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MAJOR ARTICLE

Xpert-Ultra assay on stool and urine to improve tuberculosis diagnosis in children: the Médecins Sans Frontières experience in Guinea-Bissau and South Sudan

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Background: Over half of childhood tuberculosis (TB) remains undiagnosed yearly. WHO recommends Xpert-Ultra as a first paediatric diagnosis test, but microbiological confirmation remains low. We aimed to determine the diagnostic performance of Xpert-Ultra on stool and urine in presumptive paediatric TB cases in two high-TB burden settings.

Methods: This Médecins sans Frontières cross-sectional multicentric study took place at Simão Mendes hospital, Guinea-Bissau (July 2019 to April 2020) and in Malakal hospital, South Sudan

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(April 2021 to June 2023). Children 6 months to 15 years with presumptive TB underwent clinical and laboratory assessment, with one respiratory and/or extrapulmonary sample (gold standard (GS)), one stool and one urine specimen analysed with Xpert-Ultra.

Results: A total of 563 children were enrolled in the study, 133 from Bissau, 400 from Malakal; 30 were excluded. Confirmation of TB was achieved in 75 (14.1%) while 248 (46.5%) had unconfirmed TB. Of 553 with GS specimen, the overall diagnostic yield was 12.4% (66/533). A total of 493 and 524 samples were used to evaluate Xpert-Ultra on stool and on urine, respectively. Compared to GS, sensitivity and specificity of Xpert-Ultra on stool were 62.5%(95%CI:49.4-74) and 98.3%(95%CI:96.7-99.2), whereas on urine were 13.9%(95%CI:7.5-24.3) and 99.4%(95%CI:98.1-99.8), respectively. Nine patients were positive on stool and/or urine but negative on GS.

Conclusions: Xpert-Ultra on stool showed moderate to high sensitivity and high specificity when compared to GS and an added diagnostic yield when GS was negative. Xpert-Ultra on stool was useful in extrapulmonary cases. Xpert-Ultra in urine showed low test performance.

Trial registration: NCT06239337

Key words: paediatric tuberculosis; Xpert-Ultra; stool; urine; LMIC

Key points: In this large cohort of presumptive paediatric TB cases from two high-burden TB settings, this study confirms a high diagnostic accuracy and added diagnostic yield of Xpert-Ultra on stool, while test performance of Xpert-Ultra on urine was low.

INTRODUCTION

Despite being a preventable and treatable disease, tuberculosis (TB) continues to be an important cause of morbidity and mortality in children (1), especially among those living with HIV and/or malnutrition. Over half of childhood TB remains undiagnosed every year due to several factors: low rate of microbiological confirmation, need for partly invasive procedures in young children, and low access to microbiological testing, including TB culture or Xpert-Ultra, and to chest radiology (2-5). Thus, in many contexts the diagnosis of TB in children is based solely on clinical presentation despite the poor specificity of clinical features, which ultimately contributes to the diagnostic gap.

TB is the main comorbidity and cause of mortality in people living with HIV, including children (6), and is also a common comorbidity of severe malnutrition in TB-endemic environments. Malnutrition is an independent risk factor for both development and mortality due to TB and is associated with more severe forms of the pathology (7-9).

Though the gold standard for diagnosis is TB culture, it is often unavailable and requires a high turnaround time to be used on a routine basis. Since 2013, the World Health Organization (WHO)

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recommends Xpert MTB/RIF® (Cepheid, Inc.) as first test for the diagnosis of TB in children (10, 11) considering the low sensitivity of smear microscopy (12). An international expert panel established that for study purposes the case definition of "confirmed tuberculosis" included a positive WHO-endorsed nucleic acid amplification test (such as Xpert MTB/RIF) (13-15).

Xpert MTB/RIF has been widely studied for pulmonary (16) and extra pulmonary samples (17-19), as well as for stool (20-24), which being easily obtainable, is considered a suitable complementary sample, especially for children unable to provide respiratory samples. Urine is not yet recommended and most of the related studies focus on adults with HIV (25-27).

Cepheid developed Xpert-Ultra to improve sensitivity of TB detection with a special focus on people living with HIV, children and extrapulmonary forms (27-30). The increase in sensitivity has been at the expense of a lower specificity, especially amongst patients with a history of TB treatment. Stool proved to be a suitable sample for Xpert-Ultra as well (28, 31-33) which led WHO in 2021 to recommend Xpert -Ultra in several pulmonary and extrapulmonary samples including stool, but not urine (2).

In South Sudan, TB remains a major public health concern, with an estimated TB incidence in 2021 of 227 per 100 000 population (18% affecting children under 15 years old), and an overall treatment coverage of 72% (34). HIV prevalence in the country was 2.5% with an antiretroviral (ARV) coverage of 18% in 2020 (35). Internally displaced people (IDP) living in the camps have an increased risk of developing TB (36); by the end of 2023, 67 000 IDPs lived in Malakal. Médecins sans Frontières (MSF) started support to the Ministry of Health in Malakal (Upper Nile state) by the end of 2013 due to a conflict-related humanitarian crisis. MSF is currently supporting primary and secondary health care in Malakal Protection of Civilians (POC) site and Town, while supporting the rural area through a decentralised model of health care.

Guinea-Bissau is a high burden country for HIV and TB. In 2021, the estimated TB incidence was 361 per 100 000 population (4% affecting children, likely underestimated), with an overall treatment coverage of 33% (37). HIV prevalence in the country was estimated at 5% in 2018, with an ARV coverage of 34%, albeit 8% in paediatric HIV (38). Global acute malnutrition is estimated at 5% in children (39). MSF supported the paediatric emergency and intensive care unit at Simão Mendes hospital in Bissau from 2017 to 2020.

This study evaluates the performance of Xpert-Ultra on stool and urine and its additional diagnostic yield in a cohort of children ≤15 years of age (and subpopulations) with presumptive TB in two Sub-Saharan hospital contexts.

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METHODS

Study design

This multicentric cross-sectional study took place at Malakal Teaching Hospital and PoC hospitals from November 2019 to June 2023, and at Simão Mendes National Hospital between July 2019 and April 2020. Children with presumptive TB underwent clinical and laboratory evaluation.

Study Population, Clinical, and Laboratory procedures

Children 6 months to 15 years were considered presumptive TB cases if they showed persistent cough for more than 2 weeks, unexplained fever for more than 1 week or signs of extrapulmonary TB such as: gibbous deformity of the spine, lymphadenopathy, subacute meningitis, distended abdomen with ascites, diarrhoea for more than two weeks, painless enlarged joints, or pleural effusion.

Presumptive TB cases were also identified after a week of inpatient admission, characterized by low weight gain despite nutritional treatment, persistent pneumonia or cough despite adequate antibiotic therapy, persistent fever (>38ºC), and persistent or aggravated fatigue. Patients were screened for TB based on their medical history and clinical presentation, including TB contacts, past TB treatment or HIV infection. Physical examination was conducted in all patients and included relevant anthropometric measures (see "Data collection" section). All patients with unknown HIV status were tested for HIV, and all children were tested with Xpert-Ultra for at least one pulmonary or extrapulmonary sample (considered as gold standard), and one stool and one urine samples.

Respiratory samples included naso-pharyngeal aspirate, gastric lavage, or spontaneous sputum; sample collection procedures were described in **supplementary file** 1. Extrapulmonary samples included lymph node puncture, pus aspirate, and ascetic, pleural, or cerebrospinal fluids. Stool and urine were collected from all patients as well. Standard operating procedures for Xpert-Ultra analysis of stool and urine can be found in **supplementary file 2**. All specimens were kept between 2 and 8ºC until processed, which was done within 24 hours.

All patients underwent a diagnostic evaluation and were included in one of three categories: *Confirmed TB* (patients who had an Xpert-Ultra positive on one of the samples); *Unconfirmed TB* (clinical TB diagnosis without Xpert-Ultra confirmation according to a clinical-decision based algorithm which can be found in **supplementary file 3**); *Unlikely TB* (Xpert-Ultra negative and alternative diagnosis with adequate response to alternative treatments, and TB treatment not started). Patients with TB (confirmed or unconfirmed) were categorized according to the clinical presentation into pulmonary TB (PTB), extrapulmonary TB (EPTB) or disseminated TB (when TB affected more than one site).

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Xpert-Ultra was used to determine the specimens as: *Mycobacterium Tuberculosis* (*MTB) not detected* (or negative) or *MTB detected* (positive or trace); specimens with MTB detected were determined for resistance to rifampicin: RIF-resistant *detected*, *not detected*, or *indeterminate*. Any *Indeterminate* or *Invalid* result entailed repeating the test, and only considered as *Invalid* when the second test had the same result.

In Malakal, MSF supported the TB program in collaboration with the Ministry of Health (MoH) all along the study. In Bissau, all results were communicated to MoH who were responsible for treatment initiation.

Data Collection and Analysis

All data were collected in an anonymized, structured, paper-based forms, and managed using Research Electronic Data Capture (REDCap) software. Data were analysed using SPSS version 21 (IBM Corp., Armonk, N.Y., USA) and R version 4.3.1.

Continuous variables were reported using means and standard deviations (SD) or medians and interquartile ranges (IQR) as appropriate and expressed as ordinal categories with frequencies. Frequencies were presented with corresponding 95% confidence intervals (CI). Age-appropriate anthropometric indicators were calculated using the World Health Organization (WHO) Multicentre Growth Reference. Severe acute malnutrition (SAM) was defined based on WHO criteria (SAM: weight-for-height Z-score <-3 standard deviations (SD) or MUAC <11.5 cm or presence of bilateral oedema for children <5 years and BMI-for-age Z-score <-3 SD for those 5–15 years) (40).

Diagnostic accuracy of Xpert-Ultra in stool and urine samples for TB detection was validated against Xpert-Ultra in pulmonary and/or extrapulmonary samples, which was considered as gold standard for our study. Diagnostic accuracy was calculated as sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). All measures of accuracy were expressed as percentage with 95% CI. Diagnostic yield was defined as proportion of TB positive results obtained from the test, regardless of whether those results were true positives or false positives.

Statistical differences were tested in univariable analyses using Chi Square, Fisher Exact, or Kruskal-Wallis rank sum tests, as appropriate. All estimates are presented with respective 95% CI. For statistical comparisons on secondary objectives, p-values below <0.05 were considered statistically significant.

Ethics and Patient Consent Statement

Ethics approval was obtained from the MSF Ethics Review Board, the Guinea-Bissau National Health Ethics Committee, and the South Sudan Ministry of Health Ethical Review Board. Written

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informed consent was received from a legal guardian and further verbal assent from children aged 10 years old and above.

RESULTS

Demographics and Clinical Presentation

A total of 563 patients were enrolled between July 2019 and April 2020 in Guinea-Bissau and from November 2019 till June 2023 in South Sudan. Thirty patients were excluded from the analysis due to absence of written consent (n=1) or absence of gold standard sample (n=29). For the Xpert-Ultra on stool analysis, 40 additional patients were excluded due to absence of sample or invalid results, thus a total of 493 patients were included in the sub-analysis. For the Xpert-Ultra in urine analysis, 9 patients were excluded due to absence of sample or invalid result, thus a total of 524 children were included in the sub-analysis. **Figure 1** shows the flowchart of the participants in the study.

Demographic and clinical study characteristics of the participants are shown in **table 1**. Of 533 patients with presumptive TB, 323 (61%) had a final diagnosis of TB, 75 (14.1%) presented with Xpert- Ultra confirmed TB and, among them, only one (1/75, 1.3%) had rifampicin-resistant TB. Two-hundred and forty-eight patients (46.5%) had unconfirmed TB and 210 (39.3%) patients had unlikely TB. A total of 93 (17.4%) patients presented with HIV infection and 331 (62.1%), with SAM.

Comparative data between Malakal and Bissau can be found in **supplementary table 1**. When comparing Malakal (n=400) and Bissau (n=133) cohorts, patients from Bissau were older, had more history of TB contact, presented with more HIV-infection and with lower CD4 count. Clinically, children in Malakal presented with greater weight loss, fever, diarrhoea, and prevalence of extrapulmonary TB.

When analysing the total cohort, the median (IQR) age was 48 months (18, 108) and 282 (52.9%) were under 5 years old. Demographic characteristics (including age, gender, and previous history) were similar in all TB groups. When comparing TB vs. unlikely TB patients, they presented with similar proportion of severe acute malnutrition, but patients with TB had more HIV-infection and lower CD4 count, and more exposure to TB. In terms of clinical presentation, hypoxemia, gibbous, peripheral lymph nodes, and pleural effusion, were significantly higher in TB patients.

Performance of Xpert-Ultra on stool and urine

Performance of Xpert-Ultra on stool is described in **table 2**. The overall diagnostic yield of Xpert -Ultra on stool was 8.5% (42/493), with a third of positives by trace result (14/42). Overall, sensitivity (95% CI) of stool was 62.5% (49.4, 74) and specificity (95% CI) was 98.4% (96.7,

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99.2); breakdown by HIV, nutrition and age subpopulation are shown in the table. The diagnostic accuracy was 94.3% (91.9, 96.0) and the Cohen's kappa was 0.68 (0.60 - 0.77).

Performance of Xpert-Ultra in urine is described in **table 2**. The overall diagnostic yield of Xpert-Ultra in urine was 2.3% (12/524), with 25.0% (3/12) of positives by trace result. Overall, sensitivity (95% CI) of urine was 13.9% (7.5, 24.3) and specificity (95% CI) was 99.4% (98.1, 99.8). Further analysis on subpopulations was not carried out due to the small sample size of Xpert-Ultra positive in urine. The diagnostic accuracy of Xpert-Ultra on urine was 89.1% (85.8, 91.2) and the Cohen's kappa was 0.20 (0.14 - 0.26). Among these 12 children with Xpert-Ultra positive on urine, 7 (58,3%) presented disseminated TB.

A total of 9 patients (12.0% (9/75)) were diagnosed based on an Xpert-Ultra positive on stool and/or urine alone, as gold standard was negative. In **Supplementary figure 1**, the Venn's diagram shows the concordance per type of sample and only includes patients that had GS, stool, and urine specimens (N=490) with a positive result. In **Supplementary table 2,** a descriptive table of patients who presented with only Xpert-Ultra on stool and/or urine can be found.

Diagnostic yield per type of pulmonary and extrapulmonary samples and combination of different tests

The positivity rate per sample is shown in **Supplementary table 3**. For pulmonary samples, the overall positivity was 9.8% (49/500) while 10.2% (5/49) among them had a trace result. The positivity rate between nasopharyngeal aspirate and gastric lavage was similar (9.5% vs. 9.2%). Extrapulmonary samples had a positivity rate of 32.0% (16/50) and the highest positivity were found in lymph nodes (35.0%) and pus or tissue (33.3%). Among extrapulmonary samples, 19.0% (4/21) had a trace result.

The diagnostic yield of combination of different tests is described in **table 3**, where samples from patients who did not have Xpert-Ultra on stool were excluded. For patients with pulmonary TB, the most efficient combination was sputum and stool (24.3%), which can only be obtained in older children; for younger children, gastric aspirate and stool showed a diagnostic yield of 16.4% in patients with TB; however, Xpert-Ultra on stool did not increase the diagnostic yield of nasopharyngeal aspirate (13.5%). Patients with extrapulmonary TB had higher diagnostic yield, namely 41.2% when combined with stool, with the highest increase in yield found for cervical lymph node TB (6.2%, from 35.0% to 41.2%).

Xpert-Ultra diagnostic yield per HIV, nutritional status and age

The diagnostic yield of respiratory and extrapulmonary samples was similar per age, HIV and nutritional status and is presented in **table 4**. The diagnostic yield in stool and urine were similar per category.

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DISCUSSION

To our knowledge, this is the first study to investigate the diagnostic accuracy of Xpert-Ultra in urine for the diagnosis of TB in children, and the first to assess Xpert-Ultra on stool and urine for paediatric extrapulmonary TB and in HIV subpopulations. Additionally, this study provides relevant results on the diagnostic utility of Xpert-Ultra on stool and urine in field conditions in resource-limited settings and in a large cohort of children with presumptive TB (n=533) and with final TB diagnosis (n=323). It is also the first peer-reviewed study to report TB diagnosis in paediatric population in South Sudan.

This multicentric study was conducted in two high-burden HIV, TB and malnutrition settings in Guinea-Bissau and South Sudan. Even though cohorts presented with significant differences in some relevant demographics and in clinical presentations, such as TB contact or HIV-coinfection, we found a similar proportion of final TB diagnosis (59.3-64.7%) among children with presumptive TB across sites. These were higher than those reported in other studies (31-33), a difference likely attributed to the high TB incidence in the context of an effective clinical-decision diagnostic algorithm. TB microbiological confirmation was achieved in 24.9 to 30.2% of TB cases, which is in line with WHO observations (3), and only 1.3% (1/75 confirmed patients) presented with rifampicin-resistance TB.

In our study, we found that a third of patients with confirmed EPTB were positive for Xpert-Ultra on stool, which has not been reported in other studies. Of note, patients with cervical lymph node TB experienced an increase of 6.2% in diagnostic yield when combined with stool. This may indicate either a non-symptomatic concomitant PTB or a gastrointestinal affection and would support the argument for recommending Xpert-Ultra testing in stool for all presumptive pediatric TB cases -not only in pulmonary ones.

In terms of test performance, the sensitivity of Xpert-Ultra in urine was low and its use would not be systematically recommended from a programmatic perspective at this stage, considering a low number of patients with Xpert-Ultra positive on urine (n=12). Of note, 58,3% (7/12) presented with disseminated TB though only one quarter (3/12) were living with HIV; Xpert-Ultra in urine has shown some utility in disseminated TB but has mainly been studied in people with advanced HIV (26,41). We found a non-statistically significant increase in diagnostic yield in SAM compared to non-SAM children, suggesting further studies may help identify and confirm whether in specific subpopulations Xpert-Ultra in urine could play a useful role.

Xpert-Ultra on stool showed a sensitivity of 62.5% overall, and 69.4% among PTB cases, as well as a diagnostic accuracy of 94.3%. These were higher than described in previous studies which evaluated Xpert-Ultra on stool in PTB cases compared to TB culture as reference standard, and where sensitivities ranged between 45.5 and 60.3% (31-33). The standard operating procedure for stool processing was based on the MSF operational SOP (2018, supplementary file 2). Compared to WHO-recommended stool processing methods (42), centrifugation was used, which may

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explain the higher sensitivity compared to other methods which did not use centrifugation and for which sensitivity ranged between 46.8 and 52.1% (42-44).

Additionally, we also noted an additional yield of 10.7% (8/75) patients who were diagnosed on the basis of Xpert-Ultra on stool. This suggests screening children with presumptive TB with Xpert-Ultra on stool could in some cases shorten time to TB diagnosis. Those meeting criteria and having an Xpert-Ultra positive result on stool could commence treatment. In case of a negative result, a second test in a respiratory or extrapulmonary specimen could help confirm TB disease. Of note, this may imply an increase of consumables and, consequently, in cost. Further studies on cost-benefit may be considered.

In patients with a final diagnosis of TB, the diagnostic yield of Xpert-Ultra on stool and urine was 14.1% and 3.8%, respectively. Compared to Kabir et al cohort of presumptive TB cases, diagnostic yield of Xpert-Ultra on stool was similar (31). In pulmonary TB cases, sputum had the higher diagnostic yield with 21.4%, but this sample can only be obtained in older children capable of expectorating. Induced sputum could be an alternative, but it was not available in our setting. For younger children, gastric aspirate in combination with stool presented with a diagnostic yield of 16.4%. Despite WHO latest recommendation, we did not find a significant increase when using stool in combination with naso-pharyngeal aspirate (13.5%), albeit with a low number of confirmed cases (n=5).

WHO recommends Xpert-Ultra as a first test for children with presumptive TB despite a lower specificity (28) due to its increased sensitivity compared to conventional cartridges: the effort to increase TB diagnosis in children outweighs the risk of overtreating patients (11). It is worth noting that a high proportion of patients with confirmed TB presented with a trace result in Xpert-Ultra: 10.2% in pulmonary samples, 19.0% in extrapulmonary samples, 33.3% in stool and 25.0% in urine, congruent with other studies (31). Those results were interpreted as true positives, considering the clinical condition of our pediatric cohort in field conditions with high HIV/SAM prevalence; Xpert-Ultra was consequently not repeated. Of note, a small proportion of invalid results had to be excluded from the analysis despite repeating the test (2.4%, 13/533).

When examining HIV, SAM and under 5-year-old subpopulations, we found a non-statistically significant trend suggesting greater sensitivity of Xpert-Ultra on stool in those with HIV (87.5%) and SAM (71.9%), without a substantial drop in specificity, which is similar to that described by Kabir et al who found a sensitivity of 71% children with SAM (31); unpublished data available in a Cochrane Review report sensitivity of 50% in children living with HIV (28). If confirmed in larger samples, this would support systematic use of Xpert-Ultra on stool in those key vulnerable populations. Diagnostic yield was similar in each subgroup in respiratory and extrapulmonary samples.

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LIMITATIONS

The main limitation of our study was the impossibility to access TB culture, in addition to having an imperfect gold standard for unconfirmed TB cases, which is a limitation for the calculation of specificity. The study was conducted in two settings with high TB incidence and HIV/malnutrition prevalence, which may compromise the generalizability of our results to lower prevalence settings. Additionally, trace results were not repeated, which may ultimately overestimate sensitivity and underestimate specificity, and Xpert-Ultra has a lower specificity comparted to conventional cartridges.

CONCLUSIONS

This study was carried out during routine care provision in two resource-limited and high-TB burden contexts and found that Xpert-Ultra on stool showed moderate to high sensitivity and high specificity when compared to gold standard and an added diagnostic yield when gold standard was negative. Xpert-Ultra on stool was also useful for extrapulmonary presentations. Test performance of Xpert-Ultra in urine was low.

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Contribution statement: All individuals listed as authors have contributed substantially to designing, performing or reporting the study, and every specific contribution is indicated as follows: Conception or design of the work: LMP; Data collection: JG, RG, EB, LF; Data analysis: RM; Interpretation of data analysis: LMP, RM; Drafting the article: LMP; Critical revision of the article: LMP, AL, IM, MJS, RM. All authors read and approved the final manuscript.

Potential Conflicts of Interest: No reported conflicts by the authors.

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Data sharing statement: Data is available to be shared upon request as per MSF data sharing policies.

Ethics statement: Ethics approval was obtained by the Médecins Sans Frontières Ethics Review Board (ID 18116), by the Guinea-Bissau National Health Ethics Committee (ID 009/CNES/INASA/2019) and by South Sudan Ministry of Health Ethical Review Board (ID MOH/ERB 20/2019).

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Figure 1: Flowchart of participants through the study

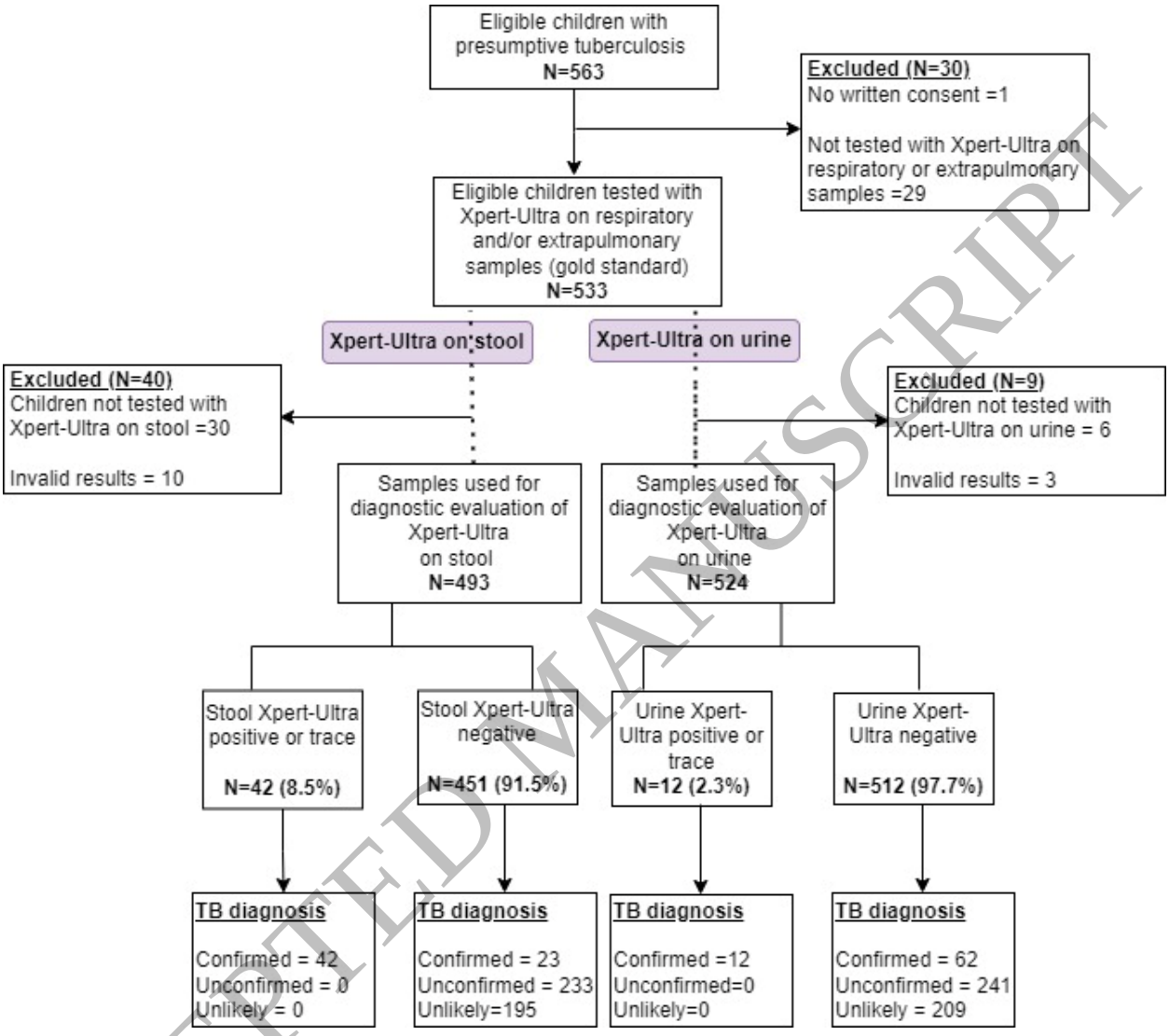

Table 1: Baseline demographic and clinical characteristics of children with presumptive TB at Simão Mendes hospital and Malakal project

Characteristic	Overall, N = 533	Confirmed TB, N = 75	Unconfirmed TB, N = 248	Total TB, N = 323	Unlikely TB, N = 210	p-value
Age group (years)						0.3
0-<2	166 (31%)	15 (20%)	92 (37%)	107 (33.1%)	59 (28%)	
2-<5	116 (22%)	23 (31%)	50 (20%)	73 (22.6%)	43 (20%)	
5-15	251 (47%)	37 (49%)	106 (43%)	143 (44.3%)	108 (51%)	

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Age (months)	48 (18, 108)	48 (24, 99)	54 (32, 108)	36 (16, 96)	60 (20, 120)	0.05
Sex female	272 (51%)	36 (48%)	130 (53%)	166 (52%)	106 (50%)	0.8
Missing	*2 (0.4%)*	*2 (1.5%)*	*0 (0%)*			
TB history present	30 (5.6%)	3 (4.0%)	17 (6.9%)	20 (6.2%)	10 (4.8%)	0.8
Missing	*3 (0.6%)*	*0 (0%)*	*2 (0.8%)*	*2 (0.6%)*	*1 (0.5%)*	
TB contact present	168 (32%)	32 (43%)	84 (34%)	116 (36%)	52 (25%)	**0.023**
Unknown	*11 (2.1%)*	*3 (4.0%)*	*3 (1.2%)*	*6 (2%)*	*5 (2.4%)*	
Children with SAM	331 (62%)*	41 (55%)	167 (68%)	208 (65%)	123 (59%)	0.167
Missing	*3 (0.6%)*	*0 (0%)*	*2 (0.8%)*	*2 (0.6%)*	*1 (0.5%)*	
Children with HIV	93 (17%)**	10 (14%)	61 (25%)	71 (22%)	22 (10%)	**<0.001**
Missing	*1 (0.2 %)*	*1 (1.3%)*	*0 (0%)*	*1 (0.3%)*	*0 (%)*	
CD4<200 cells/mm$^{3\$}$	26 (34%)	4 (44%)	15 (29%)	19 (32%)	7 (41%)	0.464
Missing	*17 (18.3%)*	*2 (20%)*	*10 (16.4%)*	*12 (16.9%)*	*5 (22.7%)*	
ART status$^{\$}$: on ART	40 (43%)	7 (64%)	23 (38%)	30 (42%)	10 (45%)	0.9
Unknown	*1 (1.1%)*	*1 (9.1%)*	*0*	*1 (1.4%)*	*0*	
TB type$^{\#}$						
Disseminated	92 (28.5%)	33 (44%)	59 (24%)	92 (28.4%)	-	
EPTB	70 (21.7%)	19 (25%)	51 (21%)	70 (21.7%)	-	
PTB	161 (49.8%)	23 (31%)	138 (56%)	161 (49.8%)	-	
Cough	399 (75%)	54 (72%)	190 (77%)	244 (76%)	155 (74%)	0.7
Tachypnoea	19 (3.6%)	5 (6.7%)	9 (3.6%)	14 (4.3%)	5 (2.4%)	0.2
Hypoxemia (SPO2 <92%)	50 (9.4%)	6 (8.0%)	34 (14%)	40 (12%)	10 (4.8%)	**0.003**
Fever	440 (83%)	60 (80%)	201 (81%)	261 (81%)	179 (85%)	0.2
Weight loss	374 (70%)	45 (60%)	181 (73%)	226 (71.3)	148 (71%)	0.4
Missing	*2 (0.4%)*	*0 (0%)*	*1 (0.4%)*	*1 (1.4%)*	*1 (0.5%)*	
Gibbous	28 (5.3%)	9 (12%)	15 (6.0%)	24 (7.4%)	4 (1.9%)	**0.005**
Lymph nodes	64 (12%)	21 (28%)	29 (12%)	50 (15%)	14 (6.7%)	**0.002**
Subacute meningitis	5 (0.9%)	0 (0%)	3 (1.2%)	3 (0.9%)	2 (1.0%)	>0.9
Abdomen distended	28 (5.3%)	3 (4.0%)	15 (6.0%)	18 (5.6%)	10 (4.8%)	0.7
Diarrhoea	49 (9.2%)	3 (4.0%)	27 (11%)	30 (9.3%)	19 (9.0%)	>0.9
Painless enlarged joints	8 (1.5%)	1 (1.3%)	5 (2.0%)	6 (1.9%)	2 (1.0%)	0.5
Pleural effusion	7 (1.3%)	1 (1.3%)	6 (2.4%)	7 (2.2%)	0 (0%)	**0.046**
Other EPTB signs	6 (1.1%)	2 (2.7%)	3 (1.2%)	5 (1.5%)	1 (0.5%)	0.4
No signs of EPTB	345 (65%)	36 (48%)	150 (60%)	186 (58%)	159 (76%)	**<0.001**

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Notes: *70/331 (21.1%) children with SAM were living with HIV. **70/93 (75.3%) children with HIV had SAM. $Excluding data of children without HIV. # Excluding data of children with unlikely TB.

Table 2: Diagnostic accuracy of Xpert MTB/RIF Ultra on stool and urine

N- Total samples, TP- True positives, FP- False positives, FN- False negatives, TN- True negatives, PPV- Positive predictive value, NPV- Negative predictive Value, 95% CI- 95% confidence interval, SAM- Severe acute malnutrition.

	N	TP	FP	FN	TN	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
Stool Xpert-Ultra (all)	493	35	7	21	430	62.5 (49.4, 74)	98.4 (96.7, 99.2)	83.3 (69.4, 91.7)	95.3 (93, 96.9)
-Children with HIV	86	7	0	1	78	87.5 (52.9, 97.8)	100 (95.3, 100)	100 (64.6, 100)	98.7 (93.2, 99.8)
-Children <5 years of age	262	14	4	11	233	59.3 (40.7, 75.5)	98.3 (95.7, 99.3)	80 (58.4, 91.9)	95.5 (92.1, 97.4)
-Children with SAM	30	2	3	9	27	71.9 (54.6, 84.4)	98.9 (96.9, 99.6)	88.5 (71, 96)	96.8 (94.1, 98.3)
*Against pulmonary samples	470	34	6	15	415	69.4 (55.5, 80.5)	98.6 (96.9, 99.4)	85 (70.9, 92.9)	96.5 (94.3, 97.9)
*Against extrapulmonary samples	50	6	1	12	31	33.3 (16.3, 56.3)	96.9 (84.3, 99.5)	85.7 (48.7, 97.4)	72.1 (57.3, 83.3)
Urine Xpert-Ultra (all)	524	45	3	58	418	13.9 (7.5, 24.3)	99.4 (98.1, 99.8)	75 (46.8, 91.1)	89.1 (86.1, 91.5)

*23 children were tested for both pulmonary and extrapulmonary samples

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Table 3: Diagnostic yield of combination of different tests

	Diagnostic yield total patients (%, n/N)	Diagnostic yield in TB patients (%, n/N)
Only Xpert-Ultra on respiratory sample	9.4% (44/470)	15.7% (44/281)
Xpert-Ultra on respiratory sample + stool	10.9% (51/470)	18.1% (51/281)
Xpert-Ultra on sputum	12.0% (15/125)	21.4% (15/70)
Xpert-Ultra on sputum + stool	13.6% (17/125)	24.3% (17/70)
Xpert-Ultra on gastric aspirate	8.5% (24/283)	14.0% (24/171)
Xpert-Ultra on gastric aspirate + stool	9.9% (28/283)	16.4% (28/171)
Xpert-Ultra on naso-pharyngeal aspirate	8.6% (5/58)	13.5% (5/37)
Xpert-Ultra on naso-pharyngeal aspirate + stool	8.6% (5/58)	13.5% (5/37)
Only Xpert-Ultra on extrapulmonary sample	32.0% (16/50)	37.2% (16/43)
Xpert-Ultra on extrapulmonary sample + stool	36.0% (18/50)	41.9% (18/43)
Xpert-Ultra on extrapulmonary sample + urine	33.9% (20/59)	40.8% (20/49)
Xpert-Ultra on lymph node	35.0% (14/40)	41.2% (14/34)
Xpert-Ultra on lymph node + stool	40.0% (16/40)	47.1% (16/34)
Xpert-Ultra in pus or tissue	33.3% (2/6)	40.0% (2/5)
Xpert-Ultra in pus or tissue + stool	33.3% (2/6)	40.0% (2/5)
Only Xpert-Ultra on stool	8.5% (42/493)	14.1% (42/298)
Only Xpert-Ultra on urine	2.3% (12/524)	3.8% (12/315)
Only Xpert-Ultra on stool and urine	9.2% (45/490)	15.3% (45/295)

Table 4: Xpert-Ultra diagnostic yield per sample and per age, HIV and nutritional status

	Overall	TB	No TB	OR (95% CI)	P value
Respiratory samples					
<5 years old	268 (53.5)	24 (49)	244 (54)	0.8 (0.5, 1.5)	0.51
≥5 years old	233 (46.5)	25 (51)	208 (46)		
SAM	321 (64.3)	32 (65.3)	289 (64.2)	1.1 (0.6, 2.0)	0.88
No SAM	178 (35.7)	17 (34.7)	161 (35.8)		
HIV	89 (17.8)	9 (18.8)	80 (17.7)	1.1 (0.5, 2.3)	0.86
No HIV	411 (82.2)	39 (81.3)	372 (82.3)		

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Extrapulmonary samples					
<5 years old	30 (50)	9 (42.9)	21 (53.8)	0.6 (0.2, 1.9)	0.42
≥5 years old	30 (50)	12 (57.1)	18 (46.2)		
SAM	23 (39)	8 (38.1)	15 (39.5)	0.9 (0.3, 2.8)	0.92
No SAM	36 (61)	13 (61.9)	23 (60.5)		
HIV	5 (8.3)	1 (4.8)	4 (10.3)	0.4 (0.01, 4.9)	0.84
No HIV	55 (91.7)	20 (95.2)	35 (89.7)		
Stool samples					
<5 years old	262 (53.1)	20 (47.6)	242 (53.7)	0.8 (0.4, 1.5)	0.45
≥5 years old	231 (46.9)	22 (52.4)	209 (46.3)		
SAM	308 (62.7)	26 (61.9)	282 (62.8)	1.0 (0.5, 1.9)	0.91
No SAM	183 (37.3)	16 (38.1)	167 (37.2)		
HIV	86 (17.5)	7 (17.1)	79 (17.5)	1.0 (0.4, 2.3)	0.94
No HIV	406 (82.5)	34 (82.9)	372 (82.5)		
Urine samples					
<5 years old	274 (52.3)	7 (58.3)	267 (52.1)	1.3 (0.4, 4.1)	0.67
≥5 years old	250 (47.7)	5 (41.7)	245 (47.9)		
SAM	322 (61.8)	11 (91.7)	311 (61.1)	7.0 (1.0, 302.9)	0.05
No SAM	199 (38.2)	1 (8.3)	198 (38.9)		
HIV	91 (17.4)	3 (25)	88 (17.2)	1.6 (0.3, 6.6)	0.7
No HIV	432 (82.6)	9 (75)	423 (82.8)		

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