TB-Speed

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RESEARCH PROJECT TO STRENGTHEN PAEDIATRIC TUBERCULOSIS SERVICES FOR ENHANCED EARLY DETECTION

TB-SPEED STUDY PROTOCOLS

Despite progress in reducing tuberculosis (TB) incidence and mortality in the past 20 years, TB is a top ten cause of death in children under 5 years worldwide. However, childhood TB remains massively underreported and undiagnosed, mostly because of the challenges in confirming its diagnosis due to the paucibacillary nature of the disease and the difficulty in obtaining expectorated sputum in children.

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TB-SPEED DECENTRALIZATION

Impact of an Innovative Childhood TB Diagnostic Approach Decentralised at District Hospital and Primary Health Care Levels on Childhood Tuberculosis Case Detection and Management in High Tuberculosis Incidence Countries

STUDY BRIEF SUMMARY

The TB-Speed Decentralisation study aims to increase childhood Tuberculosis (TB) case detection at district hospital (DH) and Primary health Care (PHC) levels using adapted and child-friendly specimen collection methods, i.e. Nasopharyngeal Aspirate (NPA) and stool samples, sensitive microbiological detection tests (Ultra) close to the point-of-care (Edge), reinforced training on clinical diagnosis, and standardized chest X-ray (CXR) quality and interpretation using digital radiography.

The TB-Speed Decentralisation study evaluated the impact of an innovative patient care level diagnostic approach deployed at DH and PHC levels, and compared effectiveness and cost-effectiveness of the two different decentralization approaches.

The hypothesis was that, in countries with high & very high TB incidence, a systematic approach to the screening and diagnosis of TB in sick children presenting to the health system will increase childhood TB case detection. The study also hypothesized that sputum collection using battery-operated suction machines and microbiological TB diagnosis using G1 (Edge) can be decentralized to PHC level, thus enabling TB diagnosis and treatment in children at PHC level.

OBJECTIVES

Primary Objective

To assess the impact of implementing decentralized diagnostic approaches on childhood TB case detection at district hospital and PHC levels compared to the pre-intervention status.

INNOVATIVE CHILDHOOD TB DIAGNOSTIC APPROACH

The intervention consisted of the following 4 components:

- Systematic TB screening: refers to asking simple specific questions at health care OPD entry point to identify children with presumptive TB.
- Clinical evaluation: refers to detailed history taking, relevant physical examination, severity of illness done for all children with presumptive.
- Xpert Ultra testing of NPA and stool (or expectorated sputum) for molecular detection of Mycobacterium tuberculosis and rifampicin resistance).

- Optimised CXR reading: using digital radiography, improvement of reading skills, simplified reading tool, and quality control of CXR reading.

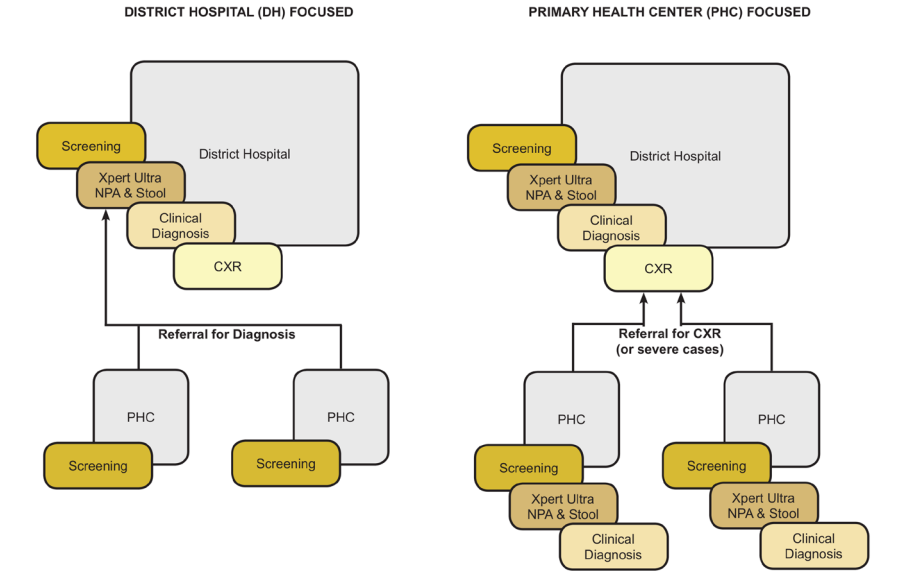
These components provided guidance to the clinician for the decision whether or not to treat for TB, and when to start treatment.

ELIGIBILITY CRITERIA

Inclusion Criteria:

Sick children seeking care at Outpatient Department (OPD) of District Hospital or Primary Health Center - Age <15 years

DECENTRALIZATION STRATEGIES



STUDY DESiGN

Study type	Operational Research - before and after cross sectional design and nested cohort
Screened	168 416
Duration of follow-up once enrolled	1 week in cross-sectional analysis, 6 months in cohort study
Study Start Date	September 13, 2019
Study Completion Date	December 31, 2021

TB-SPEED PNEUMONIA

Impact of Systematic Early Tuberculosis Detection Using Xpert MTB/RIF Ultra in Children With Severe Pneumonia in High Tuberculosis Burden Countries

STUDY BRIEF SUMMARY

Pneumonia is the leading cause of death in children under the age of 5 years worldwide. There is growing evidence that, in high TB burden settings, TB is common in children with pneumonia, with up to 23% of those admitted to hospital with an initial diagnosis of pneumonia later being diagnosed as TB.
However, the current WHO standard of care (SOC) for young children with pneumonia considers a diagnosis of TB only if the child has a history of prolonged symptoms or fails to respond to antibiotic treatments. Hence, TB is often under-diagnosed or diagnosed late in children presenting with pneumonia.

OBJECTIVES

Primary Objective

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 standard of care (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, as compared to the SOC alone.

METHODS

Study design

Multicentric, stepped wedge cluster-randomised diagnostic trial.

Implementing sites

15 hospitals from six countries with high TB incidence rate: Côte d'Ivoire, Cameroon, Uganda, Mozambique, Zambia and Cambodia.

Randomisation

2570 children were equally distributed across the two strategies using a computer generated random sequence. Randomisation was stratified on the country estimated TB incidence rate (cut-off value of 300 cases/100 000 person-years).

Follow-up

Children were followed for 12 weeks after enrolment, with systematic trial visits at day 3, discharge, 2 weeks post-discharge, and week 12. An extra TB visit was performed if children present with signs and symptoms of presumptive TB.

ELIGIBILITY CRITERIA

Inclusion criteria

- Children aged 2 to 59 months
- Newly hospitalized for severe pneumonia defined using WHO criteria as cough or difficulty in breathing with:
  - . Peripheral oxygen saturation < 90% or central cyanosis, or
  - . Severe respiratory distress, or
  - . Signs of pneumonia

TRIAL STRATEGIES AND INTERVENTION

Control arm

All children admitted in the hospital and presenting 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.

Intervention arm

The TB-Speed strategy consisted on the WHO SOC plus the study intervention consisting in rapid TB detection on the day of hospital admission using the Ultra assay performed on 1 NPA and 1 stool sample. The sample flow was organised in order to reduce time to results to 3 hours. Drugs were available at the inpatient level to enable immediate initiation of TB treatment, as soon as a positive Ultra result was available.

STUDY DESIGN

Study type	Cluster randomized trial
First inclusion	March 20th, 2019
Inclusion period	80 weeks (18 months)
Duration of follow-up once enrolled	12 weeks
Last visit of the last patient	March 30th, 2021

TB-SPEED HIV

Validation of a Tuberculosis Treatment Decision Algorithm in HIV-infected Children

STUDY BRIEF SUMMARY

TB-Speed HIV was a prospective multicentre management study evaluating the safety and feasibility of the recently proposed PAANTHER TB treatment decision algorithm for HIV-infected children with presumptive TB.
It was conducted in four countries with high and very high TB (Tuberculosis) incidence (Côte d'Ivoire, Uganda, Mozambique, and Zambia) which have not participated in the study that developed the PAATHER algorithm.

OBJECTIVES

Primary Objective

To evaluate the proportion of missed TB cases in HIV-infected children with presumptive TB not initiated on treatment as per the PAANTHER TB treatment decision algorithm (false negative cases).

METHODS

Study design

External validation study based on a prospective, multicentre management study evaluating the safety and feasibility of the recently proposed PAANTHER TB treatment decision algorithm for HIV-infected children with presumptive TB.

Implementing sites

8 tertiary level hospitals in 4 countries with high and very high TB incidence (Côte d'Ivoire, Uganda, Mozambique, and Zambia) which have not participated in the PAANTHER development study.

Methodology

- The PAANTHER algorithm was used for TB treatment decision by site clinicians in all children enrolled in the study.
- Validation of the algorithm was performed by evaluating the proportion of missed TB cases in children not initiated on treatment as per PAANTHER TB treatment decision algorithm.

Follow-up

All children were followed-up for 6 month upon enrolment, with systematic study visits at day 7, day 15, month 1, 2, 3, and 6.

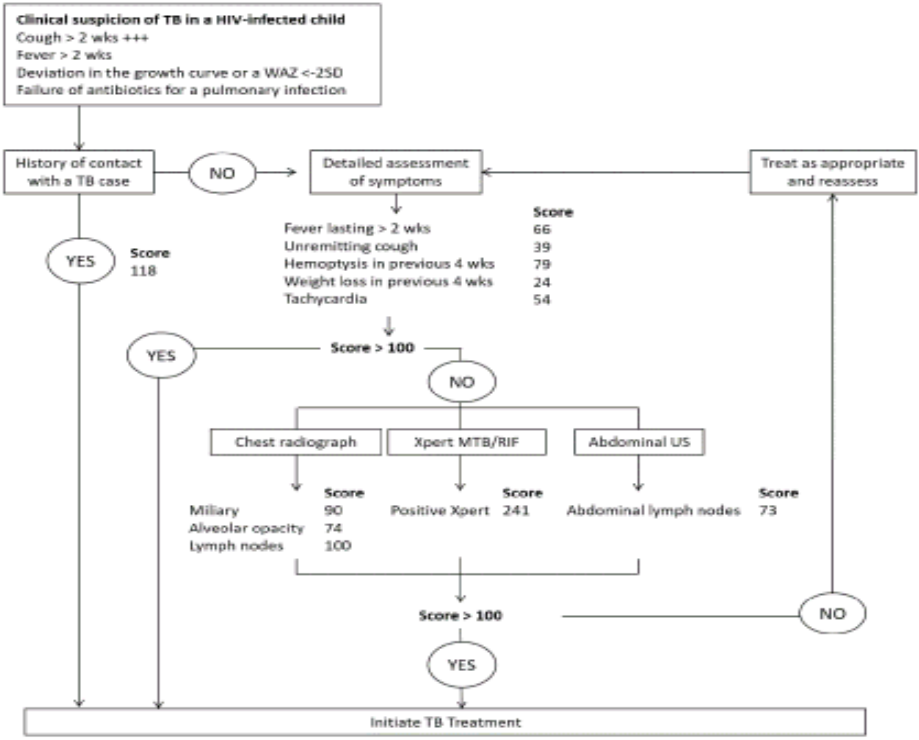
ELIGIBILITY CRITERIA

Inclusion criteria

- Children aged 1 month to 14 years
- Documented HIV-infection (i.e., confirmed before entry into the study)
- Presumptive TB based on at least one criteria among the following:

. Persistent cough for more than 2 weeks
. Persistent fever for more than 2 weeks
. Failure of broad spectrum antibiotics
. Recent failure to thrive in the last 3 months or Z score weight/age < 2)
. Suggestive CXR features

THE PAANTHER ALGORITHM



STUDY DESiGN

Study type	Prospective management study
Total enrollment	278 participants
Duration of follow-up once enrolled	6 months
Study Start Date	September 13, 2019
Study Completion Date	December 31, 2021

TB-SPEED SAM
SEVERE ACUTE MALNUTRITION

Development of a Diagnostic Prediction Score for Tuberculosis in Hospitalized Children With Severe Acute Malnutrition

STUDY BRIEF SUMMARY

TB-Speed SAM was a multicentric, prospective diagnostic cohort study conducted in two countries with high and very high TB incidence (Uganda, and Zambia). It aimed at assessing several diagnostic tests that could result in the development of a score and algorithm for TB treatment decision in hospitalised children with severe acute malnutrition (SAM).

OBJECTIVES

Primary Objective

To develop a diagnostic prediction score for TB in hospitalized children with Severe Acute Malnutrition (SAM).

METHODS

Study design

External validation study based on a prospective, multicentre management study aiming to assess several diagnostic tests that could result in the development of a score and algorithm for TB treatment decision in hospitalised children with SAM.

Implementing sites

3 tertiary healthcare hospitals in 2 countries with high and very high TB incidence: Uganda and Zambia.

Methodology

- The diagnostic strategy included an initial clinical, radiographic and bacteriological evaluation. For the purpose of the study, additional diagnostic methods were evaluated including abdominal ultrasonography, Quantiferon interferon gamma assay (QFT), monocyte lymphocyte ration (MLR), C-reactive protein (CRP) as well as alternative sample collection methods (NPA, stool samples). MLR, CRP, QFT, and abdominal ultrasound findings were made available to the clinicians.

- TB diagnosis was made according to national TB guidelines.
- At the end of the study, children were retrospectively classified as confirmed, unconfirmed, or unlikely TB, using the updated version of the Clinical Case Definition for Classification of Intrathoracic Tuberculosis.
- Using logistic regression, we developed a score for TB diagnosis in hospitalized children with SAM and, if possible, an initial symptom-based screening step to identify children with presumptive TB.
- Both scores were internally validated using resampling and were incorporated in a stepwise algorithm to guide practical implementation of the screening and diagnosis process.

Follow-up

Children were followed up for 6 months upon enrolment, regardless of their TB diagnosis with protocol visits at day 0 (TB diagnosis visit), day 15, month 1, 2, 3, and 6.

ELIGIBILITY CRITERIA

Inclusion Criteria

- Children aged < 5 years
- Severe acute malnutrition defined as weight-for-height Z score (WHZ) < -3 standard deviation (SD) or mid-upper arm circumference (MUAC) < 115 mm or clinical signs of bilateral pitting oedema in children aged <5 years
- Hospitalized per hospital clinician's decision
- Parent/guardian informed consent

STUDY DESIGN

Study type	Prospective diagnostic cohort study
Duration of follow-up once enrolled	6 months
Estimated total enrollment	603 participants
Study Start Date	September 13, 2019
Study Completion Date	December 31, 2021

TB-SPEED TB-PK - PharmacoKinetic

Impact of Malnutrition on PharmacoKinetic of Rifampicin, Isoniazid, Pyrazinamide and Ethambutol in TB-HIV co-Infected Children

STUDY BRIEF SUMMARY

TB-Speed TB-PK is a cross-sectional PK study of anti-TB treatment nested in the TB-Speed HIV and TB-Speed SAM studies aiming at assessing the impact of malnutrition on PK of rifampicin, isoniazid, pyrazinamide, and ethambutol in TB-HIV co-infected children. Children are also enrolled from routine care for TB outside of the TB- Speed HIV and TB-Speed SAM studies.

OBJECTIVES

Primary Objective

To assess the effect of severe acute malnutrition (SAM) on plasma concentration of rifampicin, isoniazid, pyrazinamide, and ethambutol in children with tuberculosis (TB).

HYPOTHESIS

. HIV-infection and SAM, each one on its own, may have an impact on TB drugs concentrations. Both conditions are also associated with poorer treatment outcomes
. SAM in children with HIV, may explain or aggravate the issue of low TB drug concentration, through mainly metabolic complications of SAM.
. Additional evidence on association between HIV and/or SAM status and optimal drug concentrations could contribute to better dosing recommendations

METHODS

Implementing sites

4 tertiary healthcare hospitals in 2 countries with high and very high TB incidence: Uganda, and Zambia.

Methodology

Intensive PK of rifampicin, isoniazid, pyrazinamide, and ethambutol is performed between 2 to 4 weeks of TB treatment in the following 4 groups of children receiving FLD anti-tuberculosis treatment:

. Group (Gr.) 1. HIV-infected with SAM (WHZ<-3SD or edematous malnutrition or MUAC <115) (HIV+/SAM+)

. Gr2. HIV-infected without SAM (none of the 3 criteria above) (HIV+/SAM-)
. Gr3. HIV-negative with SAM (WHZ<-3SD or edematous malnutrition or MUAC <115) (HIV-/SAM+)
. Gr4. HIV-negative without SAM (none of the 3 criteria above) (HIV-/SAM-)

Children from Gr.1, 2, and 3 are enrolled mostly among participants to the TB-Speed HIV and TB-Speed SAM studies in Uganda and Zambia; Gr.4 HIV-negative children without SAM are enrolled from the routine TB care cohort in Zambia and Uganda, as well as children from the other 3 groups if enrolment cannot be complemented through the TB-Speed HIV and TB-Speed SAM studies.

Follow-up

Children are followed up for 6 months upon enrolment, regardless of their TB diagnosis with protocol visits at PK visit, month 2, and 6.

ELIGIBILITY CRITERIA

Gr1.	**Gr2.**	**Gr3.**	**Gr4.**
HIV-infected children with SAM	**HIV-infected children without SAM**	**HIV-negative children with SAM**	**HIV-negative children without SAM**
INCLUSION CRITERIA			
Age 6 months to 5 years			
Diagnosed with TB and first line TB treatment to be initiated or started less than 4 weeks prior to inclusion			
HIV-infected		HIV-negative	
SAM	Absence of SAM	SAM	Absence of SAM
Ability to take drugs orally during the planned PK day			
Signed informed consent from parents or guardian			

STUDY DESIGN

Study type	PK/PD study
Estimated total enrollment	80 participants
Study Start Date	October 19, 2021
Study Completion Date	September, 2022

TB-SPEED STOOL PROCESSING

Evaluation of Four Stool Processing Methods Combined With Xpert MTB/RIF Ultra for Diagnosis of Intrathoracic Paediatric Tuberculosis

STUDY BRIEF SUMMARY

There is a growing interest for the use of stool samples as an alternative to respiratory samples for the diagnosis of intrathoracic TB in children unable to produce sputum.
Unlike respiratory samples, stool samples require processing before molecular testing. Several groups have already evaluated different processing methods. However, it is difficult to know which method has the best diagnostic accuracy and potential for use at Primary Health Care level, due to the difference in study designs and populations.
Therefore, in this study, we proposed to evaluate the diagnostic accuracy of different promising stool processing methods in the same population using the same study methodology: accuracy of Xpert MTB/RIF Ultra performed on stool samples collected from children with presumptive TB and processed using four different processing methods (Standard sucrose flotation (standard sucrose flotation method optimized sucrose flotation method (OSF), stool processing kit (SPK), and Simple One Step (SOS) against bacteriological results from respiratory specimens and to perform a head-to-head comparison of the diagnostic accuracy and feasibility of these different.

OBJECTIVES

Primary Objective

To determine the diagnostic accuracy of Xpert MTB/Rif Ultra performed on stools processed using four different sample processing methods (standard sucrose flotation, OSF, SOS and SPK methods) in children with presumptive TB.

METHODS

Study design

Multicentric, two-stage prospective diagnostic cohort study to evaluate the diagnostic accuracy of Xpert MTB/RIF Ultra performed on stool samples collected from children with presumptive TB and processed using four different processing methods (Standard sucrose flotation method, OSF, SPK, and STEP).

Implementing sites

Children were recruited from the Mbarara Regional Referral Hospital in Mbarara (Uganda, South West region), Lusaka University Teaching Hospital (Zambia) and the Arthur Davidson Children Hospital, Ndola (Zambia).

Methodology

- During stage 1 (prospective cohort) all consecutive eligible presumptive TB children were enrolled. During stage 2 (enrichment cohort) only eligible children with an Xpert positive result on a respiratory sample were enrolled.
- The diagnostic strategy included an initial clinical, radiographic and bacteriological evaluation. Gastric aspirate and stool were collected and tested with Ultra. Mycobacterial culture was also performed on the gastric aspirate. Children were then retrospectively classified as confirmed, unconfirmed, or unlikely TB, using the updated version of the Clinical Case Definition for Classification of Intrathoracic Tuberculosis.

Follow-up

Children were followed up for 2 months upon enrolment, regardless of their TB diagnosis with protocol visits at day 1 and month 2.

ELIGIBILITY CRITERIA

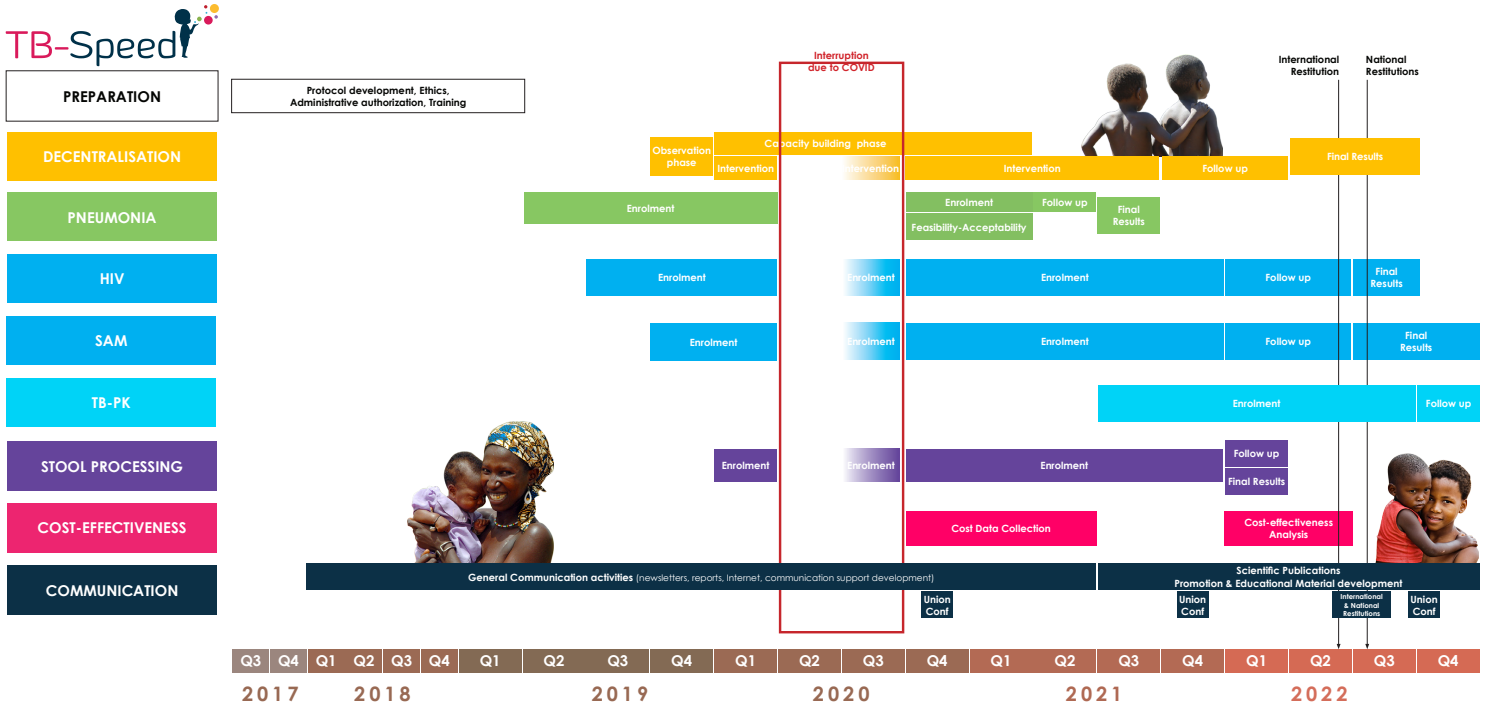
Inclusion Criteria

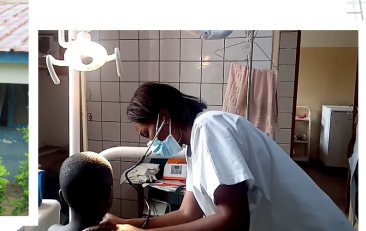
- 1. Children < 15 years old
- 2. Presumptive intra-thoracic TB based on at least one criterion among the following:
  - . Persistent cough for more than 2 weeks
  - . Persistent fever for more than 2 weeks
  - . Recent failure to thrive (documented clear deviation from a previous growth trajectory in the last 3 months or Z score weight/age < 2)
  - . Failure of broad-spectrum antibiotics for treatment of pneumonia
  - . Suggestive CXR features
  - . OR History of contact with a TB case and any of the symptoms listed under point 2 with short

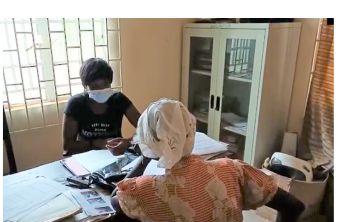
STUDY DESiGN

Study type	Prospective diagnostic accuracy study
Estimated total enrollment	261 participants
Study Start Date	January 6, 2020
Study Completion Date	December 31, 2021

TB-SPEED GLOBAL CHRONOGRAM







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