A retrospective assessment of rifampicin resistance in paediatric tuberculosis in a tertiary hospital in south west Nigeria

Otaigbe, I.I.,[1,2], Elikwu, C.J.,[1,2], Oluwole, T.O.,[1,2] Ogunlolu, A.E.,[1], Oseni, O.E.,[1], Bello, O.D.,[1] Olayiwola, P.O.[1], Dike-Israel, V.C[1], Atuk, G.J.[1]

[1]Department of Medical Microbiology, School of Basic Clinical Sciences, Benjamin Carson (Snr) College of Health & Medical Sciences, Babcock University, Ilishan-Remo, Nigeria.
[2]Department of Medical Microbiology, Babcock University Teaching Hospital, Ilishan-Remo, Nigeria.

Article Info

Article type:
Original Article

Article history:
Received: September 17, 2023
Accepted: October 31, 2023
Published: February 16, 2024

Keywords:
Tuberculosis, Rifampicin Resistance, Pediatric

Corresponding author:
Otaigbe, I.I.
ORCID-NO: https://orcid.org/0000-0003-3140-1205
otaigbei@babcock.edu.ng

The article can be accessed at:
www.rjhs.org

http://dx.doi.org/10.4314/rejhs.v12i1.6

Abstract

Objectives: Children infected with tuberculosis, including drug resistant tuberculosis serve as reservoirs for Tuberculosis (TB) and as indicators of recent or ongoing transmission in the community. The aim of this study was to evaluate the prevalence of rifampicin resistance in paediatric tuberculosis in Babcock University Teaching Hospital, Ilishan Remo, Ogun State, Nigeria
Methodology: This was a retrospective study that involved a review of medical microbiology laboratory records to analyze GeneXpert results of sputum samples obtained from pediatric patients with tuberculosis between January 2017 and March 2022. A convenience sampling method was used to select cases who met the study's inclusion criteria until the sample size was attained.
Results: The medical laboratory records of 1046 subjects were analyzed in this study of which 556 (53.2%) were males. The mean age of all the patients was 10.77±4.38 years and majority of the respondents 445 (42.5%) were in the age group 11-15 years. Fifty patients (4.8%) had positive GeneXpert results of which 3 (6.0%) were Rifampicin resistant.
Conclusion: In order to lower the burden of TB globally more efforts should be made to reduce paediatric TB.

Une évaluation rétrospective de la résistance à la rifampicine dans la tuberculose pédiatrique dans un hôpital tertiaire du sud-ouest du Nigéria

Résumé

Objectif de l'étude: Les enfants infectés par la tuberculose, y compris la tuberculose pharmaco résistante, servent de réservoirs de tuberculose (TB) et d'indicateurs de transmission récente ou en cours dans la communauté. Le but de cette étude était d'évaluer la prévalence de la résistance à la rifampicine dans la tuberculose pédiatrique à l'hôpital universitaire Babcock, Ilishan Remo, État d'Ogun, Nigéria.
Méthode de l'étude : Il s'agissait d'une étude rétrospective qui impliquait un examen des dossiers de laboratoire de microbiologie médicale pour analyser les résultats GeneXpert d'échantillons d'expectorations obtenus auprès de patients pédiatriques atteints de tuberculose entre janvier 2017 et mars 2022. Une méthode d'échantillonnage de commodité a été utilisée pour sélectionner les cas répondant aux critères d'inclusion de l'étude. Critères jusqu'à ce que la taille de l'échantillon soit atteinte.
Résultat de l'étude : Les dossiers de laboratoire médical de 1 046 sujets ont été analysés dans cette étude, dont 556 (53,2 %) étaient des hommes. L'âge moyen de tous les patients était de 10,77 ± 4,38 ans et la majorité des répondants, 445 (42,5 %), appartenaient à la tranche d'âge de 11 à 15 ans. Cinquante patients (4,8 %) ont eu des résultats GeneXpert positifs, dont 3 (6,0 %) étaient résistants à la rifampicine.
Conclusion : Afin de réduire le fardeau de la tuberculose à l'échelle mondiale, des efforts supplémentaires doivent être déployés pour réduire la tuberculose pédiatrique.

INTRODUCTION

Tuberculosis (TB) is a global health security challenge which annually accounts for about 10 million infections and 1.5 million deaths globally (1,2). TB is prevalent in low and middle income countries (LMICs) and about half of the people with TB are found in 8 countries: Bangladesh, China, India, Indonesia, Nigeria, Pakistan, Philippines and South Africa. In recent times TB has become a leading cause of antimicrobial resistance (AMR) (3-9).

Tuberculosis is caused by *Mycobacterium tuberculosis* (MTB) an aerobic, non-spore-forming, non-motile, slow growing acid-fast bacillus (10-17). No age group is speared the scourge of Tb however adult TB has typically attracted more research and policy making than paediatric tuberculosis (18-21). The data cocncerning paediatric TB are dismal as it is estimated that in 2021 there were about about 10.6 million cases of tuberculosis, globally; about 9.4 million of these cases were adults while 1.2 million were children and about 14% of these children died. (1, 5, 18-27).

Pediatric TB is a significant problem in Africa (28-32). Seventeen of the 30 high TB burden countries in the world are found in Africa (29, 31, 33). Paediatric TB in Africa accounts for about 322,000 annual cases (or a third of the global TB burden) (31). Nigeria has the highest burden of TB in Africa and is ranked 6th among high TB burden countries globally (33-40). In Nigeria, it is reported that about about 6000 cases of paediatric TB occurred in 2015 representing 6% of the estimated global burden of paediatric TB cases (30).

More importantly, infected children are a marker of recent or ongoing transmission of TB in a community (41-47). They also serve as reservoirs for TB, in addition to being likely TB cases if not diagnosed or treated (41-47). Therefore an evaluation of the burden of paediatric TB may also help to determine the efficiency of TB control programs in communities and nations (19, 28). However, in Africa and many low and middle income countries with weak health systems paediatric TB is grossly under-reported, poorly diagnosed and inadequately managed due to lack of access to care, poor specimen collection and inadequate diagnostic facilities (30, 31, 48-52) . In addition, poor disease notification and a paucity of research regarding paediatric TB makes it difficult to properly estimate the burden of paediatric tuberculosis and subsequently design effective strategies to curb the problem of paediatric TB (19,43,44,48,52,53).

Ultimately the global health challenge posed by TB has become exacerbated by the emergence of antimicrobial resistance in both adult and paediatric TB (54-56). The roll out of the GeneXpert machine in the management of TB has made it possible to rapidly diagnose TB and also identify drug resistance (57-61). In the past the diagnosis of TB, particularly in low and middle income countries (LMICs) has involved microscopy using the Ziehl Neelsen stain (61-64). More elaborate techniques like culture and drug susceptibility are expensive and beyond the technical and financial capacities of laboratories in many LMICs (62). However the introduction of molecular techniques (such as GeneXpert) in the diagnostic ecosystem of tuberculosis has made it possible to implement and scale up TB diagnosis in resource constrained settings globally (61-64). A major advantage of Genexpert is its rapid turn around time (< 2hours) in contrast to culture and drug susceptibility which may take weeks to conduct (61-64). In addition GeneXpert is able to identify Rifampicin (RIF) resistance and therefore allows expedite and optimized decision-making in TB care (61-64).

Isoniazid, rifampicin, pyrazinamide, and ethambutol are the four first-line antimicrobials often used in the standard treatment for tuberculosis (65,66). Unfortunately, over the course of treatment, resistance to these medications may arise (65,66). Point mutations in the beta subunit of RNA polymerase (rpoB) gene that determine RIF resistance are the main cause of rifampicin resistance (67-70).Rifampicin-resistant tuberculosis (RR-TB; TB resistant to at least rifampicin) or multidrug-resistant tuberculosis (MDR-TB; RR-TB with documented resistance to isoniazid) affects roughly 2 million children worldwide, and 25,000–30,000 children are believed to contract RR-TB disease each year (71-72). RIF-resistant TB in children has been the subject of continuous research globally. A study done in China between January 2013 and December 2015 showed rifampicin resistance in paediatric patients was 6.9 percent (73) Another study conducted in Ethiopia revealed that 9.9% of all TB confirmed cases and 7.9% of paediatric TB patients were rifampicin resistant (74).

The growth of drug-resistant strains and the rise in the prevalence of pediatric tuberculosis are important public health issues, particularly in developing nations like Nigeria with high burdens of TB (29, 40,75). However, in contrast

to adult TB, there is a paucity of data in on the true burden of rifampicin resistance in paediatric TB (18-21). The aim of this study therefore was to evaluate the prevalence of rifampicin resistance in paediatric tuberculosis in the hospital.

MATERIALS AND METHODS

Study site

The study was conducted in the Department of Medical Microbiology, Babcock University Teaching Hospital, Ilishan-Remo, Ikenne Local Government, Southwest Nigeria. The hospital is a 240-bed tertiary hospital involved in teaching, research and specialist services. It serves Ogun State and neighboring States in southwest Nigeria.

Study Design

This retrospective study involved a review of medical microbiology laboratory records to analyze GeneXpert results of sputum samples obtained from pediatric patients with tuberculosis between January 2017 and March 2022. The study did not involve any contact with pediatric patients. Data collection involved the use of a data collection tool specifically designed for this study. Data collected included age, gender, presence of rifampicin resistance, HIV status, site of infection and type of specimen collected. All data were anonymized to ensure patient confidentiality. Patients were apportioned study identification numbers. Informed consent was not deemed necessary in this study because there was no contact with patients as it was a retrospective study.

Study inclusion criteria

The inclusion criteria included all patients age less than 18 years who had a diagnosis of tuberculosis and had undergone Gene Xpert testing between January 2017 and March 2022. All patients who did not meet this criteria were excluded from the study.

Sample size and sampling method

A convenience sampling method was used to select cases who fulfilled the study's inclusion criteria and to determine the sample size. The laboratory records were carefully evaluated to identify all cases who met the inclusion criteria. A total number of 1046 patients fulfilled the inclusion criteria.

Data analysis

Data analysis was done using IBM SPSS software version 20.0 Descriptive statistics were used to analyze results based on frequency, gender, age, rifampicin resistance and HIV status. Bivariate analysis was done using the Chi square test and P values < .05 were considered significant.

Ethical approval

Ethical approval for this study was obtained from Babcock University Health Research and Ethics Committee (BUHREC No 693/22). As data were retrospectively obtained from the laboratory records and did not involve contact with patients nor recruitment of patients, informed consent was not deemed necessary. However, privacy and confidentiality of patients' data were protected in accordance with the Declaration of Helsinki.

RESULTS

In the 5-years, three months period under consideration, a total of 1046 paediatric patients submitted sputum samples to the medical microbiology laboratory for GeneXpert testing of which 556 (53.2%) were males. The mean age of all the patients was 10.77 ± 4.38 years and majority of the patients (445;42.5%) were in the age group 11-15 years (Table 1).

Fifty patients (4.8%) had positive GeneXpert results of which 3 (6.0%) were Rifampicin resistant. Thirty nine (3.7%) of the 1046 patients were HIV positive (Table 2). Bivariate analysis conducted showed that majority (34.0%) of TB cases were seen in age group 16-17 years with patients <1 year being the least affected (4.0%) p=0.001 (Table 3). Majority of TB cases were seen in females (56.0%) p= 0.679 (Table 3). The majority (43.6%) of HIV cases were seen in the age group 11-15 years with the least seen in <1 year (0.0%) p=0.005. HIV was more common in females (53.8%) p=0.296 (Table 4). and the prevalence of HIV-TB co-infection was 4% p=0.671 (Table 5). No patient (0%) with Rifampicin resistance was HIV positive (Table 6) and all three patients (100%) with rifampicin resistance were males (Table 7).

DISCUSSION

The prevalence of tuberculosis among children in this study was 4.8%, which is higher than the findings reported in Zambia (1.58%) (76), Mozambique (1.65) (77), South Africa (1.3%) (78), and lower than reports from Zimbabwe (8.7%) (79), Uganda (10%) (80), Ethiopia (13.6%) (81), Bangladesh (32.97%) (82). However our findings were lower than studies done in Nigeria, in which the prevalence

of tuberculosis, following genexpert testing, was 19.8% (83) and 27.8% (84) respectively. The reason for variation might be due to the difference in the prevalence of tuberculosis in the general population, methods of sputum sample collection and diagnosis. While we used results of only Xpert MTB/RIF assay, the other studies applied microscopy and culture (76-84).

In this study, HIV cases were seen most in the age group 11- 15 years (43.6%) and no cases were seen below the age of 1 year. This is statistically significant (P = 0.005). The amount of HIV cases in females (53.8%) was more than the number of cases in males (46.2%) but the difference is insignificant (P = 0.296). The prevalence of tuberculosis among HIV positive children was 4%, but 36% among HIV negatives while the prevalence of TB among patients with an unknown HIV status was 60% (30). However, data did not show a statistically significant association between pulmonary tuberculosis and HIV infection (P = 0.01). According to the study, the odds of acquiring pulmonary tuberculosis among HIV negative children was 9 times higher than HIV positives but the difference is not significant.

The presence of rifampicin-resistant TB is a serious public health issue since children can independently become infected in the community (81, 85). Therefore, molecular typing of isolates from pediatric TB patients and their possible contacts is crucial to identifying the source of transmission (86, 87). The prevalence of rifampicin-resistant pulmonary tuberculosis infection in this study was 6.0%, which is higher than the findings reported in South Africa (0.66%) (88). However, it is lower than the findings reported in Ethiopia (7.9%) (81), China (30%) (89) and Nigeria (6.4%) (83). The difference could be the result of variations in study populations, study settings, study designs, and sociocultural practices. It is necessary to improve access to TB care, including public awareness and enlightenment (90, 91). Increased vaccine coverage is also advised to reduce the occurrence of paediatric tuberculosis (92).

CONCLUSION

The prevalence of rifampicin resistance among the subjects who tested positive for childhood tuberculosis was 6%. Appropriate measures including testing, isolation and treatment should be invested into the early detection and prevention of paediatric rifampicin resistant tuberculosis (93). Further studies are required to 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 (30,94). It must be stated that Genexpert is not a stand alone in the diagnostic ecosystem of TB (95, 96). However, challenges with scaling up (such as poor power supply) have made it difficult to improve coverage of the device in many countries (97). As such many countries still rely on case management and sputum microscopy which have low indexes of diagnosis for TB in children (98-100). Culture is expensive and novel methods such as next generation sequencing are clearly out of the reach of many TB endemic countries with weak and poorly funded health systems (101,102). The way forward lies in improving surveillance efforts, early detection and treatment of paediatric TB in Nigeria and other low and middle income countries (5, 30, 48). A major limitation of this study was that it was laboratory based and not integrated with clinical records of patients.

Conflicts of interest: None

REFERENCES

1. Medecins Sans Frontières (MSF). MSF Medical Guidelines. Global Burden of Tuberculosis. https://medicalguidelines.msf.org/en/viewport/TUB/english/1-7-global-burden-of-tuberculosis-20320195.html#footnote2_aee0dgi
2. World Health Organization. Global Tuberculosis Report 2021. Geneva: World Health Organization; 2021. https://apps.who.int/iris/rest/bitstreams/1379788/retrieve
3. World Health Organization. Tuberculosis. World Health Organization. 2020. https://www.who.int/health-topics/tuberculosis#tab=tab_1.
4. Foo C, Shrestha P, Wang L, Du Q, García-Basteiro AL, Abdullah AS, Legido-Quigley H. Integrating tuberculosis and noncommunicable diseases care in low- and middle-income countries (LMICs): A systematic review. PLoS Med. 2022;19(1):1-42. https://doi.org/10.1371/journal.pmed.1003899.
5. World Health Organization. Tuberculosis. 2023. https://www.who.int/news-room/fact-sheets/detail/tuberculosis
6. Abou JGJ, Garcia BI, Nguhiu P, Siroka A, Palmer T, Goscé L, et al. Allel K, Sinanovic E, Skordis J, Haghparast-Bidgoli H. National tuberculosis spending efficiency and its

associated factors in 121 low-income and middle-income countries, 2010-19: a data envelopment and stochastic frontier analysis. Lancet Glob Health. 2022 ;10(5):e649-e660. https://doi.org/10.1016/S2214-109X(22)00085-7

7. Chowdhury K, Ahmad R, Sinha S, Dutta S, Haque M. Multidrug-Resistant TB (MDR-TB) and Extensively Drug-Resistant TB (XDR-TB) Among Children: Where We Stand Now. Cureus. 2023;15(2):e35154. https://doi.org/10.7759/cureus.35154
8. University of Liverpool Centre of Excellence for long-acting therapeutics.Reducing the burden of TB in the world's most in need communities with long-acting injectables. 2022. https://www.liverpool.ac.uk/centre-of-excellence-for-long-acting-therapeutics/blog/longevity-blog/reducing-the-burden-of-tb/
9. World Health Organization. Global tuberculosis report 2022. 2022 https://www.iom.int/sites/g/files/tmzbdl486/files/documents/2023-03/Global-TB-Report-2022.pdf
10. Jilani TN, Avula A, Zafar Gondal A, Siduqui AH. Active Tuberculosis. In: StatPearls. Treasure Island, Florida: StatPearls Publishing; p. 1-25. https://www.ncbi.nlm.nih.gov/books/NBK513246/
11. Dunn JJ, Starke JR, Revell PA. Laboratory Diagnosis of Mycobacterium tuberculosis Infection and Disease in Children. J Clin Microbiol. 2016;54(6):1434-1441. https://doi.org/10.1128/JCM.03043-15
12. Herchline ET, Amorosa JK. Tuberculosis. Medscape. 2023. https://emedicine.medscape.com/article/230802-overview
13. Nardell EA. Tuberculosis. MSD Manuals Professional Version. 2022 https://www.msdmanuals.com/professional/infectious-diseases/mycobacteria/tuberculosis-tb
14. Boston University, Research Occupational Health Program. Mycobacterium tuberculosis agent Information sheet. https://www.bu.edu/research/ethics-compliance/safety/rohp/agent-information-sheets/mycobacterium-tuberculosis-agent-information-sheet/
15. Herman P, Fauville-Dufaux M, Breyer D, Van Vaerenbergh B, Pauwels K, Thi CDD, Sneyers M, Wanlin M, Snacken R, Moens W. Biosafety Recommendations for the Contained Use of Mycobacterium tuberculosis Complex Isolates in Industrialized Countries. Scientific Institute of Public Health, Division of Biosafety and Biotechnology. 2006. https://www.biosafety.be/sites/default/files/mtub_final_dl.pdf
16. Government of Canada.Pathogen Safety Data Sheets: Infectious Substances – Mycobacterium tuberculosis and Mycobacterium tuberculosis complex. https://www.canada.ca/en/public-health/services/laboratory-biosafety-biosecurity/pathogen-safety-data-sheets-risk-assessment/mycobacterium-tuberculosis-complex.html
17. Jessenius Faculty Of Medicine in Martin. Comenius University. Bratislava, Slovakia. Microbiology 2 Practical: Mycobacteria. https://www.jfmed.uniba.sk/fileadmin/jlf/Pracoviska/ustav-mikrobiologie-a-imunologie/distancna_vyuka/VLa_mycobacteria.pdf
18. Newton SM, Brent AJ, Anderson S, Whittaker E, Kampmann B. Paediatric tuberculosis. Lancet Infect Dis. 2008;8(8):498-510. https://doi.org/10.1016/S1473-3099(08)70182-8
19. Maphalle LNF, Michniak-Kohn BB, Ogunrombi MO, Adeleke OA. Pediatric Tuberculosis Management: A Global Challenge or Breakthrough<Children (Basel). 2022 ;9(8):1-42. https://doi.org/10.3390/children9081120.
20. Hamzaoui A, Yaalaoui S, Tritar Cherif F, Slim Saidi L, Berraies A. Childhood tuberculosis: a concern of the modern world. Eur Respir Rev. 2014 Sep;23(133):278-91. https://doi.org/10.1183/09059180.00005314
21. Sandgren A, Cuevas LE, Dara M, Gie RP, Grzemska M, Hawkridge A, et al. Childhood tuberculosis: progress requires an advocacy strategy now. Eur Respir J. 2012;40(2):294-7. https://doi.org/10.1183/09031936.00187711
22. Zhuang Z, Sun L, Song X, Zhu H, Li L, Zhou X, et al. Trends and challenges of multi-drug resistance in childhood tuberculosis. Front Cell Infect Microbiol. 2023 ;13 91183590): 1-7. https://doi.org/10.3389/fcimb.2023.1183590
23. The Global Fund. Tuberculosis:the challenge. 2023. https://www.theglobalfund.org/en/tuberculosis/
24. Elizabeth Glaser Paediatric Aids Foundation. Tuberculosis: Expanding Access To Diagnosis and Treatment for TB. 2023. https://pedaids.org/our-expertise/tuberculosis/
25. Kaiser Family Foundation. The U.S. Government and Global Tuberculosis Efforts.2023.https://www.kff.org/global-health-policy/fact-sheet/the-u-s-government-and-global-tuberculosis-efforts/
26. United Nations. How TB infections increased during COVID-19.https://www.un.org/africarenewal/magazine/october-2022/how-tb-infections-deaths-increased-during-covid-19-pandemic
27. Pan American Health Organization. Tuberculosis deaths and disease increase

during the COVID-19 pandemic. 2022. https://www.paho.org/en/news/27-10-2022-tuberculosis-deaths-and-disease-increase-during-covid-19-pandemic
28. Uwishema O, Rai A, Nicholas A, Abbass M, Uweis L, Arab S, et al. Childhood tuberculosis outbreak in Africa: is it a matter of concern<Int J Surg. 2023;109(5):1539-1542. https://doi.org/10.1097/JS9.0000000000000140
29. World Health Organization Africa Region. Tuberculosis. 2023. https://www.afro.who.int/health-topics/tuberculosis-tb
30. National Tuberculosis and Leprosy Control Programme. End-Term Review of Nigeria's National Strategic Plan For Tuberculosis Control 2015-2020
https://ntblcp.org.ng/content/uploads/2023/06/Final-report-ETR-NIGERIA-1.pdf
31. World Health Organization Africa Region. African Union and WHO urge swift action against childhood tuberculosis. 2022. https://www.afro.who.int/news/african-union-and-who-urge-swift-action-against-childhood-tuberculosis
32. Bagcchi S. Reducing tuberculosis in African children. Lancet Infect Dis. 2022 Nov;22(11):1544. .
33. Federal Ministry of Health, National Tuberculosis and Leprosy Control Programme. 2019 Annual TB Report. https://www.health.gov.ng/doc/Draft-2019-NTBLCP-Annual-report-22032020.pdf
34. World Health Organization. WHO releases new global lists of high-burden countries for TB, HIV-associated TB and drug-resistant TB. 2021 https://www.who.int/news/item/17-06-2021-who-releases-new-global-lists-of-high-burden-countries-for-tb-hiv-associated-tb-and-drug-resistant-tb
35. Muanya C, Onyedika-Ugoeze N. World TB Day. Nigeria Ranks 6 among high TB Burden Countries. The Guardian. 2023, March 24 https://guardian.ng/features/world-tb-day-nigeria-ranks-sixth-among-high-tb-burden-countries/#:~:text=Nigeria%20is%20among%20the%2014,globally%20and%201st%20in%20Africa.
36. KNCV Tuberculosis Foundation Nigeria. A Major Issue With Tb In Nigeria Is The Low Tb Case Finding For Both Adults And Children. 2023. https://kncvnigeria.org/nigeria-is-among-the-14-high-burden-countries-for-tb/
37. World Health Organization Regional Office for Gearing towards a TB free Nigeria- WHO and partners scale up action. 2021 https://www.afro.who.int/news/gearing-towards-tb-free-nigeria-who-and-partners-scale-action
38. Ogbo FA, Ogeleka P, Okoro A, Olusanya BO, Olusanya J, Ifegwu KI, et al. Tuberculosis disease burden and attributable risk factors in Nigeria, 1990–2016. Trop Med Health. 2018;46:1-11. https://doi.org/10.1186/s41182-018-0114-9
39. Adebowale-Tambe N. Tuberculosis: Stigma, funding , other factors threaten disease elimination in Nigeria. Premium times. https://www.premiumtimesng.com/news/headlines/519247-2022-world-tb-day-stigma-poor-funding-other-factors-threaten-disease-elimination-in-nigeria.html
40. Ugwu KO, Agbo MC, Ezeonu IM. Prevalence Of Tuberculosis, Drug-Resistant Tuberculosis And Hiv/Tb Co-Infection In Enugu, Nigeria. Afr J Infect Dis. 2021 ;15(2):24-30. https://doi.org/10.21010/ajid.v15i2.5
41. Carvalho I, Goletti D, Manga S, Silva DR, Manissero D, Migliori G. Managing latent tuberculosis infection and tuberculosis in children. Pulmonology. 2018;24(2):106-114. https://doi.org/10.1016/j.rppnen.2017.10.007
42. Migliori GB, Nardell E, Yedilbayev A, D'Ambrosio L, Centis R, Tadolini M, et al. Reducing tuberculosis transmission: a consensus document from the World Health Organization Regional Office for Europe. Eur Respir J. 2019;53(6):1-18. https://doi.org/10.1183/13993003.00391-2019
43. United States Centers for Disease Control. TB in children. 2023. https://www.cdc.gov/tb/topic/populations/tbinchildren/default.htm
44. Thomas TA. Tuberculosis in Children. Pediatr Clin North Am. 2017;64(4):893-909. https://doi.org/10.1016/j.pcl.2017.03.010.
45. Health Protection Surveillance Centre. Guidelines on the Prevention and Control of Tuberculosis in Ireland 2010. https://www.hpsc.ie/a-z/vaccinepreventable/tuberculosistb/guidance/tbguidelines2010amended2014/tb%20guidance%20chapter%208.pdf
46. Coleman M, Martinez L, Theron G, Wood R, Marais B. Mycobacterium tuberculosis Transmission in High-Incidence Settings-New Paradigms and Insights. Pathogens. 2022;11(11):1-20. https://doi.org/10.3390/pathogens11111228.
47. Seddon JA, Shingadia D. Epidemiology and disease burden of tuberculosis in children: a global perspective. Infect Drug Resist. 2014;7:153-65. https://doi.org/10.2147/IDR.S45090
48. Linn AR, Dubois MM, Steenhoff AP. Under-Reporting of Tuberculosis Disease among Children and Adolescents in Low and Middle-Income Countries: A Systematic Review. Trop Med Infect Dis. 2023;8(6):1-16. https://doi.org/10.3390/tropicalmed8060300
49. Joshi B, De Lima YV, Massom DM, Kaing S, Banga MF, Kamara ET, et al. TB-Speed

Decentralization study group. Acceptability of decentralizing childhood tuberculosis diagnosis in low-income countries with high tuberculosis incidence: Experiences and perceptions from health care workers in Sub-Saharan Africa and South-East Asia. PLOS Glob Public Health. 2023 ;3(10):1-24. https://doi.org/10.1371/journal.pgph.0001525

50. An Y, Teo AKJ, Huot CY, Tieng S, Khun KE, Pheng SH, et al. Barriers to childhood tuberculosis case detection and management in Cambodia: the perspectives of healthcare providers and caregivers. BMC Infect Dis. 2023;23(1):1-10. https://doi.org/10.1186/s12879-023-08044-y
51. World Health Organization Regional Office for Africa. The African Regional Health Report. 2006. https://www.afro.who.int/sites/default/files/2017-06/african_regional_health_report2006_0.pdf
52. UNICEF Data. An Agenda for Action on Tuberculosis. 2018https://data.unicef.org/wp-content/uploads/2018/03/TB-Advocacy-Brochure-Final-3_21-high-Res.pdf
53. Gebremichael B, Abebaw TA, Moges T, Abaerei AA, Worede N. Predictors of pediatric tuberculosis in public health facilities of Bale zone, Oromia region, Ethiopia: a case control study. BMC Infect Dis. 2018;18(1):252. https://doi.org/10.1186/s12879-018-3163-0
54. World Health Organization. Overcoming the drug resistant TB crises in children and adolescents. 2020 https://www.who.int/news/item/20-11-2020-overcoming-the-drug-resistant-tb-crisis-in-children-and-adolescents
55. Prestinaci F, Pezzotti P, Pantosti A. Antimicrobial resistance: a global multifaceted phenomenon. Pathog Glob Health. 2015;109(7):309-18. https://doi.org/10.1179/2047773215Y.0000000030.
56. Dheda K, Gumbo T, Gandhi NR, Murray M, Theron G, Udwadia Z, et al. Global control of tuberculosis: from extensively drug-resistant to untreatable tuberculosis. Lancet Respir Med. 2014;2(4):321-38. https://doi.org/10.1016/S2213-2600(14)70031-1
57. Piatek AS, Van Cleeff M, Alexander H, Coggin WL, Rehr M, Van Kampen S, Shinnick TM, Mukadi Y. GeneXpert for TB diagnosis: planned and purposeful implementation. Glob Health Sci Pract. 2013;1(1):18-23. https://doi.org/10.9745/GHSP-D-12-00004
58. Evans CA. GeneXpert--a game-changer for tuberculosis control< PLoS Med. 2011;8(7):e1001064. https://doi.org/10.1371/journal.pmed.1001064
59. World Health Organization. Largest ever roll-out of GeneXpert® rapid TB test machines, in 21 countries 2013. https://www.who.int/news/item/11-06-2013-largest-ever-roll-out-of-genexpert-rapid-tb-test-machines-in-21-countries
60. TB Facts.org. GeneXpert- testing for TB and drug resistant TB.
61. United States Centers for Disease Control. TB Diagnostic Tool: Xpert MTB/RIF Assay Fact Sheet. 2016. https://www.cdc.gov/tb/publications/factsheets/testing/xpert_mtb-rif.htm
62. Harries AD, Kumar AMV. Challenges and Progress with Diagnosing Pulmonary Tuberculosis in Low- and Middle-Income Countries. Diagnostics (Basel). 2018 ;8(4):78.
63. Dzodanu EG, Afrifa J, Acheampong DO, Dadzie I. Diagnostic Yield of Fluorescence and Ziehl-Neelsen Staining Techniques in the Diagnosis of Pulmonary Tuberculosis: A Comparative Study in a District Health Facility. Tuberculosis Research and Treatment, 2019; 4091937: 1-6. https://doi.org/10.1155/2019/4091937
64. Chandra TJ, Selvaraj R, Sharma YV. Same day sputum smear microscopy for the diagnosis of pulmonary tuberculosis: Ziehl-Neelsen versus fluorescent staining. J Family Med Prim Care. 2015;4(4):525-8. https://doi.org/10.4103/2249-4863.174273
65. United States Centers for Disease Control. Chapter 6 Treatment of Tuberculosis Disease - CDC. https://www.cdc.gov/tb/education/corecurr/pdf/chapter6.pdf
66. Seung KJ, Keshavjee S, Rich ML. Multidrug-Resistant Tuberculosis and Extensively Drug-Resistant Tuberculosis. Cold Spring Harb Perspect Med. 2015;5(9):a017863. https://doi.org/10.1101/cshperspect.a017863 .
67. Tajbakhsh A, Ghasemi F, Mirbagheri SZ, Momen Heravi M, Rezaee M, Meshkat Z. Investigation of the rpoB Mutations Causing Rifampin Resistance by Rapid Screening in Mycobacterium Tuberculosis in North-East of Iran. Iran J Pathol. 2018 Fall;13(4):429-437.
68. Tavanaee SA, Ashna H, Kaffash A, Khaledi A, Ghazvini K. Mutations of rpob Gene Associated with Rifampin Resistance among Mycobacterium Tuberculosis Isolated in Tuberculosis Regional Reference Laboratory in Northeast of Iran during 2015-2016. Ethiop J Health Sci. 2018 May;28(3):299-304. https://doi.org/10.4314/ejhs.v28i3.7 .
69. Goldstein, B. Resistance to rifampicin: a review. J Antibiot 67, 625–630 (2014). https://doi.org/10.1038/ja.2014.107
70. Nusrath UA, Hassan S, Indira K V, Revathy R, Hanna LE. Insights into RpoB clinical mutants in mediating rifampicin resistance in Mycobacterium tuberculosis. J Mol Graph Model. 2016;67:20-32.

https://doi.org/10.1016/j.jmgm.2016.04.005.
71. Prasad R, Gupta N, Banka A. Multidrug-resistant tuberculosis/rifampicin-resistant tuberculosis: Principles of management. Lung India. 2018 Jan-Feb;35(1):78-81. https://doi.org/10.4103/lungindia.lungindia_98_17
72. Adejumo OA, Olusola-Faleye B, Adepoju V, Bowale A, Adesola S, Falana A et al. Prevalence of rifampicin resistant tuberculosis and associated factors among presumptive tuberculosis patients in a secondary referral hospital in Lagos Nigeria. Afr Health Sci. 2018;18(3):472-478. https://doi.org/10.4314/ahs.v18i3.2
73. Lu J, Li H, Dong F, Shi J, Yang H, Han S, et al. The Feasibility of Xpert MTB/RIF Testing to Detect Rifampicin Resistance among Childhood Tuberculosis for Prevalence Surveys in Northern China. Biomed Res Int. 2017;2017:5857369. https://doi.org/10.1155/2017/5857369
74. Mulu W, Abera B, Yimer M,. et al. Rifampicin-resistance pattern of Mycobacterium tuberculosis and associated factors among presumptive tuberculosis patients referred to Debre Markos Referral Hospital, Ethiopia: a cross-sectional study. BMC Res Notes. 2017;10:8 https://doi.org/10.1186/s13104-016-2328-4
75. Onyedum CC, Alobu I, Ukwaja KN. Prevalence of drug-resistant tuberculosis in Nigeria: A systematic review and meta-analysis. PLoS One. 2017;12(7):e0180996. https://doi.org/10.1371/journal.pone.0180996
76. Munthali T, Chabala C, Chama E, Mugode R, Kapata N, Musonda P, et al. Tuberculosis caseload in children with severe acute malnutrition related with high hospital-based mortality in Lusaka, Zambia. BMC Res Notes. 2017;10(1):206. https://doi.org/10.1186/s13104-017-2529-5
77. López-Varela E, Augusto OJ, Gondo K, Garcia-Basterio AL, Fraile O, Ira T,et al. Incidence of tuberculosis among young children in rural Mozambique. Pediatr Infect Dis J. 2015;34(7):686–692. https://doi.org/10.1097/INF.0000000000000710
78. Marais BJ, Obihara CC, Gie RP, Schaaf HS, Hesseling AC, Lombard C et al. The prevalence of symptoms associated with pulmonary tuberculosis in randomly selected children from a high burden community. Arch Dis Child. 2005;90(11):1166–1170. https://doi.org/10.1136/adc.2004.060640
79. Chipinduro M, Mateveke K, Makamure B, Ferrand RA, Gomo E. Stool Xpert® MTB/RIF test for the diagnosis of childhood pulmonary tuberculosis at primary clinics in Zimbabwe. Int J Tuberc Lung Dis. 2017;21(2):161–166. https://doi.org/10.5588/ijtld.16.0357.
80. Jaganath D, Zalwango S, Okware B, Nsereko M, Kisingo H, Malone LS, et al. Contact investigation for active tuberculosis among child contacts in Uganda. Clin Infect Dis. 2013;57(12):1685–1692. https://doi.org/10.1093/cid/cit645
81. Arega B, Menbere F, Getachew Y. Prevalence of rifampicin resistant Mycobacterium tuberculosis among presumptive tuberculosis patients in selected governmental hospitals in Addis Ababa, Ethiopia. BMC Infect Dis. 2019;19(1):307.30947695
82. Sultana AT, Gathia R, Huda MM, Begum JA, Amin MR. Pattern of childhood tuberculosis among the patients admitted in Dhaka Shishu (Children) Hospital. Northern Int Med Coll J. 2017;8(2):213–215. https://doi.org/10.3329/nimcj.v8i2.32552
83. Garba MA, Ogunbosi BO, Musa A, Ibraheem RM, Alao MA, Jiya-Chitumu EN et al. Trends in pediatric tuberculosis diagnosis utilizing xpert Mycobacterium tuberculosis/Rifampicin in a poor-resource, high-burden region: A retrospective, multicenter study. Int J Mycobacteriol. 2023;12(1):77-81 https://doi.org/10.4103/ijmy.ijmy_1_23
84. Ogbudebe CL, Adepoju V, Ekerete-Udofia C, Abu E, Egesemba G, Chukwueme N, et al. Childhood Tuberculosis in Nigeria: Disease Presentation and Treatment Outcomes. Health Serv Insights. 2018;11:1-7. https://doi.org/10.1177/1178632918757490
85. Fadeyi A, Desalu OO, Ugwuoke C, Opanwa OA, Nwabuisi C, Salami AK. Prevalence of Rifampicin-Resistant Tuberculosis among Patients Previously Treated for Pulmonary Tuberculosis in North-Western, Nigeria. Niger Med J. 2017;58(6):161-166. https://doi.org/10.4103/nmj.NMJ_41_17
86. Mathema B, Andrews JR, Cohen T, Borgdorff MW, Behr M, Glynn JR, et al. Drivers of Tuberculosis Transmission. J Infect Dis. 2017;216(suppl_6):S644-S653. https://doi.org/10.1093/infdis/jix354
87. Diel R, Nienhaus A. Pathways of TB Transmission in Children-A Systematic Review of Molecular Epidemiological Studies. Int J Environ Res Public Health. 2023;20(3):1737. https://doi.org/10.3390/ijerph20031737
88. Hesseling AC, Kim S, Madhi S, Nachman S, Schaaf HS, Violari A et al. High prevalence of drug resistance amongst HIV-exposed and-infected children in a tuberculosis prevention trial. Int J Tuberculosis Lung Dis. 2012;16(2):192–195. https://doi.org/10.5588/ijtld.10.0795
89. Jiao W, Liu Z, Han R, Zhao X, Dong F, Dong H.et al. Prevalence of drug resistant

Mycobacterium tuberculosis among children in China. Tuberculosis. 2015;95(3):315–320. https://doi.org/10.1016/j.tube.2015.02.041

90. Adisa R, Ayandokun TT, Ige OM. Knowledge about tuberculosis, treatment adherence and outcome among ambulatory patients with drug-sensitive tuberculosis in two directly-observed treatment centres in Southwest Nigeria. BMC Public Health. 2021 ;21(1):677. https://doi.org/10.1186/s12889-021-10698-9
91. Anochie PI, Onyeneke EC, Onyeozirila AC, Igbolekwu LC, Onyeneke BC, Ogu AC. Evaluation of public awareness and attitude to pulmonary tuberculosis in a Nigerian rural community. Germs. 2013;3(2):52-62. https://doi.org/10.11599/germs.2013.1037
92. Roy P, Vekemans J, Clark A, Sanderson C, Harris RC, White RG.Potential effect of age of BCG vaccination on global paediatric tuberculosis mortality: a modelling study. Lancet Glob Health. 2019 Dec;7(12):e1655-e1663. https://doi.org/10.1016/S2214-109X(19)30444-9
93. O'Riordan P, Schwab U, Logan S, Cooke G, Wilkinson RJ, Davidson RN, Bassett P, Wall R, Pasvol G, Flanagan KL. Rapid molecular detection of rifampicin resistance facilitates early diagnosis and treatment of multi-drug resistant tuberculosis: case control study. PLoS One. 2008;3(9):e3173. https://doi.org/10.1371/journal.pone.0003173
94. World Health Organization. Global research agenda for antimicrobial resistance in human health. Policy brief. 2023. https://cdn.who.int/media/docs/default-source/antimicrobial-resistance/amr-spc-npm/who-global-research-agenda-for-amr-in-human-health---policy-brief.pdf<sfvrsn=f86aa073_4&download=true
95. Moussa HSh, Bayoumi FS, Ali AM. Evaluation of GeneXpert MTB/RIF assay for direct diagnosis of pulmonary tuberculosis. Saudi Med J. 2016;37(10):1076-81. https://doi.org/10.15537/smj.2016.10.14998
96. Tropical Disease Research (TDR). Integrating GeneXpert molecular testing technology in national health systems – lessons from four implementation research studies. 2022. https://tdr.who.int/newsroom/news/item/17-10-2022-integrating-genexpert-molecular-testing-technology-in-national-health-systems-lessons-from-four-implementation-research-studies
97. Nalugwa T, Shete PB, Nantale M, Farr K, Ojok C, Ochom E, et al.. Challenges with scale-up of GeneXpert MTB/RIF® in Uganda: a health systems perspective. BMC Health Serv Res. 2020;20(1):162. https://doi.org/10.1186/s12913-020-4997-x.
98. Ramsay A, Harries AD. The clinical value of new diagnostic tools for tuberculosis. F1000 Med Rep. 2009;1:36. https://doi.org/10.3410/M1-36
99. Pai, M., Dewan, P.K. & Swaminathan, S. Transforming tuberculosis diagnosis. Nat Microbiol 8, 756–759 (2023). https://doi.org/10.1038/s41564-023-01365-3
100. Shin SS, Seung KJ. Tuberculosis. In:Magill AJ, Solomon T, Hill TR, Ryan ET, editors. Hunter's Tropical Medicine and Emerging Infectious Disease. 9th ed. London: Elsevier, 2013; p.416-432.
101. Dookie N, Khan A, Padayatchi N, Naidoo K. Application of Next Generation Sequencing for Diagnosis and Clinical Management of Drug-Resistant Tuberculosis: Updates on Recent Developments in the Field. Front Microbiol. 2022 Mar 24;13:775030. https://doi.org/10.3389/fmicb.2022.775030
102. Hasan Z, Shakoor S, Hasan R. Importance of next-generation diagnostics in control of tuberculosis in LMICs. EBioMedicine. 2021;74:103753.

Table 1: Demographic Characteristics

Characteristics		n=1046 (%)
1. Gender	Male	556 (53.2)
	Female	490 (46.8)
2. Age	<1 year	12 (1.1)
	1-5 years	145 (13.9)
	6-10 years	284 (27.2)
	11-15 years	445 (42.5)
	16-17 years	160 (15.3)

Table 2: Clinical Details of Tb and HIV Infection

Characteristics		n=1046 (%)
1. TB infection status	Positive	50 (4.8)
	Negative	996 (95.2)
		n=50 (%)
2. Rifampicin resistance status	RIF Resistance	3 (6.0)
	No RIF Resistance	47 (94.0)
		n=1046
	Positive	39 (3.7)
3. HIV status	Negative	319 (30.5)
	Unknown	688 (65.8)
4. Clinical site of infection	Pulmonary	872 (83.4)
	Extra-Pulmonary	8 (0.8)
	N/S	166 (15.9)

Table 3: Bivariate Analysis Showing the Relationship between Age, Gender and Tb Status of the Respondents

VARIABLES		TB STATUS n=1046 (%)		x^2	*p-value*
		Positive	**Negative**		
1. Age	<5 years	8 (16.0)	149 (14.9)		
	6-15 years	25 (50.0)	704 (70.7)	18.796	**0.001**
	16-17 years	17 (34.0)	143 (14.4)		
2. Gender	Male	22 (44.0)	468 (47.0)	0.171	0.679
	Female	28 (56.0)	528 (53.0)		

Table 4: Bivariate Analysis Showing Relationship between Age, Gender and HIV Status of the Respondents

VARIABLES			HIV STATUS n=1046 (%)			x^2	*p-value*
			Positive	Negative	Unknown		
1.	Age	<5 years	8 (20.5)	54 (17.0)	95 (13.8)		
		6-15 years	27 (69.2)	196 (61.4)	506 (73.5)	21.748	**0.005**
		16-17 years	4 (10.3)	69 (21.6)	87 (12.7)		
2.	Gender	Male	18 (46.2)	161 (50.5)	311 (45.2)	2.436	0.296
		Female	21 (53.8)	158 (49.5)	377 (54.8)		

Table 5: Bivariate Analysis Showing Relationship between Tb Infection and HIV Status

VARIABLES		TB Infection n=1046 (%)		x^2	*p-value*
		Positive	Negative		
HIV Status	Positive	2 (4.0)	37 (3.7)		
	Negative	18 (36.0)	301 (30.2)	0.789	0.671
	Unknown	30 (60.0)	658 (66.1)		

Table 6: Bivariate Analysis Showing Relationship between Rifampicin Resistance and HIV Status

VARIABLES		RIF Resistance status n=3 (%)		x^2	*p-value*
		RIF resistance	No RIF Resistance		
HIV Status	Positive	0 (0.0)	2 (4.3)		
	Negative	1 (33.3)	17 (36.2)	0.158	0.924
	Unknown	2 (66.7)	28 (59.6)		

Table 7: Bivariate Analysis Showing Relationship between Gender and Rifampicin Resistance

VARIABLES		RIF Resistance status n=3 (%)		x^2	*p-value*
		RIF resistance	No RIF Resistance		
Gender	Male	3 (100.0)	19 (40.4)	4.062	0.044
	Female	0 (0.0)	28 (59.6)		

►*Please cite this article as:*
Otaigbe, I.I., Elikwu, C.J., Oluwole, T.O., Ogunlolu, A.E., Oseni, O.E., Bello, O.D., Olayiwola, P.O., Dike-Israel, V.C., Atuk, G.J. A retrospective assessment of rifampicin resistance in paediatric tuberculosis in a tertiary hospital in south west Nigeria. Research Journal of Health Sciences, 2024; 12(1): 42-52