Midterm Review of the STEP-TB Pediatric TB Grant to TB Alliance

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Key Acronyms

AIDS	Acquired immunodeficiency syndrome
AUC	Area under the curve
BCS	Biopharmaceutics Classification System
BE	Bioequivalence
BRICS	Brazil, Russian Federation, India, China, South Africa
CDC	Centers for Disease Control and Prevention (USA)
CHAI	Clinton Health Access Initiative
FDC	Fixed-dose combination
E	Ethambutol
EBA	Early bactericidal activity
EMA	European Medicines Agency
EML	Essential medicines list
FDA	Food and Drug Administration (USA)
GCP	Good clinical practices
GDF	Global Drug Facility
GF	Global Fund
H	Isoniazid
HBCs	High-burden countries
HCW	Healthcare worker
HIV	Human immunodeficiency virus
HR	Isoniazid, rifampicin
HRZE	Isoniazid, rifampicin, pyrazinamide, ethambutol
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials Network
IP	Intellectual property
IJTLD	International Journal of Tuberculosis and Lung Disease
IUATLD	International Union against Tuberculosis and Lung Disease
KNCV	Koninklijke Nederlandse Chemische Vereniging (Royal Dutch TB Foundation)
LTBI	Latent tuberculosis infection
M	Moxifloxacin
MDR-TB	Multidrug-resistant TB
MOU	Memorandum of understanding
MSH	Management Sciences for Health
NiX	New Chemical Entities in XDR-TB
NGO	Non-governmental organization
NRA	National regulatory authority
NTP	National tuberculosis programs
Pa	PA-824 (Pretomanid)
PK	Pharmacokinetic
PmRN	Pediatric medicines Regulatory Network
PQ	Prequalified
R	Rifampicin
REMox	Rifampicin, Ethambutol, and Moxifloxacin
RTI	Research Triangle Institute (RTI International)
SHINE	Shorter treatment for minimal TB in children
SRA	Stringent regulatory authority
STAND	Shortening Treatments by Advancing Novel Drugs
STEP-TB	Speeding Treatments to End Pediatric Tuberculosis
TB	Tuberculosis
TBA	TB Alliance
UNICEF	United Nations Children's Fund
USD	United States dollars
WHO	World Health Organization
XDR-TB	Extensively drug-resistant TB
Z	Pyrazinamide

1. EXECUTIVE SUMMARY

Beginning in 2013, UNITAID granted TB Alliance USD 16.72 million over 3 years to increase and accelerate the availability of low-cost pediatric-friendly formulations of tuberculosis (TB) medicines. This is an independent midterm evaluation of the project initiated by UNITAID in February of 2015. The purpose of this review is to 1) assess the performance and impact of the project to date and 2) identify opportunities to improve the implementation of future projects.

Findings: Relevance was rated as HIGH

- **The agreement between UNITAID and TB Alliance targeted clear gaps in the pediatric TB market.** Prior to the start of the project, there were few, and widely disparate, data on the numbers of annual cases in children. Reporting gaps were recognized, but the magnitude was unclear. As a consequence of lack of data on the size of the pediatric drug market, the perceived lack of public health impact of childhood TB, and the unclear role of the private sector in treating childhood TB cases, there were few incentives for manufacturers to produce more pediatric-friendly formulations.
- **The project addressed 4 of UNITAID's strategic objectives**. The grant fulfilled 4 of UNITAID's 6 strategic objectives (Annex 1): increasing access to affordable pediatric medicines to treat TB (Annex 2); increasing access to emerging medicines and/or regimens, as well as new formulations or dosage forms that will improve treatment of HIV/AIDS and co-infections (which include TB); securing a supply of second-line TB medicines and increasing access to emerging medicines and regimens that will improve treatment of both drug-sensitive and multidrug-resistant TB; and increase access to products for the prevention of TB.

Findings: Effectiveness was rated as HIGH

- **The grant outputs were consistent with the objectives and expected outcomes described in the project plan.** When modifications were considered given budgetary allowances, UNITAID was involved in discussions about the changes. In several domains, more work was done on the grant than what was in the initial STEP-TB proposal.
- **The outputs predominantly were achieved with the timeframe specified in the initial project plan.** In some instances, timelines were delayed as an output took on a broader scope, and in other cases delays were outside the control of TB Alliance (e.g., market studies with China). That said, the vast majority of outputs were achieved either on time or earlier than the stated completion dates. Given the complexities of this project and the multidisciplinary nature of the STEP-TB project, the ability to adhere to timelines in this fashion is impressive.
- **Factors were considered to ensure that value for money has been achieved.** When some aspect of the project were under-budgeted (e.g., for output 4), TB Alliance discussed options for reallocation of those monies toward other aims; in this case, for bedaquiline studies in children. Conversations with manufacturers have emphasized the need to have affordable medicines; having 3 manufacturers producing medicines will help control prices via market competition.

Findings: Efficiency was rated as HIGH

- **TB Alliance can demonstrate that national authorities are aware and participating in grant activities at the national level.** Input was obtained from surveys sent to TB authorities in the vast majority of the 22 high-burden countries (HBCs). However, small numbers of respondents from each country and discrepancies in reporting from individual countries preclude more analyses. That said, TB Alliance increased visibility of the project during several meetings of the International Union Against Tuberculosis and Lung Disease (IUATLD), including discussion of the STEP-TB project at the meeting of the Childhood TB subcommittee. In addition, two regional meetings in Asia raised visibility among national authorities.
- **Grant implementation was cost effective and cost efficient.** As certain deliverables in the grant were found to not consume as many financial resources, these monies were redirected to new deliverables, including work on pharmacokinetic studies of bedaquiline.
- **Challenges were raised with the UNITAID Secretariat in a timely manner, and the Secretariat participated in resolving these challenges**. No issues were raised by UNITAID or by WHO. Despite the high turnover and some system changes (e.g., online reporting systems), personnel in involved in all aspects of the project were flexible and communicated well.
- **There were no issues related to potential diversion of products, counterfeit, or quality**. Medicines were supplied by manufacturers according to GCP, and WHO prequalification (PQ) will be sought (in many instances, these requirements are more stringent than national regulatory authority (NRA) requirements.

Findings: Impact and sustainability were rated as MEDIUM/HIGH

- **The grantee can report on impact as originally framed in the project plan and LogFrame.** TB Alliance found the LogFrame useful.
- **The grantee attributing UNITAID's financial support for medications purchased to patients tested and treated in each beneficiary country.** *Not applicable*.
- The impact for this study is high. My only concern for sustainability is that if TB Alliance leaves off with the stated outputs, there will still be gaps between medication availability through the GDF or other sources and uptake in the community. I feel that other measures should be considered that are currently beyond the scope of the grant as written to ensure that the drug formulations developed make it to the bedside. These are outlined more comprehensively in the Future Directions section following the review of Output 7 (Section 4).

Findings: Learning & risk mitigation were rated as HIGH

- **Lessons learnt have been documented and disseminated by TB Alliance and UNITAID**. Several white papers (Annex 3) have been published, as well as study results which have been published in the peer-reviewed medical literature. Lessons learnt also have been distributed through conferences and partner meetings. These strategies, when combined with a website accessible to clinicians, policy-makers, advocacy experts, and the lay public, allow for information to be disseminated to a broad group of persons with varying levels of knowledge of childhood TB.
- **Programmatic and financial risks have been identified and tracked over the course of grant implementation**. This was particularly the case in conversations with manufacturers, where a staged approach to fund distribution helped decrease financial risks, as monies dispensed were tied to tangible milestones for the companies.
- **The findings of the end-of-year one report have been used to improve grant performance**. These findings have been incorporated going forward.

Recommendations for future projects

Output 1:

- Develop a more robust infrastructure for gathering data on market size in terms of completeness of data for certain countries.
- Expand the consumption study to India and some sub-Saharan African countries

Output 2:

- Funding for pediatric portions of Pretomanid (PA-824) and NiX TB study
- Additional PK work on second-line drugs for MDR/XDR-TB disease and prevention

Output 3:

- Support national programs to streamline procurement. This can reduce delays between submission of applications and medicines being provided. In addition to increasing manufacturer confidence, it would reduce stock-outs of TB medicines. This may also entail ensuring funding (e.g., a bridging grant) is in place for the transition to new dosing formulations and for the scale-up of new treatments.

Output 4:

- Define 'accessibility' beyond the HBCs, as this strategy will relatively neglect Latin America, a region with relatively high incidence rates but where infrastructure cannot be compared to the BRICS.

Output 5:

- Provide technical assistance. Technical assistance can be used to help develop new treatment guidelines and training materials to support transitions to new formulations (e.g., weight-band dosing). In addition, technical support can help with forecasting, procurement, and budgeting of new treatments.
- Engage policy-makers and key opinion leaders to drive adoption at the national level

Outputs 6/7:

- Collaboration with other organizations focused on child health
- Links to TB Alliance website from UNICEF and other high-profile international organizations which focus on child health. Future goals include having childhood TB mentioned by child survival initiatives such as Promise Renewed and Double Dividend.

2. INTRODUCTION

2.1 Context

The STEP-TB grant by UNITAID to TB Alliance was novel for both organizations. For UNITAID, it was a departure from a historic focus on increasing access and optimizing the market around existing commodities already available. For TB Alliance, it was an extension of their previous work into the pediatric arena. The union came at an opportune time for childhood TB. Historically, childhood TB has been neglected under a variety of premises: 1) children are 'public health dead-ends' because they do not transmit *M. tuberculosis* as often or readily as adults; 2) difficulties in confirming the diagnosis microbiologically; 3) the difficulties of conducting studies in children; and 4) the perception that childhood TB simply was not a problem which warranted being addressed.

This situation fortunately has started to change over the last few years. While we still have innumerable gaps in data compared to what is known about TB in adults, there is now a critical mass of interest that has been generated to address these gaps and to provide better care to the most vulnerable population. The STEP-TB project is optimally positioned to address the gaps in market size using a multifaceted approach and to then use those data going forward to collaborate with industry to produce appropriately-dosed pediatric-friendly formulations of first-line TB medicines. The processes established in this study should be able to be adapted to second-line medicines.

2.2 Objectives of the Review

In early 2015, the UNITAID Secretariat initiated a mid-term evaluation of the STEP-TB grant to assess the progress of this 3-year grant over 18 months since project inception. This review was performed using in-person interviews with the TB Alliance staff in New York, telephone interviews with essential personnel at UNITAID and WHO (Annex 4), and desk review of documents (Annex 5). The objectives of this independent evaluation are two-fold:

- To assess the extent to which the project has achieved the agreed deliverables
- To recommend ways in which the lessons learned from this project could be used to improve future UNITAID projects, including certain tasks which would be logical extensions of the current grant and would fall well within the purview of what TB Alliance already has accomplished

3. FINDINGS

3.1 Output 1: Market data on the existing and potential pediatric TB market gathered to make the business case to manufacturers, donors, and governments

Table 1: Output 1 Deliverables

Deliverable	Timeline	Status
Global consultation on childhood TB estimates convened	Q4 2013	Complete
Model to estimate actual and potential market size developed	Q4 2013	Complete
Literature review of private sector pediatric TB treatment written	Q4 2013	Complete
Literature review of pediatric formulation acceptability written	Q4 2013	Complete
NTP and reported figures compared	Q1 2014	Complete
Qualitative survey of non-NTP facilities conducted	Q1 2014	Reassessed
Rapid assessment of policy and practice in HBCs conducted	Q1 2014	Complete
Sales from existing manufacturers quantified	Q2 2014	Complete
Contact tracing study finalized	Q2 2016	Reassessed
Procurement study in 19 HBCs	Q4 2014	Expanded, 2015
Consumption study in HBCs	Q4 2014	Expanded, 2015
Study on Chinese market size conducted	Q4 2014	Delayed, 2015
Procurement decisions in China analyzed	Q4 2014	Delayed, 2015

HBCs: high-burden countries; NTP: national TB program; TB: tuberculosis

Prior to approaching manufacturers, it was imperative that TB Alliance demonstrate that there was a sufficient market to justify entry into what may have been perceived of as a high-risk market. Extant data were insufficient to make this case, as it was known that childhood TB cases were underreported; what was not well recognized was the magnitude of the underreporting. To obtain a more realistic picture of the potential market, modeling studies were undertaken to provide better estimates of the burden. Collaboration with TB Alliance was reported as excellent by the WHO.

Global consultation on childhood TB estimates
A global consultation on pediatric TB was hosted by TB Alliance in New York in September of 2013 and included representatives from the WHO, UNITAID, GDF, CDC, KNCV, CHAI, the Sentinel Group, and representatives from several NTPs. The meeting was chaired by Steve Graham (Chair, Childhood TB Subgroup of the STOP TB Partnership) and Andrew Jones (Bill & Melinda Gates Foundation). Suggestions from the group included a market survey of non-NTP care in 5 Asian countries and survey manufacturers, pharmacies, and wholesalers currently selling TB medications to strengthen surveillance. In addition, several studies were recommended to better quantify the pediatric TB market. Many of these were integrated into the study output. In summary, several methods were identified to try to address the gap in existing numbers of childhood TB cases, and given that the methods address different portions of the market, the numbers should be complementary.

Model to estimate actual and potential market size
TB Alliance consulted with Peter Dodd of Sheffield University and James Seddon of Imperial College, London to model estimated cases of TB disease and infection in the 22 HBCs. Instead of starting with the usual estimates of pediatric notifications, the model used estimated numbers of cases in adults, knowledge of the population structure, household density, and epidemiologic data on numbers of latent TB infection (LTBI) cases caused by a given adult with pulmonary TB to estimate the pediatric burden of disease. Two models (transmission in the home, transmission in the community) were used and yielded similar results. Their estimates (~650,000/year) are higher than WHO estimates. Specifically, the authors noted that for children < 5 years of age, the majority of HBCs notified far fewer children than predicted by the model, likely due to: 1) difficulties in obtaining microbiologic confirmation of TB; 2) underdiagnosis as disease is attributed to pneumonia or other causes; 3) underreporting (particularly for children treated in the private sector). In addition, the authors estimated the number of children living with an adult with pulmonary TB who have acquired recent LTBI as 7.5 million. This number represents a huge pool of potentially preventable cases if effective LTBI regimens could be operationalized. The results have since been published in the *Lancet Global Health* in August of 2014. In summary, this report documented alternative numbers for burdens of TB disease in children and offered the first estimate of LTBI prevalence in HBCs.

Literature review of private sector pediatric TB
This updated literature review attempted to: 1) provide additional data on the size, structure, and market growth potential of the pediatric TB private sector and 2) to understand the availability of published research on this topic. To that end, medical literature searches (January 1990-September 2013) and searches in the grey literature were conducted using broad search terms. The former found no articles specifically addressing the study question. The grey literature search uncovered passing references to 2 Gates Foundation grants, but with scant detail. In summary, this review could not uncover data to assist in quantifying market size.

Literature review of pediatric formulation acceptability
This white paper by the TB Alliance focused on two issues that drive medicine acceptability for children: formulation type and palatability. Lessons learned from treatment of malaria and HIV in children were integrated into the document. The benefits and limitations of various formulations were reviewed. The strengths and relative lack of limitations of dispersible preparations were emphasized. Palatability of medications often has been ignored for pediatric formulations, but given the duration of therapy, adherence will decrease if parents have to fight with their children daily to take medications. One note is that flavors popular in some regions (strawberry, bubble gum) may not be recognized or be attractive in other countries. Palatability of the medication has to be balanced with not wanting to make medications

too attractive, lest children have unintentional overdoses, as formerly seen with acetaminophen. The document also reviews which flavors can mask unpleasant tastes. In summary, the research indicates that a dispersible tablet with a fruit-based (sugary) flavor would be most ideal and acceptable to children and their families.

Figures reported by national TB programs (NTPs)
At the study outset, TB Alliance planned to sample NTP facilities and their reporting to see if there were discrepancies in numbers reported to the NTPs versus numbers of children in treatment reported by NTPs to the WHO. However, this plan was reassessed after discussions with the WHO and NTP personnel indicated that such a study would be extremely time-consuming and unlikely to reveal significant reporting discrepancies. As such, the decision was made to focus on the rapid analysis of children treated outside of NTPs, where discrepancies in under-reporting and inappropriate treatment were thought to be greater. Of note, some of the effort needed around the rapid analysis was folded into the inventory studies, which will better elucidate the role of the non-NTP sector.

Qualitative survey of non-NTP facilities
This rapid assessment by 3 national consultants focused on the role of non-NTP facilities in 3 HBCs (Indonesia, Nigeria, Pakistan) to understand where children with TB may receive care, the numbers currently treated (and likely not reported to NTPs), understand how children are diagnosed and treated, and to better understand the relationship between non-NTP facilities and the NTPs. Nigeria differed from the other 2 nations in terms of having few children with TB reported to the NTP and also having a limited role for the private sector in the treatment of childhood TB. The results demonstrated the heterogeneity of where care is housed: pediatricians (Indonesia), private hospitals (Nigeria), and/or laboratories (Pakistan). In some countries, a few high-volume centers provided the majority of private-sector care, and sampling of these facilities would have added substantially to the number of cases reported to the NTP. In some countries, even if care was readily available via the NTP, caregivers continued with care in the private sector. In summary, the size of the private sector market was difficult to elucidate from this study, but was widely variable by country, and substantial reporting gaps to the NTP existed.
A second study of non-NTP facilities was conducted in South Africa in private-for-profit medical facilities. It was estimated that the role of the private sector here is low. Although 17% of the population seeks care in this venue, TB treatment is not covered by insurance, private doctors/hospitals do not manage TB patients beyond diagnosis, and long-term drug supplies are not available in this arena. However, challenges exist with many patients lost to follow-up in the transition between the private sector and the NTP. In summary, this study suggested a minimal role for the private sector, but important considerations when patients are transitioning between the 2 sectors. The timelines for the qualitative survey have been extended because it has been rolled into the larger inventory study.

Rapid assessment of policy and practice in HBCs
This online questionnaire served as a preliminary needs-assessment for HBCs to address topics in several domains: national policy; current practice; activities to increase adherence with the 2010 WHO guidelines; and the perceived role of the private sector. Sixty-three of 228 (28%) responded from 20 of 22 HBCs, with 2-4 persons answering each question for each country. The small sample size precluded subgroup analyses. While all 20 responding countries had national pediatric TB guidelines, only 50% had guidelines incorporating the 2010 WHO dosing adjustments. There was in-country heterogeneity in reporting of uptake of the new guidelines by clinicians. Variation also existed in terms of what drug formulations were available for children. The role of the private sector was deemed important by over two-thirds of respondents, but the exact role of the private sector for childhood TB was difficult to quantify. In summary, this survey demonstrated the wide variation in the available care of children with TB in HBCs.

Sales from existing manufacturers quantified
TB Alliance contracted with Results for Development (R4D) to obtain data on the existing sales of pediatric TB drugs as another way to assess market size. While a few manufacturers agreed to share data, the data obtained were insufficient to allow for more accurate market projections. Consequently, other sources of data (modeling study, procurement and inventory data) will be used to address this issue.

Contact tracing study
The decision to conduct this study was reassessed. After collaboration with global experts, the decision was made to defer this study. Several studies have indicated that contact tracing works and that it decreases time to diagnosis and initiation of effective treatment for children. With contact tracing, children are diagnosed earlier, with attendant decreases in morbidity and mortality. While the impact of contact tracing may be slightly diminished in hyper-endemic settings (e.g., the Western Cape of South Africa), the effectiveness of contact tracing is not questioned. It was decided that more effort should be on operationalizing and scaling up contact tracing in the HBCs.

Procurement studies: HBCs
This project started with the analysis of the GDF data. In December of 2014, TB Alliance entered into an agreement with Management Sciences for Health (MSH) for a procurement assessment for adult and pediatric medications for first-line therapy and for the treatment of MDR-TB. MSH will provide overall coordination for the study, but it will be conducted by different partners (CHAI, MSH, individual consultants) in 19 of the 22 HBCs (all except Indonesia, Mozambique, and Zimbabwe). MSH will address the following issues: criteria influencing procurement decisions (e.g., price, necessary approvals, policy recommendations); procurement requirements; procurement processes (NTP and private sector) and policy adoption processes in nations; current procurement practices; necessary steps to facilitate rapid procurement (including fast-track and waiver mechanisms); and identification of key stakeholders. The inception meeting has already occurred, and a report on procurement drivers, policies, and practices is expected in late February. The final reports are anticipated to be available in June of 2015.

Consumption studies: HBCs
The purpose of the consumption studies is to validate how much of the TB medicine that is procured is likely to have been dispensed to patients, including where and when. The above procurement study and the other work support broad quantification at national and international levels. The consumption study identifies gaps and problems in downstream supply mechanisms. While the STEP-TB initiative is not designed to do capacity development in local supply chains, it is important to identify any gaps in reaching people. The study will identify average consumption, stock out problems, correspondence of consumption to national forecasts and an analysis of any problems in supply mechanisms. This study, managed by WHO in collaboration with individual ministries of health, will evaluate components of the supply chain in different nations. Data on the supply chain management system will be collected from 3 levels: national; district; facilities. Attempts will be made to disaggregate pediatric and adult data. These variables will include average consumption, days of stock-outs, and the degree to which forecasted needs met actual demand.

Study on Chinese market size and procurement strategies
China was specifically selected because of the large estimated market size, the low official numbers of children reported, and in-country interest for obtaining better data. The timeline for this study has been dictated, largely, by China. As such, there are delays in some of the deliverables that are outside the control of the TB Alliance. However, significant steps have been made. Historically, the Chinese manufacturing market has not seen the pediatric market as sufficiently large to garner attention. In the last 2 years, China has participated in regional workshops on childhood TB sponsored and conducted by the WHO and TB Alliance, and Chinese participants followed this up with training sessions for pediatricians in China. China also attended another regional workshop in September of 2014 in Thailand and seems much more engaged than in the past. TB Alliance has established a relationship with one Chinese pharmaceutical, Fosun, for adult TB medicines, and linked them with one of the TB Alliance-associated manufacturers of pediatric products. China will be conducting an inventory study in 2015 with retrospective design.

Inventory workshop: HBCs
This is an additional project, in collaboration with WHO, not covered in the initial STEP-TB proposal to better evaluate where patients are treated outside of NTPs. Dr. Babis Sismanidis from WHO was interviewed about this output. A significant amount of the market research was not defined in the initial proposal but was outlined after the Global Consultation in the market plan. This survey is designed to help distinguish between under-reporting versus under-diagnosis of pediatric TB. Countries are targeted if

it is known that there is a large private sector (e.g., Indonesia, Pakistan, Philippines, Thailand, Vietnam) or if the reported numbers of cases are much lower than expected (e.g., China). In the latter, the issue is one of under-diagnosis. The first step will be mapping locations were TB is treated in a given region, and see how the numbers there compare to the numbers reported. This will both help identify sites of treatment and under-reporting. While China and Thailand's inventory studies will be retrospective (due to both countries having many laboratory or insurance data available electronically), in most of the other countries, data collection will be prospective with real-time on-the-ground data collection. The data generated here will help revise the global estimate for childhood TB in addition to allowing for better in-country estimates. Thailand is proceeding with country-level training and orientation of physicians. Indonesia, Pakistan, and Vietnam have submitted protocols currently under review by WHO; WHO is hoping to finalize the protocols for Indonesia and Pakistan in April of 2015, with the goal of starting data collection at the end of Q2 or the beginning of Q3 2015. The Chinese public health authorities are starting data collection there, and have requested statistical technical assistance from WHO to facilitate this process. Prospective data collection will be over 3 months, followed by validation and modeling estimates. The majority of countries will be completed within the project timeframe and all within budget, but there are several countries still in progress (e.g., Philippines – as this country is conducting a prevalence study this year, they may push back the inventory study until early 2016). WHO expects to have some preliminary data back from several nations by mid-2016.

Lessons Learnt:

- Market size estimates:
    - These will require data input from a number of sources to try to bridge the gap between reported and expected numbers of children with TB disease. That children remain underreported to NTPs and undiagnosed/untreated is also not in question; the issue is more of the magnitude of this under-diagnosis and underreporting.
    - There is a significant role for the non-NTP sector and building linkages to this sector will be critical for uptake of new pediatric formulations.
    - Current market size estimates from existing manufacturers is difficult to quantify, especially in countries where children receive adult formulations of medications or where TB statistics are not disaggregated.
- Inventory study:
    - A *no-cost* extension may be needed for the inventory study given the time frames for the collection of prospective data from 4 nations.

3.2 Output 2: Clinical data necessary for regulatory approval of new formulations

Table 2: Output 2 Deliverables

Deliverable	Timeline	Status
Summaries of consultation with SRAs, WHO PQ, others	Q1 2014	Data collection completed, analysis in progress; mid-2015
Report on data requirements for HRZE formulations	Q2 2014	Completed
Preliminary results from PK study of children < 5kg	Q4 2014	Completed
Dosing recommendations for children < 5kg	Q2 2015	On track
Decision on development of pretomanid (PA-824) in children	Q1 2014	Completed
Pediatric study plan for pretomanid (PA-824)	Q4 2015	Completed*
Decision on development of moxifloxacin in children	Q4 2014	Reassessed
Pediatric study plan for moxifloxacin	Q2 2015	Delayed, late 2015

HRZE: isoniazid, rifampicin, pyrazinamide, ethambutol; PK: pharmacokinetic; SRA: strict regulatory agency; WHO PQ: World Health Organization Prequalified

*study plan completed; the ability to study pretomanid in children is delayed by safety concerns (see below)

There is substantial heterogeneity and a lack of transparency in the requirements for regulatory approval for outside of SRAs, where regulatory approval processes are heterogeneous. Many of the HBCs and other high-incidence nations do not have a unified approach to adult medicines, much less pediatric medicines. Some countries use WHO PQ to bolster national regulatory processes, whereas other countries want specific BE data or data in children in their nation prior to regulatory approval. Having a better sense of what specific country requirements are will help determine the extent to which regulatory harmonization will be possible.

Summaries of consultations with SRAs, WHO PQ, other regulators, manufacturers
TB Alliance is exploring with the national regulatory authorities (NRAs) in the HBCs. TB Alliance has already determined what the WHO PQ requirements will be. The initial plan was to compile regulatory requirements for the FDA and EMA, but then it was realized that drug distribution will not be to nations covered by SRAs, so the focus was shifted to focus more on how to get the medicines prequalified. Through consultation with Dr. Valerio Reggi, who has expertise in regulatory affairs, the TB Alliance Market Access group will gather information on national requirements, opportunities for expedited review, and pediatric-specific requirements for both for new formulations of existing medicines (Output 2) and for new medicines (Output 3). This desk study will focus on HBCs outside of Africa. The reason for this is that all the HBCs within Africa, with the exception of South Africa, have signed on to the WHO collaborative registration scheme, which harmonizes registration processes for countries with WHO PQ. As the scope of the work has expanded, the timeline has been modified accordingly. In addition, the timelines have shifted, with the idea to have meetings closer to when the medicines will be available. Meetings have already been had with WHO PQ. The change from the initial proposal was to use a consultant with extensive information on regulatory authorities in HBCs to get as much information as possible before TB Alliance approaches specific regulatory authorities which would require more engagement due to stricter requirements or where the manufacturers have a challenge getting medicines into the country.

Report on data requirements for HRZE formulations
Manufacturers and TB Alliance have been consulting with regulatory agencies on registering new formulations of existing drugs; most of these conversations are confidential. However, general themes emerged. In response to concerns about what would constitute an appropriate comparator group for FDCs, comparator products and purchase information were obtained from the WHO PQ. The mechanism for obtaining a biowaiver in lieu of a performing a BE study was clarified. Follow-up on these requirements will occur when the TB Alliance meets with the Pediatric medicines Regulator Network (PmRN); this is discussed in Output 3. The study being conducted by Dr. Reggi will help support this aim as well.

PK study of first-line medicines in infants
This study, carried out in collaboration with Stellenbosch University and the University of Cape Town (UCT), evaluated the PK of HRZ in infants. Conversations began prior to grant submission, and protocol development, regulatory approval, and study initiation occurred promptly after funds were dispensed. This timeline was streamlined by several factors: 1) use of registered products avoided additional regulatory processes, as children were receiving the standard of care; 2) granting process was made easier because TB Alliance had already done prior studies with Stellenbosch; and 3) partnering with Helen McIlleron at the UCT, who already had an existing grant for PK. TB Alliance served as a liaison between Stellenbosch, which cares for a population in a hyperendemic region, and UCT, which brought PK expertise. Interim results on 19 infants were available (Table 3) in the fall of 2014. Levels of H and Z were in the therapeutic range, but rifampicin levels showed wide variation, with some infants showing little evidence of drug absorption. These findings resulted in modifications during the second part of the study, as the rifampicin dose was increased to 20mg/kg. Given that many infants enrolled weighed more than 5kg at study entry, it would perhaps be best to conceptualize this as an infant PK study. Enrollment in the entire cohort has now concluded, and study results are expected in the spring of 2015.

Pretomanid (PA-824) in children
Pretomanid, a nitroimidazole with excellent penetrance into tissue, has been shown to have good early bactericidal activity in a 14-day period in a TB Alliance-sponsored study published in the *Lancet* in 2012 (Table 3). Phase III studies in adults (STAND study) are just beginning enrollment. Certain serious adverse events (testicular necrosis, lens opacities) have been seen in murine models, but not in non-

human primate models. However, until a formal semen analysis is done in adults (a planned sub-study in STAND), the plans developed to study this medicine in children cannot move forward. It is anticipated that these data in adults will be available in Q4 2016, at which point, assuming the same effect is not seen in humans, TB Alliance will encourage PK studies in children and against dose de-escalation, realizing that this policy considerably slows down the time to approval for younger children. In the interim, a juvenile toxicity program needs to be in place if children are to be dosed with the full Pa-MZ regimen, and canine models do not work for this drug. Given the cost of using non-human primate models, these studies may be cost-prohibitive for the TB Alliance to perform using existing funding and is not part of the current scope of work of the STEP-TB project. I would suggest that UNTAID consider providing additional funds to TB Alliance for this work, under the principle of accelerating entry of medicines into the marketplace.

Moxifloxacin in children

A rate-limiting step to data on fluoroquinolones in children is that manufacturers have limited interest in seeking additional indications for medicines that are now generic. Several data elements are inadequately described for children, including: long-term adverse events; PK; and optimal dosing (with and without concomitant rifampicin administration). In recent years, moxifloxacin has been the focus, as opposed to levofloxacin, in part because of the ease of single-daily dosing of the former drug. A preliminary expert meeting was held at the 2014 IUATLD meeting in Barcelona to discuss the merits of one fluoroquinolone over the other, and this will be followed up both by webinars and by another meeting at the December 2015 IUATLD meeting in Cape Town. While the STEP-TB study has focused more on moxifloxacin as it comprises part of the PaMZ regimen and was part of the REMox study, both medicines will be in use for years, and obtaining optimal dosing data for both drugs, as well as palatability concerns for moxifloxacin, is needed. The decision to move moxifloxacin forward, though not as part of the REMox study, has been made. Efforts to date on the part of TB Alliance will focus on consultation, for example, with Anneke Hesseling's group in Stellenbosch, who will provide updated data on fluoroquinolones in advance of the 2015 IUATLD meeting.

New activities

With reallocation of funds initially earmarked for manufacturer engagement, TB Alliance has been able to extend efforts toward several other activities. These include:

- Bedaquiline: this previously UNITAID-approved collaboration with TB Alliance and Janssen has already resulted in development of a pediatric formulation for bedaquiline. PK studies (Table 3) are planned. While this study will not enroll HIV-infected children, a parallel study by IMPAACT will. This represents a shift in the drug development paradigm where medicines are only studied in children long after their use in adults has been proven, if at all.

Allied or Similar Interventions in Pediatric Tuberculosis outside the Project

- Levofloxacin: in addition to the studies mentioned above, TB Alliance has facilitated levofloxacin entry into the marketplace by facilitating Macleods' production of pediatric formulations of levofloxacin for the Stellenbosch group to use in a study of MDR-LTBI in children. Given the almost complete lack of systematic studies on use of second-line drugs for the treatment of MDR-LTBI, the findings of this study will be significant irrespective of the findings. This study is proceeding with technical support from TB Alliance, but no specific funding for this project exists in the STEP-TB grant. TB Alliance is attempting to create consensus around the use of fluoroquinolones in children; there is no budgetary impact or request for funding reallocation.
- NiX-TB study: this study of pretomanid, linezolid, and bedaquiline for patients with XDR-TB will enroll patients down to 14 years of age. Adolescents are a population that has been poorly studied in childhood TB, as their care often is fragmented between pediatric and adult providers. Having pediatric-specific data on this group is an important step in optimizing care for this historically disenfranchised group. This study is proceeding with support from TB Alliance, but no specific funding for this project exists in the STEP-TB grant and there is no request for funding reallocation.

Lessons Learnt:

- WHO PQ: Meeting PQ requirements, which in many cases are more stringent than NRA requirements, is a conservative way to try to best position a dossier for acceptance in more than one nation given the heterogeneity in regulatory processes.
- Key Opinion Leaders in NRAs: In a given region, there may be certain countries where, if regulatory approval is obtained there, other countries in the region may follow. One example is the extent to which South African policies for TB may rapidly be adopted by sub-Saharan African nations. To the extent possible, determining what the requirements are in these countries may facilitate regional adoption of medicines.

Table 3: Study Results, Output 2

Variable	Study 1	Study 2	Study 3	Study 4*	Study 5*
Research question addressed	PK of HRZ in infants	Use of pretomanid, Moxifloxacin, and Z (PaMZ) for drug-susceptible TB compared to standard regimens and bedaquiline-containing regimens (Phase IIa)	Substitution of Moxifloxacin for H or E in a 4-month regimen for pulmonary TB	Bedaquiline PK in children	NiX study: PA-824, linezolid, and bedaquiline for patients with XDR-TB disease
Target population	Infants < 5kg with suspected TB disease receiving HRZ. Of note, most of the infants were 5-10kg, not < 5kg	Treatment naïve patients with uncomplicated drug-susceptible pulmonary TB	Adults with smear-positive, pan-susceptible pulmonary TB	60 subjects, 15 in each of 4 cohorts (12-18; 5-11; 2-4; <2y)	Adolescents, adults with relapsed XDR-TB disease
Hypothesis	There is more variation in drug PK in infants than in older children	Use of newer drugs may allow for shorter treatment durations and decrease time to smear conversion	Use of Moxi can decrease regimen duration	Optimize bedaquiline dosing in younger children (oldest cohort will use adult dosing)	NiX regimen may allow for a 6-month treatment and may be a safer option for patient with XDR-TB
Methodology	Prospective observational PK cohort study using current WHO doses of HRZ.	Prospective RCT in Cape Town using multiple medication combinations	Prospective multicenter RCT	Prospective PK cohort study, age de-escalation protocol with 24 week treatment added to background regimen	N/A
Data collection	PK data: C_{max}, T_{max}, $T_{1/2}$, AUC for each of the 3 TB medications	Daily changes in CFU from sputum samples	Treatment failure or relapse; time to smear negativity	PK data: C_{max}, T_{max}, $T_{1/2}$, AUC	N/A
Results	19 infants as of 9/2014, 10 of whom HIV-exposed. Substantial variation in R levels, considerably lower C_{max}. Doses for H, Z achieved levels c/w what has been seen in older children. 3 infants developed transient transaminitis not requiring dose adjustments. In one-quarter, no evidence of R absorption. No apparent interaction with NGT administration. R dosed increased in 2nd cohort; enrollment completed, results pending	14-day EBA of the study regimen was equivalent to standard regimens and better than bedaquiline-containing regimens. One patient had treatment stopped due to QTc prolongation.	Both arms of the 4m regimen (Moxi substituted for H or E) was *not* noninferior to traditional regimen; 6 month course was noninferior	N/A (enrollment to begin in Q2 2015)	N/A (enrollment has not yet begun)
Pending research questions	R levels low because of low absorption or rapid metabolism? To what degree do lower levels impact clinical outcomes, including development of secondary resistance?	Adult trial has concluded (Lancet 9/2012). STAND Phase III study is just starting	Adult trial has concluded (NEJM 10/2014)	Multiple; few pediatric data known on optimal bedaquiline dosing	Similar to study 2, progress contingent on testicular safety data from STAND study

New research questions raised	Further study of R dosing – after interim analysis, dose increased to 20mg/kg. Can administration with orange juice increase gastric pH and increase absorption? Is weight-banded dosing appropriate for infants?	Safety and tolerability when given over longer time periods?	Would use in children, who have paucibacillary disease, yield different results?	Optimal bedaquiline dosing if administered with R? Optimal dosing in children receiving ARVs?	Safety and tolerability when given over longer time periods?
Other research questions related to hypothesis	Significance of transient transaminitis in this population (response: add another LFT measurement)	Need juvenile toxicology program before administration of multiple doses to children	SHINE study also hopes for shorter-course regimens, but with standard HRZE		Need juvenile toxicology program before administration of multiple doses to children
Related developments & policy initiatives	Does WHO dose for R need to be increased in young children?	Pediatric studies to be delayed until testicular toxicity issue addressed in a planned subanalysis of the STAND study	Will there be a lack of interest in repeating this study in children due to perceived small market size?	Currently no published data on this topic in children	How to include younger children in the study process from earlier in the study period once safety has been demonstrated and some initial PK data are available?

ARVs: antiretrovirals; AUC: area under the curve; E: ethambutol; EBA: early bactericidal activity; FDC: fixed-dose combination; H: isoniazid; LFT: liver function test; N/A: not available; PK: pharmacokinetic; R: rifampicin; RCT: randomized controlled trial; TB: tuberculosis; WHO: World Health Organization; Z: pyrazinamide

*additional study beyond those planned in the initial STEP-TB proposal

3.3 Output 3: Clear regulatory pathways used by manufacturers and regulatory agencies for new and existing pediatric TB medicines

Table 4: Output 3 Deliverables

Deliverable	Timeline	Status
Summaries of consultation with EMA, FDA, WHO PQ, manufacturers, and other regulators	Q1 2014	Data collection complete, analysis in progress; mid-2015
Report summarizing regulatory advice on the pathway for pediatric medicines	Q1 2015	Delayed, Q2 2015
Meeting summary from clinical experts meeting	Q1 2015	Revised, 2016
Pediatric development pathway white paper	Q2 2015	Completed
Written endorsement from PmRN	Q4 2015	On track

EMA: European Medicines Agency; FDA: Food & Drug Administration (USA): PmRN: Pediatric medicines Regulators Network; WHO PQ: World Health Organization Prequalification

Similar variation exists in the approval for new medicines as exists for new formulations of existing medicines, with the exception that additional data (safety, PK) will be required prior to approval. Again, these processes are not consistent across nations, nor are they always transparent. To that end, several deliverables are associated with this output.

Summaries of consultations with EMA, FDA, WHO PQ, other regulators, manufacturers
This summary will focus on understanding how global regulatory authorities approach new pediatric medications, as opposed to the new formulations of existing medicines described in Output 2. Similar to Output 2, the scope of this deliverable has expanded, necessitating alterations in the timeline. The goal here is to obtain general info on how to accelerate the field for future medicine and regimen combinations. This will start with gathering data that is already known about FDA/EMA and other agencies to see if these requirements can be harmonized. Then, NRAs will be approached for specific requirements. This will be performed by collaborating with the Research Triangle Institute International (RTI) to collect data to define the landscape. Specific questions in this domain include: the need for preclinical data prior to extrapolating adult data to children; the need for age de-escalation; if having PK and safety data alone, without accompanying efficacy data in children, will suffice; if countries would be willing to approve based on studies conducted outside their borders; is a pediatric plan necessary in each country. Following this, TB Alliance may then approach specific regulatory groups to see how aware they are of the regulatory requirements of others. Data collection for this aim was completed in March of 2015; final deliverables will be shared with UNITAID once they are available.

Report summarizing regulatory advice on the pathway for pediatric medicines
The data surrounding regulatory advice on pediatric medicines will be disseminated in a number of venues. A paper has been accepted by *Lancet Infectious Diseases* (Sharon Nachman is the first author, with several TB Alliance members as co-authors) summarizing the results of an international panel of childhood TB opinion leaders around drug development. The RTI review of discussions with the FDA and EMA will be disseminated. TB Alliance will set up meetings with NRAs, possibly via PmRN. Finally, there will be a supplement on pediatric TB drugs in IJTLD which TB Alliance will be spearheading.

Meeting summary from clinical experts meeting
The time frame on this has been revised, in keeping with modifications made the deliverables above. The plan is to meet with regulatory and harmonization experts after the above reports become available. These issues actually pertain far more to regulatory experts than to clinicians, and having the advice of the former will be more useful going forward than the latter.

Pediatric development pathway white paper
This collaboration between TB Alliance and the Solution Lab described market dynamics, challenges, and solutions in the pediatric TB drug market. Participants included TB Alliance, GF, WHO, CHAI, and 3 manufacturers, 2 of which ultimately signed MOUs with TB Alliance (Lupin, Svizera) and one which did

not (Sandoz). Table 5 summarizes potential barriers and solutions. This also meets a deliverable in Output 1.

Table 5: Barriers and Solutions to Concerns in the Pediatric TB Medication Market

Barrier	Solution
Inappropriate formulations	Development of dispersibles or other pediatric friendly formulations
Storage requirements	Stability trials in higher temperatures found in most HBCs
Poor estimates of market size	Sufficient market case and preventing market fragmentation
Variation/inefficiency in regulatory processes	Accelerate drug registration process and standardize requirements for approval across nations
Lack of HCW education resulting in underdiagnosis	HCW education via technical assistance

HBC: high-burden country; HCW: healthcare worker

Written endorsement from PmRN

There is a meeting of the PmRN in 2015 around existing products; there was not a meeting last year. At this time, the summary of consultations by RTI will be available and then TB Alliance can make a case for how to approach the pediatric drug market. One approach would be to follow FDA/EMA/WHO PQ guidelines to start and see if that approach is deemed acceptable by the HBCs. This meeting with PmRN should help guide future policy on this issue. What is desired is a regulatory pathway that includes contributions from the PmRN and options that they are willing to promote. The process to achieve this is through development of strategies that fit the regulatory frameworks of HBCs. Given that HBCs have vast differences in their regulatory environment, the overall regulatory approach includes options that would be applied to categories of country regulators based on their regulatory maturity and ability to participate in collaborative processes with other regulators. Very weak regulators will require assistance, moderate level regulators will be encouraged to rely on an information sharing scheme with WHO PQ, and more mature regulators will need a country by country approach, but one that should aim to reduce redundant clinical studies in the regulatory processes.

Lessons Learnt:

- Requirements to produce medicines in the country: some countries insist that at least part of the manufacturing process occur within their borders. While this can increase country capacity, this often sacrifices cost to achieve this goal and creates fracturing of the supply globally. One option would be to have some stages of the manufacturing process (e.g., packaging) occur in-country. For other countries, pairing a manufacturer with an in-country distributor may suffice.
- Funding of pilot data needed for approval: some countries (e.g., the Russian Federation) will require a BE study to be done in-country prior to approval being obtained, as well as a source to pay for medicine registration. The approach to this may well differ between the BRICS and the other HBCs.

3.4 Output 4: Commitment of at least 1 manufacturer secured to ensure timely and global availability of new pediatric TB formulations

Table 6: Output 4 Deliverables

Deliverable	Timeline	Status
List of potential regional and global manufacturing partners	Q3 2013	Complete
Executive summary and PowerPoint presentation outlining business case	Q3 2013	Complete
Signed MOU or agreement from first manufacturer	Q3 2013	Complete
Signed MOU or agreement from second manufacturer	Q1 2014	Complete
Manufacture of clinical supplies to support Phase I study	Q1 2015	On track
Initial abbreviated stability data	Q4 2015	On track

MOU: memorandum of understanding

The goal of this output was to ensure that more than one manufacturer was interested in developing new pediatric TB medications for at least two reasons. First, this helped assure competition in the marketplace, which will assist in assuring the UNITAID principle of *affordability* of medications. Second, this strategy will assure that the supply chain can meet the anticipated need (latter discussed in Output 1); this addresses the UNITAID principle of *accessibility*. Having too many manufacturers enter this relatively small market would have resulted in market fragmentation and decreased interest on the part of manufacturers.

TB Alliance has already secured an agreement with Macleods and MOUs with Svizera and Lupin. Several core criteria were evaluated prior to selection of these manufacturers. The core criteria included: current manufacturer of TB medications; experience formulating new dosage forms of existing medications; ability to obtain WHO prequalification; adequate production capacity; ability to export, register, and have products meet regulatory requirements in low/middle income nations; consistent and timely supply of medications to GDF and other procurement agencies; and overall interest in supply of pediatric TB drugs to the international community. These 3 companies shared some features that may have made them more amenable to working on pediatric TB medications. First, they had existing interest in TB medications in adults, and may have viewed extension into the pediatric market as complementary. Second, they had connections to the GDF already, and may have considered this a more stable market for a financially less desirable group of medications. Third, as they were accustomed to producing generic drugs, they were also more familiar with lower cost margins, and thus the risk of a niche market for pediatric TB drugs may have been considered more acceptable. Fourth, many had a history of producing fixed-dose combination tablets, and felt comfortable expanding that technology. Two other manufacturers meeting most of these requirements were considered for partnerships, but this fell through as either they had experience with FDCs but none in TB (Teva) or had experience in TB drugs but to gear them up to produce pediatric FDCs would have been prohibitive in terms of both cost and in the time frames needed (Sanofi).

To ensure broad distribution of drugs, TB Alliance is helping manufacturers pair with existing TB drug manufacturers in HBCs to obtain regulatory approval and avail themselves of established supply chain pathways. For example, Macleods is working with Fosun in China, and they will work to pair one of the 3 manufacturers with Sanofi-South Africa to address another BRICS market. This addresses the access principles of UNITAID. Finally, rediversion of surplus funds initially earmarked for approaching manufacturers has been directed toward working with Janssen to support pediatric development of bedaquiline.

Macleods

On March 7, 2014, TB Alliance and Macleods signed a manufacturer cooperation agreement to produce 2 pediatric FDCs (HR, HRZ) and 2 single tablet doses of H and E (Table 7). The understanding was that drug production would focus on taste in addition to variables embedded in good clinical practices (GCP) and that the medications produced would be produced as quickly as possible and at affordable pricing. This meets UNITAID principles of *affordability* and *accessibility*. Following drug development, bioequivalence studies for FDCs would be completed and WHO PQ would be approached for Expert Review Panel approval pending prequalification by the WHO. In addition, regulatory approvals would be sought in individual HBCs. Of note, Macleods also produces dispersible formulations for moxifloxacin, levofloxacin, and ethionamide; these are prototypes at this stage and funding has not been secured to take these products to market. However, their preliminary work indicates that this company would be an optimal partner for extension of pediatric TB medications into second-line medicines.

A telephone interview with Vijay Agarwal of Macleods revealed initial manufacturer concerns about drug development. This company had just finished obtaining PQ for the lower-dose FDCs when the 2010 recommendations were released. This led them to be concerned about market demand and they initially were unwilling to risk taking on the development costs for new formulations. This was resolved by having TB Alliance pay for some of these development costs. Second-line drugs are viewed as even riskier, as there are fewer data as to market size. Consequently, they anticipate developing new formulations of second-line drugs only if they receive external funding for this. Their only suggestion for improvement of their processes was to get administrative approvals and agreements signed in a more timely manner.

Their only intellectual property (IP) concern was about their IP being used by another company, and this was resolved by specifically mentioning in the agreement that their IP could not be used by another company unless they defaulted.

Table 7: Progress in Pediatric TB Drug Development, Macleods

Drug	Dose (mg)	Stability	Disintegration time (sec)	Taste	BE data
HRZ FDC	H 50; R 75; Z 150	3 month, satisfactory	20-30	Good (strawberry)	Underway
HR FDC	H 50; R 75	3 month, satisfactory	20-30	Good (raspberry)	Completed, results pending
H	100	2 month data pending	20-30	Good (raspberry)	Planned
E	100	12 month data pending	< 60	Good	Underway
Z*	150	1 month data pending	60-120	Good (orange)	Planned

BE: bioequivalence; E: ethambutol; FDC: fixed-dose combination; H: isoniazid; R: rifampicin; Z: pyrazinamide

*already produced for the Indian market (not under the auspices of STEP-TB); results shared with TB Alliance.

Lupin

On 1 June 2014, TB Alliance and Lupin signed an MOU to produce 2 FDCs (HRZ, HR). The understanding was that the focus would be on optimizing taste, in addition to meeting GCP requirements. In addition, the MOU discussed commercialization in terms of facilitating widespread use and low, sustainable competitive pricing for products. These meet the UNITAID principles of *access* and *affordability*. Similar to the arrangement with Macleods, BE and stability studies are planned, and WHO prequalification status will be sought. Their deadline is the end of 2015, but they are likely to have results in the fall, and in contrast to Svizera and Macleods, Lupin products have 3-year shelf lives.

Svizera

On 26 September 2013, TB Alliance signed an MOU with Svizera to produce 2 FDCs (HRZ, HR). The MOU was very similar to that described above for Lupin. At this point, Svizera is unwilling to perform BE studies for 2 reasons: 1) the possibility that they will not be needed if the drugs are categorized as BCS class 1; and 2) in the absence of an equivalent comparator product, they would prefer SRA guidance on how to best proceed for BE studies so that these studies do not need to be replicated in slightly altered format to achieve approval in other countries. That said, Svizera is preparing to do a BE study so that there will be no delay if they are required to do one. As with Lupin and Macleods, Svizera is on track to meet deliverables. Dr. Boudewijn Ploos van Amstel from Svizera was interviewed 5 March 2015. His company was comfortable taking on the financial risk of drug development because of the market size estimates provided by TB Alliance and the sense that this was their corporate responsibility; they stated feeling the same way about second-line pediatric formulations. They had no intellectual property concerns. They felt that the process by which companies were selected for partnership with TB Alliance was equitable, and had two suggestions on how to improve processes. The first was to provide more technical guidance on the regulatory processes. Svizera was hoping for more feedback on how to best proceed with a BE study (please see above), and was hoping for a more concrete pathway to have been laid out in conjunction with TB Alliance. Their second suggestion was increased transparency between the companies engaged to share lessons learned. Finally, this company's representative worried that paying for developmental costs for some companies and not others would create unequal footing between competitors, but understood why some companies needed more support than others.

Janssen

TB Alliance and Janssen are collaborating on the Bedaquiline Pediatric Program since mid-2014. However, the organizations have a track history of collaboration dating back to 2009, when TB Alliance received exclusive rights to bedaquiline for drug-susceptible TB. Janssen achieved conditional approval for bedaquiline via the EMA in March of 2014. The pediatric collaboration was a natural evolution of this and consistent with TB Alliance's unified drug development pathway from drug-susceptible to drug-

resistant TB. Phase 2 trials and conditional approval are usually achieved prior to embarking on a more extensive pediatric plan. In mid-2014, it became clear that TBA had access to funds that could be reallocated from other aspects of the STEP-TB project, and an agreement was signed to allow TBA to take a more formal role in the process of BDQ development. Janssen is still driving the regulatory process; TBA is providing support. Myriam Haxaire-Theeuwes from Janssen was interviewed on 11 March 2015. From an intellectual property standpoint, this relationship is quite different than that with other manufacturers, because in this case, TB Alliance owns the rights to marketing for a subsection of the market (those with drug-susceptible TB). The pediatric protocol was finalized in 2014 and feasibility assessments were performed, given the difficulty in recruiting children for these studies. They were looking for a few high-quality sites for clinical trials. Two sites (Durban, Moscow) were identified. Clinical trials applications have been submitted in both the Russian Federation and in the Republic of South Africa; approval is pending. There will 4 age cohorts (<2, 2-<5, 5-<12, 12-18), with 15-16/cohort who will receive 24 weeks of bedaquiline added to an optimized background regimen. The inclusion of adolescents is significant, as this population has historically been neglected as adolescent data is difficult to disaggregate from data in younger children or adults. The goal is to enroll the 1st patient in Russia in May and RSA in June of 2015. They hope to recruit an adolescent cohort by the end of 2015. The goal for this study is not solely to collect sufficient data to meet regulatory requirements. Instead, the intent is to provide more meaningful data on safety and efficacy. There are planned interim analyses that will offer the potential to update the label to allow usage for different age cohorts as the study progresses.

Lessons learnt:

- Resource utilization. This portion of the study on manufacturer engagement has actually consumed fewer resources than anticipated. In part, this was because two of the manufacturers (Lupin, Svizera) were comfortable paying for the drug development costs themselves if TB Alliance provided data on market access and helped with identifying and possibly influencing faster approval of these medicines in countries. For the 3rd company (Macleods), TB Alliance had already budgeted for these activities in the initial project plan to help fund drug development and BE studies.
- Challenges of bioequivalence studies. This stems from at least 4 considerations: 1) lack of clarity on whether they ultimately will be needed for regulatory approval (if the drugs are classified as BCS class 1 by the GDF); 2) lack of an adequate comparator product (Lupin and Macleods are comparing dispersibles to non-dispersible FDCs and comparing AUC and C_{max}); 3) concern that comparator that may be deemed acceptable to one government may not be acceptable to another government; and 4) lack of a defined pathway for regulatory approval for drugs that are new formulations of existing drugs.
- Affordable pricing and accessibility (Annex 2). The MOUs and agreements specifically indicate the importance of these 2 UNITAID principles. That said, there is no legal way to enforce them for MOUs and for agreements; litigation is a suboptimal route. The risk of poor public relations aspects of failing to meet obligations can keep companies on task. TB Alliance ensures affordability and access by enabling multiple companies to compete, which will keep prices down. When the new FDCs become available later this year, it is possible that the price will be slightly higher than that of current medicines, in large part because it is anticipated that one manufacturer will begin to supply through the GDF before the other two. As such, the new FDC could be as much as 20% more than the current cost of treatment. However, as soon as the second and third manufacturers enter the market, it is anticipated that the prices will quickly go down to current levels. This assumption is based upon historical data from the GDF with relation to previous pediatric products. In order for a manufacturer to supply via the GDF, they are going to have to offer the new products at competitive prices, as the GDF simply will not procure product at an unreasonable price. In addition, countries that purchase medicines outside the GDF also generally implement maximum acceptable prices in their tenders and won't purchase the new FDCs outside of an affordable spectrum.
- Manufacturer default. The impact of a manufacturer defaulting hopefully will be minimized by having 3 manufacturers producing medications. The likelihood of default will be lessened by the TB Alliance decision to stage fund dispersal, as opposed to dispersing funds in a lump sum. Prior to funds being dispersed, milestones are constructed by TB Alliance, and at each milestone, information from the manufacturer is downloaded, quality documents are reviewed, and payments

are only made if satisfactory progress has been demonstrated; reviews currently occur every 6 months. This is one way to limit the financial damage if default does occur. One issue that arose was the possibility of taking best practices or technology developed by one manufacturer and transferring it to another company if default were to occur. This would be challenging for at least 2 reasons. First, some of that technology was in existence prior to the agreement with TB Alliance and is thus proprietary to the manufacturer. Second, the manufacturers are starting with different building blocks to construct the FDCs, so technology transferred would have decreased value to another manufacturer.

- Market stability. Having three manufacturers for a market size of at least 500,000 children annually seems appropriate. If the case rates were substantially higher, concern would exist over the ability of 3 manufacturers to supply sufficient product. I do think (please see my recommendations for future studies) that as more pediatric-friendly formulations are not only available, but are being dispensed to children, that the perceived need will increase. Also in combination with other initiatives (Output 6) to increase awareness of pediatric TB, more cases in children are likely to be reported and/or started on therapy.
- Intellectual property (IP) considerations. IP would be more relevant for new medications, in contrast to new formulations of existing medications. As such, IP issues are less applicable to the vast majority of the aims of the STEP-TB grant. This will need to be considered more in the future, as the processes established for reformulation of first-line medications should be considered for use as new drugs enter the pipeline. The market will be protected to a certain degree because only certain partners will be licensed to commercialize the product and have the technology transfer abilities to produce it readily.
- Regional market: China. TB Alliance has recognized some of the unique challenges facing China, including a perceived lack of need for pediatric TB formulations. Several strategies have been taken (please see Output 1) to address perceptions of the market size here. The Chinese government plays a large role in determining price points, and this will help contain costs. One Chinese manufacturer, Fosun, was given licensing capacity for PaMZ within China. Concerns about IP with new medications have existed here until recently. In the last few years, there has been a paradigm shift where the Chinese government has realized that the only way to develop proprietary technology in China is to protect IP.
- GDF: This may be the best way to reach the high-incidence nations due to existing arrangements for drug procurement.

3.5 Output 5: Treatment policy and activity changed enabling uptake of new pediatric TB formulations at the country level

Table 8: Output 5 Deliverables

Deliverable	Timeline	Status
Global list of current treatment guidelines and practices at country level	Q1 2014	Completed
List of countries that have adopted WHO 2010 Pediatric Advice	Q2 2016	Revised, 2-3 years after formulations available
Updated list of countries targeted	Q4 2014, Q4 2015	On track
Updated policy documents or letters indicating policy and practice change from countries	Q2 2016	On track

Availability of new and better pediatric formulations alone will not be sufficient to ensure uptake. Medications will need to be accessible to countries, and this will be facilitated in part by addition of these medications to national essential medicines lists (EMLs), which often differ substantially from the WHO's EML. In addition, knowledge of countries' current practices toward childhood TB, including whether

countries have both adopted and integrated the 2010 dosing changes into their practice, is key to performing a needs assessment.

Global list of current treatment guidelines and practices at country level
This survey of the HBCs was conducted by TB Alliance. Data accrued thus far from qualitative surveys of the HBCs (Output 1) indicate that uptake has been variable even within nations, and that there is some reluctance to change to new dosing regimens in the absence of drug formulations that easily conform to the 2010 recommended doses. This output will be reassessed at later points in the grant funding period, as described above.

List of countries adopting 2010 Pediatric Advice; Updated policy documents or letters indicating policy and practice
Final analyses for these deliverables are targeted for Q2 2016. However, this is expected to begin 2-3 years after formulations become available. Interim analyses for the 2010 pediatric advice uptake rate have already been completed in a qualitative manner (Output 1). One issue that has arisen is the question of how one gets countries to utilize the updated WHO recommendations until drugs become available. Few countries have tried to implement the new dosing, as this would mean having to add single-dose tablets to FDCs they were receiving from the GDF. WHO was reluctant to do this, given concern for dosing errors and potential adverse events that would lead providers to be reluctant to adopt the higher-dose FDCs when they became available. One approach that has been used is regional workshops with pediatric TB experts, NTP personnel, and technical advisors to explain the justification for the change. Countries need to be presented with accurate timelines for when new formulations will become available and to develop action plans at the country level. For example, India asked TB Alliance for help with trainings and with making the transition to newer doses. TB Alliance has also added workshops to existing meetings (e.g., GDF meetings) to decrease cost to participants and to make the trainings more accessible to participants. For example, there is a planned workshop in Thailand in March of 2015 and one is planned for Africa later in 2015. It is unlikely that all HBCs can be surveyed at the same time. This process likely will be staged, starting with asking countries about satisfaction and comfort with using FDCs. Sampling will occur using existing monitoring machinery and reviews, as well as utilizing data being collected by existing partners (e.g., Global Fund, Challenge TB).

Updated list of countries targeted
This deliverable relates to modifications of the HBC list to reflect that some countries do not want WHO recommendations or support, where as some smaller nations would like both. An example of the former is the Russian Federation and examples of the latter are Papua New Guinea and Zambia. As such, it is anticipated that the list of countries targeted will be modified in the coming years.

Lessons learnt:

- Global Fund: One way to increase uptake of new formulations is to streamline the processes by which countries obtain medications from the GDF. In March 2015, there will be a task force meeting with GDF, the Global Fund, supply management partners with country-level presence (CHAI, MSH), WHO, and TB Alliance to discuss aligning processes. The TB Alliance and their partners (WHO, GDF, MSH) have been consulting with countries to ensure that the new pediatric formulations are included in all concept notes going forward. Additionally, they have engaged with GFATM directly on a regular basis (Silas Holland, Anna Scardigli) on reprogramming of current country grants, specifying what the needs are going forward for new pediatric products, and considering what's required in concept notes going forward. Through these contacts, TB Alliance has learned that the Global Fund will work with the GDF to facilitate direct procurement, as opposed to leading this effort themselves. TB Alliance participated in a Global Fund review about 'sourcing strategic dynamics' in October of 2014.
- EMLs: TB Alliance has submitted an application to add FDCs to the WHO EML, which is revised every 2 years (last revision: October 2013). While the WHO endorses the use of FDCs, none currently are on the list for children (several FDCs are included on the WHO EML for adults). In addition, the complementary list of second-line drugs does not include bedaquiline, clofazimine, delamanid, or linezolid. A portfolio application for 13 different TB medicines was submitted for consideration by the WHO EML Expert Committee. The evidence reviews and analysis were

performed by a consultant with support from WHO technical departments. The application, along with all other EML applications, will be reviewed in April 2015 by the Expert Committee for a final decision regarding their inclusion. In some cases, such as the FDC, the application is for a revision to the current listing. Also for the FDC, the information was included with a request for an exception to the normal criteria of commercial availability. As the FDC will not be commercially available in time for the 2015 EML meeting; it was still included in an application with a request to change the listing and noting that the product will be commercially available in 2015.

3.6 Output 6: Funding for appropriate pediatric treatments allocated by donors and governments

Table 9: Output 6 Deliverables

Deliverable	Timeline	Status
Presentation/Package outlining case for donors	Q1 2014	Amended, completed
Presentation/Package outlining case for governments	Q1 2014	Amended, completed
Meeting summary from stakeholders meeting	Q4 2014	Reassessed

Ramifications of a poorly understood pediatric TB market extend beyond manufacturers. Failure to recognize childhood TB as an issue in the HBCs and other high-prevalence nations can lead to decreased expenditures on childhood TB by both governments and donors, who may target efforts to diseases with apparently higher visibility. To sustain the impact of the inroads made by the TB Alliance, it is necessary to garner support from both types of organizations.

Presentation/Package outlining case for donors
This strategy has been reassessed in favor of a more tailored approach toward individual donors. For donors, use of in-country data on the burden of disease and demonstrating that there is sufficient infrastructure/capacity in place to be sure that the monies will be used wisely is paramount. Potential donors include both well-known organizations for child health (e.g., World Vision, Save the Children) as well as governments of high-income nations that could donate money to the GDF (the Canadian government is one recent example of this). In November of 2014, UNICEF signed a proposal with TB Alliance to: 1) facilitate and promote introduction of appropriately-dosed pediatric medications in priority markets; 2) to integrate TB into child health programs in the HBCs; and 3) to help drive the integration of TB into maternal/child health programs and pediatric HIV/AIDS initiatives. UNICEF has substantial impact on both donors and governments, and having this organization in particular increase awareness of childhood TB at an international level has obvious advocacy advantages. Their involvement likely will help extend the UNITAID principle of *accessibility*. The Bill and Melinda Gates Foundation does not fund childhood TB. USAID was initially involved in the project through funding (USD 500,000), and once the project began, the role of USAID was more toward technical support. At this time, USAID has been involved with Keri Lijinsky (USAID TB/HIV advisor), who is involved in the AFRO regional meeting and other efforts in Africa around pediatric TB, along with Clydette Powell, who is the pediatric TB point-person in the infectious disease department. She is also involved in Challenge TB and the Childhood TB Subgroup. I interviewed Elizabeth Pleuss from USAID, who is the Agreement Officer Representative working with TB Alliance. USAID first entered into discussions with TB Alliance regarding rolling out of REMox. These conversations then transitioned to using the same model for rolling out pediatric formulations of the FDCs. She has been very pleased with her interactions. Responses have been prompt with accurate information conveyed. Despite some staff turnover at TBA, the transition plan was very smooth and not at all disruptive to the project.

Presentation/Package outlining case for governments
This strategy also has been reassessed in favor of a more tailored approach stratified between Brazil, the Russian Federation, India, China, and South Africa (BRICS nations) and the other HBCs. BRICS nations historically do not obtain their medications though the GDF, but either purchase it elsewhere or have in-country manufacturers (e.g., India). It is important that these countries are brought into the global market so that patients in these countries have access to the new products. TB Alliance has worked with the BRICS ministries of health, who currently are discussing their joint response to TB lead by the MOH from Brazil. TB Alliance is advocating to include language specifically addressing childhood TB. As certain

BRICS nations contemplate producing generics (e.g., Brazil), the risks and benefits need to be addressed. If additional manufacturers come online, this may cause market fragmentation and increase the risk profile to the extent that manufacturers may be unwilling to enter the pediatric TB market. On the other hand, it is possible that some BRICS nations may be interested in donating their generic drugs to low and low/middle income nations.
The strategy for HBCs obtaining drugs via the Global Fund is different. Here, the rate-limiting step is not the cost of the drugs, but to have countries identify pediatric TB as a priority. Interventions here need to occur prior to the decision to treat, but across the continuum of care, from access to care to diagnosis and treatment to reporting. These governments can be targeted through in-country trainings (several of which have occurred with the support of the project), technical assistance, and in-country stakeholder meetings. The Global Fund has liaised with TB Alliance and WHO, and the Global Fund now has a point person within pediatric TB to review concept notes to be sure children are included. The Global Fund has sufficient monies to target childhood TB, but the issue is more that this organization is aware of the true burden of disease to ensure that they allocate adequate amounts of their GF funds to this issue. .

Meeting summary from stakeholders meeting
Reflecting the more tailored approach to donors and governments, this deliverable has been modified in favor of providing more specific data to individual funders and governments. TB Alliance is planning in-country stakeholder meetings (5 countries to be identified) close to product launch instead of one large meeting.

Lessons learnt:

- Partnering with organizations already working in child health: partnering with UNICEF or other large organizations with existing interests in child health offers the opportunity to raise the visibility of childhood TB more than what would be possible for TB Alliance alone. These organizations already have extensive advocacy experience (including securing funders) and do not need to be convinced of the importance of child health.
- Differing approaches for the BRICS vs non-BRICS HBCs, as well as different approaches for countries procuring medicines from the GDF vs those obtaining medicines from other sources: identifying potential barriers for countries will differ based on procurement plans and regulatory requirements. BRICS countries are more likely to have the necessary infrastructure to potentially enter the TB drug market, and this also needs to be considered given the relatively small market share of pediatric TB medicines compared to the need in adults.

3.7 Output 7: Technical, regulatory, market, and other relevant data on pediatric TB medicines shared and disseminated

Table 10: Output 7 Deliverables

Deliverable	Timeline	Status
Web portal	Q4 2014	Completed
Summary of pediatric advisory group meetings and consultations	Q1, Q3 annually	On track
Symposium description and agenda	Q4 annually	On track
Summary of lessons-learned exchanges	Q1, Q3 annually	Reassessed
Overview of media coverage of stakeholders and media event	Q2 2014	Delayed, 2015

Dissemination of information on pediatric TB is challenging given that information may be viewed by persons with very different levels of baseline TB knowledge. The strategy to website design would be very different for donors versus scientists, for example. To address the heterogeneity in persons who may be seeking childhood TB information, the TB Alliance has developed a multipronged approach to information dissemination through varied media: websites; symposia at national/international professional TB meetings; and social media. A single strategy to disseminate information would not be as successful. The dissemination of information from manufacturers has been ongoing, and has to take manufacturer comfort in visibility into consideration. For example, Svizera was interested in booths and press releases at the IUATLD meeting, while Macleods participated in the symposium. Messaging around the countries

has been more general, focusing on how partnership with them will meet 2 of the aims of UNITAID (accessibility and affordability). Please also see Annex 3 on white paper distribution.

Web portal

The website was launched on World TB Day 2014; it is one of the most visited sites on the TB Alliance website (Table 11). The site content is modified on an as-needed basis by a team from TB Alliance which includes input from both the pediatric team and the communications specialists. There is a vendor who helps with modifications involving graphics. The site modifications (which are dated) occur as new studies, resources, or numbers become available. The web portal has links to a newsletter, the LinkedIn group, Twitter, Facebook, and ready access to contact information for TB Alliance. In addition, there are podcasts and links to videos discussing childhood TB. From an education standpoint, it has hyperlinks to a number of training manuals, research papers on new/newer drugs in the TB pipeline, and details on drug development. News releases (3 in the last 2 months) discuss updates in both studies and in changes with TB Alliance. On World TB Day 2015, TB Alliance will be announcing a partnership with UNICEF, distributing a messaging/social media package, and introducing an emotive video about the problems of childhood TB, emphasizing the family-centered nature of childhood TB.

Table 11: Dissemination of Information by TB Alliance

Venue	**Created**	**Utilization**
Website, pediatric portal	March 2014	15,000 views of pediatric TB web pages
LinkedIn	October 2013	>320 members; 44 posts
Twitter	Pre STEP-TB	13,800 followers 6.8 million social media impressions in 2014 (impressions rose sharply after launch of pediatric portal and data center, and spikes in engagement coincided with STEP-TB milestones and use of #tbkids hashtag
Facebook	Pre STEP-TB	Nearly 1000 'fans' of TB Alliance
Webinars	April 2014; January 2015	April 2014: 172 attendees + web views January 2015: 255 attendees + web views
Podcast (estimating pediatric TB burden)	Fall, 2014	Coverage of content on Citizen News Service and affiliated outlets (circulation > 5000); 86 plays of full podcast from website
Video (whiteboard video to build awareness of pediatric TB)	Winter, 2014	>65,000 views; 'liked' > 4000 times; shared by 140 users

Summary of Pediatric Advisory Group meetings and consultations

The inaugural meeting of the pediatric advisory group was in June of 2014 in New York. The group is comprised of representatives from the childhood TB academic community, the pediatric HIV/AIDS community, NGOs, industry, and advocacy. The group does not meet frequently, but their value lies in the bilateral relationships developed with the groups they represent. TB Alliance can access these persons independently of meetings. For example, the advisory group has been particularly useful in preparing a sponsored supplement for the *IJTLD* (the first pediatric-specific supplement in at least a decade).

Symposium description and agenda:

TB Alliance has sponsored symposia at the last 2 IUATLD meetings. The Paris meeting (2013), presented in the childhood TB track, focused upon the WHO's pediatric data collection processes, presented market research, and discussed new formulations of existing medicines. The Barcelona (2014) meeting, presented in the adult and child lung health track, updated the group on progress of efforts to make appropriately dosed pediatric formulations, reviewed drugs in the pipeline, and discussed strategies to ensure maximum uptake of the medicines that will soon be available. At the 2015 meeting (Cape Town), the TB Alliance will be sponsoring a lunch at the childhood TB subgroup meeting focused on FDCs. By partnering with a concurrent meeting, attendance will be maximized.

Summary of lessons-learned exchanges
This deliverable has been reassessed. At study onset, it was initially perceived that there would be synergy between TB Alliance and 2 other organizations funded by UNITAID around the same time, DNDi (Drugs for Neglected Diseases Initiative) and MMV (Medicines for Malaria Venture). However, the scope of work of the projects, as well as projects being in different stages, made the possibility of synergy less evident. TB Alliance has held one-on-one meeting with both organizations and have shared information at various points that have been helpful for their mutual projects. However, co-hosting meetings would have been quite costly with little yield. However, the lessons learned from the project will be in the IJTLD supplement later in 2015.

Overview of media coverage of stakeholders and media event
TB Alliance has held stakeholder meetings at the IUATLD annual meetings, most recently in Barcelona in 2014. Here, almost 100 stakeholders attended the meeting, at which several members of TB Alliance spoke. The group was updated on progress in existing studies, planned studies, and reviewed obstacles and opportunities in drug development. The PowerPoint presentations have been made available online as enduring materials. TB Alliance is in the midst of developing a strategy for product launch which is anticipated to include a variety of communications and media outreach.

3.8 Other:

LogFrame:
The LogFrame was considered a useful document by the TB Alliance. In late February 2015, they had a conference call with UNITAID M&E to discuss how changes in formatting to the LogFrame changed how indicators were reported. TB Alliance was going to potentially ask for modifications to make sure that the indicators collected accurately reflected what they were doing and provide this feedback to M&E to see if certain variables needed to be added or adjusted. However, in general they thought the LogFrame was useful and concise.

Reallocation of funds:
TB Alliance has been able to save a significant amount of money in the grant that has then made it possible to allocate some of these monies to other activities. The cost savings have resulted from 3 major factors: 1) negotiations with manufacturers; 2) staffing of TB Alliance; and 3) collaboration for the infant PK study. First, only 1 of 3 manufacturers required funding to start producing pediatric dispersible FDCs. The other 2 companies were willing to take on that financial risk if assured by TB Alliance that the market was sufficiently strong to make products financially viable. Second, efficiency gains in the TB Alliance offices enabled decreased staff time to work on the project. Third, collaboration with Helen McIlleron at the University of Cape Town, who had an existing PK grant, allowed for cost savings for the infant PK study. Recognizing that additional monies would be available, TB Alliance discussed with UNITAID how additional activities could be accomplished that fit into the goals and objectives of the STEP-TB study.

Communication with partners:
WHO felt that they were made aware of challenges and opportunities in a timely manner. This was facilitated by monthly conference calls interspersed with working group teleconferences and emails. Certain relationships formed for activities performed under this grant have helped forge better relationships in related projects. For example, the WHO TB personnel now have joint meetings with WHO personnel working on the essential medicines list, something which had not happened prior to this grant. They felt that TB Alliance was very transparent in their communications. In addition, WHO felt that the STEP-TB project has facilitated other activities of the Childhood TB Subgroup, and resulted in many requests for technical assistance as momentum for childhood TB has been created (collaboration with UNICEF is one such example). The WHO feels that this was a model collaboration between a UN agency and a private non-profit organization.

Building Partnerships and Collaborations
A significant strength of TB Alliance is the collaborative relationships that have been formed with a number of partners. These include Stellenbosch University, the University of Cape Town, PmRN, RTI,

and the Solution Lab. Given the scope of the project, and the relatively small team at TB Alliance, forging of these collaborative relationships was not only imperative for success of this project, but also laid the groundwork for TB Alliance to continue in these collaborative relationships for future studies. In addition, the cost reductions from some of these relationships (e.g., with the University of Cape Town group for the pharmacokinetic studies) enabled resource reallocation to extend the scope of work for other portions of the project.

4. RECOMMENDATIONS FOR FUTURE DIRECTIONS

TB Alliance has accomplished, or is on track to accomplish, all of its major goals toward ensuring affordability and accessibility of pediatric TB medicine formulations. While the scope of the current project is broad, I am concerned that availability of medicines alone will not increase uptake without additional interventions. Given the success of the current project, as well as the ability that TB Alliance has demonstrated in terms of forging collaborative relationships, I believe that they would be uniquely positioned to orchestrate steps within countries that would increase uptake, if sufficient extra funding could be obtained. Some of these additional activities are possible within the confines of the current grant and would thus be budget neutral (e.g., supporting product registration in China, more in-depth trainings in India). I know that discussions for budget reallocations have already been initiated between TB Alliance and UNITAID on this topic. There is also the possibility of extending TB Alliance's work beyond the current limited geographic focus from working through the GDF (~20% of the pediatric TB market). Such an extension is important to increase market and create more scale by encompassing the majority of the potential pediatric market. Finally, it is more evident than at the time of STEP-TB inception that there are new drugs and regimens that will require assistance to get from the bench to the bedside. This is part of the current project, but the knowledge gained from this project can provide better abilities to forecast market projections. However, this would require more than the limited budget allocated to the deliverable in the current STEP-TB budget.

Interviewing personnel from WHO, they share my concern and recommendations about extending the project. From their perspective, abundant material is now available at the global level in terms of guidelines and multimedia training materials. What is now needed from their standpoint is technical assistance, identifying champions at the national level, and country-by-country follow-up to see what the uptake is of new pediatric formulations. From their perspective, additional funds to enable a 2-3 year follow-up with country-level technical assistance would achieve the goal of moving medications from the step where they are available to the stage where they are actually being used in children.

The following activities could remove obstacles that countries would face in moving from the stage of drug availability through regulatory barriers to encouraging uptake of the new formulations at the national and district levels.

Accelerating regulatory approvals in individual nations

Having appropriately dosed pediatric formulations available via the WHO PQ would be a massive improvement in the current state of affairs. Recognizing what steps countries need to take to obtain regulatory approval adds transparency to a somewhat opaque process. However, shepherding countries through the process will accelerate the timeline for medicines to reach the children. Potential activities in this area include:

- Identify champions in each country to help drive the regulatory process, and pair them with persons with expertise in this arena. This may be within the NTPs (e.g., training activities) or in-country NGOs working on childhood TB (e.g., Damien Foundation or BRAC in Bangladesh).
- Facilitating countries registering products.
- Securing agreements as to who will pay for products in non-GDF countries.
- Adding the FDCs and pediatric formulations to individual countries' essential medicines lists (EML).

Scaling the uptake, delivery, & adoption of pediatric TB products

TB Alliance is uniquely positioned based on their prior work and on the STEP-TB project to work to improve market sustainability (delivery mechanisms) and demand creation through provider and health worker training and marketing of new treatment (market access expansion). Potential activities that could

be considered to scale uptake and delivery of medicines, first for first-line drugs and later for second-line agents include:

- Operational research and demonstration projects to ensure fast uptake of newly available pediatric TB products.
- Buying drugs (become grant provider for delivery mechanisms)
- Identify delivery options and mobilize partner networks (e.g., UNICEF), which in turn aids stability. Initial collaboration between TB Alliance and UNICEF, as described above, will be announced in late March, 2015.
- Focus on new countries and regions to increase impact on the global market by expanding into new, large MDR markets (e.g., Peru) that aren't part of the 22 HBCs.
- Create community stakeholder understanding and buy-in around pediatric TB and child friendly medicines through research literacy trainings, and family friendly materials on pediatric TB.
- Collaborate with the Sentinel Group and James Seddon and colleagues to obtain disaggregated data by HIV status and to look at the market for second-line formulations for children and for scaling up isoniazid preventive therapy (IPT) for children.

MDR-TB & Novel Regimens

The lack of adequate PK studies in infants for first-line drugs, the most recent of which were introduced 50 years ago, is a cautionary tale for second-line drugs. With increased incidence of MDR- and XDR-TB, the timeline for studying these medicines in children has to begin much earlier. Potential activities in this domain include:

- Engagement of manufacturers and drug developers to produce child-friendly second-line drug formulations in appropriate dosages. Some manufacturers (e.g., Macleods) are already working on this for fluoroquinolones. Knowledge of the pediatric market size here will be even more difficult to evaluate than for childhood TB in general, and modeling likely will be required (some work on this area already has been done by the Sentinel Group). However, an incentive may be that many second-line drugs are used to treat non-mycobacterial infections, and the market share would be far greater for other, non-TB, pathogens. These drugs include bedaquiline, levofloxacin, moxifloxacin, linezolid, and pretomanid. The studies proposed could review existing drugs or drugs recently approved for adults with MDR-TB, assessing safety and dosing gaps and looking at the stability of these drugs in certain groups (e.g., HIV-infected and/or malnourished children and children with TB meningitis or other extrathoracic disease).
    - NiX-TB (New Chemical Entities in XDR-TB) will evaluate regimens composed of novel drugs in people with XDR-TB in carefully controlled conditions; this study plans to include adolescents.
- Evaluation of treatment options for children with MDR-LTBI. Given the poor uptake of LTBI treatment even for children presumably infected by drug-susceptible TB, it is unsurprising that there have been few inroads made in the study of optimal treatment regimens for MDR-LTBI. In the absence of data, there is wide practice variation, with 1 or more medicines utilized for variable durations. In part, lack of adequate pediatric formulations of second-line medications has caused stagnation on this topic.

Annex 1: UNITAID Strategic Objectives*

Strategic Objective 1:

- Increase access to simple, point-of-care diagnostics for HIV/AIDS, TB, and malaria

Strategic Objective 2:

- Increase access to affordable pediatric medicines to treat HIV/AIDS, TB, and malaria

Strategic Objective 3:

- Increase access to emerging medicines and/or regimens, as well as new formulations, dosage forms, or strengths of existing medicines that will improve the treatment of HIV/AIDS and co-infections such as viral hepatitis

Strategic Objective 4:

- Increase access to artemisinin-based combination therapies (ACTs) and emerging medicines that, in combination with appropriate diagnostic testing, will improve the treatment of malaria

Strategic Objective 5:

- Secure supply of second-line TB medicines, and increase access to emerging medicines and regimens that will improve both the treatment of drug-sensitive multidrug-resistant TB

Strategic Objective 6:

- Increase access to products for the prevention of HIV, TB, and malaria

*From: http://www.unitaid.com/images/strategy/UNITAID-Strategy_2013-2016-Full-English.pdf

Annex 2: UNITAID Access and Pricing Principles*

TB Alliance shall use its best efforts to align the implementation of the Project with UNITAID's Mission and Strategy, together with the following principles and objectives:

1.1 The major goal for TB Alliance in entering into an agreement with a Product Manufacturer is that Final Products will be developed and commercialized in such a manner that facilitates their widespread use for the treatment of children with tuberculosis in lower and middle income countries.

1.2 TB Alliance and the Product Manufacturers acknowledge and agree that it is their common intent that the Final Product(s) shall be made Globally Available as quickly as possible at Affordable Pricing to meet the needs of low and middle income countries in sufficient quantities for distribution through the Public Sector of as many low and middle income countries as possible.

1.3 Product Manufacturers selected to participate in the Project should possess known sources of supply and sufficient production capacity to ensure a continuity of supply of the Final Products to the Public Sector in the quantities requested by the Public Sector, under normal conditions (measured in terms of quantity, quality and order forecasts) and should be committed to undertake commercially reasonable efforts to manufacture the Final Products at the lowest possible cost consistent with sustainable market dynamics. Where relevant, this should include a commitment to:

a) prioritize firm orders from the Public Sector over those of the private sector;
b) pass on any significant reduction in the production and direct distribution costs of the Final Product to the benefit of the sale price for the Public Sector, and/or
c) develop a cost estimation scenario towards defining pricing of the Final Products through the Public Sector on the basis of Affordable Pricing, so as to ensure Global Availability and equitable access to all children in need of the Final Products.

1.4 It is acknowledged that it may be appropriate for Product Manufacturers to define a tiered pricing approach for the pricing of the Final Products, reflecting a need for products to be priced at a lower level in low and middle income countries.

1.5 Where relevant, Project Product Manufacturers should confirm that:

a) they have the full right, power and authority to authorize or license the use of the Project Product Manufacturer(s) Background IP;
b) they have not granted or will not grant during the term of the Development Agreements to any third party any of its right, license or interest in, to or under Project Product Manufacturer(s) Background IP or Project Product Manufacturer(s) Foreground IP that would conflict with, limit or adversely affect the rights granted to TB Alliance or TB Alliance's ability to conduct the activities assigned to it under the Development Agreements, and/or
c) to their best knowledge, the use of Project Product Manufacturer(s) Background IP as contemplated under the Development Agreements does not infringe any intellectual property rights of any third party in the country of manufacture of the Final Product, and it has not received any claim and/or been party to any proceeding of any nature by any third party claiming the existence of any such infringement. TB Alliance shall endeavour to require Project Product Manufacturer(s) to notify TB Alliance in writing promptly upon learning of any such actual or threatened claim or proceeding.

1.6 The Final Products must be developed to the quality standards and in a manner commensurate with professional standards to meet the criteria set by the WHO Prequalification Program and/or countries with a Stringent Drugs Regulatory Authority.

Annex 3: List of White Papers*

Paper	Dissemination
Distribution of first-line pediatric drugs in 22 HBCs: analysis of Global Drug Facility procurement	UNITAID, technical partners (CHAI, MSH, MSF, USAID, manufacturers); will be incorporated into an article in the IUATLD journal supplement in 2015; presentation at Union World Conference
Mathematical modelling estimates of the burden of childhood tuberculosis in the 22 high-burden countries (published in Lancet Global Health)	UNITAID; Journal circulation, press releases, podcast; social media networks; presentation in at European Pediatric Society Conference and Union World Conference; TB Alliance website
Treatment of Pediatric Tuberculosis in South Africa: How significant are the private medical sector facilities?	UNITAID, technical partners
Literature Review: The Role of the Private Sector in Treating Pediatric TB	UNITAID, technical partners
Rapid Assessments of the Treatment of Pediatric TB Outside of NTP Facilities: Summary of Multi-Country Study Findings (in review by PLOS ONE)	UNITAID, technical partners; seeking publication in peer reviewed journal; presentation at the Union World Conference
Survey of Policy and Practice in the Treatment of Pediatric TB in High Burden Countries	UNITAID, technical partners; presentation at the Union World Conference
Consideration for the Acceptability of New Pediatric TB Formulations	UNITAID, technical partners, manufacturers
Pediatric Tuberculosis Drug Market: An Insider Perspective on Supply Side Dynamics, Challenges, and Innovative Solutions	UNITAID; will be incorporated into an article in the IUATLD Journal Supplement in 2015
Towards earlier inclusion of children in tuberculosis (TB) drug trials: consensus statements from an expert panel (submitted and approved for Lancet; not published yet)	UNITAID; waiting for publication in peer reviewed journal before disseminating

*as of 25 March 2015

Annex 4: Project Interview List

Organization	Name	Title/Affiliation	Status
UNITAID	Y. Mundade	Technical Officer, Acting Portfolio Manager, TB	Interviewed
WHO	M. Grzemska	Coordinator, Technical Support Coordination	Interviewed
	B. Sismanidis	TB Monitoring and Evaluation	Interviewed
	L. Hedman	Technical Officer, Market Intelligence, Policy, & Uptake	†
	A.Brands	Global TB Programme WHO	Interviewed
USAID	Y. Mukadi	Senior TB Technical Advisor	*
	E. Pleuss	Agreement Officer Representative	Interviewed
TB Alliance	C. Scott	Director, Pediatric Programs	Interviewed
	S. Cook-Scalise	Senior Program Specialist, Market Access & External Affairs	Interviewed
	M. Spigelman	President and CEO	Interviewed
	C. Pero	Chief Administrative Officer	Interviewed
	W. Brock	Senior VP, External Affairs	Interviewed
	B. Lorette	Senior VP, Business Development	Interviewed
	S. Murray	Senior Medical Officer	Interviewed
	R. Taneja	Senior Director, Pharmaceutical Product Development	Interviewed
	S. Malhotra	Director, Market Access	Interviewed
	I. Usherenko	Program Coordinator, Pediatrics	Interviewed
	J. Breitstein	Senior Director, Communications	Interviewed
Manufacturers	Macleods	Vijay Agarwal	Interviewed
	Lupin	Shrikant Kulkarni	*
	Svizera	Boudewijn Ploos van Amstel	Interviewed
	Janssen	Myriam Haxaire-Theeuwes	Interviewed
	Sanofi	Isabelle Cieren-Puiseux	*
Other	J. Starke	Pediatric expert panel	Interviewed

CEO: chief executive officer; TB: tuberculosis; VP: vice president; WHO: World Health Organization
†contacted, communicated via email
*contacted, but not interviewed

Annex 5: Document List

Document/Output	Section	Reviewed
Original Agreement	Grant agreement	Yes
	Annexes	Yes
	Contract	Yes
	Project plan	Yes
	Annexes	Yes
UNITAID Documents	Strategy, 2013-2016	Yes
	MOU of UNITAID with WHO	Yes
	Feedback on TBA 1st annual report	Yes
TBA Reports	Inception report	Yes
	1st annual report (submitted 14 March 2014)	Yes
	Semi-annual report (submitted 15 Sept 2014)	Yes
MOU or Agreements with Manufacturers	Svizera	Yes
	Macleods	Yes
	Lupin	Yes
	Janssen	Yes
List of All Project-Related Meetings	STEP-TB Project meeting 2014	Yes
	General project meeting Dec 2013	Yes
	General project meeting March 2014	Yes
	General project meeting May 2014	Yes
	General project meeting June 2014	Yes
	General project meeting August 2014	Yes
	General project meeting October 2014	Yes
	Summary, Moxifloxacin consultation meeting	Yes
	Summary, Global consultation on pediatric TB (9/2013)	Yes
Minutes of Meetings with Manufacturers	Macleods progress update	Yes
	Macleods pediatric symposium presentation	Yes
Agreements with PIs of Studies, Trials	SOW with MSH (procurement study)	Yes
	SOW with Dr. Valerio Reggi (regulatory work)	Yes
	SOW with RTI (regulatory work)	Yes
	UNICEF proposal to TB Alliance	Yes
	University of Cape Town, Stellenbosch	Yes
Study Reports	O1: Survey of policy and practice in the treatment of pediatric TB in high-burden countries	Yes
	O1: Rapid assessments of the treatment of pediatric TB outside of NTP facilities	Yes
	O1: Mathematical modelling estimates of the burden of childhood TB in the 22 high-burden countries	Yes
	O1: Distribution of first-line pediatric drugs in 22 HBCs: analysis of Global Drug Facility procurement	Yes
	O1: Literature review: role of the private sector in treating pediatric TB	Yes
	O1: Private sector in South Africa	Yes
	O1: White paper on pediatric TB drug market	Yes
	O1: Market studies (list)	Yes
	O1: Considerations for acceptability of new pediatric TB formulations	Yes
	O1: Analysis of the consumption patterns of tuberculosis medicines	Yes
	O2: Interim analysis plan and results (infant PK)	Yes
	O2: Manuscript Pediatric TB New Drugs	Yes
	O5: List of current treatment guidelines and practices at	Yes

	country level	
Website Content, TBA	TBA Pediatric Portal	Yes
	LinkedIn Pediatric Group	Yes
	Burden Estimate Podcast	Yes
Other	O2: TBA recommendations for infant PK study	Yes
	O2: Stellenbosch response to TBA recommendations	Yes
	O2: Protocol, infant PK study	Yes
	O3: RTI technical proposal	Yes
	O4: Matrix pediatric manufacturer criteria	Yes
	O6: Concept note for accelerating access to new child TB treatment	Yes
	O6: UNICEF grant	Yes
	O7: Agendas from symposia	Yes
	O7: Summary of meeting with pediatric advisory group	Yes

HBC: high-burden country; MOU: memorandum of understanding; MSH: Management Sciences for Health; NTP: national TB program; O: output; PK: pharmacokinetic; RTI: Research Triangle Institute; SOW: scope of work; TB: tuberculosis; TBA: TB Alliance; UNICEF: United Nation Children's Fund; WHO: World Health Organization