

The Condition of Mycobacterium Tuberculosis Lineages and Resistances in Indonesia

Vivi Hendra Sutandar^{1*}, Ziske Maritska²

¹ Master Student, Biomedical Program, Faculty of Medicine, Universitas Sriwijaya

² Department of Biology Medicine, Faculty of Medicine, Universitas Sriwijaya

*Corresponding Author. E-mail: ziske_maritska@unsri.ac.id Mobile number: 0812-2480-1100

ABSTRACT

Background: Tuberculosis is a disease caused by Mycobacterium tuberculosis. Indonesia ranks second worldwide in TB incidence in the country.

Content: The spread of the disease is happening across Indonesia. Each area of Indonesia had different types of lineage *M. tuberculosis* and TB incidence number. Drug resistance is threatening to society and it needs full attention and immediate medication to control the disease. Therefore, this paper is composed of reviews from 10 journals that reported drug resistance TB in several different locations in Indonesia using different methods available.

Conclusion: The number of TB cases and their lineages differ in each area in Indonesia, one of which is due to the availability of diagnostic tools and level of self-awareness in each area. There are reported findings of drug resistance TB in Indonesia that are concerning. Currently, many TB treatments are under development to produce the best therapy to treat the disease.

Keywords: Mycobacterium tuberculosis; Indonesia; Incidence



GREEN MEDICAL
JOURNAL
E-ISSN 2686-6668

Article history:

Received: 12 July 2022
Accepted: 15 August 2022
Published: 31 August 2022

Published by:

Faculty of Medicine
Universitas Muslim Indonesia

Mobile number:

+62821 9721 0007

Address:

Jl. Urip Sumoharjo Km. 5, Makassar
South Sulawesi, Indonesia

Email:

greenmedicaljournal@umi.ac.id

Introduction

Even after the whole world has gone into a state of pandemic, tuberculosis (TB) is still the leading cause of death worldwide. It even landed in second place just after COVID-19, causing approximately 1.5 million deaths in 2020 with Indonesia in second place after India. Its high mortality rate makes TB one of the global health burdens that need to be managed.

There are several factors contributing to the high number of incidences as well as the high number of death, where one of which is multidrug resistance (MDR-TB). MDR-TB has become a world concern which caused health crises globally, including in Indonesia.¹ The high number of TB and MDR-TB incidents in Indonesia signifies the need for controlling and preventing tuberculosis.²

Indonesia is an archipelago country, with numerous islands spread from Sabang to Merauke. TB spreads differently in each area of Indonesia. Asides from geographical factors, lack of medical staff and utilities may also affect the disease spread in remote areas.³ Recent research by Noviyani et al. found that the highest prevalence of TB in Indonesia was found on Sumatra.

Due to the concerning high number of TB and MDR-TB cases worldwide and also in Indonesia, the condition of TB across Indonesia needs to be assessed to evaluate the differences in TB incidence numbers in such areas, and what are the factors contributing to the phenomenon. This brief literature review wished to discuss *Mycobacterium tuberculosis* lineage and its resistance in Indonesia.

Literature review

General Condition of TB in Indonesia

Lisdawati et al. reported the predominant family is distributed differently in Indonesia. The western region of Indonesia is predominated by the Beijing family which is the dominant family in Indonesia. While central and eastern regions are predominated by East-African-Indian (EAI) families. And the resistant strain is also found within the samples which are 6,1% with mono-resistant and 5,4% multi-drug resistant (MDR) most of which are found within Beijing family isolates.⁴ Soeroto et al. found that 288 (85%) of 339 patients are found to be resistant to rifampicin (RR-TB) from a total of 3415 patients using Xpert MTB-RIF guided diagnosis conducted in West Java, Indonesia.⁵ And from the study done by Chaidir et al. to predict *M. tuberculosis* drug resistance in Indonesia by using whole-genome sequencing for strains from 322 adult TB patients with no history of HIV, the result found that 51 (15.8%) of 322 patients had *Mycobacterium tuberculosis* resistance to MDR and extensively drug resistance (XDR) with mutation majority in *katG* and *pncA*, and some on *rpoB*, *fabG*, and *embB*. With the highest resistance in both isoniazid and rifampicin, a lower number for both ethambutol and

streptomycin. 37.5% of resistance in Indo-Oceanic lineage is higher than in other lineages such as Euro-American and East Asian strains but the latter was found to possess most of the multiple mutations. This report may portray the potential of using WGS as a rapid and comprehensive test to predict drug resistance to TB.⁶ WHO reported Indonesia is within the list of 20 countries worldwide with the highest burden of drug resistance or MDR-TB and the number of estimated incident cases. There is a significant rise of 30% of MDR TB cases in Indonesia from 2016-2017 with a total of around 5000 cases reported of MDR/RR-TB from 2009-2017.⁷

Tuberculosis resistance

The resistance of *M. tuberculosis* isolates develops in two ways, infection from the resistant bacteria or indiscreet use of antibiotics by patients may lead to resistance or metabolic problem. Guidelines for laboratory testing of *M. tuberculosis* are available.⁸ Many roles may affect the resistance of *M. tuberculosis*, therefore to prevent the increasing number of incidences, a rapid test needs to be available to prevent the further spread of the disease and reduce the fatality number in the country. Nurwidya et al. suggest using nucleic acid amplification test (NAAT) and whole-genome sequencing (WGS) may be useful because of their minimum time requirements in diagnosing TB to further help control the spreads.⁹ While Wiqoyah et al. reported that the microbiome in sputum are potential biomarker the proteobacteria microbiome is abundant in MDR-TB comorbid diabetes, and microbiome genera are more diverse in RR-TB patients.⁹ Majdawati et al. also added that the chest X-ray lesion characteristic of MDR-TB is the presence of correlation between cavities, nodules, and fibrosis.¹⁰

Tuberculosis resistance condition in Indonesia

Banten

Christopher et already reported the drug resistance TB test conducted on 600 patients in Banten, in which 4.9% of samples had the drug resistance mutation detected as RR-TB or rifampicin resistance-TB using the GeneXpert method.¹¹

West Java

Tania et al. did a WGS analysis of MDR-TB in Java, Indonesia. They found isolates resistance in the order of rifampicin, isoniazid, streptomycin, and ethambutol. And MDR-TB was commonly found in the East Asian Lineage by 63.3% and no DR-TB was found.¹² This result is consistent with Chaidir et al. in which isoniazid and rifampicin resistance is commonly found in West Java.¹³ 16 But Soeroto et al. found that besides RR-TB, MDR-TB and XDR-TB were also found in patients in West Java.¹⁴ While the gene responsible for resistance was done by Purkan et al. found from the isolate R2 which is resistant to isoniazid with a mutation in the *katG* gene, the points are C1061T, G1261 A, G1388T, G2161A.¹⁵

Papua

The TB condition in eastern Indonesia is consecutively almost similar to other areas in Indonesia. Chaidir et al. analyze the *M. tuberculosis* pattern in Papua and found 15% drug resistance mutation in patients. 7.6% of patients were resistant to rifampicin, 7.6% to isoniazid, 3.5% to ethambutol, and 2.5% to streptomycin. Additionally, 4% of patients had MDR-TB. Lineage found in the area majority is East-African India with 33.7% followed by Euro-American with 19.4% and Beijing strains, the latter proving to possess the most drug resistance mutation than the other two by 40%.¹⁶ This result was supported by another research by Chaidir et al. did genotype distribution of *M. tuberculosis* in coastal Papua using spoligotyping, from 199 isolates, modern lineage 4 had 46.9%, followed by ancient lineage 1 with 33.7% and modern lineage 2 with 19.4%. 35% of strains were found mainly in Beijing genotype by genotyping cluster analysis. The distribution of the *M. tuberculosis* strain in Papua is different from other areas in Indonesia.¹⁷ Another research was done in Papua to understand further the gene which caused the drug resistance mutation in *M. tuberculosis* in Papua by Maladan et al. found rifampicin resistance from a gene mutation in the *rpoB* gene from points S450L, D435Y, H445Y, L430P, and Q432K. isoniazid mutation in *katG* (S315T), *kasA* (312S), *inhA* (I21V), and *Rv1482c-fabG1* (C-15T). while in ethambutol mutation in *embB* gene (M306L, M306V, D1024N), and pyrazinamide mutation in *pncA* gene (W119R).¹⁸

South Halmahera

Dewi reported that 8% of drug-resistant TB was found in South Halmahera, Eastern Indonesia. 11 out of 13 patients had MDR-TB while the rest had pre-extensively drug-resistant. In which only 8 patients receive the treatment, 4 patients died and 1 lost contact.¹⁹

Makassar, South Sulawesi

Analyzing the gene responsible for drug resistance *M. tuberculosis* was done in Makassar by analyzing several genes which play roles in resistance. Umar et al. did an analysis and found rifampicin resistance in 80% of patients from a mutation in *rpoB* (S450L, H445D, D435V, S441L, I491F, and Q432P). There is an 11.42% case, in which mutation in *katG* leads to rifampicin resistance, not isoniazid resistance. Mutation points in *katG* are P280P, G279R, E340Q, T271I, E340*stop codon, R373G, and S315N. two strains mutation leading to streptomycin resistance because of mutation present in *rrs* gene (G878A and/or S514R).²⁰

Potential treatments for TB

There is a lot of potential substance to treat TB, Mudaliana found antimicrobial activity present in *Centella Asiatica* and *Gigantochloa apus* extract towards *M. tuberculosis*. Both extracts contain tannin

and alkaloids.²¹ Other than plants derivatives substances, other sources may be the potential to treat TB, the research by Daletos et al. reported the potential of marine invertebrates such as sponges and coral chemical substances had antimycobacterial activities because they contain terpenes and alkaloids which are under development as DR-TB drugs and therapies.²²

While natural substances had emerging research regarding their activity as antimicrobial. The use of gene manipulation to develop vaccine candidates is also under development because of its specificity. Indriarini et al. did research to develop vaccine candidates by cloning and protein expression on *Mce1A* gene from *M. tuberculosis* strain Beijing and standard strain (H37RV) inserted in *Escherichia coli* BL21. After the insertion, the expression was then analyzed by using a western blot, and the results are the forming of bands was found to be higher than expected.²³

Indonesia with WHO is planning to eliminate TB by 2030 with the support of the government. The recent report with WHO global held in October 2021 resulted in the six strategies to be implemented by Indonesia to achieve control of TB.²⁴

This study limitation to the limited amounts of articles available online thus the results of this study may not be able to represent the whole number of tuberculosis incidence in Indonesia. Thus, further research regarding the subject may be needed in the future.

Conclusions

The incidence of TB in Indonesia is high ranking second in the world. The number may differ in each area in Indonesia, several factors may affect those numbers one of which is the availability of tools in the area and the level of self-awareness. MDR-TB is also jeopardizing society and the numbers are also high in Indonesia. Research regarding the treatment of TB is plentiful, thus the development of MDR-TB treatment may not be far anymore for those who need it.

Conflict of Interest

There is no conflict of interest in this research

Funding Sources

There is no funding sources

Acknowledgment

There is no acknowledgment

References

1. World Health Organization. Tuberculosis. 2021. Retrieved from <https://www.who.int/news-room/fact-sheets/detail/tuberculosis>
2. Erawati, M, & Andriany M. The prevalence and demographic risk factors for latent tuberculosis infection (LTBI) among healthcare workers in Semarang, Indonesia. *J Multidiscip Healthc.* 2020;13:197–206.
3. Noviyani, A, Nopsopon, T, & Pongpirul K. Variation of tuberculosis prevalence across diagnostic approaches and geographical areas of Indonesia. *PLoS One.* 2021;16((10))
4. Lisdawati, V, Puspadari, N, Rif'ati, L, Soekarno, T, M, M, K, S., Parwati, I. Molecular epidemiology study of Mycobacterium tuberculosis and its susceptibility to anti-tuberculosis drugs in Indonesia. *BMC Infectious Diseases.* 2015; 15, 366. doi:10.1186/s12879-015-1101-y.
5. Soeroto, AY, Lestari, BW, Santoso, P, Chaidir, L, Andriyoko, B, Alisjahbana, B, .Hill. Evaluation of Xpert MTB-RIF guided diagnosis and treatment of rifampicin-resistant tuberculosis in Indonesia: A retrospective cohort study. *PLoS ONE.* 2019 14(2), e0213017. doi:<https://doi.org/10.1371/journal.pone.0213017>.
6. Chaidir, L, Ruesen, C, Dutilh, BE, Ganiema, AR, Andryani, A, Apriani, L, . . . Alisjahban, B. Use of whole-genome sequencing to predict Mycobacterium tuberculosis drug resistance in Indonesia. *Journal of Global Antimicrobial Resistance.* 2019; 16. 170-177. doi:<https://doi.org/10.1016/j.jgar.2018.08.018>.
7. Forbes , BA, Hall, GS, Miller, MB, Novak, SM, Rowlinson, M-C, Salfinger, M, . . . Wilson, ML. Practice Guidelines for Clinical Microbiology Laboratories. 2018.
8. Nurwidya, F, Handayani, D, Burhan, E, & Yunus, F. Molecular Diagnosis of Tuberculosis. *Chonnam Med J.* 2018., 54(1), 1-9. doi:10.4068/cmj.2018.54.1.1.
9. Wiqoyah, N, Mertaniasih, NM, Artama, WT, & Matsumoto, S. Microbiome in Sputum as a Potential Biomarker of Chronicity in Pulmonary Resistant to Rifampicin-Tuberculosis and Multidrug-Resistant-Tuberculosis Patients. *Int. J. Mycobacteriol.* 2021; 10(3), 260-267. doi:10.4103/ijmy.ijmy_132_21.
10. Christopher, PM, Cucunawangsih, & Widysanto, A. GeneXpert Mycobacterium tuberculosis /rifampicin assay for molecular epidemiology of rifampicin-Resistant Mycobacterium tuberculosis in an Urban Setting of Banten province, Indonesia. *Int J Mycobacteriol.* 2019; 8(4), 351-358. doi:10.4103/ijmy.ijmy_138_19
11. Tania, T, Sudarmono, P, Kusumawati, RL, Rukmana, A, Pratama, WA, Regmi, SM, . . . Faksri, K. Whole-genome sequencing analysis of multidrug-resistant Mycobacterium tuberculosis from Java, Indonesia. *J. Med. Microbiol.* 2020; 69(7), 1013-1019. doi:10.1099/jmm.0.001221.
12. Purkan, P, Ihsanawati , I, Natalia, D, Syah, Y, Retnoningrum, D, & Siswanto, I. Molecular Analysis of katG Encoding Catalase-Peroxidase from Clinical Isolate of Isoniazid-Resistant Mycobacterium tuberculosis. *J Med Life.* 2018. 11(2).
13. Chaidir, L, Sengstake, S, de Beer, J, Krismawati, H, Lestari, FD, Ayawaila, S, Alisjahbana, B. Mycobacterium tuberculosis genotypic drug resistance patterns and clustering in Jayapura, Papua, Indonesia. *Int J Tuberc Lung Dis.* 2015. 19(4), 428–433. doi:<http://dx.doi.org/10.5588/ijtld.14.0350>.
14. Chaidir, L, Sengstake, S, de Beer, J, Oktavian, A, Krismawati, H, Muhapril, E, van Creve, R. Predominance of modern Mycobacterium tuberculosis strains and active transmission of Beijing sublineage in Jayapura, Indonesia Papua. *Infect. Genet. Evol.* 2016; 39, 1 87-193. doi:10.1016/j.meegid.2016.01.019.
15. Maladan, Y, Krismawati, H, Wahyuni, T, Tanjung, R, Awaludin, K, Audah, KA, & Parikesit, AA.. The whole-genome sequencing in predicting Mycobacterium tuberculosis drug susceptibility and resistance in Papua, Indonesia. *BMC Genomics.*. 2021; 22, 844. doi:<https://doi.org/10.1186/s12864-021-08139-3>
16. Dewi, AP. Prevalence and characteristic of drug-resistant tuberculosis patients in South Halmahera District, eastern Indonesia. *European Respiratory Journal.* 2020; 56, 505. doi:1 0.1183/13993003.congress-2020.505
17. Umar, FF, Husain, DR, Hatta, MM, Natzir, RR, Sjahril, RS, Dwiyantri, RR, .Primaguna, MR. Molecular characterisation of mutations associated with resistance to first- and second-line drugs among Indonesian patients with tuberculosis. *Journal of Taibah University Medical Science.* 2020, 15(1), 54-58. doi:<https://doi.org/10.1016/j.jtumed.2019.12.003>
18. Mycobacteria. *Clinical Microbiology Reviews*, 13(2), e00038-00017. doi:1 0.1128/CMR.00038-17
19. Majdawati, A, Icksan, AG, & Lolong, D. Comparison of chest X-ray lesion characteristics of multidrug-resistant tuberculosis and non-tuberculous mycobacterial infection. *Pol. J. Radiol.* 2019. 84, e162-e170. doi:<https://doi.org/10.5114/pjr.2019.84515>
20. World Health Organization. Global tuberculosis report 2018 .World Health Organization. 2018. retrieved from <https://apps.who.int/iris/handle/10665/27445>.

21. Mudaliana, S. Antimicrobial activity of *Centella asiatica* and *Gigantochloa apus*. *J Basic Clin Physiol Pharmacol*. 2021. 32(4), 755-759. doi:10.1515/jbcpp-2020-0396.
22. Daletos, G, Ancheeva, E, Chaidir, C, Kalscheuer, R, & Proksch, P. Antimycobacterial Metabolites from Marine Invertebrates. *Pharmaceutics*, 2021; 13, 592.
23. Indriarini, D, Rukmana, A, & Yasmon, A. Cloning and expression of MCE1A gene from *Mycobacterium tuberculosis* Beijing and H37RV strain for vaccine candidate development *Afr., J. Infect.* 2018; 12(S), 127-132. doi:<https://doi.org/10.2101/Ajid.12v1S.19>
24. Organization WH. Indonesia commitment to eliminate TB by 2030 supported by the highest-level government [Internet]. 2021. Available from: <https://www.who.int/indonesia/news/detail/28-11-2021-indonesia-commitment-to-eliminate-tb-by-2030-supported-by-the-highest-level-government>.