal formulation in order to deliver the guidelines, as well as to bring everyone on the same page and have transparency and clarity about challenges
- The gaps that we are facing are clear: there is a lack of funding and a lack of capacity – therefore we need to get funders on board and give clear signals to donors and suppliers about what is needed

- Spectrum of disease: different dosages are needed, for example for levofloxacin (Lfx) for LTBI, PTB, disseminated TB, TBM – the optimal dosing is evolving: FDCs are critically important but standalone formulations are needed for special cases (e.g. children with severe disease)
- Formulations: need to be pragmatic: small, dispersible/scored, based on average child and routine standard of care, flexible use for different scenarios (dose range may change)
- Advocacy role of PADO TB:
 - Norms/standards: access to data to inform recommendations and help stratification approaches - promote the use of data
 - We might be ahead of the adult process, but adult processes will affect paediatrics as well
 - Second line formulations' cost are prohibitive and often it is easier for countries to continue crushing adult formulations – therefore advocacy is also needed to reduce prices of child-friendly formulations
 - Advocacy function is important and may be the potential of this group (e.g. advocating for BDQ for children needs more advocacy than TAG and MSF). PADO TB can enhance this advocacy.
 - Advocacy around TB is traditionally much less than for HIV: this need to be enhanced
 - Pregnant women: push for inclusion as well – is included in HIV PADO (was a natural issue once the PADO process was established, but may be challenging for the first PADO to include)
- TPMAT: already focuses on short-term priorities – what is needed is more research around long-term priorities
 - WHO forms an active part of the group, taking cues from existing norms and standards
 - TPMAT has no desire to inform guidance, and focuses more on market and procurement aspects, highlights what is currently missing looking at the guidance in place
 - Therefore, PADO should focus on what does not (yet) exist, not on market/procurement aspects with clear signals to manufacturers
 - Scope of PADO TB: TPMAT covers short-term priorities – should PADO focus on longer term?
- PADO for HIV example: PADO HIV facilitates a prioritization exercise linked to normative guidance: there has not always been agreement on how to get where we wanted to go, for example HIV had to give up certain protease inhibitors, and had to make choices. Later on in the process, the question was whether the correct ones had been chosen. For TB: should the focus be on 3HP or 1HP (which one has the best adherence, efficacy, least side effects) as both are better than what we can currently offer? At times it will be necessary to make compromises, and pick one based on available data – or risk not having any of the new options for the next 5 years.
- Illustration of how TB is different from HIV: the example of second-line paediatric formulations by one supplier, simply because they were told by one expert that these are needed.

- There is value in having a transparent process in place involving as many stakeholders as possible. Consensus on priorities keeping in mind what children need and what is technically feasible coupled with better advocacy.
- The Global Fund will soon stop paying for first line drugs. Perhaps beyond the role of PADO TB, but advocacy is urgently needed in order for countries to keep buying child-friendly formulations once GF support stops.

Day 2, Friday 15 February 2019

Summary of day 1, objectives for day 2 and introduction to group work to define short, medium and long-term priorities for the development of paediatric antituberculosis drugs and formulations

Background on HIV PADO list (Linda Lewis):

- HIV PADO list evolution (from PADO 1 to PADO 4):

PADO 1-2013	PADO 2-2014	PADO 3-2016	PADO 4-2018
LPVr 4-in-1	LPVr 4-in-1 (30/15/40/10 mg)*	In advanced development	
ABC/3TC/EFV	ABC/3TC/EFV (150/75/150 mg)*	In advanced development	
ATVr	ATVr (100/33mg)*	Removed [§]	
NVP 20 mg	NVP/AZT	NVP/AZT	Removed
RAL	RAL	RAL (50 mg scored)*	Removed
DRVr	DRVr	DRVr (120/20 mg)*	DRVr (120/20 mg)
DTG single	DTG paedts single	DTG paedts single (5 mg)*	DTG paedts single (10 mg scored) dispers tab
DTG/3TC/ABC	DTG/3TC/ABC	DTG/3TC/ABC (5/30/60 mg)*	DTG/3TC/ABC (5/30/60 mg) dispersible tab
F/TAF	F/TAF	F/TAF	XTC/TAF dispersible tablets
DTG/XTC/TAF	DTG/XTC/TAF	DTG/XTC/TAF	DTG/XTC/TAF dispersible tablets
		DTG/DRVr	Removed
		DTG/3TC	Removed
		LA	MK 8591
		bNab	Doravirine
			LA
			bNab
			New delivery technologies

- These were all products that did not exist in paediatric formulations
- Some products had specific challenges, e.g. vile taste, high alcohol %, etc.
- Learning experiences about the products themselves
- Ongoing innovations, e.g. scored, dispersible tablet
- If there was no interest from manufacturers, products could be removed or replaced
- New delivery systems
- Long-term list = Watch list: products we want as soon as we can get them
- Not many products on the lists are currently available – the list tells us what is most important but unfortunately it does not always happen

- Dolutegravir (DTG) moved from wish list in 2013 to highest priority in 2018 (as trial data available)
- Optimal formulary list: This is a list of products a country should have to treat the paediatric population. This is a different list showing what is currently available – based on WHO guidelines, publicly available for Ministries of Health to access (comparable to GDF list of product available to procure)
- Example of LPV/r 4 in 1: this product is currently in advanced development, but not yet on the formulary list. It is still in development and will hopefully get FDA approval this year. Development was delayed by technical challenges necessitating special equipment and investments in the production line. This product therefore is not on the actual priority list anymore.
- It may happen that a product that was prioritized earlier is no longer needed in light of new evidence. While preparing a list of priorities, we could consider to flag level of risk.
- Need to address technical challenges and therefore to work more closely together between originators and generic manufacturers and also for originators to file for generic registration to shorten timelines– some of these challenges led to the establishment of GAP-f

Discussions

- Does TB need to learn from HIV or the other way around?
 - GDF and WHO signalling about products needed, but not leading to sales. Priorities not defined in the same way. There is currently agreement between Global Fund Expert Review Panel (ERP) and WHO prequalification (PQ). Using existing systems, it currently takes less than three years for suppliers to come to the market. No other disease is using ERP in the same way.
 - Second-line paediatric formulations – success stories
 - TB programme seems to be doing a better job from the outcomes perspective
 - The challenge will be to agree on what the priorities are, to look at long-term gaps, while not throwing away what works well. Clear signals from the scientific community on consensus priority products.
 - TB can work with existing mechanisms, while HIV needed a different (longer and more complicated) approval pathway. E.g. in TB, we have a pooled procurement mechanism, and are already working to harmonize the signals sent to suppliers through existing mechanisms and pathways.
- There will be value in having consensus on the priorities for TB. It is realistic to assume that more investment is needed, which will also create new opportunities
- There may be value to also clearly highlight funding gaps for research and development.

Session 5: Group Work to define short/medium- and long-term priorities for the development of paediatric antituberculosis drugs and formulations.

Group 1: Drug-susceptible TB disease treatment (Jen Cohn + Sabine Verkuijl)

Output 1: 3-5 years (Short/Medium) priorities:

- Rifampicin (RIF) single dispersible
 - Data is already there that this can increase efficacy, and maybe lead to regimen shortening
 - Single rather than FDC because ratios will change across weight bands (for “top up”)
 - Ideal dose of a dispersible tab to be determined but data already there
- Rifapentine (RPT)
 - Single rifapentine (same rationale as above for single need)
 - Optimal dosage will come from PK study (not yet started/funded)
 - Formulation should be dispersible (potentially scored) – dose TBD on PK study

Output 1 >5 years (Long)

- Nothing if we can get to a 2-month regimen (especially if the same drugs can be used for LTBI [broadening applicability of a single regimen/drug across the spectrum of disease])
- Long-acting safe formulation that works across ages and disease spectrum appears

Possible watch list:

- RHZL FDC short regimen – this FDC may be useful if SHINE not successful and if studies with short FQN based regimens are successful. Lfx will be needed for CNS-TB, but we believe currently available Lfx single dispersible will be sufficient for this.
- HRZE dispersible FDC
- HPZ(E) and HP dispersible FDC – depending on results of rifapentine PK study (if same ratio between P and H are maintained across weight bands). Will also depend on harmonization of this FDC between DS-TB disease and infection indications.
- B6 dispersible FDC (in combination with first-line anti-tuberculosis drugs)
- Bedaquiline, Pretonamid – If we cannot find a short regimen using currently used drugs (e.g. RHZE or PHZE), a regimen containing B and Pa such as BPamZ may be needed

Output 2: Additional research questions, funding gaps and advocacy needs:

- Research gaps:
 - PK of high-dose daily RPT (not yet started)
 - PK/safety of antituberculosis drugs in malnourished kids
 - PK of high-dose RIF and DTG (maybe DRV/r)
- Funding gaps
 - PK of high-dose daily RPT (not yet started) – study not funded
- Advocacy needs
 - Safety of Ethambutol

- Quality B6 supply

Next steps:

- Convene subgroup of PK experts to work with available data and determine appropriate dosing of rifampicin

Group 2: Drug-resistant TB disease treatment (Jennifer Furin + Martin Van Den Boom)

Output 1: Priority products for DR-TB treatment

Medicine	Ped formulation	Comments
Bedaquiline	Trial formulation	Short term
Clofazimine	No	Short term
Delamanid	Trial formulation available for compassionate use	Short term Could be used also for LTBI
Lfx/Mfx	Yes/Yes	Formulations exist. Could also be used for DR-LTBI and treatment of INH-mono-resistant TB
Linezolid	Syrup (very expensive) 150mg dispersible tablet in development	Short term
Pretomanid	No	Short term

Watch list (based on new compounds in phase II):

- Telacebec (Q203)
- Sutezolid (PNU-100480)
- Delpazolid (LCB01-0371)
- OPC-167832

Preferred formulations:

- Scored (functional) dispersible tablet
- Under 5kg kids – compounded formulations, pragmatic use of dispersible tablets used for higher weight group
- FDC is not a priority
 - Guidelines changing frequently
 - Toxicity requiring stopping one drug
- Long acting formulations (could be also injectable version) – for the future development

Output 2: Research questions

- New delivery and administration ways
- Ongoing PK/PD studies to optimize dosing (not to be based only on age and weight)
- Understanding acceptability, adherence to administration instructions
- Explore formulations to overcome food restrictions

- Co-packing (e.g. with food)
- Optimal dosing strategies for children under 5 kg
- Flexible dosing
- Is there a need for more than one agent from each drug class (e.g. FQs, nitroimidazoles)
- Planning for paediatric studies should begin once a product is in phase II.
- Use of drugs for other indications (FQ, DIm) and maybe for adults – increasing market
- Market estimations – how many children from different weight and age groups
- Costing the research agenda to inform donors and manufacturers
- Explore potential candidates for long acting formulations

Next steps and actions:

- Follow up call to suggest the ideal strength tablet for paediatric bedaquiline and delamanid (<1 month)
- Fill out the drug score sheet (identify knowledge gaps, prioritize drugs)
- Advocacy to overcome Intellectual Property barriers and manufacturing insufficiencies
- Facilitate, advocate, negotiate with manufacturers
- Stimulate countries to collect/share data on children (disaggregated by **weight** and age). Provide generic data collection tools, collaborate with partners (MSF, Union, KNCV, PIH, and others.)
- Establish research HUBs in different regions (Belarus, Kyrgyzstan....), develop research capacity
- Harmonize the needs with the preventive market
- Regulatory harmonization (WHO+TAG+CSO) and advocacy enabling research, harmonized registration
- Orphan status of paediatric formulations (facilitate uptake in countries that require local registration)

Group 3: Latent TB infection treatment (drug-susceptible and drug-resistant) (Lisa Obimbo + Annemieke Brands)

Output 1: Short/medium term PADO TB drugs for prevention

Drug	Formulation	Comments
Short to medium term - All scored and dispersible		
Rifapentine 150mg	150 mg	DS TB
Isoniazid/Rifapentine FDC (HP)	unknown	DS TB Evidence upcoming
Delamanid	50 mg	DR-TB
(Pyridoxine)	50 mg	Minimize INH toxicity. On essential medicines list (CTX/B6 FDC for HIV)

Notes on table:

- Rifapentine stand-alone: has multiple uses and allows for flexibility to adjust dose as evidence emerges on higher dosing for LTBI and active TB treatment.

- HP FDC: Optimal ratio of H:P unknown, but preferred regimen is to optimize a 1 HP (HP once daily for one month) short course regimen (Weekly HP for 3 months [3HP] would be the second preferred short course): Multiple uses, both for LTBI and active disease.
- Delamanid stand-alone: Current trials using 25mg trial formulation berry-flavoured mandatory dispersible available. Taste is good. Not scored. Preferred for development: 50 mg scored dispersible tablet (not restricted to mandatory dispersible, but also ok to dissolve on tongue for older children).

Output 1: Long term PADO TB drugs for prevention

Drug	Formulation	Comments
Long term - All scored and dispersible		
Moxifloxacin	100 mg	DR TB Taste masked formulation required
Bedaquiline	20mg	DR TB
Pretomanid	Unknown	Guided by research

Notes on table:

- Levofloxacin: Lfx 100mg scored and dispersible tablet is already available, and it seems palatable and acceptable in ongoing trials, but needs to be given for 6 months. So this formulation could be scaled up for immediate use. No new formulation required, therefore not to be included in PADO TB list.
- Moxifloxacin: Long-term – consider development of taste masked formulation 100mg. However, Mfx is inferior to levofloxacin in safety profile, so optional to include this.
- Bedaquiline: Long-term – 20mg paediatric formulation for shortened regimens for DR-TB exposed children.
- Pretonamid: Long-term develop paediatric formulation for shorter course preventive regimens for DR-TB exposed children (there is a paediatric formulation under development – remote participant communicated). This will have multiple uses and may also be useful for treatment of DR-TB disease.

Output 2: Prevention LTBI in Children: Remaining research questions to inform development and optimal use

- Shorter preventive regimens for children
 - for DS TB (1HP, 3HP)
 - for DR TB (fluoroquinolones, delamanid and possibly bedaquiline)
- Acceptability and palatability to be assessed for all paediatric formulations early on in research
- Levofloxacin – establish PK, safety and optimal dosing for children (emerging evidence – bioavailability appears higher than expected in initial reports with 15-20mg/kg)
- Moxifloxacin formulation: taste masking
- Optimal ratio of isoniazid:rifapentine (HP) FDC
- Long-acting novel formulations for children

- Operations research to understand barriers and facilitators to uptake of treatment of LTBI in children.

Discussions:

Discussion on pursuing FDCs versus single scored and dispersible formulations:

- FDCs may pose a risk as long-term guidance and efficacy are not clear – therefore FDCs are not a short-term priority
 - More long-term priorities pending further research
 - Single drugs most important but when deciding on formulations, the pill burden needs to be kept in mind
- Discussion on delivery strategies and flexible dosing: functionally scored dispersible formulations are needed. Collect data from countries prior to updating guidelines.
- Child-friendly versus patient-friendly formulations for both children and adults

TB/HIV:

- A study on DRV/r with rifampicin seemed too unsafe and was just stopped in a study in adults which showed grade 3 and 4 hepatotoxicity

Ethambutol barriers:

- Evaluation of ethambutol safety (barrier to uptake of 4-drug regimens for first line treatment): SHINE trial not powered to evaluate this. Currently not all sub-Saharan African countries using additional ethambutol
- E is protective in areas with increasing INH resistance. However, most children are not infected with HIV and do not have severe disease and therefore do not need E.
- Ethambutol containing regimens may not be needed as most children do not have severe disease and are not infected with HIV

Prevention:

- Data are needed on preventive therapy for children living with HIV on ARVs
- We should not use “LTBI” but “treatment of TB infection”
- Merging the spectrum of LTBI and DS-TB treatment: long-term possibility of treatment for all for 2 months?
- Preventive treatment is given to children who are well and needs to be weight based, very safe, tolerable and, as short as possible.
- We need better data on how many children are eligible for preventive treatment to better shape the market.
- Prevention in youngest who are most at risk: precise dosing needed although they metabolize medicines quicker
- 3HP versus 1HP: if companies can develop for trials, they can develop for markets even though ratio H:P different in 3HP and 1HP

DR-TB:

- Levofloxacin versus moxifloxacin: the choice used to be dependent on DST results. Currently, levofloxacin is the drug of choice, as moxifloxacin causes more problems with QTc prolongation.
- Reporting on adverse events is cumbersome
- Recent publication on adverse events related to fluoroquinolones: advocacy needed on levofloxacin

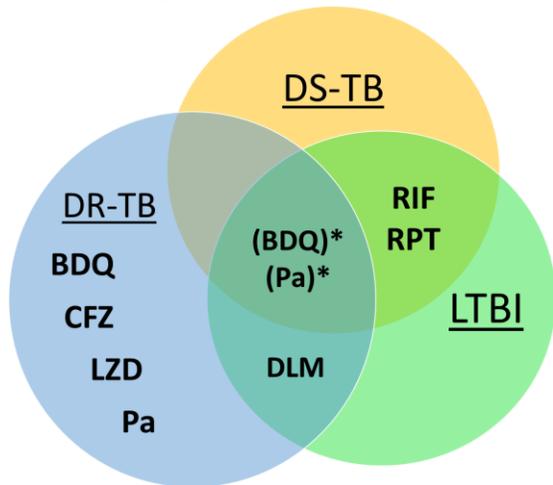
PADO lists of priorities and research needs:

- The PADO priority consensus list should contain formulations that we think can be achieved and that are better than we currently have (versus the perfect formulation)
- PADO TB consensus priority list: realistic versus wish list of ideal formulations. Products can be really expensive.
- Within each area (DS TB, DR-TB and LTBI), try to prioritize within the list of consensus priorities (try to delineate a bit more)

PADO TB 1: Summary of agreed priorities:

Formulations: All scored dispersible				
Short-term list	DS-TB	DR-TB	LTBI	Remarks
Rifampicin (RIF)	√		√	Currently 4R is not a preferred LTBI regimen for children
Rifapentine (RPT)	√		√	
Bedaquiline (BDQ)	(√)	√	(√)	Watch-list for LTBI and DS-TB
Clofazimine (CFZ)		√		
Delamanid (DLM)		√	√	
Linezolid (LZD)		√		
Pretonamid (Pa)	(√)	√	(√)	Watch-list for LTBI and DS-TB
Watch list				
Bedaquiline (BDQ)	√	(√)	√	Short-term list for DR-TB
Pretonamid (Pa)	√	(√)	√	Short-term list for DR-TB
Telacebec (Q203)		√		Currently phase IIa
Sutezolid (PNU-100480)		√		Currently phase IIa
Delpazolid (LCB01-0371)		√		Currently phase IIa
OPC-167832		√		Currently phase IIa/IIb
Moxifloxacin (MFX)	(√)	√		Taste-masked

Venn-diagram of agreed short-term priorities:



* BDQ and Pa on short-term list for DR-TB but on watch-list for LTBI and DS-TB

Session 6: Where do we go from here?

Discussion on ways to stimulate action towards the development of priority paediatric antituberculosis drugs and formulations and agreement on next steps, including priorities for GAP-f – facilitated by Jennifer Cohn

Summary of discussions:

- What signals to communicate to manufacturers, researchers, funders, regulators, advocacy groups
 - Advocacy to create demand, regional and in-country; this should be more than usual
 - Make use of existing and functional structures, for example, feed into communication by GDF/TPMAT etc.
 - It needs to be clearly communicated that rifampicin on short-term list is not necessarily for 4R LTBI regimen as 3RH and 1HP or 3 HP are preferred options for children
- Research gaps:
 - Work on dosing based on (early) PK data – e.g. for rifapentine
 - Also around patient, caregiver and healthcare worker preference (this would be done early on in the development process) – context does matter
- Experiences with dissemination after HIV PADO:
 - Meeting report
 - Webinar sharing outcomes
 - Scientific dissemination (general and specific)
 - Community representation
- Potential outputs:
 - A subgroup of PADO TB 1 to anticipate dosing requirements based on what we currently know and on early research results

- Explore funding to address research gaps and build capacity to develop and implement appropriate research in multiple sites. Develop research protocols and make them available for funding. Work towards sustainable funding for research.
- Engage the NIH (who are very active and have already expressed interest) to alert them on the PADO priorities, research questions and gaps
- GDF to facilitate messages to manufacturers (involvement of CSOs and activists) and to WHO PQ and GF ERP Expressions of interest (EOI), via established mechanisms
- GDF (through TPMAT) with WHO can provide signals to suppliers
- Advocacy role, including advocating with in-country regulatory authorities: Possible opportunities through FDA/EMA/SRA approval (e.g. sharing review documents through secure site)
- GDF can help assist with WHO PQ processes as TB medicines are almost always generics (in that sense TB is different from HIV)
- Advocate for funding for patient preference surveys.
- Explore how best to build on existing initiatives and experiences.
- The revived paediatric regulatory network convened by WHO EMP, linked to GAP-f, could convey messages on behalf of the TB community
- Medicines Patent Pool: can coordinate licensing agreements between innovators and make them available to generic companies
- GF ERP can accelerate the process, next meeting on 8 April 2019: make use of the current momentum and share the list of priorities

Next steps:

- Meeting report with wide dissemination
- Suggest establishment of sub-group of PADO TB and report to the Strategic and Technical Advisory group (STAG TB)
 - Show need for prioritization
 - Learn more from PADO HIV experiences
 - Make use of advantage of having GDF and UNITAID funding
 - Work closely with WHO HIV and WHO MVP, in particular PQ
- In future, involve more representatives from TB high burden countries as well as communities affected by TB in PADO TB
- Share outcome of PADO TB with the core team of the Child and Adolescent TB Working Group
- Participate in IAS webinar 27 February 14:00 CET (15:00 SAST; 8:00 ET)

Annex 1: Meeting agenda

Day 1: Thursday 14 February 2019		
Chair: Tony Garcia-Prats		
08:30-08:55	Welcome and introductions Optimizing paediatric TB prevention and treatment in the light of reaching UNGA HLM on TB targets	Dr Tereza Kasaeva, Director WHO GTB
08:55-09:00	Overview of meeting objectives Declaration of interests	Annemieke Brands, WHO GTB
<p>Session 1: An introduction to the size and specifics of the paediatric anti-TB drug market and to the concept of paediatric antituberculosis drug optimization</p> <p>Expected outcome:</p> <ol style="list-style-type: none"> 1) An overview of the burden of TB, DR-TB and TB infection in children and recent policy developments; 2) An understanding of the current paediatric TB market and implications for drug development; 3) Review the concept of drug optimization and lessons learned from PADO for HIV; 4) An introduction to the Global Accelerator for Paediatric Formulations (GAP-f) framework. 		
10:00-10:20	The concept of drug optimization and the Global Accelerator for Paediatric Formulations (GAP-f) framework: learning from experiences of the HIV programme	Martina Penazzato, WHO HIV
09:00-09:20	The burden of paediatric TB (infection and disease), recent policy developments and targets	Malgosia Grzemska, WHO GTB
09:20-09:40	Paediatric TB medicines market overview and coordination	Brenda Waning, GDF
09:40-10:00	Paediatric TB market specifics and implications for drug development: a community and human rights perspective	Lindsay McKenna, TAG
10:20-10:30	Discussions	All
10:30-11:00	Group photo and coffee/tea break	
<p>Session 2: Experiences with antituberculosis drug development and market-shaping</p> <p>Expected outcome:</p> <ol style="list-style-type: none"> 1) Sharing of experiences with paediatric antituberculosis drug development (first- and second line); 2) An understanding of regulatory and other barriers for drug development and market shaping; 3) Ongoing efforts to improve access to paediatric formulations; and 4) An understanding of child-friendly formulations. 		
11:00-11:20	Development of child-friendly TB Fixed-Dose Combinations: lessons learned	Shelly Malhotra, TB Alliance (remotely)
11:20-11:40	Development and introduction of TB medicines: the case of paediatrics	Brian Kaiser, GDF
11:40-12:00	Role of the WHO Access to Medicines, Vaccines and Health	Samvel Azatyan, WHO

	Products (MVP) cluster in improving access to and use of appropriate TB medicines for children	MVP
12:00-12:30	Discussion	All
12:30-13:30	Lunch break	

Session 3: Current adult and paediatric TB research and clinical trial landscape, priorities and overview of drug development

Expected outcome:

- 1) Overview of current adult and paediatric TB infection and disease, TB/HIV co-infection trials, drug pipeline and policy implications;
- 2) Ongoing efforts to improve access to paediatric formulations in other disease areas including HIV; and
- 3) An understanding of additional research priorities and needs.

Chair: Rina Triasih

13:30-13:50	An overview of the paediatric TB (infection and disease) trial landscape	Anneke Hesselings/Tony Garcia-Prats, Desmond Tutu TB Centre
13:50-14:10	An overview of the adult TB trial landscape and implications for paediatric TB drug optimization	Kelly Dooley, Johns Hopkins University (remotely)
14:10-14:30	TB/HIV-coinfection, ARVs and implications for paediatric TB drug development/Identifying synergies and alignment between TB and HIV	Helena Rabie, Stellenbosch University (remotely)
14:30-14:50	An overview of the current TB drug development pipeline and remaining research priorities	Lindsay McKenna, TAG
14:50-15:10	Discussion	All
15:10-15:30	Tea/coffee break	

Session 4: PADO for TB

Expected outcome:

- 1) Discussion on the PADO for TB mechanism and modus operandi in the context of complementary efforts in paediatric drug optimization;
- 2) Discussion on the process to reach consensus on short/medium and long-term priorities for the development of paediatric antituberculosis drugs and formulations.

15:30 -17:00	Discussions on the PADO for TB mechanism and modus operandi in the context of complementary efforts in paediatric drug optimization and to reach consensus on priorities for the development of paediatric antituberculosis drugs and formulations	Facilitated by WHO (Martina Penazzato and Martin Van Den Boom)
17:00	Summary and wrap-up	Malgosia Grzemska, WHO GTB

Day 2: Friday 15 February 2019		
08:30-09:00	Summary of day 1, objectives for day 2 and introduction to group work to define short, medium and long-term priorities for the development of paediatric antituberculosis drugs and formulations	Malgosia/Annemieke/Sabine, WHO GTB
<p>Session 5: Group Work to define short/medium- and long-term priorities for the development of paediatric antituberculosis drugs and formulations.</p> <p>Expected outcome: 1) Agree on a list of short/medium- (2-5 years) and long-term (5-10 years) priorities for the development of paediatric antituberculosis drugs and formulations according to proposed methodology; and,</p>		
09:00-10:30	<p>Group Work to define short/medium- and long-term priorities for the development of paediatric antituberculosis drugs and formulations:</p> <p>Group 1: Drug-susceptible TB disease treatment</p> <p>Group 2: Drug-resistant TB disease treatment</p> <p>Group 3: Latent TB infection treatment (drug-susceptible and drug-resistant)</p> <p>Brainstorming</p>	<p>Facilitators:</p> <p>Group 1: Jen Cohn + Sabine Verkuijl (Main room CDS65)</p> <p>Group 2: Jen Furin + Martin Van Den Boom (D46010)</p> <p>Group 3: Lisa Obimbo + Annemieke Brands (D6007 - ground floor)</p>
10:30-11:00	Coffee/tea break	
11:00-12:30	Group work continued – formulations of priorities	
12:30-13:30	Lunch break	
13:30-15:30	Report back of group work and discussion and agreement on a final list of paediatric TB drug optimization priorities	Group facilitators
15:00 -15:30	Discussion	All
15:30-16:00	Tea/coffee break	
<p>Session 6: Where do we go from here?</p> <p>Expected outcome: Consensus on next steps</p>		
Chair: Jen Cohn		
16:00-17:30	Discussion on ways to stimulate action towards the development of priority paediatric antituberculosis drugs and formulations and agreement on next steps, including priorities for GAP-f	All
17:30	Closing remarks	Malgosia Grzemska, WHO GTB

Annex 2: List of participants

1. Jay Achar
HIV/TB/Hepatitis Advisor
Médecins sans Frontières
London
United Kingdom of Great Britain and
Northern Ireland
Email: jay.achar@london.msf.org
2. Draurio Barreira
Technical Manager
UNITAID
Geneva
Switzerland
Email: barreirad@who.int
3. Grania Brigden
Deputy Director TB and HIV Department
The International Union Against TB and
Lung Disease (The Union)
Geneva
Switzerland
Email: grania.brigden@theunion.org
4. Michael Campbell
Clinton Health Access Initiative (CHAI)
Bethesda
USA
Email: mcampbell@clintonhealthaccess.org
5. Martina Casenghi
Technical Director CaP TB Project
Elizabeth Glaser Pediatric AIDS
Foundation (EGPAF)
Geneva
Switzerland
Email: mcasenghi@pedaids.org
6. Thomas Chiang (*unable to participate*)
Senior TB Technical Advisor
USAID
Washington, D.C.
USA
Email: tchiang@usaid.gov
7. Jennifer Cohn
Senior Director of Innovation
Elizabeth Glaser Pediatric AIDS Foundation
(EGPAF)
Geneva
Switzerland
Email: jcohn@pedaids.org
8. Charlotte Colvin (*unable to participate*)
Senior TB Technical Advisor
USAID
Washington, D.C.
USA
Email: ccolvin@usaid.gov
9. Sarah Cook-Scalise
Global Alliance for TB Drug Development
New York
USA
Email: sarah.cook-scalise@tballiance.org
10. Kelly Dooley (*through webex*)
Associate Professor of Medicine,
Pharmacology & Molecular Sciences
Co-Director, Fellowship Training Program
in Clinical Pharmacology
Faculty Leader, Janeway Firm of the Osler
Residency Program
Johns Hopkins University School of
Medicine
Baltimore
USA
Email: kdooley1@jhmi.edu
11. Gunta Dravniece
TB Consultant
KNCV Tuberculosis Foundation
The Hague
The Netherlands
Email: gunta.dravniece@kncvtbc.org

12. Jennifer Furin
The Sentinel Project on Pediatric Drug
Resistant TB
Boston
USA
Email: jenniferfurin@gmail.com
13. Anthony Garcia-Prats
Stellenbosch University
Cape Town
South Africa
Email: garciprats@sun.ac.za
14. Lucia Gonzalez Fernandez
Senior Manager
International AIDS Society
Geneva
Switzerland
Email: lucia.gonzalez@iasociety.org
15. Anneke Hesseling
Professor in Paediatric and Child Health
Director, Desmond Tutu TB Centre
Stellenbosch University
Cape Town
South Africa
Email: annekeh@sun.ac.za
16. Fabienne Jouberton
Médecins Sans Frontières
Geneva
Switzerland
Email: Fabienne.jouberton@geneva.msf.org
17. Sandeep Juneja
Senior Vice President, Market Access
Global Alliance for TB Drug Development
New York
USA
Email: Sandeep.juneja@tballiance.org
18. Brian Kaiser
Technical Officer, Global Drug Facility, Stop
TB Partnership
Geneva
Switzerland
Email: briank@stoptb.org
19. Alexander Kay (through webex)
Baylor International Pediatric AIDS Initiative
Mbabane
Eswatini
Email: alexander.kay@bcm.edu
20. Alexei Vladimirovich Kazakov
Senior Scientist
National Medical Research Center of
Phtisiopulmonology and infectious diseases
Ministry of Health
Moscow
Russian Federation
Email: alexeykazakov1982@yandex.ru
21. Linda Lewis
Director
Clinical and Regulatory Affairs
Clinton Health Access Initiative (CHAI)
Bethesda
USA
Email: llewis@clintonhealthaccess.org
22. Shelly Malhotra (through webex)
Director, Market Access
Global Alliance for TB Drug Development
New York
USA
Email: shelly.malhotra@tballiance.org
23. Helen McIlleron (through webex)
University of Cape Town
Cape Town
South Africa
Email: helen.mcilleron@uct.ac.za
24. Lindsay McKenna
TB Project Co-Director
Treatment Action Group
New York
USA
Email: Lindsay.mckenna@treatmentactiongroup.org

25. Hannah Moak Barron
Business Development Manager
Medicines Patent Pool
Geneva
Switzerland
Email: hmoak@medicinespatentpool.org
26. Yamuna Mundade
Unitaid
Geneva
Switzerland
Email: mundadey@unitaid.who.int
27. Elizabeth Obimbo
Professor
University of Nairobi
Nairobi
Kenya
Email: eobimbo@yahoo.com
28. Fernando Pascual
Medicines Patent Pool
Geneva
Switzerland
Email: fpascual.consultant@medicinespatentpool.org
29. Helena Rabie (through webex)
Stellenbosch University
Cape Town
South Africa
Email: hrabie@sun.ac.za
30. Rada Savic
Associate Professor
University of California San Francisco
San Francisco
USA
Email: rada.savic@ucsf.edu
31. Anna Scardigli
TB Advisor
The Global Fund to Fight AIDS,
Tuberculosis and Malaria
(The Global Fund)
Geneva
Switzerland
Email: anna.scardigli@theglobalfund.org
32. James Seddon (through webex)
Imperial College London, UK &
Stellenbosch University
South Africa
Email: james.seddon@imperial.ac.uk
33. Moorine Sekadde (through webex)
Paediatric TB Coordinator
National TB and Leprosy Program
Kampala
Uganda
Email: moorine.sekadde@gmail.com
34. Alena Skrahina
Deputy Director
The Republican Research and Practical
Centre for Pulmonology and TB
Minsk
Belarus
Email: alena.skrahina@gmail.com
35. Rina Triasih
Sardjito Hospital
Jakarta
Indonesia
Email: rina_triasih@yahoo.com
36. Anna Turkova (through webex)
University College London
London
United Kingdom of Great Britain and
Northern Ireland
Email: a.turkova@ucl.ac.uk
37. Essien Ukanna
Unitaid
Geneva
Switzerland
Email: ukannae@unitaid.who.int

38. Brenda Waning
Global Drug Facility
Stop TB Partnership
Geneva
Switzerland
Email: brendaw@stoptb.org

WHO Regional Office

39. Martin van den Boom, WHO EURO

WHO-Headquarters

- 40. Soumya Swaminathan, WHO DDG
- 41. Tereza Kasaeva, Director WHO GTB
- 42. Malgosia Grzemska, Coordinator, WHO GTB TSC
- 43. Annemieke Brands, WHO GTB TSC
- 44. Sabine Verkuijl, WHO GTB TSC
- 45. Dennis Falzon, WHO GTB THC/RTE
- 46. Matteo Zignol, Coordinator, WHO GTB THC & RTE
- 47. Avinash Kanchar, WHO GTB THC
- 48. Lice Gonzalez-Angula, WHO GTB LDR
- 49. Nebiat Gebreselassie, WHO GTB RTE
- 50. Kefas Samson, WHO GTB TSC
- 51. Martina Penazzato, WHO HIV
- 52. Samvel Azatyan, WHO MVP
- 53. Marina Plesons, WHO RHR
- 54. Vindi Singh, WHO HIV