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Spectrum of Childhood Tuberculosis: Ensuring and Making a Differential Diagnosis by Tuberculin Skin Test and Clinical Signs in Kisangani, DR Congo

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Authors' contributions

This work was carried out in collaboration between all authors. Authors ETK and NND designed the study, wrote the protocol and wrote the first draft of the manuscript. Authors JNK and ETK performed the statistical analysis and managed the analyses of the study. Author BBL managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: Early diagnosis of childhood tuberculosis (CTB) could enable rapid diagnosis and management of TB epidemic within a community at high risk. This study was undertaken to determine the performance of Tuberculin Skin Test (TST) and influencing factors in the evaluation of CTB spectrum.
Methods: This was a retrospective cross-sectional analysis of patients' medical records carried out at a tertiary health center, from 05 March 2012 to 27 December 2013, in Kisangani city. The subjects were children and adolescent 6 months to 17 years old who have been tested for tuberculosis with TST alongside chest radiograph and clinical symptoms.

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Results: The spectrum of CTB approached 40% among 593 children tested, of which 31.5% were diagnosed with TST and 8.5% by other means. TST sensitivity was 78.3%. Presence of BCG vaccination may increase the positivity of TST. The prevalence of the infection was not significantly different between male and female, but was significantly lower in old children compared with infants 6-24 months old [OR=0.740;p=0.002]. All municipalities were affected, but Makiso and Tshopo housed the majority (OR=1.25). Contact with TB adult suspect significantly increased risk of primo-infection [OR=2.13;p=0.013].
Conclusion: The spectrum of TB is actually high in the city. TST remains the faster and more accessible test to diagnosing TB in this high endemic city but other clinical approaches should be used to not miss out TST false negative cases. Free testing should be envisaged to serve poorest families who cannot afford current costs.

Keywords: Spectrum childhood tuberculosis; tuberculin skin test; chest radiograph; Kisangani.

1. INTRODUCTION

According to the World Health Organization (WHO) statistics 2016, approximately 10 % of around 9 million cases of tuberculosis (TB) recorded worldwide are children [1,2]. The surveillance of childhood tuberculosis (CTB) is very important because it is indicative of a recent infection from an adult contaminant [3]. A high prevalence of CTB in a community signals not only the circulation of the tubercle bacillus or *Mycobacterium tuberculosis* (MT) in that community but also the failure of its screening and its management [3-5]. Currently, the diagnosis of tuberculosis primary infection (TPI) in children is considered difficult even for pulmonary forms [3-5]. The actual estimates of TPI cases in children consequently remain quite biased in poor countries with a high-burden of the disease [5-7], and that is more dramatic in children living with HIV [8-10]. The underlying causes making it difficult are atypical symptoms in children, the fact that the child rarely expectorates and the paucibacillary character of infection which makes difficult the bacteriological confirmation [11-13]. Several authors [14-21] have recommended the diagnosis be based on a set of tests including, tuberculin skin test (TST), radiographic abnormalities, endoscopy, Xpert MTB/RIF assay, and use of IGRAs (interferon-γ release assays) among others. The simplest and most affordable recommended test in resources-limited countries is TST [22]. Since its first use, TST helped in epidemiological surveys for TB detection and supervision of Bacillus Calmette-Guérin (BCG) vaccination. It is applied either during a systematic screening visit of subjects living in contagious environment, or at the time of consultation motivated by TB evocative symptoms. In developing countries with well-known endemic zones of TB like the DR Congo, the validity of TST has been demonstrated in diagnosing TPI [14,22], but its performance rate and utility remain unclear yet commonly accepted and practiced. In the city of Kisangani, the clinical consensus for practicing TST in children suspected of TB is still challenging [23]. The policy for offering BCG vaccinations in DRC is to protect people who are at higher risk of becoming infected with TB. The BCG vaccine administered to newborns before getting out of the hospital but also for children up to 15 years old who did not get it before. However, not all children are vaccinated and those vaccinated are not completely prevented from acquiring TB.

The aim of this study was to evaluate the performance of TST and clinical features to diagnosing CTB for BCG vaccinated and unvaccinated children in order to establish a road map in the context of Kisangani environment.

2. MATERIALS AND METHODS

2.1 Study Design

The study took place in the town of Kisangani, the capital of the Tshopo province in eastern DR Congo. The city has a high incidence of tuberculosis as it has long been the theater of recurrent wars which led to extreme poverty and increased contact with displaced persons including civilians and all kind of military fighters. The study was designed as a retrospective cross-sectional analysis of data extracted from medical records of children aged 6 months to 17 years who have been submitted to TST at the pediatric hospital center, known as "Village de Pédiatrie", from 05 March 2012 to 27 December 2013. The Center offers TST to TB children suspects. But, given that the test is not for free, the access to all suspect cases is limited. All children of both sexes who consulted the

Pediatric Village Center during the study period were eligible. Those who underwent TST were pre-selected. Among them, we retained only those who have been registered at the Center and we excluded those who came from other medical centers. Finally we retained those diagnosed TB+ regardless of positivity or negativity to TST.

2.2 Study Sample

During the observational period, 1246 children have been given TST, of whom 593 were affiliated with the Pediatric Village and 653 children were from other medical centers. Only 593 cases found in the Register at Pediatric Village were analyzed. For TB untreated group, all three members in charge of diagnosis agreed that TST was negative, no bacteriological confirmation was obtained and no extra-thoracic TB was documented. Treated group comprised of all children who had manifestations suggestive of TB. Globally, 239 children were treated for TB and 354 children were considered for other pathologies (Fig. 1). HIV children known were not treated at the center and were in excluded cases.

2.3 Practice of Tuberculin Skin Test

Each child was injected intradermally into the anterior surface of the left forearm at the upper third junction with an exact volume of 0.1 ml (2 IU) of tuberculin solution according to the manufacturer protocol. The kit used (Serum Institute of Copenhagen) was the derivative of the purified protein RT 23 of the staten which is a protein extract of a culture of *Mycobacterium tuberculosis* and which is the reference for TST recommended by WHO. The allergy reaction result was read 72 hours after. TST was negative when the induration diameter (and not of the erythema) developed at the site of injection was <5mm. The result was positive when the cut-off diameter was ≥5 mm despite the presence of BCG scar. Generally an induration of 5 or more millimeters is considered positive in HIV-infected persons or a recent contact of a person with TB disease or persons with fibrotic changes on chest radiograph consistent with prior TB. An induration of 10 or more mm is considered positive in children < 4 years of age, infants, children, and adolescents exposed to adults in high-risk categories. An induration of 15 or more mm is considered positive in any person, including persons with no known risk factors for TB. In our case, given that Kisangani is a highly endemic area, there is a high probability of detecting both clinical silent and clinical active infection. A diameter ≥10 was considered as active TB while between 5 and 10 was taken roughly as latent form. In clinic setting, when we say latent that means infection is there but silent and contagious is low, and that will further progress to clinical disease. The patient is put under surveillance and will be treated once the medical team decides to intervene. In our case, since the area is at high-risk, we took precaution to intervene before the situation gets worse; both were treated.

2.4 Measurement Variables

Table 1 summarizes the variables used in this study to ensure and make the diagnosis of primary tuberculosis infection. Criteria for being TB+ included: TST+, Chest abnormalities conclusive or responding to TB treatment, yet being TST- and chest abnormalities inconclusive.

Table 1. Study variables

Variables	Meaning
TST performance	Sensitivity = percentage of true positive (TB+/TST+)
	Specificity= percentage of false positive (TB-/TST+)
	Discriminate ability= mean of sensitivity + specificity
TB risk factors	BCG vaccination (presenting scar or not)
	Promiscuity (more or less than 4 persons sharing a room)
	Contagion (history of living in contagious environment)
Demographics	Age, sex, residence, nutritional status
Chest images	Consolidation/opacities, cavitations/cysts, linear opacities/fibrosis, nodules/masses, miliary pattern, lymphadenopathy, pleural abnormalities, trancheobronchial abnormalities, hilar adenopathy
Blood test	Sedimentation rate (SR): > 30 min/h or <30 min/h
	Leucocyte formula (neutrophil count, lymphocyte count)
Symptoms	Fever, weight loss, cough, etc.

2.5 Statistical Analysis

For the analysis, the data collected was treated with Excel spreadsheet, Epi-info version 3.3.2 software (CDC Atlanta Georgia.) and SPSSv20 Windows to capture and perform descriptive statistics. Data are presented as mean ± SD for continuous variables and proportion and 95% confidence interval for nominal variables. Crosstabulation or logistic regression was used to calculating crude odds and odds ratio for nominal variables using Chi-square tests of Pearson, Fisher exact test or Mantel-Haenszel depending on the case with statistical significance at $p<0.05$.

3. RESULTS

3.1 Performance of Diagnosis

Fig. 1 shows the flow chart of patients. Out of 593 cases found in the register at the Pediatric village, 187 (31.54%) were TST+ positive and 406 (68.46%) were TST-negative. Among TST-, 52 (21.76%) were found TB+ by other criteria (chest abnormalities and response to TB treatment). The sensitivity of the test was then 78.24% meaning that the probability of reporting false negative cases was 21.76%. The specificity of the test was however 100% meaning that the probability of reporting false positive was negligible. The discriminatory ability of the test was then 89.12%.

Table 2 shows the findings related to basic chest abnormalities and some clinical patterns of the disease in the three groups: True positive (TP)=(TB+/TST+), False negative (FN)=(TB+/TST-) and True negative (TN)=(TB-/TST-). In general, chest abnormalities and clinical patterns were more prominent in TB+ (TP and FN) than TB- (TN).

Fig. 2 presents the distribution of continuous and interval variables. The mean value for age was 3.1(0.42-17) years; the mean values for weight were 13.55(3.3-62) kg for actual measured weight and 13.96(6.45-51) kg for ideal expected weight. Definitely, taking the margin of ± 20% of the ideal weight as normal range, there were 460(77.6%) children with normal weight, 95(16%) with underweight and 38(6.4%) with overweight for the entire population. The brachial diameter mean value was 14.83 (10.7-24) mm independently of the gender. The mean body temperature was 37.29(35.3-40.1)℃. The Induration size mean was 13.2±3.9 (5-28), mode (10), CL95% (0.59), count (187). Only 13.4% had size 5-10 (infection with late evident-clinical manifestation) against 86.6% with size >10mm= 86.6% (infection with clinical manifestation).

3.2 Impact of Patients' Characteristics on Tuberculosis Status

Table 3 describes the distribution frequencies by age, sex, residence and other characteristics. TB+ infants younger than 3 years were more affected than old children compared with TB-. The frequency in TP group steadily decreased from 38% in children aged 6-11 months to 4.3% in children 11-15 years old while in TN group, the frequency was 19.5% in 6-11 months children and 34.1% in 3-5years old. Overall there were 50.3% males and 49.7% females in the TP group; males are more likely to contact TB than females but the difference was not significant. The majority of patients came from Makiso and Tshopo communes, but the proportion of TB in these two communes is not significantly different with other communes (OR=1.159). The malnutrition status was higher in FN group (50%) than in TN group (34%). Children living in contagious environment had very high risk of developing tuberculosis than those not

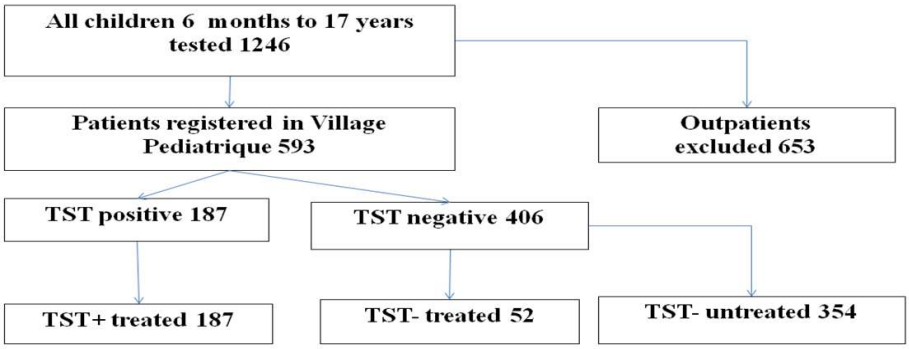

Fig. 1. Flow chart of patients

exposed (OR=2.129). Promiscuity did not significantly increase the risk to TB. The presence of BCG scar increased the probability of being tested TST positive (p=0.002) at the cut-off ≥5 mm.

4. DISCUSSION

Definitely, the likelihood of TB prevalence among children registered at the Pediatric Village Center as diagnosed by both TST and chest radiographic or clinical investigation was around 40.3%. The prevalence of reactivity to TST was 31.5% (187/593). This rate is between 27.3% found in the Central African Republic [22] and 40% reported in other countries [24,25]. The sensitivity of TST was estimated to be 78.7% and the specificity as 100%, meaning that False-negative approximated 21.3% while False-positive responses were negligible. In the study by Sohelha et al. [25] in Iran, the tuberculin skin test was positive in 73%. Also a recent study by Schumacher et al. [26] estimated the sensitivity of the TST to be 75% (95% CrI: 61, 84), and decreasing substantially among children who were malnourished and infected with human immunodeficiency virus (56%); the specificity of the TST was 69% (95% CrI: 63%, 76%). Furthermore, it was estimated in that study that 46% (95% CrI: 42, 49) of pulmonary TB-negative cases and 93% (95% CrI: 82; 98) of TB-positive cases received antituberculosis treatment, which indicates substantial overtreatment and limited under treatment.

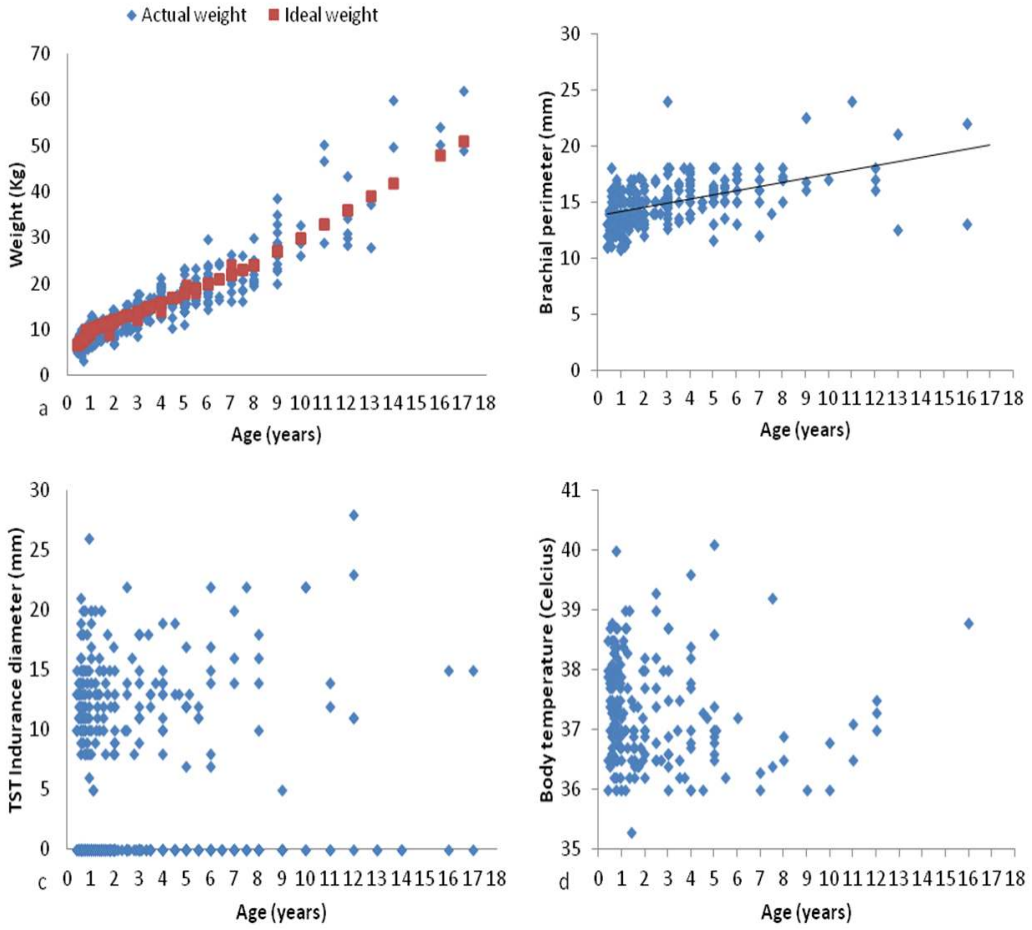

Fig. 2. Distribution of characteristic continuous variables as function of age (valid cases)

Age: mean 3.10±2.89(0.42-17), mode(3), CL95% (0.23), count (593); Actual weight: mean 13.55±7.65(3.30-62), mode (10), CL95% (0.62), count(593); Ideal weight: mean 13.96±6.74(6.45-51), mode (14), CL95% 0.54), count(593); Brachial diameter: mean 14.83±1.98(10.70-24), mode (15), CL95% (0.23), count (296); Indurance size: mean 13.2±3.94 (5-28), mode (10), CL95% (0.59), count (187); Body temperature: mean 37.29± 0.88(35.3-40.10), mode (37), CL95% (0.13), count (188)

Table 2. Diagnostic by chest X-ray and clinical patterns

	Markers	Count TN;FN;TP	TN (%)	FN (%)	TP (%)	Sign.
CXR	Densification	168;41;186	1(0.6)	0(0)	1(0.5)	0.001
	Miliary (disseminated)		1(0.6)	1(2.4)	4(2,2)	
	Opacities		35(20.8)	11(26.8)	29(15.6)	
	Hilar adenopathy		124(73.8)	17(41.5)	92(49.5)	
	Cardiomegaly		0(0)	3(7.3)	0(0)	
	Unread		7(4.2)	9(22.0)	60(32.3)	
Sedimentation	<30 mm/h	354;52;170	190(53.7)	19(36.5)	51(30.0)	0.000
	>30 mm/h		164(46.3)	33(63.5)	119(70.0)	
WBC	Lymphocyte count pattern	146;43;140	77(52.7)	21(48.8)	64(45.7)	0.493
	Neutrophil count pattern		69(47.3)	22(41.4)	76(54.3)	
Clinical signs	Cough	354;52;187	72(20.3)	18(43.6)	45(24.1)	0.027
	Fever	354;52;187	63(17.8)	10(19.2)	51(27.3)	0.034
	Sickle cell	354;52;187	0(0)	1(1.9)	1(0.5)	
	Chronic kidney disease	354;52;187	8(2.3)	3(5.8)	4(2.1)	
	Neurological signs	354;52;187	3(0.8)	0(0)	2(1.1)	
	High blood pressure	354;52;187	3(0.8)	3(5.8)	3(1.6)	

TN=true negative (TST-/TB-); FN=false negative (TST-/TB+); TP=true positive (TST+/TB+). The percentage (within column) was calculated on the basis of valid cases

Table 3. Association of patients' characteristics and tuberculosis status (percentage and odds)

Variable		TN%	FN%	TP%	Variable		TN%	FN%	TP%
1 Age	6-11 month	19.5	34.6	38.0	**4 Nutrition**	Normal	80.5	73.1	73.3
	12-24 month	31.4	28.8	27.3		Under	13.6	23.1	18.7
	3-5 year	31.1	21.2	20.9		Over	5.9	3.8	8.0
	5-11 year	15.5	15.4	9.6		Total(n)	354	52	186
	11-15 year	2.5	0	4.3		OR	1	1.118	1.313
	Total (n)	354	52	187		Sign.		0.514	0.074
	OR	1	0.756	0.740	**5 Promiscuity**	No	37.7	31.9	29.5
	Sign.		0.047	0.000		Yes	62.3	68.1	70.5
2 Sex	Male	51.1	51.9	50.3		Total(n)	313	47	173
	Female	48.9	48.1	49.7		OR	1	1.291	1.448
	Total (n)	354	52	187		Sign.		0.444	0.069
	OR	1	0.969	1.035	**6 Exposure**	No	77.4	57.6	61.6
	Sign		0.915	0.849		Yes	22.6	42.4	38.4
3 Residence	Kabondo	12.4	15.4	8.6		Total	106	33	112
	Kisangani	1.7	1.9	0		OR	1	2.518	2.129
	Lubunga	2.3	0	0		Sign.		0.029	0.013
	Makiso	61	55.8	63.1	**7 BCG scar**	No	44.3	45.8	29.9
	Mangobo	5.1	9.6	0.7		Yes	55.7	54.2	70.1
	Tshiopo	17.5	17.3	21.4		Total(n)	307	48	174
	Total(n)	354	52	187		OR	1	0.940	1.866
	OR	1	0.985	1.159		Sign.		0.842	0.002
	Sign.		0.888	0.031					

TN=true negative (TST-/TB-); FN=false negative (TST-/TB+); TP=true positive (TST+/TB+). The percent (within column) was calculated on the basis of valid cases

Some persons may not react to the TST even though they are infected with *M. tuberculosis*. The reasons for these false-negative reactions may include, but are not limited to, cutaneous anergy because of a weakened immune system; recent TB infection (within 8-10 weeks of exposure); very old TB infection (many years); very young age (less than 6 months old); recent live-virus vaccination (e.g., measles and smallpox); overwhelming TB disease; some viral illnesses (e.g., measles and chicken pox); incorrect method of TST administration; incorrect interpretation of reaction [26-29]. In this study the more likely causes may be anergy and recent

live-virus vaccination. Some other persons may react to the TST even though they are not infected with *M. tuberculosis*. The causes of these false-positive reactions may include, but are not limited to infection with non non-tuberculous mycobacteria; previous BCG vaccination; incorrect method of TST administration; incorrect interpretation of reaction; incorrect bottle of antigen used [26-30]. No case of false positive was detected in this study.

To ensure the absence of the disease in TST-group, radiographic images and other evocative symptoms were considered. The pathological patterns of lungs were more prominent in TB+ children than in TB-. Blood markers like sedimentation rate, anemia, and leukocyte formula also concurred to making differential diagnosis. The hypothesis that a rate of sedimentation can be accelerated in a child suspected of primary tuberculosis infection was verified. The theory that the leukocyte formula in adults TB+ is predominantly lymphocytic [30] has not been observed in these children. That is, the leukocyte formula is likely not characteristic in childhood primary infection. Fever and weight loss may be evocative signs, but alone are not discriminate factors in multiple co-infections cases observed in poor countries. Malnutrition as estimated by weight loss or mid-up-circumference [31] was higher in tuberculosis group than in non tuberculosis children. It was proposed that adolescent girls with triceps skinfold thickness or mid-upper-circumference 25 mm and over should be characterized as obese [31], but no one was detected obese. Other not frequent comorbidities found were sickle cell anemia, chronic kidney disease, neurological signs and high blood pressure, partially consistent of studies by others [32,33].

The analysis of the association between socio-demographic and risk of developing active intra-thoracic back studies that demonstrated that TB affects equally both sexes [10] and the housing with adult ill person increases the risk of contaminating a child [34]. The odd of having pulmonary TB being male was not significant [OR=1.035 (95% CI: 0.87–1.30)]. Young age (<2 years) significantly increases the risk of TPI. The odds of having TPI was significantly higher [2.13 (95% CI:1.41–4.97)] in children living in contact with adult infected compared with those in non contagious exposure.

In this analysis, the effect of having a BCG scar on TST reactivity was statistically significant (0.002) at the cut-off ≥5 mm. This result is not consistent with other studies [35-37] which found that BCG vaccination does not induce sensitivity to TST. Seddon et al. [38] found that "a 5 mm TST cut-off demonstrated good sensitivity and specificity in BCG-unvaccinated children, and an excellent negative predictive value but was associated with low specificity (62.7%; 95% CI 56.1% to 69.0%) in BCG-vaccinated children; for BCG-vaccinated children, a 10 mm cut-off provided a high negative predictive value (97.7%; 95% CI 94.2% to 99.4%) with the positive predictive value increasing with increasing age of the child". They concluded that "BCG vaccination had little impact on TST size in children over 5 years of age. The revised TST cut-off recommended in the recent revision to the UK TB guidelines demonstrates good sensitivity but is associated with impaired specificity in BCG-vaccinated children". However, in endemic areas, that might not interfere with interpretation of TST results and justify the use of TST for estimating prevalence and infection rate regardless of vaccination status.

5. CONCLUSIONS

The study found that the spectrum of childhood tuberculosis is actually high in the city, striking both sexes and more particularly younger children under 3 years old. Tuberculin skin test remains the faster and more accessible test to diagnosing tuberculosis in higher endemic communities but other clinical patterns of the disease should be evocated to not miss out false negative cases. In addition, advocacy is needed to make TST available free of charges and accessible in the package offered by partners in support of the TB program. It is the responsibility of the government, the national tuberculosis control program and the partners to give importance to the diagnosis of tuberculosis in children, as it remains a prominent indicator of the circulation of *MT* in the community.

CONSENT

It is not applicable.

ETHICAL ISSUE

The study protocol has been cleared by the hospital ethical committee (AUTORISITION DE RECHERCHE N°O5/ PED/2013).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. WHO Global Tuberculosis report; 2016. Available:http://www.who.int/tb/publications/global_report/en/
2. Mukanyangezi MF, Kadima NJ, Musemakweri A. Determination of isoniazid acetylator phenotype and its Clinical Implication in Rwandan Tuberculosis patients. Rwanda Journal Series F: Medicine and Health sciences; 2015;2(1). Available:http://dx.doi.org/10.4314/rjhs.v2i1.1F
3. Khan EA, Starke JR. Diagnostic of Tuberculosis in Children increased Need for better methods. Emerg Infect Dis. 1995; 1(4):115–123. DOI: 10.3201/eid0104.950402
4. Perez-Velez CM, Marais BJ. Tuberculosis in children. N Engl J Med. 2012;367348-61. (Google Scholar) PMID: 22830465
5. Hatherill M, Hanslo M, Hawkridge T, Little F, Workman L, Mahomed H, et al. Structured approaches for the screening and diagnosis of childhood tuberculosis in a high prevalence region of South Africa. Bull World Health Organ. 2010;88:312–20. PMID: 20431796 DOI: ORG/10.2471/BLT.09.062893 (PubMed Google Scholar)
6. Marais BJ, Graham SM. Childhood tuberculosis: A roadmap towards zero deaths. J Paediatr Child Health. 2016; 52:258–61. PMID:24923706, DOI: org/10.1111/jpc.12647. (PubMed Google Scholar)
7. Marais BJ, Gie RP, Schaaf HS, Hesseling AC, Enarson DA, Beyers N. The spectrum of disease in children treated for tuberculosis in a highly endemic area. Int J Tuberc Lung Dis. 2006;10:732–8. PMID: 16848333. (PubMed Google Scholar)
8. Kiwanuka J, Graham SM, Coulter JBS, et al. Diagnosis of pulmonary tuberculosis in children in an HIV-endemic area, Malawi. Ann Trop Paediatr. 2001;21:5–14. (PubMed)
9. Corbett EL, Watt CJ, Walker N, et al. The growing burden of tuberculosis. Global trends and interactions with the HIV epidemic. Arch Intern Med 2003;163:1009-1021. (Google Scholar Cross Ref PubMed)
10. Harries AD, Hargreaves NJ, Kemp J, et al. Deaths from tuberculosis in sub-Saharan African countries with a high prevalence of HIV-1, Lancet. 2001;357: 1519-1523 (Google Scholar CrossRef PubMed)
11. Hesseling AC, Schaaf HS, Gie RP, Starke JR, Beyers N. A critical review of diagnostic approaches used in the diagnosis of childhood tuberculosis. Int J Tuberc Lung Dis. 2002;6:1038–45. PMID: 12546110 (PubMed Google Scholar)
12. Cruz AT, Starke JR. Clinical manifestations of tuberculosis in children. Paediatr Respir Rev. 2007;8:107–17. PMID: 17574154 DOI: ORG/10.1016/J.PRRV.2007.04.008 (PubMed Google Scholar)
13. Roya-Pabon CL, Perez-Velez C. *M. Tuberculosis* exposure, infection and disease in children: A systematic diagnostic approach. Pneumonia. 2016; 8:23. DOI: 10.1186/s41479-016-0023-9
14. Watkins RE, Brennan R, Plant AJ. Tuberculin reactivity and the risk of tuberculosis: A review. Int J Tuberc Lung Dis. 2000;4(10):895–903. (PubMed)
15. Marais BJ, Gie RP, Hesseling AC, Schaaf HS, Lombard C, Enarson DA, et al. A refined symptom-based approach to diagnose pulmonary tuberculosis in children. Pediatrics. 2006;118:e1350–9. PMID:17079536 DOI: ORG/10.1542/PEDS.2006-0519 (PubMed Google Scholar)
16. Chiang SS, Swanson DS, Starke JR. New diagnostics for childhood tuberculosis. Infect Dis Clin North Am. 2015;29:477–502. PMID:26188605. DOI: ORG/10.1016/J.IDC.2015.05.011 (PubMed Google Scholar)
17. Denkinger CM, Schumacher SG, Boehme CC, Dendukuri N, Pai M, Steingart KR. Xpert MTB/RIF assay for the diagnosis of extrapulmonary tuberculosis: A systematic

review and meta-analysis. Eur Respir J. 2014;44:435–46.
PMID:24696113
DOI: ORG/10.1183/09031936.00007814
(PubMed Google Scholar)

18. Mutetwa R, Boehme C, Dimairo M, Bandason T, Munyati SS, Mangwanya D, et al. Diagnostic accuracy of commercial urinary lipoarabinomannan detection in African tuberculosis suspects and patients. Int J Tuberc Lung Dis. 2009;13:1253–9.
PMID: 19793430
(PubMed Central Google Scholar)
19. Graham SM. The use of diagnostic systems for tuberculosis in children. Indian J Pediatr. 2011;78:334–9.
PMID: 21165720
DOI: ORG/10.1007/S12098-010-0307-7
(PubMed Google Scholar)
20. Tebruegge M, Dutta B, Donath S, Ritz N, Forbes B, Camacho-Badilla K, et al. Mycobacteria-specific cytokine responses detect tuberculosis infection and distinguish latent from active tuberculosis. Am J Respir Crit Care Med. 2015; 192:485–99.
PMID: 26030187
DOI: Org/10.1164/Rccm.201501-0059oc
(PubMed Google Scholar)
21. Ankrah AO, van der Werf TS, de Vries EF, Dierckx RA, Sathekge MM, Glaudemans AW. PET/CT imaging of *Mycobacterium tuberculosis* infection. Clin Transl Imaging. 2016;4:131–44.
PMID:27077068
DOI: ORG/10.1007/S40336-016-0164-0
(PubMed PubMed Central Google Scholar)
22. Minime-Lingoupou F, Ouambita-Mabo R, Komangoya-Nzozo AD, Senekian D, Bate L, Yango F, Nambea B, and Manirakiza A. Current tuberculin reactivity of schoolchildren in the Central African Republic. BMC Public Health. 2015;15:496
DOI: 10.1186/s12889-015-1829-8
23. Tebandite Kasaï E, Alworong'a Opara JP, Batina Agasa S, et al. Déterminants de la réponse à l'intradermoréaction à la tuberculine à Kisangani, RDC. Kisangani Médical. 2016;7(1):269-274.
24. Raharimanga V, Ratovoson R, Ratsitorahina M, Ramarokoto H, Rasolofo V, Talarmin A, et al. Tuberculin reactivity in first-year schoolchildren in Madagascar. Trop Med Int Health. 2012;17(7):871-6.
DOI: 10.1111/j.1365-3156.2012.03013.x
(PubMed)(Cross Ref)
25. Soheila Khalilzadeh, Nooshin Baghaie, Mohammed Reza Boloorsaz, Mohammed Hakimi, Siamak Amari, Ali Akbar Velayati, Screening of tuberculosis in symptomatic close Contact Children. NRITLD, Tanoffos. 2003;2(5):51-56.
26. Schumacher SG, van Smeden M, Dendukuri N, Joseph L, Nicol MP, Madhukar Pai M, Zar HJ. Diagnostic test accuracy in childhood pulmonary tuberculosis: A bayesian latent class analysis. Am J Epidemiol. 2016;184(9): 690–700
DOI: 10.1093/aje/kww094
27. Steiner P, Rao M, Victoria MS, et al. Persistently negative tuberculin reactions: Their presence among children with culture positive for *Mycobacterium tuberculosis* (tuberculin-negative tuberculosis). Am J Dis Child. 1980;134:747.
28. Farhat M, Greenaway C, Pai M, Menzies D. False-positive tuberculin skin tests: What is the absolute effect of BCG and non-tuberculous mycobacteria? Int J Tuberc Lung Dis. 2006;10:1192–204.
PMID: 17131776.
(PubMed Google Scholar)
29. Kiwanuka JP. Interpretation of tuberculin skin-test results in the diagnosis of tuberculosis in children. Afr Health Sci. 2005;5(2):152–6.
(PMC free article) (PubMed)
30. Neul-Bom Yoon, Choonhee Son, Soo-Jung Um. Role of the neutrophil-lymphocyte count ratio in the differential diagnosis between pulmonary tuberculosis and bacterial community-acquired pneumonia. Ann Lab Med. 2013;33(2):105–110.
DOI: 10.3343/alm.2013.33.2.105
31. Carl C. Seltzer, Ralph F. Goldman, Jean Mayer. The triceps skinfold as a predictive measure of body density and body fat in obese adolescent girls. Pediatrics. 1965;36(2):212–218.
(PMID 14320030)
32. Cruz AT, Merchant O, Zafar A, Starke JR. Tuberculosis exposure, infection and disease among children with medical comorbidities. Pediatr Infect Dis J. 2014; 33:885–8. PMID:24642517.
DOI: Org/10.1097/INF.0000000000000343
(PubMed Google Scholar)
33. Gonzales Saldana N. At all pulmonary tuberculous: Symptoms, diagnosis and treatment. 19 year experience in third level pediatric hospital. BMC Infect Dis. 2014;19 (14):401.

34. Schaaf HS, Michaelis IA, Richardson M, Booysen CN, Gie RP, Warren R, et al. Adult-to-child transmission of tuberculosis: Household or community contact? Int J Tuberc Lung Dis. 2003;7:426–31.
PMID:12757042.
(PubMed Google Scholar)

35. Mudido P, Guwatudde D, Nakakeeto M, Bukenya G, Nsamba D, Johnson J, et al. The effect of bacille Calmette-Gue´rin vaccination at birth on tuberculin skin test reactivity in Ugandan children. Int J Tuberc Lung Dis. 1999;3:891–5. (PubMed)

36. Sleiman R, Al-Tannir M, Dakdouki G, Ziade F, Assi NA, Rajab M. Interpretation of the tuberculin skin test in bacille Calmette-Guerin vaccinated and nonvaccinated school children. Pediatr Infect Dis J. 2007;26(2):134–8.
DOI: 10.1097/01.inf.0000253058.48277.86
(PubMed) (Cross Ref)

37. Gopi PG, Subramani R, Nataraj T, Narayanan PR. Impact of BCG vaccination on tuberculin surveys to estimate the annual risk of tuberculosis infection in south India. Indian J Med Res. 2006; 124(1):71–6. (PubMed).

38. Seddon JA, Paton J, Nademi Z, Keane D, Williams B, Williams A, Welch SB, Liebeschutz S, Riddell A, Bernatoniene J, Patel S, Martinez-Alier N, McMaster P, Kampmann B. The impact of BCG vaccination on tuberculin skin test responses in children is age dependent: evidence to be considered when screening children for tuberculosis infection. Thorax 2016;71:932–939.
DOI: 10.1136/thoraxjnl-2015-207687
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