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# SECONDARY BACTERIAL INFECTIONS IN PULMONARY TUBERCULOSIS: MICROBIAL SPECTRUM, ANTIMICROBIAL SUSCEPTIBILITY PATTERN, AND ASSOCIATED RISK FACTORS.A OBSERVATIONAL CROSS-SECTIONAL STUDY

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ABSTRACT

**Background: Aim:** To Identify and isolate various pathogenic bacteria from all Pulmonary tuberculosis positive patients and to know their pattern of anti-microbial susceptibility. **Objective:** Pulmonary tuberculosis (TB) remains a major global health challenge and is frequently complicated by secondary bacterial infections that worsen morbidity and treatment outcomes. These infections, driven by host factors such as smoking, alcohol use, and comorbidities, along with emerging antimicrobial resistance, pose significant clinical and therapeutic challenges. Understanding their prevalence, microbial spectrum, and resistance patterns is essential for guiding effective management and antibiotic stewardship.

**Materials and Methods:** This is a hospital based cross sectional observational study conducted in the Microbiology department of R. D. GARDI Medical College and C.R.G. Hospital in Ujjain, (M.P.) from March 2023 to February 2025. Study was started after obtaining the approval of the institutional ethical committee and IEC Ref. number is 02/2023. A total of 525 clinical samples (sputum, BAL and ETT) from pulmonary tuberculosis patients were received in a sterile container were processed and antimicrobial susceptibility testing performed as per standard guidelines. Analyzed the association between demographic (age, sex), risk factors, co-morbidities with secondary bacterial infection in pulmonary tuberculosis patients by using chi square test and if p-value <0.05 is considered as statistically significant. Isolates were classified as MDR and XDR as per standard definitions.

**Results:** Among 525 pulmonary tuberculosis patients, 72 (13.7%) developed secondary bacterial infections, more frequent in males 381(73%) and 144 (27%) female. Smoking 52 (19%) and alcohol use 34(14%) were the predominant behavioral factors. Among the co-morbidities, HIV 14 (9.3%), diabetes mellitus 8(12.7%), chronic kidney disease 2(17%), and chronic liver disease 1(12.5%) were observed. The overall association of these factors with secondary bacterial infections was statistically highly significant ($p < 0.05$).Pseudomonas aeruginosa was predominant 35 (49%), followed by Klebsiellapneumoniae 20 (28%), E. coli 8 (11%), S. aureus 5 (7.1%), Acinetobacter spp. 1 (1.4%), and Candida spp. 3 (4.2%). MDR was highest in K. pneumoniae 18 (90%) and E. coli 7 (88%). XDR strains were detected in S. aureus 1(20%), E. coli 1(12.5%), P. aeruginosa 2 (6%), and K. pneumoniae 1(5%). ESBL production was common in E. coli 4 (50%), K. pneumoniae 7 (35%), and P. aeruginosa 7 (20%). P. aeruginosa remained fully susceptible to piperacillin–tazobactam and meropenem, 35(100%) while K. pneumoniae and

E. coli showed poor susceptibility to cephalosporins and carbapenems. In S.aureus, MRSA 4(80%) retained complete sensitivity to vancomycin, linezolid, and teicoplanin.
**Conclusion:** Secondary bacterial infections in tuberculosis patients were significantly associated with demographic, behavioral, and co-morbid factors ($p < 0.05$). Predominantly caused by P. aeruginosa and K. pneumoniae, with high rates of MDR, XDR, and ESBL production. Preserved susceptibility of P. aeruginosa to carbapenems and anti-MRSA agents highlights the need for vigilant antimicrobial stewardship and targeted therapy.
**Keywords:** Multi drug resistant(MDR), extensive drug resistant (XDR), Extended spectrum β-lcatamase(ESBL), Chronic kidney diseases(CKD), Chronic liver diseases (CLD), Methicillin resistant Staphylococcus aureus (MRSA).

## INTRODUCTION

Tuberculosis (TB) continues to be a major public health challenge in India, which accounts for over a quarter of the global TB burden. While the primary focus is on controlling Mycobacterium tuberculosis, a significant and often overlooked complication is the development of secondary bacterial infections. These co-infections are a critical concern as they can worsen a patient's clinical condition, complicate management, and lead to poor treatment outcomes, including increased morbidity and mortality.

The relationship between TB and secondary bacterial infections is symbiotic. Active TB infection compromises the host's immune system, particularly local defenses in the lungs. The structural damage to lung tissue, such as cavity formation, creates an ideal environment for opportunistic bacteria to colonize and thrive.[1] This makes TB patients highly susceptible to co-infections, which can manifest as pneumonia, empyema, or sepsis. This challenge is particularly acute in settings like India, where delayed diagnosis and the high prevalence of drug resistance in both TB and other bacterial pathogens complicate treatment.

Recent studies from tertiary care centers in India highlight the significant prevalence of these co-infections. Prevalence rates vary, with studies reporting figures ranging from around 10% to over 50%.[2,3] A considerable proportion of these infections are caused by Gram-negative bacteria. A recent study found that Klebsiellapneumoniae was the most common pathogen, followed by Acinetobacterbaumannii and Pseudomonas aeruginosa.[2] Other studies, however, identify Streptococcus pneumoniae and Staphylococcus aureus as the predominant culprits, reflecting regional variability in pathogen profiles.[3] This diversity underscores the need for local microbiological surveillance to guide appropriate empirical therapy.

The rise of antimicrobial resistance (AMR) in these co-infecting pathogens is a major concern. Many of these bacteria show high rates of resistance to common antibiotics. For instance, studies have noted significant resistance in Acinetobacterbaumannii to drugs like ciprofloxacin and carbapenems.[2] This "double-whammy" of resistance—in both the TB organism and the secondary pathogen—severely limits treatment options and contributes to the overall burden of AMR in the country.

Several factors increase the risk of secondary bacterial infections in TB patients. These include advanced age, male gender, a history of smoking, malnutrition, and co-morbidities such as diabetes mellitus and HIV/AIDS.[3,4] Clinically, patients with co-infections may present with worsening symptoms like a persistent cough, increased breathlessness, and fever despite being on anti-tuberculosis therapy. These patients may also show laboratory markers of a heightened inflammatory response, such as elevated white blood cell counts.[3]

The lack of a strong clinical suspicion and standardized diagnostic guidelines for these infections often leads to delayed diagnosis and inappropriate antibiotic use. Therefore, a comprehensive understanding of the microbiological profile and antibiotic susceptibility patterns is crucial for effective and timely management. The findings from studies like this one can provide up-to-date data, which is essential for tailoring targeted treatment protocols and contributing to the broader national effort to combat TB and antimicrobial resistance in India.

The aim of this study is to isolate and identify pathogenic microorganisms in pulmonary tuberculosis patients from clinical samples (sputum, BAL, and ETT) and their antimicrobial susceptibility pattern, and to study various risk factors and their association with secondary bacterial infection in tuberculosis-positive patients.

## MATERIALS AND METHODS

This is a hospital-based cross-sectional observational study conducted in the Microbiology department of R. D. GARDI Medical College and C.R.G. Hospital in Ujjain (M.P.) from March 2023 to February 2025. Study was started after obtaining the approval of the institutional ethical committee (IEC Ref. number 02/2023).

**Sample size calculation**: According to study by E. Shaddock et al,[5] prevalence of bacterial infection among TB-positive cases is 36%. To calculate the sample size, the following formula was used:
n=Z2×P×(100−P)e2n = \frac{Z^2 \times P \times (100-P)}{e^2}n=e2Z2×P×(100−P)
Where:

- Z=1.96Z = 1.96Z=1.96 at 95% confidence interval
- P=36%P = 36\%P=36% (assumed prevalence)
- e=5%e = 5\%e=5% (absolute error)

369n=52(1.96)2×36×(100−36)=369
Sample size was n = 369 tuberculosis-positive samples.

**Inclusion Criteria:**Pulmonary clinical samples (sputum, BAL, and ETT) received from pulmonary tuberculosis-positive patients (old and new) were included.

**Exclusion Criteria:** Clinical samples from extrapulmonary tuberculosis, pulmonary tuberculosis-negative patients, and repeated samples were excluded.

**Data Collection:** Data were collected via a structured platform that included demographic and clinical variables. The demographic data included age, sex, history of substance use (tobacco and alcohol), and co-morbidities like diabetes mellitus, HIV, chronic liver disease, and chronic kidney disease. These factors were chosen based on their potential associations with TB and secondary infections.[3,6,7,8,9,10,11]

**Sample Processing:** Pulmonary samples were received in sterile containers and processed under strict aseptic precautions. All samples underwent initial microscopic examination using Gram staining and acid-fast staining. Acid-fast positive samples were confirmed with CBNAAT. Samples were cultured on Blood Agar, MacConkey Agar, and Sabouraud Dextrose Agar (SDA) incubated aerobically at 37ºC, and Chocolate Agar plates incubated in 5% CO2. Bacterial growth was checked after 24 hours, and pathogens were identified based on Gram stain and biochemical properties.[12,13] Antimicrobial susceptibility testing (AST) was performed using the modified Kirby-Bauer disk diffusion method on Mueller-Hinton Agar according to CLSI guidelines.[14] Quality control strains included *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922, and *Pseudomonas aeruginosa* ATCC 27853.[14] MDR and XDR bacteria were defined according to Magiorakos et al.[15]

**Statistical Analysis:**All calculations were done using SPSS version 21. Data were described in terms of percentages where appropriate. Chi-square tests were applied to detect p-values; $p < 0.05$ was considered statistically significant.

## RESULTS

A total of 525 samples were received from tuberculosis patients, of which 381 (73%) were males and 144 (27%) females. Secondary bacterial infections were detected in 72 patients (13.7%), predominantly the >30–45 years 21(15%) and >45-60; 19(14%) compared to younger or elderly groups. (Table/Figure1)

Smoking 270 (51.4%) and alcohol use 240 (46%) were the most common behavioral factors, with secondary infection rates of 52 (19%) and 34 (14%), respectively. Among comorbidities, HIV 150 (28.5%), diabetes mellitus type II 63 (12%), CKD 12(2.2%) and CLD 8 (1.5%) showed secondary infection rates of 14(9.3%), 8(12.7%), 2(17%) and 1(12.5%), respectively. In this study, gender, age, smoking, alcoholism, HIV, diabetes, chronic kidney disease, and chronic liver disease showed a statistically significant association with secondary bacterial infections in tuberculosis patients ($p < 0.05$).(Table/Figure1)

The majority of specimens were; sputum 475(90.4%), BAL 40(7.6%), and endotracheal aspirates 10(2%). (Table/Figure2)

The most common isolate was Pseudomonas aeruginosa 35(49%), followed by Klebsiellapneumoniae 20(28%), E. coli 8(11%), S. aureus 5(7.1%), Acinetobacter spp. 1(1.4%) and Candida spp. 3(4.2%). In pulmonary tuberculosis, sputum yielded 59 (82%) isolates. Within sputum cultures, P. aeruginosa was isolated in 28 (47.4%), K. pneumoniae in 17 (29%), E. coli in 7 (12%), S. aureus in 4(7%), Candida spp. in 3 (5%). Bronchoalveolar lavage (BAL) contributed 12 (16.7%). The predominant organism in BAL was P. aeruginosa 7(58%), followed by K. pneumoniae 3(25%), E. coli 1(8.3%), and S. aureus 1(8.3%). Only one ETT aspirates (1.3%) yielded growth, which was Acinetobacter spp.(Table/Figure 3)

Multidrug resistance (MDR) was highest in K. pneumoniae 18 (90%) and E. coli 7 (88%), followed by S. aureus 4(80%) and P. aeruginosa 5 (14.2%). XDR strains were detected in S. aureus 1(20%), E. coli 1(12.5%), P. aeruginosa 2 (6%) and K. pneumoniae 1 (5%), and ESBL production was noted in E. coli 4(50%), K. pneumoniae 7(35%), and P. aeruginosa 7(20%).(Table/Figure4)

Antimicrobial susceptibility pattern ofisolates; P. aeruginosa showed complete susceptibility to piperacillin–tazobactam 35(100%) and meropenem 35(100%), with high susceptibility to tobramycin 34(97%), minocycline 34(97%), cefepime 32 (91%), imipenem 28(80%), aztreonam 28 (80%), and ceftazidime and levofloxacin 25 (71%) each. K. pneumoniae exhibited declining susceptibility: piperacillin–tazobactam 13(65%), imipenem 10(50%), meropenem and ertapenem 15 (75% ) each, tobramycin15 (75%), gentamicin 14 (70%), and amikacin 13(65%). Susceptibility to third-generation cephalosporins was markedly reduced,

cefotaxime and ceftriaxone 4 (20%) each. E. coli showed poor susceptibility to third-generation cephalosporins, cefotaxime and ceftriaxone1(13%) each and carbapenems (imipenem 2(25%); meropenem and ertapenem 4(50%) each, but retained good susceptibility to amikacin and gentamicin7 (88%). Acinetobacter spp. was susceptible to all tested agents 1 (100%).(Table/Figure5) S. aureus isolates included 4 (80%) MRSA and 1 (20%) MSSA. All MRSA isolates were susceptible to vancomycin, linezolid, and teicoplanin, with full susceptibility to erythromycin 4 (100%) and reduced susceptibility to gentamicin, chloramphenicol, tetracycline, and cotrimoxazole 3(75%) each. The single MSSA isolate was susceptible to all tested agents.(Table/Figure6)

**Table 1: Association of Demographic, clinical, Behavioral Characteristics and Co-morbidities of study population with Secondary bacterial infection (n=525)**

| Risk Factors | Total no. (n= 525) | Category n(%) | Occurrence n(%) | Secondary Bacterial infection | | Chi square value | p-value* |
|---|---|---|---|---|---|---|---|
| | | | | Present n(%) | Absent n(%) | | |
| Demographic | | | | | | | |
| Gender | 525 | Male | 381(73) | 61 (16) | 320 (83) | 6.189 | 0.0129 |
| | | Female | 144(27.4) | 11(8) | 133(92) | | |
| Age group(years) | 525 | <=18 | 17(3.2) | 3 (18) | 14 (82) | 1.1406 | 0.2855 |
| | | >18-30 | 116(22) | 13 (11) | 103(89) | | |
| | | >30-45 | 137(26) | 21(15) | 116 (85) | | |
| | | >45-60 | 138(26.2) | 19 (14) | 119 (86) | | |
| | | >60 | 117(22.2) | 16 (14) | 101 (86) | | |
| Behavioral | 525 | | | | | | |
| Smoking | | Yes | 270(51.4) | 52 (19) | 218 (80) | 14.44 | 1.44 |
| | | No | 255(49) | 20 (8) | 235 (92) | | |
| Alcohol use | | Yes | 240(46) | 34(14) | 206 (86) | 0.0765 | 0.7821 |
| | | No | 285(54) | 38 (13) | 247 (87) | | |
| Co-morbidities | 525 | | | | | | |
| HIV | 525 | Yes | 150(28.5) | 14(9.3) | 136(91) | 3.406 | 0.065 |
| | | No | 375(71.4) | 58(15.5) | 317(84.5) | | |
| | | | | 8(12.7) | 55(87.3) | | |
| Diabetes mellitus Type II | 525 | Yes | 63(12) | 64(14) | 398(86.1) | 0.0624 | 0.8027 |
| | | No | 462(88) | | | | |
| Chronic kidney diseases* | | | | 2(17) | | | |
| (CKD) | 525 | Yes | 12(2.2) | 70(14) | 10(83.3) | 0.0905 | 0.7635 |
| | | No | 513(98) | | 443(86.3) | | |
| Chronic liver | | | | 1(12.5) | | | |
| diseases*(CLD) | 525 | Yes | 8(1.5) | 71(14) | 7(87.5) | 0.0101 | 0.9199 |
| | | No | 517(98.4) | | 446(86.2) | | |

Chronic kidney diseases* and Chronic liver diseases* were co-morbidities not the adverse reaction of Anti tubercular treatment.
p-value *- is <0.05 is statistically highly significant.

**Table 2: Types of Pulmonary samples (n=525)**

| Clinical Samples | Total number 525 (%) |
|---|---|
| Sputum | 475(90.4) |
| Bal fluid | 40 (7.6) |
| ET | 10(2) |

**Table 3: Distribution of Microorganisms isolated in Secondary Bacterial Infection from various clinical samples (n=72)**

| Samples n(%) 72 (%) | *P.aeruginosa* 35 (49) | *K.pneumoniae* 20(28) | *E.coli* 8(11) | *Acinetobacterspp* 1(1.4) | *S.aureus* 5(7.1) | *Candida spp* 3(4.1) |
|---|---|---|---|---|---|---|
| Sputum 59 (82) | 28 (47.4) | 17(29) | 7(12) | 00 | 4(7) | 3(5) |
| BAL* 12(17) | 7(58) | 3(25) | 1(8.3) | 00 | 1(8.3) | 00 |
| ETT* 1 (1.3) | 00 | 00 | 00 | 1(100) | 00 | 00 |

BAL*-Broncho alveolar lavage, ETT*- Endotracheal tube aspirate

**Table 4: Distribution of MDR, XDR and ESBL producers isolates in Secondary Bacterial Infection,[15] (n=68)**

| Microorganisms | Frequency n(%) | MDR n (%) | XDR n (%) | ESBL producers n(%) |
|---|---|---|---|---|
| *Klebsiella pneumonia* | 20 (28) | 18 (90) | 1(5) | 7(35) |
| *E.coli* | 8 (11) | 7(88) | 1(12.5) | 4(50) |
| *Pseudomonas aerugiinosa* | 35 (49) | 5(14.2) | 2(6) | 7(20) |

| | | | | |
|---|---|---|---|---|
| *Staphylococcus aureus* | 5 (7) | 4(80) | 1(20) | - |
| **Total** | 68 (100) | 34(50) | 5(7.3) | 18(26.4) |

**Table 5: Antimicrobial susceptibility pattern of Gram negative bacteria (n=64)**

| Antimicrobial agents | *Pseudomonas aeruginosa* 35(%) | *Klebsiellapneumoniae* 20 (%) | E.coli 8(%) | *Acinetobacter spp.* 1 (%) |
|---|---|---|---|---|
| Ampicillin-Sulbactam | - | 7 (35) | 3(38) | 1(100) |
| Amoxclave | - | 4 (20) | 3(38) | - |
| Piperacillin-Tazobactam | 35(100) | 13(65) | 4(50) | 1(100) |
| Cefoxitin | - | 4(20) | 1(13) | - |
| Ceftazidime | 25(71) | 8(40) | 1(13) | 1(100) |
| Cefuroxime | - | 3(15) | 1(13) | - |
| Cefotaxime | - | 4(20) | 1(13) | 1(100) |
| Ceftriaxone | - | 4(20) | 1(13) | 1(100) |
| Cefoperazone-Sulbactam | - | 8(40) | 5(62) | - |
| Cefepime | 32(91) | 5(25) | 00 | 1(100) |
| Imipenem | 28(80) | 10(50) | 2(25) | 1(100) |
| Meropenem | 35(100) | 15(75) | 4(50) | 1(100) |
| Ertapenem | - | 15(75) | 4(50) | - |
| Ciprofloxacin | 23(66) | 3(15) | 1(13) | 00 |
| Levofloxacin | 25(71) | 7(35) | 1(13) | 1(100) |
| Tetracycline | - | 7(35) | 2(25) | - |
| Minocycline | 34(97) | 14(70) | 6(75) | 1(100) |
| Amikacin | - | 13(65) | 7(88) | 1(100) |
| Gentamicin | - | 14(70) | 7(88) | 1(100) |
| Tobramicin | 34(97) | 15(75) | 7(88) | 1(100) |
| Aztreonam | 28(80) | 7 (35) | 2(25) | 1(100) |
| Cotrimoxazole | - | 4(20) | 1(13) | 1(100) |

**Table 6: Antimicrobial susceptibility pattern of Staphylococcus aureus % (n=5)**

| Antimicrobial agents | MRSA 4 ( 80%) | MSSA 1 (20%) |
|---|---|---|
| Benzyle penicillin | 00 | 1(100) |
| Chloramphenicol | 3(75) | 1(100) |
| Ciprofloxacin | 00 | 00 |
| Levofloxacin | 1(25) | 1(100) |
| Erythromycin | 4(100) | 00 |
| Clindamycin | 4(100) | 1(100) |
| Gentamicin | 3(75) | 1(100) |
| Linezolid | 4(100) | 1(100) |
| Teicoplanin | 4(100) | 1(100) |
| Vancomycin | 4(100) | 1(100) |
| Tetracyclin | 3(75) | 1(100) |
| Cotrimoxazole | 3(75) | 1(100) |
| Inducible Clindamycin resistant (ICR) | 00 | 00 |

## DISCUSSION

Secondary bacterial infections were observed in 72 (13.7%) pulmonary tuberculosis patients. Males 381 (73%) showed higher secondary infection rates 61(16%) compared to females 11(8%), likely due to higher prevalence of smoking, alcohol use, and exposure to environmental risk factors.[6,7] Secondary infections were more frequent in patients aged 30–45 years 21 (15%) and 45–60 years 19(14%), consistent with studies showing the working-age population is more exposed to risk factors and may have undiagnosed co-morbidities.[8] Smoking 52 (19%) and alcohol consumption 34(14%) were significantly associated with secondary bacterial infections.[3,6,7,16] Tobacco smoke impairs mucociliary clearance and alveolar macrophage function, while alcohol suppresses immunity, facilitating bacterial superinfection in TB-damaged lungs.

Among comorbidities, HIV infection 14 (9.3%) and diabetes mellitus type II 8(12.7%) were associated with higher secondary infection rates, consistent with previous reports.[9,17,18,19,20] CKD 2 (17%) and chronic liver disease 1(12.5%) also showed higher infection rates, in line with studies showing immune dysfunction and higher TB susceptibility in these populations.[10,11]

The most common isolates were P. aeruginosa 35(49%) and K. pneumoniae 20(28%), consistent with prior Indian studies.[2,21,22,23] Structural lung damage from TB predisposes to colonization by Gram-negative opportunistic pathogens.[21] MDR was observed in 34 (50%), XDR in 5 (7.3%), and ESBL production in 18 (26.4%) of isolates, reflecting high resistance rates among Gram-negative bacteria.[2,8,21,24,25]

P. aeruginosa retained high susceptibility to piperacillin–tazobactam, meropenem, aminoglycosides, and minocycline, likely due to minimal exposure to broad-spectrum antibiotics in TB therapy.[26] In contrast, E. coli and K.

pneumoniae exhibited extensive resistance due to prior exposure to cephalosporins, fluoroquinolones, and β-lactam/β-lactamase inhibitors.[27,28,29]

**Limitations**

This single-center study with a limited sample size may not be generalizable. Culture-based methods could have missed fastidious or slow-growing pathogens, and molecular resistance mechanisms and long-term outcomes were not evaluated.

## CONCLUSION

Secondary bacterial infections were observed in a considerable proportion of pulmonary tuberculosis patients, with higher prevalence among males, older age groups, smokers, alcohol users, and patients with comorbidities such as HIV, diabetes, chronic kidney disease, and liver disease. P. aeruginosa and K. pneumoniae were the predominant pathogens, with alarming levels of MDR, XDR, and ESBL production. P. aeruginosa remained relatively susceptible to carbapenems, piperacillin–tazobactam, and aminoglycosides, whereas E. coli and K. pneumoniae showed extensive resistance. These findings highlight the need for routine microbiological surveillance, early diagnosis, and targeted antibiotic stewardship, alongside comprehensive management of behavioral and metabolic risk factors, to improve outcomes in TB patients with secondary infections.

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