Diagnostic performance and feasibility of implementing newly recommended treatment decision algorithms for pulmonary tuberculosis in children

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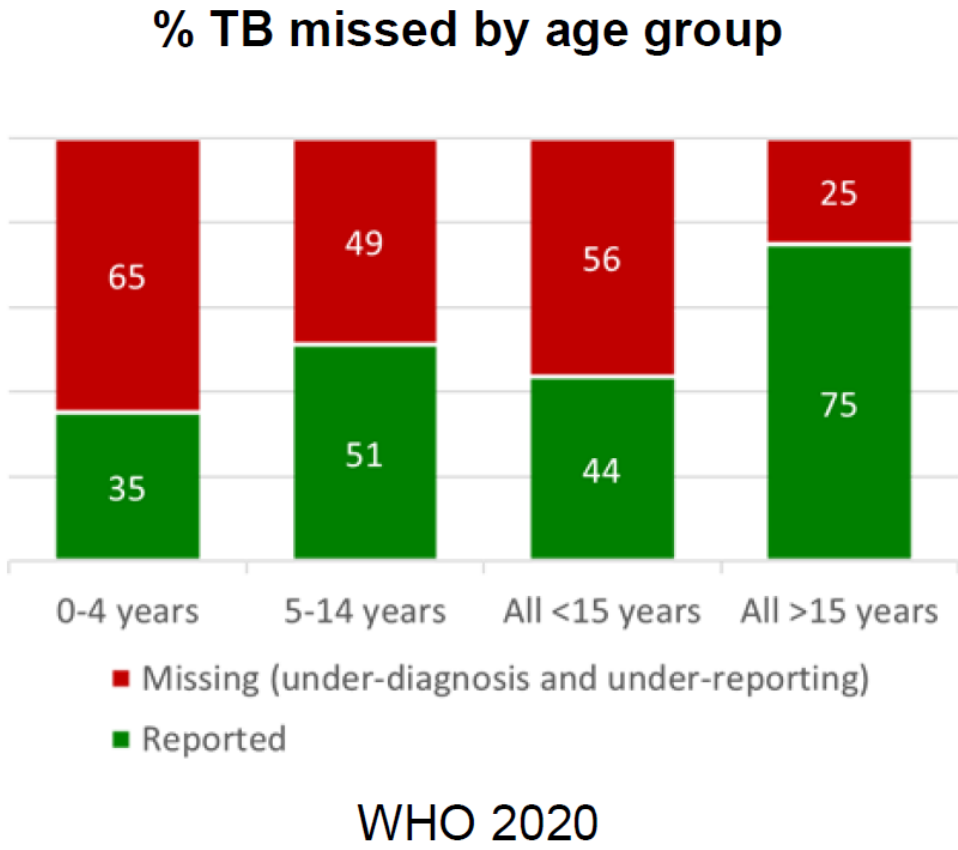
epicentre
ÉPIDÉMIOLOGIE • EPIDEMIOLOGY

MEDECINS SANS FRONTIERES

Background

Tuberculosis (TB) in children is often underdiagnosed.

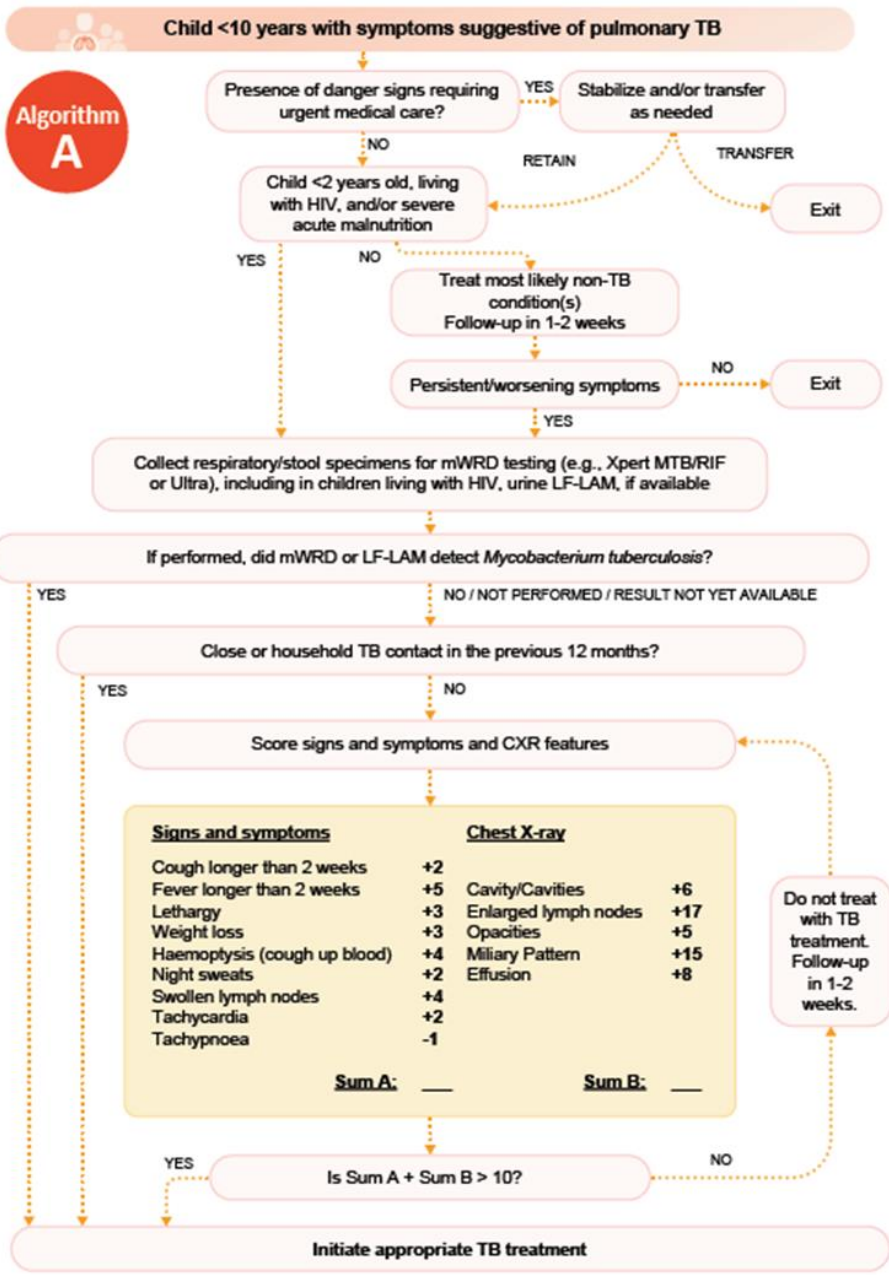
- 60% of children with TB are not diagnosed
- 96% of children who die with TB were not on treatment

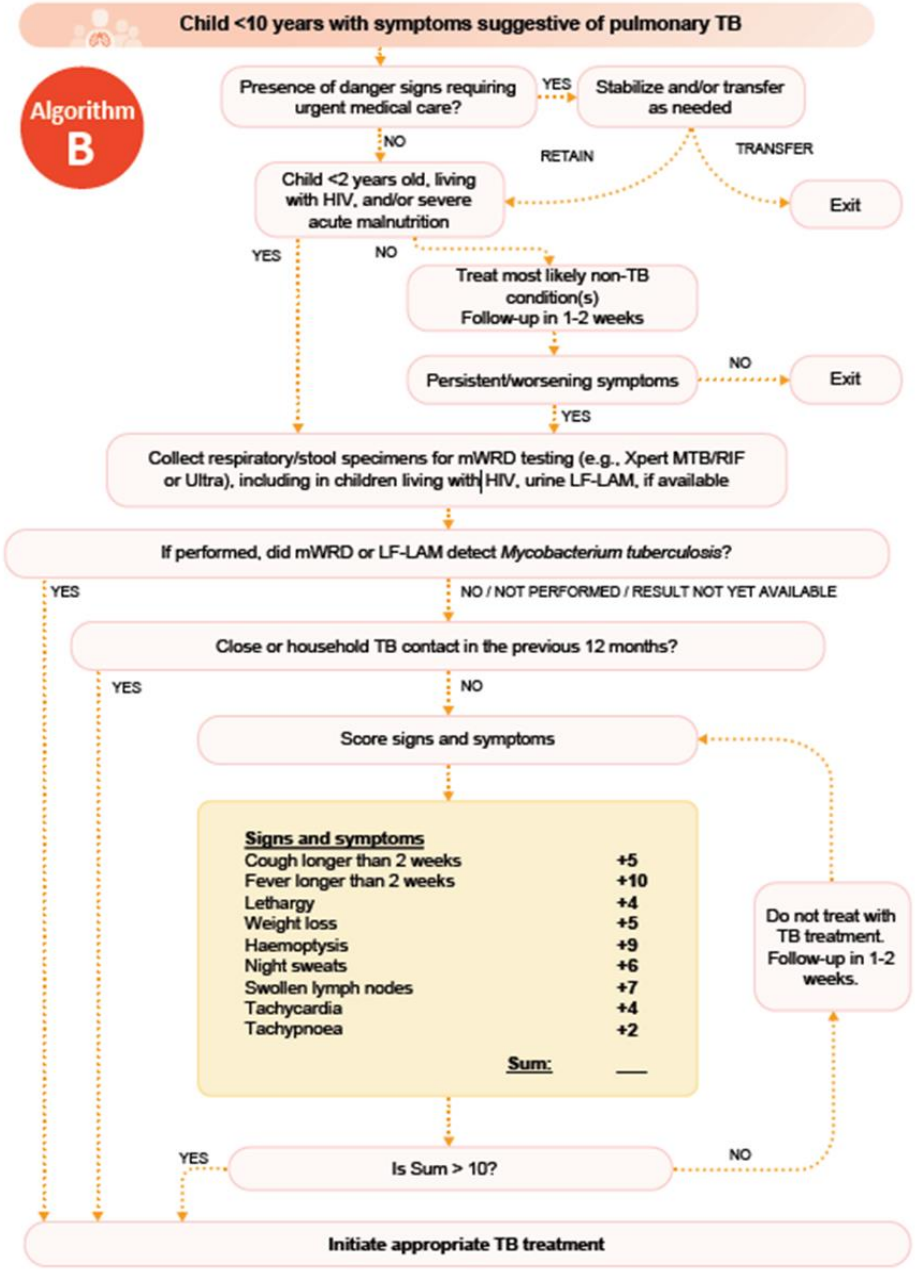


WHO new recommendations for diagnosis and management of TB in children in 2022

More kids diagnosed	Shorter treatments	Shorter prevention
Treatment decision algorithms Rapid treatment initiation	**4 months treatment for non severe TB** Using existing children's formulations	**3 months treatment to prevent TB** for household contacts

New TB treatment decision algorithms (with and without X-ray)





Background

- The new algorithms have not been implemented and their diagnostic performance and feasibility has not been evaluated.
- WHO made a call for generation of evidence on the new treatment decision algorithms to inform future recommendations.
- MSF/Epicentre responded to the WHO call and proposed a multi-country study to assess the diagnostic performance and the feasibility of the new algorithms in real conditions.

Primary objectives

1. **To assess the diagnostic accuracy** of the 2022 WHO treatment decision algorithms against a reference standard.

2. **To document the diagnostic cascade** using the 2022 WHO algorithms (frequency of children undergoing each step of the algorithms, started on TB treatment etc).

3. **To assess health workers and patients/caregivers' perspectives** on the 2022 WHO treatment algorithms including challenges and enablers to the introduction of the recommended algorithms.

Secondary objectives

1. To assess clinical evolution, TB treatment initiation, and **mortality at 2 months** of follow-up.
2. To assess the diagnostic performance of **TB-LAM** in HIV-positive and HIV-negative children.
3. To assess the diagnostic performance of **POCUS** (only specific study sites).
4. To compare the actual TB treatment algorithms' recommendations with the **potential recommendation** that would have been reached if chest X-ray or laboratory results were not available.
5. To assess the number and the proportion of children potentially **eligible for a 4-month treatment** regimen.
6. To report changes on paediatric aggregated **case notification rates** 12 months prior to, and 12 months following the implementation of the algorithms.

Study design

- **Observational prospective multi-country study** to assess the algorithms' diagnostic performance.
- **Mixed-methods study** to document the algorithms' implementation and to assess their feasibility and acceptability.
- **Analysis of routine program data** to assess case notification rates 12 months before and after the implementation of the algorithms.

Study sites

1. Madarounfa (Niger) – MSF OCP
2. Maiduguri (Nigeria) – MSF OCB
3. Conakry (Guinea) – MSF OCB
4. Malakal (South Sudan) – MSF OCBA
5. Mbarara (Uganda) – Epicentre
6. Mumbai (India) – OCB (in discussion)

Population

- Observational study: **children under 10 years with symptoms of TB**
- Mixed-methods study: **health workers, program managers, key informants, and parents.**

	Population	Age (years)	Type of care	Algorithm assessed	Feasibility evaluation
Malakal, South Sudan	General	<10	Ambulatory (District Hospital OPD) Hospitalized (District level)	B B	No
Mbarara, Uganda	General	<10	Ambulatory (Health Center) Ambulatory (District Hospital OPD) Hospitalized (District level)	B A A	Yes
Madarounfa, Niger	Malnourished	<5	Ambulatory (ATFC) Hospitalized (District level ITFC)	B A	Yes
Maiduguri, Nigeria	Malnourished	<10	Hospitalized (District level ITFC)	A	No
Conakry, Guinea	Living with HIV	<10	Ambulatory (Health Center)	A	Yes

Procedures

Observational prospective study:

- Medical history, contact with TB, clinical exam.
- GeneXpert MTB/RIF in gastric aspirate and stool.
- TB-LAM in urine.
- Chest X-ray if available.
- MTB culture (only Uganda).
- Ultrasound (only South Sudan).

	Study enrolment	Initial visit (D1, D2)	Follow up visit (Day 7-14)	Follow up visit (Month 2)
Screening for study eligibility criteria	X			
Informed consent	X			
Enrolment	X			
All children				
Anamnesis and history of TB contact		X		
HIV testing[1]		X		
Clinical exam		X	(X)	X
Children at high risk of disease progression				
Specimen collection for Xpert MTB/RIF and culture		X	(X)	
Collection of urine sample for TB-LAM test		(X)		
Chest X-ray (algorithm A)		X		
Ultrasound		(X)		(X)
Treatment for TB or non-TB conditions		X	X	
Appointment for visit at D7-D14 or M2		X	(X)	
Children at low risk of disease progression				
Specimen collection for Xpert MTB/RIF and culture			(X)	
Collection of urine sample for TB-LAM test			(X)	
Chest X-ray (algorithm A)			(X)	
Ultrasound			(X)	(X)
Treatment for TB or non-TB conditions		X	(X)	
Appointment for visit at D7-D14 or M2		X	(X)	
All children				
Discharge from study				X

Procedures

Mixed-methods study:

- Direct observations on the use of algorithms
- Health workers' diaries
- Individual interviews
- Focus group discussions

Mixed methods study

Phase 1 Context analysis

As soon as the protocol is validated by the ethics committee

Assessment of community and health system perceptions and strategies for TB diagnosis -before implementation of the algorithms

Phase 2 Implementation analysis

Within **6 months** of implementation

Evaluation of the implementation process and perceptions of the algorithms

Phase 3 Post-implementation analysis

Within **12 months** of the start of the implementation

Evaluation of the evolution of practices regarding new algorithms (e.g. ownership, maintenance and support of practices over time)

Sample size

- Observational prospective study: 2 020 children with presumptive TB
  - 500 in Uganda, 230 in South Sudan, 600 in Niger, 350 in Nigeria, 340 in Guinea.
- Mixed-methods study:
  - Phase 1: 10-15 interviews per group of population
  - Phase 2: 10-15 health workers' diaries; 3 focus group discussions with 4-8 people each; 10-15 interviews per group of population
  - Phase 3: 3 focus group discussions with 4-8 people each; 10-15 interviews per group of population

Ethical aspects

- Caregivers will be asked written consent for their children's participation in the study.
- Assent will be asked to children 8-9 years in Uganda.
- The multi-site study protocol has been approved by the MSF Ethics Review Committee.
- Site-specific study protocols have been approved by the National Ethics Review Committees in Nigeria, Niger, and Guinea, and are under review in Uganda and South Sudan.

Funding

- MSF internal funding for costs in MSF sites – OCP, OCB, OCBA
- ANRS funding obtained for Mbarara
- Submission to the MSF TIC initiative for additional funding as part of a bigger project (TACTiC)

TACTiC: Test, Avoid, Cure TB in Children

- An MSF intersectional approach to improving the management of TB in children.
- Main objective of TACTiC is to help MSF missions and project teams start implementing WHO's latest recommendations.
- Aim at supporting the reduction of pediatric TB diagnosis and treatment gaps by:
  - Offering support and guidance to MSF teams and their partner MoH/NTP.
  - Strengthening the capacities of medical and paramedical staff.
  - Developing evidence-based advocacy including through operational research, for the implementation and scaling-up of the recommendations.

Timelines – Total study duration 2,5 years

- Protocol writing: December 2022- March 2023
- ERB approvals (MSF & 6 countries): April - September 2023
- Patient's enrolment (6-12 months depending on the country): August 2023 - October 2024
  - Nigeria: August 2023 (started)
  - Niger & Guinea: September 2023 (planned)
  - Uganda & South Sudan: October 2023 (planned)
- Patient's follow-up (2 months): last patient's follow-up in December 2024
- Documentation and feasibility assessment: September 2023-December 2024 (in 3 phases).
- Data management and analyses: January-March 2025
- Report and dissemination of results: April-December 2025

Study Team & Partners

- Médecins Sans Frontières, France
- Médecins Sans Frontières, Belgium
- Médecins Sans Frontières, Spain
- Epicentre, France
- Ministry of Health, Nigeria
- Ministry of Health, Niger
- Ministry of Health, Guinea
- Ministry of Health, Uganda
- Ministry of Health, South Sudan
- University of Tübingen, Germany
- ANRS, France