

The Resistance Trends in Mycobacterium kansasii Pulmonary Isolates and identification of risk factors for drug resistance in Taiwan

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Benjamin Sobkowiak , Meng-Hsuan Cheng , Wei-Chang Huang ,
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Highlights

- Most *M. kansasii* isolates in Taiwan remained susceptible to the first-line agents.
- Resistance to ciprofloxacin, doxycycline, and minocycline raised concern.
- The presence of fibrocavitary lesions is associated with resistance.
- Region-specific and individualized therapies are crucial for treating *M. kansasii* pulmonary disease.

Journal Pre-proof

**The Resistance Trends in *Mycobacterium kansasii* Pulmonary Isolates
and identification of risk factors for drug resistance in Taiwan**

Sheng-Bin Fan^{1,2*}, Hung-Ling Huang^{1,2,3,15*}, Hung-Pin Tu⁴, Benjamin

Sobkowiak⁵, Meng-Hsuan Cheng^{1,2,3}, Wei-Chang Huang^{6,7,8#}, Yi-Wen Huang^{9,10},

Shang-Yi Lin^{1,12,13}, Inn-Wen Chong^{1,2,14}, Po-Liang Lu^{1,11,15,16#}

¹ Department of Internal Medicine, Kaohsiung Medical University Hospital,
Kaohsiung, Taiwan

² Division of Pulmonary and Critical Care Medicine and Department of Internal
Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan.

³ Graduate Institute of Medicine, College of Medicine, Kaohsiung Medical University,
Kaohsiung, Taiwan.

⁴ Department of Public Health and Environmental Medicine, School of Medicine,
College of Medicine, Kaohsiung Medical University, Taiwan

⁵ Department of Infection, Immunity and Inflammation, University College of London
(UCL) Great Ormond Street Institute of Child Health (GOS), London, United
Kingdom

⁶ Division of Pulmonary Immunology & Infectious Disease, Department of Chest
Medicine, Taichung Veterans General Hospital, Taichung, 407219, Taiwan

⁷ Department of Post-Baccalaureate Medicine, College of Medicine, National Chung Hsing University, Taichung, 402202, Taiwan

⁸ School of Medicine, Chung Shan Medical University, Taichung, 40201, Taiwan

⁹ Division of Chest Medicine, Department of Internal Medicine, Changhua Hospital, Ministry of Health and Welfare, Changhua, 513, Taiwan

¹⁰ Institute of Medicine, Chung Shan Medical University, Taichung 402, Taiwan

¹¹ Department of Post-Baccalaureate Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan

¹² Graduate Institute of Clinical Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan

¹³ Department of Laboratory Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan

¹⁴ Department of Respiratory Care, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan.

¹⁵ Center for Liquid Biopsy and Cohort, Kaohsiung Medical University, Kaohsiung, Taiwan.

¹⁶ Center for Tropical Medicine and Infectious Disease Research, Kaohsiung Medical University, Kaohsiung, Taiwan.

*** Corresponding author**

Dr. Po-Liang Lu

Department of Internal Medicine

Kaohsiung Medical University Hospital

16F, No.100, Tzyou 1st Rd., Sanmin Dist., Kaohsiung City 80756, Taiwan

Email: d830166@gmail.com

Tel: +886-7-3121101, ext 5675

Fax: +886-7-3222461

* Sheng-Bin Fan and Hung-Ling Huang contributed equally

Wei-Chang Huang and Po-Liang Lu contributed equally

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Objectives: *Mycobacterium kansasii* (*M. kansasii*) pulmonary disease is an emerging global health concern, and the pathogen's resistance to antimicrobial agents is challenging. Understanding the epidemiology of drug resistance rates and the associated risk factors is useful for guiding antimicrobial agent selection for *M. kansasii* treatment.

Methods: This retrospective cohort study analysed 361 pathogenic *M. kansasii* isolates collected from patients with *M. kansasii* pulmonary disease in two tertiary medical centers in Taiwan between 2011 and 2022. Antimicrobial susceptibility testing was performed using Sensititre™ SLOMYCO1 or SLOMYCO2, and MIC breakpoints were according to CLSI 2018. We applied multivariate logistic regression and Cochran-Mantel-Haenszel test to assess the factors associated with drug resistance.

Results: Most *M. kansasii* isolates in Taiwan remained susceptible to the first-line agents, including rifampin (92.2%) and clarithromycin (98.6%). High resistance rates were observed in ciprofloxacin (42.7%), doxycycline (56.2%), and trimethoprim/sulfamethoxazole (87.8%). The drug resistance rates of tested antibiotics for *M. kansasii* increased notably in 2018-2022 compared to those between 2015-2017. *M. kansasii* isolates from central Taiwan exhibited significantly higher resistance rates in all drugs compared to those in southern Taiwan. Pulmonary

fibrocavitary lesion was an independent risk factor for resistance to rifampin and ciprofloxacin.

Conclusions: The study reveals increasing resistance to the first- and second-line agents in *M. kansasii* isolates across Taiwan. Resistance epidemiology differed between regions. Fibrocavitary lung lesion was significantly associated with drug resistance. These findings underscore the importance of region-specific surveillance to undergo individualized treatment strategies for *M. kansasii* pulmonary disease.

Keywords: *Mycobacterium kansasii*, resistance, drug susceptibility, risk factor, Taiwan.

Running title: Drug susceptibility trend of *M. kansasii* in Taiwan.

1. INTRODUCTION

Nontuberculous Mycobacterium (NTM) has become a significant global pathogen. Treating NTM diseases requires prolonged multidrug regimens, often leading to adherence issues due to adverse effects and treatment failure.

Although the correlation between drug susceptibility and clinical outcomes remains inconsistent due to limited studies (1), certain drugs, such as macrolides for *Mycobacterium avium* complex (2) and rifampin for *Mycobacterium kansasii* (3), have demonstrated clinical relevance. Drug resistance rates in various NTM species have increased over decades (4), with notable regional variations in susceptibility (5). Understanding updated regional resistance patterns is crucial for optimizing antimicrobial selection, especially given the lack of routine susceptibility testing.

M. kansasii, a slow-growing NTM, commonly causes pulmonary disease resembling tuberculosis, characterized by lower respiratory symptoms and upper lobe cavitation. Risk factors for *M. kansasii* pulmonary diseases include smoking, chronic obstructive pulmonary disease, alcohol abuse, bronchiectasis and prior tuberculosis infection (6). Standard treatment comprises rifampin, ethambutol, and either macrolide or isoniazid for at least 12 months, achieving cure rates of 80–100% (1, 6). However, prolonged treatment poses challenges, including adverse effects, high costs, and poor adherence. Rifampin is a key drug, as resistance correlates with treatment failure (1), while resistance to

isoniazid or ethambutol appears less impactful (7). Previous studies have shown that prior exposure to rifampicin can induce resistance (3), and the demographic variation of drug resistance has been reported (8-13). In Iran, rifampin resistance in *M. kansasii* isolates reaches 50% (8), while in Taiwan, Wu et al. reported a 21.6% resistance rate to rifampin among 37 isolates from Northern Taiwan (2000–2004) (12). In China, the rates range from 0% to 20% across regions (9-11, 13). In rifampin-resistant *M. kansasii* or first-line drug intolerance cases, second-line agents like fluoroquinolones and linezolid are considered as clinical treatment, though their in-vitro susceptibility remains underexplored.

As both the *M. kansasii* isolates and its pulmonary disease patients increased annually in Taiwan (14), alongside the recent rising use of broad-spectrum antibiotics, it is essential to elaborate the drug susceptibility profiles and unravel the sequential annual trend change of drug resistance, which can be crucial for guiding optimized treatment strategies for *M. kansasii* disease.

2. MATERIAL AND METHODS

2.1 Case and strain selection

This retrospective cohort study analyzed 396 clinical isolates of *M. kansasii* obtained from pretreatment sputum or bronchoalveolar lavage fluid of patients. These isolates were collected between 2011 and 2022 from two tertiary medical centers in central and southern Taiwan, including Taichung Veterans General Hospital (TVGH) in central Taiwan and Kaohsiung Medical University

Hospital (KMUH) in southern Taiwan. The institutional ethics committees of each site approved the study. Of the 396 isolates, 9 containing mixed NTM species and 26 colonization isolates were excluded, leaving 361 *M. kansasii* isolates for final analysis. All patients met the ATS/IDSA diagnostic criteria for *M. kansasii* pulmonary disease (1). Baseline demographics, comorbidities, sputum acid-fast smear results, radiographic patterns, and lesion extent were recorded. We collected imaging studies, including chest radiographs and computed tomography scans, performed within six months before and after the diagnosis of NTM pulmonary disease. The images were independently reviewed by two radiologists from our medical team who were blinded to the patients' clinical information. Subsequently, two pulmonologists re-evaluated the images and corresponding reports.

2.2 Strain culture and drug susceptibility test

The *M. kansasii* isolates were initially retrieved from frozen vials containing 7H9 stock solution supplemented with 15% glycerol (VWR) and OADC (Oleic Albumin Dextrose Catalase; CMP). The strains were streaked onto 7H11 solid agar plates (Becton Dickinson) and incubated at 37°C in a 5% CO₂ incubator until reaching the log phase. The colonies were then selected for species identification using Matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) spectrometry with Bruker Biotyper system, Mycobacteria Library v3.0 (Bruker Daltonics GmbH & Co. KG., Bremen, Germany).

Subsequently, the antimicrobial susceptibility testing of *M. kansasii* isolates was performed using commercially available Sensititre™ SLOMYCO1 and SLOMYCO2 plates (Trek Diagnostic Systems Ltd., East Grinstead, UK). The testing medium consisted of Cation-Adjusted Mueller-Hinton Broth with 5% (v/v) OADC supplement (Trek Diagnostic Systems Ltd.). The SLOMYCO1 plate included the following antibiotics: amikacin, ciprofloxacin, clarithromycin, doxycycline, ethambutol, ethionamide, isoniazid, linezolid, moxifloxacin, rifabutin, rifampin, streptomycin, and trimethoprim/sulfamethoxazole (SXT). The SLOMYCO2 panel featured the same drugs, except ethambutol, ethionamide, and isoniazid, while adding clofazimine, minocycline, and a higher concentration of amikacin (The detailed difference was shown in Table S1).

Due to discontinued production of the SLOMYCO1 panels during the study period, different testing strategies were employed in sites because of the testing kit supply issue. At TVGH, 59 isolates were tested using the SLOMYCO1 panel. At KMUH, the first 56 isolates were initially tested with the SLOMYCO1 panel; however, as this panel was subsequently discontinued, all 302 isolates from KMUH, including these initial 56 isolates, were retested using the SLOMYCO2 panel to ensure consistency. Consequently, with the exception of ethambutol, which was assessed only in SLOMYCO1, all reported minimum inhibitory concentration (MIC) results from KMUH were derived from the SLOMYCO2 panel. The process of antimicrobial susceptibility testing was

performed according to the product instructions, and the MIC, defined as the lowest dilution concentration resulting in a 99% reduction in growth, was determined visually. The breakpoint of antimycobacterial agents is according to the Clinical and Laboratory Standards Institute (CLSI) guideline 2018 (15). Results were categorized into three classifications: susceptible, intermediate, or resistant. Antibiotic agents and their interpretive ranges for slow-growing mycobacteria are summarized in the corresponding tables.

2.3 Literature review

Given the limited data on *M. kansasii* drug susceptibility, we compared our findings with published studies. A comprehensive literature search was conducted on PubMed using the keywords "Mycobacterium kansasii AND drug susceptibility" across all search fields, with a restriction to English-language publications. The final search was completed on 8 December 2024. Two authors independently reviewed the identified articles, screening titles, and abstracts to select studies that assessed drug susceptibility profiles using broth microdilution methods and applied breakpoints defined by the CLSI. Of 212 identified articles, 15 met the inclusion criteria. Resistance rates were extracted independently by two authors and summarized in Table 1.

2.4 Outcome assessment

The primary objective was to analyze demographic variations in *M. kansasii* drug susceptibility in Taiwan. The secondary objective was to identify

predictors of drug resistance and compare MIC profiles with global studies.

2.5 Statistical analysis

Intergroup differences in continuous variables were analyzed using the Student t-test or the Mann-Whitney U test, depending on normality. Categorical variables were compared with the χ^2 test or Fisher exact test, as appropriate. Multivariate logistic regression was used to determine adjusted odds ratios (aOR), 95% confidence intervals (CI), and p-values to assess potential risk factors for each drug resistance. Statistical significance was defined as a two-sided p-value of < 0.05 . Considering the substantial difference in sample sizes between the two hospitals, we further applied additional statistical methods, including the Cochran–Mantel–Haenszel (CMH) test and the Breslow–Day test, to minimize potential bias arising from the sample size disparity. All statistical analyses were performed using SPSS, version 20.0 (SPSS Inc., Chicago, Illinois, USA).

3. RESULTS

3.1 Baseline characteristics of enrolled population

The clinical characteristics of 361 patients with *M. kansasii* pulmonary disease, including 302 from KMH in southern Taiwan and 59 from TVGH in central Taiwan were presented in Table 2. The mean age was 65.6 ± 17.8 years, with 67.3% male ($n = 243$). Among the patients, 54.8% were never-smokers. The most common comorbidity was chronic obstructive pulmonary disease (COPD)

(30.0%), followed by diabetes mellitus (20.8%) and prior pulmonary tuberculosis (17.5%). A fibrocavitary pattern was observed in 19.9% of cases ($n = 72$).

Baseline characteristics were comparable between the two hospitals, except for a higher prevalence of fibrocavitary lesions at TVGH (47.5% vs. 14.6%, $p < 0.001$). Fibrocavitary lesions were associated with smoking (adjusted OR: 1.54 [1.04–2.30], $p = 0.033$) and prior pulmonary tuberculosis (adjusted OR: 2.00 [1.04–3.86], $p = 0.038$) (Table S2).

3.2 Results of drug susceptibility

Detailed results of drug susceptibility are shown in Table 2 and Table S3. Most drugs exhibited low resistance rates in Taiwan, including rifampin (7.8%), rifabutin (2.5%), clarithromycin (1.4%), amikacin (9.1%), linezolid (5.8%), and moxifloxacin (6.9%). In contrast, high resistance rates were observed for ciprofloxacin (42.7%), doxycycline (56.2%), trimethoprim/sulfamethoxazole (87.8%), and ethambutol (100%). *M. kansasii* isolates from central Taiwan exhibited significantly higher resistance rates in all drugs compared to those in southern Taiwan, suggesting regional differences in drug susceptibility (Table 2).

Figure 1 and Table S4 illustrate the annual trends in drug resistance, showing increased resistance from 2018–2022 compared to 2015–2017, particularly for ciprofloxacin (77.3% vs. 30.4%), doxycycline (83.3% vs. 46.9%), and minocycline (34.6% vs. 8.8%).

3.3 Predictors for drug resistance of each antimicrobial agents

was demonstrated in Table S5-S12. Baseline characteristics were similar between groups, except that the patients with pulmonary fibrocavitary lesions have higher resistance to rifampin, clarithromycin, amikacin, linezolid, moxifloxacin, ciprofloxacin, and doxycycline when compared to those without pulmonary fibrocavitary lesions. Table 3 further highlights the impact of fibrocavitary lesions on drug resistance. Among patients with prior tuberculosis, those with fibrocavitary lesions showed higher ciprofloxacin resistance than those without (47.4% vs. 20.5%, $p < 0.05$). In patients without prior tuberculosis, more patients with fibrocavitary lesions were associated with increased resistance to clarithromycin (5.7% vs. 0.4%, $p < 0.05$), rifampin (26.4% vs. 4.5%, $p < 0.05$), amikacin (18.9% vs. 7.3%, $p < 0.05$), ciprofloxacin (75.5% vs. 39.2%, $p < 0.05$), doxycycline (71.7% vs. 55.5%, $p < 0.05$), linezolid (15.1% vs. 4.9%, $p < 0.05$), moxifloxacin (18.9% vs. 5.3%, $p < 0.05$), and rifabutin (9.4% vs. 1.6%, $p < 0.05$). These findings indicate that fibrocavitary lesions, regardless of tuberculosis history, are linked to resistance to many drugs. In overall, table S13 showed the fibrocavitary lesions is the independent risk factor for each offending drug, including rifampin (aOR [% CI]: 7.98 [3.2 – 19.90], $p < 0.001$), rifabutin (aOR [% CI]: 11.1 [2.14–57.81], $p < 0.001$), clarithromycin (aOR [% CI]: 14.56 [1.45–146.04], $p = 0.023$), amikacin (aOR [% CI]: 2.55 [1.19–5.47], $p = 0.016$), linezolid (aOR [% CI]: 3.78 [1.51–9.47], $p = 0.005$), moxifloxacin

(aOR [% CI]: 4.93 [2.08–11.68], $p < 0.001$), ciprofloxacin (aOR [% CI]: 4.71 [2.62–8.47], $p < 0.001$), and doxycycline (aOR [% CI]: 1.89 [1.08–3.32], $p = 0.026$).

Table 4 and Table S14 demonstrated the common odds ratio (OR) across different medical centers, estimated using the CMH test to adjust for stratification by center. After adjustment using the CMH test, pulmonary fibrocavitary lesions remained associated with resistance to rifampin (common OR 2.82, 95% CI: 1.05–7.56, $p = 0.039$) and ciprofloxacin (common OR 2.44, 95% CI: 1.33–4.50, $p = 0.004$). Additionally, COPD was also linked to an increased risk of ciprofloxacin resistance (common OR 2.28, 95% CI: 1.39–3.75, $p = 0.001$). The combined effect of both COPD and fibrocavitation was associated with an even greater risk of ciprofloxacin resistance, with an adjusted OR of 7.07 (95% CI: 2.01–24.93, $p = 0.002$). (Table S15)

3.4 Literature review

Data from 15 literature publications were systematically listed in Table 1. The considerable diversity in drug resistance patterns is noted not only between different countries but also within different regions of a country that regions of China have different resistance patterns within the same country (9-11, 13). High resistance rates (>20%) to rifampin and clarithromycin are noted in Iran, India, and some regions of China (8-10, 16, 17). In contrast, low resistance rates to both drugs are found in Europe (18-20). In East Asia, Taiwan, Korea, and China all

showed high resistance rates to ciprofloxacin and doxycycline (9, 11-13, 21).

Moreover, Taiwan and China share similar high resistance rates to trimethoprim/sulfamethoxazole (9, 11, 13). Wu et al. reported a drug resistance profile in northern Taiwan distinct from our findings (12), with higher resistance to rifampin (21.6% vs. 7.8%) and moxifloxacin (40.5% vs. 6.9%) but lower resistance to amikacin (2.7% vs. 9.1%) and trimethoprim/sulfamethoxazole (18.9% vs. 87.8%).

4. DISCUSSION

Although *M. kansasii* generally responds well to first-line antibiotics, emerging resistance remains a concern in some regions (4, 22, 23). Knowing the epidemiology of drug resistance is useful for optimizing *M. kansasii* treatment, particularly when resistance necessitates second-line agents. This study analyzes the drug susceptibility trends of *M. kansasii* in Taiwan over the past decade. Our findings revealed that although most *M. kansasii* isolates remain susceptible to first-line agents like rifampin and clarithromycin, an annual increase in resistance rates is evident. Rifabutin and linezolid may serve as key alternatives for rifampin-resistant strains. Notably, despite a 100% resistance rate to ethambutol in Taiwan, current guidelines emphasize that resistance does not correlate with clinical outcomes, supporting its continued use in first-line regimens.

Although the resistance rate to ethambutol in Taiwan has reached 100%, treatment guidelines continue to recommend its inclusion in first-line regimens (1, 7), as resistance has not been shown to correlate with clinical outcomes. This paradox underscores the limited clinical utility of ethambutol drug susceptibility testing (DST) and suggests that its value may reside primarily in the context of combination therapy rather than as a single agent, highlighting the need to refine the interpretation of DST results in guiding treatment decisions.

The increasing resistance to second-line agents such as ciprofloxacin and doxycycline limits their roles as the preferred therapeutic options in Taiwan. These insights can help clinicians select appropriate second-line antibiotics for *M. kansasii* treatment. Additionally, we observed the significant regional difference in drug resistance rates across regions within Taiwan, a small island country. We also summarized the drug resistance epidemiology of *M. kansasii*, which differed between countries from the literature review. The above indicated the need of local epidemiology and emphasized the impact of regional differences on drug susceptibility patterns. Furthermore, pulmonary fibrocavitary lesions were identified as predictors of multidrug resistance, underscoring the importance of clinical and radiographic factors in guiding therapy. Even after adjusting for potential bias arising from the disparity in sample size between the two medical centers, pulmonary fibrocavitary lesions remained associated with

antimicrobial resistance, particularly to rifampin, which is a key drug in the treatment of *M. kansasii*.

Regional difference in drug resistance of *M. kansasii* is presented in Table 1. In Europe, resistance rates to first-line agents such as rifampin and clarithromycin are generally low, while resistance to amikacin, isoniazid, and ethambutol varies widely. However, resistance to isoniazid and ethambutol is clinically insignificant due to minimal impact on treatment outcomes. In contrast, Asia exhibits higher rifampin resistance but lower amikacin resistance. For example, rifampin resistance in China ranges from 0% to 56% (9-11, 13), while linezolid resistance in Iran varies from 0% to 89% (4, 8). Our data similarly show higher resistance rates in central Taiwan compared to the south, aligning with previous studies, such as Wu et al. (12), which reported higher rifampin and moxifloxacin resistance but lower TMP-SMX resistance in northern Taiwan. These findings underscore the need for region-specific treatment strategies. Additionally, progressive increase in resistance rates over time, as observed in Italy (22, 23), supports the rising trend of resistance identified in our study.

The mechanisms of resistance in NTM can be classified as innate or acquired. Innate resistance is driven by variations in cell wall structures, intracellular enzymes, and inducible resistance genes, contributing to the diversity in drug sensitivity among strains (24). Acquired resistance is often influenced by regional antibiotic usage patterns (5, 22), explaining variations

within geographically close areas. A retrospective cohort study reported an increase in drug resistance of rifampin, ethambutol and isoniazid in *M. kansasii* following two months of presumptive antimycobacterial treatment (25). Rifampin resistance, a key determinant of *M. kansasii* treatment failure (1) and primarily results from *rpoB* gene mutations, is likely driven by antibiotic selection pressure (26). Alternative mechanisms, such as drug inactivation via ADP-ribosylation mediated by the *arr* gene, may also play a role (26). In Iran, the routine administration of first-line anti-TB drugs to all mycobacterial disease patients may contribute to high rifampin resistance (8). Similarly, Wu et al. hypothesized that the widespread use of antituberculosis drugs, driven by the high prevalence of TB in Taiwan, could explain the elevated rates of rifampin resistance (12). Differently, our study found no correlation between rifampin resistance and prior pulmonary TB. Our result does not provide supportive evidence to prove selection pressure and the major underlying mechanisms.

Fluoroquinolone resistance is rising globally (27), with our findings highlighting a particularly rapid increase in resistance rates for *M. kansasii*. High fluoroquinolone resistance rates are also reported in other bacterial species in Taiwan, such as *Salmonella enterica* (28). This trend may be linked to widespread fluoroquinolone use in healthcare, agriculture, and aquaculture (28), emphasizing the urgent need for judicious antibiotic use and regulatory

oversight. Further research is needed to elucidate resistance mechanisms, particularly through genetic analysis.

We observed that pulmonary fibrocavitary lesions were associated with increased drug resistance, particularly in patients without prior pulmonary TB (Table 3). We hypothesize that *M. kansasii* infections leading to fibrocavitary lesions may promote drug resistance, mirroring trends observed in pulmonary TB (29, 30). This phenomenon could be attributed to higher bacterial loads within cavitory lesions (31) and reduced antibiotic penetration (29), both of which increase the likelihood of spontaneous gene mutations and resistance development. Interestingly, a retrospective cohort study reported that the resolution of pulmonary cavities during treatment was associated with treatment success (32). Imaging findings, both before and during treatment, may provide valuable clues for physicians in evaluating treatment efficacy. Whether the patients' experience of antimicrobial agents is heavier, or the disease duration is longer in cases with fibrocavitary pattern was not clearly elucidated in the study for the limitation of retrospective design. However, it warrants further investigation.

Our study has several limitations. First, the sample size discrepancy between central and southern Taiwan may have exaggerated resistance rate differences. Therefore, we further applied additional statistical methods, including the Cochran–Mantel–Haenszel test and the Breslow–Day test, to

minimize potential bias arising from the sample size disparity. Second, although we know the drug resistance rate increased, the treatment efficacy regarding to each offending drug is not reported in our study. Third, spatial-genotypic analyses of *M. kansasii* strains were lacking, limiting our understanding of resistance mechanisms and regional variations. Fourth, the lack of routine drug susceptibility testing for *M. kansasii* limited data availability from northern and eastern Taiwan, potentially introducing selection bias. Fifth, the transition from the SLOMYCO1 to SLOMYCO2 panel, necessitated by the discontinuation of the former, may have introduced minor variability in MIC determination, although this change has been noted in prior study (33).

Our study demonstrates evolving antimicrobial resistance patterns of *M. kansasii* isolates across Taiwan, with rising resistance rates over the past decade. Although susceptibility to rifampin and clarithromycin remains high, increasing resistance to second-line agents such as ciprofloxacin and doxycycline presents important therapeutic challenges. Geographic variability and the presence of pulmonary fibrocavitary lesions emerged as key factors shaping resistance profiles. These findings underscore the importance of region-specific surveillance and individualized treatment approaches. To our knowledge, this represents the most comprehensive dataset on *M. kansasii* resistance trends in Taiwan, providing a valuable reference to inform clinical decision-making and guide future treatment strategies.

Author contributions:

Manuscript writing and figure preparation: SBF, HLH, WCH, PLL

Study design: SBF, HLH, WCH, PLL

Data collection: SBF, HLH, MHC, YWH, SYL, IWC, WCH, PLL

Data analysis and interpretation: SBF, HLH, HPT, BS, WCH, PLL

Manuscript revision: WCH, PLL, IWC

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Declaration of Generative AI and AI-assisted technologies in the writing process:

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Table 1. Literature review of anti-mycobacterial resistance rates (%) using broth microdilution for *M. kansasii* isolates in different countries

Continent	Country	Specimen (number/source)	Period	CLSI	CLA	RIF	AMI	CIP	MIN	DOX	LZD	MXF	RFB	SXT	INH	EMB	STR
Europe	Spain (20)	104/Mixed	1994-2005	2003	0	1.9	-	-	-	-	0	0	-	-	2.9	2.9	-
	Poland (18)	62/ Unknown	2000-2015	2011 ^a	0	0	0	25.8	-	-	0	0	0	0	-	100	-
	Portugal (19)	36/ Mixed	2003-2016	2011	-	0	-	-	-	-	-	-	-	-	2.9	0	-
	Italy (22)	48/ Mixed	2016-2020	2018 ^a	0	12.5	7	53.2	-	72.7	2.3	4.4	2	62.5	-	-	-
	Italy (23)	9/ Mixed	2018-2023	2018 ^a	0	78	11	44	-	55	22	0	22	89	-	-	-
Americas	Brazil (34)	69/ Respiratory site	2008-2016	2011	1	12	0	51	-	-	-	0	-	96	-	75	-
Asia	Iran (8)	40/ Mixed	2010-2014	2003	0	50	5	50	-	100	0	0	50	8	0	0	35
	Iran (16)	46 /Respiratory site	2017-2020	2011	17.4	43.5	0	-	-	-	89.1	13	-	-	97.8	30.4	-

India (17)	18/ Respiratory site	2017-2020	2011 ^a	17	39	11	33	-	72	11	11	11	39	-	-	-
China (10)	78/ Unknown	2008-2015	2011	20.5	56.4	5.1	-	-	-	32.1	16.7	34.6	16.7	-	20.5	-
China (9)	60 /Respiratory site	2018-2020	2011 ^a	1.7	20	10	73.3	-	-	8.3	11.7	0	31.7	-	76.7	-
China (11)	31 /Respiratory site	2013	2018 ^a	0	6.5	0	25.8	-	77.4	3.2	0	3.2	51.6	-	-	-
China (13)	14 /Respiratory site	2019-2021	2018 ^a	0	0	0	0	-	100	0	0	0	64.3	-	43	-
Korea (21)	23/ Mixed	2016-2020	2018	0	4	0	52	-	61	0	0	-	17	-	-	-
Taiwan (12)	37/Respiratory site	2000-2004	2003	0	21.6	2.7	29.7	-	-	-	40.5	2.7	18.9	27	73	5.4
Our study	361 /Respiratory site	2011-2022	2018^a	1.4	7.8	9.1	42.7	12.9	56.2	5.8	6.9	2.5	87.8	-	100	-

^a The drug susceptibility testing was performed with Sensititre™ SLOMYCO panel.

Abbreviations: AMI: amikacin; CIP: ciprofloxacin; CLA: clarithromycin; DOX: doxycycline; EMB: ethambutol; LZD: linezolid; MXF: moxifloxacin; RIF:

rifampin; RFB: rifabutin; SXT: trimethoprim/sulfamethoxazole;

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Table 2: Clinical information and susceptibility results of isolates from patients**with *M. kansasii* pulmonary disease, stratified by geographic distribution in****Taiwan**

	Total (n=361)	Southern (n = 302)	Central (n = 59)	p- value
Age (year)	65.6 ± 17.8	61.4 ± 19.4	65.9 ± 17.6	0.456
male sex	243 (67.3%)	200 (66.2%)	43 (72.9%)	0.319
Smoking status				
Never smoker	198 (54.8%)	170 (56.3%)	28 (47.5%)	0.212
Current	62 (17.2%)	61 (20.2%)	1 (1.7%)	0.001
Ever	101 (28.0%)	71 (23.5%)	30 (50.8%)	0.001
Specimen categories				
Expectorated sputum	350 (97.0%)	294 (97.4%)	56 (94.9%)	
Bronchoscopic alveolar lavage	11 (3.0%)	8 (2.6%)	3 (5.1%)	
Comorbidities				
Old pulmonary tuberculosis	63 (17.5%)	57 (18.9%)	6 (10.2%)	0.107
Diabetes mellitus	75 (20.8%)	66 (21.9%)	9 (15.3%)	0.253
COPD	101 (30.0%)	88 (29.1%)	13 (22.0%)	0.266
Acid-Fast smear grading				

<2	74(20.5%)	51(16.9%)	23(39.0%)	
≥ 2	60(16.6%)	45(14.9%)	15(25.4%)	
Radiographic pattern				
Fibrocavitary	72 (19.9%)	44 (14.6%)	28 (47.5%)	<0.001
Drug-Resistance (R)				
Rifampin-R	28 (7.8%)	4 (1.3%)	24 (40.7%)	<0.001
Rifabutin-R	9 (2.5%)	2 (0.7%)	7 (11.9%)	<0.001
Clarithromycin-R	5 (1.4%)	1(0.3%)	4 (6.8%)	<0.001
Amikacin-R	33 (9.1%)	13 (4.3%)	20 (33.9%)	<0.001
Linezolid-R	21 (5.8%)	5 (1.7%)	16 (27.1%)	<0.001
Moxifloxacin-R	25 (6.9%)	6 (2.0%)	19 (32.2%)	<0.001
Ciprofloxacin-R	154 (42.7%)	101 (33.4%)	53 (89.8%)	<0.001
Doxycycline-R	203 (56.2%)	148 (49.0%)	55 (93.2%)	<0.001
Minocycline-R*	39(12.9%)	39(12.9%)	-	-
SXT-R	317 (87.8%)	260 (86.1%)	57 (96.6%)	0.027

Data are presented as mean $\pm$ standard deviation or number (%).

* The drug susceptibility test for minocycline was performed using Sensititre™

SLOMYCO 2. However, at Taichung Veterans General Hospital, the drug

susceptibility test was conducted using Sensititre™ SLOMYCO1, which did not

include minocycline testing. Consequently, the total number of tests conducted for

minocycline was 302.

p value for the comparison of data from southern and central Taiwan was calculated

using Student's t test, chi-square test, or Fisher's exact test.

Abbreviations: COPD: chronic obstructive pulmonary disease; SXT:

trimethoprim/sulfamethoxazole

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tuberculosis status

Drug Resistance	With history of pulmonary TB		Without history of pulmonary TB	
	FC (n, %)	Non-FC (n, %)	FC (n, %)	Non-FC (n, %)
Patient number	19, 100%	44, 100%	53, 100%	245, 100%
CLA-R	1, 5.3%	0	3, 5.7%*	1, 0.4%
RIF-R	2, 10.5%	1, 2.3%	14, 26.4%*	11, 4.5%
AMI-R	2, 10.5%	3, 6.8%	10, 18.9%*	18, 7.3%
CIP-R	9, 47.4%*	9, 20.5%	40, 75.5%*	96, 39.2%
MIN-R [#]	2, 13.3%	3, 7.1%	3, 10.3%	31, 14.4%
DOX-R	11, 57.9%	18, 40.9%	38, 71.7%*	136, 55.5%
LZD-R	1, 5.3%	0	8, 15.1%*	12, 4.9%
MXF-R	2, 10.5%	0	10, 18.9%*	13, 5.3%
RFB-R	0	0	5, 9.4%*	4, 1.6%
SXT-R	18, 94.7%	34, 77.3%	47, 88.7%	218, 89.0%
EMB-R [#]	4, 100%	2, 100%	24, 100%	29, 100%

* The statistical significance ($p < 0.05$) in the group (FC vs. Non-FC in patients with history of pulmonary tuberculosis, or FC vs. Non-FC in patients without history of pulmonary tuberculosis)

[#] Due to discontinued production of the SLOMYCO1 panels during the study period, different testing strategies were employed at different sites. At TVGH, 59 isolates were tested using the SLOMYCO1 panel, while at KMUH, the initial 56 isolates were tested with the SLOMYCO1 panel before all subsequent 302 isolates were retested using the SLOMYCO2 panel. Therefore, the number of specimens in these two groups differed from that in the other group.

Abbreviations: AMI: amikacin; CIP: ciprofloxacin; CLA: clarithromycin; DOX: doxycycline; EMB: ethambutol; FC: fibrocavitation; LZD: linezolid; MXF: moxifloxacin; RIF: rifampin; RFB: rifabutin; SXT: trimethoprim/sulfamethoxazole; TB: tuberculosis.

with the Cochran-Mantel-Haenszel test

Drug resistance (R)	Predictors	Common OR [95% CI]	<i>p</i> -value
Rifampin-R	Fibrocavitation	2.82 (1.05-7.56)	0.039
Rifabutin-R	Fibrocavitation	2.02 (0.5-8.17)	0.325
Clarithromycin-R	Fibrocavitation	5.62 (0.67-46.84)	0.111
Amikacin-R	Fibrocavitation	1.14 (0.46-2.83)	0.773
Linezolid-R	Fibrocavitation	1.21 (0.43-3.37)	0.720
Moxifloxacin-R	Fibrocavitation	1.76 (0.65-4.78)	0.267
Ciprofloxacin-R	COPD	2.28 (1.39-3.75)	0.001
	Fibrocavitation	2.44 (1.33-4.50)	0.004
Doxycycline-R	Fibrocavitation	1.14 (0.62-2.09)	0.679

The Cochran-Mantel-Haenszel (CMH) test was used to estimate the common odds ratio across different medical centers, adjusting for potential confounding due to center-specific differences.

Abbreviations: CI, confidence interval; OR, odds ratio.

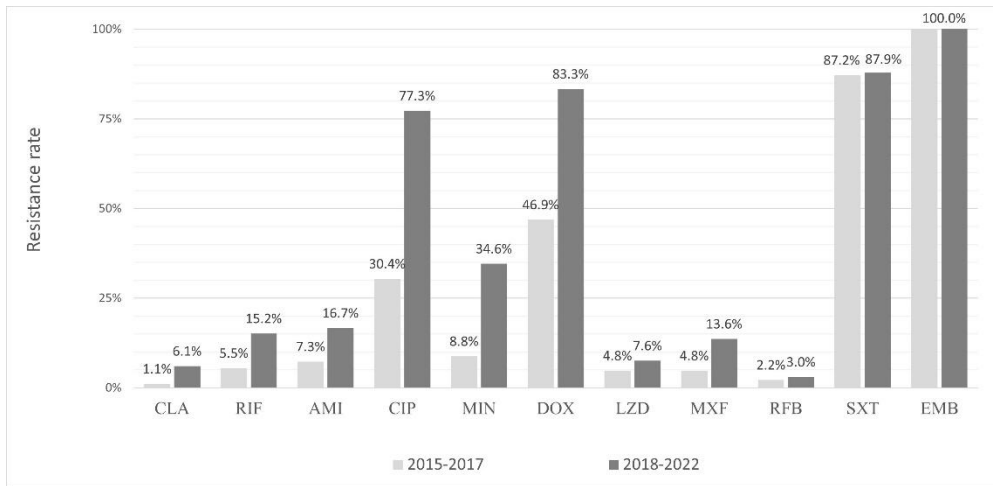


Figure 1. The annual change in drug resistance rate of *M. kansasii*, stratified by year-period, before and after 2018

Abbreviations: AMI, amikacin; CIP, ciprofloxacin; CLA, clarithromycin, DOX, doxycycline, E, ethambutol; LZD, linezolid; M, moxifloxacin; RIF, rifampin; RFB, rifabutin; SXT, Trimethoprim / sulfamethoxazole

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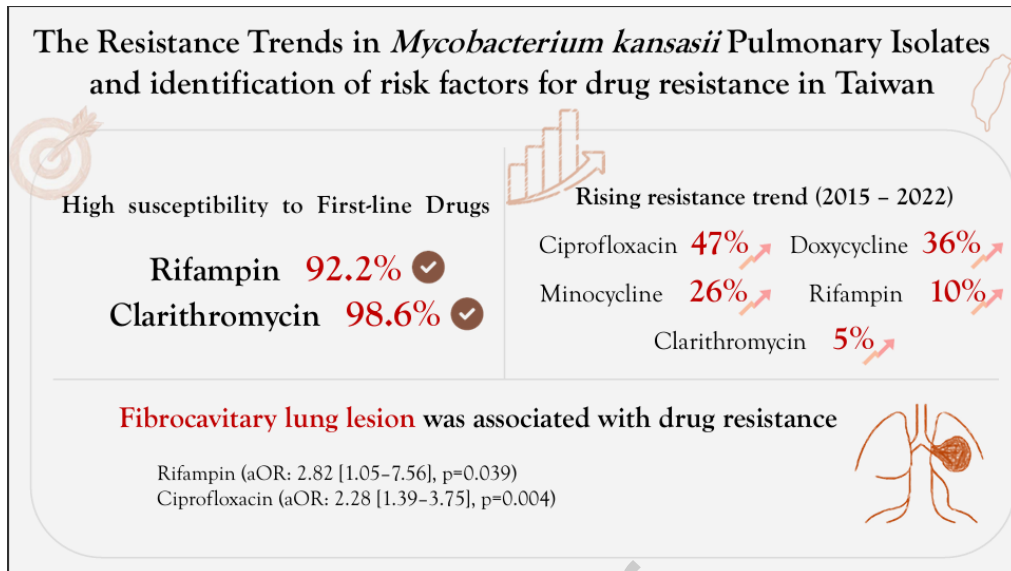
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