

The Impact of the COVID-19 Pandemic on the Resistance Level of *Mycobacterium Tuberculosis* in Suspected Tuberculosis Patients at the Surakarta Central General Hospital

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ABSTRACT

Background: Analysis of the impact of the COVID-19 pandemic on the resistance level of *Mycobacterium tuberculosis* (MTb) isolates to Anti Tuberculosis Drugs (ATD) needs to be carried out considering the level of MTB resistance is an important factor in the occurrence of Multidrug-Resistant TB (MDR-TB) in Indonesia. The purpose of the study was to analyze the impact of the Covid-19 pandemic on the level of resistance of MTb isolates of patients with suspected TB in Surakarta.

Subjects and Method: This research is a quantitative descriptive study with a retrospective Cohort based on the medical record data of suspected TB patients at Surakarta Central General Hospital in 2020 – 2021. The sampling technique was random sampling with a total of 200 samples each year. Data analysis used the SPSS 21 program.

Results: Characteristics of respondents with suspected TB patients who visited the Surakarta Central General Hospital in 2020 and 2021, mostly in men and occurring in productive ages 36-55 years. The most effective type of ATD against MTb isolates is Rifampicin with a mean rank of 6.00 and a $p=0.035$. While Ethambutol is ineffective as an ATD with a mean rank of 58.00 and a $p<0.001$. The results of the Wilcoxon test analysis showed there was a significant difference in the level of resistance or sensitivity of MTb isolates in 2020 and 2021 with a p -value=0.000.

Conclusion: There is a significant effect of the impact of the Covid-19 pandemic on the level of resistance or sensitivity of MTb isolates of patients with suspected TB in the Surakarta area in 2020 and 2021.

Keywords: pandemic, COVID-19, resistance, MTb isolates, ATD

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BACKGROUND

Coronavirus disease 2019 (Covid-19) is an acute respiratory syndrome caused by Coronavirus 2 (SARS-CoV-2) known as a global pandemic and the Covid-19 case in Indonesia occurred in early March 2020.

The Covid-19 pandemic had an impact on all aspects of life. Aspects directly and or indirectly to various other infections including TB. The latest data on October 21, 2021, shows that there are 301 cases of TB in

Indonesia per 100,000 population, placing Indonesia in the 3rd position with the most TB cases globally.

The World Health Organization said that TB cases increased again globally in the midst of the Covid-19 pandemic and it was estimated that the Covid-19 pandemic had worsened the situation for TB sufferers, in addition to health funds being diverted to deal with Covid-19 and difficult access to care due to the lockdown. As a result, there is a decrease in the number of people seeking TB preventive treatment by 2.8 million in 2020, or a decrease of about 21% compared to 2019. The target of a world free from the TB epidemic in 2030 can be reduced to 80 percent, it is feared that it will not be achieved due to the Covid-19 pandemic (WHO, 2020).

The distribution of the rate of TB and MDR-TB in Indonesia is influenced by various factors that contribute to the occurrence of germ resistance to ATD, including respondent characteristics, treatment programs, culture, socio-economic and environmental conditions including the impact of the Covid-19 pandemic. The initial Covid-19 case in Indonesia was detected in March 2020 with various causes of the Coronavirus variant until it was updated, namely the Omicron delta type. From April 2021 to date, the Government of Indonesia has intensively implemented a national and free vaccination program for all Indonesians through the 1st and 2nd vaccination programs, and even now, a booster program is still being implemented to prevent the spread of Covid-19.

Prolonged MDR-TB therapy can have side effects, namely a correlation between the cure rate and changes in the bacterial profile related to resistance to ATD. Based on data from the Ministry of Health of the Republic of Indonesia in 2020, only 271,750 TB cases were found in Indonesia. This

number decreased sharply when compared to 2019 which was 568,987 cases. In fact, the estimated number of TB cases in Indonesia in 2020 is around 840,000. It is estimated that there will be an addition of 6.3 million cases and 1.4 million deaths of TB patients in the world during 2020-2025 with an achievement of 65 cases per 100 thousand population and a decrease in mortality to 6 per 100 thousand population in 2030 (Indonesian Ministry of Health, 2020).

Research on the analysis of the development of resistance levels of MTb isolates in patients with suspected TB who visited the Surakarta Central General Hospital as a result of the Covid-19 pandemic and the vaccination program has been carried out by the Indonesian Government nationally, needs to be done considering the level of resistance is an important factor in the occurrence of MDR-TB in Indonesia. Based on this, the general objective of the study is to analyze the impact of the Covid-19 pandemic on the resistance level of MTb isolates of patients suspected of having TB in the Surakarta area from March 2020 to December 2021.

SUBJECT AND METHOD

1. Study Design

The study was conducted from January to March 2022 at the Surakarta Central General Hospital with a quasi-experimental study design with a retrospective Cohort was based on medical record data of suspected TB patients who visited the Surakarta Central General Hospital from March 2020 to December 2021.

2. Population and Sample

The population based on medical record data from suspected TB patients who visited Surakarta Central General Hospital in 2020 with a total of 370 subjects and in 2021 a total of 243 subjects.

The research sampling technique was random sampling with a sample of 200 subjects each year in the period March 2020 (the beginning of the emergence of Covid-19 in Indonesia) to December 2020; and the period January 2021 (beginning of the implementation of the national vaccination program) to December 2021 in Surakarta Central General Hospital.

3. Study Variables

The independent variable was the type of ATD including Streptomycin, Isoniazid, Rifampicin, and Ethambutol (SIRE), while the dependent variable was the level of resistance or sensitivity of MTb isolates.

4. Operational Definition of Variables

Anti Tuberculosis Drugs (ATD) is a type of anti-tuberculosis drug that is used as a regimen in TB therapy. SIRE includes first-line ATD that given at the intensive stage given every day.

TCM (Molecular Rapid Test) as a biomolecular-based MDR-TB diagnostic examination (Genexpert) recommended by WHO in 2018 as a new revolution for rapid diagnosis of TB and MDR-TB cases within 2 hours.

DST (Drug Sensitivity Test) is a method of testing the sensitivity or resistance of MTB to the type of ATD used as a TB therapy regimen in vitro, based on the presence or absence of growth of MTB isolates from positive screening results on LJ medium so that the percentage level of resistance of MTB to ATD types can be determined if the results are positive. < 1% then the conclusion is sensitive to drug concentration and if the result is > 1% then the conclusion is resistant to drug concentration.

5. Study Instruments

The stages of the research consist of handling inspection materials; isolation and identification of MTB isolates; MTb sensitivity test in vitro on Lowenstein Jensen (LJ)

medium containing the test preparation and SIRE.

MTB isolates were obtained based on the results of a positive screening test for MTB based on microscopic examination of BTA staining Ziehl Nelson, rapid test MPT 64 and Rapid Molecular Test (TCM) Genexpert method and Drug Susceptibility Testing (DST) from sputum samples of patients suspected of TB at the Surakarta Regional General Hospital for the period from March 2020 to December 2021.

6. Data analysis

From the primary data, the editing, coding, scoring, and tabulating stages were carried out and then statistically analyzed using SPSS 21, namely univariate and bivariate analysis to determine the relationship between the independent variable and the dependent variable with a significance level of = 0.05. In univariate analysis, the characteristic sample is continuous data presented in the parameters n, mean, standard deviation, minimum, and maximum. Categorical data are presented in terms of frequency and percentage. Bivariate analysis was carried out with Wilcoxon because the data scale was ordinal.

RESULTS

1. Characteristics of Respondents

Characteristics of respondents from the medical records of suspected TB patients who visited the Surakarta Central General Hospital from March 2020 to December 2021 as listed in table 1.

2. Effectiveness of ATD against MTb Isolate Resistance or Sensitivity

The results of the research related to the effectiveness of the types of ATD namely Streptomycin, Isoniazid, Rifampicin, and Ethambutol (SIRE) used at the Surakarta Central General Hospital against MTb isolates for the period March 2020 to December 2021 as listed in table 2.

Table 1. Distribution of respondent’s characteristics

Characteristics	2020 Year		2021 Year	
	Frequency	Percentage	Frequency	Percentage
Gender				
Male	125	62.5%	110	55.0%
Female	75	37.5%	90	45.0%
Age				
< 18 years old	2	1.0%	2	1.0%
18-25 years old	29	14.5%	21	10.5%
26-35 years old	24	12.0%	30	15.0%
36-45 years old	45	22.5%	44	22.0%
46-55 years old	45	22.5%	49	24.5%
56-65 years old	38	19.0%	40	20.0%
> 65 years old	17	8.5%	14	7.0%

Table 2. The level of effectiveness of ATD against MTb isolates in 2020-2021

Variable	Resistance	%	Sensitivity	%	Mean	SD	Mean Rank	p
2020								
Streptomycin	108	54.0	92	46.0	1.46	0.500	9,99	0.000
Isoniazid	50	25.0	150	75.0	1.75	0.434	1,83	0.000
Rifampicin	2	1.0	198	99.0	1.99	0.100	0,27	0.035
Ethambutol	143	71.5	57	28.5	1.29	0.453	6,38	0.000
2021								
Streptomycin	70	35.0	130	65.0	1.65	0.478	20,535	0.000
Isoniazid	14	7.0	186	93.0	1.93	0.256	7,32	0.000
Rifampicin	9	4.5	191	95.5	1.96	0.208	0,06	0.035
Ethambutol	72	36.0	128	64.0	1.64	0.481	26,97	0.000

3. Distribution of MTb isolate Resistance or Sensitivity Levels

The distribution of the description of the level of resistance or sensitivity of MTb

isolates during the period March 2020 to December 2021 at the Surakarta Central General Hospital is listed in table 3.

Table 3. Distribution of resistance and sensitivity of MTb isolates in 2020-2021

Variable	2020					2021					p
	Total	%	Mean	SD	Mean Rank	Total	%	Mean	SD	Mean Rank	
Resistance	159	79.5	1.42	0.494	5,1175	117	58.5	1.21	0.405	2892,5	0.000
Sensitivity	41	20.5				83	41.5				

DISCUSSION

Based on table 1 shows the characteristics of the respondents by gender, the most suspected TB patients in 2020 were male as many as 125 people (62.5%), and in 2021 as many as 110 people (55.0%). The characteristics of respondents based on age are at most 36-45 and 46-55 years old as many as 45 people (22.5%) in 2020 and 46-55 years old as

many as 49 people (24.5%) in 2021. The incidence of TB can be influenced by factors of age, gender, nutritional status, education level, socioeconomic and lifestyle, including smoking habits. TB infection is more common in men because smokers are generally dominated by men as a result, men are more easily exposed to the risk of TB. Smoking habits can reduce the immunity of smokers

because of the toxins in cigarettes that are harmful to health, namely tar, nicotine, CO, and NO gases from tobacco so that the person becomes more susceptible to MTB bacterial infection. The results of research conducted in 2016-2017 at the Surakarta Hospital showed that TB cases in men occurred 1.5–1.9 times more compared in women (Sutanto, 2021c).

The study results showed that the age of the respondents was dominated by adults and productive ages, namely 36-55 years. Age as an independent factor in the incidence of MDR-TB. Productive age to adulthood is the respondent's optimum activity age-related to work activities and socio-economic conditions. The distribution of TB patients generally shows that more than at 50% occur at productive ages, namely 20-50 years, this is related to the social relations and working conditions of the respondents (Lu et al., 2017). The level of resistance to ATD in respondents aged over 60 years and reinfection cases showed significantly lower in other than age groups due to an imbalance of drug resistance between different age groups, mainly due to medication history (Ullah et al., 2016; Lan et al., 2016). The 45-64 year age group has a significant 2.4 times risk with the incidence of drug-resistant TB compared to the 15-24 year age group (Farihatun, 2018).

The distribution of the occurrence of MTB and MDR-TB in patients with suspected TB is influenced by various factors that contribute to the occurrence of bacterial resistance to drugs, characteristics of respondents, treatment programs, culture, socio-economics, and the environment. Variables that affect the incidence of MDR-TB include family support, knowledge, regularity of taking medication, and the role of health workers. In addition, TB patients who do not regularly take ATD are at risk of 11,218 times experiencing MDR-TB. The knowledge of

pulmonary TB patients about TB disease, the required treatment, and the length of treatment that must be carried out affect the patient's adherence to complete treatment. Patients with low levels of knowledge will be at risk of treatment failure more than twice compared to patients who have high knowledge. Respondents with poor medication adherence had a risk of 2486 times MDR-TB disease compared to respondents who adhered to taking ATD in TB treatment. Factors of education, knowledge, behavior, social support, and self-efficacy of TB patients are related to the level of adherence to treatment of TB patients (Muhammad, 2019).

Diagnosis of drug-resistant TB (TB-RO), MDR-TB, and XDR-TB can be done using TCM with PCR (Xpert MTB/RIF) methods, culture examination, and DST. DST is an in vitro susceptibility test method for *M. tuberculosis* as one of the laboratory diagnostic parameters used in determining the level of bacterial resistance. DST is performed after the results of a positive smear microscopic examination or a positive TCM examination result. DST uses Lowenstein Jensen (LJ) solid media containing in vitro (Harti et al., 2018). The ideal examination method is to meet the criteria of specificity, sensitivity, and representativeness so that each method has advantages and disadvantages. The results of the sample culture are part of the sensitivity test of *M. tuberculosis* to drugs and determine the potential for MDR-TB (Lu et al., 2018).

TB can be cured by giving the right ATD, however, recently many MTB strains have been found to be resistant to two or more ATDs known as MDR-TB strains. TB treatment lasts quite a long time, namely at least 6 months of treatment, making patients drop out of treatment or take treatment irregularly. Both of these things have fatal consequences, causing treatment to fail and the bacteria to become resistant, known as

MDR, which results in multiple costs and makes it more difficult to treat TB for the sake of eradicating TB in Indonesia.

Based on the data in table 2 shows that in 2020 and 2021 shows that the most effective type of ATD against MTb isolates is Rifampicin, namely in 2020 only 2 MTb isolates (1%) were resistant and in 2021 there were 9 resistant MTb isolates (4.5%) with a mean rank = 6.00 and a p-value = 0.035. While Ethambutol is ineffective as an ATD, in 2020 there were 143 resistant MTb isolates (71.5%) and in 2021 there were 72 resistant MTb isolates (36.0%) with a mean rank = 58.00 and a p-value of 0.000. The varying levels of resistance or sensitivity of MTb isolates to ATD were influenced by several factors, including the different characteristics of respondents related to the level of TB infection from respondents who suspected early TB or the MDR-TB group. MDR-TB is one type of MTB resistance to at least two first-line antiretroviral drugs, namely isoniazid and rifampin, the two most effective antiretroviral drugs. The effectiveness of ATD against MTb isolates was also influenced by the biomolecular mycolic acid resistance gene (trehalose dimycolate) which functions equivalently to lipopolysaccharide in Gram-negative bacterial cells. The presence of mycolic acid content in MTB plays an important role in the level of resistance of bacteria to host immune cells and drugs; namely inhibiting the fusion of macrophages in host cells against pathogens. Initial treatment of pulmonary TB caused by MTB usually uses isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA), and ethambutol (EB) or streptomycin (SM) as the mainstay. Resistance encourages the use of alternative drugs that are more toxic, namely ethionamide, aminosalicylic acid, cycloserine, capreomycin, ciprofloxacin, or ofloxacin (Kobayashi, 2017).

Many factors contribute to the resistance of bacteria to drugs and the occurrence of MDR-TB. Resistance of MTb isolates to ATD can be in the form of primary resistance and secondary resistance. Resistance of germs to ATD can occur if the administration of drugs is not appropriate namely the patient does not complete the treatment given, health workers provide inappropriate treatment in terms of combination, dose, duration of treatment, and quality of drugs, as well as problems with the supply of drugs that are not always available (Sun et al., 2019).

MDR-TB is a TB infection caused by MTB and is resistant in vitro to isoniazid (H) and rifampin with or without other drug resistance (Li et al., 2018). The emergence of *M. tuberculosis* strains that are resistant to two or more ATD causes the failure rate of tuberculosis therapy to be high (Wu et al., 2019). The use of natural ingredients-based galenic preparations has potential as an alternative to ATD therapy. The results showed that the combination of snail seromucoid and chitosan has potential as a bioimmunostimulator and bioimmunodulator in TB therapy (Sutanto et al., 2020; Sutanto et al., 2021a; Sutanto et al., 2021b). Durian peel extract polysaccharides and chitosan have the potential to an antimicrobial against MTb isolates (Sutanto et al., 2022).

Determination of the incidence rate of MDR-TB and MTB is a useful determinant for early and accurate detection of mortality rates and the effectiveness of therapy in TB patients. Early detection of MDR-TB and starting therapy as early as possible are important factors for achieving successful therapy. The existence of side effects in MDR-TB therapy and the correlation between cure rates and ATD resistance requires a social psychological management approach in MDR-TB patients and the need to know the profile of MTB bacteria related to ATD

resistance (Migliori et al., 2020). The most dominant variable influencing the incidence of MDR-TB is medication adherence; therefore, it is necessary to improve the outreach program to patients and families about the importance of medication adherence and the consequences arising from non-adherence to taking medication so that this can be used to control the increase in the incidence of MDR-TB (Ama, 2020). The results showed that the distribution of the incidence of MDR-TB and MTB in 2016 and 2017 at the Surakarta Central General Hospital was relatively varied. In 2016 the percentage of MDR-TB (45.21%) was lower than MTB (54.79%) while in 2017 the incidence rate of MDR-TB (76.14%) was higher than MTB (23.86%) (Sutanto et al., 2020).

The presence of resistance factors from MTB bacteria to the effectiveness of the ATD used can affect the incidence of MTB and MDR-TB in an area. Therefore, predictions or indicators of the determinants of the incidence of MDR-TB in TB patients, including the characteristics and risk factors that make a person susceptible to early detection of TB disease, are important factors for achieving the success of TB therapy on the mortality rate and effectiveness of therapy in patients. TB. To achieve this, a number of strategies were carried out by the Ministry of Health Republic Indonesia assisted by related institutions through 3 things namely prevention, detection, and therapy. The preventive strategy is carried out by increasing BCG immunization in children which have been carried out so far. BCG coverage in the last 3 years has decreased in achievement due to the impact of the Covid-19 pandemic, namely in 2018 as much as 37%, in 2019 as much as 50%, and in 2020 as much as 32%. The detection strategy includes the availability of laboratory inspection facilities at the community health center or Hospital level, namely the molecular rapid test (TCM)

examination which is constrained because not every community health center has this equipment with data there are 1,168 TCM devices spread over 34 provinces and 496 regencies and cities. The detection strategy can also be carried out through tracing per village, sub-district to the province of patients with suspected TB. While the therapeutic strategy is carried out by administering an appropriate anti-tuberculosis drug regimen (ATD), considering that TB treatment includes long-term treatment related to the profile of MTb bacteria which has unique physiology in the cell wall and the emergence of MDR-Tb strains (Li et al., 2018).

Based on table 3 shows that the resistance level of MTb isolates decreased from 79.5% in 2020 and 58.5% in 2021 or inversely proportional to the sensitivity level of MTb isolates which increased from 20.5% in 2020 to 41.5% in 2021. The results of the Wilcoxon test analysis showed mean rank of 44.50 and a p-value 0.000 so there was a significant difference in the level of resistance or sensitivity of MTb isolates in 2020 with 2021. Based on the results of this study, the resistance level of MTb isolates in 2021 tends to decrease compared to that of 2015. 2020 while the sensitivity of MTb isolates tends to increase. The decrease or increase in this percentage cannot be used as a guideline or reference that MDR-TB cases are lower than MTB due to various factors that affect the rate of MDR-TB in an area. The decrease in MTb isolates resistance was possible because of the Covid-19 vaccination program as immunoprophylaxis which had an impact on increasing the immune system of probands or MTB patients, namely bioimmunomodulators, thereby suppressing the resistance of MTb isolates. The emergence of MDR-TB can be caused by comorbid factors or other comorbidities, including HIV, PTM infection, metabolic disorders;

non-adherence to taking medication due to the relatively long TB treatment period of 6 months, and environmental conditions related to the epidemiology of the impact of the Covid-19 pandemic.

This result is a problem that should be observed during the period of the Covid-19 pandemic case that appeared in Indonesia in March 2020 and reached a peak on July 14, 2021, and the vaccination program in Indonesia began to be run nationally on January 13, 2021. Coronavirus disease 2019 (Covid-19) or acute respiratory syndrome caused by Coronavirus 2 (SARS-CoV-2), is a global pandemic, including in Indonesia. Symptoms and signs of Covid-19 include pneumonia, lymphopenia, lymphocyte deficit, and the occurrence of a cytokine storm that results in acute respiratory distress which can ultimately lead to death. Detection of Coronavirus infection can be carried out based on the patient's clinical profile (signs and symptoms) and laboratory diagnosis results, including lung x-rays, hematology, rapid antigen or antibody tests, measurement of IgM, and IgG antibodies, PCR (Polymerase Chain Reaction). Cytokine storm profile plays an important role in the Covid-19 infection process (Yao et al., 2020). The results of research by Zhao et al. (2019) on 463 patients with Covid-19 showed a decrease in the number of total lymphocytes, CD3+, CD4+, and CD8+ in T lymphocytes resulting in lethal pneumonia.

TB cases that have not been found have a very high transmission potential, such as Covid-19. There are similarities and differences between TB and Covid-19, namely, transmission can occur through droplets and the location of the infection in the respiratory tract, but the differences are in terms of etiology, symptoms, pathogenesis, diagnosis, and different ways of handling. The etiology of TB is the bacterium *Mycobacterium tuberculosis*, the etiology of

Covid-19 is the Coronavirus or known as SARS-Cov2. Symptoms of TB include onset or chronic attack of more than 14 days with symptoms of fever less than 38°C accompanied by coughing up phlegm, blood spots, gradually worsening shortness of breath, weight loss, and night sweats. Meanwhile, the symptoms of Covid-19 include acute onset symptoms of less than 14 days accompanied by a fever of more than 38°C with dry cough, shortness of breath appearing immediately after onset, joint pain, runny nose, headache, impaired smell or taste. The TB and Covid-19 diagnosis processes have similarities, namely using the TCM and Polymerase Chain Reaction (PCR) methods, but the difference is in the sampling. For the diagnosis of Covid-19, you must go through a swab, while TB is enough with phlegm. TB treatment uses the ATD regimen that already exists and has been developed to date, while for Covid-19 there is currently no cure, and is still in the exploration stage as a Covid-19 drug. Control of Covid-19 infection can be carried out through the application of the 5M health protocol, namely wearing masks, washing hands, maintaining distance, staying away from crowds and limiting mobility, chemotherapy using effective anti-virus drugs, and increasing body immunity, and vaccination programs. The vaccination program related to the Covid-19 pandemic intensified by the Government of Indonesia, which began in 2021 until now, aims to improve the body's immune system, which has an impact on the occurrence of a person's herd immunity.

The limitations of the study are the number of samples that are not the same every year and the absence of medical record data from patients suspected of TB whether they have carried out a complete vaccination program or not so that supporting data is needed regarding the effectiveness of the COVID-19 vaccination program after the

COVID-19 pandemic on the resistance level of MTB isolates. The conclusion of the study showed that the characteristics of the respondents suspected of TB who visited the Surakarta City Hospital in 2020 and 2021, mostly men and occurred in the productive age of 36-55 years. The most effective type of ATD against MTB isolates was Rifampicin, while Ethambutol was ineffective as an ATD. The results of the Wilcoxon test analysis showed a p-value = 0.000 so there was a significant impact on the impact of the Covid-19 pandemic on the level of resistance or sensitivity of MTB isolates from 2020 to 2021. This is recommended for health service units to complete medical record data for TB patients who have been diagnosed with TB. carry out the Covid-19 vaccination so that the effectiveness of the vaccination program against the level of MTB isolate resistance of patients with suspected TB can be known.

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AUTHOR'S CONTRIBUTION

All authors contributed to drafting, research design, data analysis, and discussion

CONFLICT OF INTEREST

There was no conflict of interest in this study.

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