Title Page

Title: Prevalence of pulmonary tuberculosis among presumptive cases in Rivers State, Nigeria.

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Abstract:

Background: Tuberculosis (TB) is a leading cause of death in children but it is underdiagnosed and underreported in children.

Objective: To determine the prevalence of pulmonary TB in children among presumptive cases of TB and to compare the diagnostic efficacy of different screening tool for TB in children.

Materials and Methods

This study was a descriptive prospective study carried out over one year in nine general health facilities that can provide diagnosis and treatment for tuberculosis in Rivers State, Nigeria. Children aged 0 – 18 years with presumptive TB were explored. They were explored by carrying out a clinical assessment with chest radiograph, sputum or gastric aspirate for microscopy and XpertMTB/RIF screening. Sociodemographic data and results of the screening tests was retrieved from their case records as well as the National Tuberculosis registers. Ethical approval for the study was obtained from the Rivers state Ministry of Health. Those with confirmed pulmonary TB were commenced on anti TB medications and followed up for at least 6months. Obtained data was analysed by SPSS version 20 and expressed as percentages, proportions and frequencies. A test of significance (chi square and t-test) was conducted between proportions and means as appropriate. In all a p value of less than 0.05 was considered significant.

Results

Nine hundred and sixty three patients aged 0-18years had presumptive diagnosis of TB, 394 (40.9%) were males while 569 (59.1%) were females. The commonest presenting symptom was chronic cough which occurred in 735 (76.5%) of the patients. The prevalence of pulmonary TB was 19.1%. Significantly more males (60.9%) than female (39.1%) had confirmed tuberculosis (X^2= 37.431, p-value <0.001). Significantly more children (54.3%) from the low socioeconomic class had confirmed pulmonary. Seventy two (39.1%) and 29 (15.8%) of the patients were AFB and XpertMTB/RIF positive respectively. Children aged 0-5 years were neither AFB nor XpertMTB/RIF positive. Of the children with confirmed TB, 170 (92.4%) had suggestive clinical features while 14 (7.6%) had suggestive X-ray features. About a third of the children aged 0-5 years had their TB confirmed by suggestive X-rays and Clinical features. All the patients with TB were commenced on anti TB medications, 40 (21.7%) were lost to follow up (LTFU), 21 (11.4%) were transferred to other centres while 123 (66.8%) completed the treatment.

Conclusion

The prevalence of pulmonary TB among presumptive TB cases in this study was comparable to findings from other studies and clinical diagnosis of Pulmonary TB remains very relevant in its management. Improving the clinical skills of physicians involved in TB care and treatment and the need for community/ facility collaboration to reduce cases of LTFU is advocated.

Introduction:

Tuberculosis (TB) is a common human disease. Worldwide, it is the second leading cause of death from a single infectious disease. [1] In 2017, TB caused an estimated 1.3 million deaths among HIV-negative people with an additional 300 000 deaths among HIV-positive people.[2] Children (aged <15 years) accounted for 15% of total deaths among HIV negative people and 10% of total deaths in HIV positive people.[2]

Tuberculosis affects all countries and all age groups and the World Health Organisation (WHO) has listed Nigeria as one of the countries with very high TB burden and it is hoped that this will stimulate targeted interventions and advocacy for funding to improve TB control. [4]

The actual burden of Tuberculosis in children in Nigeria is not known, however, it is estimated by the WHO that 30,000 children get TB in Nigeria each year. Study show that sputum microscopy smear-positive TB in children (<14 years old) is low.[3] and because the majority of children are sputum microscopy smear negative, these data underestimate the true burden of childhood TB.

Tuberculosis in children is underdiagnosed and underreported as microscopical examination of sputum smears is the cornerstone of diagnosis in most resource limited countries, but its usefulness is limited in young children who have paucibacillary disease and are unable to expectorate sputum. These children with undetected TB form a large pool that eventually becomes adult cases of TB. To reduce cases of missed diagnosis, children with presumptive diagnosis of TB are pooled and screened for TB by both bacteriological method and strong clinical assessment combined with chest radiograph.

A recent and a more reliable screening tool and the first line WHO recommended screening tool for TB the XpertMTB/RIF screening, is an important advance in rapid detection of TB disease and drug resistance TB. Studies have shown that it is much more sensitive than microscopy, with sensitivity being reported from 75 to 90% on sputum samples and nearly 70% on gastric aspirates, with comparable performance in HIV positive and HIV negative children. [5,6]

The study therefore was carried out to determine the prevalence of pulmonary TB disease among presumptive cases of TB and to compare the diagnostic efficacy of different screening tool for TB in children.

Methodology:

This study was a descriptive prospective study. It was carried out in Rivers state in Southern Nigeria among nine general health facilities that can provide diagnosis and treatment for tuberculosis in Rivers State, Nigeria. The diagnosis and treatment of TB in these centres follow the National guidelines for Tuberculosis and Leprosy control programme and the WHO directly observed treatment short course (DOTs) strategy. Ethical approval for the study was obtained from the Rivers state Ministry of Health. The study population consisted of children aged 0 – 18 years who presented in these health facilities from 1st of April 2016 to 31st of March 2017. All children with presumptive TB were explored. Presumptive TB refers to a patient who presented with one or more of the following symptoms: cough for >2 weeks; cough not responding to adequate dose of first line antibiotics after 7days; unexplained fever for >2 weeks; failure to thrive (FTT) or weight loss; a contact with a suspected or confirmed case of pulmonary TB. FTT was defined as a weight or height measurement that fall below the 3rd or 5th percentile for age or sex or a downward change in growth that crosses two major growth percentile on a growth chart (this is mainly for under-fives). They were explored by

carrying out a chest x-ray, sputum or gastric aspirate for microscopy and XpertMTB/RIF screening and by noting the number of symptoms and signs that they presented with. Sociodemographic data and results of the screening tests was retrieved from their hospital record files as well as the various National Tuberculosis registers kept in the DOTS clinic. All patients with extra pulmonary TB and those with Rifampicin resistance following XpertMTB/RIF test were excluded from the study while those with rifampicin resistance were referred to Drug resistant TB centres. Individual with confirmed pulmonary TB (clinically and or bacteriologically) were commenced on standard first line anti TB medications and followed up for at least 6months. Follow up was done to ensure compliance to treatment and to prevent lost to follow up (LTFU) through phone calls to patients or their caregivers at least once a week (a day before their medication pick up). Obtained data was entered into an excel sheet and analysed by SPSS statistical software version 20. Data was expressed as percentages, proportions and frequencies. A test of significance (chi square and t-test) was conducted between proportions and means as appropriate. In all a p value of less than 0.05 was considered significant.

Result

Nine hundred and sixty three patients aged 0-18years had presumptive diagnosis of TB, 394(40.9%) were males while 569(59.1%) were females. The mean age was 7.05 ±4.53 years, the mean age for males was 7.3±4.6 while the mean age for females was 6.9 ± 4.9, the age difference was not statistically significant (t= 0.793 , p value = 0.120). The commonest presenting symptom was chronic cough which occurred in 735 (76.5%) of the patients. Table 1

One hundred and eighty four had confirmed TB giving a prevalence of 19.1%. More males (60.9%) than female (39.1%) had confirmed tuberculosis and the difference was statistically

significant (X^2= 37.431, p-value <0.001). More children (54.3%) from the low socioeconomic class had confirmed TB and there was a statistically significant different between TB and social class. Age groups 1-5 years, 6-10 years, 11-15 years and 16-18 years constituted 28.3%, 17.4%, 26.6% and 22.8% respectively of children with confirmed TB (Table 2).

Seventy two (39.1%) of the patients were AFB positive. More males (53.7%) than females (40.3%) were smear positive for AFB, however this difference was not statistically significant. Table 3. Of the patients with confirmed TB, XpertMTB/RIF was positive in only 29 (15.8%) of them. Seventeen (58.6%) of them were males while 12 (41.4%) were females. There was no gender difference in proportion in children with positive XpertMTB/RIF test, (p value = 0.787). Table 4. All (100%) the children aged 0-5 years had undetectable TB antigen by both AFB and XpertMTB/RIF. Children aged 11-15 years constituted, 62.1% and 44.4% of bacteriologically detectable TB by XpertMTB/RIF and AFB respectively (Table 5).

More than half and nearly half of the children with bacteriologically detectable TB by XpertMTB/RIF and AFB respectively were between 11-15years. Table 5

Out of the children with confirmed TB, 98 (53.3%) had suggestive clinical features while 86(46.7%) had suggestive X-ray features. More than a third (33.2%) of the children aged 0-5years had their TB confirmed by suggestive X-rays and Clinical features. Table 6

All the one hundred and eighty four identified TB cases were commenced on appropriate doses of standard six months first line anti TB medications (Rifampicin, Isoniazide, Pyrazinamide and Ethambutol) under DOTs strategy. One month into treatment, 17 (9.2%) were lost to follow up and by the second month, a total of 40 (21.7%) were lost to follow up.

Twenty one (11.4%) relocated out of Rivers state and were transferred to centres closest to them while 123 (66.8%) completed the treatment.

Discussion:

The diagnosis of TB is protean and requires a high index of suspicion. This is because there is a wide variation in presentation and severity of disease. A presumptive TB case is any person whether adult or child, with signs and/or symptoms suggestive of TB (pulmonary or extra-pulmonary, or those with chest x-ray findings suggestive of active TB disease. Presumptive diagnosis of TB increases the pool of patients with clinical risk factors for TB who are subsequently screened to confirm the presence of disease. Nine hundred and sixty three patients had a presumptive diagnosis of TB in this study with more females (59.1%) than males (40.9%) being affected. Presumptive diagnosis over diagnoses TB but however ensures that any case of TB that presents to health facilities are not left undiagnosed. Study show varying proportion of confirmed TB disease from this pool. [7, 8]

The presentation of pulmonary TB disease in children depends on many factors that include age, immunization status to the bacillus Calmette-Guerin (BCG), immune status, co-existing disease, virulence of the infecting organism and host-microbe interaction. [9] Chronic cough as was found in 76.3% of this study was the commonest presenting symptom in these children and this is similar to findings in other studies in children with pulmonary TB. [10, 11] This cough is initially unproductive but with progressive inflammation and tissue necrosis, sputum is produced. None of the patient had hemoptysis but this is occasionally a presenting symptom especially in older children but usually results from previous disease and may not indicate active tuberculosis. It may arise from rupture of a dilated vessel in the wall of a cavity (Rasmussen's aneurysm), tuberculous bronchiectasis, bacterial or fungal infection (especially *Aspergillus* mycetoma) in a cavity or erosion into an airway (broncholithiasis). [10, 11] The

duration of cough in older children and adults has been shown to affect transmission, with other children more likely to be infected if the source case has been coughing for a longer period of time. [12, 13] Children who present with chronic cough especially when not responding to simple antibiotics should raise the suspicion for Pulmonary TB, this is more so when there are other suggestive symptoms like weight loss/failure to thrive (FTT) that 20.6% of our patients presented with. It is quite common not to get the history of contact with an adult with TB or chronic cough as was found in this study. This may probably be due to the fact that many people still feel stigmatised by TB and so relations refuse to volunteer the history or hide it even when asked**.** Poor knowledge and cultural beliefs about TB may also contribute to this and these all lead to poor health seeking behaviour, delay or failure to access the health services. [14, 15] The fact that TB is a curable disease especially with early presentation calls for increased public health enlightenment so that any associated stigma and misconceptions could be addressed.

This study found a pulmonary TB disease prevalence of 19.1% among children with presumptive diagnosis of TB. This compares with 20.7% prevalence reported by Kolapo in Lagos state [7] but contrasts with findings from Nwachukwu et al who found a prevalence of 12.3% among presumptive cases of TB in Anambra atate. [8] These studies were among adults as there are limited studies in children. The methodology used by Nwachukwu et al may have contributed to the lower prevalence as cases of confirmed TB was by sputum microscopy only while a combination of microscopy, XpertMTB/RIF and radiological and clinical findings were used in our study.

Males were diagnosed more than females with TB in this study which is statistically significant as is reported in other studies. [16, 17] Males may be more predisposed due to a yet unidentified genetic risk or the fact that parents have a better health seeking behaviour for their male children especially in our part of the world. Other studies have also reported a

female predominance of TB among older children aged 11years and above.[18-21] This age group has been found to have a higher prevalence of TB due to hormonal and reproductive changes. Among adults however, two thirds of TB cases occur in men and globally, men are significantly more at risk of contracting and dying from TB than women. [22, 23]

It is not surprising that more children from the lower social class were diagnosed with TB as TB has been described as a disease of poverty. These individuals are more likely to live in areas with high population and overcrowded environments. High population density will increase the risk of a child coming into contact with an infectious TB case, as more dense populations lead to more human encounters and encounters of more intense and prolonged physical proximity. [24]

The age of a child influences the risk of TB exposure and eventual disease. There was a near equal representation of the TB cases among the different age groups in this study, however, children aged 0-5 years constituted over a third of the cases of TB. The immunity of children in this age group is low and so progression from latent TB to TB disease is higher among them once exposed to an infectious source. However, because pre-school children interact with fewer sadults, and generally come into contact with adults only in their family units, their chances of exposed to an adult with infectious TB is reduced. Older children interact with more adults in their day-to-day life, they can therefore be exposed to infectious cases of TB at home or in the community.

Bacteriological confirmation of TB disease in children is difficult and this is more so in younger children. This is because children have paucy bacillary disease and find it difficult to produce sputum. The skill of acquiring sputum by gastric aspirate for AFB and or XpertMTB/RIF is quite invasive and poorly done by many health workers on outpatient basis. Many do a gastric lavage instead and the required minimum 4hours fast before the

procedure is not usually practiced. Sputum yield becomes poor and so the XpertMTB/RIF and AFB yield. All these contribute significantly to misdiagnosis, underdiagnoses and underreporting in children. This study found a positive yield of 39.1% and 15.8% for AFB and XpertMTB/RIF respectively. Studies have shown that XpertMTB/RIF is rapid and more sensitive to microscopy with sensitivity as high as 75-90% on sputum samples and as high as 70% on gastric aspirates. [25, 26] Despite the low yield to both microscopy and XpertMTB/RIF in this study there was a higher sensitivity to microscopy in contrast to reported findings. This may be due to poor specimen collection in younger children or poor expertise on the use of the recently introduced XpertMTB/RIF test by its users or both. The low bacteriological yield that was found in this study has been reported in other studies. [27, 28] Improvement on the quality of this Mycobacterium TB gene detection by XpertMTB/RIF test, improvement on the expertise of its use or use of other specimen like stool and urine specimen for detection of TB in children is advocated.

All children aged 0-5years had undetectable bacteriological test. This clearly suggest that either the sputum yield was poor, that the bacteriological screening methods lacked sensitivity or both. It may also depict the paucibacillary nature of TB in children and the fact that most children in this age group have primary TB which is not commonly associated with cavitatory lesions. However many children in this age group had clinical and radiological evidence of TB and responded to anti TB medications. It then follows that many children who are managed by clinicians without expertise on clinical diagnosis of TB may go undetected and progress to severe disease with poorer outcome. Over 80% of children with detectable bacteriological tests were aged 11years and above confirming the appropriateness and usefulness of these diagnostic methods in older children.

Nearly 50% of children with TB were diagnosed by clinical evaluation and use of chest radiograph. These children had two or more suggestive symptoms and sign and augmented

with chest radiographs findings. The low diagnostic yield of sputum microscopy and XpertMTB/RIF in children especially the very young makes them an unreliable method of diagnosis in children when used solely. A high index of suspicion and clinical expertise becomes vital in making a diagnosis of pulmonary TB in children especially in children 0-5years. These very young children with low immunity are more likely to develop severe disease and to succumb to it if diagnosis and treatment is delayed in many due to lack of experienced physicians. TB diagnosis therefore requires clinical expertise and early screening of children who presents with worsening and unrelenting cough lasting for 2 weeks or more with associated fever, weight loss or poor weight gain and a positive history of contact with an adult case of TB.

The DOTs strategy in TB treatment requires that patients visit TB treatment centres (closest to them) on daily basis and are observed to take their medications. This strategy guarantees compliance and adherence knowing the importance of completing TB medications or achieving cure. However, this is practically difficult in many areas as each DOTs centres covers a wide expanse of area. Therefore, Patients are given drugs on weekly basis and followed up with regular phone calls. Diagnosed patients with TB and or their caregivers are however properly counselled about the disease and drug adherence before commencement of medications and this is reinforced at every visit. Despite these measures, about a quarter of them were lost to follow up (LTFU)s. In a Kenyan study, Kibango et al reported a lower LTFU rate of 13%. [29] Reasons proffered for LTFU included no salaried employment, lack of family support and the male gender. Other studies proffered reasons such as financial limitation, transportation costs, lack of job, feeling better after few weeks of treatments, knowledge deficit about duration of treatment, poor patient-health worker relationship. [30-35] Home visits by health workers and collaboration with community health workers may overcome some of these reasons but is quite cost intensive. However, this should be explored

and properly integrated into the end TB strategy milestone for 2025 that calls for a reduction in number of TB deaths by 75% and TB incidence by 50%.

Conclusion:

The prevalence of pulmonary TB among presumptive TB cases in this study was comparable to findings from other studies and clinical diagnosis of Pulmonary TB remains very relevant in its management. Improving the clinical skills of physicians involved in TB care and treatment and the need for community/ facility collaboration cannot be overemphasized.

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Tables:

Table 1: Socio demographic characteristics and presenting symptom of presumptive TB

Socio-demographic of presumptive TB cases	Frequency (N =963)	percentage (%)
Gender		
Males	394	40.9
Females	569	59.1
Social class		
Upper	2I0	21.8
middle	339	35.2
Lower	414	43.0

Symptoms		
Chronic cough> 2weeks	735	76.3
Weight loss/FTT	198	20.6
Contact with a TB case	30	3.1
Age years		
< I	20	2.1
1-5	477	46.8
6- 10	201	20.8
11-15	214	22.3
16-18	51	5.3
Mean age (years)	**7.01 ± 4.53**	

Prevalence of Tuberculosis:

One hundred and eighty four had confirmed TB giving a prevalence of 19.1%. More males (60.9%) than female (39.1%) had confirmed tuberculosis. This difference was statistically significant (X^2 =37.431, p-value <0.001). More children (54.3%) from the low socioeconomic class had confirmed TB and there was a statistically significant different between TB and social class. There was a near equal representation of children with confirmed TB in the different age groups after one year of age.

Table 2. Prevalence of Tuberculosis

Variables	**Unconfirmed Cases N (%)**	**Confirmed cases N (%)**	**Total N (%)**	χ^2	**df**	**p value**
Gender						
Males	282 (36.2)	112(60.8)	394(40.9)	**37.431**	**1**	**< 0.001**
Females	497 (63.8)	72 (39.1)	569(59.1)			
Total	**779**	**184**	**963**			

Social class						
Upper	171(22.0)	39 (21.2)	210(21.8)	**12.952**	**2**	**0.002**
Middle	293 (37.6)	46 (25.0)	339 (35.2)			
Lower	315(40.4)	99 (53.8)	414(43.0)			
Total	**779**	184	963			
Age years						
< I	11 (1.4)	9(4.9)	20(2.1)	**164.752**	**4**	**<0.001**
1-5	425 (54.5)	52(28.3)	477(49.5)			
6- 10	169 (21.7)	32(17.4)	201 (20.9)			
11-15	165(21.2)	49(26.6)	214(22.2)			
16-18	9 (1.2)	42(22.8)	51(5.3)			
Total	**779 (100.0 %)**	**184(100.0%)**	**963 (100.0)**			

Proportion of subjects with positive AFB test by gender

Seventy two (39.1%) of the patients were AFB positive. More males (53.7%) than females (40.3%) were smear positive for AFB, however this difference was not statistically significant. Table 3

Table 3: Proportion of subjects with positive AFB test by gender

Gender	AFB		
	Detected	Not detected	Total
	N (%)	N (%)	N (%)s
Males	43(59.7)	69(61.6)	112(60.9)
Females	29 (40.3)	43(38.4)	72(39.1)
	72(100.0)	112(100.0)	184 (100.0)

$\chi 2$ = 0.065 , df = 1 p value = 0.799

Proportion of subjects with positive XpertMTB /RIF by gender

Of the patients with confirmed TB, XpertMTB/RIF was positive in only 29(15.8%) of them. Seventeen (58.6%) were males while 12 (41.4%) were females. There was no gender difference in proportion of positive XpertMTB/RIF test, (p value = 0.787). Table 4

Table 4: Proportion of subjects with positive XpertMTB/RIF test by gender

Gender	XpertMTB/RIF		
	Detected	Not detected	Total
	N (%)	N (%)	N (%)
Males	17 (58.6)	95 (61.3)	112(60.9)
Females	12 (41.4)	60(38.7)	72(39.1)
Total	29(100.0)	155(100.0)	184 (100.0)

$\chi 2$ = 0.073 , df = 1 p value = 0.787

Comparism between age and Microbiological results

All (100%) the children aged 0-5years had undetectable TB antigen by both AFB and Gene XpertMTB/RIF. More than half and nearly half of the children with detectable TB antigen by XpertMTB/RIF and AFB respectively were between 11-15years.

Table 5: Comparism between age and Microbiological results

Microbiological results:	**XpertMTB/RIF**		**AFB**	
	Detected N (%)	Not detected N (%)	Detected N (%)	Not detected N (%)
Age years				
< I	0(0.0)	9 (5.8)	0(0.0)	9(8.0)
1-5	0(0.0)	52 (33.5)	0 (0.0)	52(46.4)
6- 10	4(13.8)	28 (18.1)	9 (12.5)	23(20.6)
11-15	18(62.1)	31(20.0)	32(44.4)	17(15.2)
16-18	7(24.1)	35(22.6)	31(43.1)	11(9.8)
	29(15.8)	**155(84.2)**	**72(39.1)**	**112 (60.9)**

Age and Clinical diagnosis of TB:

Out of the children with confirmed TB, 98 (53.3%) had suggestive clinical features while 86(46.7%) had suggestive X-ray features. More than a third (33.2%) of the children aged 0-5years had their TB confirmed by suggestive X-rays and Clinical features. Table 6

Table 6: Age and Clinical diagnosis of TB:

Age years	**Suggestive CF**	**Suggestive Xray**	**Total**
	N (%)	N (%)	N (%)
< I	5(5.1)	4(4.6)	9(4.9)
1-5	30(30.6)	22(25.6)	52(28.3)
6- 10	16(16.3)	16(18.6)	32(17.4)
11-15	27(27.6)	22(25.6)	49(26.6)
16-18	20(20.4)	22(25.6)	42(22.8)
Total	**98(53.3)**	**86 (46.7)**	**184 (100.0)**

$\chi 2$ = 1.17 , df = 4 p value = 0.883

CF-Clinical features