

Pulmonary tuberculosis and fungal coinfection during 2018–2022: a single center study in Jakarta, Indonesia

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ABSTRACT

BACKGROUND Pulmonary tuberculosis (TB) is among the top 10 causes of death worldwide. Prolonged use and noncompliance with TB treatment have a potential risk for pulmonary fungal coinfection. This study aimed to evaluate fungal coinfection in pulmonary TB patients in Indonesia referred to the Clinical Microbiology Laboratory, Faculty of Medicine, Universitas Indonesia, Jakarta, during 2018–2022.

METHODS A cross-sectional study was conducted to compare 5 years of data collected at the Clinical Microbiology Laboratory, Faculty of Medicine, Universitas Indonesia. A total of 7,440 sputum specimens from various clinical sites were examined from 2018 to 2022. Sputum specimens from TB patients were prepared for microscopic examination using ZN staining to detect AFB. Culture and antimicrobial susceptibility of TB were performed on LJ agar. Fungal detected on microscopic examination and culture were assessed as coinfections.

RESULTS ZN staining to detect *M. tuberculosis* in clinical specimens has high specificity (98.4%) but low sensitivity (60.6%). Drug resistance in TB patients remains a problem, which can increase the risk of fungal infections. In 2018–2019, TB and fungal coinfections were more common in polyresistant TB cases. In 2020–2021, TB and fungal coinfections were found in all resistant TB cases, most commonly in XDR-TB cases. In 2022, TB and fungal coinfections were found in monoresistant and polyresistant patients. *Candida* spp. was found in 6.2% of positive TB cases, and all were found in resistant TB.

CONCLUSIONS Increasing MDR- and XDR-TB are risk factors for fungal coinfection and must be detected early for better TB management in Indonesia.

KEYWORDS antimicrobial susceptibility, culture, fungal infections, sputum, tuberculosis

Pulmonary tuberculosis (TB) is a major cause of mortality attributed to the *Mycobacterium tuberculosis* complex, and is one of the top 10 global causes of death.^{1,2} Before the coronavirus disease 2019 (COVID-19) pandemic, efforts to combat TB in several countries were relatively stable. This is reflected in the 9% and 14% decrease in incidence and mortality, respectively, from 2015 to 2019. According to the latest 2020 global TB report, data from more than 200 countries showed a significant decline in

TB case notifications. A 25–30% decline was reported between January and June 2020 compared with the same period in 2019 in three high-burden countries, including Indonesia, which has a high TB burden and limited diagnostic and therapeutic resources.³

The Ministry of Health of the Republic of Indonesia compiled a roadmap for eradicating TB in Indonesia from 2020 to 2030, including a target to reduce the incidence of TB to 65 cases per 100,000 people by 2030. In Indonesia, there were 845,000 TB cases in 2019, of

which only 67% reported to have received treatment. Of these cases, an estimated 24,000 were patients with drug-resistant TB (DR-TB), with an enrollment rate of 48% (5,531 patients) among 11,463 confirmed DR-TB cases. This remained below the 90% treatment target. Therefore, this falls short of the targets required to achieve TB elimination by 2030.^{3,4}

Long-term treatment of TB with anti-TB drugs, as well as long-term use of immunosuppressive agents or antibiotics, can lead to fungal infections. In patients who are administered anti-TB medications in the presence of fungal coinfection, healing may be prolonged. Bacteria can affect the growth and physiology of fungi; however, fungi can also control bacterial activity. Various *Candida* species are associated with pulmonary TB and are considered pathogenic in patients with TB. The coexistence of pulmonary TB and fungal infection can affect treatment and increase mortality because it is challenging to distinguish between infection and fungal colonization.^{5,6} Therefore, timely diagnosis of fungal infection in patients with TB is essential for treatment. Studies on the coexistence of fungi and *M. tuberculosis* in Indonesia are limited. Therefore, this study aimed to evaluate TB and coinfection with pulmonary fungal pathogens in patients with multidrug-resistant (MDR)-TB in Indonesia who were referred to the Clinical Microbiology Laboratory, Faculty of Medicine, Universitas Indonesia, Jakarta, between 2018 and 2022. Fungal coinfection in TB patients often occurs, particularly in immunocompromised patients with MDR-TB. This finding indicates the need for comprehensive management that not only focuses on TB bacteria but also opportunistic fungi that worsen the patient's condition.

METHODS

This cross-sectional study was conducted to compare data collected over a 5-year period (2018–2022) at the Clinical Microbiology Laboratory, Faculty of Medicine, Universitas Indonesia. Samples were collected using a consecutive sampling method. A total of 7,440 sputum specimens from various clinical sites, examined between 2018 and 2022, were included in this study. The study was approved by the Ethics Committee of the Faculty of Medicine, Universitas Indonesia – Cipto Mangunkusumo Hospital (No: KET-683/UN2.F1/ETIK/PPM.00.02/2024).

Clinical specimens and microscopic examination

The sputum specimens were examined at the Clinical Microbiology Laboratory, Faculty of Medicine, Universitas Indonesia to confirm the diagnosis of pulmonary TB. Ziehl-Neelsen (ZN) staining was used for direct examination to detect acid-fast bacilli (AFB).⁷ Microscopic examination was performed both before and after decontamination. The digested and decontaminated specimens were mixed using a vortex and divided into two equal parts. The modified Petroff's method was used to process the specimens, which were then inoculated directly onto Lowenstein-Jensen (LJ) agar for *M. tuberculosis* culture.⁸

Modified Petroff's method

Approximately 3–5 ml of sputum and an equal volume of 4% sodium hydroxide (NaOH) were homogenized using a shaker for 15 min. The homogenized suspension was centrifuged at 3,000 g for 15–20 min. The pellet was then neutralized using 20 ml of sterile distilled water or aquadest pro injection. The specimen was re-centrifuged at 3,000 g for 15–20 min. The pellet was inoculated onto LJ slant agar and subjected to microscopic examination using ZN staining. Culture on LJ agar was incubated at 35–37°C.⁹ Where fungi were detected on microscopic examination, the culture was classified as a coinfection.

TB identification

TB identification was performed using positive culture results. Colony growth on the LJ agar was observed daily during the first week. Observations were subsequently made weekly for 8 weeks. The colonies were identified based on their growth rate, optimal growth temperature, colony morphology, and pigmentation. Chromatographic tests were used to detect the presence or absence of Mycobacterium protein tuberculosis (MPT)-64 antigen, and p-nitrobenzoic acid (PNB) tests were used to determine the presence of *M. tuberculosis* or non-tuberculous mycobacteria (NTM). If no growth was observed on the LJ agar after 8 weeks of evaluation, the culture result was considered negative.

Susceptibility testing for TB

Drug susceptibility testing (DST) was conducted on LJ agar using the proportion method. LJ agar was prepared with and without anti-TB drugs according to the manufacturer's instructions. The suspected

colonies were then tested for susceptibility to streptomycin, isoniazid, rifampicin, and ethambutol in LJ agar containing 1.0 µg/ml, 0.1 µg/ml, 1.0 µg/ml, and 5.0 µg/ml, respectively. Stock solutions of the anti-TB drugs were prepared aseptically in a medium with a pH of 6.8. To perform DST, suspected colonies were scraped from the LJ agar, homogenized in sterile distilled water using glass beads, and mixed using a vortex. The turbidity of each suspension was adjusted to 0.5 to 1 McFarland. Two dilutions of the homogenized bacterial suspensions, 10^3 and 10^5 , were inoculated onto each medium containing anti-TB drugs. Both bacterial suspensions were inoculated onto the medium without an anti-TB drug as a positive control. The control strain of H37Rv for the susceptibility testing of streptomycin, rifampicin, isoniazid, and ethambutol was also included in each DST batch. All tubes were incubated at $35^\circ\text{C} \pm 2^\circ\text{C}$ for 6 weeks. Colony growth was observed and the number of cells were compared between the media containing an anti-TB drug and the control. The comparison of the results was calculated as a ratio and expressed as a percentage. This semi-quantitative analysis revealed the proportion of the mycobacterial population resistant to each drug tested. Isolates with growth of more than 1% on the medium containing an anti-TB drug, compared to the control, were categorized as resistant strains. Isolates with growth of less than 1% on the medium containing anti-TB drugs, compared to the control, were categorized as sensitive. The resistance patterns were categorized as monoresistant, polyresistant, MDR, or extensively drug-resistant (XDR). The definitions of each criterion are listed in Table 1.

Fungal microscopic examination

Fungal identification was performed by microscopic examination. Gram staining was used to

observe yeast morphology, and lactophenol cotton blue staining was used for mold identification.

RESULTS

ZN staining for detecting *M. tuberculosis* in clinical specimens had high specificity (98.4%) but low sensitivity (60.6%), as shown in Table 2. The positive predictive value was 79.1% and the negative predictive value was 96.1%.

Table 3 shows the proportion of positive ZN results and corresponding culture results from 2018 to 2022. At the beginning of the COVID-19 pandemic in 2020, the proportion of TB appeared to decrease compared to the levels observed in 2018 and 2019. *M. tuberculosis* was more common than NTM. The rate of resistance to more than one drug was consistently more than 10% every year. Between 2018 and 2022, a total of 241 (35.6%) polyresistant TB cases were found.

Figure 1 shows the susceptibility profile of *M. tuberculosis* to streptomycin, isoniazid, rifampicin, and ethambutol between 2018 and 2022 as reported by the Clinical Microbiology Laboratory, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia.

The susceptibility of *M. tuberculosis* to streptomycin, isoniazid, rifampicin, and ethambutol anti-TB drugs was more than 60% annually from 2018 to 2022. In this study, the resistance pattern was predominantly observed in monoresistant strains; however, cases of polyresistant, MDR-, and XDR-TB were also observed (Figure 2).

Patients with DR-TB are at risk of fungal pulmonary coinfection. A total of 7,440 sputum samples collected from patients with suspected TB were examined at the Clinical Microbiology Laboratory, Faculty of Medicine, Universitas Indonesia.

Table 1. Criteria of TB resistance

Resistance pattern	Criteria
Monoresistant	Resistance to one of anti-TB drugs, such as isoniazid resistance (H).
Polyresistant	Resistance to more than 1 drug, other than a combination of isoniazid (H) and rifampin (R), for example isoniazid and ethambutol (HE) resistance, rifampin-ethambutol (RE), isoniazid-ethambutol and streptomycin (HES), and rifampin-ethambutol and streptomycin (RES).
MDR	Resistance to isoniazid and rifampin, with or without other first-line drugs, e.g HR, HRE, or HRES resistance.
XDR	MDR-TB with resistance to one of the fluoroquinolones and one of the second-line injectable drugs (capreomycin, kanamycin, and amikacin).

MDR=multidrug-resistant; TB=tuberculosis; XDR=extensively drug-resistant

Table 2. Microscopic versus culture of TB patients during 2018–2022 referred to Clinical Microbiology Laboratory, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia

Positive		TB culture (gold standard)		
		Positive	Negative	Total
Microscopic examination (AFB staining)	Positive	412	109	521
	Negative	268	6,651	6,919
	Total	680	6,760	7,440

AFB=acid-fast bacilli; TB=tuberculosis

Of the 678 positive TB cases, *Candida* spp. were found in 42 (6.2%) of the positive TB cases, and all were found in DR-TB cases. Figure 3 shows TB and fungal coinfections, as reported by the Clinical Microbiology Laboratory, Faculty of Medicine, Universitas Indonesia. In 2018–2019, TB and fungal coinfections were more common in polyresistant TB cases than in MDR-TB cases. TB and fungal coinfections were not observed in monoresistant TB. In 2020, TB and fungal coinfections were detected in all DR-TB cases. The most common was found in XDR-TB cases. In 2021, TB and fungal coinfections were more common in monoresistant TB than in polyresistant and MDR-TB. In 2022, TB and fungal coinfections were found in equal proportions in monoresistant and polyresistant cases.

The characteristics of patients with TB and fungal coinfections during 2018–2022 who were referred to the Clinical Microbiology Laboratory, Faculty of Medicine, Universitas Indonesia are shown in Table 4. TB and fungal coinfections were more common in patients aged >45 years. There was no evidence of TB or fungal coinfection in the 437 patients with drug-sensitive TB. TB and fungal coinfections were also predominant in polyresistant TB cases, which were resistant to more than one drug other than a combination of isoniazid (H) and rifampin (R).

DISCUSSION

At the beginning of the COVID-19 pandemic in 2020, global TB case detection declined, including in Indonesia. Significant reductions in notified cases have been seen globally in India (25%), South Africa (26%), Indonesia (31%), and the Philippines (37%).¹⁰ The reduction in case detection in this study was 8%, which is lower than the reported reduction in Indonesia. This may be attributed to a decrease in the number of TB samples referred to our laboratory during the COVID-19 pandemic.

ZN smear microscopy is a widely used, rapid, and low-cost laboratory technique for diagnosing TB; however, it is known to have low to moderate sensitivity compared to culture methods. A sensitivity of 60.6% was observed in this study. This result is similar to that of Dzodanu et al¹¹ and Barik et al¹² who reported sensitivities of 54.8% and 66.67%, respectively. A high specificity of 98.4% for ZN smear was observed in this study. Roswidianah et al¹³ and Dzodanu et al¹¹ reported a specificity of 100% for ZN in supporting TB diagnosis, whereas Kelamane and Mispah¹⁴ reported a specificity of 98.5%.

The positivity rate of the TB culture was 678 (9.1%) cases among the 7,440 clinical specimens suspected of TB. In this study, the LJ agar was essential for isolating *M. tuberculosis* because of its ability to support slow growth and its low cost. Other benefits of the LJ agar include low contamination rates and the potential to provide high-quality isolates for confirming diagnosis and DST. Although liquid culture methods are faster than LJ solid medium, Pestariati and Rachmawati¹⁵ reported no difference in results between solid (LJ) and liquid media (mycobacteria growth indicator tube).

The MPT-64 antigen and PNB tests were used to distinguish TB from NTM.^{4,15} Overall, the positivity rates for NTM using these tests was 0.3%. Unlike

Table 3. Proportion of TB patients during 2018–2022 referred to Clinical Microbiology Laboratory, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia

Year	Examined (N)	Positive TB, n (%)	Positive NTM, n (%)	Sensitive >1, n (%)	Resistance >1, n (%)
2018	2,157	148 (6.9)	7 (0.3)	76 (51.4)	72 (48.6)
2019	1,335	205 (15.4)	3 (0.2)	99 (48.3)	106 (51.7)
2020	1,185	87 (7.3)	3 (0.3)	60 (69.0)	27 (31.0)
2021	1,227	124 (10.1)	4 (0.3)	103 (83.1)	21 (16.9)
2022	1,536	114 (7.4)	4 (0.3)	99 (86.8)	15 (13.2)

NTM=non-tuberculous mycobacteria; TB=tuberculosis

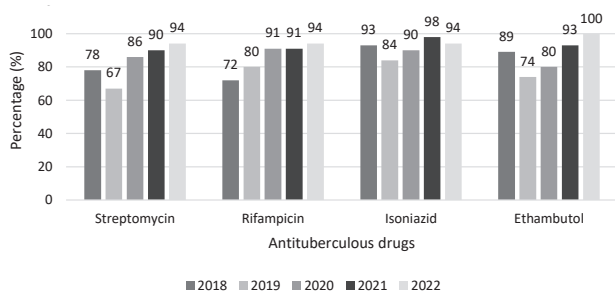


Figure 1. Susceptibility profile of *M. tuberculosis* to antituberculous drugs during 2018–2022 referred to Clinical Microbiology Laboratory, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia

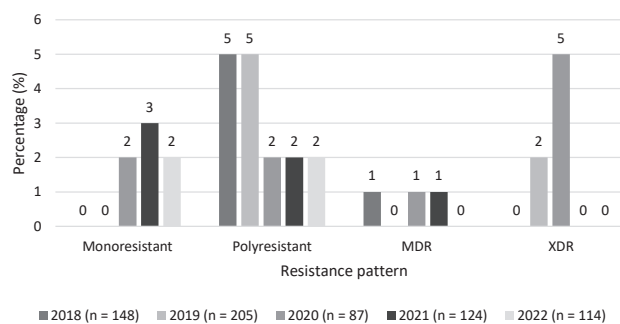


Figure 2. Resistance pattern of TB cases referred to Clinical Microbiology Laboratory, Faculty of Medicine, Universitas Indonesia, Jakarta in 2018–2022. MDR=multidrug-resistant; TB=tuberculosis; XDR=extensively drug-resistant

Table 4. Characteristics of TB and fungal coinfections in patients during 2018–2022 referred to Clinical Microbiology Laboratory, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia (N = 42)

Age (years)	Mono-resistant TB/fungal	Poly-resistant TB/fungal	MDR-TB/fungal	XDR-TB/fungal
<18	0	0	0	0
18–45	1	2	0	4
>45–60	5	11	2	0
>60	2	10	1	4

MDR=multidrug-resistant; TB=tuberculosis; XDR=extensively drug-resistant

M. tuberculosis, NTM are opportunistic pathogens widely found in water, soil, and dust. Healthcare professionals should carefully analyze and assess whether a detected NTM is pathogenic, a contaminant, or a transient colonizer.

DST is crucial for TB management to ensure effective treatment by identifying whether *M. tuberculosis* is susceptible or resistant to specific drugs. However, drug resistance remains a significant

problem in cases referred to microbiology laboratories in Jakarta, with more than 30% of cases affected each year. Between 2018 and 2022, 241 (35.6%) DR-TB cases were found. Changes in the resistance patterns, particularly the emergence of MDR/XDR-TB, may increase the risk of TB and fungal coinfection and contribute to higher mortality rates.^{5,16}

In 2018, resistance patterns were more common in monoresistant strains than in polyresistant and MDR strains. Isoniazid and rifampin, which are bactericidal drugs, are still used as first-line therapies for TB. Resistance to more than one drug, other than the combination of isoniazid (H) and rifampin (R), began to increase in 2019, and patients were at increased risk of TB and fungal coinfection. The resistance patterns in 2020 were more diverse than in previous years. Monoresistant, polyresistant, MDR-, and XDR-TB cases were reported in 2020. Meanwhile, in 2021 and 2022, resistant cases were predominantly monoresistant rather than polyresistant or MDR cases. No XDR cases were recorded during these years.

In 2018, Tjekyan et al¹⁷ reported that the proportion of MDR cases was 1.4% in Palembang City, Western Indonesia. In the same year, another study found that the proportion of MDR-TB was higher in Jakarta (5%). In 2018, 2.4% of new TB cases and 13% of retreated TB cases were reported in Indonesia, with a treatment success rate of 48%. The 2018 global MDR-TB report shows that Indonesia is included among the 30 countries with the highest MDR-TB burden in the world. Indonesia is ranked 9th in terms of MDR-TB incidence, after India, China, Russia, Pakistan, South Africa, the Philippines, Ukraine, and Kazakhstan.¹⁸ We reported MDR-TB rates of 6% and 2% in 2019 and 2020, respectively. The decrease in MDR-TB cases in 2020 correlated with a reduction in TB case detection during the COVID-19 pandemic. The detection of XDR cases in 2019–2020 may have complicated TB eradication efforts. Moreover, patients with XDR-TB are at a higher risk of transmitting DR-TB bacteria to healthy individuals than patients with active pulmonary TB.

DR-TB cases are at risk of fungal colonization, which can lead to fungal infections.^{19,20} Reports of TB and fungal coinfection in DR *M. tuberculosis* cases in Indonesia are limited, although many cases of resistance have been found. The coexistence of pulmonary TB and fungal infections can affect treatment and increase mortality it is challenging to distinguish between infection and fungal colonization.

Therefore, in cases of DR-TB, fungal examinations should be performed.

To detect TB and fungal coinfections, the quality of sputum specimens should be considered. A high neutrophil count increases confidence in the interpretation of positive culture results.^{21,22} An AFB smear prepared using the ZN technique was used for microscopic detection of mycobacteria. ZN staining is preferred because of its relative simplicity, high specificity, low cost, and simple microscopic requirements. However, fungal morphology was difficult to observe using ZN staining. Fungal growth was easier to detect in TB culture media from decontaminated specimens. Modified Petroff's method was used as an effective simplified decontamination technique for *M. tuberculosis* culture and DST.⁸

Fungal examinations should be considered in patients with TB, especially those with DR-TB. The diagnosis of fungal coinfections in patients with pulmonary TB is of critical importance. Pulmonary fungal infection complicates TB treatment and increases the mortality rate in patients with TB.^{5,23} Factors such as immunodeficiency, chronic course of the disease, and destroyed lungs contribute to the worsening of fungal coinfection in patients with TB. Missed pulmonary fungal coinfection in TB cases, due to a lack of specific clinical manifestations, may lead to high morbidity and mortality rates.^{24–27} Our findings suggest that fungal coinfection in patients with resistant pulmonary patients and TB in Indonesia should be considered for better management in the future.

In this study, all TB and fungal coinfections were found in DR-TB cases. TB and fungal coinfections were most commonly observed in XDR-TB cases. To reduce the incidence of XDR-TB, rational therapy, adequate clinical care, and easy-to-access facilities that support diagnosis and treatment should be implemented. Reducing the risk of DR-TB may also lower the risk of fungal infection, representing a more effective strategy for TB control in Indonesia.

The limitations of this study include: 1) its retrospective design, which may not represent all the risk factors, and 2) since this study was based on available laboratory records, there was missing information regarding clinical and pulmonary radiological examinations that could further support the presence of TB and fungal coinfection, especially in resistant cases. In conclusion, the proportions of MDR

cases referred to the Clinical Microbiology Laboratory, Faculty of Medicine, Universitas Indonesia in 2018–2022 were 5%, 6%, 2%, 2%, and 1%, respectively. TB and fungal coinfections were more common in patients with DR-TB. *Candida* spp. was the most common fungal agent isolated from sputum of patients with TB as a colonizer that may act as a risk factor for fungal infection. Pulmonary fungal infections complicate TB treatment, resulting in an increased mortality rate among patients with TB. Fungal coinfections in Indonesian patients with resistant pulmonary TB should be considered for better management in the future. Handling coinfection of TB with fungi requires a dual approach, considering that long-term TB treatment can weaken immunity and facilitate fungal infections, such as the integrated administration of anti-TB drugs and antifungals. Monitoring and managing side effects that arise during therapy as well as the immune system are necessary.

Conflict of Interest

The authors affirm no conflict of interest in this study.

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