TB-Speed

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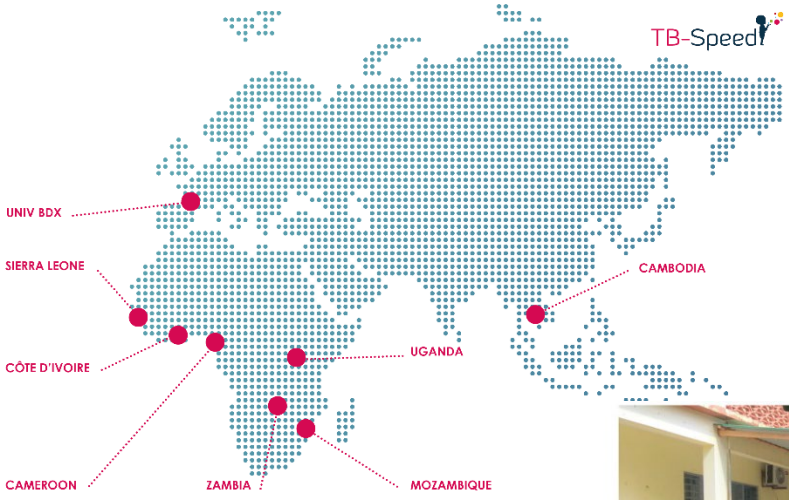
Research project to strenghen paediatric tuberculosis services for enhanced early detection

TB-SPEED PRELIMINARY TECHNICAL REPORT

September 5, 2022



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Content

Abbreviations

AUS: Abdominal Ultrasound
CXR: Chest X Ray
DH: District Hospital
DALY: Disability-Adjusted Life Year
HCW: Health Care Workers
HIV: Human Immunodeficiency Virus
NPA: Nasopharyngeal Aspirate
NTP: National Tuberculosis Programme
OR: Odds Ratio
OSF: Optimized Sucrose Flotation method
PHC: Primary Health Center
SAB: Scientific Advisory Board
SAM: Severe Acute Malnutrition
SOC: Standard Of Care
SOS: Simple One Step method
SPK: Stool Processing Kit method
TB: Tuberculosis
TDA: Treatment Decision Algorithm
UBx: University of Bordeaux
WHO: World Health Organisation

Introduction

Tuberculosis (TB) is an infectious disease caused by the agent *Mycobacterium tuberculosis,* which essentially affects the lungs and is transmitted through the air. TB affects 10 million globally each year, including a stable proportion of around 11% cases occurring in children, i.e. more than 1 million children. Of those, only four hundred thousand were diagnosed and two hundred and twenty-six thousand died. (https://www.who.int/news-room/fact-sheets/detail/tuberculosis)

Figure 1: childhood TB burden 2020 (source WHO, Global TB report)

Since 2016, the start year of the TB-Speed project, the situation has not changed significantly. Indeed, in 2016, the number of new TB cases was 1 000 000, only 450 000 cases were notified and 250 000 children died.

A majority of children dying from TB are not treated because they are not diagnosed with the disease, especially among young children[1]. This diagnostic gap is explained by the difficulty to confirm TB in children due to 1) the paucibacillary nature of the disease in children affecting the performance of existing microbiological tests 2) the difficulty to collect sputum in young children unable to self-expectorate, and 3) low access to alternative sputum specimen collection methods such as gastric aspirate or induced sputum at low level of healthcare. Therefore, most children are diagnosed with TB based on history of exposure to TB, and clinical and radiological suggestive signs. The low specificity of clinical signs, limited access to good quality X-ray, and lack of training of clinician on clinical and radiological diagnosis of childhood TB results in high numbers of underdiagnosed childhood TB cases. TB diagnosis is even more complicated in children suffering from comorbidities such as HIV (Human Immunodeficiency Virus) infection and malnutrition due to the even lower specificity of clinical signs in this group of vulnerable children[2, 3]. Due to the cellular immunodeficiency, these children are more likely to present severe forms of TB, have an increased risk of fatal outcome, and therefore need rapid TB treatment decision. Childhood intra-thoracic TB can also present with or as severe pneumonia in young children but often TB is only considered in children with TB contact history, with chronic symptoms or non-response to antibiotic[4]. This leads to diagnostic delays and missed diagnosis of TB and increases the risk of death.
In addition, in most high burden and resource-limited countries, pediatric TB diagnosis remains centralized at reference hospital at secondary or tertiary level with poor involvement of PHC (Primary Health Center) level where most sick children will seek cares first.

In that context, the Unitaid and L'Initiative - funded TB-Speed project aimed **to contribute to the reduction in childhood mortality from tuberculosis by delivering an available, feasible, cost-effective, and decentralized childhood tuberculosis diagnostic approach to enhance case-finding and access to treatment.** The project focused on two major axes:

1. Increasing access to diagnosis through decentralized pediatric TB diagnosis at district and sub-district levels
2. Increasing systematic and rapid TB detection in vulnerable children, i.e. those with severe pneumonia, HIV infection and/or with SAM (Severe Acute Malnutrition).

Figure 2: The two major axes of the TB-Speed project

Objective of the technical report

The objective of the technical report is to provide a summary of the project findings in terms of scientific evidence, tools developed and material and economic impact, in order to provide funders, National Tuberculosis Programs, national and international policy makers with scientific and practical evidence to establish or update strategic plans and policies on childhood TB for high burden and resource-limited countries.

This preliminary report is based on results presented at the TB-Speed international restitution symposium held in Maputo, Mozambique, on June 9 and 10, 2022. It is intended to be a support document for national restitution symposia that will be held in all TB-Speed project countries. The final report will include final TB-Speed study results. It will be available in November 2022.

Project Overview

TB-Speed project outputs

The project had 6 outputs or work packages, which collectively contributed to the achievement of its goal, including 3 outputs with human subject researches, or "clinical outputs", and 3 technical outputs, aiming to develop new tools and provide more evidence and support for communication of TB-Speed results.

The TB-Speed Output were the following:

Output 1: New decentralized childhood tuberculosis diagnostic approaches were tested at district health system level (output leader: MUJHU, under the responsibility of UBx (University of Bordeaux))

This was an operational research to implement and evaluate decentralized childhood TB diagnostic approaches at district health systems level. This research implemented with the support from NTPs (National Tuberculosis Programs) will used an innovative diagnostic approach based on Xpert MTB/RIF (using the newly developed Xpert Ultra and battery-operated GeneXpert G1 Edge) performed on a combination of easy to collect samples (NPA (Nasopharyngeal Aspirate) and stool), systematic symptoms screening and CXR (Chest X Ray) interpretation.

Output 2: Evaluation of an early tuberculosis detection strategy in children with severe pneumonia (output leader: UBx)

This was a pragmatic cluster randomized clinical trial to evaluate the impact on mortality and case detection of adding systematic early detection of TB by Xpert MTB/RIF Ultra performed on NPA and stools to the WHO (World Health Organisation) recommended SOC (Standard Of Care) for children with severe pneumonia. Additional co-funding has been obtained from the French 5% initiative for implementation of output 2 in Cambodia, Cameroon, Côte d'Ivoire, and Mozambique, which allows the consortium to increase the scale of the TB-SPEED project.

Output 3: Validation of diagnostic tools and algorithms in highly-vulnerable groups with presumptive tuberculosis, specifically HIV-infected and severely malnourished children (output leader: UBx)

This was a diagnostic cohort study enrolling HIV-infected children and hospitalized severely malnourished children. The study included a validation component of a recently a proposed score/algorithm for diagnosis of TB in HIV-infected children with presumptive TB (developed in the ANRS 12229 PAANTHER 01 study) and the evaluation of several diagnostic tests in hospitalized severely malnourished children, that could result in the development of a score/algorithm for TB diagnosis in severely malnourished children.

Output 4: Identification of optimized, suitable, and affordable specimen processing and collection methods for childhood tuberculosis diagnosis in resource limited countries (output leader: IRD, under the responsibility of UBX)

This involved microbiological and technological optimization work to identify and test simple and affordable specimen processing and collection methods for childhood TB diagnosis that can be deployed at low health care level in resource-limited countries.

Output 5: Evaluation of cost-effectiveness of the proposed diagnostic approaches (output leader: UBx)

Cost-effectiveness analysis of the proposed approaches and modeling of their market impact built evidence for public health decision-making.

Output 6: Dissemination, communication and stakeholders' engagement (output leader: IRD, under the responsibility of UBx)

This included communication on the project progresses, advocacy towards the relevant stakeholders, and dissemination of results to support future scaling-up.

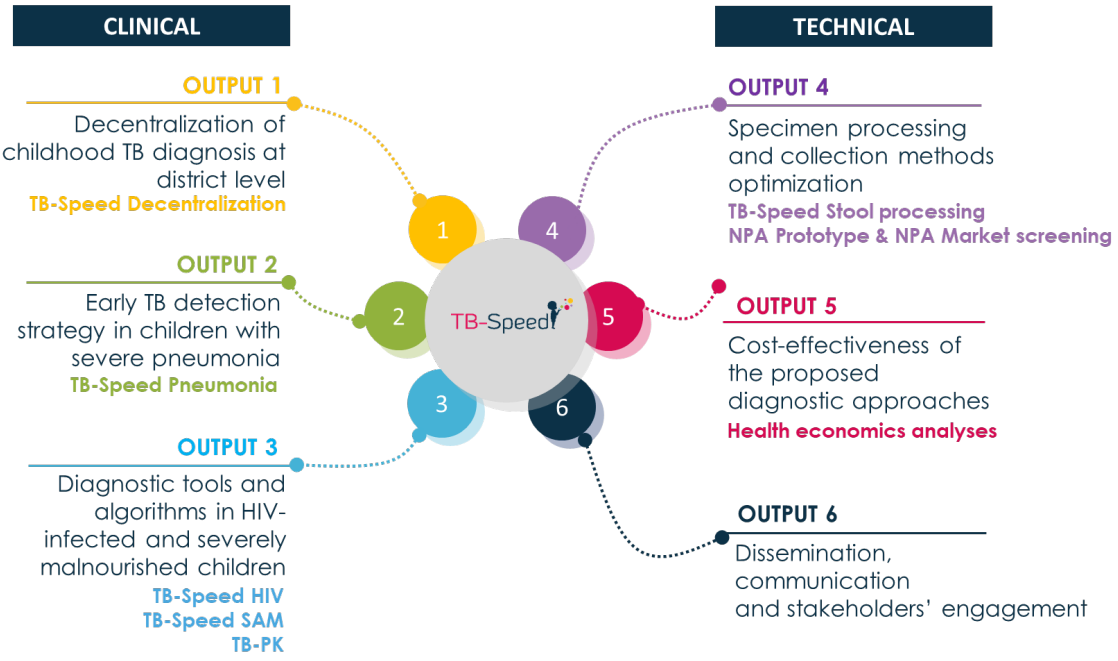


Figure 3: The 6 TB-Speed Outputs

The TB-Speed project was implemented between 2017 and 2022 in 7 countries with high (100 to 300 TB cases per 100,000 population) and very high (>300 TB cases per 100,000 population) TB incidence: Cambodia, Cameroun, Cote d'Ivoire, Mozambique, Sierra Leone, Uganda and Zambia.

The project was implemented by a multidisciplinary consortium and technical partners associating researchers, technical experts, health professionals, public health program managers and Non-Governmental Organizations from both high-income countries and low- and middle-income countries. The consortium members included: University of Bordeaux (France), Institut Pasteur Cambodia, IRD (*Institut de Recherche pour le Développement*) (France and Cameroon), PAC-CI (Cote d'Ivoire), Instituto Nacional de Saude (Mozambique), Solthis (France and Sierra Leone), Makerere University - Johns Hopkins University (Uganda) and University of Zambia (Zambia), Epicentre (Uganda). Additional technical partners included: MSF-Log (*Médecins Sans Frontières-Logistique*) (France), CAMTech (Uganda), Team/SPI (France), Adera (France). The project was lead and coordinated by the University of Bordeaux. More than a hundred staff have been hired by the TB-Speed project, and overall several hundred persons were involved in the project.

The TB-Speed project received scientific supervision and guidance from the TB-Speed SAB (Scientific Advisory Board) that included the following members: Steve Graham (University of Melbourne, Melbourne, Australia, SAB chair), Anneke Hesseling (Stellenbosch University, Cape Town, South Africa), Luis Cuevas (Liverpool School of Tropical Medicine, UK), Christophe Delacourt (Hôpital Necker-Enfants Malades, France), Malgorzata Grzemska and Sabine Verkuijl (WHO, Switzerland), Philippa Musoke (Makerere University, Uganda), Mark Nicol (University of Western Australia, Perth, Australia), Elizabeth Maleche-Obimbo (University of Nairobi, Kenya), Abdulai Abubakarr Sesay (CISMAT-SL, Sierra Leone.

TB-Speed recieved funding from Unitaid (14.6 M$) and L'Initiative (1.5M€) and received support from the ANRS-MIE (*Agence Nationale de Recherches sur le Sida et les hépatites virales | Maladies Infectieuses Emergente*). Studies were sponsored by the INSERM (*Institut National de la Santé et de la Recherche Médicale)*.

Increasing the number of children initiated on TB treatment trough decentralization of pediatric TB diagnosis at district hospital and primary health care center

Study	TB-Speed Decentralization (Output 1)
Countries involved	Cambodia, Cameroon, Côte d'Ivoire, Mozambique, Sierra Leone, Uganda
Study period	August 2019 - March 2022 (Inclusions March 2020 – September 2021)
Participants	442,618 children attending care screened for TB 3106 children enrolled < 15 years with presumptive tuberculosis

The objectives of this study were 1) to assess the impact on childhood TB case detection of decentralizing an innovative childhood TB diagnostic approach as compared to the pre-intervention SOC, and 2) to compare the effectiveness, feasibility and acceptability of two decentralization strategies: at DH (District Hospital) level and at PHC level.

The innovative childhood TB diagnostic approach included 1) systematic screening at triage of any sick child entering the facility to identify children with presumptive TB, followed by 2) clinical evaluation, 3) systematic Xpert MTB/RIF Ultra (Ultra) testing of one NPA, one stool, and or one expectorated sputum and 4) CXR in children with presumptive TB.

Table 1: Description of the screening, biological testing, clinical evaluation and Chest Xray for Decentralisation study

What?	To whom?	How?
Systematic screening	All sick children	Who: nurse or lay worker How/screen questions: 1) Cough for more than 2 weeks 2) Fever for more than 2 weeks 3) Documented weight loss 4) History of TB contact with any duration of cough
Ultra testing on NPA + stool and or ES	Children w/ presumptive TB	NPA collection using mucus extractors connected to a suction machine NPA Ultra testing at PHC (G1 Edge) or DH laboratory (GX4) Sucrose flotation stool processing at DH laboratory level for stool Ultra testing
Clinical evaluation and treatment decision	Children w/ presumptive TB	TB-Speed algorithms based on the Ugandan NTP Clinical mentoring
Chest-radiography	Presumptive TB at DH Presumptive TB still symptomatic at day 7 at PHC	Digital CXR using DR-plates on analog X-ray machines Simplified reading system using 6 features (1) Enlarged lymph nodes (2) Alveolar opacity of the lung tissue (3) Airways compression (4) Miliary (5) Cavitation (6) Pleural or pericardial effusion

Two districts including one DH and 4 (PHCs) were selected per country. In one district, the diagnostic approach was deployed at DH only and children with presumptive TB identified by symptom screening at PHC were referred to the DH for diagnosis (DH-focused strategy). In the other district, the approach was implemented both at DH and PHC and children were only referred for CXR when indicated (PHC-focused strategy). Districts were randomly selected at country level to implement either the DH or the PHC-focused strategy.

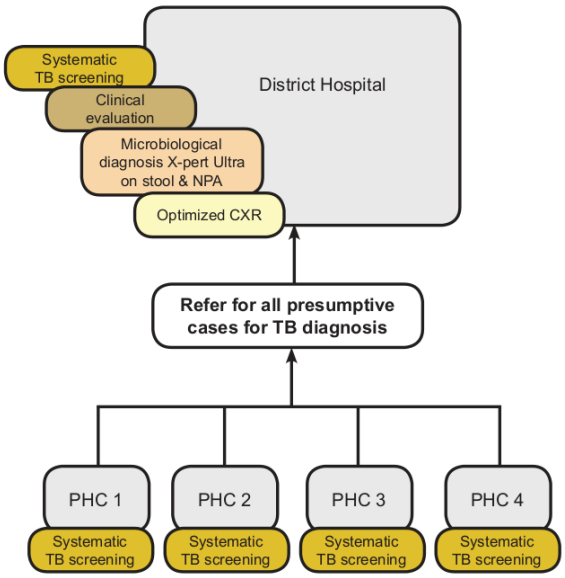


Figure 4: DH-Focused strategy

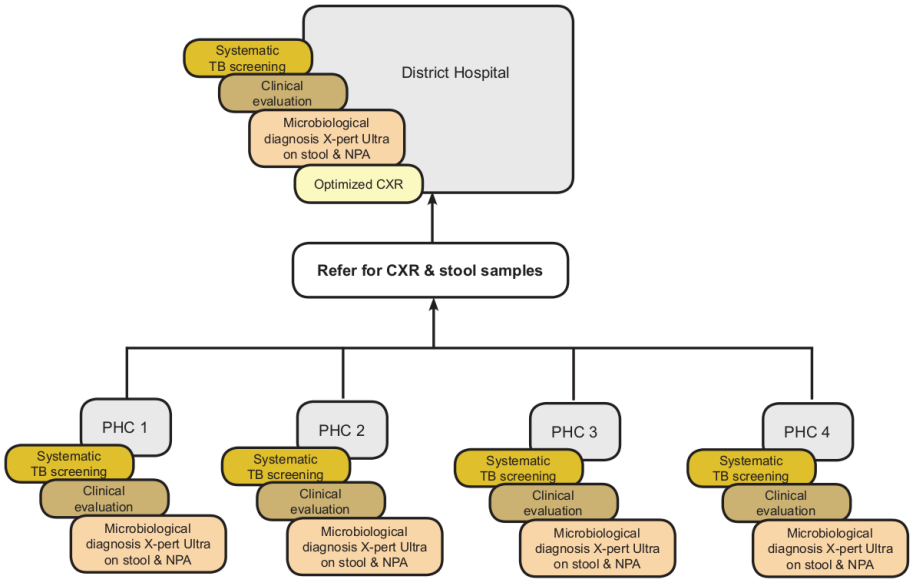


Figure 5: PHC-focused strategy

Facilities were equipped with GeneXpert machine (4 modules and 1 module battery operated), battery operated mucus aspirator for NPA and DR plate for digitalization of the radiography. Facility staff were trained on clinical examination, specimen collection, Ultra testing on both stool and NPA and CXR reading with support to clinical mentors. Several hundred people were trained using national and TB-Speed specific curricula. The quality of CXR reading was assessed by an external quality assurance system relying on national re-readers set up with the TB-Speed technical partner Team/SPI and local consortium partners. Implementation of the intervention was coordinated by district, regional and national coordination meeting with NTLP and supervised by site support supervision visits together with the NTLP. Clinical mentoring visits were performed to support clinicians and improve their skills for clinical decision making.

Equipment by facility level	DH	PHC
DR plates for CXR*	√	-
Oxygen concentrator	√	√
Suction machine	√	√
Oximeter	√	√
G1 edge	-	√
G4	√	-
Centrifuge	√	√
Tablets	√	√
Vortex	√	√

*some DH (N=2) provided with analog X-ray machine

Figure 6: Equipement provided to sites

Summary of main results

255,512 and 186,224 children attended health care in TB-Speed project DH-focused and PHCs focused and 217 and 411 were diagnosed with TB during the observation and the intervention period, respectively. Hence decentralizing pediatric TB diagnosis at district level increased from 0.08% to 0.22% the proportion of sick children diagnosed with TB as compared to pre-intervention data (OR=3.17, [1.79; 5.61]). The effect was more pronounced in the DH-focused approach (OR=4.02, [1.83-8.84]) than the PHC-focused approach (OR=1.99, [0.96; 4.17]) where there was no significant effect observed.

In terms of uptake for the different components of the innovative childhood TB diagnostic approach, more than 80% of sick children were screened for TB and 2% had symptoms suggestive of TB. Of the 3106 children enrolled in the study with presumptive TB, 92% had NPA sample tested with Xpert Ultra but only 73% had stools collected, and 65% had stool sample tested with Ultra, mainly due to the difficulty to obtain stool at initial visit and to the necessity to send samples to the DH for specimen processing and testing as compared to NPA that could be tested at PHC. The TB detection yield, i.e. the proportion of children with presumptive TB diagnosed with TB, using of Ultra on NPA was 2.3% in the DH-focused and 1.5% in the PHC-focused strategy. The TB detection yield for stool Ultra testing was 2.5% in the DH-focused and 0.7% in the PHC focused-strategy. Overall, HCW (Health Care Workers) at DH and PHC-levels perceived and experienced decentralized childhood TB diagnosis as acceptable but implementation could be hampered by feasibility issues. Main challenges were the drop-out of children with presumptive referred from PHC to DH in the DH-focused approach, the staff turnover and unavailability of trained staff onsite, and technical issues with equipment as digital Radiology or GeneXpert.

Compared to the pre-intervention SOC, decentralizing the innovative childhood TB diagnostic approach with DH-focused strategy was cost-effective under a threshold of $200 per DALY (Disability-Adjusted Life Year) averted. The DH-focused approach was more cost-effective than the PHC-focused approach.

Key message:

- **Decentralizing TB diagnosis at district level (with capacity building including equipment and training and making diagnostic tools available) increases case detection**
- **Triage based screening is highly feasible, more so in PHC than DH (facility) leading to identification of 2.7% presumptive TB**
- **The DH-focused strategy, despite challenges with referral to DH, has a better impact on case detection overall than the PHC-focused strategy**
- **NPA and stool sample collection and testing with Ultra is highly feasible both at DH and PHC level, with more challenges in stool collection and testing**
- **The yield of Ultra testing on microbiological samples is low overall in these decentralized settings**
- **The DH-focused and the PHC-focused strategy are both likely to be cost-effective compared to the SOC, according to country thresholds**
- **Decentralized strategies were well accepted in all countries**

Improving diagnosis of tuberculosis in highly vulnerable children

Systematic and rapid TB detection in children admitted with severe pneumonia

Study	TB-Speed Pneumonia (Output 2)
Countries involved	Cambodia, Cameroon, Côte d'Ivoire, Mozambique, Uganda, Zambia
Study period	March 2019 – June 2021 (Inclusions: March 2019- March 2021)
Participants	2570 children admitted with WHO-defined severe pneumonia

The objective of this study was to evaluate the impact on all-cause mortality at 12 weeks of adding systematic early detection of TB with Xpert MTB/RIF Ultra performed on one NPA and one stool sample to the WHO SOC in young children with severe pneumonia, followed by immediate anti-TB treatment initiation in children with a positive Ultra result, in high TB incidence countries.

The study was a multicentric, stepped wedge cluster-randomised diagnostic trial implemented in 15 hospitals from six countries with high TB incidence rate. All children admitted with WHO-defined severe pneumonia were immediately managed as part of routine care per the WHO SOC, including broad spectrum antibiotics, oxygen therapy if required, additional supportive care and specific therapies for comorbidities such as HIV infection. In addition, in the intervention arm children had one NPA and one stool collected and tested with Ultra followed by immediate initiation of TB treatment if positive. Ultra results were available on NPA in less than 3 hours after collection.

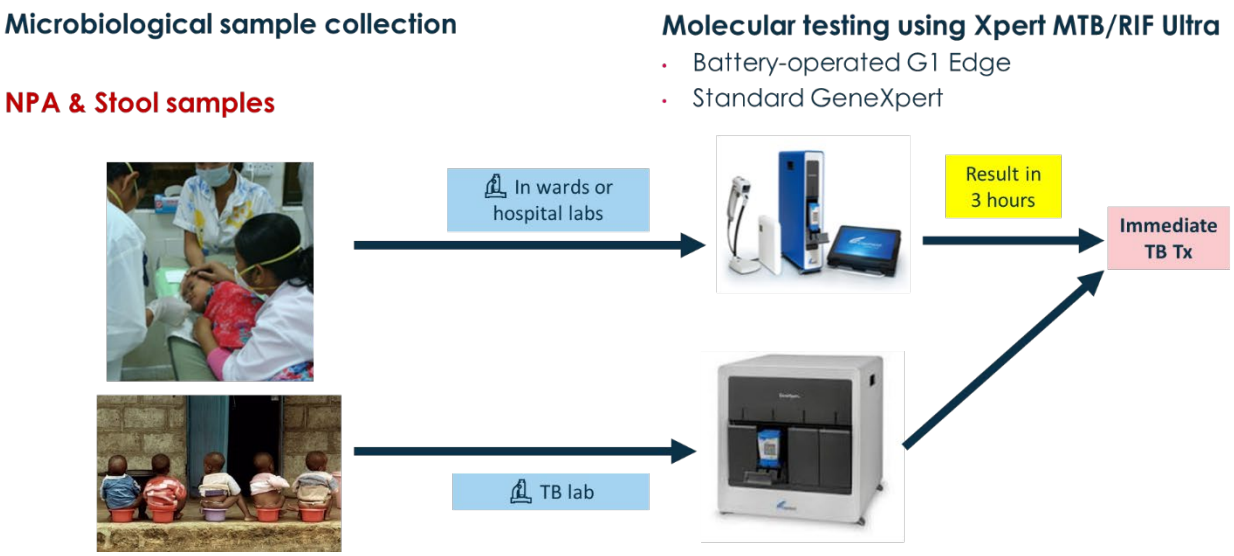


Figure 7: The TB-Speed Pneumonia intervention

Summary of main findings:

Overall, 1401 and 1169 children were enrolled in the control and the intervention arms, respectively. In the intervention arm, 1007 (97%) and 850 (82%) children had NPA and stool collected, respectively, and 24 (2.1%) had positive Ultra. Mortality at 12 weeks was not different between the intervention arm (7.9%) and the SOC (7.7%) arm [adjusted OR: 0·95 (95%CI 0·58 – 1·58)]. Overall, 5.1 % and 7.4% of children were diagnosed with TB in the control and intervention groups, respectively. There was more microbiologically confirmed TB in the intervention group compared to the SOC (2.1% vs 0.9%). NPA was well tolerated with no serious adverse event reported due to NPA. The mortality and tuberculosis diagnosis rates were 4-5-fold higher in children with SAM. In children with SAM, mortality rates were 57/240 (23.8%) and 53/297 (17.8%), and TB diagnosis rates were 36/240 (15.0%) and 56/297 (18.9%) in the control and the intervention arm, respectively.

Key message

- **Introducing systematic TB rapid molecular detection using Xpert MTB/RIF Ultra on one NPA and one stool sample in addition to the WHO SOC did not lead to a reduction in 12-week all-cause mortality in children with severe pneumonia.**
- **Collection and testing of NPA and stool samples was highly feasible and well tolerated in children with severe pneumonia.**
- **Trend of lower mortality, high rates of tuberculosis treatment initiation and microbiological confirmation support the more systematic use of Ultra in in children with SAM**

Validated TB treatment decision algorithm for use in children living with HIV

Study	TB-Speed HIV (Output 3)
Countries involved	Côte d'Ivoire, Mozambique, Uganda, Zambia
Period of inclusion	December 2019 – December 2021
Participants	278 children living with HIV presenting with presumptive TB

The objective of this study was to externally validate a TB TDA (Treatment Decision Algorithm), the PAANTHER algorithm, that was developed before for children living with HIV with presumptive TB [2]. A treatment algorithm is a system that enables standardizing and simplifying complex treatment decision making to make it feasible for HCW with limited clinical skills at lower level of healthcare. The PAANTHER algorithm combined history of exposure and symptoms assessment, clinical signs, NPA and stool testing with Ultra, CXR and AUS (abdominal ultrasound) features. Points were allocated to each signs and test results based on the initially developed predictive model. A TB treatment decision is taken for an individual patient as soon as the score reaches 100.

Table 2: Scoring points for the PAATHER TDA items

Exam/assessment	Features/items	Points
Contact history	History of contact with a smear + TB case	118
Symptoms	Fever lasting > 2 weeks	66
	Unremitting cough	39
	Hemoptysis in previous 4 weeks	79
	Weight loss in previous 4 weeks	24
Clinical signs	Tachyardia	54
Xpert MTB/RIF Ultra	Positive Xpert MTB/RIF Ultra result	241
Chest radiography	Miliary	90
	Alveolar opacity	74
	Lymph nodes	100
Abdominal ultrasound	Abdominal lymph nodes	73

The treatment decision by the score was compared with the TB classification by an independent expert panel in order to determine the proportion of missed TB cases not initiated on treatment as per the PAANTHER TB TDA and the proportion of unlikely TB among those initiated on treatment as per the PAANTHER TB TDA.

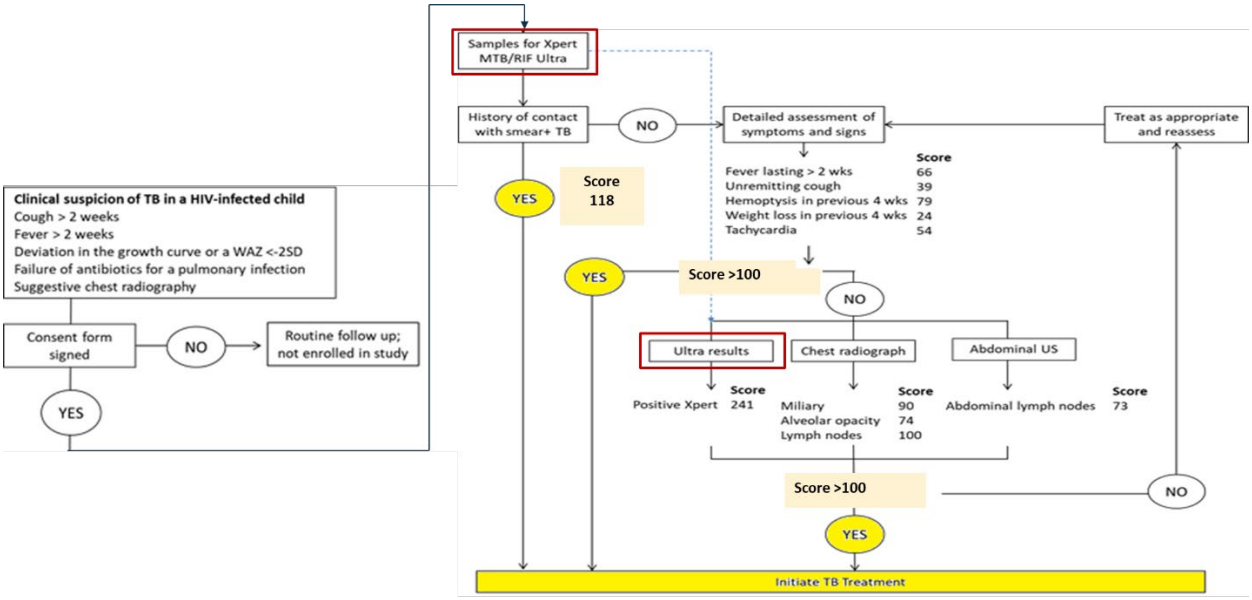


Figure 8: The PAANTHER algorithm as applied in the TB-Speed HIV study

Summary of main findings:

Of 277 enrolled children, 214 (77.3%) had a score > 100, and of them 183 (85.5%) were treated for TB. Among the 63 children with a score <100, 13 (20.6%) were started on TB treatment secondarily by the clinician. The negative predictive value of the PAANTHER TDA was 84.1%, [95%CI: 73.2; 91.1], its positive predictive value was 82.2% [76.6; 86.8], sensitivity was 94.6% [90.4; 97.1] and specificity 58.2% [48.0; 67.8]. Time to treatment initiation for children with a score > 100 was 1.0 day, interquartile range [0, 3.0].

Key messages:

- **The use of the PAANTHER algorithm for TB diagnosis and treatment decision was highly feasible in this population**
- **Most children with detected TB initiated TB treatment within a day**
- **Only few TB cases were missed by the score**
- **The study confirmed the high sensitivity and specificity of the PAANTHER treatment decision algorithm**
- **The use of the PAANTHER score should allow rapid treatment decision and could reduce mortality in CLHIV**

Additional evidence to come by October 2022:

- **Final analysis**
- **Compared diagnostic accuracy with that of the WHO-suggested TDA (childhood TB operational handbook 2022).**
- **Outcome data (mortality)**

Newly developed TB treatment decision algorithm for children admitted with SAM

Study	TB-Speed SAM (Output 3)
Countries involved	Uganda, Zambia
Study period	January 2020 – June 2022 (Inclusions: January 2020 - December 2021)
Inclusion	603 children hospitalized with severe acute malnutrition

The objective of this study was to develop a specific TDA in children aged <5 years admitted for SAM. WHO defines SAM as children with a weight-for-height Z score (WHZ) < -3 standard deviation (SD) or mid-upper arm circumference (MUAC) < 115 mm (in children over 6 months) or clinical signs of bilateral pitting oedema[5]. As for the TB-Speed HIV study, the diagnostic tools included combined history of exposure to TB and symptoms assessment, clinical exam, NPA and stool tested with Ultra, CXR and AUS. The diagnostic accuracy of the different tools and of the diagnostic algorithm were evaluated against validated standard case definitions of intra-thoracic TB in children.

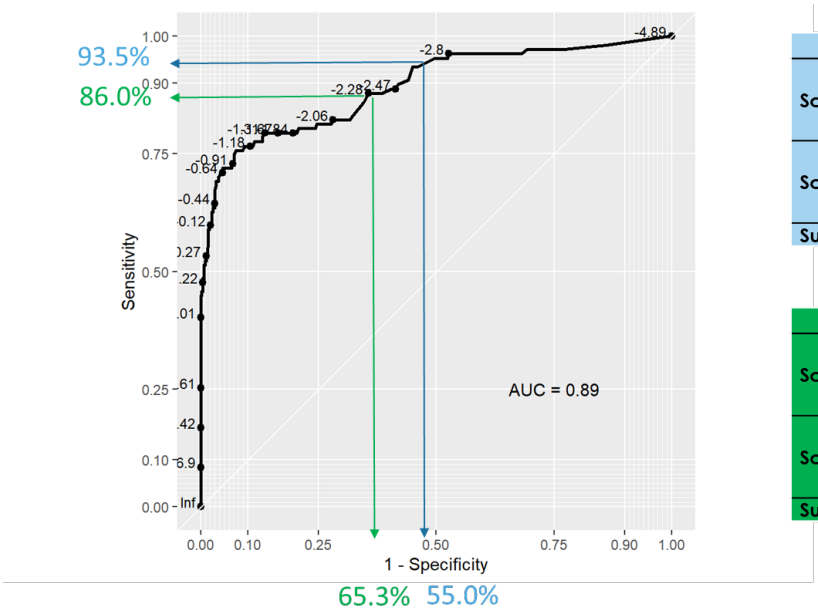
Summary of the main results:

Of the 603 enrolled children, 114 (19%) were diagnosed with TB (22% in Zambia and 17% in Uganda). Of them, 42 (37%) were confirmed by Ultra. A diagnostic prediction model was developed including all features previously associated with TB in children, notably those with SAM, and associated in the study in those with confirmed TB as compared with those alive not treated and in follow-up, i.e. with excluded TB. Variables associated with TB and hence that would be included in the diagnostic score and algorithm to be developed soon are shown in the table below. The relative importance of each item in the score is reflected by its OR (Odds Ratio).

Table 3: Variables associated with TB that would be included in the score

	OR
Xpert result Positive	753.704
Contact with adult TB case*	4.280
HIV infection	2.995
Cough >3 weeks	2.651
Loss of appetite >2 weeks	1.592
Temperature >38°C	2.702
Chest indrawing	3.789
Drepressed level of consciousness**	1.358
Cervical or supra clavicular adenopathy	8.900
CXR_Alveolar opacity	2.079
CXR_Hilar mediastinal lymphadenopathy	2.915
CXR_Pleural effusion	8.339
CXR_Pericardial effusion	0.141
AUS_Splenic micro abscesses	6.068
AUS_Pericardial or pleural effusion	2.333
AUS_Peritoneal effusion ascites	1.756

When setting the sensitivity at 86%, the model combining different tools had a specificity of 65% that decreased to 55% when sensitivity increased to 94% (see figure below). The diagnostic score for the TDA is under development and will be available in October 2022. Only 30% of children with TB had chronic cough (> 2 weeks) and almost 20% of them presented with acute severe respiratory symptoms.



	TB	Not TB	Sum
Score ≥100	100	192	292
Score <100	7	235	242
Sum	107	427	534

	TB	Not TB	Sum
Score ≥100	92	148	240
Score <100	15	279	294
Sum	107	427	534

Figure 9: Sensitivity and specificity of the model

Key messages:

- **There is a high TB prevalence in children hospitalized with SAM and a high TB microbiological confirmation rate in both countries calling for particular attention to this vulnerable population.**
- **Usual TB symptoms with chronic cough are less common and children with SAM can present with pneumonia-like presentation**
- **The diagnostic model is able to keep a specificity above 60% for a sensitivity of 85% but needs to be confirmed with the final data analysis and to be moved to a treatment decision algorithm as we did for HIV-positive children.**

Additional evidence to come by October 2022:

- **Development of the final treatment decision algorithm (TDA)**
- **Attempted screening algorithm without CXR, Ultra and Ultrasound to identify those with presumptive TB that would benefit from additional testing**
- **Compared diagnostic accuracy with that of the WHO-suggested TDAs (Childhood TB operational handbook 2022)**
- **Outcome data (mortality)**

Pediatric TB diagnostic tools

Nasopharyngeal aspirate

Suitable mucus suction device

NPA is recommended by WHO as a suitable sample for diagnosis of intra-thoracic TB in children using Xpert Ultra in the last pediatric TB guidelines 2022 [6]. TB-Speed has shown that NPA is highly feasible and well accepted with more than 90% of sample collected and tested among children with presumptive TB, including highly vulnerable children admitted with SAM, severe pneumonia or with HIV infection (see section *"Summary of findings on Ultra testing of combined NPA and stool samples"* below with summary results). Tolerability was good even among seriously ill children. NPA requires a suction device to aspirate mucus but there is a lack of guidance on what type of machine can be used. Procedures and instruction of use for NPA have been developed by the TB-Speed project and are available on the TB-Speed website https://www.tb-speed.com/wp-content/uploads/2020/09/TB-Speed_SOP_NPA.pdf). To facilitate purchase of suction devices for NPA at country level by NTPs and other stakeholders, TB-Speed developed a Target Product Profile for suction device and performed a market screening to identify a robust, affordable and well distributed battery-operated device. The preferred machine for use at country level is the ATMOS LC27 device that can be purchased from the Atmos company for a non-negociated price of 399 euros. Additional information can be obtained from the TB-Speed partner MSF-Logistique.

Table 4: Specification of the ATMOS LC27

Price	**399 euros**
Dimension	28,6 x 24,3 x 11,8 cm
Weight	3,5 kg
Pressure Range	37 à 600 mmHg
Air Flow	27 l / min
Container Capacity	800ml (reusable)
Continuous Working Time	60 min
Charging time	50% in 3 h / Max in 12h
Classification	CE ISO 13485
Spare Part Availability	Yes
Operating Temperature	0 °C / 40 °C
Power Supply	100-240V / 50-60 Hz or 12 VCC
Battery	Lead
Guarantee	2 years
Minimum Order	1

Figure 10 : ATMOS LC27. Link to ATMOS website : https://atmosmed.com/lc27/index_en.html

Alternatively, the project developed a MOAP (Manual Operated Aspiration Pump). Prototype specification and instructions for fabrication at country level will be available in October 2022.

Figure 11: Nurse using the MOAP

Stool testing using Xpert

A simplified specimen processing methods

Use of Xpert Ultra from stool sample is recommended by WHO for diagnosis of intrathoracic TB in children [7]. PCR inhibitors in stools can result in invalid Ultra results and debris can lead to errors in the Ultra test run. Therefore, stool sample need to be processed prior to Ultra testing, which may require a well-equipped laboratory. TB-Speed has developed, based on the centrifuged-based sucrose flotation method that has been shown to be sensitive from detection of TB in children, a simplified centrifuge-free method in an *in vitro* study (Optimized sucrose flotation, OSF method). The project has evaluated the diagnostic accuracy and feasibility of the method in children with presumptive TB in Uganda and Zambia. Two other simplified method (Simple One Step (SOS) and Stool Processing Kit (SPK)) were evaluated in the same study.

In 176 enrolled children, the sensitivity of the OSF, SPK and SOS was 69%, 56% and 58% and specificity was at least 95% for the 3 methods when compared to Xpert and culture from respiratory samples. The three methods were considered easy to performed by laboratory technicians with more favorable attitude toward the SOS method.

The OSF method is recommended by WHO and instruction of use is available in the Global Laboratory Initiative manual for stool testing. (https://www.who.int/publications/i/item/9789240046764)

Summary of findings on Ultra testing of combined NPA and stool samples

The following table summarizes TB-Speed project results on the feasibility and yield of collecting and testing with Ultra NPA and stool samples for Decentralization and Pneumonia studies. HIV and SAM studies results will be presented in the final technical report.

Table 5 : NPA and stool samples Ultra testing findings

Study	Decentralization	Decentralization	Pneumonia
Health facility level	DH	DH and PHC	UTH and tertiary RH
Population	Presumptive TB from general paediatric population	Presumptive TB from general paediatric population	WHO defined severe pneumonia
N enrolled	1938	3106	2570 (**1169** Intervention arm)
Median age	3.5 [1.33-7.17]	3.75 [1.33-7.46]	11 [6-20]
NPA collected	1830 (94.4%)	2873 (92.5%)	1139 (97.4%)
NPA tested	1746 (90.1%)	2873 (92.5%)	1133 (96.9%)
NPA Ultra +	41 (2.1%)	50 (1.6%)	21 (1.8%)
Stool collected	1506 (77.7%)	2235 (72%)	943 (80.7%)
Stool tested	1342 (69.2%)	2010 (64.7%)	934
Stool Ultra +	27 (1.4%)	32 (1%)	16 (1.4%)
NPA or stool Ultra +	58 (3.0%)	71 (2.3%)	24 (2.0%)

Chest X-ray quality improvement package

To support clinicians with reading and interpreting CXR features from children with presumptive TB seen at DH and PHC (Decentralization study), the TB-Speed technical partner TeAM/SPI has developed a 1.5 day course on CXR interpretation adapted to HCW at low level of health care including nurse clinicians, with the support of the TB-Speed CXR working group. The course included training for clinicians on 1) how to recognize a normal CXR in children and 2) how to identify 6 radiological features known to be suggestive of intrathoracic TB in children:

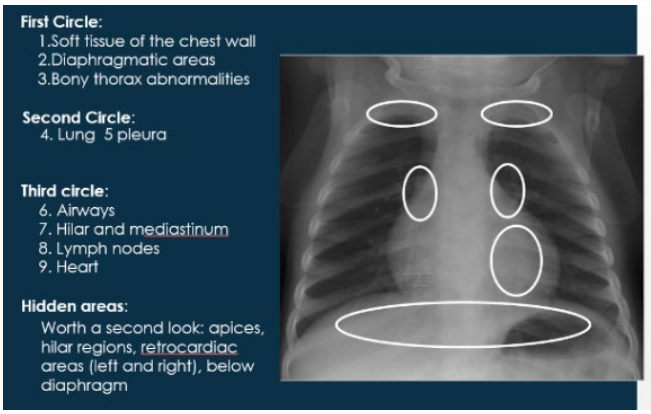


Figure 12: Support of course for CXR reading

- Enlarged lymph nodes
- Alveolar opacity of the lung tissue
- Airways compression
- Miliary
- Cavitation
- Pleural or pericardial effusion

Twelve sessions were conducted in 6 countries for 217 health staff (74 doctors, 85 nurses, 28 Xray technicians, 30 other staff) from DH and PHC with 68% pre-post-test increase and 1/3 of participants who scored 15 or more after the training on a set of 15 tested X-rays. The module is available on the project website (https://www.tb-speed.com/wp-content/uploads/2021/04/TB-Speed_Interpret-Child-CXR.pdf).

Android application for the PAANTHER algorithm

For programs considering implementing the PAANTHER TDA in HIV-positive children with presumptive TB, the project developed an android application to help clinicians calculating the PAANTHER score that can be used on any smartphone. This technology could be adapted to any other TDA with score.

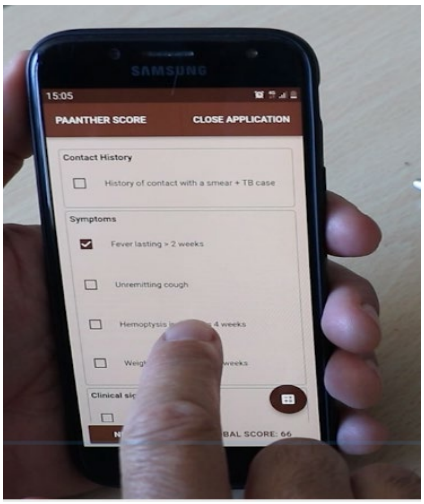


Figure 13: PAANTHER score android application

Conclusion

To conclude this preliminary report, and as discussed with the TB-SAB, the following general recommendations can be broadly done and discussed in project countries during restitution symposia. TB-Speed results have to be also integrated with the new WHO recommendations to 1) decentralize childhood TB services, 2) shorten TB treatment regimen in children with less severe forms of the disease, and 3) use TDAs at lower level of health care for childhood TB treatment decision.

- Childhood TB diagnostic approaches can be successfully decentralized either at DH or at PHC level, depending on the country priorities. Implementing the innovative childhood TB diagnostic approach including systematic screening, clinical evaluation, Ultra testing on NPA and stool samples, and simplified CXR reading at DH is particularly effective and needed as more children with more severe forms of TB will present there, as compared to the PHC level
- Childhood TB diagnosis has to be systematically implemented in children from vulnerable groups:
    - In children admitted to hospital with severe pneumonia, all children should be systematically screened for prolonged symptoms and history of exposure; those with SAM diagnosed either using a MUAC bracelet of weight of height curves, NPA and stool testing should be systematically done
    - Specific TDAs should be sued for TB diagnosis in children living with HIV and those hospitalized with SAM in order of a better diagnose in these populations.
- In the general paediatric population, WHO suggested TDAs should be used to strengthen clinical evaluation and decision making (conditional recommendation)
- NPA and stool combined collection and testing with Ultra is highly feasible and effective for microbiological confirmation in different populations. In those hospitalized with SAM, the combination of gastric aspirates, that are facilitated by the fact that children often have nasogastric tubing in place for renutrition, and stool samples seem to be the best combination.

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TB-Speed

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