Detection Yield and Tolerability of String Test for Diagnosis of Childhood Intrathoracic Tuberculosis

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Background: Difficulty to obtain sputum in children complicates diagnosis of intrathoracic tuberculosis (TB). The intragastric string test (ST) used for retrieval of enteric pathogens might be an alternative specimen collection method but requires further evaluation of its utility in TB diagnosis. We conducted a cross-sectional study comparing the TB detection yield and the tolerability of ST and sputum induction (SI) in children.

Methods: Two ST and SI procedures were performed in children (3–14 years of age) who were clinically suspected of having TB. The string was removed after a 2-hour gastric downtime, and SI was done after a maximum of 20 minutes nebulization with 5% saline solution. LED-fluorescence microscopy and mycobacterial cultures were performed on all specimens, and XpertMTB/RIF assay was performed on stored specimen sediments. Tolerability questionnaires were administered to parents of children.

Results: Of 137 included children (median age: 8.1 years; 33.3% with HIV infection), 14 (10.2%) were diagnosed with TB, 10 (71.4%) by ST and 12 (85.7%) by SI. Among 105 children with both ST and SI performed, 5 (4.8%) versus 4 (3.8%) were smear positive using ST and SI, respectively (McNemar $P = 1.00$). Nine (8.6%) in each group had positive cultures ($P = 1.00$). Of 64 children tested with XpertMTB/RIF, 3 (4.7%) of the ST group versus 4 (6.3%) of the SI group were TB positive ($P = 1.00$). No adverse serious events were reported. ST could not be performed in 22 of 137 (16.1%) children because they were unable to swallow the capsule.

Conclusions: TB detection yield was comparable between ST and SI. The tolerability of ST in young children might be improved by the reduction of the size of the capsule.

Key Words: tuberculosis, children, diagnosis

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The diagnosis of intrathoracic tuberculosis (TB) in children is a challenge for timely detection and treatment, especially in low resource settings.[1] It can be difficult to obtain a respiratory specimen because children tend to swallow what they cough up and bacteriologic confirmation is seldom achieved due to predominantly paucibacillary nature of childhood TB.[2] Consequently, the decision to treat children for TB is often empiric based on clinical presentation, history of recent TB exposure, positive tuberculin skin test (TST) and judgment on chest radiography.[3,4] The development of alternative methods for retrieving a specimen for bacteriologic confirmation of intrathoracic TB in these patients is desirable.

Procedures such as sputum induction (SI), bronchoalveolar lavage and gastric aspiration (GA) have been used to obtain specimens in children.[5–9] Bronchoalveolar lavage is invasive, requires specialized training and is not feasible in most resource-poor setting. Both SI and GA show good detection yields in the hands of experienced health professionals in limited resources countries but may be challenging to implement on a large scale, especially in rural areas and at places with limited facilities.[5–8,10] This is particularly true for GA that is usually not performed in outpatients setting.

One little-explored option is the "string test" (ST), a procedure approved by the US Federal Drug Administration for retrieval of the enteric pathogens *Giardia* and *Helicobacter pylori*.[11–13] The device is not labeled for the use for diagnosis of TB. ST uses a weighted gelatin capsule containing a coiled absorbent nylon string, with 1 end of the string protruding from a small hole on 1 side of the capsule. The trailing part of the string is taped to the patient's cheek, and the capsule is swallowed. The string is then retrieved by gentle traction and placed in 0.9% saline solution for TB diagnosis. Results from 2 studies in adults suggest that ST is comparable with SI for the detection of TB.[14,15] Prior study showed good tolerance of the ST in 4 years and older children with clinical suspicion of TB. There is no published data on TB detection yield using ST in children.[16] Further evaluation of the diagnostic values of ST in children is therefore warranted.

In this study, we compared the TB detection yields using microscopy, culture and XpertMTB/RIF assay (Cepheid, Sunnyvale, CA) between ST and SI in children who were clinically suspected of having TB. We also assessed the tolerability of these 2 methods.

PATIENTS AND METHODS

Study Design and Population

All children (3–14 years) referred to the Mbarara Regional Referral Hospital who were clinically suspected of having TB were eligible for the study. Suspicion of TB was defined by the combination of at least 1 of the following symptoms: cough for longer than 2 weeks, persistent wheezing, unexplained loss of weight or fever, failure to thrive, persistent or recurrent diarrhoea, painless swelling in a group of superficial nodes, not regaining normal health after measles or whooping cough; either a history of contact to a confirmed TB case; a positive TST defined as a TST >5 mm induration; a chest radiogram suggestive of TB or the absence of clinical improvement after 1 week of antibiotics targeting respiratory infection.

Patients were excluded if they had received TB treatment or a fluoroquinolone for at least 1 week within the month before enrollment, had contraindications to SI (asthma, chronic obstructive pulmonary disease, restrictive airway disease or oxygen saturation <92%) or were too unwell to tolerate procedures. Written consent was obtained from parent or guardian and assent was received from children older than 7 years. A medical questionnaire on symptoms

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and TB exposure history was obtained from the parents. Physical examination and anteroposterior chest radiogram were performed. A TB suggestive radiograph was defined by the presence of hilar or mediastinal lymphadenopathy, local collapse/consolidation, severe bilateral but asymmetric disease, cavitation, miliary changes or pleural effusion.[17] All children diagnosed as TB were started on TB treatment following national guidelines.

Sample Collection and Laboratory Procedures

For optimal yield, SI was systematically performed after ST. One ST followed by one SI procedures were performed at enrolment ("spot" samples), and both procedures were repeated in the same order the next morning ("morning" samples) by the same trained nurses. For ST, a 2-hour fasting was required before sample collection. Pediatric ST from the HDC Corporation (San Jose, CA) was used according to the manufacturer's guidelines, except that the intragastric downtime was reduced from 4 to 2 hours to improve feasibility of the procedure. Results from a laboratory-based study revealed similar *Mycobacterium tuberculosis* (*MTB*) detection from STs retrieved after 2-hour and 4-hour intragastric downtime from smear-positive patients.[18] A ST failure was defined as failure to swallow the capsule despite 2 attempts. For the SI, 5% hypertonic saline solution was nebulized using an ultrasonic nebulizer for a maximum of 20 minutes. For children who could not expectorate, nasopharyngeal aspiration was used after induction. An SI procedure was defined as failure if no specimen was obtained after 20 minutes. Procedures were performed in an adequately ventilated area of the clinic to limit the risk of TB transmission.

For both SI and ST, samples were immediately transported to the laboratory and processed within 2 hours after collection. Same diagnostic tests were performed on all collected specimens. Smear microscopy was performed on freshly induced sputum and on sediment after decontamination and centrifugation of ST samples. Specimens were decontaminated for 20 minutes using the *N*-acetyl-L-cysteine, 0.5%–Sodium hydroxide, 1.5% method (final NaOH concentration of 1.5%) followed by addition of 45 mL of phosphate buffer solution for neutralization to make a total of 50 mL. Centrifugation was done at 5°C for 20 minutes at 3000*g*, and the sediment was resuspended with 2.5 mL phosphate-buffered saline. From March 2011 (the approximate midpoint of the study), the sediment remaining after centrifugation of 1 ST sample and 1 SI sample per patient was frozen at −20°C. They were then tested with the XpertMTB/RIF assay that became available on the site at the end of the study. Auramine-stained smears were read with LED-fluorescence microscope (FluorescenS® LED system, Bergman Labora, Danderyd, Sweden) under 200/400 magnification according to international standards.[19] For each collected sample, 2 drops of resuspended sediment were inoculated into 2 tubes with Löwenstein–Jensen (LJ) medium and 1 with Mycobacteria Growth Indicator Tube (MGIT; Becton, Dickinson, Franklin Lakes, NJ) containing a cocktail of antibiotics: polymyxin amphotericin B nalidixic acid trimethoprim azlocillin and supplement oleic acid albumin dextrose catalase. For *MTB* identification and detection of contamination, culture-positive samples were processed with Ziehl–Neelsen smear microscopy, blood agar inoculation, the *p*-nitrobenzoic acid test and then tested with the SD TB Ag MPT64 rapid test (Standard Diagnostics, INC, South Korea). For XpertMTB/RIF assay, 0.5 mL of the sediment was added to 1.5 mL of test reagent and processed according to the test manufacturer's instructions. The laboratory was monitored by the Tropical Medical Institute in Antwerp (Belgium), whereas external quality assurance for microscopy and culture was done at the National Health Laboratory Service in South Africa.

Tolerability Assessment

Tolerability was assessed using standardized questionnaires administered to the parent or guardian by a nurse during SI and ST procedures. The ST procedure was divided into 7 time points (before insertion, during insertion, 10 minutes after insertion, 1 hour after insertion, 10 minutes before removal, during removal and 10 minutes after removal) and the SI into 3 time points (before SI, during SI and 10 minutes after SI). A behavioral pain scale (Detroit Medical Center 2000, Campbell, CA) was used to establish the total tolerability (pain) scores at these designated time points. Discomfort was rated by the parent or guardian at same time points using a visual analog scale of 0–10 (0 = no discomfort and 10 = worst possible discomfort).[16,20] During SI, oxygen saturation and the occurrence of adverse events were recorded.

Statistical Analysis

We needed to recruit 112 children to show equivalence between the TB detection yield of ST and SI with a maximum tolerated difference of 7.5%, an expected proportion of discordant results of 8%; 80% power and 5% 2-sided significance level (N Query Advisor; paired test of equivalence of proportions). Taking into account 20% refusals or dropouts, we aimed to recruit 140 children.

A confirmed pulmonary tuberculosis case was a patient with at least 1 positive TB result on any collected specimens (ST or SI) using microscopy or culture. For calculating the *MTB* culture detection yield, contaminated results were excluded and results with non-TB mycobacteria (NTM) were classified as culture negative results for *MTB*. The comparison of detection yields using microscopy, culture and XpertMTB/RIF assay between ST and SI were done in patients who had at least one ST and one SI sample result, using the McNemar test for paired data.

TB culture detection yield was presented by children's characteristics, type of culture method and degree of TB suspicion defined by the presence of 1, 2, 3 or 4 TB suggestive criteria. These criteria included history of TB contact, suggestive chest radiogram, positive TST and nonresponse to antibiotic course at the entrance in the study.

The indicators of tolerability were described using proportions for dichotomous variables and means with standard deviation (SD) for continuous variables.

Data were double entered in a Voozanoo database (Epiconcept, Paris, France), and statistical analysis was performed using Stata software (v. 11, College Station, TX).

Ethical Approvals

The study was approved by The Mbarara University Faculty of Research and Ethics Committee, The Mbarara University Institutional Review Board, The Uganda National Council for Science and Technology and The Comité de Protection des Personnes of Ile de France XI, Saint-Germain, Laye, France.

RESULTS

A total of 140 children were enrolled between July 19, 2010 and March 1, 2013. Three children were secondarily excluded for not fulfilling inclusion criteria (cough without additional criteria; Fig. 1). Almost half of children enrolled were 10–14 years old, and 19% were younger than 5 years. About half of children were female, and one third of children tested were HIV infected (Table 1). Of the 74 outpatients, 31 were referred from the outpatient hospital department, 13 from the hospital HIV clinic, 14 from peripheral clinics and 12 were symptomatic child contact cases referred for TB investigation. Most of the children were clinically suspected of having TB based on symptoms and 2 other conditions. The median

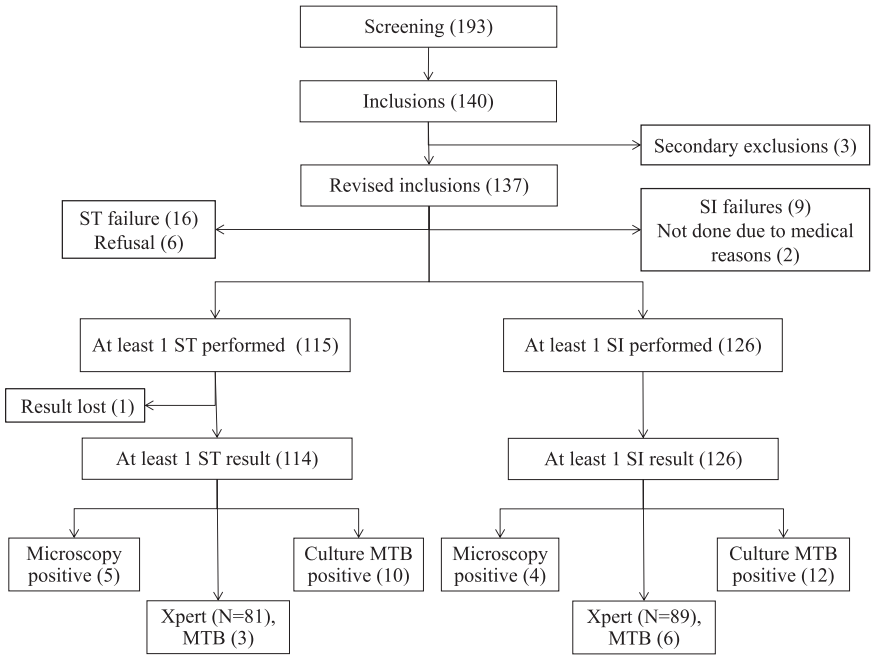

FIGURE 1. Study profile.

number of symptoms suggested of TB per child was 2 (1–3), and 59 of 137 (43.1%) children did not respond to a nonspecific antibiotic course (Table, Supplemental Digital Content 1, http://links.lww.com/INF/C299). In total, 96 of 137 (70.1%) children had a chest radiogram suggestive of TB. Predominant radiological feature was lung infiltrations (84/96; 87.5%) and lymphadenopathy (16/96; 16.7%).

TABLE 1. Patients' Characteristics

Characteristic, N = 137	n (%)
Median (IQR) age in years	8.1 (5–11)
Age categories in years	
<5	26 (19.0)
5–9	49 (35.8)
10–14	62 (45.2)
Gender	
Male	66 (48.2)
Female	71 (51.8)
HIV status	
Positive	43 (31.0)
Negative	86 (63.0)
Unknown	08 (06.0)
Patient type	
Inpatients	63 (46.0)
Outpatients	74 (54.0)
Nutritional status (weight for height Z score)	
Normal, SD > −1	99 (72.3)
Mild malnutrition, SD, −2 to ≤−1	22 (16.1)
Moderate malnutrition, SD, −3 to ≤−2	11 (8.0)
Severe malnutrition, SD ≤3	05 (3.6)
Symptoms at inclusion	
Cough >2 weeks	94 (68.6)
Persistent wheezing	17 (12.4)
Unexplained weight loss	51 (37.2)
Reported fever	58 (42.3)
Failure to thrive	31 (22.6)
Persistent or recurrent diarrhoea	11 (8.0)
Painless swelling in a group of superficial nodes	35 (25.5)
Not regaining normal health after measles or whooping cough	2 (1.5)

IQR indicates interquartile range.

Among the 137 children included in the analysis, 115 (83.9%) and 126 (92.0%) had at least 1 ST and 1 SI attempted, respectively (Fig. 1). XpertMTB/RIF assay was performed on 81 (59.1%) and 89 (65.0%) sediments from ST and SI samples, respectively.

Overall, a total of 14 of 137 children (10.2%) were diagnosed with TB, and all were started on TB treatment. Of them, 13 (92.9%) were diagnosed from the first (spot) collected specimen; 4 (28.6%) were smear positive, and 14 (100%) were culture *MTB* positive. Two SI samples were culture positive for NTM. There was no NTM-positive culture result with ST. Five patients were smear positive, 4 (80%) were confirmed *MTB* culture positive, and 1(20%) had NTM growth (SI sample). There was no case of final culture contamination result after using all the 3 culture methods (2 LJ and 1 MGIT). There were 10 of 14 (71.4%) patients diagnosed with TB using ST and 12 of 14 (85.7%) using SI.

Among the 137 patients, 105 had at least 1 ST and 1 SI sample result available for microscopy and culture. Of them, 5 (4.8%) and 4 (3.8%) had a smear-positive result from ST and SI, respectively (exact McNemar test, $P = 1.00$). *MTB* culture detection yield was the same with each method (9/105; 8.6%). XpertMTB/RIF results from both ST and SI were available for 64 patients. *MTB* was detected in 3 (4.7%) cases from ST and 4 (6.3%) cases from SI ($P = 1.00$; Table 2). None was resistant to rifampicin. Table 3 presents the *MTB* culture detection yield for ST, SI and the combination of both by different patients' and specimens' characteristics. Children older than 4 years were more likely to be culture positive than younger children.

In term of feasibility, 22 children did not swallow the ST capsule: 5 (22.7%) in the 3 years old group, 8 (36.4%) in the 4 years old group, 2 (9.1%) in the 5 years old group, 1 (4.5%) in the 6 years old group and 6 (27.3%) in children older than 6 years. The SI was not attempted in 2 children because of their poor clinical condition and did collect any sample in 9 other children.

Tolerability was assessed in 115 children for ST and 126 children for SI. The mean pain and discomfort scores quoted by the parent or the guardian for ST was higher during the insertion and removal of the capsule but remained below 3 out of 10 during

TABLE 2. Comparison of Microscopy and Culture Detection Yield Between SI and ST in Children With at Least 1 SI and 1 ST Results

	Microscopy (N = 105)			Culture (N = 105)			Xpert (N = 64)		
	ST+	ST−	*P* Value*	ST+	ST−	*P* Value*	ST+	ST−	*P* Value*
SI+	4	0	1.00	8	1	1.00	3	1	1.00
SI−	1	100		1	95		0	60	

*Exact McNemar's χ^2 test.

Culture result with nontuberculosis mycobacteria was classified as negative *Mycobacterium tuberculosis* culture results for the analysis.

the other phases of the procedure. The scores were below 2 at the different times of assessment for the SI (Fig. 2). Cough was reported in 8 of 115 (7.0%) children with ST and 1 of 126 (0. 8%) with SI. Tachypnea occurred in 4 children (3.2%) during SI. The mean oxygen saturation was 98.8% (SD, 2.7) before starting SI, changed to 98.0% (SD, 6.4) during the procedure and was 98.1% (SD, 2.8) at the end of the procedure. No serious adverse event was reported.

DISCUSSION

This is the first study that evaluated TB detection yield from samples collected with the ST in children. The TB recovery rates between ST and SI were comparable but remained very low with approximately 5%, 10% and 7% detection yields for microscopy, culture and XpertMTB/RIF, respectively. The culture detection yields from SI were similar to results reported in previous studies and very close to results obtained from GA.[5,21] Detection yield using the XpertMTB/RIF assay on ST or SI samples were also comparable with results on SI samples from others studies.[21–23] Detection yields were lower in young children (3–4 years old) compared with older children (5 years and above). On the other hand, the yield was not different according to children's HIV status and nutritional condition. It increased to more than 50% in children with higher pretest probability for TB.

Studies that evaluated SI, GA or nasopharyngeal aspirate in children report an average increase of 20% of TB detection yield when using 2 specimens compared with 1 specimen.[24] Surprisingly in our study, the gain of detection of the examination of the second specimen was very low (7%). On the other hand, we showed that the combination of SI and ST at the first visit (14/137; 10.2%) had similar detection yield than the examination of 2 SI or 2 ST specimens collected during 2 consecutive days (10/137; 7.3% for ST and 12/137; 8.8% for SI). This is consistent with results reported by previous studies using different specimen collection methods.[25,26] The combination of different specimen collection methods might offer a possibility of a 1-day TB diagnosis in children. In our study, the SI was always performed after the ST assuming that the ST would optimize the yield of the SI. Further investigation to assess the combination of different specimen collection methods in children and the best order of the tests to maximize the detection yield would be required.

TABLE 3. Tuberculosis Detection by Patients' Characteristics, Type of Specimen and Culture Using SI and ST

	ST		SI		ST or SI	
	n/N (%)	*P*	n/N (%)	*P*	n/N (%)	*P*
Age, yr						
3 and 4	0/12 (0)	0.26	0/25 (0)	0.07	0/26 (0)	0.05
5–14	10/102 (9.8)		12/101 (11.9)		14/111 (12.6)	
HIV status						
Positive	2/32 (6.3)	0.47	4/40 (10.0)	0.98	5/43 (11.6)	0.84
Negative	8/75 (10.7)		8/79 (10.1)		9/86 (10.5)	
Nutrition/malnutrition*						
Normal	7/86 (8.1)	0.49	7/90 (7.8)	0.44	9/99 (9.1)	0.66
Mild	1/15 (6.7)		3/20 (15.0)		3/22 (14.0)	
Moderate	1/8 (12.5)		1/11 (9.1)		1/11 (9.0)	
Severe	1/5 (20.0)		1/5 (10.0)		1/5 (20.0)	
Degree of TB suspicion						
1 condition	3/62 (4.8)	0.18	4/66 (6.1)	0.04	5/71 (7.0)	0.05
2 conditions	5/42 (11.9)		5/46 (10.9)		6/51 (11.8)	
3 conditions	1/8 (12.5)		1/11 (9.1)		1/12 (8.3)	
4 conditions	1/2 (50.0)		2/3 (66.7)		2/3 (66.7)	
Culture type†						
LJ1 + LJ2	7/114 (6.1)	0.13	8/126 (6.3)	1.00	9/137 (6.6)	
MGIT	9/113 (8.0)	1.00	10/125 (8.0)	0.50	12/137 (8.8)	
LJ1 + LJ2 + MGIT	10/114 (8.8)		12/126 (9.5)		14/137 (10.2)	
Specimen‡						
Spot	10/107 (9.3)	1.00	9/120 (7.5)	0.13	13/132 (9.8)	1.00
Morning	7/110 (6.4)	0.25	9/117 (7.7)	0.50	11/129 (8.5)	0.25
Spot + morning	10/114 (8.8)		12/126 (9.5)		14/137 (10.2)	

*Weight for height Z score.

†*P* values for comparison with LJ1 + LJ2 + MGIT using McNemar test.

‡Comparison with spot + morning.

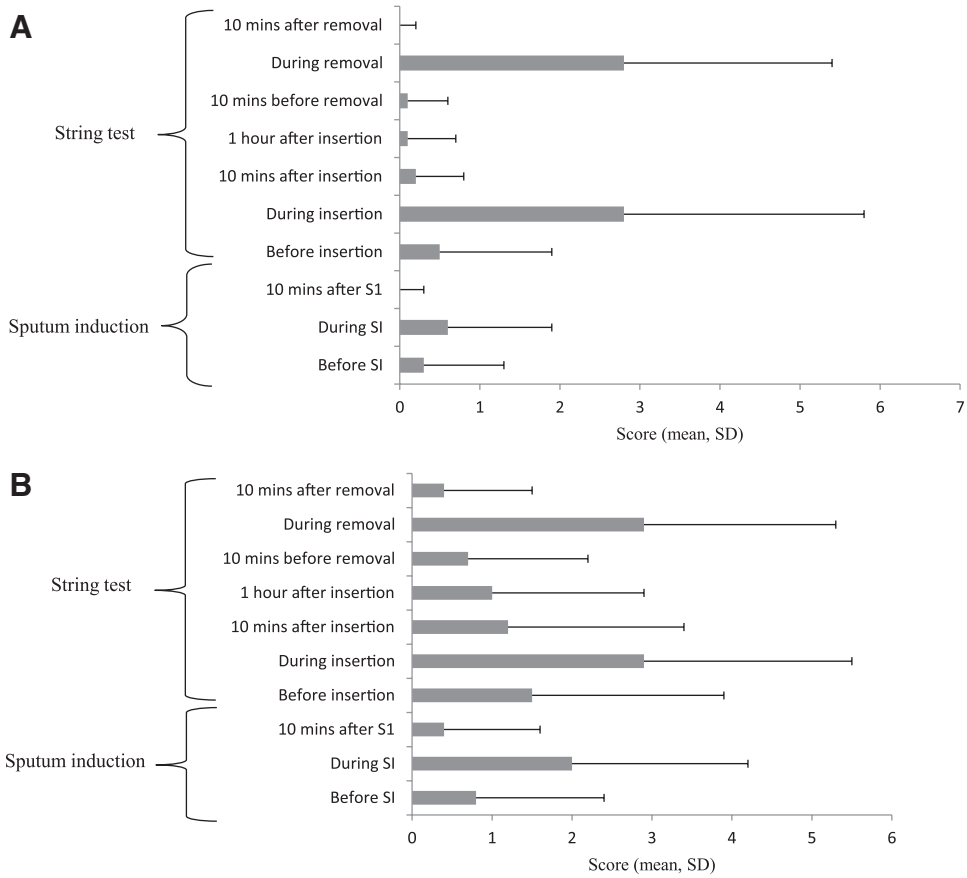

FIGURE 2. Tolerability and discomfort scores during ST and SI procedures. A, Tolerability scores at various times during ST and SI procedures. B, Mean discomfort scores for child and guardian at various times during ST and SI procedures.

The ST was not very well tolerated by children, especially during the insertion and removal of the string. The size of the capsule was definitely a serious limiting factor in our study, especially in children below 5 years. Indeed, 60% of the children unable to swallow the ST capsule were 3 or 4 years old. The use of ST in children in programmatic conditions should consider the access to smaller capsules. This is particularly important in high HIV-burden countries where the median age of children diagnosed with TB is lower than 4 years.[23] There were very few adverse events reported with the ST and SI procedures, and none was serious. SI did not impede oxygen saturation in our study but very sick children were not included in the study.

Regarding operational aspects for the implementation of the ST, it requires very limited training of the nursing staff. The requirement of 2-hour fasting and 2-hour gastric downtime of the string can be a limiting factor for the use of the test in an outpatient setting. The need of the sample centrifugation before smear microscopy is also a constraint for microscopy laboratory setting, which do not have centrifuge. However, this is probably not needed for the XpertMTB/RIF assay. In term of availability, today, there is only 1 manufacturer of the ST device in US for the cost of $1 per test. The device is extremely simple and could be easily produced locally as shown in Peru, where in-house tests were developed for less than $0.20 per test using market-purchased gelatine capsules.[16]

Our study had several limitations. The comparison of TB detection yield between SI and ST was hampered by the relatively low numbers of enrolled patients who were tested with both SI and ST because of an unexpected high proportion of children who failed to swallow the ST capsule. The study was not initially designed to use the XpertMTB/RIF assay, which was only available later after starting the study. Therefore, the XpertMTB/RIF assay could only be performed on samples collected in a subgroup of patients. Finally, our study was not designed to compare the ST with the GA. It is important to assess if these 2 sample collection methods for the intragastric retrieval of *MTB* have similar TB detection yield. However, the evaluation of several semiinvasive sample collection methods in children is challenging. In this study, we used the SI as comparator because it had similar TB detection yield than the GA, and we considered it more suitable to outpatient setting than the GA.

CONCLUSION

The ST might be a good alternative to SI in children who are old enough to swallow the capsule. Its use could be optimized with the development of smaller capsules and the reduction of the duration of the intragastric downtime. More research on biomarkers is needed to obtain more sensitive nonsputum-based TB diagnostic test for children.[27]

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