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Characteristics of Drug-sensitive and Drug-resistant Tuberculosis Cases among Adults at Tuberculosis Referral Hospitals in Indonesia

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Abstract. As Indonesia's rifampin resistance testing rates are lower than global testing rates per the 2020 WHO global tuberculosis (TB) report, prevalence of multidrug-resistant TB may be underestimated. Our study aimed to evaluate prevalence and patterns of TB drug resistance (DR) within Indonesia. We conducted a cross-sectional analysis of baseline data collected from 2017–2018 as part of a cohort study of adults with presumed pulmonary TB at 7 DR-TB referral hospitals in Indonesia. Bacteriological examinations (acid-fast bacilli, GeneXpert, sputum culture) and drug-susceptibility testing were performed following the guidelines of the National TB Program. Of 447 participants with complete bacteriological examinations, 312 (69.8%) had positive sputum cultures for *Mycobacterium tuberculosis*. The proportion of MDR and pre-extensively drug-resistant was higher in previously treated compared with newly diagnosed participants (52.5% [73/139] versus 15% [26/173]). Compared with drug-sensitive case, drug-resistant TB was associated with cavities. Given the difference between rates of DR in TB referral hospitals from our study compared with the WHO survey in 2019 that showed 17.7% and 3.3% DR among previously treated and newly diagnosed participants globally, further characterization of Indonesia's TB epidemiology in the general population is needed. Strategies, including public policies to optimize case finding, strengthen capacity for resistance testing, and prevent loss to follow-up will be critical to reduce the burden of TB in Indonesia.

INTRODUCTION

Tuberculosis (TB) remains a significant global public health problem, particularly in low- and middle-income countries. In 2020, the WHO estimated that there were 10 million cases and 1.5 million deaths attributable to TB worldwide. Compared with 2000, this represents a 15% decrease in incidence and 35% decrease in mortality.[1] Similar to the global trend, new TB cases in Indonesia decreased from 370 to 312 cases per 100,000 people from 2000 to 2019. During the same period, annual mortality fell from 119,000 to 96,000 deaths.[2] Despite decreasing rates and scientific advances, concerns related to TB-HIV coinfection[3] and emergence of drug-resistant *Mycobacterium tuberculosis* (MTB) persist.[4,5]

The global incidence of multidrug-resistant/rifampicin (RIF)-resistant (MDR/RR) TB has increased 20% annually to reach 650,000 cases, with the proportion of MDR and RR-TB higher in previously treated patients (17.7%) versus new cases (3.3%) in 2019.[4] These numbers may be underestimated because RR testing rates for microbiologically confirmed cases, particularly among those with newly diagnosed TB, were lower than among previously treated cases (59% versus 81%, respectively).[4] Data from the most recent drug-resistant TB (DR-TB) surveys conducted between 2004 and 2007 reveal varying MDR prevalence among newly diagnosed TB cases (1.8% in Central Java,[6] 2% in Jayapura, Papua,[7] and 4.1% in Makassar[8]) and previously treated TB cases (11.7% in Central Java[6] and 19.2% in Makassar[8]). Data on DR-TB, including extensively drug-resistant (XDR) TB, from other geographic areas are lacking in Indonesia. Our study aimed to provide more accurate data on the prevalence of DR-TB among newly diagnosed TB or previously treated TB cases in Indonesia. These data can be used by Indonesia's National TB Program (NTP) to facilitate achievement of the WHO EndTB goals.

METHODS

Study design and population. This is a cross-sectional analysis of baseline data from a prospective cohort study that enrolled participants from February 2017 to November 2018 at seven DR-TB referral hospitals in seven large cities in Indonesia (Dr. Soetomo, Surabaya; Sanglah, Denpasar; Dr. Sardjito, Yogyakarta; Dr. Kariadi, Semarang; Persahabatan, Jakarta; H. Adam Malik, Medan; and Dr. Wahidin Sudirohusodo, Makassar). These hospitals received referral patients from primary health centers and private clinics. Referral patients met suspected DR-TB criteria, including standard anti-TB treatment failure, no sputum conversion after the intensive phase of standard anti-TB treatment, receipt of non-standard anti-TB treatment, disease relapse, return after

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being lost to follow-up, close contact with DR-TB patients, or having TB-HIV coinfection and not responding to anti-TB treatment.

Enrollment criteria included age ≥ 18 years, presumptive pulmonary TB with cough for at least 2 weeks and at least one other TB symptom (fever, unexplained weight loss, loss of appetite, hemoptysis, shortness of breath, chest pain, night sweats, or fatigue). Participants were excluded if they received TB treatment of more than 7 days in the past month or had any serious underlying conditions (e.g., chronic liver disease, chronic kidney disease, or psychiatric illness). Women were tested to ensure that they were not pregnant at enrollment.

Study procedures. Participants signed informed consent on day 0. A baseline visit occurred between days 0 and 5. Demography, TB history, contact history, tobacco use, treatment-seeking behavior, clinical data, physical examination including body weight and height, and chest x-ray were collected. Sputum was obtained for acid-fast bacilli (AFB) smear, GeneXpert, and culture examination. Sputum was induced if necessary; failure to collect sputum at baseline was considered as end of study for the participant. Blood was drawn for clinical and research purposes.

Microbiological work-up. AFB smear and GeneXpert were performed at the microbiology laboratory of the study sites. Culture and drug susceptibility tests were conducted at appointed National TB Program Reference Laboratories.

AFB smear microscopy. Sputum smears were stained for acid-fast microscopic examination using the Ziehl-Neelsen stain. Smear-positive specimens were reported semi-quantitatively using the standard scale from the International Union Against Tuberculosis and Lung Disease as recommended by the U.S. CDC.[9]

GeneXpert. The GeneXpert MTB/RIF cartridge was processed according to the manufacturer's recommendations (Cepheid, Sunnyvale, CA). GeneXpert MTB/RIF software was used to generate results.

Culture and drug susceptibility tests. Sputum was decontaminated with NaOH-NALC and inoculated into Lowenstein Jensen (LJ) media prepared according to manufacturer's instructions (BD BBL, BD, Sparks, MD)[10] or a Mycobacteria Growth Indicator Tube (BBL MGIT, BD), which contains PANTA supplemented modified Middlebrook 7H9. MTB was identified using TB Antigen MPT64 and para nitrobenzoic acid. First-line drug susceptibility was tested against streptomycin 1.0μg/mL, isoniazid (INH) 0.1 μg/mL, RIF 1.0 μg/mL, ethambutol 5.0 μg/mL in all participants. Second-line drug susceptibility was tested against ofloxacin 2 μg/mL, amikacin 1 μg/mL, and kanamycin 1 μg/mL, in previously treated participants and/or when GeneXpert detected MTB with RIF resistance. If isolates were MDR or resistant to three or four anti-TB drugs, MGIT drug-susceptibility testing (DST) was repeated to confirm resistance. Confirmed RIF, INH, and streptomycin-resistant MTB from clinical isolates and H37Rv ATCC 27294 were used as the positive and negative control, respectively.

Case classification. On the basis of microbiological examinations, participants were classified as 1) clinically diagnosed TB when none of the laboratory results were positive and 2) bacteriologically confirmed TB when at least one of the three examinations was positive. Among those with positive MTB culture, participants were further categorized as having drug-sensitive/susceptible TB (DS-TB), RR-TB, monoresistant TB (MR-TB), MDR-TB, polydrug resistance TB (PDR-TB), pre-XDR-TB, and XDR-TB based on WHO criteria.[11,12] Operational definitions are provided in Supplemental Table 1.

Statistical analysis. Descriptive data are presented as mean (SD) and frequencies (percentages). Cases are classified into new or previously treated TB based on the participant's report and/or hospital record.

Study approvals. Ethical clearance for this study was provided by the Indonesia National Institutes of Health and Research Development Health Research Ethics Committee. The study has been registered at ClinicalTrials.gov (registration number NCT02758236).

RESULTS

Classification of TB cases. Of 490 enrolled participants, 43 (8.8%) were excluded from analysis. Details are described in Figure 1. Among 447 participants with complete AFB, GeneXpert MTB/RIF, and sputum culture results, 260 (58.2%) were classified as newly diagnosed TB and 187 (41.8%) as previously treated TB cases. Sputum culture was positive in 173 (66.5%) newly diagnosed TB and in 139 (74.3%) previously treated TB cases. The proportion of MDR and pre-XDR was 46% and 6.5% in previously treated TB and 13.3% and 1.7% in newly diagnosed TB.

Participant characteristics. Age was not significantly different between previously treated TB and newly diagnosed TB cases, including when stratified by bacteriological and drug-resistance results. Participants were predominantly male (61%), which was not significantly different between newly diagnosed TB and previously treated TB groups. Most participants were nonsmokers. Only four of the 193 microbiologically confirmed new TB cases had prior contact with DR-TB patients. Of those 4, one had DS-TB and three had DR-TB. Thus, of the 58 new TB cases with DR-TB, 55 (94.8%) did not have a clearly identifiable source of resistance. Diabetes mellitus (DM) was the most common comorbidity (31.8%), with high proportions in all DR-TB subgroups (33.3%– 56.5%). Participants with negative culture results were also more likely to be diagnosed with extrapulmonary TB than other subgroups (15% in newly diagnosed TB and 19% in previously treated TB cases). Previous contact with TB patients was more common in newly diagnosed TB than previously treated TB (14% and 9%, respectively) among bacteriologically confirmed cases. By chest x-ray, the proportion of affected lung was highest in DR subgroups among previously treated TB cases (60%–85%), followed by DR subgroups in newly diagnosed TB cases (50%–57.5%), DS-TB subgroups (40%), culture negative (32.5%–37.5%), and clinical TB subgroups (27%–37.5%). All participants had opacities; cavities were more frequent in DR subgroups (53%–78%) and least frequent in clinical TB subgroups (12%–31.3%). Additional details are shown in Table 1.

TB status and drug-resistant pattern in each hospital. Due to differences in study duration, four hospitals contributed 85.2% of the 447 participants (Soetomo: 123 participants [27.5%], Kariadi: 103 [23%], Persahabatan: 80 [17.9%], and Sardjito: 75 [16.8%]). Of 447 TB cases, 78% were bacteriologically confirmed, ranging from 36% in Sardjito to 93% in Soetomo. Newly diagnosed TB cases were more commonly enrolled at most sites, except in Kariadi and

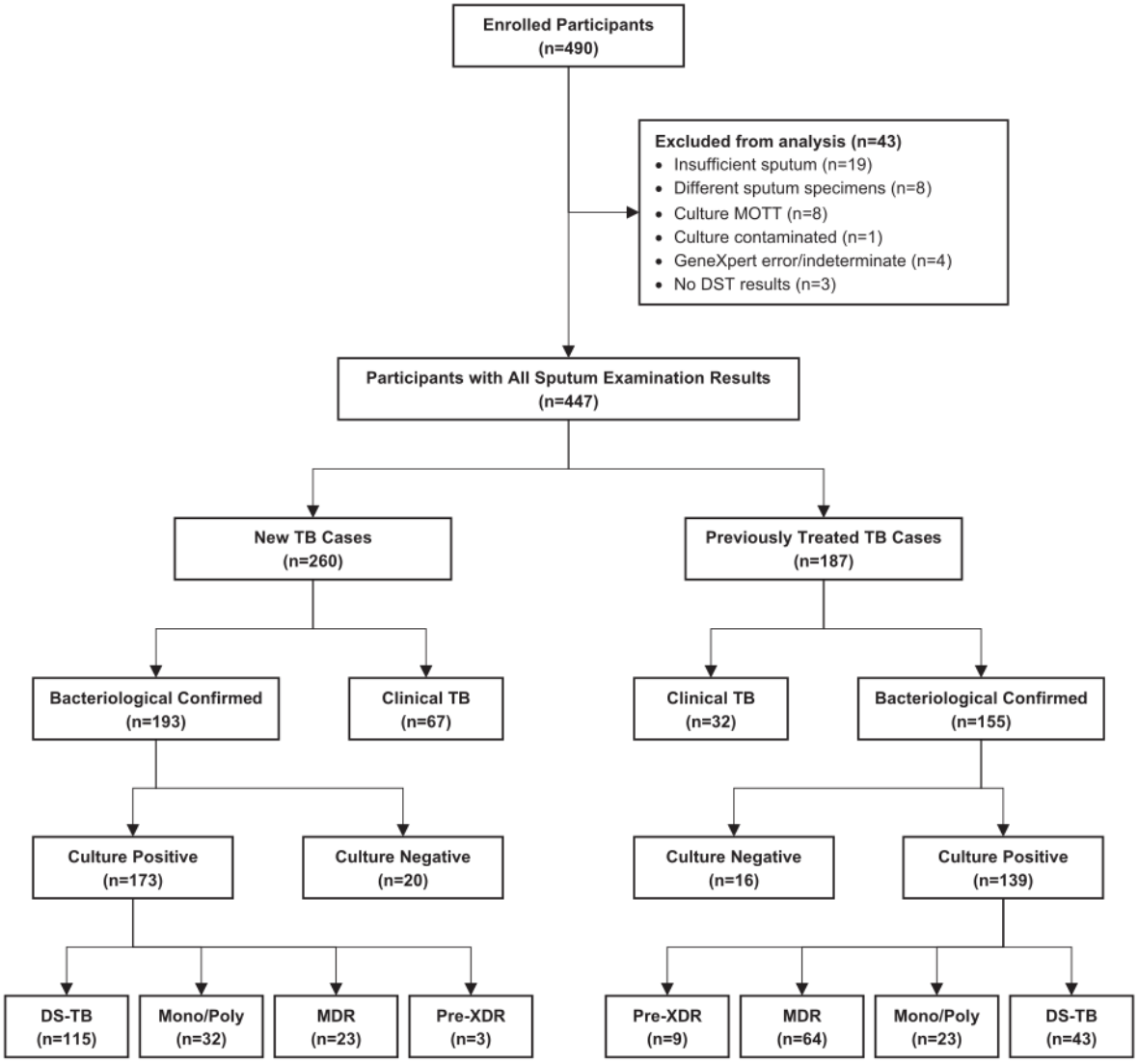

FIGURE 1. Flowchart of participants showing categorization by treatment history, results of bacteriological examination, and antituberculosis drug sensitivity test. DS-TB = drug sensitive/susceptible TB; DST = drug-susceptibility testing; MDR = multidrug-resistant; MOTT = *Mycobacterium* other than tuberculosis; Pre-XDR = pre-extensively drug resistance.

Adam Malik, where previously treated TB cases constituted the majority (65% and 76%); these hospitals also had the highest proportion of MDR cases (61% and 64%). Study site profiles are shown in Table 2 and Supplemental Table 2.

Drug-resistant patterns in newly diagnosed TB and previously treated TB cases. Figure 2 shows the distribution of the 58 newly diagnosed TB and 96 previously treated TB cases with drug resistance. Mono resistance was more frequent in newly diagnosed TB versus previously treated TB cases (32.8% versus 14.6%). MTB resistant to either rifampicin or isoniazid dominated the mono- and poly-resistant subgroups for both newly diagnosed TB (73.7% and 61.5%) and previously treated TB (64.3% and 88.9%) cases. Three (5.2%) pre-XDR isolates were detected in newly diagnosed TB cases and nine (9.4%) in previously treated TB cases.

DISCUSSION

This is the first multicenter study assessing new and previously treated TB cases at major TB referral hospitals in Indonesia. The proportion of MDR-TB among newly diagnosed TB and previously treated TB cases was much higher than reported in the WHO Global TB Report 2020.[4] Among culture-positive cases, we identified 13.3% MDR-TB among newly diagnosed TB and 46% among previously treated TB compared with 3.3% and 17.7%, respectively, reported by the WHO. These proportions were also higher compared

TABLE 1

Participant characteristics by treatment history, bacteriological examination, and drug susceptibility results

	New TB cases (N = 260)						Previously treated TB cases (N = 187)						
Participant Characteristics	DS N = 115	Mono/Poly N = 32	MDR N = 23	Pre-XDR N = 3	Negative culture N = 20	Clinical TB N = 67	DS N = 43	Mono/Poly N = 23	MDR N = 64	Pre-XDR N = 9	Negative culture N = 16	Clinical TB N = 32	All N = 447
Age (mean ± SD)	39 ± 15.3	37.6 ± 14.1	46.2 ± 10.1	42 ± 16.5	35.5 ± 14.7	42.6 ± 15.4	39.9 ± 11.8	39.7 ± 11.9	43.6 ± 11.1	43.4 ± 14.9	42.3 ± 16.1	48 ± 14.7	41.3 ± 14.1
Sex, *n* (%)													
Male	67 (58)	20 (62)	9 (39)	1 (33)	15 (75)	38 (57)	32 (74)	16 (70)	42 (66)	3 (33)	13 (81)	18 (56)	274 (61)
Female	48 (42)	12 (38)	14 (61)	2 (67)	5 (25)	29 (43)	11 (26)	7 (30)	22 (34)	6 (67)	3 (19)	14 (44)	173 (39)
Previous history of smoking, *n* (%)													
Nonsmoker	93 (80.9)	29 (90.6)	22 (95.7)	3 (100)	17 (85)	56 (83.6)	36 (83.7)	20 (87)	61 (95.3)	9 (100)	14 (87.5)	30 (93.8)	390 (87.2)
Daily smoker	18 (15.6)	2 (6.3)	0 (0)	0 (0)	2 (10)	7 (10.4)	5 (11.6)	3 (123)	2 (3.1)	0 (0)	1 (6.3)	1 (3.1)	41 (9.2)
Occasional smoker	4 (3.5)	1 (3.1)	1 (4.3)	0 (0)	1 (5)	4 (6)	2 (4.7)	0 (0)	1 (1.6)	0 (0)	1 (6.3)	1 (3.1)	16 (3.6)
Previously sought treatment, *n* (%)													
None	21 (18.3)	3 (9.4)	1 (4.4)	0 (0)	4 (20)	12 (17.9)	5 (11.6)	1 (4.4)	0 (0)	1 (11.1)	3 (18.8)	5 (15.6)	56 (12.5)
Public facilities	42 (36.5)	13 (40.6)	7 (30.4)	2 (66.7)	4 (20)	9 (13.4)	18 (41.9)	9 (39.1)	20 (31.2)	1 (11.1)	5 (31.2)	5 (15.6)	135 (30.2)
Private facilities	19 (16.5)	7 (21.9)	4 (17.4)	1 (33.3)	5 (25)	36 (53.7)	4 (9.3)	5 (21.7)	17 (26.6)	3 (33.3)	4 (25)	8 (25)	113 (25.3)
Public and private	33 (28.7)	9 (28.1)	11 (47.8)	0 (0)	7 (35)	10 (14.9)	16 (37.2)	8 (34.8)	27 (42.2)	5 (44.4)	4 (25)	14 (43.8)	143 (32)
Previous contact with TB patients, *n* (%)	14 (12)	3 (9)	4 (17)	1 (33)	5 (25)	3 (4)	7 (16)	1 (4)	5 (8)	0 (0)	1 (6)	2 (6)	46 (10.3)
Previous contact with DR-TB patients, *n* (%)	1 (0.9)	1 (3)	2 (9)	0 (0)	0 (0)	0 (0)	2 (5)	0 (0)	3 (5)	0 (0)	0 (0)	1 (3)	10 (2.2)
Comorbidities, *n* (%)													
HIV	3 (2.6)	1 (3.1)	0 (0)	0 (0)	2 (10)	15 (22.4)	2 (4.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	23 (5.2)
DM	34 (29.6)	14 (43.8)	13 (56.5)	1 (33.3)	4 (20)	9 (13.4)	11 (25.6)	9 (39.1)	28 (43.8)	5 (55.6)	6 (37.5)	8 (25)	142 (31.8)
Cancer	2 (1.7)	0 (0)	0 (0)	0 (0)	0 (0)	6 (9)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3.1)	9 (2)
HIV + DM	0 (0)	0 (0)	0 (0)	0 (0)	1 (5)	2 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (0.7)
DM + cancer	0 (0)	0 (0)	1 (4.4)	0 (0)	0 (0)	4 (6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	5 (1.1)
Chest X-ray findings, *n* (%)													
Opacity	115 (100)	32 (100)	23 (100)	3 (100)	19 (95)	67 (100)	43 (100)	23 (100)	64 (100)	9 (100)	16 (100)	32 (100)	446 (99.8)
Cavity	40 (35)	17 (53)	18 (78)	2 (67)	3 (15)	8 (12)	25 (58.1)	14 (60.8)	40 (62.5)	7 (77.8)	6 (37.5)	10 (31.3)	190 (42.5)
Mediastinal lymphadenopathy	3 (5)	0 (0)	0 (0)	0 (0)	1 (6)	2 (3)	1 (4)	0 (0)	1 (3.3)	0 (0)	0 (0)	0 (0)	8 (2.8)
Hilar lymphadenopathy	4 (6)	1 (5)	0 (0)	0 (0)	4 (24)	4 (6)	1 (4)	0 (0)	3 (9.7)	0 (0)	0 (0)	0 (0)	17 (5.9)
Pleural effusion	15 (13)	7 (22)	5 (22)	0 (0)	7 (35)	15 (22)	11 (25.6)	6 (26.1)	19 (29.7)	5 (55.6)	3 (18.8)	8 (25)	101 (22.6)
Proportion of affected lung (median, IQR)	40 (22–55)	57.5 (35–68.5)	50 (33–80)	50 (10–65)	32.5 (15–47.5)	27 (15–40)	40 (30–60)	65 (40–80)	60 (40–80)	85 (40–90)	37.5 (30–60)	32.5 (18–51.5)	50 (30–70)
Presence of extra pulmonary TB (n, %)	13 (11)	3 (9)	1 (4)	0 (0)	3 (15)	6 (9)	4 (9)	3 (13)	0 (0)	0 (0)	3 (19)	2 (6)	38 (8.5)

DM = diabetes mellitus; IQR = interquartile range; MDR = multidrug-resistant; Mono = mono resistant; Poly = poly resistant; Pre-XDR = pre-extensively drug resistance TB = tuberculosis.

TABLE 2
Treatment history, bacteriological examination, and drug resistance profiles by study sites

	Sanglah	Wahidin	Kariadi	Soetomo	Sardjito	Persahabatan	Adam Malik	All
Enrolled participants, *n*	32	25	108	128	83	89	25	490
Analyzed participants, *n*	25	20	103	123	75	80	21	447
Treatment history (*N* = 447)								
New, *n* (%)	22 (88)	19 (95)	36 (35)	70 (57)	59 (79)	49 (61)	5 (24)	260 (58)
Previously treated, *n* (%)	3 (12)	1 (5)	67 (65)	53 (43)	16 (21)	31 (39)	16 (76)	187 (42)
TB status (*N* = 447)								
Bacteriological confirmed, *n* (%)	17 (68)	15 (75)	95 (92)	114 (93)	27 (36)	66 (82)	14 (67)	348 (78)
Clinical, *n* (%)	8 (32)	5 (25)	8 (8)	9 (7)	48 (64)	14 (18)	7 (33)	99 (22)
Culture results (*N* = 447)								
Culture positive, *n* (%)	16 (64)	12 (60)	90 (87)	106 (86)	18 (24)	56 (71)	14 (67)	312 (70)
Drug susceptible, *n* (%)	12 (75)	10 (83)	9 (10)	67 (63)	11 (61)	46 (82)	3 (21)	158 (51)
Drug resistant, *n* (%)	4 (25)	2 (17)	81 (90)	39 (37)	7 (39)	10 (19)	11 (79)	154 (49)
Mono resistant, *n* (%)	1 (6)	2 (17)	9 (10)	15 (14)	1 (6)	5 (9)	0 (0)	33 (11)
Poly resistant, *n* (%)	3 (19)	0 (0)	10 (11)	5 (6)	2 (1)	1 (2)	1 (7)	23 (7)
Multidrug resistant, *n* (%)	0 (0)	0 (0)	55 (61)	17 (16)	4 (22)	2 (4)	9 (64)	85 (27)
Pre-extensively drug resistant, *n* (%)	0 (0)	0 (0)	7 (8)	2 (1)	0 (0)	2 (4)	1 (7)	10 (3)
Culture negative, *n* (%)	9 (36)	8 (40)	13 (13)	17 (14)	57 (76)	24 (29)	7 (33)	135 (30)
TB category based on TB treatment history and DST results (*N* = 312)								
New case DS-TB, *n* (%)	11 (69)	9 (75)	7 (8)	47 (44)	9 (50)	31 (55)	1 (7)	115 (37)
Previously treated DS-TB, *n* (%)	1 (6)	1 (8)	2 (2)	20 (19)	2 (11)	15 (27)	2 (14)	43 (14)
New case DR-TB, *n* (%)	3 (19)	2 (17)	27 (30)	14 (13)	4 (22)	5 (9)	3 (21)	58 (18)
Previously treated DR-TB, *n* (%)	1 (6)	0 (0)	54 (60)	25 (24)	3 (17)	5 (9)	8 (57)	96 (31)

DR-TB = drug-resistant tuberculosis; DS-TB = drug-susceptible tuberculosis; DST = drug-susceptibility testing; TB = tuberculosis.

with other studies from Indonesia (1.8% to 4.1% among newly diagnosed TB, and 17.1% to 19.2% among previously treated TB, respectively).[6–8] The large discrepancy between our results and the WHO Global Report 2020 estimate may be attributable to lack of recent TB surveillance in Indonesia, which was last conducted in 2013–2014.[4,5] Additionally, our participants were recruited from referral hospitals, whereas previous surveys recruited from community health centers. Most participants had sought treatment both in public and private facilities before being sent to the referral hospitals, suggesting our population represented more difficult cases.

A higher proportion of MDR-TB among previously treated TB patients compared with newly diagnosed TB patients has been reported in other low- to middle-income countries.[8,13–16] In neighboring Papua New Guinea, MDR-TB was detected in 2.7% and 19.1% of new and previously treated TB cases, respectively, with no case of XDR-TB being detected.[17] Additionally, DST coverage is higher among previously treated TB versus newly diagnosed TB patients globally (81% versus 59%)[4] and in Indonesia (100% versus 16%).[18] Thus DR is more likely to be detected in previously treated TB cases due to higher testing rates.

FIGURE 2. Distribution of drug resistance patterns among newly diagnosed and previously treated tuberculosis cases from all sites. AMK = amikacin; EMB = ethambutol; INH = isoniazid; KAN = kanamycin; OFX = ofloxacin; Pre-XDR = pre-extensively drug resistance; RIF = rifampicin.

Identification of 58 (33.5%) participants with DR (32 mono/poly-resistant, 23 MDR, and three pre-XDR) among those without previous exposure to anti-TB drugs supports reports that primary DR-TB has increased up to 80% in some settings.[19] This is bolstered by molecular epidemiology studies that show high degrees of strain clustering.[20] However, we cannot exclude the possibility that patients were incorrectly categorized as treatment naive because prior anti-TB drug use may not have been accurately reported.

Participants in our study were predominantly male, similar to the TB Global Report,[4] which has shown men (aged ≥ 15 years) accounted for 56% of the people who developed TB in 2009. Meta-analysis of 56 TB prevalence surveys, including 2.2 million participants in 28 countries, also shows that TB prevalence is higher among men, with case notification data reflecting a higher male-to-female ratio.[21]

The prevalence of cavities in our study was similar to that from a review of 17 studies. Cavities occurred in approximately 70% of previously treated MDR-TB patients and in approximately 30% of DS-TB patients.[22] Thus, detection of cavities may facilitate risk stratification. Duration of TB disease may affect the likelihood of cavity formation, although cavities may develop early after infection, particularly in immune-competent adults.[23,24] This may explain the high proportion of cavities in our newly diagnosed TB participants. Among bacteriologically negative cases, cavities may be associated with other pulmonary processes such as fungal (histoplasmosis, aspergillosis, etc.) and parasitic (*Echinococcus*, paragonimiasis) infections.[25] Characterization of this relationship merits further exploration.

Mandatory DST to first-line drugs in our study enabled detection of a high proportion of MTB isolates resistant to isoniazid in non-MDR/XDR groups (22 of 213 patients (10.3%). Access to DST remains low particularly for newly diagnosed TB patients, consequently INH resistance is often undetected in daily practice because the more readily available rapid diagnostic test (GeneXpert) detects only rifampicin resistance. If INH resistance is not seen, patients will receive drugs for DS-TB, which is suboptimal for DR-TB and increases the risk of treatment failure, relapse, or acquiring RR. In our study, among 167 patients with Xpert Rif susceptibility, 15 (9%) were INH resistant by DST. On the other hand, patients with mono-RR TB may be treated inappropriately as MDR; they will receive second-line TB drugs, which are less effective, more toxic, and have longer duration, when highly effective isoniazid might actually be used. In our study, we found 8% patients (11/137) with mono-RR based on GeneXpert results.

Surveillance to better estimate the prevalence and incidence of RR, INH-susceptible TB and to monitor the progression of mono-INH and RIF resistant cases to MDR is needed. A recent large whole genome sequencing study revealed that INH resistance may predate rifampicin resistance. Therefore, INH resistance may be a precursor to MDR-TB.[26] Modalities to identify INH resistance are also essential to distinguish between RR-TB and MDR-TB. These would facilitate appropriate treatment of RR-TB and minimize development of further drug resistance. However, it is difficult for high TB-burden countries to perform routine INH-resistance tests because line-probe assays and liquid cultures are only available at reference laboratories. The newly released GeneXpert MTB/XDR cartridge (Cepheid, Sunnyvale, CA), which includes resistance testing for INH, fluoroquinolones, and second-line injectables, is a potential solution because the cartridge can be used in the GeneXpert machines already used in Indonesia. Other automated rapid diagnostic tests for direct detection of MTB complex with INH and/or RIF resistance from sputum samples should also be considered.[27] In addition, the reference laboratory may perform next-generation, high-throughput molecular tests that can simultaneously detect RIF and INH resistance.

Our study highlights the need to improve current public health approaches to TB in Indonesia. Because primary DR-TB was relatively high, community transmission must be addressed by screening programs and tracking of case contacts followed by more liberal use of DST, for which Indonesia has low uptake. Comprehensive drug-resistant data will allow patients to be treated with effective drugs, reduce development of drug resistance and toxicity, and inform public health program treatment algorithms. Early detection and adequate treatment will reduce transmission, morbidity, and mortality.[28] In addition, strengthening public–private partnerships and improving coordination between the national health insurance scheme and the National TB Program will reduce diagnostic delays and minimize costs.[29,30] Decentralized care after diagnosis can also be considered because it demonstrates better treatment outcomes and reduced costs compared with centralized care in some circumstances.[31]

The high incidence of DS- and DR-TB cases in previously treated individuals underlines the high risk of recurrent TB in this population and contributes substantially to disease burden. Post-treatment follow-up that anticipates TB relapse and secondary preventive therapy may accelerate reduction of TB incidence and save resources for TB control.[32,33] Because molecular tests may remain positive for genetic material even after cure, caution is warranted in interpreting a positive GeneXpert MTB/RIF or other molecular tests post-treatment.[33]

The present study has several limitations. First, we collected data from only seven TB referral hospitals in Indonesia, limiting generalizability and biasing the patient population toward more complicated cases. Nevertheless, our results reflect real-world circumstances of the National TB Program in larger, provincial hospitals in Indonesia. Our study was also limited to adults ≥ 18 years. Because prevalence of MDR-TB in younger age groups is variable from country to country and often poorly understood,[34] the prevalence of new and previously treated TB may not be similar if a broader age range were captured. Another limitation is the exclusion of some participants from analysis because AFB, GeneXpert, and culture examinations used different specimens. It is possible that these participants would have shown a different result profile. Given our real-world National TB Program setting, the use of different specimens for some cases was unavoidable. Lastly, we did not test for Group A drugs because our study was conducted before the updated definition of XDR was released by the WHO. The new definition should encourage health authorities in Indonesia to initiate testing for Group A drugs.

The difference in DR TB incidence in our study compared with previous surveys or WHO estimates highlights the need to conduct a national survey of DR-TB in Indonesia. Our data also inform strategies to improve diagnosis and management of MDR-TB for new and previously treated cases. Contact tracing, early detection, and early treatment based

on DST results will reduce transmission, morbidity, mortality, and disease burden. All test results should be reported to the national system. Future public health policies should consider additional strategies to reduce costs for TB control, including public–private partnerships, decentralized services, and utilization of national health insurance.

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