Childhood Tuberculosis in Nigeria: Disease Presentation and Treatment Outcomes

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ABSTRACT

OBJECTIVES: Understanding the factors that influence tuberculosis (TB) treatment outcomes in children is key to designing interventions to address them. This study aimed to determine the case category distribution of childhood TB in Nigeria and assess which clinical and demographic factors are associated with different treatment outcomes in childhood TB.

MATERIALS AND METHODS: This was a retrospective cohort study involving a review of medical records of children (0-14 years) with TB in 3 states in Nigeria in 2015.

RESULTS: Of 724 childhood TB cases registered during the review period, 220 (30.4%) were aged 0–4 years. A high proportion of patients had pulmonary TB 420/724 (58.0%), new TB infection 713/724 (98.5%), and human immunodeficiency virus (HIV) coinfection 108/724 (14.7%). About 28% (n = 201) were bacteriologically diagnosed. The proportion of TB treatment success was 601/724 (83.0%). Treatment success was significantly higher in children aged 5–14 years than those 0–4 years (85.3% vs 77.7%, $P = .01$). Factors associated with unsuccessful outcomes in patients aged 0–4 years are male sex (adjusted odds ratio [aOR]: 1.2), HIV-positive status (aOR: 1.2), and clinical method of diagnosis (aOR: 5.6).

CONCLUSIONS: Efforts should be made to improve TB treatment outcomes in children by ensuring early and accurate diagnosis, focused training of health workers on childhood TB-HIV care, and effective adherence counseling of caregivers.

KEYWORDS: Nigeria, children, tuberculosis, treatment outcomes, cohort review

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Background

Childhood tuberculosis (TB) and human immunodeficiency virus (HIV) syndrome are major public health concerns contributing to significant child morbidity and mortality. Globally, about 1 million incident childhood TB cases occur annually, only 359 000 were notified in 2014 indicating that two-thirds of the children who developed TB worldwide were not notified.[1,2] It is believed that these missing childhood TB cases were neither diagnosed nor initiated on TB treatment. The actual magnitude of childhood TB epidemic is difficult to assess, mainly due to diagnostic difficulties and noninclusion of children in most surveys.[1] Poor access and delay in diagnosing and initiating appropriate TB treatment in children have implications on child morbidity and mortality. In 2014, 136 000 children aged <15 years died of TB and about 40 000 of the deaths were in HIV-coinfected children.[1]

Childhood TB is a good indication of ongoing transmission of TB in the community. Tuberculosis in children has been shown to occur mostly among infant and young children aged <5 years.[3,4] These younger children are at higher risk of progressing to TB disease after infection as well as developing more severe forms of TB such as TB meningitis.[5,6] For those HIV positive, the situation is even worse.[6] However, childhood TB is not adequately recognized in some countries, based on the reported number of childhood TB cases. The World Health Organization (WHO) estimates that around 10% to 20% of total TB case notification is expected to occur in children and even higher in settings with high burden of TB.[1] Commonly, many national TB programs report numbers well below the estimated average. Reported treatment outcomes also vary, especially in children who are younger than 5 years of age. Studies from sub-Saharan Africa have reported outcomes for children ranging from 77.4% to 79.2%.[7,8] In Ethiopia and South Africa, children with some clinical features such as HIV coinfection have also been reported to have poorer outcomes.[9,10]

Nigeria has one of the highest burdens of TB and HIV-associated TB in the world. About 6000 children aged <15 years were notified to have TB in 2015, and this represented 6% of the estimated incident childhood TB cases.[1] The

Nigerian National Tuberculosis Program (NTP) is well established. However, the NTP routine surveillance data do not disaggregate reported childhood TB cases in terms of type, site of disease, method of diagnosis, and previous treatment history, among others, which make programmatic interventions targeting specific childhood TB cases difficult. Among children, striking variations have been reported in the distribution of TB cases, and this has important implication for program interventions for childhood TB. Although important progress has been made in the overall treatment outcome with treatment success in the general population (all ages) exceeding 85% in recent time, poor outcomes have been reported among children, and even poorer outcomes are reported among younger children aged <5 years.[1,11] This suggests that there are underlying clinical and demographic factors associated with childhood TB that need to be explored.

Furthermore, little is known about the case distribution of childhood TB for different age groups. Treatment outcome measurement has historically focused on individuals with smear-positive TB, which is much less common in children—especially infants and young children who often have difficulty producing sputum. There are also few studies in Nigeria that evaluated treatment outcomes of childhood TB and risk factors. The few studies that undertake this task are limited to either a small cohort or geographical area and are not age specific.

Given this paucity of information on childhood TB in sub-Saharan Africa, this study focuses on providing information on childhood TB in Nigeria. The specific aims of this study are (1) to determine the case category distribution of childhood TB in Nigeria and (2) to assess which clinical and demographic factors are associated with different treatment outcomes in childhood TB.

Methods

Data

The research was conducted in Lagos, Ondo, and Osun states in Southwest Nigeria. Review of medical records of all childhood patients with TB undergoing treatment under the public and private health facilities between January and December 2015 was carried out. There are 726 designated TB treatment facilities across the 3 states, serving an estimated population of 21.7 million people, of which 7.5 million (35%) were children. These TB treatment facilities are located in 68 local government areas (LGAs) across the 3 states. Each LGA is supervised by a designated LGA TB supervisor. The study population consisted of all children aged <15 years who were diagnosed and treated of TB under the NTP. Information and data on demographic and clinical variables were extracted quarterly from the TB treatment cards and TB registers maintained in the TB treatment facilities by the LGA TB supervisors and entered into a designated LGA recording tool. These data were then extracted by 10 trained data entry clerks using a structured data extraction Microsoft Excel tool. The variables extracted include TB registration, type and category of TB, HIV status, sex, age (years), treatment category, and treatment outcome. Information on age-specific population was obtained from the National Population Commission Census Data 2006 and adjusted for annual population growth rate of 3.2%.[12]

This was a retrospective cohort study. States were selected based on convenience and to reflect a range of TB and HIV burdens and population coverage. Nigeria is one of the 30 countries with highest TB burden, with a TB incidence rate of 322 (189-488) per 100 000 population and HIV-associated TB incidence rate of 55 (31-85) per 100 000 population.[1] Tuberculosis incidence in children (0-14 years) was estimated at 586 (345-890) per 100 000. The NTP follows the WHO-recommended Directly Observed Therapy, Short Course (DOTS) strategy for TB treatment.[13] Samples were collected from symptomatic children for GeneXpert or acid-fast bacilli microscopy. For children who could produce sputum, sputum samples were collected for either GeneXpert or microscopy, whereas other samples (gastric lavage, cerebrospinal, and pleural biopsy) were collected for GeneXpert when a child could not produce sputum. The national program also approved clinical and radiologic diagnoses of childhood TB based on decision of a medical doctor to treat with full course of anti-TB treatment.

In 2015, the NTP intensified screening for TB among children attending health care facilities across the states and released guidelines endorsing GeneXpert MTB/RIF assay as the priority diagnostic tool for children with signs and symptoms of TB.[13] The national policy included recommendations for referral of samples (including gastric lavage) from health facilities where GeneXpert MTB/RIF services are not available to designated testing facilities with GeneXpert MTB/RIF services. Children diagnosed with TB received a standard treatment regimen consisting of Isoniazid (H), Rifampicin (R), Pyrazinamide (Z), Ethambutol (E) for 2 months, followed by R and H for 4 months (2RHZ + E/4RH).

Measurement

Dependent Variables. Outcome variables were categorized as successful (cured and treatment completed) and unsuccessful (died, failure loss to follow-up, and not evaluated). Treatment outcomes categories (cured, treatment completed, died, treatment failure, loss to follow-up, and not evaluated) were assigned based on NTP/WHO guidelines.[13] Patients were followed up using laboratory or clinical evaluations at regular intervals, ie, second, fifth, and sixth months during chemotherapy.

Independent variables. Children were defined as those aged <15 years, with additional subcategories of younger (0-4 years) and older (5-14 years) children. Tuberculosis diagnosis was based on standard WHO/NTP methods, using any of sputum microscopy, clinical examination, chest X-ray, and GeneXpert for diagnosis.[13] Bacteriologically diagnosed cases included

Table 1. Demographic and clinical characteristics of childhood TB cases registered.

VARIABLES	CHILDREN 0-4Y, NO. (%)	CHILDREN 5-14Y, NO. (%)	TOTAL, NO. (%)	*P* VALUE[a]
Total	220 (30.4)	504 (69.6)	724	
Demographics				
Gender				
Female	107 (48.6)	293 (58.1)	400 (55.2)	
Male	113 (51.4)	211 (41.9)	324 (44.8)	.02
State				
Lagos	193 (87.7)	373 (74.0)	566 (78.2)	
Ondo	13 (5.9)	70 (13.9)	83 (11.5)	
Osun	14 (6.4)	61 (12.1)	75 (10.3)	<.01
Presentation and medical history				
Anatomic site of TB				
Pulmonary TB	137 (58.0)	283 (56.2)	420 (58.0)	
Extrapulmonary TB	83 (42.0)	221 (43.8)	304 (42.0)	.14
Method of diagnosis				
Bacteriologically diagnosed	14 (6.4)	187 (37.1)	201 (27.8)	<.01
Clinically diagnosed	206 (93.6)	317 (62.9)	523 (72.2)	
Category of patients with TB				
New TB cases	219 (99.5)	494 (98.0)	713 (98.5)	
Retreatment TB cases	1 (0.5)	10 (2.0)	11 (1.5)	.11
HIV status				
HIV positive	39 (17.7)	69 (13.7)	108 (14.9)	.17
HIV negative	181 (82.3)	435 (86.3)	616 (85.1)	

Abbreviations: HIV, human immunodeficiency virus; TB, tuberculosis.
[a]Fisher's exact test.

those who were diagnosed using either GeneXpert or sputum microscopy.

Analysis strategy

Data were double entered, checked, and analyzed using Epi Info 7 (Centers for Disease Control and Prevention, Atlanta, GA, USA). The analyses were based on intention to treat. Outcome variables were categorized as primary (rate of successful outcomes) and secondary (proportion of treatment failures at the end of chemotherapy). Descriptive statistics was used to determine the characteristics of the study population. Demographic and clinical characteristics and treatment outcome (successful and treatment failures) variables were compared using χ^2 test and Fisher exact or mid-*P* exact as appropriate, with a *P* value of .05 assumed to be statistically significant. Unadjusted odds ratios (ORs) and adjusted ORs (aORs) with their 95% confidence intervals were estimated using multivariable logistic regression analysis, with unsuccessful outcomes as the dependent variable and sex, age, site of disease, method of diagnosis, and HIV status as the predictor variables.

Protection of human subjects

Because the study was based on a retrospective review of existing records, did not include any patient interaction, and did not involve the collection of individual identifying information, the study involved no risk to participants. Clearance for exemption was granted by the Ethical Committee, State Ministry of Health. Institutional approval was obtained from the respective state and local government TBL Control program managers.

Results

Of the 724 childhood TB cases registered, 220 (30.4%) were aged 0–4 years and 504 (69.6%) were aged 5–14 years. The

Table 2. Treatment outcomes of childhood TB cases stratified by demographic and clinical characteristics.

CATEGORY	UNSUCCESSFUL OUTCOMES, NO. (%)*	SUCCESSFUL OUTCOMES, NO. (%)†	X^2	*P* VALUE
Total	123 (17.0)	601 (83.0)		
Sex				
Female	75 (18.7)	325 (81.3)		
Male	68 (21.0)	256 (79.0)	0.49	.45
Age				
0–4	49 (22.3)	171 (77.7)	6.23	.01
5–14	74 (14.7)	430 (85.3)		
Site of disease				
Pulmonary TB	49 (11.7)	371 (88.3)	1.84	.21
Extrapulmonary TB	26 (8.5)	278 (91.5)		
Method of diagnosis				
Bacteriological diagnosed	19 (9.5)	182 (90.5)		
Clinically diagnosed	104 (19.9)	419 (80.1)	11.19	<.001
Type of patient				
New TB cases	122 (17.1)	591 (82.9)	0.49	.70
Retreatment TB cases	1 (9.1)	10 (90.9)		
HIV status				
Positive	31 (28.7)	77 (71.3)	13.34	<.001
Negative	92 (14.9)	524 (85.1)		

Abbreviations: HIV, human immunodeficiency virus; TB, tuberculosis.
†Successful outcomes = cured and treatment completed; *Unsuccessful outcomes = died, failure, and not evaluated.

ratio of male to female was 1:1.2 (Table 1). Among these, 566 (78.2%) were registered in Lagos, 83 (11.5%) registered in Ondo and 75 (10.3%) in Osun states. About 58% (n = 420) were pulmonary TB cases, whereas 42% (n = 304) had extrapulmonary TB (EPTB). Most (98.5%; n = 713) were new TB cases and the remaining 11 (1.5%) cases had been treated for TB in the past. Nearly a third (27.8%; n = 201) were bacteriologically diagnosed, whereas 72.2% (n = 523) were diagnosed clinically. The TB/HIV coinfection rate was 14.9% (n = 108).

The treatment outcomes of patients are shown in Table 2. Of the 724 patients enrolled, the overall treatment success rate was 83% (n = 601). Children aged 5–14 years had higher treatment success rate than those aged 0–4 years ($P = .01$). Patients who were bacteriologically diagnosed and HIV negative had higher treatment success rates than those clinically diagnosed ($P < .001$) and HIV positive ($P < .001$), respectively. Treatment outcomes among male patients were worse compared with female patients but this difference was not statistically significant. There were no significant differences in treatment outcomes between patient type ($P = .07$) and site of disease ($P = .21$; Table 2).

Multivariable logistic regression analysis was used to identify significant predictors of unsuccessful treatment outcomes among childhood patients with TB as shown in Table 3. Clinically diagnosed, HIV-positive, and young children aged 0–4 years were significantly associated with unsuccessful treatment outcomes. After adjusting for confounders, aged 0–4 years (aOR: 1.4), clinically diagnosed (aOR: 2.1), and HIV-positive status (aOR: 1.9) remained independent predictors of unsuccessful outcomes (Table 3).

Further multivariable analysis showed that in children aged 0–4 years, male sex, HIV-positive status, and clinical method of diagnosis were significantly associated with treatment outcomes. After adjusting for confounders, male sex (aOR: 1.2), HIV-positive status (aOR: 1.2), and clinical method of diagnosis (aOR: 5.6) remained independent predictors of unsuccessful outcomes in patients aged 0–4 years (Table 4). No association was found between site, type of TB disease, and treatment outcomes. However, clinical method of diagnosis was associated with unsuccessful outcomes in patients aged 5–14 years (aOR: 0.6).

Table 3. Factors associated with unsuccessful treatment outcomes among childhood TB cases.

CATEGORY	OR (95% CI)	*P* VALUE	AOR (95% CI)	*P* VALUE
Sex				
Male	1.3 (0.7–1.6)	.22	1.1 (0.5–1.4)	.25
Female	1.0			
Age				
0–4	1.6 (1.1–2.4)	.009	1.4 (1.01–2.3)	.017
5–14	1.0			
Site of disease				
Pulmonary TB	1.4 (0.8–2.3)	.10	1.4 (0.7–2.3)	.21
Extrapulmonary TB	1.0			
Method of diagnosis				
Bacteriological diagnosed	1.0			
Clinically diagnosed	2.3 (1.4–3.9)	<.001	2.1 (1.3–4.0)	<.001
Type of patient				
New TB cases	2.0 (02–16.2)	.2	2.2 (0.3–45.5)	.41
Retreatment TB cases	1.0			
HIV status				
Positive	2.2 (1.4–3.6)	<.001	1.9 (1.1–3.4)	.001
Negative	1.0			

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; TB, tuberculosis.

Discussion

This study described the case distribution of childhood TB and treatment outcomes in Nigeria and assessed the relationship between demographic and clinical variables with treatment outcomes. We found that childhood TB treatment was characterized by relatively poor outcomes. Age, HIV status, and method of diagnosis were associated with unsuccessful treatment outcomes. Given that this study was designed to assess childhood TB distribution and care under program conditions, our study provides valuable insights into the underlying challenges of childhood TB management in high-burden, resource-limited settings. Although the proportion of children with previous history of TB treatment in our study is smaller (1.5%) compared with previous studies, our cohort had similar clinical features consistent with severe disease[5,6,14] such as smear positivity (30%-60%)[6] and abnormal radiography (40%-51%).[6,14,15] Compared with other studies, a higher proportion of children in our study were HIV positive (14.9% vs 11.3%)[16] and had EPTB disease (42% vs 34.6%)[17] suggesting differences in clinical presentation and complication in case management. The age-specific distribution of TB in our study showed that TB was most common among children aged 5–14 years, similar to findings from previous studies in Nigeria.[11] This is in contrast to the expected epidemiology of TB and findings of other studies which reported high proportions of childhood TB cases in the 0–4 years age group.[4,6,14] The reason for this difference is not clear; it may be due to under-notification of TB in the age group of 0–4 years as a result of diagnostic difficulties and the consequent passive health care sector in Nigeria.

We also found that the overall treatment success rate was 83.0%, which is consistent with the national average. However, the measure treatment success was lower than findings from Bhutan and India, which reported 93% to 96% treatment success rates.[15,17] The Nigerian NTP applies a standardized daily treatment regimen, and its policy guidelines rely on DOTS to be practiced throughout the duration of chemotherapy either by a DOTS provider or by a trained treatment supporter. Globally, studies have shown that early detection of TB and effective implementation of DOTS with good adherence counseling and patient education would result in high treatment success rate and reduce death.[3,4,6] The Roadmap for Childhood TB in this and similar settings should therefore focus on implementing key strategies to raise suspicion of TB among clinicians,[16] strengthen techniques for sputum collection for accurate bacteriological diagnosis, and improve overall

Table 4. Factors associated with unsuccessful treatment outcomes among childhood TB cases stratified by age group.

CATEGORY	AOR-1 (95% CI)[a] (N = 220)	AOR-2 (95% CI)[b] (N = 504)
Sex		
Male	1.2 (0.8-1.6)*	0.9 (0.7-1.1)
Female	1.0	1.0
Site of disease		
Pulmonary TB	1.1 (0.8-1.4)	0.9 (0.8-1.3)
Extrapulmonary TB	1.0	1.0
Method of diagnosis		
Bacteriological diagnosed	1.0	1.0
Clinically diagnosed	5.6 (3.3-10.3)*	0.6 (3.5-0.9)*
Type of patient		
New TB cases	0.6 (0.08-2.4)	1.1 (0.4-2.9)
Retreatment TB cases	1.0	1.0
HIV status		
Positive	1.2 (0.8-1.9)*	0.9 (0.7-1.3)
Negative	1.0	1.0

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; TB, tuberculosis.
[a]ORs adjusted for age group 0-4 years.
[b]ORs adjusted for age group 5-14 years.
*$P < .05$.

treatment outcomes via effective adherence counseling of caregivers.

Human immunodeficiency virus–positive status, age 0–4 years, and clinical method of diagnosis independently predicted unsuccessful treatment outcomes. The HIV-coinfected patients would require closer monitoring in an effective program. Poor treatment outcomes in childhood TB cases coinfected with HIV are consistent with findings of other studies.[10,18–20] This may be due to the predominant respiratory comorbidity which increases risk of delayed diagnosis and treatment, missed diagnosis, atypical presentation, and mortality in HIV-coinfected children, particularly those at the advanced stage of HIV disease.[3–21] Age-specific outcomes showed that treatment was less successful among children who are younger than 5 years of age, especially those HIV positive and male sex. Diagnosis and treatment for TB in children in resource-limited settings are associated with significant difficulties often due to presence of immature immune response, poorer cell-mediated immunity, unrestrained bacteria proliferation, parenchymal damage, and disseminated disease which are common in children, particularly in HIV-coinfected children.[22] A program that substantially reduces TB death and improves treatment success would considerably reduce the burden of TB.[23] An increasing prevalence of HIV infection in Nigeria provides the basis for greater collaboration, prioritization, and commitment by both TB and HIV programs to tackle childhood TB.

Limitations

Our study population was limited to childhood TB cases diagnosed and treated at health facilities under the NTP but did not include childhood TB cases managed outside the NTP system. Due to its retrospective nature, additional information such as antiretroviral therapy initiation, baseline and follow-up CD4 percent, and distance to health facility which could support deeper analysis were unavailable. Despite these, our study highlights the burden of TB in children in Nigeria particularly among younger children aged 0–4 years and provides insight that could form part of the roadmap to reducing treatment failures among childhood TB cases in Nigeria and in similar low-resource high-burden settings.

Conclusions

This study highlights the need for a renewed focus on strategies to reduce burden of TB in children, particularly among young children aged 0–4 years and HIV-coinfected children in this and other similar settings. The Nigerian TB control program should pay greater attention to early diagnosis and case management of childhood TB/HIV coinfection through investment on newer TB diagnostic technology and training of general health care workers on childhood TB/HIV

comanagement. Routine screening for TB and comorbidities such as HIV should also be intensified among children aged 0-4 years.

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Authors Contributions

CLO, VA, NC, MG and GE conceived and designed the study. EA, CE-U, VA, and CLO conducted data collection. VA, CLO, and EA analyzed and interpreted the data and wrote the first draft of the manuscript. All authors carefully reviewed and revised the manuscript for intellectual content. All authors read and approved the final manuscript.

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