



Global Alliance for TB drug development (TB Alliance) Speeding Treatments to End Paediatric Tuberculosis (STEP – TB) End of Project Evaluation

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ABBREVIATIONS AND ACRONYMS

CHAI	Clinton Health Access Initiative
DNDi	Drugs for Neglected Diseases Initiative
E	Ethambutol
EMA	European Medicines Agency
ERP	Expert Review Panel
FDA	United States Food and Drug Administration
FDC(s)	Fixed Dose Combinations
GDF	Global Drug Facility
GF	Global Fund
H	Isoniazid
HBC(s)	High Burden Country(ies)
HIV	Human Immunodeficiency Virus
IUATLD	International Union Against Tuberculosis and Lung Disease
IJTL	International Journal of Tuberculosis and Lung Disease
LICs	Low-income country
LMICs	Low- and middle-income countries.
LTBI	Latent tuberculosis infection
MDR-TB	Multi Drug Resistant TB
MMV	Medicines for Malaria Venture
MoU	Memorandum of Understanding
MSH	Management Sciences for Health
NCE	No cost extension
NTP	National Tuberculosis Programme
P	Rifapentine
pK	Pharmacokinetic
PaMZ	PA-824 (Pretomanid), Moxifloxacin and Pyrazinamide regimen
PmRN	Paediatric medicines Regulators Network
R	Rifampicin
REMox	'Rapid Evaluation of Moxifloxacin' in the treatment of sputum smear positive tuberculosis' in relation to the trial REMoxTB
RTI	Research Triangle Institute
STEP-TB	Speeding Treatments to end Paediatric Tuberculosis
TAG	Treatment Action Group
TB	Tuberculosis
TB Alliance	Global Alliance for TB Drug development
TORs	Terms of Reference
UNICEF	United Nations Children's Fund
WHO	World Health Organization
WHO EM	World Health Organization Essential Medicines
WHO GTB	World Health Organization Global Tuberculosis Programme
WHO PQ	World Health Organization Prequalification
Z	Pyrazinamide

EXECUTIVE SUMMARY

Background

The challenge addressed by the project was the lack of child-friendly formulations in the correct dosages aligned to the WHO 2010 revised guidelines. To fill this gap, in December 2012, the UNITAID Executive Board committed up to USD 16.7 million to the Global Alliance for TB Drug Development (TB Alliance) over three years to support the development and production of appropriate new paediatric formulations.

The present end-of-project evaluation was to provide UNITAID with an assessment of the implementation of the project with a particular focus on the project's overall market and public health impact.

Evaluation Approach

The evaluation team reviewed the project documentation, collected data and information through interviews with key stakeholders, conducted an online survey covering all 22 project countries, searched for additional external documentation as needed and finally synthesized information from these various sources to address the different objectives of the present evaluation.

Findings

Using the UNITAID grant evaluation framework, the evaluators rated the various criteria as following:

Relevance is rated as high:

- 1- The project targeted several gaps in the TB paediatric market, contributing to much better and reliable estimates of the burden of childhood TB. The new estimate is that there are around 1 million TB patients in children, whereas the previous 2013 estimates were about half of that.
- 2- The project resulted in two new correctly dosed fixed dose combinations of first line drugs. The new formulations have an ERP review for time limited procurement and are today globally available through the GDF mechanism of supply.
- 3- The project contributed to two of UNITAID's six strategic objectives in a short term: objective 2 to increase access to affordable paediatric medicines for tuberculosis, and objective 6 to increase access to products for the prevention of TB. It also contributed to objective 5 in a longer term from additional paediatric development activities around Moxifloxacin, PA-824 and Bedaquiline.

Effectiveness: rated medium to high

- 1- The outputs of the grant were consistent with the objectives and expected outcomes as described in the project plan. All activities were developed as per project plan and most deliverables were completed.
- 2- UNITAID was regularly informed about the progress of the project through regular updates sent on a semi- and annual basis, regular quarterly meetings and email or calls if needed, and has been involved in discussions and decision making on the changes. One major change has been the integration of the Bedaquiline study under output 4 from reallocation of unused fund initially dedicated to engage the manufacturers.
- 3- The outputs of the project were largely achieved within the timeframe specified in the project plan and even ahead for some activities. Two main activities could not be completed within the overall project timeframe or as expected: 1- The pharmacokinetic study in infants under output 2 that needed further investigation of Rifampicin dosing. A follow-up study was initiated during the NCE phase and is ongoing. 2- Announcement on the readiness of dispersible Ethambutol from MacLeods and of the two FDCs from Lupin's was expected early 2017, but this has not been done yet.

4- Efforts were made throughout the project to ensure that the overall goal is achieved. A weakness we can see is that it might have been good to anticipate certain steps earlier, especially steps for implementation of the formulations.

Efficiency: rated as medium

1- National authorities were aware of and participated in certain project activities TB Alliance undertook during the Union conferences, and meetings organised, such as the initial meeting in 2013, and another meeting in June 2016. However, national authorities do not seem to have been involved in project planning, implementation and assessment.

2- Implementation of the grant could have been much more effective and efficient had implementing partners and partners such as GDF been involved in an earlier stage.

3- Implementation arrangements of the grantee and co-implementers have not been very clear.

Impact: rated as medium

1- The grantee has been able to report on impact as originally framed in the project plan and Log-Frame. In relation to the two impact indicators of the logframe, GDF included the new formulation into its products list and removed the old formulations. The importance however, is that countries order the new formulations, which has occurred as well: 11 of the 22 project countries have ordered the products.

2. The grantee can attribute UNITAID's financial support to patients treated to a limited degree. Now that the project has ended, it is unsure whether further implementation will be supported and by whom, which may limit that the new formulations reach children with TB.

3. The evaluators could not assess direct impact of the project in the sense of improved treatment outcomes and increased numbers of children initiated on TB treatment with the new formulations. Because this is the most important impact, the project was rated as medium.

Learning and risk mitigation: rated as medium

The project disseminated much information and has certainly contributed to the visibility of childhood TB. It is not clear to the evaluators however, whether this sharing did contain lessons learnt, and how certain lessons contributed to improved implementation. This had been a lack of documentation throughout the project.

Market Impact

On the availability dimension the impact of the project was significant. The STEP-TB project made new dispersible child-friendly FDCs (RH 75/50 mg and RHZ 75/50/150 mg) available, and contributed to development of single drug formulations of Ethambutol 100 mg and Isoniazid 100 mg. To some extent, it also contributed to paediatric development of second line drugs from activities around Moxifloxacin, PA-824 and Bedaquiline. The new formulations are globally available through the GDF mechanism of supply, at a reasonable price and have an ERP review for time limited procurement. All 22 high burden countries except China and the Russian Federation have adopted the WHO 2010 revised recommendations and most countries are now in a transition phase towards replacing the 'old' formulations with the 'new' ones. Some uncertainty however remains in relation to the new formulations reaching the children with TB.

There is no direct impact of the STEP-TB Project on the supply and delivery dimension, and this could not be expected as it was not part of the project design. However, there is indirect impact on some operational aspects.

The concern is, and this is a high-level goal not achieved, that only one manufacturer MacLeods has launched the two new FDCs within the timeframe of the project and at present, the new formulations are available from MacLeods only.

Today, childhood TB can no longer be ignored, and with this the market for paediatric TB products. Raising global awareness for childhood TB is seen as a major achievement as underlined in most

interviews. Advocacy activities have contributed to this achievement significantly but also market research and to a lesser extent consultations around regulatory activities.

Public Health Impact

Assessment of direct public health impact was impossible. A positive step towards public health impact is that 20 of the 22 project countries have adopted plans or frameworks for the introduction of, and transition to the new formulations, which was the best possible achievement given the reluctance of two countries - China and the Russian Federation - to use fixed dose combinations at all. A direct public health assessment in terms of patients/people reached or lives saved was not possible because of the recent introduction of the formulations, and many uncertainties involved. Furthermore, 13 of the 22 project countries ordered the new formulations, of which 7 received them and three started using them therefore an assessment of impact is not possible at this point in time.

Project weaknesses

From the evaluators' view, the project 1) lacked sufficient focus on the main objective that was introduction of the new formulations, 2) documentation that was an important part of the project has not been produced in an optimal and comprehensive way, 3) the market landscape analysis is incomplete and 4) criteria for partners' selection remains to be documented.

Recommendations

1. Most of the project countries have adopted the revised childhood TB dosage recommendation that are reflected in national guidelines and are in transition to the new dosage; dissemination of critical information and collaborative methods of working with countries has much contributed to this. In addition, the implementing partners have run an effective marketing campaign around the new fixed-dose combinations that has significantly contributed to the adoption of these new paediatric formulations. These activities have been important success factors in the STEP-TB project that future projects focusing on introduction of new products could draw upon.
2. In spite of this major achievement, a number of issues however remain to be addressed so that the product arrives where it should: the child with TB. Future projects should continue to design a number of implementation steps, and related budget allocations. Product implementation steps should be built in to the design phase of the project.
3. The STEP-TB project has confirmed that the major driving force to engage the manufacturers is market demand. Provision of financial incentives as a tool to engage manufacturers, as defined in the STEP-TB Project, can help to reach product development targets, especially time targets, but was not seen as a major driving force. Therefore, it is recommended that UNITAD conduct research even further into what motivates manufacturers to develop new products for a small market such as the paediatric TB medicines and use the findings to better inform future project design.
4. The assumptions used in the theory of change are grounded in the concept that with increased access to optimal paediatric TB medicines, more children would receive treatment, better adhere to long treatment and have better treatment outcomes. However, early on in the project it became clear that although the existing medicines were not ideal for children and form a barrier to initiate treatment, the medicines themselves were not the only challenge to overcome. It is recommended that a more comprehensive approach to developing the theory of change (the blueprint of project design) which underpins all of the assumptions around implementation is undertaken in order to effectively address, and ultimately change, the landscape of childhood TB.

5. Future project design should take into consideration the complexity of implementing a new formulation and the need to focus on just one objective - the introduction of the new fixed-dose combinations rather than spreading itself too thin with other activities. Potential models of introduction of medicines could include smaller grants allocated with clearly outlined steps from development up to registration. Selection of partners, through a clearly documented process, would need to be aligned with these steps to ensure partners with required skills and experience are selected.
6. The long lag time from the launch of a new drug for adults to the launch of the childhood formulation is a constant barrier to introducing new medicines for children. The results from activities around Moxifloxacin and PA-824 (Pretomanid) that were conducted under Output 2, suggest that it might have been good to focus on very specific activities built upon consolidated study results in adults or not include these activities at all at this development stage in adults. This is an interesting finding that can serve future projects in the design of the most optimal timing for the development of new paediatric medicines from advanced new drug developments in adults to the corresponding formulations adapted to children.
7. The evaluation of STEP-TB project has identified a certain lack of visibility and acknowledgment of UNITAID's grant throughout the project. Future projects should clearly acknowledge the donor in all its output and UNITAID should consider including this aspect in the grant agreement.

Conclusions

The overall goal to make new better adapted correctly dosed paediatric formulations has been achieved although a number of high-levels goals remain only partially achieved. Looking more broadly however, the STEP-TB Project has fostered a real and significant momentum for change to addressing childhood TB. The project successfully filled the gap: today, childhood TB is a global agenda. The project also helped to ensure that most of the targeted countries have adopted the WHO 2010 revised guidelines and the concept of treatment with fixed-dose combinations.

1 STEP-TB Project Background

Tuberculosis (TB) is a significant driver of childhood mortality, and one of the top 10 causes of death among children worldwide. Globally, children are estimated to represent around 10% of the more than 10 million estimated TB patients annually. The World Health Organization (WHO) reported in 2016 that approximately 210,000 children died of TB in 2015, the majority in the 22 high-burden countries, 18 of which are low-income country (LICs) or low- and middle-income countries (LMICs). Children represent up to 20-40% of the notified TB patients in some of these countries.

TB is a significant threat to all, but children are particularly vulnerable, especially those in LICs and LMICs, and those co-infected with Human Immunodeficiency Virus (HIV). Compared to adults, children's less developed immune systems are more susceptible to TB. In infants and children younger than five years of age, TB is much more likely to spread throughout the body and, consequently, children are at much greater risk of developing extra-pulmonary forms of TB, especially with meningeal involvement.

Supply and availability of paediatric medicines face significant challenges and vary by country. The situation leading to the inception of the STEP-TB project included the lack of child-appropriate formulations to treat diagnosed patients, which is a critical shortcoming. Prior to 2010, WHO recognized that the dosing recommendations for paediatric TB medications were too low and therefore revised these recommendations. Since WHO published the revised dosing recommendations, no child-appropriate formulations were available before the STEP-TB project. As a result, treatment was either delivered at lower than recommended dosage level using existing formulations, or was arrived at using a complex adjustment of existing paediatric formulations plus adult formulations. It was obvious that new TB formulations were needed for children—not only correctly dosed formulations of the first-line therapy, but also paediatric for new medicines that were in the pipeline.

In light of these challenges, in December 2012, the UNITAID Executive Board committed up to USD 16.7 million over a period of three years to the Global Alliance for TB Drug Development (TB Alliance) to support the development and production of appropriate paediatric TB medicine formulations, along a theory of change based on the following framework and assumptions:

Goal/Impact: Increase access to optimal paediatric TB medicines

Outcome: Improved access to correctly dosed, properly formulated, affordable, high quality TB medicines for children

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

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

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

Output 4: Commitment of at least one manufacturer secured to ensure timely and global availability of new paediatric TB formulations

Output 5: Treatment policies and practices changed enabling uptake of new paediatric TB formulations at the country level

Output 6: Funding for appropriate paediatric treatments allocated by donors and governments;

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

2 Objectives of the Present Evaluation

The overall objective of this end of STEP-TB project evaluation was to provide UNITAID with an assessment of the implementation of the project, co-funded by the US Agency for International Development, with a particular focus on the project's overall market and public health impact. The full terms of reference (TORs) are included in Annex 1.

More particularly, this evaluation aimed to inform on the project achievements and lessons learnt as a result of the implementation of the UNITAID grant along with the following objectives:

1. **Assessment of progress** made towards the achievement of results at the impact, outcome and outputs under the UNITAID Grant Evaluation Framework that is addressing the different questions of relevance, effectiveness, efficiency, impact and learning & risk mitigation as outlined in Annex 2. We have performed this assessment for each of the seven project outputs and related activities.
2. **Evaluation at impact** from two perspectives:
 - Market impact (intentional and unintentional) for the products provided under the project agreements; and
 - Public health impact for the beneficiaries of the medicines, diagnostics and related products provided through the project.
3. **Country assessment:** The evaluation should cover **all 22 project countries**, namely Afghanistan, Bangladesh, Brazil, Cambodia, China, Democratic Republic of Congo, Ethiopia, India, Indonesia, Kenya, Mozambique, Myanmar, Nigeria, Pakistan, Philippines, Russian Federation, South Africa, Tanzania, Thailand, Uganda, Viet Nam and Zimbabwe.
4. **Project time frame:** The evaluation should cover the full period of the project from 1 August 2013 to 31 January 2017 that is including the no-cost extension (NCE) of the project from the initial closing date of 31 July 2016 to 31 January 2017 even though most activities ended in October 2016.

3 Evaluation approach and tools

3.1 Approach Overview

The evaluation team reviewed the project documentation, collected data through interviews with key stakeholders based on questionnaires and finally, synthesized information from these various sources to address the different objectives of the present evaluation. The team sought to review as much documentation and obtain feedback from as many stakeholders as possible over the eight-

week duration of the evaluation, in order to develop a comprehensive overview of the project achievements and lessons learnt.

This included:

- **Meetings (online or in person) and discussions** with UNITAID staff, the TB Alliance team, and key persons from the WHO pre-qualification team, the Global TB program department, Global Drug Facility (GDF) and the Global Fund (GF) in Geneva;
- Desk review and analysis of **project documentation**, web sites, and external documents related to the STEP-TB Project;
- **Interviewing** key informants of organizations, manufacturers, consultants, and countries via telephone/skype;
- **Conducting** an online survey covering all 22 countries; and
- **Documenting findings** – both quantitative and qualitative, recording project accomplishments against frameworks, activities, timelines and results including highlighting challenges and successes.

The team used both qualitative and quantitative data collection methods to analyse results and lessons learned since commencement of the STEP-TB Project. Interview findings were triangulated across respondents and documents where applicable to ensure any potential bias was managed.

3.2 Evaluation Tools

The evaluation team used various tools and methods to ensure a robust collection and analysis of information from a wide range of sources and respondents, including:

- Selection of a broad spectrum of respondents within the different categories of beneficiaries from the STEP-TB Project; criteria for selection included representation of the widest range of stakeholders as possible including implementing partners, manufacturers, beneficiaries (countries), advisors to the project, and of course the lead implementer TB Alliance and co-implementer WHO, and the donor UNITAID.
- Guided questionnaires for interviews and discussions with stakeholders, manufacturers, and regulatory organisations
- Online survey questionnaire as outlined in Annex 4.

3.3 Limitations

The reader of the present evaluation should bear in mind that the evaluation was conducted over a limited amount of time that did not allow for more in depth evaluation of certain aspects of the project. However, other limitations have been identified and should be taken into consideration when viewing this report, these include:

1. To obtain views of the 22 project countries, the evaluators conducted an online survey. The survey had a very poor response rate (n=8) despite several reminders to potential respondents.
2. To further obtain country views, the evaluators approached the National Tuberculosis Programme (NTP) managers from six countries with the highest number of estimated childhood TB patients: Bangladesh, China, India, Indonesia, Nigeria and Pakistan. Despite reminders by email, only one NTP manager participated in a telephone interview.
3. Interviews with the manufacturers could not be completed as planned. Only one out of the three manufacturing partners – Svizera - participated in a telephone interview within the timeframe of the evaluation, despite introduction of the evaluators by UNITAID and several reminder emails. Ultimately MacLeods and Lupin were interviewed after submission of the draft report which fortunately left just sufficient time to incorporate the information into this final report.

4. The evaluators could not access some documentation, notably the manufacturers' assessments and progress reports that TB Alliance cited the reason as a breach of confidentiality agreements with the manufacturers (output 1 and output 4). As a result, the evaluation team was not able to access what was perceived to be information that would have assisted in the overall analysis and triangulation of information along with development of findings for this review.
5. The evaluators could not get answers to all questions raised within the timeframe of the evaluation. In particular, the evaluators did not conduct an in-depth assessment of cost efficiency and cost effectiveness of the project as this merits a full analysis that could not be done under the terms that were agreed.
6. When the evaluators started work in mid-January 2017, the TB Alliance team had limited availability to talk to the evaluators because of the project end date of 31 January 2017. This created an unfavourable situation where the evaluators were not completely familiar with the project documentation at the time of talking to the lead implementer, which led to inefficient use of the limited available time. Fortunately, TB Alliance recognized that this situation was not optimal and were available for further conversations.

4 Findings/Results

4.1 Overview

The evaluators' findings from this evaluation of the STEP-TB project are presented in the following sections: first on progress made towards achievement of the targeted goal, outcomes and outputs against the project plan (project proposal dated 17 July 2013 and NCE transition plan dated 19 February 2016); second on market impact and public health impact as a result of the implementation of the grant.

The evaluation of the progress made is reported in two separate sections. A brief summary of the achievements against the project plan are given in the following 'Project outputs' paragraphs, and per each output activity. Answers to the questions of relevance, effectiveness, efficiency, impact and learning and risk mitigation as outlined in the UNITAID grant evaluation framework are given in the following 'Evaluation discussion' section. Lessons learnt are developed in the same 'Evaluation discussion' paragraph.

Assessment of the financial implementation is based on the interim financial report dated June 2016. The final project report is not yet submitted and therefore a full assessment of financial implementation cannot be made.

The market and public health impact are treated in separate sections.

4.2 Project Outputs

Achievements under each output and deliverable were assessed against the project plan (project proposal dated 17 July 2013 and NCE transition plan dated 19 February 2016) from documentation review that was complemented with interviews as needed.

This evaluation report includes project outputs in the following section. Each output is briefly described against the project plan; indicator results against targets are presented in a summary table.

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

	Indicator	End of Project Target (year)	Results
Indicator O1.1	Number of market studies conducted	10 (2016)	17 studies ^{a)}
Indicator O1.2	Name and number of HBC where market sizing estimates completed	4 (2014)	20 countries ^{a)}
Indicator O1.3	Global paediatric market size calculated	Market size calculated (2016)	Completed

a) Number of studies and of High Burden Countries (HBC)¹ as indicated in the semi-annual report 2016. The evaluators observed some discrepancies between sources which have not yet been clarified.

Output 1 was designed with the intention to gain a comprehensive picture of the market, with the idea to use this information to raise more awareness from countries and other key stakeholders about childhood TB and the unmet needs that have to be addressed, and importantly, to engage manufacturers.

Several studies and consultations were planned to establish this comprehensive view of the paediatric market that goes beyond patient numbers and the potential size of the market by identifying gaps in programmatic implementation of paediatric treatments and barriers to market entry from the manufacturers' perspectives. The idea to consult all players in the market was foreseen, these included: patients, providers, suppliers, and procurers, be they in the private or the public sector.

Overall, the activities under Output 1 have been conducted as per the project plan, with a major achievement of contributing to ensuring consolidated and better estimates of the paediatric TB market size. The targets of the two indicators O1.2 and O1.3 were fully achieved in a timely fashion as indicated in the table above. Indicator O1.1 has been also achieved timely but at a much higher level than the target that let raise the question whether a more ambitious target could have been set at the start and/or that a number of studies that are included here may be out of the scope as defined in the project plan.

The activities (studies, reviews, and surveys) that were conducted under this output have generated a wealth of information and data that have contributed to improving estimates of the childhood TB burden and to gaining a better understanding of key questions around policy and practice. However, there was a missed opportunity to create a knowledge sharing product that provides a comprehensive overview of findings of the different studies in order to highlight the major outcomes to help guide programming.

Global consultation on childhood TB estimates

Hosted by the STEP-TB Project and among the first steps to guide the estimation of market size, the TB Alliance project team convened a global consultation on childhood TB estimation ('Global

¹ HBC are a list of 22 countries where in total 80% of the global burden of TB occurs. These countries served as project countries and include Afghanistan, Bangladesh, Brazil, Cambodia, China, Democratic Republic of Congo, Ethiopia, India, Indonesia, Kenya, Mozambique, Myanmar, Nigeria, Pakistan, Philippines, Russian Federation, South Africa, Tanzania, Thailand, Uganda, Viet Nam and Zimbabwe

Consultation on Paediatric Tuberculosis: Disease Burden Estimation and Quantification of Its Drug Market’) in New York in September 2013 gathering some 50 representatives from relevant organisations and from NTPs of Pakistan, Nigeria, Ethiopia, Indonesia and South Africa. This meeting could have been a good place to encourage and share knowledge with the manufacturers however they were not invited.

The meeting is well documented in a summary report which provides a comprehensive overview of different approaches used and/or to be developed for the estimation of the disease burden and quantification of the market. In addition, the report includes a number of proposed actions for next steps to improve the estimation of the TB drug market for paediatric TB. This activity has been fully achieved though follow-up actions were less clearly documented. For example, it was not clear that an action plan has been presented at the Q2-3 2014 Taskforce Meeting as announced in the summary report. It was confirmed later by TB Alliance that a detailed market research plan was presented and approved by UNITAID in 2013, however, the evaluators were not provided any such documentation clearly.

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 estimate, through modelling, numbers of childhood TB disease and TB infection in the 22 HBCs. The model also provided some first estimates of latent tuberculosis infection (LTBI) prevalence in HBCs from estimates of household exposure and cumulative infection suggesting an enormous opportunity for preventive treatment.

This modelling study is documented in a report and published in the *Lancet Global Health* August 2014.

TB Alliance chose these two partners as ‘During the Global Consultation held in September 2013 (reference meeting summary), two groups of modellers presented on proprietary methods around estimating the burden of child TB. The groups were 1) Pete Dodd/James Seddon, and 2) Ted Cohen (initially at Harvard, now at Yale) and his group who were working on another approach. WHO had used an alternate estimation method with notable limitations around estimating the child TB burden. During the consultation and after the consultation, these three methods were assessed and ultimately integrated into one approach that WHO used in its improved estimates published in their TB Report 2015 and 2016.’

Literature review of the private sector paediatric TB

The aim of the literature review was 1) to provide additional understanding of the size, structure and potential for growth in the market for paediatric TB medicines and 2) to understand the availability of published research on treatment provision for paediatric TB in the private sector with the ultimate goal to better understand the role of the private sector in the treatment of paediatric TB, and how it impacts the market for paediatric-specific medicines. Covering the period from January 1990 to September 2013, this literature review could not provide any data to assist in quantifying the private sector. The author of the review suggested targeted studies as an alternative to increase understanding of the role of the private sector in treating paediatric TB patients, in terms of the numbers of patients seen and other market dynamics.

The group conducted a rapid follow-up assessment in three countries (Indonesia, Nigeria, and Pakistan) where the private sector was expected to be large and helped to propose a new study plan.

Literature review of paediatric formulation acceptability

The aim of this activity was to establish a thorough evidence base for the preferred formulations of paediatric essential medicines, based upon research on patient, caregiver and provider preferences for paediatric TB as well as HIV and malaria. The end-goal was to inform TB Alliance and other

relevant stakeholders as to the preferred paediatric TB formulations that should be developed for resource-limited settings.

The result of this investigation is a well written and comprehensive White Paper with the clear conclusion that a dispersible tablet in fruit-based flavour familiar to target populations appears to have been the most ideal and acceptable product type to develop for the paediatric TB population. It also highlights that field assessments of acceptability would need to be conducted to better understand palatability and how it differs across countries and continents - the target for taste masking need not necessarily be good tasting medicines, but perhaps simply a taste that is acceptable by as many countries as possible.

Considering the date of delivery of the paper (30 April 2014), the evaluators questioned how much of the findings of this evaluation have informed the manufacturers' development of the new fixed dose combination (FDCs) product profile.

NTP and reported figures compared

This activity of cross-checking NTP numbers against the numbers reported to WHO that was planned at the study outset, was reassessed after discussions with the WHO and NTP personnel for the reason that such a study would be extremely time-consuming and unlikely to reveal significant reporting discrepancies. The decision was made to rather focus on the rapid analysis of children treated outside of NTPs, where discrepancies in under-reporting and inappropriate treatment were thought to be greater.

Qualitative survey of non-NTP facilities

The aim of this study was to 1) understand where children are taken for treatment, 2) obtain an idea of the numbers of children treated in the private and public sectors and not reported to the NTP, 3) understand the diagnosis and treatment pathways for these children and 4) learn about the reporting relations between these facilities and the NTP, with the overall goal to assess the likely magnitude and sources of under-reporting and under-diagnosis.

This qualitative survey was initially planned to be conducted in five countries, which would be selected from the seven countries with the highest numbers of incident TB patients reported in 2012 (i.e. Bangladesh, China, India, Indonesia, Nigeria, Pakistan and South Africa). It was finally conducted in Indonesia, Nigeria and Pakistan which is well documented, and in South Africa which is documented separately.

Given concerns about representativeness with the initially proposed research design of this qualitative study, TB Alliance and WHO jointly decided to switch to an Inventory study design to be conducted in five countries in which there was believed to be significant underreporting in official case notification data. Inventory studies were planned in six countries: China, Indonesia, Pakistan, Philippines, Thailand, and Viet Nam. In Indonesia, Pakistan and Viet Nam. The studies are in various stages of implementation, with the Pakistan study most advanced. The study in China is also in progress. Philippines and Thailand were supposed to start in 2017, for the Philippines after their prevalence survey has finished.

Rapid assessment of policy and practice in HBCs

This rapid assessment of policy and practice in the 22 high-burden countries used a short online questionnaire of seven questions to inform progress towards the adoption of the WHO 2010 revised guidelines on dosage recommendations for the treatment of paediatric TB. This online questionnaire provided some first answers to questions about practices and adoption of the WHO revised guidelines by the countries that served as a good baseline of information for additional research under the STEP-TB Project.

Contact investigation study

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

Procurement study in high TB burden countries

This activity comprised a first analysis of GDF Sales on a country by country basis that should be complemented by in-country follow-up work to understand supply chains where paediatric procurement practices are not available via the GDF, WHO or other sources. At the same time the follow-up work should also gather information on any concerns related to product switching.

The analysis of GDF sales was conducted during the first year of the project by TB Alliance in partnership with GDF and is well documented.

Sales from existing manufacturers quantified

TB Alliance contracted Results for Development to obtain data on the existing sales of paediatric TB drugs which, through triangulation with NTP treatment figures and GDF procurement data, could provide further insight into treatment volume across high burden countries. While a few manufacturers agreed to share data, the data obtained were insufficient to allow for more accurate market projections. TB Alliance selected Results for Development through a process which entailed approaching “4 market intelligence firms (Aptis, iGH, GfK, and R4D) with extensive experience and existing tools. This was based on internal decision to use consultancy firms with a broader reach and staff base as opposed to individual consultants for the work around market sizing due to the nature of the work. Based on their internal expertise in select areas and proposed budget, we divided the work around market sizing between the two of the firms. GfK was contracted to focus on development of the market tool (included in as Annex to 2014 semi-annual report) and R4D for compiling the sales data” (quote from TB Alliance).

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

	Indicator	End of Project Target (year)	Results
Indicator O2.1	Clinical data on H, R, Z, E ^{a)} in children <5 kg obtained and submitted to WHO PQ* and other regulators	Yes (2016)	pK study completed (2015), see below
Indicator O2.2	Decision to pursue PaMZ regimen use in children determined	Yes (2016)	Reassessed (see below)
Indicator O2.3	Decision to pursue REMox regimen use in children determined	Yes (2016)	Reassessed (see below)

a) H=Isoniazid, R=Rifampin, Z=Pyrazinamide, and E=Ethambutol. These are the first line TB medicines. (*) WHO PQ = World Health Organization Prequalification

This output was designed along three groups of activities. The first activity A2.1 was to clarify clinical data requirements and develop a strategy for registering new H, R, Z, and E formulations allowing introduction of the new formulations in the countries. The second activity A2.2 aimed to gain more evidence to determine the recommended dose for children weighing less than 5 kg. The third group of activities A2.3 and A2.4 aimed to investigate new paediatric developments from ongoing development around PA-824 (Pretomanid) and Moxifloxacin in adults.

Summaries of consultations with SRAs, WHO PQ, other regulators, and manufacturers

Overall, the first activity A2.1 has been conducted in an efficient way through numerous consultations with regulatory authorities and with regulatory expert consultants that helped to rapidly clarify national regulatory requirements and to develop a strategy to best address these requirements for registration and approach national regulatory authorities accordingly. According to the mid-term evaluation, the initial plan was to compile regulatory requirements for the European Medicines Agency (EMA) and United States Food and Drug Administration (US FDA), however, because the drug distribution would not be to nations covered by these authorities, the focus was shifted to obtain WHO PQ for these formulations.

Report on data requirements for H, R, Z, E formulations

According to the 2014 TB Alliance semi-annual report and the mid-term evaluation, manufacturers and TB Alliance have been consulting with regulatory authorities on registering new formulations of existing drugs but most of the discussions between the manufacturers and the regulatory authorities is confidential. However, some general themes on the new H,R,Z,E formulations emerged from TB Alliance discussions with the regulatory authorities which are summarized in TB Alliance semi-annual report 2014. From the understanding of the evaluators, this may explain why the deliverable 'report on data requirements for H,R,Z,E formulations' is not documented as such.

Based on document review and discussions with key informants, the evaluators observed that regulatory information and experience that was available from registration of the previous formulations has not been used in the design and development of activity A2.1. This represents a missed opportunity, especially considering that the prequalified previous formulations were from the same manufacturers MacLeods and Lupin. In addition, it is unclear why these activities have been included considering that the submission of a dossier for prequalification and registration of the new FDCs in the countries have been under the sole responsibility of the manufacturers from the understanding of the evaluators.

Preliminary results from pK study of children <5kg; Dosing recommendations for children <5kg

The infant pharmacokinetic study has been conducted as per project plan, the outcomes were presented at the 46th Union World Conference in Cape Town in December 2015 and have been published in different papers (Bekker *et al*; Pharmacokinetics of Rifampin, Isoniazid, Pyrazinamide, and Ethambutol in Infants Dosed According to Revised WHO-Recommended Treatment Guidelines. Antimicrobial Agents and Chemotherapy 2016). The results demonstrated levels of mean maximum plasma concentrations in the infants tested similar to those in adults for all drugs except rifampicin (R). Rifampicin was measured in lower than expected and variable doses that required further clinical investigation. The clinical relevance of this finding is not yet clear because the children had good treatment outcomes. A follow-up study was initiated during the no cost extension (NCE) phase and is ongoing. This finding was beyond the control of TB Alliance or the researchers and highlights the need for dose optimisation studies for Rifampicin, one of the most important first line medicines. Should future dosing studies result in different dosing recommendations, development of new formulations or adaption of the existing ones will be necessary.

Study and Development plan for PA-824 and moxifloxacin in children

These two parallel activities (A2.3 and A2.4), mainly desk work and consultations, have been reassessed throughout the project and are still at an investigation stage. One decision taken has been to tie Pretomanid and moxifloxacin into the regimen development of Pretomanid-Moxifloxacin-Pyrazinamide (PaMZ).

From the understanding of the evaluators, this last group of activities A2.3 and A2.4 were included to build on ongoing studies in adults with the same drugs however what precisely was planned, expected and finally developed remains unclear which makes some progress assessment difficult. The following information has been provided by TB Alliance in response to questions posed by the evaluators: TB Alliance:

- a) 'Results from the REMox trial were published in September 2014; the regimens failed to meet their endpoints and therefore did not move forward to registration. As such, any further development of REMox for pediatric patients was abandoned.
- b) 'The STAND trial, which is a Phase III trial of the PaMZ regimen, was initiated in March 2013 and put on clinical hold in 2015. Regulators, including the US FDA, were consulted concerning the pediatric development of pretomanid; due to some observed toxicity observed in rats, additional studies were requested, including in juvenile animals and in healthy males before pretomanid could enter studies involving adolescents and children. With the advancement of PaMZ into phase 3, the TB Alliance committed to the pediatric development of pretomanid in PaMZ and subsequent regimens--as safety would allow--realizing that required toxicity studies would somewhat delay its development in comparison to adults. STAND was taken off hold in 2016 and the decision was made to move forward with an expanded regimen of BPaMZ instead of PaMZ alone, based on extremely positive results from the NC-005 trial. Plans for pediatric development of pretomanid remain intact and will move forward with the NC-008 trial of BPaMZ. Information on the pretomanid pediatric development plan was included in reporting information from 2014 onwards.'
- c) 'For moxifloxacin, its further development for children was dependent on expert review of data concerning its safety and efficacy in children. It was identified that there still exist significant gaps in knowledge around moxifloxacin in children. There is more data for levofloxacin, a drug in the same class of fluoroquinolones, which is well tolerated in children. For TB Alliance, the pediatric development of moxifloxacin will continue to move forward as part of our regimen development in combination with pretomanid, not as a single agent.'
- d) 'A single drug product of moxifloxacin could be brought to market by Macleods, as they have a prototype, but it is dependent on additional outside investment.'

In view of the results from these activities, it would have been good to focus on very specific activities built upon consolidated study results in adults or not include these activities at all under the project at this stage of development in adults.

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

	Indicator	End of Project Target (year)	Results
Indicator O3.1	Paediatric medicines Regulators Network (PmRN) endorses regulatory requirements	Yes (2016)	Completed 2015. See more below
Indicator O3.2	FDA and/or EMA requirements for paediatric medicines outlined and made public	Yes (2016)	Completed 2015. See more below.

This output was designed along two groups of activities. The first group of activities (A.3.1) were to clarify and get advice on ways to streamline the overall regulatory process to make paediatric TB medicines available closer to the time of the launch of the adult product, for both new formulations and in general. This information was meant to be collected from consultations with US FDA, EMA and WHO PQ which have well-established processes through which to request advice, followed by consultations with various in-country regulatory authorities (including, but not necessarily limited to: the Chinese Food and Drug Administration, the Central Drugs Standard Control Organization of India and the South African Medicine Control Council) and the manufacturers. Every consultation should be documented and at the end, all advice received compiled in a summary report made available to the public.

The second group of activities (A3.2) is complementary to Activity A3.1, and was designed with the idea to produce a comprehensive and integrated paediatric development plan or guidance to inform about the requirements for safety, dosing, bioavailability, and other studies needed to obtain product approval for future paediatric TB medicines coming to market. The Clinical/Regulatory team was to draft a paediatric development pathway white paper to be disseminated in Q2 2015 and submitted to the Paediatric medicines Regulators Network (PmRN) for review in Q4 2015. The Clinical and Regulatory Team was to seek endorsement of the “white paper” from the PmRN.

It turned out that output 2 and output 3 have some overlapping areas and could have been designed as one output.

Summaries of consultations with EMA, US, FDA, WHO PQ, manufacturers and other regulators; Report summarizing regulatory advice on the pathway for paediatric TB medicines

Consultations around regulatory advice on the pathway for paediatric TB medicines have been conducted as per the project plan, with some slight alterations in the timeline due to some extension of the scope. The results have been made publicly available as per the project plan; they have been disseminated in a number of venues, notably as part of the IJTLD supplement that was published in concurrence with the 46th Annual Union World Conference on Lung Health (Int. J Tuberc Lung Dis 19(12) 2015 S69-S74 paper). From the understanding of the evaluators, there has been no such report summarizing regulatory advice on the pathway for paediatric TB medicines as planned aside from the IJTLD publication indicated above.

Meeting summary from clinical experts meeting; Paediatric development pathway white paper; Written endorsement from PmRN;

There was a general agreement between clinical and regulatory experts consulted that it would be difficult to elaborate a comprehensive and integrated paediatric development plan or guidance that applies to all paediatric medicines, an approach specific to the product remains. This is the reason no such Paediatric development pathway white paper has been produced and even less endorsed from the PmRN. The results of consultations is included in the same IJTLD 2015 supplement indicated above.

Considering that the initial plan was shifted to prequalification of the new formulations by WHO rather than registration by the European Medicines Agency (EMA) or United States Food and Drug Administration (US FDA), that the medicines would not be used in the USA, and most likely not in countries under EMA regulations, the indicator O3.2 is therefore not relevant. It would have made more sense to align the indicator with WHO Prequalification.

Output 4: Commitment of at least one manufacturer secured to ensure timely and global availability of new paediatric TB formulations

The STEP-TB Project plan defined global availability as follows “Global Availability or Globally Available means, at a minimum, the new paediatric formulations can be purchased from the GDF or the Global Fund or such organization that assume the mission of the GDF, and that the Final Products meet the quality standards established by the WHO Prequalification Programme and/or Stringent Regulatory Authorities” (Ref.: project plan dated 17July2013).

	Indicator	End of Project Target (year)	Results
Indicator O4.1	# of signed agreements/MoUs* for formulation development by manufacturer name	3 (2016)	2 MoUs signed - Svizera (Sept 2013) and Lupin (June 2014); 1 agreement signed – Macleods (March 2014)
Indicator O4.2	Date of manufacturer(s)' submission to WHO PQ or other regulators	2015	Completed for 2-FDC HR, 3-FDC HRZ and E-100(MacLeods), see below

*MoU= Memorandum of Understanding

Output 4 was designed along a number of consecutive steps and included the following targets and timelines to get manufacturing partners on board in a way to ensure rapid introduction of the formulations:

- signed agreements with three manufacturers within the timeframe of the project, with the first agreement signed by Q3 2013 and a second agreement signed by Q1 2014; that is in other words two signed agreements by the end of 2014;
- submission of a dossier for the two FDCs to WHO PQ, or another regulatory agency, by 2015 with a first dossier by Q2 2015 and a second one by Q3 2015.

From the project plan, the selection and approach to manufacturing partners was supposed to be conducted using different tools, the first tool was a ranking against a number of selection criteria for an ideal manufacturer profile including:

- Current manufacturer of one or more TB drugs, preferably H, R, Z, E;
- Manufacturer experienced with formulating new dosage forms of existing drugs;
- Ability to obtain WHO PQ and/or International Conference for Harmonization (ICH) regulatory approval for finished product and the ability to export that product;
- Adequate production capacity and/or ability to scale capacity to meet market demands; and
- Regulatory track record at country level.

The second tool made use of a push and pull mechanism to address the specific concerns raised by each company to develop the new FDCs. In particular, information from Output 1 market research activities together with other documents and data available through Output 7 would serve discussions with the manufacturers. Also part of possible push mechanisms, a financial incentive of USD 1.5 million per manufacturer was budgeted to support engagement of the manufacturers.

All activities under output 4 have been conducted as per the project plan; details of indicator O4.1 (achieved against the target in a timely manner) can be seen below:

- In September 2013, soon after the launch of the grant, TB Alliance signed a MoU with Svizera as per the initial plan, targeted at the development of the two fixed dose combinations (HR

and HRZ). Svizera is a Dutch company and a division of Maneesh Pharmaceuticals of India; the company has three FDCs for TB that are prequalified by WHO;

- In March 2014, TB Alliance signed a manufacturer cooperation agreement with MacLeods to perform a number of activities. As a priority goal, MacLeods would develop, produce and submit a dossier to WHO by March-April 2015 for prequalification of the two fixed dose combinations (HR and HRZ). In addition, MacLeods committed to develop and produce dispersible tablets of the single drugs Isoniazid 100 mg (H-100) and Ethambutol 100 mg (E-100) and to the extent possible within the same timeframe of the two FDCs. MacLeods is an Indian company and a leading manufacturer of TB drugs. Out of the 93 TB medicines that are prequalified by WHO, 26 are from MacLeods. MacLeods has been supplying the previous paediatric FDCs to GDF.
- TB Alliance pursued discussions with manufacturers in 2014 aiming to engage one or more additional manufacturing partner and ensure regional and country-specific coverage. TB Alliance signed a MoU with Lupin in June 2014 targeted at the development of the two FDCs. Lupin has been a longstanding leading manufacturer of TB drugs and is the leading manufacturer of APIs for all first line drugs except Isoniazid. Out of the 93 TB medicines that are prequalified by WHO, 11 are from Lupin. Lupin has been supplying the previous paediatric FDCs to GDF.

In view of the company profiles, the selection criteria are met. All three manufacturers were approached at different times and in different ways. For instance, it is TB Alliance that approached Lupin but MacLeods approached TB Alliance when the company heard about the grant (declaration of interest) at a UNION conference in Paris. Svizera was ahead with the development of the FDCs and had been identified as a potential partnering manufacturer before the launch of the grant.

TB Alliance approached other companies like Sandoz and Sanofi and initiated discussions with three companies in China: Fosun Pharmaceuticals, Honz and Long March. None of the other companies has entered into collaboration with TB Alliance.

In 2013 annual report, the TB Alliance team confirmed that market data produced by the project in 2013 contributed significantly to their conversations with manufacturers. This is perfectly in line with the project plan on the basis that output 1 activities were integrated with the idea to serve engaging the manufacturers to enter the small market for paediatric TB medicines.

As part of the strategy to engage manufacturers, a financial incentive was offered. Only MacLeods agreed to the financial incentive. The two other companies refused the incentive stating that it was not in line with the corporate policy of the company (Svizera) or that the company wanted to remain independent (not tied to a financial agreement) and did not see any need for external resources (Lupin). Some of the unused budget (USD 1.5 million) was reallocated to the integration of Bedaquiline development studies. These new activities were integrated under output 4 (more below). UNITAID informed the evaluators that MacLeods received USD 1.5 million however, there are some additional payments waiting to be paid as part of the project closeout. The evaluators thus could not assess the budget part of this output fully.

All three manufacturers have developed the new FDCs but only one manufacturer – MacLeods - has submitted a dossier to WHO PQ and has launched the new FDCs within the timeframe of the project. Svizera has not finalised the submission of the dossier and Lupin has encountered some unexpected delays in submission of the dossier linked to the bioequivalence study. Submission by Lupin is now likely to be in Q2-Q3 2017. In view of this, the indicator O4.2 and the high level goal of having at least two suppliers are thus partially achieved, though there is potential for full achievement in 2017.

MacLeods has developed all four dispersible products (RH 75/50, RHZ 75/50/150, H-100 and E-100), has submitted a dossier for the 2-FDCs and E-100 and launched the two FDCs in line with the manufacturer cooperation agreement, and even ahead of the targeted timelines for submission of a dossier to WHO PQ.

- 2-drug FDC: dossier submitted on 2 December 2014, acknowledged by WHO PQ 18 December 2014 (source of information: TB Alliance)
- 3-drug FDC: dossier submitted on 19 January 2015, acknowledged by WHO PQ 12 February 2015 (source of information: TB Alliance)
- Ethambutol E-100: dossier submitted end of 2016 (source of information: TB Alliance)

The FDCs were launched in December 2015, available from GDF from January 2016.

	Indicator	End of Project Target (year)	Results
Indicator O4.3	Date of completion of product development of Bedaquiline for Phase I & II clinical studies	100% ^{a)}	completed
Indicator O4.4	Date of availability of Phase I data on safety, pharmacokinetics, bioequivalence of Bedaquiline	100% ^{a)}	completed

a) as written in the logframe document dated October 2015.

Not part of the initial project plan, the above two activities under Output 4 were integrated into the STEP-TB Project in mid 2014. Funding for the activities came from unused funds initially designated for manufacturer engagement. Janssen and TB Alliance signed a first agreement in 2009 to develop Bedaquiline for drug susceptible and Multi Drug Resistant TB (MDR TB). A fifth amendment was signed between TB Alliance and Janssen to cover the new paediatric development integrated in the STEP-TB Project, mainly a paediatric pharmacokinetic and safety study of Bedaquiline.

From our understanding of the documentation available, a Bedaquiline phase II trial opened to enrolment mid 2016.

TB Alliance informed ‘that Janssen modified its paediatric plan to collapse the two oldest age groups moving toward a more accelerated development plan than initially put forward by the company. This is a direct result of the involvement of the project and will provide faster results than doing these age groups via a traditional age de-escalation paradigm’.

Output 5: Treatment policies and practices changed enabling uptake of new paediatric TB formulations at the country level

	Indicator	End of Project Target (year)	Results
O5.1	Country guidelines reflect WHO 2010 paediatric advice	20	20
O5.2	Countries have national frameworks and/or plans in place, which include 2010 paediatric advice and implementation strategies for new paediatric formulations	10	20

The indicators for this output have been achieved according to plan, for indicator O5.2 to a level much higher than the target, suggesting that a more ambitious target could have been set at the

start. The indicators related to the presence of frameworks and/or plans at country level. These plans or frameworks should include WHO's 2010 dosing recommendations and be based on the 2014 WHO guidance for NTPs on management of childhood TB.² WHO collected this information through country visits and other occasions where WHO met NTP staff.

China and the Russian Federation do not have these plans or frameworks in place because at present both countries do not intend to use fixed-dose combinations. Furthermore, both countries procure from national companies that do not necessarily have an interest to serve the global market. Other countries consider it important that medicines appear on the WHO essential medicine list, which is reviewed every two years. The new formulations developed in part of the STEP-TB Project have been submitted for inclusion into the next revision of the WHO essential medicine list.

The evaluators consider it a missed opportunity to have not worked on a child friendly formulation including the four medicines, as exists for adults. Though this had not been identified as an unmet need, such formulations would make treatment easier at the patient level in those parts of the world where children should be treated with the four medications. WHO recommends giving ethambutol in all children with TB in high HIV-prevalent settings, and in settings where resistance to isoniazid is high, as well as to children with extensive disease. The high HIV-prevalent setting applies to most of the WHO African region, representing 30% of the estimated global burden. However, when developing the recommendations, WHO considered that the 3-FDC and a single E-100 formulation would serve all countries best. One of the manufacturers considered a 4-FDC for children an additional complication to an already small market.

It is therefore hoped that a dispersible E-100 tablet, which was part of the agreement with the manufacturers and is now under assessment for prequalification by WHO, will become available soon. It seems from earlier GDF product catalogues that dispersible E-100 has been available in the past; although not any longer for reasons which are not clear.³ Based on discussions with TB Alliance and GDF it was evident that they were not aware that E-100 tablets had been available earlier.

Under Output 7 additional information on advocacy and dissemination activities can be found. TB Alliance and partners used various mechanisms to report on the project's progress, such as UNION meetings and WHO regional meetings. UNICEF organised a global meeting on the subject in June 2016. These meetings served as advocacy events for countries to change their guidelines and contributed to achievement of indicator O5.1. Through interviews and the document review, it has become clear that the project catalysed the global focus on childhood TB.

Activities under Output 5 were highly relevant and effective at achieving the introduction of plans and guidelines around new paediatric formulations. The importance of this Output is reiterated in the study from Malhotra et al. which indicates the importance for countries to update their guidelines for use of a new product. TB Alliance realised the activities within the available budget (around 30% was not spent by the end of the project), based on a forecasting of expenditure in June 2016, showing high efficiency. This output contributed substantially to the overall project goal of increasing access to optimal paediatric TB medicines.

² WHO 2014. Guidance for national TB programmes on the management of TB in children – 2nd ed. (WHO/HTM/TB/2014.03)

³ GDF product catalogue 2011 and 2014.

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

	Indicator	End of Project Target (year)	Results
O6.1	Case for purchasing new paediatric formulations made to donors and governments	11 countries/donors (2016)	No info.
O6.2	Countries allocate funds to procure new formulations	8	13
O6.3	Donors allocate funds to procure new formulations	2	1

The activities under this output were reassessed during grant implementation resulting in more direct support to countries from WHO and Management Sciences for health (MSH) for adoption of the new formulations.

The STEP-TB project collaborated with GF and the GDF and to date 13 of the 22 HBC have ordered, and 7 of these have received, the new formulations (Table 1). The evaluators obtained the data through various sources, which were triangulated to arrive at the final figures in Table 1. At least three countries started to treat children - Kenya, Pakistan and Zimbabwe - though numbers of children started on the new medicines are not yet known.

The GDF did not provide the evaluators with quantities ordered and received per country. Therefore, the table below does not contain this information .

Table 1: HBC countries status on ordering and reception of new formulations

COUNTRY	ORDERED AND RECEIVED / PROJECTED DELIVERY TIME
Afghanistan	Dec-16
Bangladesh	Nov-16
Cambodia	May-June 2017
DRC	Nov-17
India	Nov-16
Kenya	Quarter 4 2016
Mozambique	Sep-17
Myanmar	Nov-16
Pakistan	Jan-17
Philippines	Nov-16
Tanzania	May-June 2017
Uganda	May-June 2017
Zimbabwe	Nov-16

Source: TB Alliance, GDF

In addition to the 13 project countries, 23 non-project countries ordered the new formulations. These findings suggest that funding is available to procure the new formulations.

The Global Fund (GF) follows WHO recommendations on treatment, and uses the GDF price as a reference for negotiations. The latest version of the Global Fund list of TB pharmaceutical products,

dated 14 February 2017, still includes the old formulations to allow countries procuring these to prevent treatment interruption. However, whether GF performs checks to assess whether new orders of the old formulations are intended to prevent treatment interruption is not clear. Partners developed a guidance note⁴ for countries to develop a transition plan focusing on availability of medicines and minimal wastage. In addition, GF intends to support countries that want to re-program their grants to include the new formulations.

Three countries (of the 22 HBC) reported using the new formulations. Challenges that have emerged in the first phase are insufficient information and training. In addition, it is difficult to co-administer the dispersible FDC with the non-dispersible Ethambutol. This is probably a challenge in many countries where HIV is also prevalent because the WHO recommendation in high HIV prevalent settings is to treat children with HRZE. The dispersible Ethambutol has been developed and currently in the WHO prequalification process.

This output is of low to medium relevance. Most governments and donors follow WHO guidance with regard to treatment recommendations. GF is the most important donor and always follows WHO guidance, but the GF does not allocate funding for specific activities such as childhood TB. Indicator O6.1 was therefore not well chosen, and overlapping with indicator O6.2. The target for indicator O6.2 was not ambitious as seen by a 62% over achievement. With regard to indicator O6.3 only one donor, Global Affairs Canada, committed funding specifically for 140,000 treatment courses in eligible countries with procurement through the GDF. Overall Output 6 was conducted effectively and efficiently, however because of the limited relevance this is of little importance to achieving the overall goal.

TB Alliance expended only about 20% of the available budget for this output. Of the budget, 54% was available for manufacturing support and “other” costs which was not used at all. Given all the funding that was available for manufacturer support under Output 4, allocating additional budgets for manufacturers under this output seems unnecessary.

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

	Indicator	End of Project Target (year)	Results
Indicator O7.1	# of paediatric stakeholders provided access to market data, business case, and other information	No targets: STEP-TB will track and report on various engagement activities with the following: governments, donors, NGOs/advocates, media, clinicians/regulators, and manufacturers	Information given remains to clarify
Indicator O7.2	Web portal developed and launched	Yes (2014)	Launched on World TB Day (24 March 2014)

Web-portal

The web portal was launched on World TB Day (24 March 2014) <https://www.tballiance.org/child-survival/child-tb-resources>. The website brings together various materials relevant to childhood TB

⁴ Technical briefing note: Technical step process to switch to new paediatric tuberculosis formulations. WHO, Stop TB Partnership GDF, Global Fund. WHO/EMP/PAU/2016.04

and is similar to the UNION's website

https://childhoodtb.theunion.org/info/additional_resources?locale=en.

The website contains links to guidelines for diagnosis and treatment of childhood TB from several countries, as well as global guidelines. The information seems very relevant for countries and organisations working in childhood TB although is probably of little interest to manufacturers of paediatric TB medicines.

Summary of Paediatric Advisory Group meetings and consultations

The project participated in several meetings on childhood TB including the UNION conferences and other regional meetings. The project supported participants that would not have participated otherwise. For example, in some of the regional meetings organised by WHO, the project invited paediatricians or representatives from Paediatric Associations to participate. These participants may not have otherwise been selected by the Ministry of Health for WHO organised meetings.

Symposium description and agenda

TB Alliance has actively participated in the World Conferences on Lung Health since the inception of the project. TB Alliance participated in the childhood TB sub-working group, organised symposia and brought implementers from around the world together.

The impact of these activities is not assessable in quantitative terms, however, in according to interviews conducted respondents confirmed the importance of these activities. The activities contributed to childhood TB being firmly placed on the global agenda, achievement of 20 of 22 project countries have adapted their guidelines and to the fact that 13 countries ordered, 7 received and 3 have started using the new formulations.

Summary of lessons-learned exchange

The lessons learnt sharing was included because of synergies that were thought to exist between the STEP-TB project and other TB Alliance projects. In practice, there were not so many synergies, and information sharing was limited to ad-hoc sessions mainly with individuals when useful.

Overview of media coverage of stakeholders and media event

The targeted timeline of Q2 2014 for the delivering an overview of media coverage seems not well thought out as this should have been a recurring activity, similar to the summary of lessons learnt exchange. In fact, TB Alliance did report on an ongoing basis on this activity in their semi- and annual reports. Several interviewees confirmed that the project had contributed to visibility of childhood TB, not only internationally but also within organisations. UNICEF is a good example as although for UNICEF the well-being of children is the very reason for their existence, their work related more to child health in general and to children's rights. Because of familiarity with the STEP-TB Project, UNICEF realised that as an organisation it should include TB in its work.

No cost extension (NCE) phase July 2016 – October 2016

TB Alliance discussed a NCE beginning of 2016 that was finalized under a Memorandum signed on 16 June 2016 for a six month extended timeframe up to 31 January 2017 (see timing in the workplan table below).

TB Alliance confirmed that all planned activities as per table 2 have been completed except the submission of a dossier to WHO prequalification of the two FDCs by Lupin and the pharmacokinetic study in infants (as discussed further below).

Table 2: Timelines for completion of remaining project deliverables (NCE transition plan)

Deliverable	Project Output	Jan-Mar	Apr-July	Aug-Oct	Nov-Jan*
Finalized model including country level burden estimates, TB/HIV and MDR-TB	Output 1	■	■		
Provision of paediatric drug supply and technical assistance to the SHINE Trial	Output 2	■			
Manuscript on current expert opinion the use of fluoroquinolones in children	Output 2	■	■		
Initiation of phase 2 trial of Bedaquiline for use in children	Output 4	■	■		
UNICEF consultation held on advancing integration of TB into MCH programs/initiatives	Output 5	■	■		
New and adapted job aids and technical resources available to TA providers and training conducted	Output 5	■	■		
Updated map of The Global Fund grants, Challenge TB work plans, national budgets and other funding sources.	Output 6	■	■		
Identification of countries with delays/shortfalls in funding needed to procure the FDCs	Output 6	■	■		
Convene Paediatric Advisory Group to inform strategy for product introduction/adoption	Output 7	■	■		
Thought Leader Webinar	Output 7	■	■		
Workshop with countries included in first iteration of MAP-IT to get feedback and test	Output 7	■	■		
Mid-term review and data analysis workshops with countries conducting inventory studies	Output 1	■	■	■	
Additional data on the weaknesses and needs in national capacity to access supply pipelines at least 7 countries	Output 1	■	■	■	
Report from the PmRN meeting highlighting countries committed to using the WHO Collaborative Registration Procedure	Output 3	■	■	■	
Evidence obtained showing registration process initiated for Macleods' FDCs in the 15 countries	Output 4	■	■	■	
Report of engagement with manufacturing partners (i.e., Macleods, Lupin, Janssen) and feedback on market sustainability	Output 4	■	■	■	
Stakeholder meetings in Bangladesh, Tanzania, Philippines, and Ethiopia	Output 5	■	■	■	
Transition plans developed in 8 priority countries	Output 5	■	■	■	
Availability of funding to provide one time support for activities related to first order and availability of new FDCs in early-adopter countries	Output 6	■	■	■	
Joint Symposium on Paediatrics at the Union World Conference	Output 7	■	■	■	
UNICEF co-sponsorship of an event on childhood TB at a global MCH conference	Output 7	■	■	■	
Interim Data generated on the non-NTP sector through inventory studies in Indonesia, Pakistan, and Vietnam.	Output 1	■	■	■	■
Interim clinical study report of the follow-on pK study to clarify the dosing recommendation for rifampicin for infants	Output 2	■	■	■	■
ASEAN Countries agree to joint review of the dossiers for the new FDCs through the WHO harmonization initiative	Output 3	■	■	■	■
Evidence obtained showing Macleods' completes the BE study and files application for fast track approval of the FDCs with the South African regulatory agency	Output 4	■	■	■	■

Deliverable	Project Output	Jan-Mar	Apr-July	Aug-Oct	Nov-Jan*
Annual report from TAG highlighting the investments globally in child TB	Output 6	■	■	■	■
Extended awareness campaign in conjunction with other partners on child TB treatment	Output 7	■	■	■	■
Announcement on dispersible ethambutol and Lupin's new FDCs	Output 7	■	■	■	■
Finalize MAP-IT and formally launch and promote through networks and social media.	Output 7	■	■	■	■
UNICEF to include TB two of their major child campaigns	Output 7	■	■	■	■
Timeline: ■ Active ■ Completed and Report Submitted ■ Completed ■ Partner Handover					
*Administrative close-out period for the project					

4.3 Market impact

Impact assessment framework

The evaluators followed UNITAID's recommendations and looked at the market impact along the five effective market dimensions as used in the UNITAID strategy framework which are: 1) innovation and availability, 2) quality, 3) affordability, 4) demand and adoption and 5) supply and delivery.

Definitions of each dimension as agreed with the GF can be seen in Annex 5.

In addition, we thought important to evaluate whether the STEP-TB project has achieved the market outcomes that were expected from the implementation of the grant and are outlined in the project plan.

Our findings from this two-pronged approach are given in the following paragraphs.

Innovation and availability

There is more to say about availability than about innovation. The new medicines have been strongly advertised as new child friendly dispersible tablets but they are not such an innovation; they differ from the previous formulations in the dosages only. Someone new to the TB area might even not know that some dispersible tablets of the same FDCs were already on the market though in different dosages.

That said, the uptake of the new formulations has taken off much better than the previous formulations. India for example did not use FDCs before, and has in 2016 accepted this form of treatment. A contributing factor to the uptake of the new formulations is that grant implementers have run an effective marketing campaign which has also influenced the adoption of the concept of treatment with fixed-dose combinations.

Thus, there is more to say about the impact at the availability dimension that is given below including some assessment in a short to long term

1 Introduction of new paediatric FDCs of first line drugs (achieved)

Two new FDCs (RH 75/50 mg and RHZ 75/50/150 mg) have been developed by the manufacturer MacLeods as per the cooperation agreement between MacLeods and TB Alliance, offering new paediatric TB medicines that meet the needs of end users. The new paediatric formulations are in the right doses aligned with WHO 2010 revised dosing guidelines. They are easy to administer as dispersible tablets, and have an added fruit-based flavour, raspberry for the 2-FDC and strawberry for the 3-FDC to distinguish the 2- and 3-drugs combinations. Currently, the new formulations from

MacLeods are globally available through the GDF supply mechanisms and introduction and use at country level has started. To date, about 15 months after the launch of the product, 13 of the 22 HBCs have ordered and 7 of these have received the new formulations (see Table 1). The two new products are under assessment for prequalification by the WHO.

2 Introduction of a new paediatric formulation of ethambutol 100 mg and of Isoniazid 100 mg (short term)

MacLeods has completed the development of a dispersible formulation of Ethambutol 100 mg (E-100) and of Isoniazid 100 mg (H-100) as per their manufacturer cooperation agreement. The new dispersible tablet of E-100 is under assessment for prequalification by the WHO. Due to its higher price, there are uncertainties that the new dispersible tablet of H-100 will replace the non-dispersible form that is currently used. MacLeods has the dispersible tablet H-100 in their catalogue but has not submitted a dossier to the WHO for prequalification yet.

3 Introduction of new regimens of second line drugs (medium to long term)

The long lag time from the launch of a new drug for adults to the launch of the childhood formulation is a constant barrier to getting new medicines for children. By integrating activities A2.3 and A2.4 aimed at investigating new paediatric developments from ongoing developments around Moxifloxacin and PA-824 in adults, and also activities towards paediatric development of Bedaquiline (associated with Indicator O4.3 and O4.4) though it was not initially planned, the STEP-TB project has contributed to further development of these medicines though they are not yet available.

4 Project high level goal partly achieved (short to longer term)

One of the five high-level goals of the project was 'Each of the three needed new paediatric formulations (HRZ, HR and E) made globally available by at least two manufacturers'. The end of project target of two manufacturers for dispersible ethambutol was revised to only one manufacturer with agreement from UNITAID. Based on this, at this end of project stage, the goal is partly achieved with potential for fuller achievement in the short term:

- The new paediatric FDCs RH 75/50 mg and RHZ 75/50/150 mg from MacLeods were launched in December 2015 ahead of the planned timeframe of the project.
- MacLeods has also completed the development of a new paediatric dispersible formulation of E-100 mg and a dossier is under assessment for prequalification by the WHO.
- During the first year of the project, TB Alliance entered into collaboration with three manufacturers under signed agreements: Lupin, MacLeods and Svizera, and all three have completed the development of improved dispersible formulations of the 2-FDCs RH 75/50 and 3-FDCs RHZ 75/50/150. However, only one manufacturer, MacLeods, has launched the two new FDCs within the timeframe of the project. Lupin has not submitted a dossier to WHO for prequalification, due to unexpected delays in completion of the needed bioequivalence study, submission is now planned Q2-Q3 2017. Svizera has not finalized the submission of the dossier for reasons that to the evaluators' understanding are not directly linked to the notice of concern (NOC) that is on Svizera, as was stated by TB Alliance in the last semi-annual report 2016 ('Due to quality violations, no new submissions from Svizera are accepted by WHO until violations are addressed').

5 Uncertainties around availability of the new paediatric formulations (medium to longer term)

From the evaluators' interviews with key stakeholders, there is a high level of confidence that another manufacturer will enter the market in 2017. In view of MacLeods engagement to develop the new formulations, there is also no doubt that the manufacturer would respond to new orders. In view that India is the largest TB market, that the leading manufacturers of TB drugs are based in India, and that the Indian government is committed and has been very collaborative with the STEP-TB project, we could assume that progress will continue to be made towards establishing a sustained

supply of the new formulations. However, at this point, we can not disregard a number of uncertainties that are linked to a situation of having just one supplier or this would assume that all factors that could affect the supply, quality and price sustainability of the new product available are well under control with no threat of supply disruption. This question needs to be further evaluated; likewise the question around what is the 'ideal' number of suppliers. Based on stakeholder interviews there are different opinions about the latter point. Of note, there are currently two dossiers for each FDC under assessment for prequalification by WHO. This should help to sustain the availability of the new formulations.

6 Regional aspects

As defined in the project plan, results from market research under Output 1 activities were expected to be utilized to encourage more manufacturers from different countries and regions to enter the market. It was also expected that both China and India would be brought into the process of creating appropriate formulations. Though much has been done, the STEP-TB Project has not fulfilled these expectations within the timeframe envisioned. From the evaluators' assessment, there is also little probability that there will be new market players coming from other regions in the short term, maybe with exceptions linked to the development of new TB drugs (e.g. Otsuka in Japan).

- All three manufacturers – Lupin, MacLeods and Svizera - have headquarters and production plants for TB drugs in India with the exception of Svizera which have headquarters in the Netherlands but also production plant in India. India is the place of the leading manufacturers of TB medicines. Lupin has been a leading manufacturer of TB drugs for decades and is the leading manufacturer of APIs for all first line drugs except Isoniazid. MacLeods entered the market more recently (1986) but is also a leading manufacturer of TB drugs. Out of the 93 TB medicines that are prequalified by WHO, 26 are from MacLeods, 11 are from Lupin. The two companies have been supplying the previous paediatric FDCs to GDF.
- From the evaluators' understanding, Indonesia is producing paediatric FDCs but the products are not WHO prequalified or ERP reviewed.
- China is unlikely to become an important market place for the production of paediatric formulations. Chinese manufacturers have been approached at the inception of the STEP-TB Project but none have entered into collaboration with TB Alliance. Fosun Pharmaceuticals could be one potential manufacturer and has been approached by the STEP-TB team (it is a partner of TB Alliance on other projects). However, the discussions have been more towards distribution purposes rather than manufacturing possibilities. Finally, China is not ready to adopt the new paediatric formulations for reasons given in the 'public health' impact section of this report.

From a rapid screen of the WHO list of prequalified TB drugs, the evaluators identified one potential manufacturer outside India that has not been approached by TB Alliance, Antibiotice SA in Romania. Antibiotice SA has all first line drugs and a FDC of Isoniazid and Rifampicin that are prequalified (date of prequalification 23 February 2013). Based on interviews with TB Alliance they "are unfamiliar with Antibiotice SA so did not approach them".

Quality

MacLeods' new FDCs have been approved by the WHO Expert Review Panel (ERP) and are currently in the GDF list of ERP reviewed products which are permitted for procurement during a limited period of time: expiry date of ERP review validity is 17/10/2017 for the 2-FDC and 31/01/2018 for the 3-FDC. The prequalification by WHO is still ongoing, however no indication about progress and likely timelines for completion of the prequalification step were made available due to confidentiality reasons.

Affordability

The introduction price of the new formulations was USD 2.41 per 84 tablets of RH 75/50 ex-works and USD 2.95 per 84 tablets RHZ 75/50/150 ex-works. The average treatment costs were USD 15 so in the range of the treatment costs with the previous formulations: USD 13 - 22 for a full course of treatment. This initial price was listed in the GDF catalogue in November 2015 and was the negotiated price between TB Alliance and Macleods.

Based on discussions with UNITAID the evaluators understood that a subsidy was given to the manufacturers to allow for a price reduction, however the evaluators could not clarify the price negotiations any further due to limited information. TB Alliance stated the following: ‘...the strategy and decisions made around the negotiations on the pricing of the new FDCs were agreed upon with UNITAID with input from the USAID and Global Fund. ... The initial strategy was to have two manufacturers launch within months of each other to enable competition to drive an affordable price...’ that could not be used due to the situation, ‘an alternative strategy was devised to ensure the market-entry price was affordable during the period where the product would be available from only one source’. Therefore, the evaluators cannot draw firm conclusions on what led to the price that was finally set.

The evaluators do not have price forecast information or any other information that allows making a ‘best guess’ on the FDCs price in the medium to long term. The existing available information on price indicates a slight increase between February 2016, just after launch of the product, and as of today one year later. Based on interviews, the evaluators were informed that this price increase is mainly due to slight increases in production costs.

Box of 84 tablets	February 2016 (source technical document for transition WHO/GDF/GF)	Current price February 2017 (GDF catalogue)
2-FDC RH 75/50	USD 2.41	USD 2.50
3-FDC RHZ 75/50/150	USD 2.95	USD 3.04

In the short term, information from interviews indicates that a price reduction is foreseen for 2017, but the evaluators have no specific information on when this will take place and to what level.

See also paragraph above ‘innovation and availability’ above.

Demand and adoption

All 22 high burden countries except China and the Russian Federation have adopted the WHO 2010 revised recommendations. Most countries are now in a transition phase towards replacing the ‘old’ formulations with the ‘new’ ones. Introduction of FDCs is unlikely in China for several reasons cited in the ‘public health impact’ section below and Russia where individualised treatment is the most usual treatment practice. Indonesia procures only from local producers.

The adoption of the recommendations, and on-going registration processes have occurred rather rapidly, however, this does not guarantee availability of the new formulations to end-users. Use of the new FDCs by non NTP healthcare providers is even less clear.

Supply and delivery

Impact on the supply and delivery dimensions is not expected under the project. Firstly, these were not objectives of the project and therefore it was not setup to address supply and delivery, and secondly, prior to the project a global supply and delivery chain system was already in place through the GDF. However, there has been indirect impact for different reasons as seen below.

First, there have been significant efforts to develop integration strategies for procurement and supply chain. Roadmaps were developed for several countries, WHO also held training of trainee workshops for in-country partners to create similar roadmaps in other countries, all these activities contributed to some impact on the supply and delivery dimensions.

Second, The STEP-TB Project contributed to identification of suboptimal functioning of the supply chain such as inadequate quantification and forecasting, and procurement of medicines as a mechanism to spend unspent grant money, which raised issues that could then be addressed.

Furthermore, the market research activities under Output 1 have provided a better understanding of the supply chain in the non-NTP sector.

Other Market impact

Today, childhood TB can no longer be ignored, and with this the market for TB products. Raising global awareness for childhood TB is seen as a major achievement as underlined in most interviews. Advocacy activities have contributed to this achievement significantly but also market research and to a lesser extent consultations around regulatory activities. In spite of all this, the childhood TB market remains small however, one would hope to see continued commitment from all stakeholders including the manufacturers, at least from a social responsibility perspective by contributing to global health, if not from an economic perspective.

Impact from advocacy activities

Strong advocacy efforts were included in the STEP-TB Project that has helped raised awareness about childhood TB. This happened in part driven by media coverage of the project and the product introduction, but also from increased interaction among all the non-governmental organisations and civil society groups during the product launch. This strengthened and increased collaboration has created a real momentum for change.

Impact from market research

The childhood TB burden estimates, prior to the project, were unprecise. The STEP-TB Project has helped to consolidate better estimates of the paediatric TB market size which the manufacturers can now use with more confidence to forecast sales. Through project activities, WHO and partners improved methods to estimate the childhood TB burden, which resulted in an estimated 1 million children with TB in 2015. Not only did methods for burden estimates improve, reporting from countries also improved and contributed to the revised estimates. The revised burden estimates should not be interpreted as a doubling of the burden, but as a much better estimate of the burden.

Impact from regulatory activities

The STEP-TB Project was expected to support the manufacturers in their development by providing a clear and efficient regulatory pathway. The evaluators could not assess the real impact here but can confirm that manufacturers are keen to receive further guidance as expressed by one manufacturer.

4.4 Public Health impact

Impact assessment framework

Jonathan Golub, associate professor at John Hopkins University Centre for Tuberculosis Research wrote: “You see the numbers of TB globally declining, but declining very slowly. And we’re very focused on new drugs, new drug regimens, new diagnostics, but we’re not focused enough on how

to implement what we currently have. Because I do believe that if we implemented everything we have optimally, then we would have a much stronger impact on global TB incidence.”⁵.

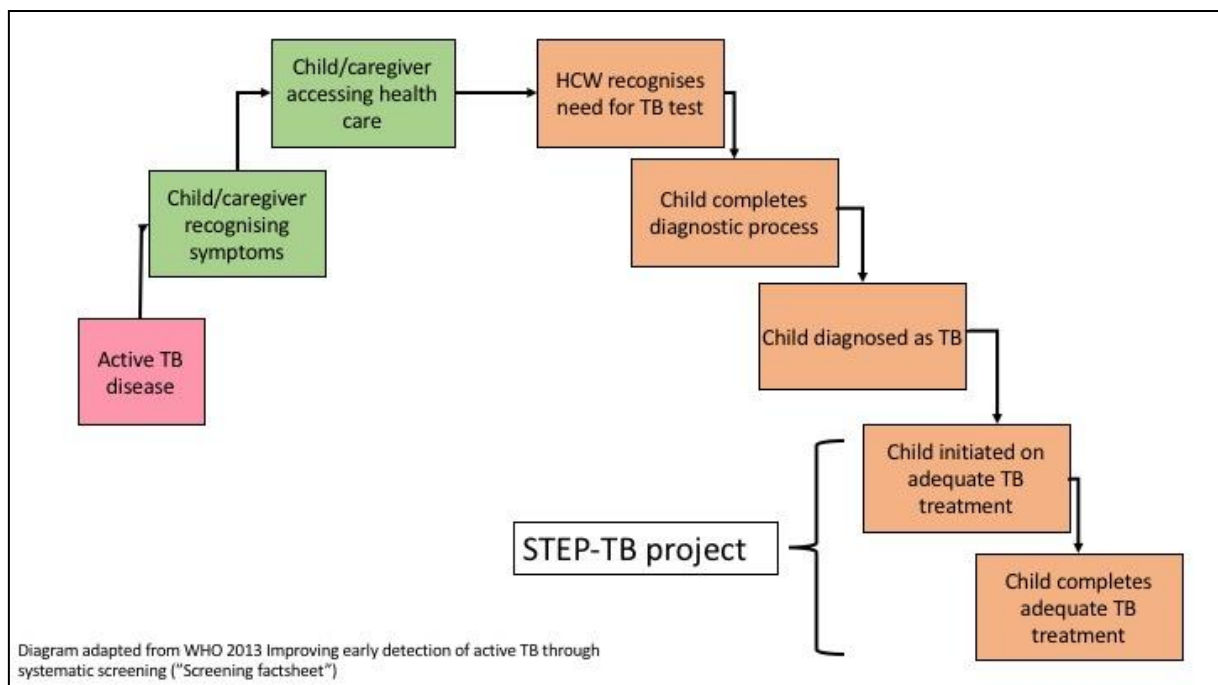
This certainly holds true for paediatric TB for which diagnosis is more challenging, even in well-resourced settings, let alone in countries where resources are scarce. Furthermore, children may not even access services where diagnosis is possible. To have public health impact, implementation of medication is a must.

Figure 1 shows that the STEP-TB Project has the potential to influence the last two parts of the TB care cascade with an emphasis of the adequacy of the treatment. Medicines for children with TB were available at the start of the project, however not in the correct dosage. It follows from this figure that direct public health impact could reasonably not be expected by the end of the project.

Assessment of the direct public health impact is not possible within the context of this evaluation. It would require patient level data of children treated with the new formulations which are not yet available. The first countries using the new formulations only started doing so in the second half of 2016, and treatment outcome data are not yet available.

The following looks at the public health impact related to the STEP-TB Project from two perspectives. The first is the change in policy guidance, often an important first step for implementation and subsequent public health impact. The second perspective explores issues such as future coverage of the products resulting from this project, potential decrease in morbidity and mortality, impact from regulatory aspects and availability of funding to use the products for the 22 project countries.

Figure 1: TB Care cascade: from existence of active TB to completion of treatment in children.



Green steps are the responsibility of the child or caregiver, orange steps are the responsibility of the for the health system. Some steps may be replaced by community systems (not shown)

⁵ Quote from: Treatment Action Group 2016 Report on Tuberculosis Research Funding Trends, 2005–2015: No time to lose.

Change in policy guidance

Output 5 focused on the change in policy guidance. Initially countries showed reluctance in changing their policies because of non-availability of the new medicines, as well as the introduction of the previous formulations which occurred just before the STEP-TB Project. This reluctance is understandable because of the steps that countries have to go through for the introduction of new medicines. The project conducted an assessment of the steps countries need to take to introduce new medicines.⁶ On average countries reported 10 steps relevant to this process, ranging from 7 in China to 13 in Bangladesh and Viet Nam. Core steps could take as long as 18-71 months.

Several factors influence adoption of new treatments such as reduction of the number of pills and cost of treatment, as well as the ease of administration of the medication and the recommendation by WHO. Of the 19 countries assessed, 11 considered the addition of the medicines to the essential medicine list by WHO relevant. This may have hampered introduction of the old formulations because these were not included in the WHO essential medicine list 2013 nor in 2015. WHO has since submitted an application for inclusion of the new child formulations to the list of essential medicines to be reviewed in 2017.

In all but two of the 22 project countries, frameworks or plans for transition that reflect the 2014 WHO treatment in children recommendations are in place. The two remaining countries, China and the Russian Federation, consider FDCs not ideal for treatment of TB in adults and children. These countries represent 11% of the estimated burden of childhood TB in the 22 project countries.

Future coverage of the project products

The order information of the new formulations (see table 1) shows that the countries where the products were delivered represent 52% of the estimated 2015 burden in HBC. With the order knowledge available at present, by the end of 2017, this percentage will have increased to 62%. It is critical that a large market such as India has accepted the new formulations. TB Alliance stated in their end of project presentation that globally countries had purchased 325,900 treatments and 240,000 been delivered. However, the order and procurement information available does not allow assessing coverage in the countries presently or for the near future. Reasons are that this coverage depends on several factors, amongst which are:

- Many countries will introduce the new formulations in a phased manner, and will use existing stocks of the old formulations in other places, even though WHO and UNICEF have issued a statement that old formulations should not be used anymore, and encourage countries to switch to the new ones.⁷ This statement is much stronger in recommending that the old formulations should no longer be used, than the technical briefing note from 2016.
- Countries may have funding left that needs to be spent, and procurement of medicines is a relatively easy way of spending grant money.
- When ordering, countries include buffer-stocks at times up to 100% or more.
- Availability in the country does not mean use in the country. Several interviewees cited medicines not being used due to inadequate and insufficient diagnosis, inadequate knowledge on how and when to use, and because the prescribing health worker does not know that the medicines are available in his area.

⁶ Malhotra S *et al.* From availability to uptake: planning for the introduction of new, child-friendly anti-tuberculosis formulations. *Int J Tuberc Lung Dis.* 2015 Dec; 19(12): S32–8.

⁷ WHO and UNICEF. [Statement on the use of child-friendly fixed-dose combinations for the treatment of TB in children.](#) 2017.

It is encouraging though to know that since the launch of the STEP-TB Project in Kenya in October 2016 (as an example) they have initiated more than 1,300 children on the new formulations, representing 21% of the number of children with TB notified in 2016 (preliminary data). It also shows that a specific launch, or a campaign bringing the new formulations under attention of all that need to know, may play an important role in uptake in countries. Implementing partners for TB and for child health could play an active part in supporting countries in such a campaign or launch.

The STEP-TB Project supported a TB technical officer at UNICEF's headquarters in New York. Although child health is one of the important parts of UNICEF's work, TB was not very visible in this. Through the support of the TB technical officer, TB has become much more integrated into the community tools that UNICEF develops and uses in countries which should contribute to increased future use of the products.

The new formulations became available at the end of 2015, and two factors could potentially have contributed to speeding up uptake:

1. Inclusion of procurement within the grant, compared to the previous UNITAID paediatric grant: if there had been a mechanism allowing eligible countries to receive the new formulations within the grant (for free), countries may have seen faster uptake.
2. If government and donors would have allowed countries to discard their existing stocks of the old formulations, countries may have ordered earlier. Because this did not occur, although GF would have allowed countries to re-programme their existing GF grants, countries were very reluctant to discard their existing stocks. This is among the reasons why GDF advocates for more frequent ordering of smaller quantities. A similar situation exists for countries wanting to shift to the shorter MDR-TB regimens.

Although most project countries are eligible to receive GF funding, more and more countries use domestic funding to cover first line medications. They may then procure the medicines where they want, and may not continue to use the new formulations.

Potential number of lives saved

This evaluation did not try to assess the number of potentially saved lives because of too many uncertainties as outlined below.

The most recent WHO estimation of the mortality of children is 210,000 of the estimated 1 million children that developed TB in 2015.⁸ However, a recent published systematic review suggests that most of this mortality may be because of children not starting treatment.⁹ The review found mortality in treated children is low (1%) compared to non-treated children (22%). This would suggest that improved medicines may not contribute much to reduced mortality.

There are several limitations to this systematic review. It included mainly studies from low TB prevalence countries. Of these studies only five (of the 18) were from the 22 project countries of which three from China. All but one of the five studies consisted of small groups. The non-China studies were from Africa, where the mortality rate was 3%. The WHO mortality estimates are substantially higher and differ by region from 2% in the European to 34% in the African region. The

⁸ WHO Global tuberculosis report. 2016.

⁹ Jenkins *et al.* Mortality in children diagnosed with tuberculosis: a systematic review and meta-analysis. *Lancet Infect Dis.* 2016 Dec 7.

global mortality estimate is 22%. The estimates make no distinction between treated and non-treated children, and therefore make assessment of the impact of an improved formulation impossible.

Furthermore, it is not clear whether the new formulations will improve treatment adherence, and even more importantly, treatment outcomes. When the evaluators discussed this issue in interviews, responses varied between ‘yes possibly these formulations will improve adherence’ and ‘we would hope so’. A trial comparing the treatment outcomes between the old formulations and the new ones would not be ethical, and therefore a direct comparison impossible to do.

Lastly, when children on TB treatment die, they may die of TB or they may die with TB but of other causes. This distinction is not important at the individual level, but may be relevant when accessing impact of the new formulations on lives saved. One would expect a larger impact on children dying with TB.

To assess impact of the new formulations on lives saved, one would need at least patient level data comparing groups treated with the old formulations and groups treated with the new formulations. This is only possible through observational studies and has therefore some limitations. In addition, one would need to collect data on adherence with both old and new formulations.

Availability of funding to use the project products

Output 6 discusses briefly the availability of funding for products. In 2017, many countries will submit concept notes or plans to continue activities to GF. As outlined above, GF is committed to support introduction of and transition to the new formulations. In theory, funding would not be a limiting factor. However, for countries ordering directly from manufacturers or with their own funding, GF cannot oblige countries to procure the new formulations.

Challenge TB, a USAID funded project for TB care and prevention, implemented by a coalition of partners from 2014 to 2019, is also committed to support the scale up of the new formulations in children. USAID was also a donor in the STEP-TB Project, and the results of the STEP-TB Project have supported annual plan development in the Challenge TB Project countries, of which 15 are also STEP-TB Project countries.

5 Evaluation discussion

5.1 Progress Assessment under the UNITAID Grant Evaluation Framework

In conclusion, using the UNITAID grant evaluation framework, the evaluators rated the various criteria as follows:

Relevance: rated as high

1. The project targeted several gaps in the TB paediatric market. The project contributed to better estimates of the burden of childhood TB, which is important information for medicine manufacturers. The new estimate is that there are around 1 million child TB patients, whereas previous estimates were about half of that. Obviously, this does not mean that the incidence of childhood TB has doubled; it means that the estimates are much more reliable. This has not resulted in a decrease of the uncertainty intervals reported in the WHO Global TB reports compared to previous years, however, the figures as reported in the 2013-2016 reports cannot be compared. The methods used to estimate the differences are not the same and therefore the

uncertainty intervals. This can be seen in the WHO database¹⁰ where age and sex disaggregated estimates are only provided for 2015.

2. In addition, at the launch of the project there were no child friendly formulations in the market in the correct dosage. Manufacturers were hesitant to develop these because they had just received prequalification for the previous dose recommendations. The project encouraged at least one manufacturer to develop these formulations within a short timeframe which, although not prequalified yet, have an ERP review for time limited procurement.
3. The project contributed to two of UNITAID's six strategic objectives: Objective 2 to increase access to affordable paediatric medicines for tuberculosis, and Objective 6 to increase access to products for the prevention of TB, because the best prevention of TB is prompt and adequate treatment of diagnosed patients. Although the project did not secure supply of second-line TB medicines, nor did it increase access to emerging medicines and regimens (Objective 5), the project contributed towards Objective 5 by integrating additional paediatric development activities from ongoing development in adults such as around Moxifloxacin, PA-824 and Bedaquiline.

Effectiveness: rated medium to high

1. The outputs of the grant were consistent with the objectives and expected outcomes as described in the project plan. All activities were developed as per project plan and most deliverables were completed within the timeframe of the project. Some deliverables were reassessed throughout the project as a result of the implementation of the activities that is intrinsic to every project progressing. The project was conducted in an effective way with regular evaluations and rethinking of some activities as needed, in light of results generated from various studies and challenges encountered.
2. UNITAID was informed about the progress of the project through reports sent on a semi- and annual basis, quarterly meetings and emails or calls with TB Alliance. UNITAID has been involved in discussions and decision making on the changes. One major change has been the integration of the Bedaquiline study under Output 4 from reallocation of unused funds initially dedicated to engage the manufacturers.
3. The outputs of the project were largely achieved within the timeframe specified in the initial project plan and even ahead for some activities. In early 2016, a no cost extension phase was agreed with UNITAID to further achieve the outcomes anticipated from the implementation of the grant and to maximize the impact in the longer term. Two main activities could not be completed within the overall project timeframe as expected: 1- Results from the pharmacokinetic study in infants under Output 2 showed lower than expected and variable levels of Rifampicin plasma concentration that required further clinical investigation. A follow-up study was initiated during the NCE phase and is ongoing; 2- Announcement on dispersible Ethambutol from MacLeods and on Lupin's new FDCs was expected early 2017, this has not been done yet. As a result of this latter point not achieved, the high level goal initially defined- each of the 3 formulations (HRZ, HR and E) made globally available by at least 2 manufacturers - is only partially fulfilled.
4. Factors were considered to ensure that value for money has been achieved. Efforts were made throughout the entire project to ensure the overall goal is achieved, and to some degree, that anticipated next steps are in place to ensure the new formulations are not only available but also used. The NCE phase was particularly illustrative in this sense. A potential weakness is that it might have been good to anticipate certain steps earlier, such as steps related to implementation of the formulations.

¹⁰ Accessed January 16th, 2017 via <http://www.who.int/tb/country/data/download/en/>.

Efficiency: rated as medium

1. National authorities were aware of the project through the activities TB Alliance undertook during the Union conferences, and organized meetings including an initial meeting in 2013 and again in June 2016. However, national authorities do not seem to have been involved in project planning, implementation and assessment. For the assessments described in the paper by Malhotra *et al*, as well as Management Sciences for Health's (MSH) work in countries, it seems that national authorities were on the receiving end of the activities, but not really involved in their planning and development. And although much work has been done in the project countries as well as during international meetings, one of the NTP managers of a project country replied to the evaluators that his country was not involved in the STEP-TB Project, when he received the evaluation on-line survey questionnaire.
2. Implementation of the grant could have been much more effective and efficient had implementing partners, and partners such as UNICEF, been involved from an earlier stage. Partners such as the Challenge TB have country presence in 15 of the project countries, and earlier involvement may have led to earlier uptake and use of the medicines.
3. Implementation arrangements of the grantee and co-implementers have not been clear. Selection of partners to conduct part of the activities has not been documented. The evaluators requested this information from TB Alliance which helped to clarify selection of partners to a certain extent. However, integrating such information into the reports would provide more transparency.

Impact: rated as medium

1. The grantee has been able to report on impact as originally framed in the project plan and Log-Frame to some extent. The original log frame contained two impact indicators: 1) GDF and/or other procurement agencies include new formulations in procurement plans; and 2) At least 25% of the total GDF paediatric allocation is directed towards new formulations. To that extent, GDF included the new formulation into its products list and removed the old formulations. However, the importance is that countries order the new formulations, which has occurred as well: 11 of the 22 project countries have ordered the new products.
2. The grantee can attribute UNITAID's financial support to patients treated to a limited degree. The launch of the medicines in Kenya was supported through grant money, but to the evaluators' knowledge that is the only country that received such support. Introduction and use in other countries may be indirectly attributable to grant money because of advocacy that the grantee conducted which led to increased awareness in many countries. However, now that the project has ended, it is unsure whether further implementation will be supported and by whom, which may limit the use of the new formulations for children with TB.
3. The evaluators could not assess direct impact of the project in the sense of improved treatment outcomes and increased numbers of children initiated on TB treatment with the new formulations for reasons previously stated - as this is the most important impact, the project was rated as medium.

Learning and risk mitigation: rated as medium

1. The project disseminated information and has contributed to the visibility of childhood TB. It is not clear to the evaluators however, whether this visibility contained lessons learnt, and how certain lessons contributed to improved implementation. This has been a lack of documentation throughout the project.
2. The mid-term evaluation report included recommendations for future projects rather than for this project. This seems a missed opportunity because the project still had 18 months of implementation left at the time of the report publication in March 2015. However, some of the recommendations were pertinent to the project such as supporting national programmes to streamline procurement and providing technical assistance and cooperation with other

organisations focusing on child health. To a certain extent, the project did provide technical support including to national programmes on procurement, but not to all countries.

5.2 Project Weaknesses

Insufficient focus on the main objective

By including many activities as defined in the STEP-TB Project, the project may have had insufficient focus on the main objective of making new child friendly formulations available, e.g. activities around PA-824 and moxifloxacin under Output 2 or some new activities that were initially not planned, such as development of a child formulation for Bedaquiline. Though interesting, these parallel activities give the impression of having diluted the activities that were essential to reach the main objective of the project, likewise the budget associated to these activities. In the evaluators' view, the project may have had more impact thrived under a different grant design focussing on just one objective being the, introduction of new FDCs that are in line with the revised WHO guidelines and from clearly outlining steps from development to registration and implementation of the new medicines. The other activities then could be the subject of different independent grants.

Documentation

The project has generated a great deal of information and data from implemented studies or consultations with experts and most of these outcomes have been reported or published in different sources of information. Reporting on the activities and making the information available to public was also part of the project plan. However, from the evaluators' view, this important part of the project has not been produced in an optimal way as highlighted below.

The information resulting from the project, mainly studies, has been made available in a fragmented manner and is dispersed in many different sources of information making it more difficult to dig out the key outcomes of the studies. First, the tremendous amount of results and data has to be seen as a 'value for money' product from the implementation of the project. The value for UNITAID would have been in part to receive a full package of information including all publications that came out from the project and organized in such a way that specific outcomes of the project can be retrieved easily by anybody new to the project and at any time.

In addition, it would have been good if the project had generated an overview of the achieved work showing how the different pieces had all contributed to the overall goal of increasing access to optimal paediatric TB medicines. An additional deliverable to cover these added values: compile and organize the full documentation produced throughout the project and produce an overview of the achieved work as described would have supported knowledge transfer and lessons learnt.

Furthermore, the information should not only be available to UNITAID but also to stakeholders in the childhood TB community in a comprehensive manner as per signed agreements with UNITAID. However, some information is tied by confidentiality agreements of TB Alliance with the manufacturers and by WHO confidentiality policy on the dossiers under assessment for prequalification which limits access to useful information such childhood TB medicines that are under development.

Finally, UNITAID has not been acknowledged systematically in published documentation, for instance the paper of Malhotra *et al.* does not acknowledge UNITAID as the funder.

Market research

There is a general agreement that the STEP-TB Project has contributed significantly to better understanding of the TB burden among children. It also built a strong community of methodological specialists and an analytical framework has been developed. Today a more solid basis to keep

working on improved estimates and updates exists due to the project. In parallel, the STEP-TB Project has gathered more information about the players in the TB medicines market and fostered collaboration with a number of manufacturers.

The picture is however not complete. First, significant effort has been put into market research, but the outputs remain as stand-alone dispersed studies and we do not see the final conclusions and do not get a complete overview of what has been done and the results of these activities. A comprehensive compilation and analysis of the findings from all different studies performed would have been useful and could have been included in Output 1.

Second, it would have been useful to conduct a market study by market research experts in order to generate a more comprehensive overview of the childhood TB market. There have been efforts in this direction with Results for Development but with little success. Some of this information may be also hidden in the manufacturers' assessment that TB Alliance declined to provide to the evaluators based on confidentiality clauses with the manufacturers. For all these reasons, important information is "missing" from the market assessment activities such as a list of all potential manufacturers including a company profile (including information on – amongst others - TB drugs produced and under development, WHO PQ drugs, site of the manufacturing plant, capacity, turnover, expertise in paediatric TB, and in developing formulations) as part of the STEP-TB Project which can serve future projects. There is also a lack of clarity regarding why some companies are in this market that is constantly described as a very small market, why other companies are not.

Partner involvement and selection

The project reports did not contain information on co-implementer or partner selection therefore the selection criteria are unknown to the evaluators and responses from TB Alliance did not always clarify why a certain partner was selected. The WHO is a very obvious co-implementer and conducted activities as such, however, Challenge TB may have been another obvious co-implementer with their presence in 15 of the project countries. Challenge TB was not directly involved, although one of the Challenge TB partners, MSH, did work on national level procurement and transition plans. They did this in 8 of the 22 project countries. In addition, USAID, the funder of the Challenge TB Initiative, was a co-donor on the STEP-TB Project. Challenge TB did include the new formulations in their work plans.

Several interviewees mentioned that TB Alliance worked in isolation initially, which may have resulted in implementation delays. The kick off meeting could have been a good place to encourage the manufacturers – being the most important target of the project – however they were not invited. As a product developer TB Alliance has a different relationship with manufacturers compared to an organisation such as the GDF. GDF has worked with manufacturers for many years, and may have been better placed to conduct certain activities, such as price negotiations, than TB Alliance.

5.3 Implementation of the new products in country

Most of the project countries have adopted the revised childhood TB dosage recommendation that are reflected in national guidelines, or countries have plans in place to transition to the new dosage. This is a great achievement of the project, however, adopting a guideline does not necessarily mean that the product arrives where it should: the child with TB. Of the project countries, Kenya and Pakistan confirmed use of the new formulations in children. Bangladesh and the Philippines received the new formulations but did not provide information on their use.

Processes or issues that may delay actual use of the new formulations for all children in the country include: registration issues, training and mentoring on correct use, distribution to all health facilities where children with TB receive treatment, and using existing stocks first are among them. It is not clear how these processes and issues will be dealt with now that the project has ended. Challenge TB

will encourage all countries where they work to use the correct formulations, however, some countries such as Nigeria still has a stock of the old formulations lasting until February 2018. If donors including UNITAID and governments consider a speedy implementation and use of the new products important, they may need encouragement to write off existing stocks.

5.4 Manufacturers' engagement and Supply Diversity

TB Alliance has signed an agreement with three manufacturers to develop the new formulations in two different types of agreements: A MoU was signed with Lupin and Svizera whereas a manufacturer cooperation agreement was signed with MacLeods. The MoU signed with Lupin and Svizera was limited to the two 2-FDCs RH 75/50 and 3-FDCs RHZ 75/50/150 whereas the cooperation agreement signed with MacLeods also included the dispersible formulations of the two single drugs E-100 and H-100. A financial incentive was budgeted in the project plan as part of a strategy to engage manufacturers. Lupin and Svizera declined the incentive while MacLeods took the incentive. Svizera did not accept the financial incentive mainly because this was not in line with the corporate policy of the company, whereas Lupin declined because the company wanted to remain independent (free of financial agreements) and did not see any need of external resources.

All three manufacturing partners – MacLeods, Lupin and Svizera – have completed the development of improved dispersible formulations of the 2-FDCs RH 75/50 and 3-FDCs RHZ 75/50/150 within the timeframe of the project, and one manufacturer - MacLeods - has also completed the development of the single drugs formulations H-100 and E-100 as per manufacturer agreement. However, only one manufacturer - MacLeods – has completed the submission of a dossier to WHO for prequalification of the two FDCs, likewise for the single drug E-100, and also launched the two new FDCs within the timeframe of the project. Lupin has encountered some unexpected delays and is likely to submit a dossier for prequalification of the two FDCs in Q2-Q3 2017. Svizera was very committed and has made progress towards the development of the new formulations, but has not completed the submission of a dossier for prequalification of the two FDCs.

In fact, what appeared as a solid basis towards moving efficiently to achieve the project goal with three manufacturing partners on board turned out to be less successful. At present, none of the high-level goals are fully achieved: each of the 3 formulations (HRZ, HR and E) made globally available by at least 2 manufacturers and a minimum of 2 but a target of 3 manufacturers enter the market.

One immediate conclusion seems to be that one gets the product if one pays for it. However, it remains unclear the potential effects of not providing a financial incentive, except that the launch of the new FDCs could have been delayed. Manufacturers were asked if they would have included the development of the new FDCs in their product development pipeline, without the STEP-TB Project. The answers were clearly yes. Svizera had been aware of the WHO revised guidelines and was already engaged at the inception of the project in developing new dispersible correctly dosed FDCs. As leading manufacturers of TB medicines, Lupin and MacLeods would also have moved into that direction of adapting to the new WHO guidelines.

From the manufacturers' experience of the previous formulations, in particular of sporadic orders that were below their production capacity, their major concern was about the market demand. By consolidating the demand, the STEP-TB Project has addressed this concern. In addition to this, the financial incentive that was taken by MacLeods has played a significant role in catalysing the development steps and helped to achieve product development targets within the timeframe of the project. This contribution of the financial incentive was confirmed in interviews. In the meantime, by providing financial support to one company and not to the others, there is the risk of creating an unfavourable situation by creating an unequal basis of collaboration; this was expressed in one interview even though it was the companies themselves that declined the incentives.

Moving a bit further into this discussion, we can also question the amount of the financial incentive, if any. The initial project proposal was built on the assumption that the product development costs would be shared between the manufacturer (60%) and UNITAID funding (40%). The agreement signed with MacLeods includes the full development process up to adoption of the new formulations by the countries, that is including submission of a dossier to WHO for prequalification of the new medicines and registration in the countries. The evaluators did not have sufficient information to determine the percentage of the total costs that has been shared by MacLeods. Depending on this cost sharing, it could be considered that MacLeods has been cooperating more like a service provider or more like a committed manufacturer. Another scenario could be that the company would have covered all product development costs, which MacLeods seems to be doing with second line drugs (ref TAG 2016 Report on Tuberculosis Research Funding Trends, 2005–2015: No Time to Lose), steps of registration and implementation would be covered by the grant.

In short, the STEP-TB project has confirmed that the major driving force to engage the manufacturers is the ‘market demand’. It has also shown that a strategy based on some financial incentive can help to reach product development targets especially time targets but this is not the main driving force. This is an interesting outcome of the project that clearly merits to be further evaluated by UNITAID to serve future projects.

Interestingly, two dossiers per each dispersible FDC RH 75/50 and RHZ 75/50/150 are currently under assessment for prequalification by WHO. One dossier is from MacLeods that is a direct result from the STEP-TB project. However, the second dossier is not from any of the two other manufacturing partners engaged in the project which are Lupin and Svizera. Whether this second dossier can be some indirect result of the STEP-TB project remains to be clarified. In any case, it would be good to know what main motivations have pushed this second manufacturer to develop the new FDCs, especially considering that the paediatric TB medicines is described as a market that is too small to be of interest for a manufacturer.

5.5 Adopt a more comprehensive theory of change

The theory of change was based on the framework and assumptions as described in ‘Background of the STEP-TB project’.

The assumptions used in the theory of change seemed to be based on the concept that with increased access to optimal paediatric TB medicines, more children would receive treatment, better adhere to long treatment and have better treatment outcomes. However, early on in the project it became clear that although the existing medicines were not ideal for children and form a barrier to initiate treatment, the medicines itself were not the only challenge to overcome. Consultation with countries and implementing agencies revealed that diagnosing children posed and continues to pose a more serious bottleneck. Diagnosis of TB in children is challenging because children often have a low bacteriological load and young children cannot produce a sputum sample. In addition, children with TB are often not reported to NTPs, and may or may not receive adequate treatment outside the NTP.

Looking at the TB care cascade (Figure 1), the STEP-TB project would probably have most impact at the final two steps: initiation and completion of treatment. The figure makes clear that even with increased access to optimal paediatric TB medicines, the public health impact in terms of children put on treatment and lives saved would be limited.

To change the landscape of childhood TB, a much more comprehensive approach is required, as outlined in the roadmap for childhood TB.¹¹ The roadmap includes several steps that align with the outcomes listed in the theory of change, partly or completely: collect and report better data is part of output 1; develop policy guidance for health care workers is reflected in output 5; output 1 and 2 pertain to addressing research gaps; and output 6 contributes to meeting the funding needs for childhood TB.

The last key priority action identified in the roadmap is “form coalitions and partnerships to improve tools for diagnosis and treatment”. Though the STEP-TB project did not set out to contribute to this last key priority action, this evaluation has shown that in fact the project had a considerable contribution to putting childhood TB firmly on the agenda. The project brought stakeholders together that before usually did not meet such as national paediatric associations’ representatives, NTPs and implementing partners. A shared understanding that collaborative efforts are needed to work towards the ambitious goals of the END TB Strategy and the roadmap for childhood TB has catalysed forces.

This shows that for future initiatives related to childhood TB to effectively serve as a game changer, a more comprehensive theory of change should be developed, involving a wider range of actors and including more steps of the TB care cascade. This is not to say that the full cascade should be addressed by one project, however, the more aspects of the cascade projects cover, the higher the public health impact will be.

6 Recommendations

1. Most of the project countries have adopted the revised childhood TB dosage recommendation that are reflected in national guidelines and are in transition to the new dosage; dissemination of critical information and collaborative methods of working with countries has much contributed to this. In addition, the implementing partners have run an effective marketing campaign around the new fixed-dose combinations that has significantly contributed to the adoption of these new paediatric formulations. These activities have been important success factors in the STEP-TB project that future projects focusing on introduction of new products could draw upon.
2. In spite of this major achievement, a number of issues however remain to be addressed so that the product arrives where it should: the child with TB. Future projects should continue to design a number of implementation steps, and related budget allocations. Product implementation steps should be built in to the design phase of the project.
3. The STEP-TB project has confirmed that the major driving force to engage the manufacturers is market demand. Provision of financial incentives as a tool to engage manufacturers, as defined in the STEP-TB Project, can help to reach product development targets, especially time targets, but was not seen as a major driving force. Therefore, it is recommended that UNITAD conduct research even further into what motivates manufacturers to develop new products for a small market such as the paediatric TB medicines and use the findings to better inform future project design.

¹¹ WHO/IUATLD/CDC/UNICEF/TAG/USAID. Roadmap for childhood tuberculosis: towards zero deaths. ((WHO/HTM/TB/2013.12). WHO; 2013.

4. The assumptions used in the theory of change are grounded in the concept that with increased access to optimal paediatric TB medicines, more children would receive treatment, better adhere to long treatment and have better treatment outcomes. However, early on in the project it became clear that although the existing medicines were not ideal for children and form a barrier to initiate treatment, the medicines themselves were not the only challenge to overcome. It is recommended that a more comprehensive approach to developing the theory of change (the blueprint of project design) which underpins all of the assumptions around implementation is undertaken in order to effectively address, and ultimately change, the landscape of childhood TB.
5. Future project design should take into consideration the complexity of implementing a new formulation and the need to focus on just one objective - the introduction of the new fixed-dose combinations rather than spreading itself too thin with other activities. Potential models of introduction of medicines could include smaller grants allocated with clearly outlined steps from development up to registration. Selection of partners would need to be aligned with these steps to ensure partners with required skills and experience are selected.
6. The long lag time from the launch of a new drug for adults to the launch of the childhood formulation is a constant barrier to introducing new medicines for children. The results from activities around Moxifloxacin and PA-824 (Pretomanid) that were conducted under Output 2, suggest that it might have been good to focus on very specific activities built upon consolidated study results in adults or not include these activities at all at this development stage in adults. This is an interesting finding that can serve future projects in the design of the most optimal timing for the development of new paediatric medicines from advanced new drug developments in adults to the corresponding formulations adapted to children.
7. The evaluation of STEP-TB project has identified a certain lack of visibility and acknowledgment of UNITAID's grant throughout the project. Future projects should clearly acknowledge the donor in all its output and UNITAID should consider including this aspect in the grant agreement.

Annexes

ANNEX 1: TERMS OF REFERENCE

Terms of Reference as received from UNITAID



TORs

ANNEX 2: UNITAID EVALUATION FRAMEWORK

<p>Relevance</p> <ol style="list-style-type: none"> 1. Are the outcome(s) and impact(s) of the grant aligned with UNITAID's overall mission to contribute to the scale up of and access to treatment for HIV/AIDS, malaria and TB for the most disadvantaged populations in developing countries using innovative global market based approaches? 2. How did the grant contribute to one or more of UNITAID's six strategic objectives? (Refer to Annex 3 for the strategic objectives)
<p>Effectiveness</p> <ol style="list-style-type: none"> 1. Are the outputs of the grant consistent with the objectives and expected outcomes as described in the project plan? If changes have been made, has the UNITAID Secretariat been involved in discussions and decision making on the changes? 2. Were the outputs of the project for the evaluation period fully achieved within the timeframe and budget specified in the initial project plan? 3. What are the main factors influencing the achievement or non-achievement of the outputs or overall outcomes across all countries and within each beneficiary country? 4. What factors have been considered to ensure that value for money has been achieved?
<p>Efficiency</p> <ol style="list-style-type: none"> 1. Have the grant implementer and co-implementers ensured project planning, implementation and assessment in collaboration with the national authorities? Can the grant implementers and their partners demonstrate that national authorities were aware and participating in grant activities at the national level? 2. How cost efficient and cost effective was grant implementation? 3. Were challenges raised with the UNITAID Secretariat in a timely manner and did the Secretariat participate in resolving these challenges? 4. Was the grant's procurement model designed to identify and solve procurement-related problems (where applicable)? 5. Were there any concerns or reported instances related to potential diversion of products, counterfeit products or poor quality products? 6. Is the grantee implementation arrangement and coordination with co-implementers and national and sub-national authorities efficient?
<p>Impact</p> <ol style="list-style-type: none"> 1. Has the grantee been able to report on impact as originally framed in the project plan and Log-Frame? If not, has the grant impact been measured in another way? 2. Where relevant, can the grantee attribute UNITAID's financial support for medicines, diagnostics or preventive products purchased to patients tested or treated in each beneficiary country?
<p>Learning & Risk mitigation</p> <ol style="list-style-type: none"> 1. Have lessons learnt been documented and widely disseminated by grantees and UNITAID? 2. Have programmatic and financial risks been identified and tracked over the course of grant implementation? 3. Have the findings and recommendations of audits (where relevant) been used to improve grant performance?

ANNEX 3: 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 paediatric 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

ANNEX 4: ONLINE SURVEY QUESTIONNAIRE



Survey as
published.pdf

ANNEX 5: EFFECTIVE MARKET DIMENSIONS



Effective market
dimensions.pptx

ANNEX 6: INTERVIEWS LIST

Organization	Name	Title/Affiliation	Status
UNITAID	Y. Mundade	Program Manager	Interviewed
	O. Mwerinde	Monitoring and Evaluation Officer, Strategy & Results	Interviewed
	L. L. Witherspoon	Senior Advisor, Procurement & Supply Chain Management	Interviewed
	G. Ramachandran	Grant Finance Officer	Interviewed
TB Alliance	C. Scott	Director, Paediatric Programs	Interviewed
	S. Cook-Scalise	Senior Program Specialist, Market Access & External Affairs	Interviewed
	R. Taneja	Senior Director, Pharmaceutical Product Development	Interviewed
	S. Malhotra	Director, Market Access	Interviewed
	I. Usherenko	Program Coordinator, Paediatrics	Interviewed
WHO	A. Brands	WHO GTB Technical Officer Technical Support Coordination	Interviewed
	B. Sismanidis	WHO GTB, TB Monitoring and Evaluation	Email communication
	L. Hedman	WHO EM, Access and supply chain, group lead	Facilitated some interview
	W. Z. Worku	WHO PQ, Technical officer, Prequalification Team- Medicines	Interviewed
Manufacturers	Macleods	Vijay Agarwal, Business Development Director	Interviewed
	Lupin	Mukul Jerath, General manager	Interviewed
	Svizera	Boudewijn Ploos van Amstel, Managing director	Interviewed
GDF	B. Waning,	Head of GDF	Interviewed
	A. Zagorski	Manager	Interviewed
GFATM	A. Scardigli	TB technical officer	Interviewed
	A. Perez	Senior Specialist, Health Products Management, Southern Africa Team Africa and Middle East Department	Email communication
	A. Prat	Quality Assurance Specialist	Email communication
UNICEF US	A. Detjen	Health Specialist, Childhood TB	Interviewed
TAG	L. McKenna	Lindsay McKenna, Senior TB/HIV Project Officer;	Interviewed
	E. Lessem	TB/HIV Project Director	Interviewed
MSH	M. Soucy	Technical Advisor, Pharmaceuticals and Health Technologies Group	Interviewed
	P. Paredes	Deputy Director, Technical Strategy and Quality Unit Pharmaceuticals and Health Technologies Group	Interviewed
USAID	Y. Mukadi	Senior TB Technical Advisor	Interviewed
KNCV Tuberculosis	C. Erkens	Senior Consultant	Interviewed

Foundation			
Advisors, Childhood TB working group	S. Graham	University of Melbourne, Centre for International Child Health, Dept of Pediatrics/International Union Against Tuberculosis and Lung Disease, France	Email communication
	F. Maqbool	Pediatric TB Program, Interactive Research and Development (IRD), Associate Director	Email communication
Mapping Health, questions about China	Ioana Ursu PharmD, MSc	Director	Interviewed

ANNEX 7: DOCUMENTS LIST

Document/Output	Section	Reviewed
Grant Agreements and project plans	Grant agreement between UNITAID and TB Alliance signed July 2013	Yes
	Grant agreement between UNITAID and WHO signed November 2013	Yes
	Project proposal	Yes
	Project plan dated 17 July 2013	Yes
	No cost extension (NCE) transition plan and amendment	Yes
	Project Logframe	Yes
UNITAID Documents	UNITAID's Feedback on TB Alliance annual report 2013 and semi-annual report 2014	Yes
	STEP-TB mid-term review 2015	Yes
	Effective market dimensions as agreed between GF and GDF	Yes
TB Alliance Reports	Annual reports 2013, 2014, 2015	Yes
	Semi-annual report 2014, 2015, 2016	Yes
	Project LogFrame updates	Yes
MoU or Agreements with Manufacturers	Svizera (MoU) signed September 2013	Yes
	Macleods (manufacturer cooperation agreement) signed March 2014	Yes
	Lupin (MoU) signed June 2014	Yes
	Janssen (5 th amendment) signed June 2016	Yes
Agreements with other partners	Statement Of Work with MSH signed November 2015	Yes
	Agreement with UNICEF	yes
Project-Related Meetings or consultations	Meeting Summary, Global consultation on paediatric TB September 2013	Yes
	Global Consultation on Childhood TB for HBCs in the Eastern Mediterranean, South East Asia and Western Pacific regions, 29Sept. 1Oct. 2014	Yes
	UNICEF consultation on childhood TB integration: strengthening community and PHC for TB, September 2016	Yes
	Summary, Moxifloxacin consultation meeting, November 2014	Yes
	STEP-TB project Close out meeting 31 January 2017 presentation and meeting summary	Yes
Study Reports	O1: Survey of policy and practice in the treatment of paediatric TB in high-burden countries	Yes
	O1: Rapid assessments of the treatment of paediatric TB outside of NTP facilities	Yes
	O1: Mathematical modelling estimates of the burden of childhood TB in the 22 high-burden countries (report and Lancet paper by P. Dodd <i>et al.</i>)	Yes
	O1: Distribution of first-line paediatric drugs in 22 HBCs: analysis of Global Drug Facility procurement	Yes
	O1: Literature review: role of the private sector in treating paediatric TB	Yes
	O1: Treatment of Paediatric Tuberculosis in South Africa: How significant are the private medical sector facilities?	Yes
	O1: Considerations for acceptability of new paediatric TB formulations	Yes
	O2: pK study (AAC paper by Bekker <i>et al.</i>)	Yes
TB Alliance webportal	https://www.tballiance.org/child-survival/child-tb-resources	Yes
	Burden Estimate Podcast	Yes

Document/Output	Section	Reviewed
Other	MSH Report of Advances and Programmed Activities in Selected High Burden Countries, Jan2016.	Yes
	International Journal of Tuberculosis and Lung Disease 2015 supplement S1 to S75	Yes
	Market size of paediatric TB Indonesia Nigeria and Pakistan PLOS paper 2015	Yes
	Presentation by Brenda Waning/GDF Global Drug Facility Update on New Pedi TB FDC Procurement; December 2016	Yes
	WHO/GDF/GF Technical Briefing note: Technical step process to switch to new paediatric tuberculosis formulations February 2016	Yes
	Papers and documents included in this report	Yes