

1 **Title:** Tuberculosis in Children aged 0-5years at the University of Port Harcourt Teaching
2 Hospital (UPTH), Nigeria - How common is HIV in children with Tuberculosis.

3

4 **Abstract**

5 Background

6 Tuberculosis (TB) is a leading cause of death in young children and the risk of progression from
7 infection to disease is higher in the very young especially among those with Human
8 Immunodeficiency Virus (HIV) infection. This study therefore aimed to examine the method of
9 TB diagnosis and how common HIV infection is among children 0-5years with tuberculosis at
10 the University of Port Harcourt Teaching Hospital (UPTH).

11 **Methods**

12 Information of children aged 0-5years from 1st January, 2011 to 31st December 2014 were
13 retrieved from the TB register of the Directly Observed Treatment Short course (DOTS) clinic of
14 UPTH. This included the age, sex, HIV status, Sputum AFB status, method of diagnosis of
15 tuberculosis and the treatment outcome of the patients.

16 **Results**

17 Three hundred and thirty five children were treated for TB and 179 (53.43%) of them were aged
18 0-5years. There were 93 (51.96%) males and 86 (48.04%) females, with male: female ratio of
19 1.08:1. Their mean age was 1.96 ± 1.45 . The sputum or gastric lavage of 21 (11.73%) were
20 positive for acid fast bacilli (AFB). The common method of TB diagnosis was clinical/
21 radiological method and this constituted 158(88.27%) of the patients with TB. Ninety (50.28%)
22 children with TB were less than one year of age and there was no statistical significant
23 relationship between age and method of TB diagnosis ($\chi^2 = 2.78$, $p = 0.249$). More males
24 93(51.96%) than females 86(48.04%) had TB but more females 13(61.90%) than males
25 8(38.10%) were AFB positive, however, these were not statistically significant. ($\chi^2 = 1.26$ p -
26 value=0.262). Seventy two (40.22%) of the children with TB were HIV positive. One hundred
27 and thirty five (75.42%) of the children recovered following treatment while 44(24.58%) were
28 referred to Dots centres closest to the patients. No child died.

29 **Conclusion**

30 The prevalence of TB among under-fives especially among infants is high. Clinical and
31 radiological methods were the common method of TB diagnosis. HIV prevalence among
32 children with TB was lower than expected by the authors, however, the treatment outcome was
33 good. Re-training of clinicians to improve their expertise on clinical diagnosis of TB and a more
34 in depth search of TB in the community among children 0-5years who are HIV sero negative
35 with persistent cough is advocated.

36 Key words: Tuberculosis, children 0-5 years, HIV

37 **Introduction:**

38 Worldwide, tuberculosis (TB) is the ninth leading cause of death, and the leading cause from a
39 single infectious agent (above HIV/AIDS) and millions of people continue to fall sick with the
40 disease each year. ¹ In 2017, TB caused an estimated 1.3 million deaths (range, 1.2–1.4 million)
41 among HIV-negative people. ¹

42 Human immunodeficiency Virus (HIV) disease continues to be a serious health issue worldwide
43 especially in sub-Saharan Africa. There are about 36.9 million people living with HIV around the
44 world. Approximately 1.8 million children worldwide are living with HIV or Acquired immune
45 deficiency syndrome (AIDS) with over 90% of them living in sub-Saharan Africa. ²

46 Tuberculosis (TB) and HIV have been closely linked since the emergence of AIDS. It is not
47 surprising to find that many children with tuberculosis are HIV positive, same also hold that
48 many children with HIV infection have tuberculosis especially in areas where tuberculosis is
49 endemic. Worldwide, TB is the most common opportunistic infection affecting HIV-seropositive
50 individuals and it remains the most common cause of death in patients with AIDS. ^{3, 4} HIV
51 infection has contributed to a significant increase in the worldwide incidence of TB. ^{3, 4} and the
52 reported sero-prevalence of HIV in children with TB in countries with moderate to high
53 prevalence ranges from 10% to 60%. ⁵⁻⁸

54 **This HIV/PTB co-infection is multi factorial** in aetiology but has been commonly postulated to
55 be due to the fact that HIV infection causes significant immunosuppression causing a flare up of
56 tuberculosis disease which prior to now remained quiescent. By producing a progressive decline
57 in cell-mediated immunity, HIV alters the pathogenesis of TB, greatly increasing the risk of
58 disease from TB in HIV-coinfected individuals and leading to more frequent extra pulmonary

59 involvement, atypical radiographic manifestations, and paucibacillary disease, which can impede
60 timely diagnosis.

61 Although HIV-related TB is both treatable and preventable, **incidence continues to climb** in
62 developing nations where HIV infection and TB are endemic and resources are limited.
63 Interactions between HIV and TB medications, overlapping medication toxicities, and immune
64 reconstitution inflammatory syndrome (IRIS) complicate the cotreatment of HIV and TB.

65 In an infected child, risk of progression to disease is multifactorial and this includes age,
66 nutritional and immune status, genetic factors, magnitude of initial infection, virulence of the
67 organism, and maturity of immune response.⁵

68 Studies on the natural history of TB conducted before the chemotherapy era, revealed that age is
69 a strong determinant of which children will progress to disease following infection. Infected
70 infants have a 50% risk of progression to disease and this progressively declines to a 2% risk in
71 children 5-10 years of age.⁹⁻¹² Also, young children are more likely to develop severe forms of
72 TB, like military TB and TB meningitis. Despite these facts there is paucity of study in TB in
73 children 0-5years especially in South-South Nigeria. It is therefore pertinent to study TB in the
74 younger child.

75 This study therefore examined TB in children aged 0-5years, method of TB diagnosis in this age
76 group, age and sex correlates of TB, Treatment outcome and especially, how common HIV
77 infection is among children 0-5years with tuberculosis at the University of Port Harcourt
78 Teaching Hospital (UPTH). It also tries to answer the question “Is HIV the primary risk factor
79 for TB or are there other underlying risk factors to tuberculous infection in young children at the
80 UPTH?”

81 **Methods:**

82 This was a retrospective study carried out **over a one Month period** from the 1st to 31st October
83 2018. The National TB register and the Acid Fast Bacilli (AFB) register at the Directly Observed
84 Treatment Short course (DOTs) clinic of the university of Port Harcourt Teaching hospital
85 (UPTH) were the data source. The DOTs clinic follows the National Tuberculosis and Leprosy
86 control programme and the WHO directly observed treatment short course strategy. Relevant
87 information on all children 0-5years with tuberculosis **were retrieved**. Information retrieved
88 included the age, sex, HIV status, method of diagnosis of tuberculosis and the treatment outcome
89 of the patients. Diagnosis of TB was based on presence of AFB on Zeil Nelson stain of sputum
90 specimen (AFB-positive), clinical and radiological diagnosis. Children diagnosed with TB
91 received Rifampicin, Isoniazid, Ethambutol and Pyrazinamide for 2 months, followed by 4
92 months of Rifampicin and Isoniazid. Obtained data was entered into an excel data sheet and
93 analysed using SPSS version 20 and presented as descriptive statistics and proportions. Chi-
94 square test was used to show the association between method of TB diagnosis and age, sex and
95 HIV status. The test of statistical significance was at p-value <0.05.

96 **Results:**

97 Three hundred and thirty five children aged 0- 18 years were treated in the DOTS clinic of the
98 University of Port Harcourt Teaching Hospital over a 4 year period from 1st January 2011 to 31st
99 December 2014. Children 0-5years made up 179 (53.43%) of the children treated for TB within
100 the period. There were 93 (51.96%) males and 86 (48.04%) females, with male: female ratio of
101 1.08:1. Their mean age was 1.96 ±1.45. Ninety (50.28%) were aged 0-1years, 53 (29.61%) were
102 **>1 to 3 years** and 36 (20.11%) were **aged >3 to 5 years**. The sputum or gastric lavage of twenty
103 one children were positive for acid fast bacilli (AFB) giving an AFB-positive prevalence of

104 11.73%. Table 1. The common method of TB diagnosis was clinical/ radiological method and
105 this constituted 158 (88.27%) of the patients with TB. Table 1. More of the children 90(50.28%)
106 with TB were less than one year of age and there was no statistical significant relationship
107 between age and method of TB diagnosis ($\chi^2 = 2.78, p= 0.249$). Table 1. Table 1 also shows
108 that more males 93(51.96%) than females 86(48.04%) had TB and also that more females
109 13(61.90%) than males 8(38.10%) were AFB positive, however, these was not statistically
110 significant. ($\chi^2 = 1.26$ p-value=0.262). Seventy two (40.22%) of the children with TB were HIV
111 positive. Eight (38.10%) out of HIV positive children were AFB positive. There was no
112 statistical significant relationship between TB and HIV sero-positivity. (p=0.832) Table . The
113 mean duration of treatment with anti-TB drugs was 6 months. One hundred and thirty five
114 (75.42%) of the children recovered following treatment while 44(24.58%) were referred to Dots
115 centres closest to the patients. No child died.

116 **Discussion:**

117 This study show that more (56.11%) of the children who were treated for TB, were aged 0-
118 5years This is in tandem with other studies.^{12, 13} At this age, due to poor immunity in children,
119 progression from infection to active disease is very high compared to the older children.¹³ This
120 age group must be carefully searched out and screened for TB in the community in any case of
121 adult TB. Tuberculosis in children is mainly due to failure of TB control in adults and therefore
122 exists in the shadow of adult TB.

123 Over 80% of the children were AFB negative with an AFB prevalence rate of 16.3%. The low
124 AFB rate in this study is common in children and have been reported in other studies.¹⁴This is
125 partly why diagnosis of TB in children is difficult especially in settings where this is the only
126 confirmatory laboratory screening tool for TB. This is worse in the under-fives as many children

127 with TB have primary TB which is not usually associated with cavitatory lesions. However, this
128 age tend to have more severe forms of the disease like milliary TB and TB meningitis and yet are
129 more difficult to diagnose with available diagnostic tool in resource limited settings. Lack of
130 resources makes accurate diagnosis of TB cases more difficult, and in many countries, TB
131 control programs rely almost exclusively on sputum microscopy for the diagnosis of TB, as part
132 of WHO TB control strategies. This means that TB in children is both undiagnosed and
133 underreported especially in resource limited settings.

134 The common method of TB diagnosis was by clinical evaluation and use of chest radiograph.
135 The low diagnostic yield of AFB makes it an unreliable method in children. It therefore requires
136 a high index of suspicion and clinical expertise to make a diagnosis of TB in this age group,
137 meanwhile this is the age group that is froth with severe disease and who are more likely to
138 succumb to the disease if TB is not detected early and treatment commenced. Despite the
139 endemicity of TB in this part of the world, the paucity of physicians with the clinical expertise
140 for its diagnosis makes it more worrisome. Tuberculosis is a significant childhood problem but is
141 neglected because many cases are usually smear negative and therefore not considered a major
142 contribution to its spread. However, children with latent infection become the reservoir for future
143 transmission following disease reactivation in adulthood, fueling future epidemics. TB diagnosis
144 requires clinical expertise and early screening of children who presents with worsening and
145 unrelenting cough lasting for 2 weeks or more with associated fever, weight loss or poor weight
146 gain and a positive history of contact with an adult case of TB. Screening includes; Tuberculin
147 sensitivity Testing (TST)-Mantoux test, chest radiograph, sputum for Acid fast bacilli (AFB)
148 using the Zeil Nelson stain, Sputum culture and more recently, using the polymerase chain
149 reaction tests such as Xpert MTB/RIF screening for mycobacterium TB (MTB) detection and

150 Rifampicin and Isoniazide (INH) drug resistance. Sputum for AFB using the Zeil Nelson stain
151 for detection of AFB is diagnostic of TB but its yield in children is low due to their
152 paucibacillary nature and difficulties in specimen collection. The more reliable screening tool
153 and the first line WHO screening tool for TB the Xpert MTB/RIF screening which has been recently
154 introduced in the researchers study area, was not rife when the subjects for this study were being
155 screened. This test is an important advance in rapid detection of TB disease and detection of drug
156 resistance. Studies have shown that it is much more sensitive than microscopy, with sensitivity being
157 reported from 75 to 90% on sputum samples and nearly 70% on gastric aspirates, with comparable
158 performance in HIV positive and HIV negative children.^{15,16} However, despite its high sensitivity, Xpert
159 MTB/RIF test cannot be used to rule out TB, as substantial proportion of children with negative test had
160 positive MTB cultures. MTB culture remains a necessary diagnostic tool. The current use of only sputum
161 or gastric aspirate for this screening in the researchers study area also limits its usefulness in children
162 considering the rigors and invasive nature of gastric lavage. Making available the use of less or non
163 invasive methods of sample collection, such as naso-pharyngeal aspirates (NPA) and stool samples for a
164 PCR-based diagnostic test is highly advocated.^{17,18}

165 More than half 90(50.28%) of all under-fives who were treated for TB were infants. This
166 prevalence decreased with increasing age in concordance with other studies.^{13, 19} It is not
167 surprising why more infants than other under-fives are diagnosed with TB. Tuberculosis in
168 children usually follow an adult source and since many of these infants are still in close contacts
169 with the adult source- parents, caregivers and relatives, transmission of the disease among them
170 is high. This close contact with the adult source most likely increases their contact with
171 aerosolized tuberculous droplets and coupled with their low immunity increases their
172 susceptibility to the disease. Also, in TB endemic areas such as ours, sociodemographic factors

173 such as overcrowding and a predominant young population there is increased exposure of
174 children to adults with pulmonary TB.^{20,21}

175 This study showed that among under-fives, TB was commoner in males, however this was not
176 statistically significant. Mayank et al in India reported a male: female ratio of 1.8:1 among
177 children less than 8years.¹⁹ Also, Blount et al reported a higher male prevalence among males in
178 a Vietnam study.²² Males may be more predisposed due to a yet unidentified genetic risk or the
179 fact that parents have a better health seeking behaviour for their male children especially in our
180 part of the world. Other studies have also reported a female predominance of TB cases among
181 children but female predominance in these studies were among older children aged 11years and
182 above.²³⁻²⁶ This age group has been found to have a higher prevalence of TB due to hormonal
183 and reproductive changes in this age group. Generally however, there is no significant difference
184 in sex distribution of TB in young children as was found in this study. The age range of 5-
185 14 year is often called the “favored age,” because in all human populations this group has the
186 lowest rate of tuberculosis disease.²⁷ Among adults however, two thirds of TB cases occur in
187 men and globally, men are significantly more at risk of contracting and dying from TB than
188 women.^{27,28}

189 Only 72(40.22%) of the children with TB were HIV seropositive in this study. This finding is
190 within the WHO estimate of 10-60% of HIV prevalence among children with TB in countries
191 with moderate to high prevalence of TB.⁷ Other studies have shown prevalence ranging from
192 16-56% of HIV among children with TB.²⁹⁻³⁵ However, a retrospective review of TB
193 notifications in the Kilimanjaro region of Kenya showed that of the minority of children who
194 were tested for HIV infection, 82% tested positive. The HIV epidemic is a key factor behind the
195 resurgence in TB incidence worldwide and HIV is the pre-eminent risk factor for the

196 development of TB. However, Nearly 60% of the children with TB in this study were HIV
197 negative. This means that among under-fives, there are more factors other than HIV that
198 increases TB susceptibility and for effective TB control in children, these must be elucidated and
199 dealt with. Though factors such as poverty, overcrowding, poor living conditions and the
200 nutritional status of the child were not part of this study design, they may be strong and
201 contributory factors to high prevalence of TB in under-fives. These factors cannot be overlooked
202 by any coordinated TB control strategy if a lasting and holistic solution is desired.

203 About three quarter (75.42%) of these children were treated successfully for TB in this study
204 while the remaining one quarter were referred to the health facilities closest to them for
205 continued treatment. This high successful treatment outcome may be due to early presentation of
206 these children to the DOTs clinic and is similar to findings in a Kampala study where the success
207 rate was 78% in 2011 and this increased to 83% in 2015. ³⁶ Adejumo et al also reported a a
208 similar treatment success rate of 79.2% in TB/HIV-negative children and 73.4% in TB/HIV
209 positive. ³⁷

210 As highlighted earlier, the risk of progression of TB to disease in an infected child is
211 multifactorial and includes other factors such as the age of the child, nutritional status, genetic
212 factors, magnitude of initial infection, virulence of the organism, and maturity of immune
213 response.⁵ TB control especially among this vulnerable group must therefore involve a holistic
214 approach with strategies to address these factors.

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218 **Conclusion:**

219 It is concluded that the prevalence of TB among under-fives especially among infants is high and
220 that the AFB prevalence is low. HIV prevalence among children with TB was lower than
221 expected by the authors, however, the treatment outcome was good. Re-training of clinicians in
222 this region to improve their expertise on clinical diagnosis of TB and a more in depth search of
223 TB in the community among children 0-5years who are HIV sero negative is advocated.

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355 **Table 1:** Method of diagnosis of TB and its association between Age distribution and sex

Age group	Method of diagnosis		Total	Chi-square (X ²) (p-value)
	AFB- Positive	Clinical diagnosis		
≤1	8 (38.10)	82 (51.90)	90 (50.28)	2.78 (0.249)
2-3	6 (28.57)	47 (29.75)	53 (29.61)	
4-5	7 (33.33)	29 (18.35)	36 (20.11)	
TOTAL	21	158	179	
SEX				
Male	8 (38.10)	85 (53.80)	93 (51.96)	1.26 (0.262)
female	13 (61.90)	73 (46.20)	86 (48.04)	
TOTAL	21	158	179	

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358 No statistical significant association between age, sex and method of TB diagnosis. ($p>0.05$).359 **Table 2: Distribution of Age, Sex, AFB status, HIV status, treatment outcome of TB cases**
360 **in children 0-5years over the 4 years (2011-2014)**

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Characteristics	2011 (n=48) Freq (%)	2012 (n=56) Freq (%)	2013 (n=35) Freq (%)	2014 (n=40) Freq (%)	2011-2014 (n=179) Freq (%)
Age					
Mean \pm SD	2.06 \pm 1.60	1.55 \pm 1.24	2.26 \pm 1.41	2.18 \pm 1.47	1.96 \pm 1.45
Age group					
≤ 1	28 (58.33)	32 (57.14)	13 (37.14)	17 (42.50)	90 (50.28)
>1-3	7 (14.58)	18 (32.14)	14 (40.0)	14 (35.0)	53 (29.61)
>3-5	13 (27.08)	6 (10.71)	8 (22.86)	9 (22.50)	36 (20.11)
Sex					
Male	30 (62.50)	23 (41.07)	17 (48.57)	23 (57.50)	93 (51.96)
Female	18 (37.50)	33 (58.93)	18 (51.43)	17 (42.50)	86 (48.04)
AFB					
Positive	5 (10.42)	8 (14.29)	4 (11.43)	4 (10.0)	21 (11.73)
Negative	43 (89.58)	48 (85.71)	31 (88.57)	36 (90.0)	158 (88.27)
HIV					
Positive	15 (31.25)	29 (51.79)	16 (45.71)	12 (30.0)	72 (40.22)
Negative	33 (68.75)	27 (48.21)	19 (54.29)	28 (70.0)	107 (59.78)
Treatment Outcome					
Treated	39 (81.25)	42 (75.0)	29 (82.86)	25 (62.50)	135 (75.42)
Referred	9 (18.75)	14 (25.0)	6 (17.14)	15 (37.50)	44 (24.58)
Died	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

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