Pattern of Diagnosis and Treatment of Childhood Tuberculosis in a Teaching Hospital in Southern Nigeria

***Oloyede IP,[1] Johnson OE,[2] David U,[3] Edem KB[3]**

ABSTRACT

The diagnosis of tuberculosis (TB) in childhood is challenging due to the paucibacillary nature of childhood TB and the difficulty in getting sputum samples from young children. The objective of this study was to determine the prevalence, diagnosis, anatomic type and treatment of tuberculosis in children admitted into the Paediatric ward. A retrospective review of clinical data of children admitted for tuberculosis in the paediatric ward of University of Uyo Teaching Hospital, Uyo, Nigeria from 2013-2017 was carried out. The data were analysed using STATA version 15.1.Among 3276 ward admissions, 32 patients (1.0%) had Childhood TB. There was a preponderance of TB in children aged 0-5 years (56.0%) with a male: female ratio of 2.6:1. Cough (71.9%), weight loss (63.0%) and fever (63.0%) were the commonest symptoms. Two out of 32 patients (7.0%) had a positive sputum Acid and Alcohol Fast Bacilli (AAFB) test and one out of five patients (20.0%) had a positive gastric aspirate GeneXpert result. The chest radiograph was suggestive of TB in 21 out of 25 patients (84.0%). Mean (SD) tuberculin skin test was 10±7mm. Pulmonary tuberculosis (67.0%) was the commonest form of TB seen. The six-month standard TB treatment option was the commonest regimen used as first-line in 28 out of 32 (88.0%) patients. Twenty five (78%) patients completed their treatment - the regime used was well tolerated. Our study has shown a 1% prevalence of Paediatric TB. There is therefore a need to tackle the issue of under diagnosis of childhood tuberculosis in our environment.

Keywords: Childhood, Tuberculosis, Diagnosis, Treatment

INTRODUCTION

Tuberculosis (TB) is the commonest chronic respiratory disease among Nigerian children. Nigeria was among the six countries accounting for 60% of the estimated 10.4 million new tuberculosis cases seen in 2015.[1] Globally 10% of new TB cases in 2015 occurred in childhood, however, the World Health Organisation (WHO) estimated that 20% of TB cases in Nigeria occurred in children.[1] Considering that TB detection in children is a sentinel event, the importance of early diagnosis and treatment in children cannot be underestimated.

The End-TB strategy has been put in place to reduce TB deaths by 90%, reduce the new cases of TB incidence rate by 80% and reduce the number of TB- affected families facing catastrophic costs due to TB to zero by 2030 compared to the 2015 levels.[2] One of the pillars underlying the End-TB strategy is early diagnosis of tuberculosis and universal drug susceptibility testing. The WHO recommends that bacteriological confirmation of TB should be sought whenever possible by microscopy, culture or WHO-endorsed genotypic (molecular) testing (i.e. Xpert MTB/RIF) of respiratory or non-respiratory samples as indicated by clinical presentation.[1,3] This is however not usually possible due to the paucibacillary nature of childhood TB and the difficulty in getting sputum from young children. Also, the cost and complexity of the new diagnostic tools make it prohibitive in resource-constrained settings of low and middle-income countries (LMIC). This has led to the development of different algorithms for the initial screening and diagnosis of TB in LMIC settings.[4]

In Nigeria at present, the diagnosis of TB in children is made using the TB score chart and the TB score algorithm which is based on clinical findings, family history of contact with a smear-positive case, x-ray examination and tuberculin skin test (TST) and culture (if available).[5] However, the symptomology and chest x-ray (CXR) findings in children with tuberculosis are non-specific and the CXR may be normal. Furthermore, in most cases of childhood TB there is no known contact and tuberculin skin test may be negative especially in children with HIV.[6] It is

Department of Paediatrics,[1] University of Uyo and University of Uyo Teaching Hospital.
Department of Community Health,[2] University of Uyo and University of Uyo Teaching Hospital.
Department of Paediatrics,[3] University of Uyo Teaching Hospital.

*Corresponding author: : isooloyede@yahoo.com

widely known that the bacteriologic yield of children with TB is low.[7]

Childhood TB is usually treated for six months with first-line drugs which include Isoniazid (H), Rifampicin (R), Pyrazinamide (Z), Ethambutol (E) and Streptomycin (S) for TB meningitis. There is usually an intensive phase of two months using four drugs and a continuation phase of four months using two drugs. The major side effects of these medications are: hepatotoxicity and neurotoxicity, allergic reactions, gastrointestinal disturbance, non-gouty polyarthralgia, gouty arthritis and retrobulbar neuritis. Various studies have however shown that these side effects are rare in children and at the recommended doses anti-tuberculous medications are well tolerated in children.[8,9] In southern Nigeria, the prevalence of microbiologically confirmed pulmonary TB was 2% among rural children.[10]

The University of Uyo Teaching Hospital (UUTH) is one of the centres endorsed by the National Tuberculosis and Leprosy Control Programme (NTBLCP) for the delivery of Directly Observed Treatment Short-course (DOTS) with anti-tuberculosis medication provided at no cost to the patient by the German Leprosy and TB Relief Association (GLRA) and HIV treatment for the 3.9million inhabitants of the State.[11,12]

In addition, the institution's microbiology laboratory is well equipped for the detection of alcohol and acid fast bacilli (AAFB) with a GeneXpert machine, which is donor driven.

The Department of Paediatrics is one of the four core clinical departments and is comprised of two main wards, the children emergency unit, the children outpatient unit and two neonatal wards.

Children diagnosed with tuberculosis are usually treated in the Department of Paediatrics in close collaboration with the Directly Observed Treatment Short-course (DOTS) unit of the Community Health Department. This study was therefore conducted to assess the pattern of diagnosis, type of tuberculosis and treatment of childhood tuberculosis in Uyo, Southern Nigeria.

MATERIALS AND METHODS

This was a retrospective cross sectional study. Data were extracted by two of the authors from the case notes of children managed for tuberculosis in the Paediatric ward over a five year period, from January 2013 to December 2017. Information extracted from the case records included the patients' age, gender, history of BCG vaccination, history of contact, duration of illness, signs and symptoms, TB score, chest radiograph findings, microbiological diagnosis, Mantoux test (A positive Mantoux test was defined as measurements ≥5mm in HIV positive children and ≥10mm in HIV negative children),[3] treatment, complications and outcome. Pulmonary tuberculosis was defined as a symptomatic child with: (1) bacteriologically confirmed tuberculosis, (2) radiologically certain tuberculosis, or (3) probable tuberculosis (as defined). Probable TB was defined as a TB score >7, radiologic certainty and a good clinical response to anti-tuberculosis treatment in the absence of bacteriologic confirmation. Radiologically certain TB was defined as an agreement between two independent radiologists that the CXR indicated certain tuberculosis and a TB score 1-6 in the absence of bacteriologic confirmation and a good clinical response to anti-tuberculosis treatment.[3]

Data were analysed using STATA version 15.1. Descriptive statistics (mean and standard deviation) were calculated for continuous variables. Categorical variables were presented as frequency and percentages. Chi-square test or Fisher's exact test was used to test for association between categorical variables. Mann-Whitney U test was used for non-parametric data. A p-value of <0.05 was taken as statistically significant.

Ethical clearance for the conduct of the study was obtained from the Ethics committee, UUTH, Uyo. The addresses, names, hospital number and other identifiers of the patients were omitted in order to maintain confidentiality.

RESULTS

A total of 61 folders were retrieved with a diagnosis of TB from the paediatric ward of UUTH. However, only 32 patients met the criteria for TB as defined in this study and received treatment at the DOTS unit of UUTH. The total inpatients for all paediatric conditions from January 2013 to December 2017 was 3276, while the total number of respiratory cases for this period was 1307. Therefore, the prevalence of TB was 1.0% and 2.5% of the total ward admissions and respiratory admissions respectively for the period studied.

Table 1A shows that 18 of the patients (56.0%) were in the 0-5 year age group, with a predominance of males (72.0%). Only ten patients (31.0%) had a positive history of contact with an adult with chronic cough and majority of the patients (94.0%) had BCG vaccination. Table 1B shows that there was no statistically significant difference in age, gender, history of contact and BCG vaccination between children with pulmonary and extra-pulmonary TB (p= 0.39; 0.07; 0.65 and 0.11 respectively). Nine (45%) out of 20 children with pulmonary TB were HIV positive while no child with extra-pulmonary TB was HIV positive. The difference was statistically significant (p=0.01).

Cough was the commonest (72.0%) symptom recorded with a mean duration of 13 weeks, followed by weight loss (63.0%) and fever (63.0%) (Table 2).

The mean weight of the patients was 19.8 ± 1.9kg with a range of 4.4- 66kg. The mean height was 104±40cm with a range of 63- 180cm. Pallor (47.0%) was the commonest clinical sign, followed by lymphadenopathy (44.0%). Only nine (28.0%) of patients had abnormal chest signs (Figure 1).

Table 3 shows that only two patients out of 32 (7.0%) had a positive sputum AAFB result and GeneXpert was positive in the gastric aspirate of only one out of five patients and negative in all sputum and lymph node aspirate results. The chest radiograph was suggestive of TB in 21 out of 25 patients (84.0%), while TB-HIV co-infection was present in nine out of 31 patients (29.0%). All patients with TB meningitis had a positive cerebrospinal fluid (CSF) AAFB.

Tuberculin skin test (Mantoux) was done in 17 patients. The measurement ranged from 0-23mm with a mean ± SD of 10±7.8mm. Nine out of 17 patients (53.0%) had a Mantoux result of 10mm and above. Eight of the patients who did not have a Mantoux done were HIV- positive. The TB score ranged from 6 to 17 with 96.0% of the patients having a TB score of seven and above. Pulmonary tuberculosis (67.0%) was the commonest form of TB seen, followed by disseminated TB in four patients (13.0%) (Figure 2).

The commonest chemotherapy was an initial two month intensive phase using rifampicin, isoniazid, pyrazinamide and ethambutol followed by a four months consolidation phase using rifampicin and isoniazid, in 28 out of 32 patients (88.0%) (Table 4). Twenty-five patients completed their treatment; four absconded from treatment while three patients were transferred to other DOTs centres close to their residence. The only complication of TB treatment observed in this study was drug-induced Hepatitis in one patient.

Table 1A: Sociodemographic characteristics of Paediatric TB patients in UUTH from 2013-2017

Socio-demographic Characteristic	Frequency n=32	Percent (%)
Age group (years)		
0-5	18	56
6-10	4	13
11-18	10	31
Gender (n=32)		
Male	23	72
Female	9	28
Contact history		
Yes	10	31
No	22	69
BCG vaccination		
Yes	30	94
No	2	6
Past /Current family history		
Yes	6	18
No	26	82
HIV Status (n=30)		
Positive	9	30
Negative	21	70

Table 1B: Comparison of type of TB with selected characteristics of the respondents

Variable	Type of TB				p-value
	Pulmonary TB		Extra-pulmonary TB*		
Age in months (mean±SD)	74± 64.5		86.5±64		0.39**
Gender (n=31)	Female 8(40%)	Male 12 (60%)	Female 1(9%)	Male 10(91%)	0.07#
History of contact (n=32)	Yes 15 (71%)	No 6 (29%)	Yes 4(36%)	No 7 (64%)	0.65#
BCG vaccination (n=32)	21 (100%)	0(%)	9 (82%)	2 (18%)	0.11##
HIV test (n=30)	Negative 11(55%)	Positive 9(45%)	Negative 10(100%)	Positive 0(0%)	0.012##

*Extrapulmonary TB: disseminated, Abdominal TB, Tb Adenitis, TB meningitis
**Mann Whitney U test
#Pearson chi2
##: fisher exact test

Table 2: Frequency and duration of symptoms in paediatrics TB cases in UUTH

Symptoms	N=32 (%)	Duration (weeks) [range; ±SD]
Cough		
Yes	23 (71.9)	24-104; [13±22]
No	9 (28.1)	
Weight loss		
Yes	20 (63)	2-104; [13±27]
No	12 (37)	
Fever		
Yes	20 (63)	0.5- 104;[8±19]
No	12 (37)	
Night sweats		
Yes	8 (25)	2-104; [4±18]
No	24 (75)	
Chest pain		
Yes	3 (9)	1-8; [0.4±1.5]
No	29 (91)	
Haemoptysis		
Yes	2 (6)	1-60; [1.9±10.6]
No	30 (94)	
Loss of appetite		
Yes	2 (6)	1
No	30 (94)	
Abnormal lethargy/fatigue		
Yes	2 (6)	1-3;
No	30 (94)	
Difficulty in breathing	N=31	
Yes	3 (10)	1-24; [1±4]
No	28 (90)	

Table 3: Types and characteristics of investigations carried out in paediatrics TB cases in UUTH

Investigation	Frequency (%)	Investigation	Frequency (%)
Chest radiograph (n=25)		HIV test (n=30)	
Normal	4(16)	Positive	9(30)
Suggestive	21(84)	Negative	21(70)
Sputum AAFB (n=32)		Sputum GeneXpert (n=33)	
Positive	2(7)	Negative	33(100)
Negative	30(93)		
Lymph node aspirate GeneXpert (n=3)		Lymph node aspirate AAFB (n=1)	
Negative	3(100)	Negative	1(100)
Lymph node aspirate histology (n=3)		Gastric aspirate GeneXpert (n=5)	
Suggestive	2(67)	Positive	1(20)
Not suggestive	1(33)	Negative	4(80)
Cerebrospinal fluid AAFB (n=2)		Tuberculin skin test (n=17)	
Positive	2(100)	Positive	9(53)
		Negative	8(47)

(n=X): X are the actual number of patients who did the investigations and had results recorded in their folders

Table 4: Chemotherapy regimen, treatment outcome among childhood Tuberculosis cases in UUTH

Chemotherapy	Frequency (n=32)	Percentage (%)
2RHZE 4RH	28	88
2RHE 4RH	1	3
2SRHZ 4RH	1	3
2RHZE 10RH	1	3
2RHZE	1	3
Treatment outcome		
Completed	25	78
Absconded	4	13
Transferred	3	9
Treatment complication		
Drug induced Hepatitis	1	3
None	31	97

R- Rifampicin; H- Isoniazid; Z- Pyrazinamide; E- Ethambutol; S- streptomycin

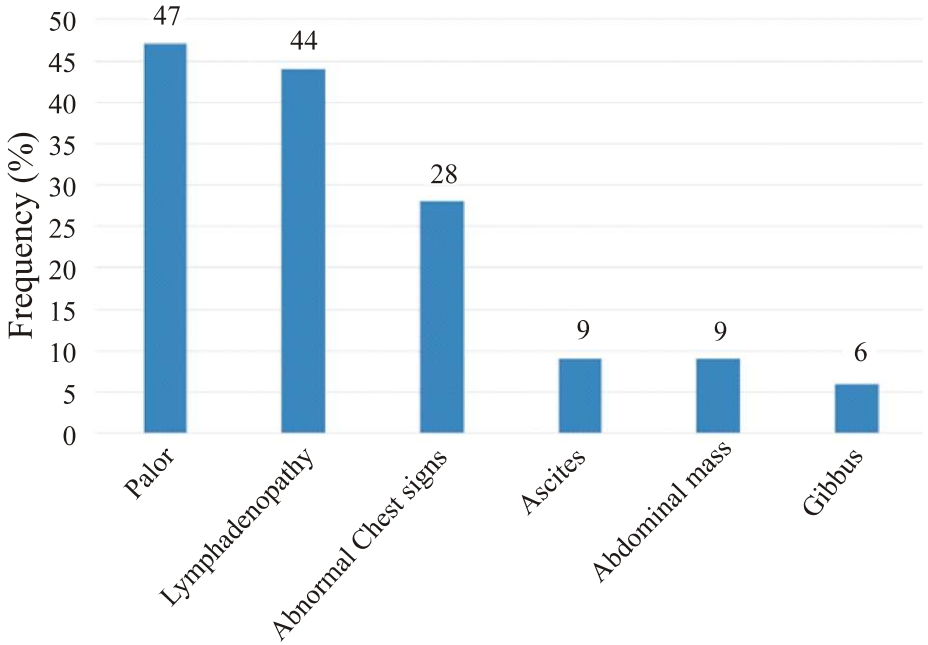

Figure 1: Distribution of clinical signs among Paediatric tuberculosis patients in UUTH

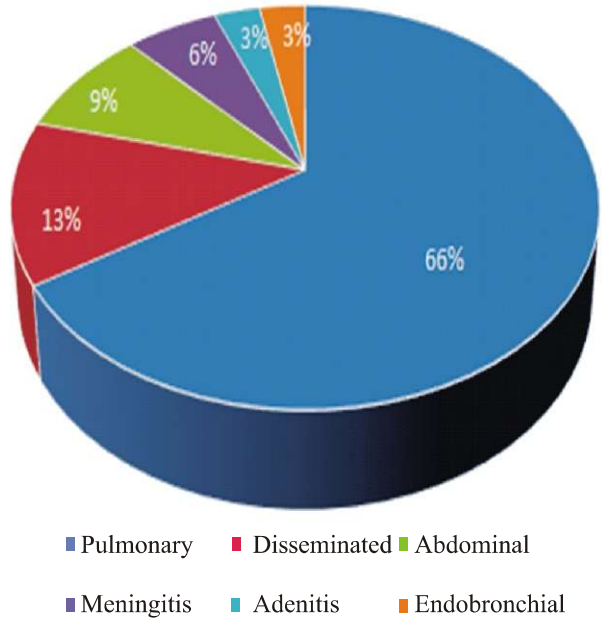

Figure 2: Anatomic classification of tuberculosis in UUTH

DISCUSSION

Our study showed a 1.0% prevalence of TB among all the paediatric ward admissions. A hospital study in DRC showed a higher prevalence (1.7%) than our study.[9] The low prevalence in our study may not be unconnected to the very low level of suspicion of childhood TB in Nigeria leading to limited identification, diagnosis and recording of cases.[13] In addition, the differences in prevalence could be explained by the different case definitions used for TB in the different studies, the differences in the burden of undiagnosed TB in various communities and the differing sample sizes in the different studies.

The higher prevalence of TB in children 0-5 years can be explained by the immaturity of the immune system of children in this age range.[14] The increase in TB disease in adolescence may be linked to the increased independence, mobility and risk taking behaviour in this age group.[15] Our study showed that more males had TB than females. There was however no significant gender difference between children with extrapulmonary and pulmonary TB. This is

similar to the results seen in children in Kilimanjaro and in a Beijing hospital study, both attributing their results to increased male birth rates.[14,16] We however suggest that this finding may be attributed partly to the better health seeking behaviours of mothers accorded to male children in our community.[17]

A contact history was not readily determined among our patients and this is probably due to the high endemicity of TB in our environment. BCG vaccination rates (94.0%) were high among our patients, further confirming the fact that in highly endemic areas BCG vaccination is only protective against severe forms of TB. In addition, the administration of impotent vaccines due to the break in cold chain or wrong administration of vaccines intramuscularly rather than intradermally by poorly trained staff cannot be completely ruled out. Furthermore, our study had higher BCG vaccination rates compared to studies in Northern Nigeria that reported lower BCG vaccination rates (12-46%) and this is probably a reflection of the effect of culture, religion, poverty, education and ignorance on vaccination uptake.[18,19]

Cough, weight loss and fever were the major symptoms found among TB patients in our study. This finding is in keeping with a previous Nigerian and South African studies.[19,20] The latter showed that the combination of cough and weight loss was the most significant (OR=5.4, 95% CI 1.7 to 16.9) predictor of newly diagnosed TB and the presence of more than one symptom in addition to weight loss increased the odds of tuberculosis.[20] However, because of our small sample population we could not ascertain the predictive values of these symptoms in our study population.

Pallor (47.0%) and peripheral lymphadenopathy (44.0%) were the commonest clinical signs while only 28.0% of patients had abnormal chest signs. The occurrence of pallor in our study may be due to other endemic illnesses like malaria and helminthiasis in addition to the anaemia of chronic disease seen in tuberculosis. The peripheral lymphadenopathy in the present study is however lower than the 74.0% reported in Congo.[9] This may be because the facility in Congo is a major referral centre for the management of TB.[9] Another study in South Africa[21]also noted lymphadenopathy as the commonest form of extrapulmonary TB.[21]

All children in our study had microbiological tests for sputum in contrast to other investigations and this is because, GeneXpert and sputum AAFB are done free as part of the National TB program that is largely donor driven. The bacterial yield was however very low which is consistent with other studies and is likely due to the paucibacilliary nature of childhood TB.[7,22] The low microbiologic yield in our study was however in contrast to the high yield which was seen in the study by Marias et al[23] and reasons adduced for the high yield included the stringent inclusion criteria of only children with radiographic evidence of intrathoracic TB; diligence in sample collection and processing; community based approach and the presence of advanced disease in most of their patients.[23]

Lymph node and Cerebrospinal fluid are commonly used extrapulmonary samples.[7]In the present study, all lymph node aspirates for AAFB and GeneXpert were negative, while 100% of CSF samples were confirmatory. In addition there was a 20.0% positive AAFB yield from gastric aspirate and a 7.0% positive yield for sputum AAFB. Oludiran *et al.,* however, had a higher smear positive result from other samples (gastric washings and lymph node aspirate).[22] This is however in contrast to some studies that have shown a higher yield from respiratory samples than non-respiratory samples.[24]

Tuberculin skin test was positive in about half of our patients and this value is lower than the 69.7% that was reported from Northern Nigeria.[19] This difference could be explained by the varying cut-off points used in both studies, while the index study had a cut off of 10mm for a positive Tuberculin skin test irrespective of a BCG scar, the latter study had a cut off of 5mm for children with no BCG scar and 10mm for children with a BCG scar.

The chest x-ray findings were suggestive in most of the children with TB and this further buttresses the fact that in children with TB, their chest radiographs may be suggestive even in the absence of chest signs. A South African study had suggestive chest radiographs in 69.9% of children with TB.[25] The higher percentage of children with suggestive X-rays in the present study may be due to our small sample size which may tend to exaggerate positive results.

HIV and TB co-infection was 30.0% in our study and is similar to the 29.2% obtained in

children in Lagos but higher than the 8.1% recorded by Marais *et al.*[25] In addition, all patients with HIV and TB co-infection had pulmonary TB and this was significant (p=0.01). This result could be explained by the low immunity of this subset of patients with increased susceptibility for the progression of TB infection to disease.[6]

Pulmonary TB (67.0%) and disseminated TB (12.0%) were the commonest forms of TB in our study. This result is similar to the report from Northern Nigeria.[18] In our study location, the six months TB treatment option was most often used. The commonest combination chemotherapy was 2 RHZE/4RH which is in accordance with the National TB guidelines of Nigeria.[5] The use of four medications for the intensive phase of TB chemotherapy is well documented in literature. Rifampicin, isoniazid and pyrazinamide have strong bactericidal properties that are necessary for the killing of fast growing extracellular bacteria during the intensive phase, while the addition of ethambutol is useful whenever there is extensive radiographic disease with or without cavitation and in reducing the risk of isoniazid resistance. The use of multiple drugs in combination, during the intensive phase of treatment, drastically reduces the risk of treatment failure despite a high organism load. The use of isoniazid and rifampicin during the four months continuation phase has been shown to sufficiently ensure organism eradication once the organism load is sufficiently reduced.[26]

The proportion of children who completed anti- TB medication was high (79.0%) with no mortality and this is similar to the 70.0% completion rate in studies conducted in Kinshasha and Lagos.[9,27] This is probably an indication of good case management, efficacy and adherence to medication and low drug resistance. Our study reported no mortality and this could be attributed to the small sample size and the fact that most of our patients did not have severe disease. The default rate in our study of 12.0% is higher than the 7.0% reported from Kinshasha and lower than the 15.0% reported from Lagos State.[9,27] Absconding from treatment is particularly common in our environment and is usually associated with poverty, ignorance, unavailability of a reliable caregiver and far distance of the health facility from the patients residence. The differences in treatment outcomes in the above studies are probably as a result of differences in settings, disease presentation, HIV prevalence and parental adherence to treatment.

The only complication of treatment observed in our study was drug induced Hepatitis, which was however not severe enough for treatment to be discontinued, as the transaminase levels were less than five times the upper levels of normal.

CONCLUSION

Our study has shown a 1.0% prevalence of Paediatric TB. The under-five age group was most affected with a higher predominance in males. Fever, cough and weight loss were the most common symptoms. Majority of the patients had a suggestive chest x-ray and positive tuberculin skin test. There was a low uptake of bacteriologic confirmation and low yield from respiratory samples. Most patients completed their treatment and the treatment was well tolerated.

The diagnosis of tuberculosis in Nigerian children is still largely symptom based. However, the predominant emphasis of the DOTS strategy on sputum smearpositive disease excludes/ delays treatment in the vast majority of children. There is therefore a need to improve service delivery for children in endemic areas by providing well defined symptom definitions for childhood TB, objective measurements of the potential diagnostic values of different symptom definitions with particular emphasis on the validation of the TB score, providing better diagnostic methods for TB, developing a pragmatic classification of childhood tuberculosis that incorporates the diverse spectrum of disease and providing child friendly fixed dose combinations of anti-tuberculous medications.

The limitations of this study were the small sample size, the retrospective nature of the study and incomplete data.

REFERENCES

1. World Health Organization. Global tuberculosis report 2016. Geneva: *World Health Organisation;* 2016 p. 1-201 [WHO/HTM/TB/2016.13]
2. World Health Organization. Implementing End-TB strategy: Geneva: *World Health Organisation* 2015p. 1-112. [WHO/HTM/TB/2015.31]

3. Graham SM, Ahmed T, Amanullah F, Browning R, Cardenas V, Casenghi M *et al*. Evaluation of tuberculosis diagnostics in children: 1. Proposed clinical case definitions for classification of intrathoracic tuberculosis disease. Consensus from an expert panel. *J Infect Dis*. 2012;205:S199-208.
4. 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-e9.
5. Adamu I, Adelusi A, Adesigbin O, Agborubere D. National Tuberculosis and Leprosy Control Programme: Workers' manual 5th edition. Abuja: *FMOH*;2008.
6. Marais B, Graham S, Cotton M, Beyers N. Diagnostic and management challenges for childhood tuberculosis in the era of HIV. *J Infect Dis*. 2007;196:S76-85.
7. Zar HJ, Hanslo D, Apolles P, Swingler G, Hussey G. Induced sputum versus gastric lavage for microbiological confirmation of pulmonary tuberculosis in infants and young children: a prospective study. *Lancet*. 2005;365:130-4.
8. Frydenberg AR, Graham SM. Toxicity of first-line drugs for treatment of tuberculosis in children. *Trop Med Int Health*. 2009;14:1329-37.
9. Aketi L, Kashongwe Z, Kinsiona C, Fueza SB, Kokolomami J, Bolie G *et al*. Childhood tuberculosis in a sub-saharan tertiary facility: epidemiology and factors associated with treatment outcome. *PloS One*. 2016;11:e0153914.
10. Oloyede IP, Inah GB, Bassey DE, Ekanem EE. Comparative study of radiological findings in pulmonary tuberculosis and paragonimiasis in children in a Southern Nigeria fishing community. *W Afr J Radiol* 2014;21:17-20.
11. Commission NNP. 2006 population and housing census of the Federal Republic of Nigeria: national and state population and housing tables: priority tables: *National Population Commission*; 2009.
12. Ikpeme E, Etukudo O, Ekrikpo U. Seroprevalence of HBV and HIV co-infection in children and outcomes following highly active antiretroviral therapy (HAART) in Uyo, South-South Nigeria. *Afr Health Sci*. 2013;13:955-61.
13. Coghlan R, Gardiner E, Amanullah F, Ihekweazu C, Triasih R, Grzemska M *et al*. Understanding market size and reporting gaps for paediatric TB in Indonesia, Nigeria and Pakistan: supporting improved treatment of childhood TB in the advent of new medicines. *PloS One*. 2015;10:e0138323.
14. Mtabho CM, Irongo CF, Boeree MJ, Aarnoutse RE, Kibiki GS. Childhood Tuberculosis in the Kilimanjaro region: lessons from and for the TB Programme. *Trop Med Int Health*. 2010;15:496-501.
15. Ahmed P, Ulonnam C. Clinical presentation of tuberculosis in adolescents as seen at National Hospital Abuja, Nigeria. *Nig J Paediatr*. 2014;41:331-6.
16. Wu X-R, Yin Q-Q, Jiao A-X, Xu B-P, Sun L, Jiao W-W *et al*. Pediatric tuberculosis at Beijing children's hospital: 20022010. *Pediatrics*. 2012; 130: e1433-e1440.
17. Noordam AC, Carvajal-Velez L, Sharkey AB, Young M, Cals JWL. Care seeking behaviour for children with suspected Pneumonia in countries in sub- Saharan Africa with High Pneumonia mortality. *PLoS ONE*. 2015;10: e0117919. Doi:10.171/journal.pone.0117919
18. Orogade AA, Ahmed P, Onazi SO, Abubakar U, Isa H. BCG status in children with tuberculosis: A multicenter study in Northern Nigeria. *J Med Tropics.* 2013;15:126-30
19. Jiya N, Bolajoko T, Airede K. Pattern of Childhood Tuberculosis In Sokoto, Northwestern Nigeria. *Sahel Med J.* 2008; 11:110-3.
20. Marais BJ, Obihara CC, Gie RP, Schaaf HS, Hesseling AC, Lombard C *et al*. The prevalence of symptoms associated with pulmonary tuberculosis in randomly selected children from a high burden community. *Arch Dis Child*. 2005;90:1166-70.
21. Marais B, Gie R, Schaaf H, Hesseling A, Enarson D, Beyers N. The spectrum of disease in children treated for tuberculosis in a highly endemic area

[Unresolved Issues].*Int J Tuberc Lung Dis*. 2006; 10:732-8.

22. Oludiran KA, Eziuka OR, Mayowa IO, Ajani BR, Kikelomo O. Bacteriology of childhood tuberculosis in Ibadan, Nigeria: a five-year review. *Trop Med Health.* 2008;36:127-30.
23. Marais BJ, Gie RP, Obihara CC, Hesseling A, Schaaf H, Beyers N. Well defined symptoms are of value in the diagnosis of childhood pulmonary tuberculosis. *Arch Dis Child*. 2005;90:1162-5.
24. World Health Organization. Laboratory services in tuberculosis Control Microscopy Part II. 1998; *World Health Organization*. 1998. [WHO/TB/98.258:63].
25. Marais B, Hesseling A, Gie R, Schaaf H, Enarson D, Beyers N. The bacteriologic yield in children with intrathoracic tuberculosis. *Clin Infect Dis*. 2006;42:e69-e71.
26. Marais BJ, Gie RP, Schaaf HS, Beyers N, Donald PR, Starke JR. Childhood pulmonary tuberculosis: old wisdom and new challenges. *Am J Res Crit Care Med.* 2006;173:1078-90.
27. Adejumo OA, Daniel OJ, Adebayo BI, Adejumo EN, Jaiyesimi EO, Akang G *et al*. Treatment outcomes of childhood TB in Lagos, Nigeria. *J Trop Pediatr.* 2015;62:131-8.