

Prevalence and Multi-Drug Resistance of *Streptococcus pneumoniae* Infection Among Presumptive Tuberculosis Adult Cases at Dilla University Referral Hospital, Dilla, Ethiopia

Benyam Kaloro Halala¹, Musa Mohammed Ali², Moges Desta Ormago²

¹Referral Hospital, Dilla University, Dilla, Ethiopia; ²School of Medical Laboratory Science, College of Medicine and Health Sciences, Hawassa University, Hawassa, Ethiopia

Correspondence: Moges Desta Ormago, Email moges22@gmail.com

Introduction: *Streptococcus pneumoniae* is the leading cause of community-acquired pneumonia in Africa. The simultaneous occurrence of both infections leads to delayed diagnosis and inadequate treatment. The study aimed to determine the prevalence, antimicrobial susceptibility pattern and associated factors of *Streptococcus pneumoniae* infection among presumptive Tuberculosis adult cases at Dilla University Referral Hospital, Dilla, Ethiopia.

Methods: An institution-based cross-sectional study was conducted on 422 presumptive TB cases visiting TB clinic at Dilla University Referral Hospital from April to June 2021. Following the Bartlett's criteria, the accepted sputum samples were cultured on Blood agar plate and chocolate agar plate. *Streptococcus pneumoniae* was identified and confirmed by typical colony morphology, alpha-hemolysis, gram staining, optochin susceptibility and bile solubility tests. Antimicrobial susceptibility test was done by using the Kirby-Bauer disc diffusion method. Semi-structured questionnaires were used to collect data. Bivariate and multivariate logistic regression analyses were done by using SPSS version 23.0, computer software.

Results: The overall prevalence of *S. pneumoniae* in presumptive tuberculosis adult cases was 21.4% (95% CI: 17.7–25.5). *S. pneumoniae* has a high level of resistance to penicillin (74.1%), tetracycline (78.7%) and Trimethoprim-sulfamethoxazole (46%). Multidrug resistance was observed in 46.1% of bacterial isolates. Being primary education, more than five family size and one or two rooms in the house had more likely to cause *S. pneumoniae* infection.

Conclusion: This study revealed a relatively high prevalence of multidrug resistance of *Streptococcus pneumoniae* infection. Primary educational status, living in a crowded family, below two rooms in the house, had a significant association with *S. pneumoniae* infection.

Keywords: *S. pneumoniae*, antimicrobial susceptibility, tuberculosis, Dilla, Ethiopia

Introduction

Tuberculosis and pulmonary pneumonia are both lower respiratory tract infections that affect almost all classes of people mostly in developing countries.¹ Pneumonia can be spread in the nose or throat and can infect the lungs if they are inhaled. They may also spread via airborne droplets from a cough or sneeze. In addition, pneumonia may spread through contact and blood, especially during and after birth.^{2,3} *S. pneumoniae* (pneumococcus) is a major cause of the disease, ranging from uncomplicated respiratory tract infections to severe invasive pneumococcal disease (IPD).⁴

Streptococcus pneumoniae (*S. pneumoniae*) is the major cause of morbidity and mortality in the world.^{5,6} It contributes to 120 million new pneumonia infections worldwide, 14 million of which were severe enough to require hospitalization.⁷ Surveillance data on *S. pneumoniae* infections are few if available to health care providers¹. *S. pneumoniae* (pneumococcus) is a major cause of disease, ranging from uncomplicated respiratory tract infections to severe invasive pneumococcal disease (IPD).² Studies in Hawassa, Ethiopia, reported that among commonest microbes

causing pneumonia, the proportion of *S. pneumoniae* was 6%⁸ and 18.1%, and another study in Addis Ababa, Ethiopia, showed the proportion of *S. pneumoniae* was 18.5%.⁹

Tuberculosis in men is caused by *Mycobacterium tuberculosis*, and according to the 2021 global TB report, ten million people were estimated to have TB cases, and 1.3 million TB deaths were among HIV-negative and 214,000 TB deaths were among HIV-positive people every year though TB drugs are effective and given freely to patients in developing countries including Ethiopia.¹⁰

Antimicrobial-resistant strains of *Streptococcus pneumoniae* have become one of the greatest challenges to global public health today, and inappropriate use of antibiotics and high level of antibiotic use are probably the main factors driving the emergence of resistance worldwide. The susceptibility of penicillin (61.7%) to *S. pneumoniae* globally was the lowest one of all antibiotics in the TEST panel. Africa, Asia, and the Middle East were the sources of isolates with 43.5%, 29.9%, and 20.7% susceptibility, respectively.¹¹ Study in two regions of Ethiopia showed that of the 57 isolates, 17.5% were fully resistant to penicillin, and multidrug resistance (MDR) was seen in 33.3% isolates.¹²

Mortality due to pneumonia is strongly linked to poverty-related factors such as undernutrition, lack of safe drinking water and sanitation, indoor and outdoor air pollution, and inadequate access to health care.^{13,14} A timely diagnosis of pneumonia is an essential step in the prevention process of the disease. X-ray and laboratory identification of the causative agent is the confirmatory tools to certainly establish the diagnosis of pneumonia.¹⁵ While these are largely unaffordable in resource-poor settings like Ethiopia¹⁶ and it cannot be assumed that all respiratory symptoms have bacterial pneumonia and should receive antibiotics, the data indicate a big gap between the rich and the poor in the treatment of symptoms of pneumonia, receiving care for pneumonia symptoms from a healthcare provider. Furthermore, in sub-Saharan Africa, where most deaths from pneumonia occur, only 47% of children with pneumonia symptoms are taken for care, with the lowest proportions in Western and Central Africa.¹⁴

However, Ethiopia is among the highest burden of pneumonia.¹⁷ Co-infection with tuberculosis (TB) and bacteria has not been widely reported. Although the superadded bacterial infection can occur in TB patients, the simultaneous occurrence of both infections leads to delayed diagnosis and inadequate treatment. Tubercular-bacterial co-infection needs to be considered, especially if TB occurs in atypical pulmonary or extra-pulmonary locations.¹⁸ Hence, information on *Streptococcus pneumoniae* infection and drug susceptibility patterns are very important for the proper selection and use of antibiotic agents. Therefore, this study aimed to determine the prevalence and multi-drug resistance of *Streptococcus pneumoniae* Infection among Presumptive Tuberculosis Adult Cases at Dilla University Referral Hospital, Dilla, Ethiopia.

Materials and Methods

Study Setting

The study was conducted at Dilla University Referral Hospital (DURH) from April to June 2021. The Hospital is found in Dilla town which is the capital city of Gedeo zone, South Nations Nationalities and People Region (SNNPR), and it is located at 5°27' N latitude and 38°8' to 38°30' east longitude with an elevation of 1570m above sea level. The town is 365 km far away from Addis Ababa and is located on the main road from Addis Ababa to Nairobi at the eastern edge of the Rift valley. Dilla University Hospital in its laboratory diagnostic department provides microbiological analysis including bacterial culture, identification and drug susceptibility testing from clinical samples. Patients visiting the outpatient department of the hospital with signs and symptoms suggestive of TB or with CXR abnormalities suggestive of TB were bacteriologically confirmed by using Xpert MTB/RIF assay.

Study Design and Participants

A facility-based cross-sectional study design was conducted among presumptive tuberculosis adult patients attending DURH. Since there was no previous study in the area, sample size was determined by considering the following: prevalence of *Streptococcus pneumoniae* infection = 50%, margin of error = 5%, 95% confidence level = 95%, and non-response rate = 10%. Accordingly, the total sample size was 422.

Systematic random sampling technique was applied to select 422 respondents for interview. The interval (K) was obtained by dividing the total number of patients attending the medical OPD for LRTI during the study period by sample size. According to information found from the database of DURH, the average daily patient flow due to LRTI at OPD is 19. The study period took 3 months, which contain 66 days and 19 times 66 gives 1254. Therefore, the total patient flow during the study period is 1254.

$$K = 1254/422 = 2.9 \approx 3$$

One of the first three presumptive tuberculosis cases was selected by a simple random sampling method. So, every 3rd presumptive tuberculosis case who came to the adult OPD in the study period was recruited until the required amount of sample was attained.

Data Collection and Laboratory Processing

Socio-demographic and clinical data were collected by trained nurses through face-to-face interviews with the patient using a semi-structured questionnaire from 422 respondents whose sputum samples fulfill Bartlett's criteria on Grams stain. Single sputum samples were collected using dry, sterile, leak-proof, translucent, and screw-capped plastic containers with a capacity of 30 mL and brought to the Microbiology Laboratory of Dilla University Referral Hospital for laboratory processing.

Gram's Stain

Quality of sputum samples was checked macroscopically for color, volume, viscosity, and odor and microscopically based on Bartlett's criteria, and any positive score (sum of + and – values assigned) on Gram's stain was considered an acceptable result to be cultured.¹⁹

Cultivation and Identification of Isolates

The purulent part of the accepted sputum samples was cultured on Blood agar plate (Oxoid, Hampshire, UK) and chocolate agar plate (Oxoid, Hampshire, UK) with a sterile wire loop and incubated in CO₂ enriched atmosphere at 37°C for 24 hours. *Streptococcus pneumoniae* was then identified and confirmed by typical colony morphology, alpha-hemolysis, gram staining, optochin susceptibility and bile solubility tests.²⁰

Antibiotic Susceptibility Testing

The disk diffusion method (Kirby–Bauer) was carried out using Muller Hinton agar (Oxoid, Hampshire, UK) supplemented with 5% sheep's blood for fastidious organisms as recommended by the Clinical and Laboratory Standard Institute (CLSI, 2020). Similar pure colonies were sub-cultured into the nutrient broth, mixed, and incubated for 2–6 hours at 35–37°C.²¹ The suspension was evenly inoculated onto Mueller–Hinton agar. Antibiotics tested include trimethoprim-sulfamethoxazole (SXT) (1.25/23.75µg), erythromycin (ERY) (15µg), vancomycin (VAN) (30µg), tetracycline (TTC) (30µg), chloramphenicol (CHL) (30µg) and clindamycin (CLM) (2µg). The zone of inhibition was measured after 18–24 hours of incubation at 35–37°C and interpreted as susceptible, intermediate, or resistant.²²

Quality Control

The consistency of the questionnaire was assured by pre-testing 5% of the questionnaires before the actual data collection. For quality control, a reference strain *S. pneumoniae* ATCC 49619 was used. Before use, all culture media were tested for sterility.

Data Entry and Analysis

Entry, cleaning and analysis of data were done by using SPSS version 23 software. Descriptive statistics were done using frequency and percentage to present the findings in the form of graphs and tables. Variables with a p-value <0.25 on bivariate analysis were selected for multivariate analysis. The multivariate analysis was used to determine the association between covariates and the outcome variables. Odds ratio (OR) with 95% CIs calculated from the multivariate logistic

regression adjusting for possible confounding (AOR) was used to determine the presence and strength of the association between dependent and independent variables, and P-values <0.05 was considered as a cut point.

Results

Socio-Demographic, Environmental and Behavioral Characteristics

A total of 416 presumptive tuberculosis adult cases were participated with a response rate of 98.6%. The mean age was 27.3 (± 9.6). Two hundred one (48.3%) were in the 18–24-year age category, 230 (55.3%) were males, 274 (65.9%) were urban dwellers, 210 (50.5%) were single and 77 (18.5%) were illiterate. Regarding environmental and behavioral characteristics, the majority 289 (69.5%) were living in a Mud/soil floor house, 295 (70.9%) had at least two windows, 27 (6.5%) had ever used any tobacco products, 14 (3.4%) were smoke cigarettes in last 30 days and 71 (17.1%) had ever drunk alcohol (Table 1)

Table 1 Socio-Demographic, Environmental and Behavioral Characteristics of Presumptive Tuberculosis Adult Cases at Dilla University Referral Hospital, Dilla, Ethiopia, 2021 (n = 416)

Variables		Frequency	Percent (%)
Sex	Male	230	55.3
	Female	186	44.7
Residence	Urban	274	65.9
	Rural	142	34.1
Age	18–24	201	48.3
	25–34	138	33.2
	≥ 35	77	18.5
Marital status	Married	181	43.5
	Single	210	50.5
	Divorced	15	3.6
	Widowed	10	2.4
Educational status	Illiterate	77	18.5
	Primary	223	53.6
	Secondary and above	116	27.9
Occupational status	Housewife	93	22.4
	Merchant	147	35.3
	Employed	74	17.8
	Farmer	86	20.7
	Others	16	3.8
Household monthly income	<2517 ETB*	278	66.8
	2517–4172 ETB	102	24.5
	>4172 ETB	36	8.7
Total household size	<5	228	54.8
	≥ 5	188	45.2
Waste disposal	Pit-hole	28	6.7
	Open field	245	58.9
	Burning	51	12.3
	Garbage	92	22.1
Floor material of the living house	Mud/soil floor	289	69.5
	Cement	125	30.0
	Wood	2	0.5
Number of rooms in the house	≤ 2	295	70.9
	>2	121	29.1

(Continued)

Table 1 (Continued).

Variables		Frequency	Percent (%)
Ownership of the latrine	Private	105	25.2
	Shared with neighbors	311	74.8
History of hospitalization	No	248	59.6
	Yes	168	40.4
Use any tobacco products	Yes	27	6.5
	No	389	93.5
Smoke cigarettes in the last 30 days	Yes	14	3.4
	Never	402	96.6
Ever drunk alcohol	No	345	82.9
	Yes	71	17.1

Abbreviation: *ETB, Ethiopian birr.

The Prevalence and Antimicrobial Susceptibility Pattern of *S. pneumoniae*

The overall prevalence of *S. pneumoniae* in presumptive tuberculosis adult cases was 89 (21.4%) (95% CI: 17.7–25.5). The prevalence of *S. pneumoniae* among illiterate participants (29.9%) was higher than participants with primary education (20.2%) and *S. pneumoniae* infection among participants living in one or two rooms in the house (27.5%) were fourfold higher than participants living in more than two rooms in the house (6.6%).

Twenty-three (25.8%) isolates of *S. pneumoniae* were susceptible to all of the antibiotics tested, 16 (18%) were resistant to one antimicrobial agent, 9 (10.1%) were resistant to two antimicrobial agents and 41 (46.1%) were resistant to three or more antimicrobial agents (multi-drug resistant). *S. pneumoniae* isolates were resistant to erythromycin 43 (48.3%), trimethoprim-sulfamethoxazole 36 (40.4%), tetracycline 36 (40.4%) and susceptible to clindamycin 76 (85.4%) and chloramphenicol 73 (82%) (Table 2).

Associated Factors of *S. pneumoniae* Infections

The variables that had a P value <0.25 by bivariate analysis and became a candidate for multivariate analysis were residence, age, educational status, total household size, number of rooms in the house, ownership of the latrine, history of hospitalization and ever-drunk alcohol were found to be potentially associated with the prevalence of *S. pneumoniae*. In the multivariate analysis, the study participants who had primary educational status were about three times more frequently exposed to *S. pneumoniae* with [AOR = 2.95, 95% CI (1.39, 6.27)] as compared with secondary and above education. Family size of more than five [AOR = 1.85, 95% CI: (1.11, 3.08)] and two or fewer rooms in the house [AOR = 5.69, 95% CI: (2.59, 12.53)] had high odds of exposure to *S. pneumoniae* infection as compared to their counterparts. Furthermore, the

Table 2 Antimicrobial Susceptibility Pattern of *S. pneumoniae* Isolates from Sputum Samples Collected from Presumptive Tuberculosis Adult Cases at Dilla University Referral Hospital, Dilla, Ethiopia, 2021 (n = 89)

Antimicrobials	<i>S. pneumoniae</i>		
	Susceptible n (%)	Intermediate n (%)	Resistant n (%)
Vancomycin	83 (93.3)	0 (0.0)	6 (6.7)
Erythromycin	60 (67.4)	5 (5.6)	24 (27)
Trimethoprim-sulfamethoxazole	77 (86.5)	0 (0.0)	12 (13.5)
Tetracycline	66 (74.2)	0 (0.0)	23 (25.8)
Chloramphenicol	79 (88.8)	1 (1.1)	9 (10.1)
Clindamycin	78 (87.6)	0 (0.0)	11 (12.4)

Table 3 Bivariate and Multivariate Logistic Regression Analyses of Factors Associated with *S. pneumoniae* Infection Among Presumptive Tuberculosis Adult Cases at Dilla University Referral Hospital, Dilla, Ethiopia, 2021 (n = 416)

Variables	<i>S. pneumoniae</i>		COR (95% CI)	P-value	AOR (95% CI)	P-value
	Yes Freq. (%)	No Freq. (%)				
Sex						
Male	49 (21.3)	181 (78.7)	I			
Female	40 (21.5)	146 (78.5)	1.012 (0.632, 1.621)	0.960		
Age						
18–24	35 (39.3)	166 (50.8)	1.737 (1.029, 2.935)	0.039*	1.736 (0.981, 3.070)	0.058
25–34	37 (41.6)	101 (30.9)	1.344 (0.701, 2.575)	0.373	1.116 (0.556, 2.237)	0.758
≥35	17 (19.1)	60 (18.3)	I		I	
Residence						
Rural	40 (44.9)	102 (31.2)	I		I	
Urban	49 (55.1)	225 (68.8)	1.801 (1.116, 2.906)	0.016*	1.628 (0.961, 2.759)	0.070
Educational status						
Illiterate	23 (25.8)	54 (16.5)	1.144 (0.644, 2.032)	0.647	1.569 (0.828, 2.972)	0.167
Primary	45 (50.6)	178 (54.4)	1.927 (0.977, 3.801)	0.058	2.953 (1.390, 6.271)	0.005*
Secondary and above	21 (23.6)	95 (29.1)	I		I	
Family size						
<5	40 (44.9)	188 (57.5)	I		I	
≥5	49 (55.1)	139 (42.5)	1.657 (1.034, 2.655)	0.036*	1.846 (1.107, 3.080)	0.019*
Number of rooms in the house						
≤2	81 (91.0)	214 (65.4)	5.346 (2.497, 11.447)	<0.001*	5.692 (2.586, 12.529)	<0.001*
>2	8 (9.0)	113 (34.6)	I		I	
Ownership of the latrine						
Private	12 (13.5)	9 (28.4)	I		I	
Shared with neighbors	77 (86.5)	234 (71.6)	2.550 (1.326, 4.905)	0.005*	2.469 (1.227, 4.972)	0.011*
History of hospitalization						
No	41 (46.1)	207 (63.3)	I		I	
Yes	48 (53.9)	120 (36.7)	2.020 (1.258, 3.243)	0.004*	1.562 (0.928, 2.628)	0.093
Ever drunk alcohol						
No	68 (76.4)	277 (84.7)	1.711 (0.963, 3.039)	0.067	1.461 (0.781, 2.733)	0.235
Yes	21 (23.6)	50 (15.3)	I		I	

Note: NB; *Statistically significant on multivariate analysis p-value (<0.05).

Abbreviations: COR, crude odds ratio; AOR, adjusted odds ratio; CI, confidence interval; I, reference; Freq, frequency.

study participants who shared a latrine with a neighbor also had about 2.5 times more frequently exposed to *S. pneumoniae* [AOR = 2.47, 95% CI (1.23, 4.97)] when it compared with those who had a private latrine (Table 3).

Discussion

The overall prevalence of *S. pneumoniae* infection in presumptive Tuberculosis adult cases at Dilla University Referral Hospital, Dilla, Ethiopia, was 89 (21.4%) (95% CI: 17.7–25.5). This study finding was comparable to results reported from Biratnagar, Nepal (21.3%),²³ and Beira, Mozambique (23%).²⁴ Our finding is higher than findings reported from Ekpoma, Nigeria (6.4%),¹ Ogun state, Nigeria (8.8%),²⁵ Sokoto, North-Western Nigeria (5.6%), and 7.3% in Kano teaching hospital, northern Nigeria.²⁶ On the other hand, the finding of this study is lower than the one reported from Jimma, South-west Ethiopia (43%).²⁷ The reason could be due to geographical distribution, sample size, educational background, and other socio-economic factors.

In this study, *S. pneumoniae* was sensitive to clindamycin (87.6%), vancomycin (93.3%), trimethoprim-sulfamethoxazole (86.5%), chloramphenicol (88.8%). The higher sensitivity of *S. pneumoniae* was reported in Hawassa, Ethiopia, for clindamycin (88.9%),²⁸ and in Arsi, Ethiopia, for vancomycin (97.7%) and chloramphenicol (94.3%).²⁹

In our study, *S. pneumoniae* was resistant to erythromycin (27%) and tetracycline (25.8%). Resistant to *S. pneumoniae* was reported in Addis Ababa, Ethiopia, for erythromycin (40%)⁹ and Gonder, Ethiopia, for tetracycline (31.3%).³⁰

The overall magnitude of multidrug resistance (MDR) was 46.1%. This result was higher than the previous studies which were conducted in Hawassa, Ethiopia (11.1%),²⁸ Addis Ababa and Amhara region, Ethiopia (33.3%),¹² and lower than other studies in Addis Ababa, Ethiopia (66.7%).⁹

This may be due to the wide use of this antibiotic in the communities because of its dose convenience, cost-effectiveness, easy availability in any pharmacy and the trend of sharing the drugs in the community. In addition to this, remarkable differences might have occurred because of the random use of antibiotics, the poor implementation of antibiotic policy and control in the study area may aggravate the situation.

History of hospitalization had a higher prevalence of *S. pneumoniae* infection (53.9%) among presumptive tuberculosis adult cases. This study result also agreed with the study report on *S. pneumoniae* infection and history of hospitalization in Hawassa, Southern Ethiopia (53.8%)³¹ and in Gondar University Hospital, Northwest Ethiopia (76.6%).³⁰ This may be due to acquiring the infection from the hospital environment during management of the patient for different reasons of admission.

This study also showed that the study participants who had primary school participants were three times more likely to be exposed to *S. pneumoniae* than participants with secondary and above education. This study result was consistent with the study report in Mekelle Zone, Tigray, Northern Ethiopia³² and in Ogun State, Nigeria.²⁵ The possible explanation for this may be that lower educational status was more exposed to environmental contaminants, like dust, animal dung, and lack of information.

In addition to this, presumptive tuberculosis adult cases from more than five family size had twice likely to be exposed to *S. pneumoniae* than those having less than five family size. This study result agreed with the study report from Wolaita-Sodo, Ethiopia.³³ The possible reason for more likely to be exposed to *S. pneumoniae* infection is that high family size may increase the chance of the transmission of the *S. pneumoniae* among the family members.

Limitation of the Study

As the patient him/herself collects the sputum, it was difficult to avoid contamination. Since participants may forget some information asked, there might be a recall bias.

Conclusions

Multi-drug resistance of *Streptococcus pneumoniae* infection in presumptive tuberculosis adult cases was prevalent. Therefore, culture and susceptibility test is vital for appropriate management of *Streptococcus pneumoniae* infection of the lower respiratory tract in the study area.

Abbreviations

LRTI, Lower respiratory tract infection; MDR-TB, Multi-Drug Resistant Tuberculosis; OPD, Outpatient department; SPSS, Statistical Package for Social Science; TB, Tuberculosis; WHO, World Health Organization.

Data Sharing Statement

The data that support the findings of this study will be available from the corresponding author upon reasonable request.

Ethics Approval and Informed Consent

Before initiation of the study, ethical clearance was obtained from the Institution Review Board Hawassa University College of Medicine and Health Sciences (Ref. No IRB/126/13). Participants were recruited after informed written consent was obtained. This study was conducted in accordance with the Declaration of Helsinki.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that there are no competing interests.

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