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Determinants of Multidrug-Resistant Pulmonary Tuberculosis in Indonesia: A Spatial Analysis Perspective

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ABSTRACT

Tuberculosis is caused by Mycobacterium Tuberculosis (MT). MT usually attacks the lungs and causes pulmonary-tuberculosis. Tuberculosis cases in Indonesia keep increasing over the years. The presence of Multidrug-Resistant Tuberculosis (MDR-TB) has been one of the main obstacles in eradicating tuberculosis because it couldnt be cured using standard drugs. In fact, the success rate of MDR-TB treatment in 2019 at the global level was only 57 percent. Research on MDR-TB can be related to the spatial aspect because this disease can be transmitted quickly. This study aims to obtain an overview and model the number of Indonesias pulmonary MDR-TB cases in 2019 using the Geographically Weighted Negative Binomial Regression (GWNBR) method. The independent variables used in the model are population density, percentage of poor population, health center ratio per 100 thousand population, the ratio of health workers per 10 thousand population, percentage of smokers, percentage of the region with PHBS policies, and percentage of BCG immunization coverage. The finding reveals that the model forms 12 regional groups based on significant variables where GWNBR gives better results compared to NBR. The significant spatial correlation implies that the collaboration among regional governments plays an important role in reducing the number of pulmonary MDR-TB.

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A. INTRODUCTION

Tuberculosis is caused by Mycobacterium tuberculosis (MT). These bacteria can infect people around them, and it occurs when people with tuberculosis excrete the MT. MT is spread through the air, for example, by coughing. MT usually attacks the lungs and causes pulmonary tuberculosis (pulmonary TB). However, this bacterium does not rule out the possibility that it can attack other areas outside the lungs and become extra-pulmonary tuberculosis. Pulmonary TB cases dominate more than extra-pulmonary TB at the global level by 84 percent. Pulmonary TB is transmitted through saliva or phlegm that contains MT. On the other hand, extra-pulmonary TB is generally not contagious. However, tuberculosis is generally an infectious disease and one of the top ten causes of death globally, among other infectious diseases (WHO, 2020).

MT infects about a quarter of the world's population. In 2019, it was estimated that there were 10 million tuberculosis cases worldwide. Of these, 7.1 million cases were diagnosed with tuberculosis and recorded at the public health care/hospital where 1.2 million of them died. Meanwhile, of the 7.1 million diagnosed with tuberculosis, pulmonary TB cases dominate more than extra-pulmonary TB, which is 84 percent (5.9 million). The highest number of tuberculosis cases, both pulmonary TB and extra pulmonary TB in 2019 was in the Southeast Asia region, reaching 44 percent of the total number of sufferers in the world. The highest number of tuberculosis cases, both pulmonary TB and extrapulmonary TB in 2019 was in the Southeast Asia region, reaching 44 percent of the total number of sufferers in the world.

Indonesia is a country in the Southeast-Asia region with the second largest contributor to tuberculosis cases globally, so Indonesia is included in the High Burden Country for tuberculosis cases. The world cannot move toward tuberculosis control if these countries, including Indonesia, do not move towards tuberculosis control. The number of tuberculosis cases in Indonesia continues to increase yearly, where the estimated total incidence of tuberculosis in 2019 being 845 thousand (WHO, 2020).

In evaluating the tuberculosis cases in Indonesia, there is a national commitment called RPJMN (National Medium-Term Development Plan) 2020-2024, which states that tuberculosis in Indonesia is targeted at 190 per 100 thousand population, with the success rate of the tuberculosis treatment reaching 90 percent. The targeted coverage of tuberculosis discovery and treatment will reach 90 percent in 2024. This target is still very far from accomplished compared to Global Tuberculosis Report 2020. According to the report, tuberculosis cases in Indonesia keep increasing. The prevalence rate in 2019 reached 312 per 100 thousand population, with the coverage of tuberculosis discovery and treatment only 67 percent with the success rate of the treatment only 83 percent. It is certainly a tough challenge for the world, especially Indonesia as the second-largest contributor to the world's tuberculosis cases. The high incidence of this disease can cause various problems (Marselia, 2017).

The main obstacle to providing treatment and eradicating tuberculosis is Multidrug-Resistant Tuberculosis (MDR-TB). MDR-TB is a type of resistant tuberculosis to rifampicin and isoniazid, the most potent drug to cure tuberculosis (Yang et al., 2014), (Prakash et al., 2016). MDR-TB has been linked with an increased risk of death during therapy (Chung-Delgado et al., 2015). MDR-TB can be cured, but it takes 18 to 24 months. In fact, the price of its drug is higher, can cause severe side effects, and the treatment is much more complicated than non-drug-resistant tuberculosis (Marks et al., 2014) (Li et al., 2016).

Indonesia is in the top 20 countries with the highest MDR-TB cases. Precisely, Indonesia is the fifth largest country that contributes to MDR-TB (WHO, 2020). The coverage of people initiating MDR-TB treatment in Indonesia is only 48 percent. With that being said, the low rate of this treatment coverage indicates that 52 percent of them havent received any treatment and still mobilize freely. Transmission of MDR-TB is the same as non-drug-resistant TB, where the transmission is spread through the air containing germs from phlegm when MDR-TB patients cough or sneeze. This transmission can cause a person not only to suffer from ordinary TB but directly MDR-TB (Devi et al., 2019). Thus, it is necessary to prevent MDR-TB transmission and break the chain of transmission so that it does not become a public health problem.

The prevention and control of the infectious pulmonary MDR-TB can be improved by prioritizing the control of risk factors. A dense population is one of the factors that can cause the massive spread of pulmonary MDR-TB (Pratama, 2015). Meanwhile, people with lower economic status can increase the risk of drug-resistant tuberculosis exposure including pulmonary MDR-TB. It is in line with research (Narasimhan et al., 2013) that poverty is also a contributor to the burden of tuberculosis. Another important social factor influencing TB is smoking (Chakaya et al., 2020). Patients who smoked had a higher chance of having TB than non-smokers did (Hapsari et al., 2021).

The healthcare facility is the first healthcare level service to identify tuberculosis cases. It must cooperate between medical, nursing, and pharmaceutical personnel to carry out comprehensive management of MDR-TB cases (Irawansa et al., 2020). The emergence of infectious diseases, particularly the progression of tuberculosis to TB-MDR, is linked to clean and healthy living habits (Mulyanto, 2014). On the other hand, tuberculosis prevention can be done early in infants by giving Bacillus CalmetteGurin (BCG) vaccine. A strategy to combat TB in general, and drug-resistant TB in particular, must include the development of new medications, enhanced diagnostics, and new TB vaccinations (Manjelievskaia et al., 2016). Bacillus CalmetteGurin (BCG) vaccination protects children from severe and disseminated forms of TB (Chakaya et al., 2020).

Based on the problems, MDR-TB, especially pulmonary MDR-TB, is still a major problem that needs to be controlled because there are various obstacles and quite severe side effects. In addition, the proportion of cases that occur in the lungs is more dominant than extra-pulmonary cases, as well as the ease of transmission of pulmonary MDR-TB compared to extra-pulmonary MDR-TB. According to the 2020-2024 Strategic Planning Working Group of the Health Ministry, strong governance is needed by the local Health Office to deal with this problem (Kemenkes RI, 2020). The regional-based national development is necessary to reduce the number of cases of pulmonary MDR-TB at the provincial level. Research on MDR-TB can be related to the spatial aspect because this disease can be transmitted easily and is not limited to administrative areas. Several studies on MDR-TB have revealed substantial spatial variation (Marselia, 2017).

The number of cases of pulmonary MDR-TB is classified as discrete data. To analyze the count or discrete data, the Poisson regression model is used if the mean and variance of the response variables are equidistant. However, if the value of the variance is greater than the mean (overdispersion), the Poisson regression model is not appropriate to use. One approach that can accommodate the overdispersion problem is to use the Negative Binomial regression model. When the regression is applied to model response variables that have spatial dependencies and heterogeneity, the appropriate method used is Geographically Weighted Poisson Regression

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(GWPR) or Geographically Weighted Negative Binomial Regression (GWNBR). This method is a development of the Geographically Weighted Regression (GWR) method (Collins, 2010).

At the global level, several studies have been conducted to examine MDR-TB and the variables that influence it by considering the spatial relationship, namely the research (Alene et al., 2017) and (Jenkins et al., 2013). At the national level, several research TB using GWNBR namely (Mumtaz and Utomo, 2018) and (Nisa et al., 2020) but only discuss TB in general. So far, in Indonesia, no study has been found that explains the incidence of MDR-TB cases, especially pulmonary MDR-TB, by taking into account the spatial relationship at the provincial level. In this regard, it is necessary to conduct research on the number of cases of pulmonary MDR-TB which is a discrete data to determine the distribution pattern of pulmonary MDR-TB in Indonesia. The study aims to analyze the spatial effect of pulmonary MDR-TB cases using Geographically Weighted Negative Binomial Regression in Indonesia at the provincial level.

B. LITERATURE REVIEW

1. Poisson Regression

Poisson regression is included in the Generalized Linear Model (GLM), a nonlinear model to model the relationship between response and predictor variables (Nelder and Wedderburn, 1972). The response variable in the Poisson regression is in the form of count (Cameron and Trivedi, 2013). Poisson regression has an assumption that must be fulfilled, namely equidispersion.

2. Overdispersion

If the variance value is greater than the mean value $\{Var(y) > E(Y)\}$, it means that the data does not meet the equidispersion condition. This can lead to variability in response probability from one group to another and the correlation between response variables within groups (McCullagh and Nelder, 2019). This overdispersion causes the standard error of the count data to decrease (underestimate) (Hilbe, 2011).

3. Negative Binomial Regression

Negative Binomial Regression is a regression model used to analyze the relationship between response variables in the form of count data and one or more predictor variables and can handle cases of overdispersion. This can be caused because the Negative Binomial model uses a dispersion parameter. Negative Binomial Regression is a combined model of the Poisson and Gamma distribution (Hilbe, 2011). NBR was chosen because it has the smallest AIC compared to other methods.

4. Non-Multicollinearity

This assumption is used to select the predictor variables to be included in the model so there is no linear correlation. Multicollinearity is one of the violations that can cause the model to be less good for forecasting and estimation. There are several ways to determine the presence of multicollinearity, namely by looking at the Variance Inflation Factor (VIF) value. Non-multicollinearity is indicated by a VIF value of less than 10 (Gujarati, 2011).

5. Spatial Effect

Spatial effects are divided into two, namely spatial dependence and spatial heterogeneity. Spatial dependency is the correlation of the response variable error (dependency/spatial autocorrelation). Spatial heterogeneity is the spatial diversity between each observation location (Anselin and Rey, 2007). This can be caused by the location of the adjacent area so that it is possible to have a relationship.

6. Geographically Weighted Regression (GWR)

The GWR model is a development of the multiple linear regression model. This model is local and can accommodate the influence of spatial effects, both in terms of spatial dependencies and spatial heterogeneity (Fotheringham et al., 2003).

7. Geographically Weighted Negative Binomial Regression (GWNBR)

GWNBR modeling is carried out when the data has spatial heterogeneity and overdispersion occurs. The parameter generated by the GWNBR method is the same as the GWR, which is local (Da Silva and Rodrigues, 2014). The GWNBR equation can be written as follows:

$$E(Y_i) = \hat{\mu}_i = \exp\left\{\hat{\beta}_0(u_i, v_i) + \sum_{k=1}^{p} \hat{\beta}_k(u_i, v_i) X_{ik} + \alpha(u_i, v_i)\right\} \quad (1)$$

$i = 1, 2, \ldots, n$
where y_i is the observed value of the i-th response variable, x_{ik} is the observed value of the k predictor variable at the location observation (u_i, v_i), $\beta_k(u_i, v_i)$ is regression coefficient of the k predictor variable for each location (u_i, v_i), $\alpha(u_i, v_i)$ is dispersion parameters for each location (u_i, v_i).

8. GWNBR Model Parameter Estimation

Formulating the spatial weighting matrix by first finding the optimum distance and bandwidth matrix in each region using the Gaussian kernel adaptive function. In a gaussian kernel, for example, the weighting function is given by (Fotheringham et al., 2003):

$$w_{ij} = \exp\left[-\frac{1}{2\left(\frac{d_{ij}}{b}\right)^2}\right]$$

In the GWNBR modeling, parameter estimation was done using the MLE approach using the Newton Raphson iteration method and Hessian information until it converged. The log-likelihood function can be written in the following form:

$$\begin{aligned} L(\beta(u_i, v_i)|x_{ik}, y_i, \alpha_i) = \sum_{i=1}^{n} \Bigg\{ & y_i \log(\alpha_i \mu_i) - \left(y_i + \frac{1}{\alpha_i}\right) \times \log(1 + \alpha_i \mu_i) \\ & + \log\left[\Gamma\left(y_i + \frac{1}{\alpha_i}\right)\right] - \log\left[\Gamma\left(\frac{1}{\alpha_i}\right)\right] - \log\left[\Gamma\left(y_i + 1\right)\right]\Bigg\} \end{aligned} \quad (2)$$

9. GWNBR Model Evaluation

NBR modeling is carried out when the data is in an overdispersion condition. NBR generates global parameters. However, when the data also experience spatial heterogeneity and overdispersion occurs, the appropriate modeling is GWNBR. The parameters that will be generated by the GWNBR method are local. Model evaluation is carried out to see which model is better used to model the data by comparing the NBR and GWNBR methods. One method that can be used to determine the best model is to compare the Akaike Information Criterion (AIC) values of each model. The AIC value is written with the following formula (Gill et al., 2019) :

$$AIC = -2l\left(\hat{\beta}|y\right) + 2p \quad (3)$$

where $l\left(\hat{\beta}|y\right)$ is the maximum log-likelihood value, and p is the number of parameters. The smallest AIC indicates that the model is better.

C. RESEARCH METHOD

This study covers 34 provinces in Indonesia using secondary data in 2019. The population study is the residents who have experienced pulmonary MDR-TB in Indonesia in 2019. The dependent variable used is the number of pulmonary MDR-TB cases in 2019 from the Sub-directorate of Tuberculosis, Ministry of Health. The predictor variables come from the Ministry of Health and Statistics Indonesia. This study uses seven predictor variables, including population density (X_1) from the publication of Statistics Indonesia 2020, the percentage of poor people (X_2) from the publication of Statistics Indonesia 2020, the ratio of health facilities per 100 thousand inhabitants (X_3) from the Decree of the ministry of Health and The BPS website, the ratio of health workers per 10 thousand population (X_4) is from Statistics Indonesia 2020 and the BPS website, the percentage of smokers (X_5) is from the

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People's Welfare Statistics 2020, the percentage of districts/cities with clean and healthy lifestyle policies (X_6) comes from the 2019 Indonesian Health Profile, and the coverage of BCG utilization (X_7) which comes from the 2019 Indonesian Health Profile.

This research uses descriptive analysis to describe the distribution of the number of pulmonary MDR-TB cases in Indonesia in 2019 and the variables that influence it. The inferential analysis is also conducted to model and explain the number of pulmonary MDR-TB cases in Indonesia with a suitable method based on the data characteristics. In global regression, a single model describes all parts of a study region. But when the data is substantial heterogeneity, the relationships between variables can not be spatially constant (Da Silva and Rodrigues, 2014). The spatial method for obtaining information affects the effect of space or location (Pratiwi et al., 2020). An inference analysis appropriate to model the number of pulmonary MDR-TB cases is Geographically Weighted Negative Binomial Regression (GWNBR) because the type of response variable is discrete data (Gomes et al., 2017). The response variable in GWNBR is predicted by predictor variables in each location where the data is observed. Estimating parameter needs information from other locations with weighting (Suryani et al., 2021). This study uses a 5 percent significance level. The steps in conducting inferential analysis can be refer to the Figure 1 and are explained below:

1. Testing the non-multicollinearity assumption using the Variance Inflation Factor (VIF) value. A VIF value of more than 10 indicates the presence of multicollinearity (Gujarati, 2011).
2. Modeling pulmonary MDR-TB cases using the Poisson Regression Model.
3. Overdispersion testing (Hilbe, 2011).
4. Modeling pulmonary MDR-TB cases using the Negative Binomial Regression Model (Hilbe, 2011).
5. Testing the spatial effects by examining spatial dependence and spatial heterogeneity of pulmonary MDR-TB cases. Moran's Index generates the spatial dependencies test (Anselin, 1988). Meanwhile, spatial heterogeneity is tested using Breusch Pagan (Breusch and Pagan, 1979).
6. Formulating the spatial weighting matrix by first finding the optimum distance and bandwidth matrix in each region using the Gaussian kernel adaptive function considering that it has the smallest AIC. (Fotheringham et al., 2003).
7. Modeling pulmonary MDR-TB cases using GWNBR. In general, it can be written as follows:

$$\begin{aligned}\ln(\hat{\mu}) = [&\hat{\beta_{0i}}(u_i,v_i) + \hat{\beta_{1i}}(u_i,v_i)X_{1i} + \hat{\beta_{2i}}(u_i,v_i)X_{2i} + \hat{\beta_{3i}}(u_i,v_i)X_{3i} \\ &+ \hat{\beta_{4i}}(u_i,v_i)X_{4i} + \hat{\beta_{5i}}(u_i,v_i)X_{5i} + \hat{\beta_{6i}}(u_i,v_i)X_{6i} + \hat{\beta_{7i}}(u_i,v_i)X_{7i}]\end{aligned} \tag{4}$$

   Where μ_I = the observed value of i-th response, X_{ik} = the observed value of the k-th predictor variable at the observation location (u_i, v_i), $\hat{\beta}_k(u_i, v_i)$ = regression coefficient of the k-th predictor variable in the region i.
8. Simultaneous testing of the GWNBR model using the likelihood ratio test.
9. Testing the significance of GWNBR parameters in each region (u_i, v_i).
10. Model selection between the NBR model and the GWNBR model using AIC. The parameters that will be generated by the GWNBR method are local parameters while the resulting NBR parameters are global.

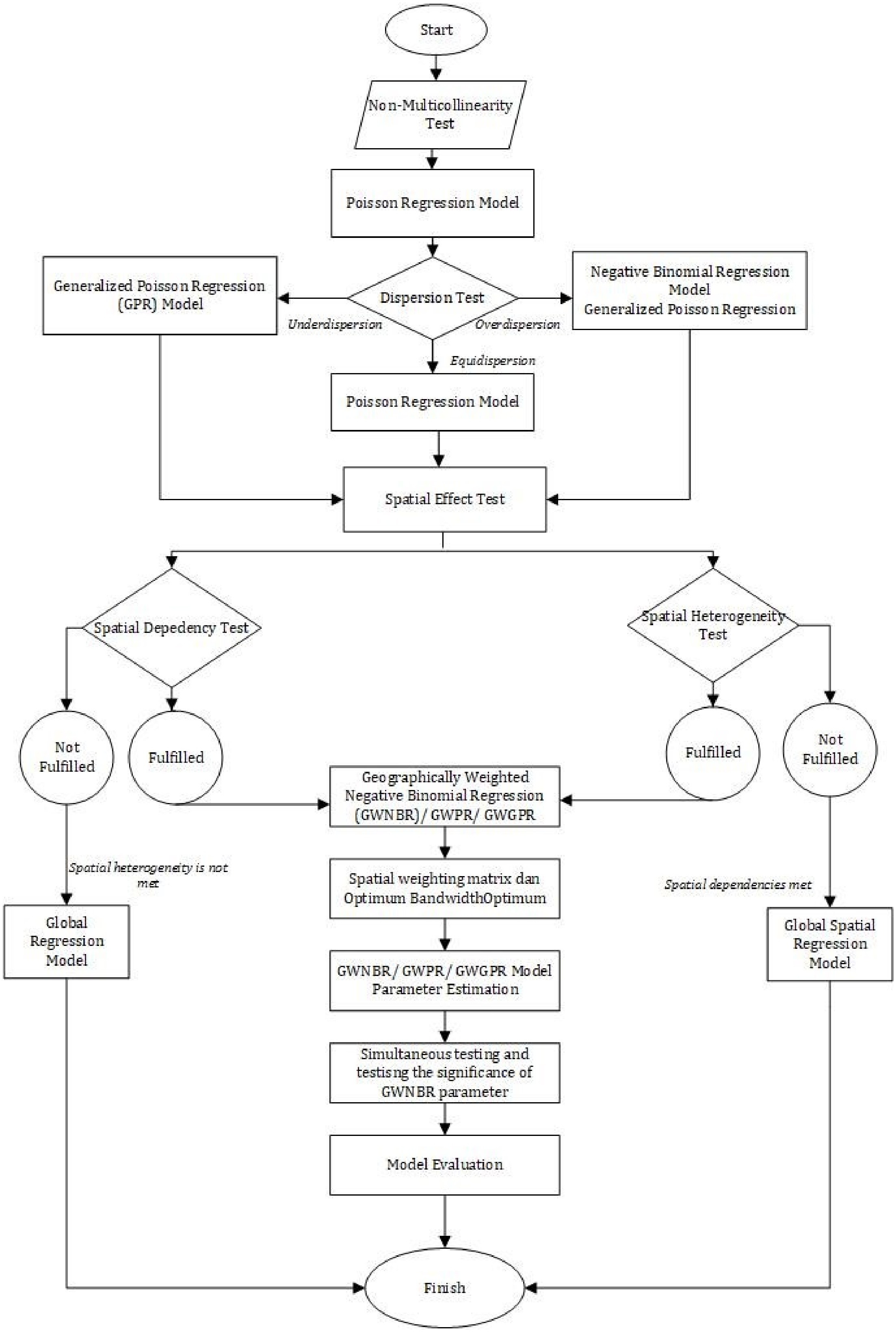

Figure 1. Inferential analysis flowchart

Source: (Hilbe, 2011), (Bustaman et al., 2013), dan (Fotheringham et al., 2003)

D. RESULTS AND DISCUSSION

1. Overview of Pulmonary MDR-TB Cases

Figure 1 shows the interval number of pulmonary MDR-TB cases in each province in Indonesia, indicated by a different color. The darker the color, the higher the pulmonary MDR-TB cases in that area. Provinces with low cases of pulmonary MDR-TB (0 to 2 cases) are Bali, East Nusa Tenggara, Gorontalo, West Sulawesi, and West Papua. On the other hand, DKI Jakarta and West Java have high MDR-TB cases (more than 274 to 311 cases). Gorontalo is a province with zero cases of pulmonary MDR-TB. It can be seen that there is a grouping in the number of cases of pulmonary MDR-TB in Indonesia, indicating that there is a spatial dependence and spatial diversity between these regions.

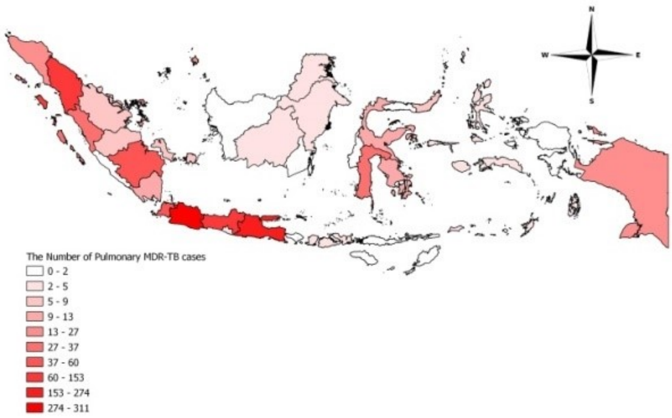

Figure 2. The distribution of pulmonary MDR-TB cases in each region in 2019

Based on the predictor variables, population density for medium to high category concentrated on the Java Island, percentage of the poor people shows a grouping where Eastern Indonesia has a higher percentage of poor people than Western Indonesia. The ratio of healthcare facilities per 100 thousand population shows that the distribution in Eastern Indonesia is higher than in Western Indonesia. Meanwhile, the ratio of health workers per 10,000 population shows that it is not evenly distributed. The percentage of the population who smokes tends to vary between regions. The percentage of districts/cities with clean and healthy living behavior policies in each province in Indonesia shows that Western Indonesia is categorized as a middle to high percentage. Meanwhile, the Eastern Indonesia region is dominated by the middle to low category. The variable percentage of BCG immunization coverage in Indonesia in 2019 shows that Western Indonesia is higher than Eastern Indonesia.

2. Geographically Weighted Negative Binomial Regression (GWNBR) Modeling

Based on tabel 1 the non-multicollinearity test, it can be concluded that there is no high correlation between predictor variables.

Table 1. VIF value of predictor variable

X1	X2	X3	X4	X5	X6	X7
(1)	(2)	(3)	(4)	(5)	(6)	(7)
1,753190	2,145962	3,305769	2,334917	1,262542	2,416101	1,712867

Furthermore, because the number of pulmonary MDR-TB is a count data, it is possible to construct a Poisson regression model first. After forming the Poisson regression model, the test of overdispersion is carried out. It shows that the dispersion parameter was 26.20037. It indicates that the value is greater than 1. In addition, a p-value is 0.0008904 (reject H_0), so it can be concluded that there is an overdispersion problem in the model. The violation of overdispersion can result in biased parameter estimation. To overcome the overdispersion in Poisson regression is by using Negative Binomial regression. Tabel 2 shows the estimated regression coefficient of NBR.

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Table 2. Coefficient estimation summary of NBR

Variable	Min	Mean	Max
Intercept	1.077691	6.87069	9.822939805
Population Density (X1)	-0.0004	0.000738	0.002302943
Percentage of The Poor (X2)	-0.09773	0.01509	0.078884459
Ratio of Health Centers per 100 Thousand Population (X3)	-0.42826	-0.20647	0.007285155
Ratio of Health Workers per 10 Thousand Population (X4)	-0.19321	-0.08888	-0.00883395
Percentage of Smokers (X5)	-0.09789	0.007922	0.098634327
Percentage of Regency/City with Clean and Healthy Living Behavior Policy (X6)	-0.07153	-0.02799	-0.00481823
Percentage of BCG Immunization Coverage (X7)	-0.0137	0.010568	0.07909134

Spatial effect testing is carried out before performing spatial modeling. In spatial testing, there are two tests, namely spatial dependence and spatial heterogeneity. The value of Moran's Index is 0.495, which means that there is a positive autocorrelation between observations. To prove the existence of spatial dependencies, the Moran's Index value was tested through randomization with 999 permutations. In this result, a p-value of 0.008 (less than = 0.05) was obtained, so with a significance level of 0.05, it indicates that there is a spatial dependency between regional observations, meaning that the number of cases of pulmonary MDR-TB in one location is observed at other locations close to each other. .Next, spatial heterogeneity testing is carried out to detect spatial diversity in the number of pulmonary MDR-TB cases and the factors that influenced it. The Breusch Pagan value is 17.605, with a p-value of 0.01388. It shows that Breusch-Pagan ¿ $\chi^2(0.05; 7) = 14.06713$, and It can be deduced that the observation regions are spatially heterogeneous. So the GWNBR model is used. The parameter estimation for the GWNBR model is carried out using adaptive Gaussian weighting. By estimating the parameters of the GWNBR model, it is possible to know the magnitude and difference in the effect of each predictor variable on the number of MDR-TB cases in each region. Table 1 shows a summary of the estimated parameters of the variables used. The estimation of the GWNBR parameters is different for each location. Furthermore, parameter testing is carried out simultaneously on the model to determine whether there is at least one predictor variable that significantly affects the number of pulmonary MDR-TB cases in Indonesia in 2019. The deviance value in the GWNBR model with an adaptive Gaussian weighting is 151.8285. Gaussian adaptive weighting deviance value is greater than $\chi^2(0.05; 7)$, which means there is at least one predictor variable that significantly affects the model.

Subsequently, a partial test is carried out to determine the significant variables at each observation location. The partial test results obtained different values and significance in each region, and it is possible to categorize each province in Indonesia based on the similarity of the significant variables. Table 2 shows that the variables that influence the number of pulmonary MDR-TB cases in Indonesia in 2019 are different for each province. There are 12 regional groups with a specific significant variable for each region.

Table 3. Province grouping based on significant predictor variables using Adaptive Gaussian kernel weighting

Group	Province	Significant Variable
1	Central Java	X1, X4, X6
2	East Java	X1, X3, X4, X6
3	Lampung, Banten	X1, X5, X6, X7
4	Central Sulawesi, Southeast Sulawesi, North Maluku, West Papua	X1, X2, X3, X4, X6
5	East Kalimantan	X1, X2, X4, X6, X7
6	Bali, Gorontalo	X1, X3, X4, X5, X6
7	DI Yogyakarta, West Kalimantan, North Kalimantan, North Sulawesi	X1, X3, X4, X6, X7
8	West Java	X1, X4, X5, X6, X7
9	West Nusa Tenggara, East Nusa Tenggara	X1, X2, X4, X5, X6, X7
10	South Sumatera, Bengkulu, Central Kalimantan, South Sulawesi, West Sulawesi, Maluku, Papua	X1, X2, X3, X4, X6, X7
11	Bangka Belitung Islands	X1, X3, X4, X5, X6, X7
12	Aceh, North Sumatera, West Sumatera, Riau, Jambi, Riau Islands, DKI Jakarta, South Kalimantan	X1, X2, X3, X4, X5, X6, X7

The result in Table 3 shows that each region has different predictor variables that affect the cases of pulmonary MDR-TB. Figure 3 is a map of the distribution of provincial groupings based on significant predictor variables.

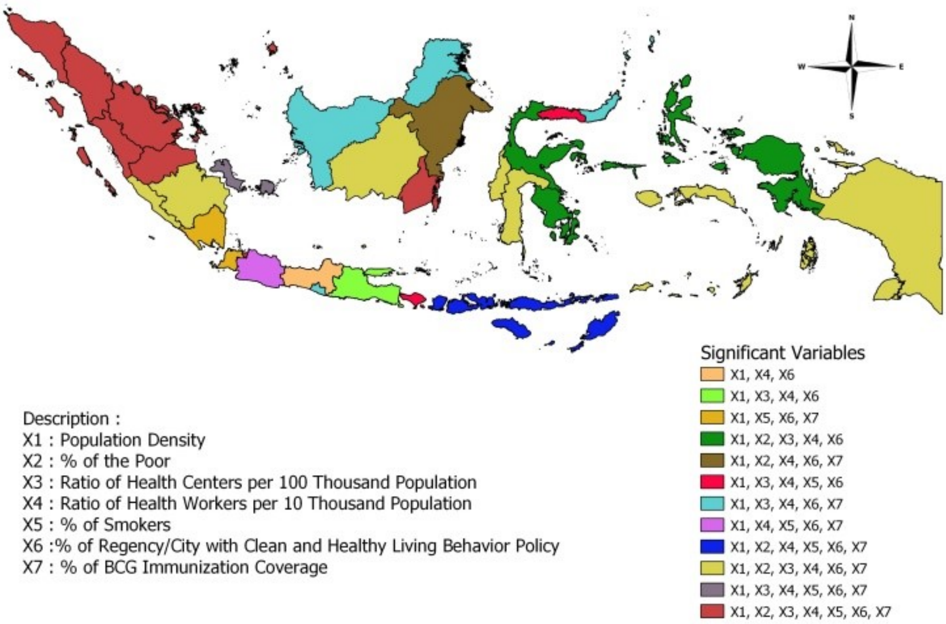

Figure 3. The distribution of the grouping of provinces in Indonesia based on significant variables using the GWNBR method

Furthermore, the GWNBR model can be obtained for each observed area. For example, the GWNBR model for the 31st observation location (u_{31}, v_{31}), namely DKI Jakarta, is in the equation below:

$$\ln(\hat{\mu}_{31}) = 7.00763 + 0.0003X_1^* + 0.0309X_2^* - 0.25204X_3^* - 0.08105X_4^* + 0.098634X_5^* - 0.03556X_6^* - 0.00609X_7^* \quad (5)$$

Note: *) significant at 0.05

3. GWNBR Model Evaluation

The model evaluation aims to choose the best model by considering the AIC value in every model. AIC value of the NBR is 288.0554, whereas the AIC value of GWNBR is 267.1734. The GWNBR model has a smaller AIC compared to the NBR. This means that the GWNBR model is better for modeling the number of pulmonary MDR-TB cases in Indonesia in 2019 than the NBR because the response variable in GWNBR is predicted by predictor variables in each location where the data is observed.

4. Discussion

Based on Table 1, the estimated population density coefficient averages 0.00073. On average, each increase in population density by one unit will increase the number of cases of pulmonary MDR-TB by $\exp(0.00073) = 1.0007$ times, assuming the other variables are constant. This population density variable has significant conditions in all regions. It is in line with research by (Zulaikha et al., 2018) that found population density has a significant and positive effect on the number of tuberculosis cases in West Java. Thirty-one provinces have a positive coefficient estimate. It means that the population density can increase the risk of the massive spread of tuberculosis. The same result is obtained from research (Pratama, 2015) on mapping and modeling tuberculosis in West Java using the GWNBR method. This study shows that the population density is significant and positive in several districts/cities in West Java. The infectious diseases can be easily transmitted to the surrounding community in densely populated areas. Based on these results, the Government in each province can enhance their efforts to distribute population density by doing such as transmigration and industrial development in less populated areas.

The coefficient estimation for the percentage of the poor has an average estimate of 0.01509. On average, when the percentage of poor people increases by one unit, the number of pulmonary MDR-TB will increase $\exp(0.01509) = 1.01520$ times, given the other variables are constant. People with low economic conditions tend to be reluctant to check their health at the hospital or healthcare facility (Zulaikha et al., 2018). This can worsen the ones health condition and cause drug-resistant tuberculosis, such as pulmonary MDR TB. The percentage of the poor has a significant value in 22 provinces in Indonesia. The percentage of poor households has significance in different areas to the number of TB RO (drug-resistant tuberculosis) cases. Areas with a significant percentage of poor people can be the government's focus to reduce this number with social assistance programs (Zulaikha et al., 2018).

The average estimated coefficient of the ratio of healthcare facilities per 100 thousand population is -0.20647. Each additional health center ratio per 100 thousand populations by one unit will reduce pulmonary MDR-TB cases by 1 unit $\exp(-0.20647) = 0.81345$ times, given the other variables are constant. Using a significance level of 0.05, the ratio of healthcare facilities per 100 thousand population is significant in 27 provinces in Indonesia. It is in line with the increasing number of healthcare facilities that will increase the Case Notification Rate (CNR) of tuberculosis. More cases can be handled, and pulmonary MDR-TB disease can be prevented (Zulaikha et al., 2018).

The average estimated coefficient of the ratio of health workers per 10 thousand population is -0.08888. Every increase in the ratio of health workers per 10 thousand population by one, on average it will reduce the number of cases of pulmonary MDR-TB by $\exp(-0.08888) = 0.91495$ times, given the other variables are constant. This variable is significant in 32 provinces in Indonesia. It is in line with those (Zulaikha et al., 2018), which studies the prevalence of tuberculosis and its influencing factors using the GWR method. The results show that the percentage of health workers significantly influences several regions. The negative estimated coefficient means that every increase in health personnel will decrease the pulmonary MDR-TB. The addition of the ratio of health workers is expected can reduce the number of pulmonary MDR-TB cases.

The percentage of smokers has an average estimated coefficient of 0,007922. It means, on average, every increase in the percentage of smokers in an area will increase the number of pulmonary MDR-TB by $\exp(0.007922) = 1.00795$ times given the other variables constant. This condition is in line with the result of smoking behavior can increase the risk of getting infected TB. (Hapsari et al., 2021). The estimation shows the significant influence of the variable in several areas of observation.

The coefficient estimation for the percentage of districts/cities with clean and healthy living behavior policies has an average of -0.02799. This means, on average, when the percentage of districts/cities with clean and healthy living behavior policies increases by one unit, it will decrease $\exp(-0.02799) = 0.97239$ times the number of pulmonary MDR-TB cases given other variables are constant. The variable percentage of districts/cities with clean and healthy living behavior policies is significant in every province in Indonesia, and each region has a negative coefficient. The study is in line with the results that showed that every increase in households using clean and healthy living behavior would reduce tuberculosis cases (Pratama, 2015).

The estimated coefficient of the percentage of BCG immunization coverage has an average of 0.010568. When the percentage of BCG immunization coverage increases by one unit, it will increase the number of pulmonary MDR-TB cases by $\exp(0.010568) = 1.01062$ times. The sign of this coefficient estimate is not as expected. It can be presumably because the effectiveness of BCG immunization in each individual varies. Immunization can protect or prevent infections by 51.02 percent (Kurniawansyah, 2007). The BCG immunization significantly affects the number of pulmonary MDR-TB cases in several provinces. The BCG vaccine can be effective or successful when a person does not have tuberculosis (Zuardy et al., 2020). The study results are in line with (Murniasih, 2007), which state a relationship between BCG immunization and the incidence of tuberculosis. However, research by (Briassoulis et al., 2005) stated that BCG immunization is ineffective in preventing primary tuberculosis but can prevent more severe complications (Rahajoe et al., 2010). BCG immunization is effective in the prevention of tuberculosis in the first place. However, someone immunized has not been entirely immune to tuberculosis. This is because tuberculosis transmission is effortless from person to person.

E. CONCLUSION AND SUGGESTION

The number of pulmonary MDR-TB cases in Western Indonesia tends to be higher than in Eastern Indonesia. There are spatial dependencies and spatial heterogeneity in the number of pulmonary MDR-TB cases in Indonesia in 2019. At the national level, so far, no research references have been found that explain the determinants of the incidence of MDR-TB cases, especially pulmonary MDR-TB by taking into account the spatial linkages at the provincial level The estimation of local parameters in each province is obtained using the GWNBR model. There are 12 regional groupings based on variables significantly influencing the number of pulmonary MDR-TB cases in Indonesia in 2019. The population density variable and the percentage of districts/cities with clean and healthy living behavior policies significantly influence the number of MDR-pulmonary TB cases in 34 provinces in Indonesia. Meanwhile, the rate of poor people, the ratio of healthcare facilities per 100 thousand people, the ratio of health workers per 10 thousand people, the percentage of smokers, and the rate of BCG immunization coverage were significant in several different areas.

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