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Spatial Distribution of Drug-Resistant Tuberculosisin Makassar City, South Sulawesi Province, Indonesia

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Abstract

This study aims to determine the domicile distribution, find out the high-risk areas, and determine the risk of drug-resistant tuberculosis patients based on patient location in 15 districts of Makassar City from Tuberculosis register data of South Sulawesi Provincial Health Office in December 2017 – April 2019 period. Gen Xpert rapid or drug sensitivity examinations were used to define drug-resistant tuberculosis. The domicile location of patients was geocoded by maps in Google Earth and aggregated per area by using Kernel Density analysis using ArcView GIS 10.3 software. We found that drug-resistant tuberculosis cases tended to be clustered in the western part of Makassar City, an area with a fairly high population density. There were areas with the highest concentration of predicted cases as a high risk of transmission of drug-resistant TB, around the Bontoala District, Makassar District, and Mamajang District. Healthcare facilities located in hot spots area need to be equipped with molecular rapid test facilities and conduct drug sensitivity tests for all suspected tuberculosis patients. Further research needs to be carried out to determine the distribution of tuberculosis patients who are sensitive and resistant to drugs.

Introduction

Currently, drug-resistant tuberculosis affects half a million people worldwide in 2018. This problem requires a longer treatment time with higher medical costs. Globally, 3.5% of new TB cases and 18% of previously treated cases had drug-resistant tuberculosis (WHO, 2019b) . In Indonesia, it is estimated that there are 8.8 patients with drug-resistant tuberculosis per 100,000 population. The success rate for drug-resistant tuberculosis treatment is also very low in Indonesia, with only 45% of patients experiencing the successful treatment of all treated patients (WHO, 2019a) .Diagnosis and treatment need to be supported by efforts to prevent the transmission of drug-resistant tuberculosis. Most incidence of drug-resistant tuberculosis is caused by the transmission of drug-resistant Mycobacterium tuberculosis from other patients (Kendall et al., 2015)

Tuberculosis transmission often occurs in communities with a high prevalence of untreated tuberculosis patients (Kompala et al., 2013). Based on these considerations, active case finding in areas at risk is a prompt implementation strategy (Yuen et al., 2015). Synergy in halting tuberculosis transmission may be attainable by combining interventions that prevent tuberculosis progression, shorten the period between disease onset and treatment initiation (case finding and diagnosis), and prevent transmission in key settings, such as the built environment (infection control) (Dowdy et al., 2017).

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We hypothesized that information about the location of patients with drug-resistant tuberculosis can be assess the risk of transmission to predict drug-resistant tuberculosis. We analyzed programmatic data collected in Makassar City, South Sulawesi Province, Indonesia by geographic mapping to see incidence spatially and to detect clusters of areas that are at high risk (hot spots) for the transmission of drug-resistant tuberculosis. In the health sector, geospatial is often used to identify geographical areas and communities with a higher risk of sickness or premature mortality and which therefore require higher preventive care or health information and disease monitoring in time and space (Banerjee, 2016)

Methods

This research was conducted based on Tuberculosis register data from December 2017 - April 2019 (unpublished data, South Sulawesi Provincial Health Office). We selected data from 15 districts of Makassar City. The selection of the location of this study was based on the drug-resistant tuberculosis location. Data collection at the District Health Office and South Sulawesi Provincial Health Office. Data processing conducted at the Department of Community Medicine and Preventive Medicine, the Faculty of Medicine, Hasanuddin University. The study protocol was approved by the ethics committee of Faculty of Medicine Hasanuddin University (Makassar, Indonesia), with number 401/UN4.6.4.5.31/PP36/2020.

The research will be divided into 2 phases: 1) Making a spatial-based related to drug-resistant tuberculosis, 2) Data analysis and mapping based on patient domicile for drug-resistant tuberculosis patients. The first phase was the development of spatial-based related to drug-resistant tuberculosis with the aim of producing direct information about symptoms experienced by the community quickly and efficiently. The data obtained will later reflect the real condition of the community by using ArcGIS from Esri.

The rest phase was data analysis and mapping to assess drug-resistant tuberculosis patients' distribution. The spatial analysis carried out is kernel density analysis, which aims to see the density index indications of drug-resistant tuberculosis patient distribution based on data validation results. Kernel Density analysis is one of the tools in Arc GIS spatial analysis, which calculates the force area per unit of a feature point or polyline using the kernel function to adjust the smooth surface tapered to each point whose output value represents the predicted density value (Seaman and Powell 1996).

Kernel Density analysis is determined by the following formula:

$$Density = \sqrt{\frac{1}{(radius)^2} \sum_{i=1}^{n} \left[\frac{3}{n} \cdot popi \left(1 - \left(\frac{disti}{radius} \right)^2 \right)^2 \right]}$$

$$\text{For } dist_i < radius \qquad (1)$$

information:

- $i = 1, \ldots, n$ is a point. Only include points in the number if they are within a radius of a (x, y) location.
- *popi* is the field value resident of point I, which is an additional parameter.
- *disti* is the distance between point i and location (x, y).

The spatial analysis of drug-resistant tuberculosis patients aims to see the distribution of TB transmission throughout Makassar City, so it can be used as a reference in making immediate break-up decisions, such as whether or not a place is needed for a quick preventative. The spatial analysis carried out is kernel density analysis which aims to see the density index of the distribution based on drug-resistant tuberculosis incidence data, which data is sourced from the South Sulawesi Provincial Health Office. The study protocol was approved by the ethics committee of Faculty of Medicine Hasanuddin University (Makassar, Indonesia) with number 401/UN4.6.4.5.31/PP36/2020.

Results And Discussion

We selected 68 drug-resistant tuberculosis patients in 15 districts of Makassar City from TB program data from December 2017 – April 2019. Gen Xpert rapid examination or drug sensitivity examinations were used to define drug-resistant tuberculosis. The domicile of patients was geocoded by using maps on Google Earth. The geospatial coding aggregated per area and used Kernel Density analysis using ArcView GIS 10.3 software. This analysis shows an area with the highest concentration of predicted cases can be used as the basis for planning TB control management.

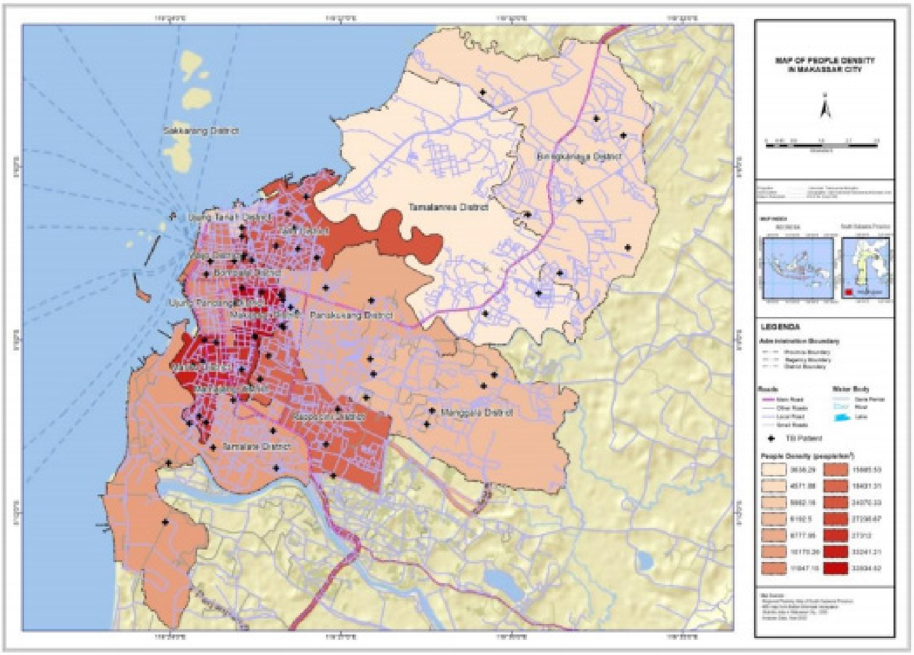

Figure 1. Map of People Density in Makassar City

The highest number of drug-resistant tuberculosis was found in Biringkanaya and Rappocini Districts, with 9 cases. Meanwhile, no finding in Sangkarrang Island and Ujung Pandang Districts. We found that drug-resistant tuberculosis cases tended to be clustered in the western part of Makassar City, an area with a fairly high population density (Figure 1). However, the ratio of drug-resistant tuberculosis cases per 1,000 population differs from the number of cases. The highest case ratio per 1,000 population was found in Bontoala District, Makassar District, and Mariso District with 0.087 cases per 1,000 population, 0.082 cases per 1,000 population, and 0.066 cases per 1,000 population, respectively.

Table 1. Number of Drug-resistant Tuberculosis Cases and Ratio of Drug-resistant Tuberculosis Cases Per 1.000 population

Districts	Cases	Population	Cases per 1.000 population
Biringkanaya	9	220,456	0.041
Bontoala	5	57,197	0.087
Makassar	7	85,515	0.082
Mamajang	4	61,452	0.065
Manggala	6	149,487	0.040
Mariso	4	60,499	0.066
Panakukang	5	149,664	0.033
Rappocini	9	170,121	0.053
Sangkarrang Island	0	14,531	0.000
Tallo	7	140,330	0.050
Tamalanrea	2	115,843	0.017
Tamalate	7	205,541	0.034
Ujung Pandang	0	29,054	0.000
Ujung Tanah	1	35,534	0.028
Wajo	2	31,453	0.064

The highest ratio of cases per 1,000 population was in areas directly adjacent and tended to be clustered, such as Bontoala District, Makassar District, Mariso District, Mamajang District, and Wajo District. The Kernel Density map of drug-resistant tuberculosis cases (Figure 2) showed that there were areas with the highest concentration of predicted cases (marked with red hot spots) around the Bontoala District, Makassar District, and Mamajang District. As previously known, this area was densely populated area, so there was a high risk of transmission of drug-resistant TB. This finding shows risk of transmission of drug-resistant tuberculosis based on domicile in Makassar City.

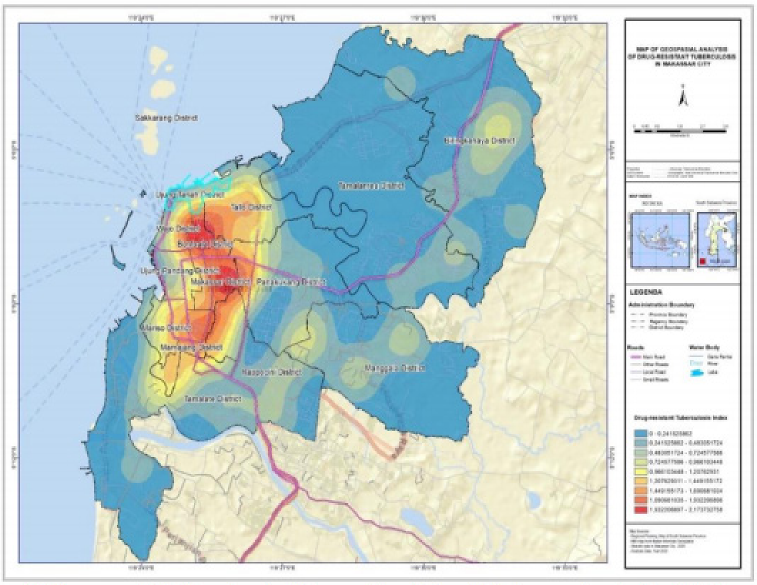

Figure 2. Map of Geospatial Analysis Drug-Resistant Tuberculosis in Makassar

We found that transmission of drug-resistant TB was geographically clustered in the western part of Makassar City. We also found several characteristics of the districts that were associated with a higher transmission rate of drug-resistant TB, including urbanization and population density. However, it does not obtain details on the baseline characteristics of patients, such as gender and age, since the information was mainly collected based on the domicile and the spread of TB.

There are studies supporting those results, Bastida et al. reported that the distribution pattern of TB patients was spatially clustered in the State of Mexico, Mexico and identified by using two types of analysis: spatial and spatial-temporal (Zaragoza-Bastida et al., 2012). Similar research by Alene KA, in Norwest Ethiopia (Alene et al., 2017). Yang S, et al in Nanchang, China, and MaO Q, et al. used a wide population in China to find clustered distribution patterns for TB cases (Mao et al., 2019). Locations with a higher percentage of TB cases also have a greater risk of becoming an MDR-TB hotspot(Jenkins et al., 2013).

The clustering of drug-resistant TB in the community is due to the transmission of drug-resistant strains (i.e. primary resistance) and was not a new case or responsiveness of first-line treatment. Further studies are needed to explore whether the spatial clustering of drug-resistant TB in the districts is due to the primary transmission of drug-resistant strains as a result of urbanization and high population density or due to poor first-line TB treatment, lack of health care services or behavioral and environmental factors (Alene et al., 2017).

The dominant causes of drug resistance are the patient's low motivation, inadequate treatment history, and sociodemographic factors so comprehensive management and the application of a Directly Observed Treatment Shortcourse (DOTS) are needed. ((Lima et al., 2020; Nugrahaeni, 2015; SR et al., 2012) In addition, both MTB ethnicity and lineage differed significantly in distribution by patient location. The lineage diversity of MTB and the detection of new sublineages suggest that this small area is already inhabited by a heterogeneous population group that is actively transmitting disease (Maung et al., 2020).

WHO recommends the test of rifampicin and/or isoniazid resistance in the following groups at the start of all patients with a history of anti-tuberculosis drugs. Drug-resistant TB is commonly found in patients with a history of treatment failure. Assessments of drug resistance conducted with criteria: all patients with Human Immunodeficiency Virus (HIV)) diagnosed with active TB, especially those who live in the area with a moderate or high prevalence of drug-resistant TB, patients with active TB after getting exposed to drug-resistant TB patients, and all new patients in the area with >3% primary drug-resistant TB cases (Kemenkes, 2013).

Conducting an assessment of drug resistance possibility based on medical history, exposure sources, and prevalence in the community should be performed on all patients. Drug resistance testing should be conducted at the initial treatment for previously treated patients. Furthermore, patients whose sputum smears gave positive results after completing three months of treatment, patients who have failed treatment, dropped out, or relapsed after treatment should always be assessed for drug resistance (Kemenkes, 2013).

For patients with possible drug resistance, drug sensitivity/resistance tests at least to isoniazid and rifampicin should be carried out immediately to minimize the possibility of transmission. Adequate infection control measures should be in place (Kemenkes, 2013). However, research conducted in Surakarta City, Central Java, Indonesia found the effect of Streptomycin, Isoniazid, and ethambutol treatment types on TB isolate resistance in patients with suspected TB (Sutanto et al., 2021). By using the spatial mapping of multidrug-resistant TB (MDR-TB), it can expand information on the prevalence of drug resistance in the community, establish specific TB management in the high-density area of MDR-TB by conducting drug resistance tests, and the efficiency of drug distribution and diagnostic tools related to TB. In the meantime, it will strengthen the preparedness of the health authorities to reduce the number of TB cases.

The transmission of drug-resistant Mycobacterium tuberculosis needs to be assessed so that patients can be early diagnosed and given prompt treatment. One of the methods is to identify clusters or locations of high-density drug-resistant tuberculosis cases. MDR-TB incidence and transmission are site-specific and often different from those in non-MDR-TB settings. (Alene et al., 2017; Lin et al., 2012) Therefore, the need for specific control and prevention planning for MDR-TB and non-MDR-TB is a top priority and includes geographic criteria in the control of MDR-TB (Oliveira et al., 2022; Oliveira et al., 2020).

We could include only drug-resistant tuberculosis patients and could not detect primary or acquisition of drug resistance. Further research needs to be carried out to determine the distribution of tuberculosis patients who are sensitive and resistant to drugs and should be carried out temporally. It can be a prior reference for the evaluation of case management and treatment in an area

Conclusion

Based on these findings, we assume there was a risk of transmission of drug-resistant tuberculosis in that area. These results suggest modification of guidelines, especially in hot spot areas. Healthcare facilities located in hot spots area need to be equipped with molecular rapid test facilities and conduct drug sensitivity tests for all suspected tuberculosis patients.

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