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Epidemiology of Tuberculosis and Multidrug-Resistance Tuberculosis In Indonesia: A Systematic Review and Meta-analysis

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ADMINISTRATIVE INFORMATION

Support - There is no financial support for this systematic review.

Review Stage at time of this submission - Data analysis.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 06 September 2023 and was last updated on 06 September 2023.

INTRODUCTION

Review question / Objective To analyze and synthesize epidemiological burden (Prevalence, Incidence, and Mortality), determinant factors, and Intervention program and treatment outcome of TB and MDR TB in Indonesia.

Rationale Tuberculosis (TB), an infectious disease caused by Mycobacterium tuberculosis, is one of the leading causes of death worldwide and causes more deaths than HIV/AIDS. Approximately 9.9 million people (8.9 – 11 million) developed TB (WHO, 2021). The proportion of TB deaths was a 27% reduction from 1.7 million in 2000 to 1.2 million (1.1-1.3 million) among HIV-negative people in 2018. Indonesia is one of eight countries with 8% accounting for two-thirds of the global cases and the third rank globally in estimated incident cases per year (WHO, 2019). Based on TB prevalence surveys in 2013-2014, WHO estimated that Indonesia had 1,600,000 TB cases, 391 cases per 100,000 population (MoH RI, 2018).

Implementation of TB control in Indonesia faces challenges. Only 63% of patients received treatment from Government Facilities, more than 50% of patients seeking care in the private sector visited level 0 facilities, such as drug shops and pharmacies, and 40.2% of patients did not continue taking the drug before it was declared cured by health personnel (MoH RI, 2018; Surya A et al., 2017). Patients who fail to follow up (default) or fail in treatment are magnified at increased risk for drug resistance with limited treatment options. These conditions also raised the morbidity and mortality of TB and contributed to the transmission of Multidrug-Resistant (MDR) TB in the community (Gler MT et al., 2012).

The burden of drug-resistant TB is a primary national, regional, and global concern. MDR TB is caused by bacteria resistant to at least both isoniazid and rifampicin, the two most potent anti-TB drugs (WHO, 2019; WHO, 2014). In 2018, there were about half a million new cases of rifampicin-resistant TB (of which 78% had multi-drug-resistant TB). The gap between the number of people enrolled in treatment and the estimated

incidence was equivalent to only 32%, and Indonesia, one of the countries, accounted for 32% of the global gap between incidence and treatment enrolments (WHO, 2019).
Indonesia is one of the 20 countries with the highest number of TB, TB-HIV, and MDR-TB cases. Among the 30 countries with an MDR-TB burden, only seven countries had treatment success rates of more than 75% in cohorts of 2016, and Indonesia only had treatment success rates of 48%. The high rates of death (17%) and loss of follow-up (26%) were the reasons for these lower success rates (WHO, 2019).
The Directly Observed Treatment Short Course Strategy (DOTS) was launched in 1994 to address the problem of TB globally. DOTS implementation has helped countries to improve national TB control programs (NTPs)(WHO, 2006). Directly Observed Therapy (DOT) is key to monitoring the treatment process. Second-line anti-TB drugs have more side effects than first-line anti-TB drugs. Close patient monitoring is needed to ensure that side effects of second-line anti-TB drugs are recognized quickly (WHO, 2014). A systematic review revealed that using full DOT had significantly higher pooled treatment success rates (67.4%, 95% CI: 61.4–72.8%) than those reporting self-administration therapy (46.9%, 95% CI: 41.4–52.4%) (Yin J et al., 2016).
There were only a few systematic reviews about TB and MDR TB in Indonesia, and they were limited only to diagnostic methods, latent tuberculosis, and tuberculosis treatment (Apriani L et al., 2019; Asyary A et al., 2019; Rewata L et al., 2009; Susilawati TN et al., 2019). A comprehensive systematic review in Indonesia is needed to understand the problem in the local context. Therefore, we aimed to conduct a systematic review to analyze and synthesize epidemiological burden (Prevalence, Incidence, and Mortality), determinant factors, and Intervention program and treatment outcomes of TB and MDR TB in Indonesia.

Condition being studied The studied conditions are prevalence, incidence, mortality, determinant factors, interventions, and treatment outcomes for tuberculosis (TB) or multidrug resistance tuberculosis (MDR TB). TB prevalence is the number of tuberculosis cases (all forms) in a population at a particular time (mid-calendar year), expressed as a rate per 100,000 population. Meanwhile, the prevalence of MDR-TB is the proportion of new TB cases with MDR-TB/RR. The incidence of TB is the number of new cases of TB per 100,000 people per year. TB deaths are TB patients who die for any reason before starting or during treatment. The TB mortality rate is the number of deaths caused by TB per 100,000 people in one year. For determinant factors, we identified four perspectives: patient characteristics, TB history and treatment, disease or comorbidities, and lifestyle and environment. Each intervention was studied, and treatment outcomes were measured in terms of cure, treatment completion, treatment failure, death, loss to follow-up (default), and treatment success.

METHODS

Search strategy This systematic review and meta-analysis used PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyzes: guidance for reporting systematic reviews and meta-analyses). The literature search included in this research was a study that contains information on the prevalence, incidence, mortality, and determinant factors of TB and MDR TB.
The Pubmed / Medline and Scopus databases retrieved potentially eligible studies in Indonesia. The keywords in the search term used are “Tuberculosis”, “Pulmonary Tuberculosis”, “Multidrug-Resistant Tuberculosis”, “Prevalence”, “Incidence”, “Mortality”, “Risk Factors”, “Association”, “Causal”, “Determinant”, “Epidemiologic Factors”, “directly observed therapy”, “directly observed treatment”, “DOT*”, “tuberculosis intervention”, “tuberculosis program”, “default”, “failure”, “adherence”, “death”, “successful treatment”, “unsuccessful treatment”, “treatment outcome”, and “Indonesia”. A combination of search terms used Boolean Operators (AND, OR, NOT). All studies were uploaded into the EndNote X9 reference manager program and removed duplicate studies by this program and manually.

Participant or population TB and MDR TB patients in Indonesia.

Intervention Determinant Factors of TB and MDR TB, and any intervention program to promote treatment success.

Comparator Non determinant factors of TB and MDR TB, and routine practice.

Study designs to be included A descriptive study that provides the prevalence, Incidence, or Mortality of TB or MDR TB will be considered to include in this study. For determinant factors, studies conducted with cross-sectional, ecological study, case-control, and cohort in adult TB or MDR TB patients. All intervention treatments or programs that provided treatment outcomes such

as cure, complete, failure, default, and dead for the intervention study.

Eligibility criteria Any study provide prevalence or Incidence, Mortality or determinant factors or intervention and treatment outcome for TB or MDR TB that was conducted in Indonesia and published in English or Indonesian language was considered to include in this study. A cross-sectional, ecological study, case-control, and cohort in adult TB or MDR TB patients were included for determinant factors. We compared the risk factors of DS-TB and MDR TB patients and those of healthy people and TB patients. We included all intervention treatments or programs that provided treatment outcomes such as cure, complete, failure, default, and dead for the intervention study. Studies that are restricted to the specific population, such as childhood, HIV, or DM population, extrapulmonary TB, qualitative study, book, guideline, protocol, commentary, letter, news, report, review, clinical study to test a new drug or a new vaccine, do not have full text, were excluded.

Information sources We will use electronic databases such as Pubmed/Medline and Scopus. If we cannot find the article, we will contact the Author through email.

Main outcome(s) The outcomes of interest in this study were pulmonary tuberculosis (PTB) and MDR-TB. PTB implies a bacteriologically confirmed or clinically diagnosed TB case involving the pulmonary parenchyma or tracheobronchial tree. Bacteria-confirmed PTB cases were those whose biological specimens were positive by smear, culture, or molecular test such as Xpert MTB / RIF. Clinically diagnosed PTB cases did not meet the criteria for bacteriological confirmation but have been diagnosed with active TB by a doctor or other medical practitioner who has decided to provide complete TB treatment to the patient. Another outcome is MDR-TB. MDR-TB was defined as resistance to at least both isoniazid and rifampicin, the first-line TB drug. MDR-TB status was verified by bacteriological confirmation using rapid molecular tests, culture methods, or sequencing technologies. Lastly, treatment outcome was measured in terms of cured, treatment completed, treatment failed, died, lost to follow-up (default), and treatment success.

Data management Eligible studies were extracted based on a database format compiled in Microsoft Excel 2013 with the following format: for epidemiological burden (Prevalence, Incidence, and Mortality, we provided Study ID, Title of study, First Author, Journal name, Publication Year, Language, Study area (Setting), Study design, Study population, Study period, Total sample, Source of data, Objective, Finding, and Implication. For determinant factors were about Study ID, Title of study, First Author, Journal name, Publication Year, Language, Study area (Setting), Study design, Study population, Study period, Source of data, Number of case, Number of non-case, Total sample, OR/RR and 95%CI, Objective, and Determinant factor identified. Finally, for intervention and treatment outcome, we kept Study ID, Title of study, First Author, Journal name, Publication Year, Language, Study area (Setting), Study design, Study population, Study period, Source of data, Number of Intervention, Number of comparisons, Total sample, RR and 95% CI, Objective, type of Intervention, Duration of intervention, Type of treatment outcome, Finding, and Conclusion. From included studies, data were extracted by the first reviewer and evaluated by the second reviewer.

Quality assessment / Risk of bias analysis We assessed the risk of bias using The Newcastle-Ottawa Scale (NOS) to assess the quality of non-randomized studies in meta-analysis for case-control by using The Newcastle-Ottawa Scale (NOS) to assess the quality of non-randomized studies in meta-analysis for case-control studies and cohort studies. Whereas the National Institute of Health (NIH) quality assessment tools for other studies.

Strategy of data synthesis We will use qualitative and quantitative synthesis. For all included studies, we will start the analysis with qualitative synthesis and continue with quantitative synthesis using meta-analysis if appropriate. We will use pooled odds ratio (ORs) and 95% confidence intervals (CI) for categorical outcomes in the fixed effect or random effect model depending on heterogeneity assessment by calculating the I-square. If the I-square ≥50% and the p-value of heterogeneity <0.05, we consider heterogeneity present. For continuous outcomes, we will use either pooled unstandardized mean difference (USMD) or standardized mean difference (SMD) depending on the measurement using the same scale or not. We will use Stata version 15 to analyze the data using "metan" and related commands in meta-analysis. If data about determinant factors are only available in one study, we will calculate the Odds ratio or mean difference using "cci" or "ttesti" command.

Subgroup analysis We will perform a subgroup analysis to identify heterogeneity sources. The geographic area based on the Province in

Indonesia will be used for stratification in subgroup analysis. We will perform a subgroup analysis to identify heterogeneity sources. The geographic area based on the Province in Indonesia will be used for stratification in subgroup analysis.

Sensitivity analysis We will perform sensitivity analysis for determinant factors with heterogeneous data that exclude a high risk of bias study to get the robustness of the result. The degree of heterogeneity and direction of effect size between groups will be considered in determining the effect estimate in the sensitivity analysis. We will use Stata version 15 to analyze study effect sizes.

Language restriction Language restrictions apply to searches by only selecting articles in English or Indonesian.

Country(ies) involved This study was conducted in Indonesia, with Indonesia and Thailand as the Author's Nationality.

Keywords Epidemiology; tuberculosis (TB); multidrug-resistant tuberculosis (MDR-TB); risk factors; intervention; Indonesia.

Dissemination plans The completed manuscript will be published in an International peer-reviewed Journal.

Contributions of each author

Author 1 - Renti Mahkota - Author 1 drafted the study protocol, designed the study, and conducted the literature search, data extraction, quality assessment, and data analysis.
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