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Predictors of Unfavorable Treatment Outcome Among Childhood Tuberculosis Patients in Ede Town Health Centers, Sub-District of Osun, Nigeria

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Abstract:-

➢ ***Background:***

Tuberculosis in children is a consequence of adult TB, but it's often neglected. Understanding treatment outcomes in children is crucial for designing effective interventions.

➢ ***Aim:***

This study is aimed at evaluating some predicting factors associated with and responsible for successful and unsuccessful treatment in the Ede town health centers of the sub-district of Osun State, Nigeria.

➢ ***Methods:***

This retrospective study involved analyzing statistically reviewed TB records of patients aged 0–14 years that were reported and enrolled between April 2018 and July 2021 at selected health facilities in Ede town, including the laboratory Gene Xpert site.

➢ ***Results:***

Of the 102 enrollees, 24/102 were aged 0–4 years, with the mortality ratio (MR) being 0.35% (95% CI 0.17–0.56), and 45/102 [MR]:0.26% (95% CI 0.13-0.36) were aged 5–9 years. 33/102 [(MR): 0.46% (95% CI 0.21-0.76)] were aged 10–14 years. 52/102 (51%) had a household contact, while 45% represented other contacts. One-quarter of our total respondents were co-infected with HIV, while 75.5% had extra-pulmonary tuberculosis. The treatment failure rate decreased with increasing age, with 0–4 years having the worst treatment failure rate at 50% and 10–14 years having the highest treatment success rate at 60.6% compared to the remaining age group. Respondents with good drug adherence status had 100% treatment success, which was statistically significant (p value < 0.01).

➢ ***Conclusion:***

The study found that drug adherence status in children aged 0–14 in Ede Health Centers, Osun, Nigeria, is a major predictor of unsuccessful tuberculosis treatments. Factors such as difficulty understanding instructions, parental supervision, taste, formulation, side effects, developmental changes, and inconsistent routines contribute to these outcomes.

➢ ***Recommendation:***

To improve drug adherence in children, healthcare providers, parents, and children should improve education, communication, and technology use. Collaboration between professionals, researchers, and policymakers is essential for identifying barriers and implementing evidence-based strategies.

Keywords:- *Childhood Tuberculosis, HIV Co-Infection, Extra-Pulmonary Tuberculosis.*

I. INTRODUCTION

Tuberculosis is the 13th leading cause of death[1] with the causative agent called Mycobacterium tuberculosis. It is the second leading infectious killer disease until the outbreak of COVID-19 and ranked above Human Immune Deficiency Virus and Acquired Immune Deficiency Virus (HIV/AIDs).[2] Tuberculosis is transmitted when an infected person expels the bacteria (Mycobacterium tuberculosis) by coughing and another person inhaling the droplet. Primarily it affects the lungs (pulmonary tuberculosis) but can be transmitted to other sites of the body. In this case it is referred to as extra-pulmonary tuberculosis (EPTB).

In 2020 according to WHO, an estimate of 10 million people were victims of tuberculosis infection globally, of which 5.6 million are men, 3.3 million are women and 1.1 million are children[1,3] and is presented in all countries and age groups[1.] Annual TB cases in Nigeria are predicted to reach 460,000 [2]. Due to the growing correlation between TB and HIV/AIDS, the prevalence of TB among patients with HIV/AIDS rose from 10.5 to 40%[3]. The incidence and mortality rates of tuberculosis in the nation are 219/100,000 and 39/100,000, respectively, with a 24% treatment coverage percentage in 2016, the nation has the lowest global TB treatment coverage rate[2]. With a drug resistance TB frequency of 4.3% among new cases and 25% among those who have already received treatment, Nigeria is ranked eighth among the 30 nations with the highest burden of multi drug-resistant tuberculosis (MDR-TB).

Historically, childhood TB has been given low priority in most national programme because it contributes little to disease transmission[6,7,8]. While about 1.1 million children are diagnosed with tuberculosis globally in 2020, mostly in low and middle income countries, children as a vulnerable population are frequently left out of randomized trials of novel treatments[9].

As one of the top 10 causes of death, childhood TB is a silent killer, with risk of mortality being particularly high in children aged <5years and HIV co-infected children not receiving Antiretroviral therapy (ART)[10,11]

Difficulties in making a tuberculosis diagnosis (particularly the absence of microbiological confirmation), a protracted course of treatment, lack of simple access to fixed-dose palatable pediatric formulations, the burden of pill-taking, and drug side effects are significant obstacle in treating children[9].

Pai et al., 2022 reveal that the majority of pediatric cases start out as mild illnesses with little bacillary burden on smear and molecular tests. It was suggested in his report that it is likely unnecessary to utilize microscopy to rule out situation where a smear is tested positive. A surrogate for smear-negative tuberculosis in a way to simultaneously rule-out rifampicin resistance low, very-low or trace positive readings is by GeneXpert test which has also been micro-biologically proven[9]. Bearing in mind at this juncture that in TB treatment cascade, children constitute the "missing face" of TB due to diagnostic dilemma. The use of sputum as a biological specimen for pediatric TB diagnosis in past constitute a dilemma in specificity, sensitivity and accuracy in the result produced. Sputum is difficult to obtain especially those of aged <5years and are unable to effectively expectorate requiring laryngopharyngeal aspiration followed by sputum induction.

The process of gastric aspirations, sputum induction and nasal/bronchial lavage are technical, painful and invasive and very difficult to implement in resource-constrained settings. With a multisectoral concerted efforts, the WHO endorsed and recommends innovative solutions with the use of Xpert MTB/RIF and Xpert Ultra (where available) to detect MTB DNA and Rif resistance in stool of children. The Xpert MTB/RIF as mentioned earlier is an automated cartridge-based nucleic acid amplification test (NAAT) for simultaneous rapid tuberculosis diagnosis and rapid antibiotic sensitivity test.

The stool Xpert test hold a positive promise as an alternative to sputum Xpert testing since stool collection is easier and relatively safer compared to sputum collection in children.

One recurring challenge that still persists in health data among this vulnerable group is Multi-Drug Resistant Tuberculosis (MDR-TB), as this was attributed to health provider not paying detailed attention to this age group[1]. Management of childhood and adolescent TB is still a pressing challenge even in low incidence countries[6,12].

To achieve comprehensive and excellent treatment outcomes in children, it is therefore essential to scale up more flexible diagnostic techniques, and a more pediatric friendly fixed-dose formulations to overcome difficulties in diagnosis and treatment as well.

Hence, This study aimed to evaluate some predicting factors associated and responsible for unsuccessful treatment of childhood tuberculosis in Ede town Health Centers, Osun subdistrict, Osun state, Nigeria.

- *Aim*:

This study is aimed at determining the associated factors responsible for unsuccessful treatment of childhood tuberculosis in Ede town Health Centers Osun subdistrict, Osun state, Nigeria.

- *Objectives:*

- To determine the baseline clinical and laboratory status of tuberculosis in children
- To access treatment outcomes (favorable-completed treatment and unfavorable treatment)
- To determine the association between baseline clinical and laboratory on treatment outcome
- To access predictors of unfavorable outcome using appropriate statistical test

II. MATERIALS AND METHODS

This was a retrospective study. The extraction of data was done using pro-formal that was designed to extract information from the case history of children treated for tuberculosis in the Chest clinic, Paediatric ward at the health centers over a period of 35 months, from April 2018 to March 2021. Variable extracted from the archive included the patients' age, gender, history of BCG vaccination, history of contact, classification based on anatomical site into pulmonary and extra-pulmonary, chest radiograph findings, GeneXpert results, HIV test results including CD4 values, drug adherence, and treatment outcome[15]

In terms of diagnosis, children that are symptomatic have sputum collected for geneXpert or acid-fast bacilli microscopy while those who could not produce sputum had other samples such as gastric lavage, stool, examined also using Xpert. These according to National Program are classified as bacteriological while those diagnosed mainly based on clinical findings or radiological investigations according to decision are classified as clinical[14]

Concerning classification, Pulmonary tuberculosis cases was defined as symptomatic child with: (1) bacteriologically confirmed tuberculosis using sputum AFB, (2) Sputum with MTB detected using GeneXpert, (3) radiologically confirmed tuberculosis, or (4) Probable tuberculosis. Probable tuberculosis was said to be a TB score >7, radiologic certainty and a good clinical response to anti-tuberculosis treatment in the absence of bacteriologic confirmation. Radiologically confirmed pulmonary tuberculosis was defined as an agreement between two independent radiologists that the Chest X-ray indicated certain tuberculosis and a TB score 1-6 in the absence of bacteriologic confirmation and a good clinical response to anti-tuberculosis treatment[13]

Standard treatment regimen under National program consist of 2 regimen namely Regimen 1 and Regimen 2. Regimen 1 has 2 months of Isoniazid (H), Rifampicin (R), Pyrazinamide (Z), Ethambutol (E) followed by R and H for 4months (2RHZ+E/4RH) while Regimen 2 has 2 months of Isoniazid (H), Rifampicin (R), Pyrazinamide (Z), Ethambutol (E) followed by R and H for 10 months (2RHZ+E/4RH)

Treatment outcomes were categorized as successful (treatment completed and cured) and unsuccessful (treatment failure, died, loss to followup, not evaluated) based on National tuberculosis program guideline adopted from World Health Organization depending on outcome of laboratory investigations at regular intervals 2^{nd} , 5^{th} and 6^{th} month for those under regimen 1 or 2^{nd} and 10^{th} month for those under regimen 2 during course of treatment.

These include respondents age, sex, nutritional status, method of diagnosis (clinical or Radiological), HIV status (Positive or Negative) and Anatomical site (Pulmonary or Extra-pulmonary).

- *Data Collection*

Data collected using a Pro formal from the case note were checked for errors before entry and analyzed using Statistical Product for service solution version 23. Regarding study population, descriptive statistics (mean and standard deviation) were calculated for continuous variables while categorical variables were presented as frequency and percentages in a tabular form. Chi-square test or Fisher's exact test was used to test for association between demographic, clinical characteristics with treatment outcome (Successful and treatment failure). A p-value of <0.05 was taken as statistically significant. Multivariate analysis was done to assess predictors of unsuccessful treatment outcome.

- *Ethical Clearance*

Ethical clearance for the conduct of the study was obtained from the Ethical clearance review committee, Osun State University, Osogbo. The addresses, names, hospital number and other identifiers of the patients were omitted in order to maintain confidentiality.

III. RESULT

Out of the 102 pediatric tuberculosis cases reported, Children in the range of 5-9 years have the highest proportion (44.1) and 0-4 years have the lowest proportion (23.5). The ratio of males to females was 1:1. When we

compared the nutrition, two third of the children reported being malnourished, and one-third were not malnourished. Also, when the history of the patients was tracked, there was no difference between the percentage of those with household contact and those whose connection was from other sources. Nearly three-quarters of our respondents were HIV-negative, and one-quarter were co-infected with HIV. From the classification of tuberculosis, 24.5% were pulmonary tuberculosis, while 75.5% were extrapulmonary tuberculosis. The respondents were checked for the history of the Bacille Calmette Guerin vaccine (BCG) vaccine. The ratio of those that took BCG and those that did not was 1:1. The methods for diagnosis captured in this study are clinical and bacteriological, with 40.2% and 59.8%, respectively.

The treatment failure rate decreased with increasing age, with 0-4 years having 50% with the worst treatment failure rate, 5-9 years at 44.4%, and 10-14 years at 39.4%. On the contrary, the treatment success rate increased with age, with 0-4 years having 50%, 5-9 years having 55.6%, and 10-14 years, with 60.6% being the age group with the highest treatment success rate compared to the remaining age group.

There was no statistically significant difference between the male and the female success and failure rates of the treatment. Patients who are HIV positive have more success rate than patients with HIV negative, and the difference between the two was slightly significant. The treatment success rate of malnourished patients was higher than usual, with 61.2% and 45.7%, respectively. Normally nourished patients were seen with more failure in their treatment, while malnourished patients have high treatment success rates which are both significant in their differences. Those who adhere to their drugs achieve 100% success in the treatment, while an insignificant proportion of success rate (4.3) was recorded from patients with poor adherence. Pulmonary tuberculosis patients responded well (60%) to treatment compared to extra-pulmonary tuberculosis patients, and there was no significant difference in their failure in response to treatment.

Furthermore, patients with a history of household contact reacted at the same rate to treatment success and failure (50%,50%). In contrast, those with connections other than households had a significant treatment success rate (82%). Patients identified with the Bacille Calmette Guerin (BCG) vaccination history and those not exhibited higher treatment success than failure (52.1%, 59.3%, and 47.9%, 40.7%). However, there was no statistically significant in their comparison.

Table 3 shows that successful treatment outcome among patients that adequately adheres to their prescription (Good adherence status) was more than patients who poorly adhere to their drug prescription (Poor adherence status). The difference is statistically significant with p value < 0.01. Hence, the drug adherence status of respondents is a significant predictor of successful treatment outcomes among respondents.

IV. DISCUSSION

A call for emergency response to protect children from TB and preventable deaths from this disease brings to the rising attention being paid to the global epidemic of childhood TB[17] . This study described the case distribution of childhood TB and predictors to successful and unsuccessful treatment outcomes in Ede Town Health Centres located in the South Western part of Nigeria, and assessed the relationship between demographic and clinical status with treatment outcomes.

Age range, nutritional status, HIV status, drug adherence status, history of contact has a strong interplay with treatment outcomes. Though the WHO estimated the TB prevalence rate[19] infected children are at higher risk of developing active TB when exposed to adults with smear-positive TB[20].

This study however provides valuable insights into the underlying challenges of childhood TB management in high-burden, resource-limited settings.

Children under the age of five represented the majority of childhood TB cases in earlier studies conducted in Africa[32,33], and young children had the highest risk of developing active TB, particularly those under the age of two years [31]. However, in our study, older children with age range (5 - 9 years) represented the highest distribution of the

age group and about 44.1%. The increase in TB disease in adolescence is linked to the increased independence, mobility and risk taking behaviour in this age group[18].

The treatment failure rate decreased with increasing age group, with 0 - 4 years having the worst treatment failure rate, while treatment failure rate increased with age, with 10 - 14 years having the best treatment success rate. This is primarily due to dependence on guidance or care-giver after drug prescription which then facilitate drug adherence at age group (5 - 9) years[18]

Also, in this study, no significant gender difference between children with extra-pulmonary and pulmonary TB was observed. Previous study by Oloyede *et al.*, had shown conformance with the above that there is no significant gender difference between children with extra-pulmonary and pulmonary TB in 2019 as published in World Journal of Biomedical Research.

This study showed that TB patients who are co-infected with HIV recorded more success in their treatment outcomes, that is patients who are HIV positive have more success rate than patients with HIV negative, and the difference between the two was slightly significant. A joint combinational efforts and an integration in treatment care cascade with strong monitoring evaluation of the individual in TB/HIV clinic activities and a biased keen interest in the desired end results could be responsible for this.

In addition, there is no statistical significance in the correlation of age and sex with the TB treatment outcome and this could be as result of low volume of data recorded for statistical presentations. Though, study by Chaves-Torres *et al.*, 2021 and some others had indicates that these factors are associated with unfavorable TB treatment outcomes.

Malnutrition can detrimentally affect the treatment of TB, but there is more to explore regarding the complex interactions between malnutrition and TB. Patients with TB may suffer from malabsorption because of malnutrition and/or comorbidities such as diabetes and human immunodeficiency virus/AIDS[22]. This study revealed a higher percentage of malnourished TB patients affecting the treatment outcome but showed no statistical significant. As stated by Sinha *et al.*, (2018), the WHO has stressed that all patients with active TB should receive individualized nutritional assessment and management, including dietary counseling and nutritional interventions, to prevent treatment failure.

Nutritional status and anti-TB drug exposure should both be assessed and monitored over time, as both nutritional status and pharmacokinetics change[29]. In addition, there is more to be done on the drug adherence status of other TB patients to ensure there is low risk of transmission. This can be achieved by therapeutic drug monitoring (TDM)[30], combined with drug susceptibility testing, to improve outcomes and reduce drug toxicity by tailoring treatment[27]. Exploration of a TDM program for malnourished TB patients may be helpful to assess the relationship between malnutrition and bioavailability of TB drugs.

BCG vaccination significantly reduced the progression to severe TB among children with active TB[24]. Studies have concluded that BCG is a cost-effective intervention against severe childhood TB, one that is only slightly less cost-effective than the treatment of active disease with short-course chemotherapy, especially in southeast Asia, Africa, and the western Pacific region where TB infection rates are high[25]. Thus, BCG vaccination of high-risk populations can potentially contribute to the vision of “zero tuberculosis” deaths in children. This study showed no significant difference on the history of BCG vaccination in treatment outcomes, and thus could be attributed to lack of knowledge about BCG vaccination record by the patient mother or care giver.

It was previously stated scaling up more flexible diagnostic techniques that accommodate a pediatric friendly fixed-dose in diagnosis and treatments are essential for successful treatment outcomes.

Though method of diagnosis had no or little impact in treatment outcomes and the overall objectives unlike in other similar studies. In Nigeria the diagnosis of TB in children is done using the TB score chat and TB score algorithm which is based on clinical findings, family history

of contact with a smear -positive case, x-ray examination, tuberculin skin test (TST), molecular techniques (GeneXpert), TB Quantiferon and culture[29]

V. CONCLUSION

This study assessed the factors responsible for unsuccessful tuberculosis treatments in children (0 - 14 years) in Ede Health Centers, Osun sub-district, osun state, Nigeria, and it was determined that drug adherence status of the respondents showed a major predictor to unsuccessful treatment outcomes. This was primarily due to difficulty of children of this age group understanding and following medication instructions, rely on parental supervision and support for medication administration, face challenges with the taste and formulation of medications, experience side effects and discomfort, struggle with developmental changes in medication needs, and inconsistency routines that makes it harder to adhere to prescribed drug regimes.

RECOMMENDATION

To enhance drug adherence in children, it is recommended to improve education and communication between healthcare providers, parents, and children. This can be achieved by providing clear and simplified instructions for medication administration to parents and developing child-friendly educational resources. Additionally, technology could play a role by incorporating applications and reminder systems to help parents and children remember medication schedules. Collaboration between healthcare professionals, researchers, and policymakers is also crucial to identifying and addressing barriers to drug adherence, as well as implementing evidence-based strategies to improve health outcomes.

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Table 1 Demographic and Clinical Status of Respondents (N=102)

Variable	Frequency	Percentages
Age in Categories		
0-4 years	24	23.5
5-9 years	45	44.1
10-14 year	33	32.4
Sex of respondents		
Male	49	48
Female	53	52
Respondent Nutritional Status		
Malnourished	67	65.7
Normal	35	34.3
History of TB contacts		
Household members	52	51
Other source of contacts	50	49
Respondents HIV status		
HIV positive	23	22.5
HIV negative	79	77.5
Classification of Tuberculosis		
Pulmonary	25	24.5
Extra-pulmonary	77	75.5
History of BCG Vaccine		
Known		
known	48	47.1
Not known	54	52.9
Method of diagnosis		
Clinical	41	40.2
Bacteriological	61	59.8

Mean age is 7.7 $\pm$ 3.4 years with age range of 2- 14 years.

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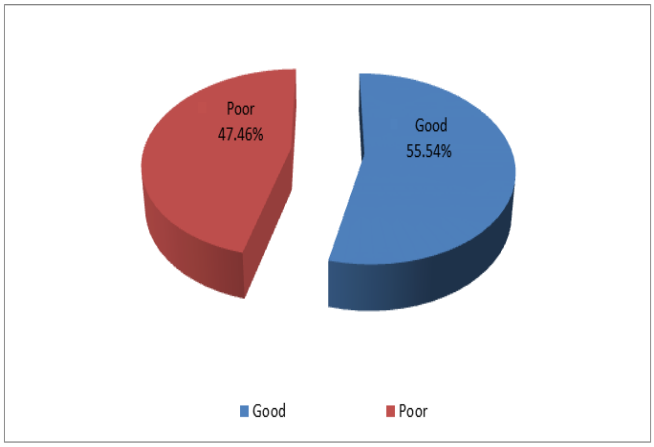

Fig 1 Drug Adherence Status Among Respondents

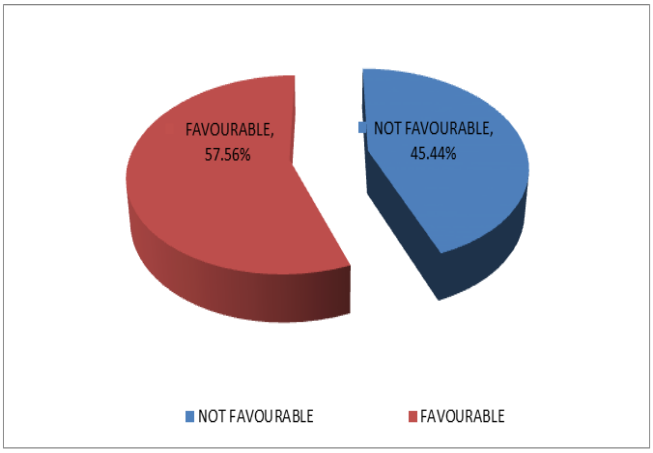

Fig 2 Treatment Out come Among Respondents

Table 2 Association between Demographic and Clinical Status and Treatment Outcome

Variables	**Treatment failure**	**Treatment success**	X^2	DF	OR	P
Age in Categories						
0-4 years	12(50%)	12(50%)	0.64	1	0.53-4.45	0.43
5-9 years	20(44.4%)	25(55.6%)	0.19	1	0.49-3.07	0.66
10-14 year (R)	13(39.4%)	20(60.6%)				
Sex						
Male	22(44.9%)	27(55.1%)	0.023	1	0.49-2.32	0.88
Female	23(43.4%)	30(56.6%)				
HIV Status						
HIV positive	7(30.4%)	16(69.6%)	2.26	1	0.18-1.27	0.13
HIV negative	38(48.1%)	41(51.9%)				
Nutritional Status						
Malnourished	26(38.8%)	41(61.2%)	2.24	1	0.23-1.22	0.14
Normal	19(54.3%)	16(45.7%)				
Drug adherence status						
Good	0(0%)	55(100%)	94.38	1	6.06-81.21	< 0.01
Poor	45(95.7%)	2(4.3%)				
Classification of Tuberculosis						
Pulmonary	10(40%)	15(60%)	0.23	1	0.32-2.0	0.65
Extra-pulmonary	35(45.5%)	42(54.5%)				
History of Contact						
Household contact	26(50%)	26(50%)	1.49	1	0.74-3.59	0.22
Other contacts	19(38%)	31(82%)				
History of BCG vaccination						
Known	23(47.9%)	25(52.1%)	0.54	1	0.61-2.93	0.53
Unknown	22(40.7%)	32(59.3%)				
Method of diagnosis						
Clinical	17(41.5%)	24(58.5%)	0.19	1	0.38-1.86	0.84
Bacteriological	28(45.9%)	33(54.1%)				

Table 3 Predictors of Unsuccessful Treatment Outcome

Variable	**Treatment failure**	**Treatment success**	**X^2**	**AOR**	**CI**	**P**
Drug adherence status						
Good	0(0%)	55(100%)	94.38		6.06-81.21	< 0.01
Poor (R)	45(95.7%)	2(4.3%)				