

Markovian modelling of transmission of tuberculosis cases in Indonesia

Andini Setyo Anggraeni* , Faradiba Jabnabillah

Institut Teknologi Batam, Indonesia

ARTICLE INFO ABSTRACT

Article History

Received : 18-05-2024 Revised : 23-06-2024 Accepted : 31-07-2024 Published : 30-08-2024

Keywords:

Life Expectancy; Markov Chain; Probability Transition; Steady State; Tuberculosis.

*Correspondence: E-mail: andini@iteba.ac.id

Doi:

10.24042/djm.v7i2.23477

Indonesia is ranked as the second highest contributor to global cases of Tuberculosis (TB), which requires a focused approach to the transmission of tuberculosis within the country. This research aims to model and analyze the spread of TB cases in Indonesia. This research uses a discrete-time Markov chain with S-I-T-R-D states and Maximum Likelihood Estimation to model the transmission of TB cases. This research provides innovation in modeling the transmission of TB cases with a more complex model by including the possibility of relapse and treatment outcomes using historical data of TB cases in Indonesia. This research produces a matrix of transition probabilities for each state, first transition probabilities, steady state states, expected times for each transition and lifetime.

<http://ejournal.radenintan.ac.id/index.php/desimal/index>

INTRODUCTION

Tuberculosis (TB), caused by the bacteria Mycobacterium tuberculosis complex, is one of the oldest diseases known to affect humans and is the leading cause of death worldwide. The disease spreads when people with TB release the bacteria into the air, for example by coughing. TB usually affects the lungs, i.e. Pulmonary TB, but can also affect other sites, i.e. extrapulmonary TB (Natarajan et al., 2020). The word tuberculosis appears to be derived from the Latin word *tubercula* (Dubos R.J ., 1987) (Sharma & Mohan,

2013)*.* M. tuberculosis bacilli have infected nearly 1/3rd of the world's population with 10% lifetime risk of developing TB disease (Bhardwaj et al., 2015). EPTB epidemiology studies have found that affected sites in the human body vary by geography and population (Makaju et al., 2010). Until the coronavirus (COVID-19) outbreak, TB was the leading cause of death from an infectious agent, ahead of HIV/AIDS (World Health Organization, 2022). The humankind had to wait for more than 60 years after Robert Koch's momentous announcement of the discovery *Mycobacterium tuberculosis* for drug(s) that could cure TB to become available (Peter R. Donald & Paul D. van Helden., 2012)(Dubos, 1939)(Feldman & Hinshaw, 1944)(Hinshaw et al., 1946)(Feldman et al., 1945)(Long & Ferebee, 1950)(Houghton et al., 1950)

WHO reports that the estimated number of people diagnosed with TB in 2021 worldwide is 10.6 million cases, an increase of around 600,000 cases from the 2020 estimate. Of the 10.6 million cases, there are 6.4 million (60.3%) people who have been reported and are receiving treatment, and 4.2 million (39.7%) others were not found and reported. Out of a total of 10.6 million cases in 2021, at least 6 million cases are adult men, 3.4 million cases are adult women and 1.2 million cases are children. Deaths from TB as a whole are also quite high, at least 1.6 million people died from TB, an increase from the previous year which was around 1.3 million people.

Based on WHO estimates, Indonesia ranks second as the country with the highest TB burden. In 2021 the incidence rate of TB is 354 per 100,000 population. In 2020, Indonesia ranks third with the highest number of cases (Kementerian Kesehatan RI, 2022). This shows an increase in TB cases in Indonesia from 2020 to 2021. TB cases in Indonesia are estimated at 969,000 cases (one person every 33 seconds), an increase of 17% from 2020, which is 824,000 cases. The incidence of TB cases in Indonesia is 354 per 100,000 population, meaning that for every 100,000 people in Indonesia, there are 354 of them suffering from TB. The death rate from TB in Indonesia has reached 150,000 cases (one person every 4 minutes), an increase of 60% from 2020 when there were 93,000 cases of death from TB. With a death rate of 52 per 100,000 population. This shows that TB cases in Indonesia need more attention from various parties. Based on this information, the analysis or modeling of the transmission of TB cases in Indonesia is very important.

There are several mathematical epidemiological models to study the dynamics of infectious diseases, these models help to understand the spread of disease infections (Kementerian Kesehatan RI, 2022). Various studies on cases of Tuberculosis have been studied before. Previous studies that have similar methods, theories or research subjects are used as references in this research. The following is previous research that discusses the case of Tuberculosis: (Alim et al., 2019) and (Anggraeni, 2019) conducted research on the modeling of various states and the calculation of critical illness and chronic illness insurance premiums in Indonesia. Modeling the transmission of TB cases in Indonesia can also be done using a multistate model. A previous study on the modeling of various TB disease states was conducted by (Twimasi,2019). However, the study was conducted in Ghana and did not consider the likelihood of relapse and treatment outcomes. Therefore, it is necessary to conduct further research on TB modeling in Indonesia with a more complex model.

Another research by Debanne (Debanne, 2000) on Multivariate Markovian modeling of tuberculosis: Predictions for the United States. The study used a Markov chain to predict the spread of TB in the US. However, this research uses projected data, not historical data. Apart from that, there is research by Zhang and Hoad (Zhang, 2022) (Hoad, 2009) on Clearance of tuberculosis infection: A continuous-time Markov chain model in the host. Research has been conducted using Markov chains in the US. Both studies use the Markov chain model, but neither study was conducted in Indonesia. The estimation method used has also not yet used MLE.

Previous research on TB in Indonesia on Modeling Risk Factors for Pulmonary Tuberculosis in West Sumatra (Masnarivan, 2022). This research uses regression analysis. There is another study on Factors Affecting the Cure Rate of Pulmonary Tuberculosis Patients Using Bayesian Mixed Survival. The method used is Bayesian Mixture Survival (Atsilah Hasibuan et al., 2022). Meanwhile, Noorcintami and Lestari et al (Noorcintami, 2021) (Lestari, 2020) conducted TB research in Java. No research on TB in Indonesia still uses a complex multi-state model with a Markov chain.

However, some models fail to estimate critical illness-related metrics such as the probability of first infection and recovery. Therefore, research is needed on the transmission of TB cases in Indonesia using multi-state modeling, Markov chain methods, and parameter estimation using MLE. This study aims to estimate the transition of TB disease at discrete time steps for future and steady state forecasting. It will estimate the transition probabilities of first infection, first treatment, first recovery, and first relapse. Additionally, it will calculate the expected time for suspected, infected and treated individuals to move between different states and their life expectancy.

In this research, the transmission of TB cases in Indonesia will be modeled using a multi-state model. Contagion cases will be classified into five states: Suspect, Infected, Treatment, Recovery and Death. A Discrete Time Markov Chain with S-I-T-R-D modeling will be used to estimate the *n*-th step probability transition matrix, estimate future case transitions at the steady state, estimate the first transition probability, and calculate expected times and lifetimes. The maximum likelihood estimation method will be used to estimate transition probabilities and standard errors. This research provides innovation in modeling the transmission of TB cases with a more complex model by including the possibility of relapse and

treatment outcomes using historical data of TB cases in Indonesia. The results of this study can guide health care strategies and interventions to effectively manage and reduce the effects of Tuberculosis in Indonesia.

This study will be divided into several parts, namely the background of the problem, research methods, results and discussion, as well as conclusions and recommendations. In the research method section, data sources, model development, the definition of each status in the model, the assumptions used, and the formulas used in the calculations will be explained. In the results and discussion section, the results of the study will be presented and a discussion of these results will be presented. The final section will explain the conclusions of the study and the recommendations obtained from this research.

METHOD

Flowchart of this research can be seen in Figure 1.

Figure 1. Flowchart

The data used in this study were obtained from the TB case database in Indonesia, which is provided under the WHO data sharing policy and is subject to WHO terms and conditions. The WHO global TB database is constantly updated, with the latest data published by the WHO in the database categorized by country and region after the release of the Global Tuberculosis Report 2022. The required data include information on suspected cases of TB, the number of new cases notified (including lung- Additional lung, Bacteriology and clinically diagnosed cases), the number of recurrent cases (including Additional lung, Bacteriology and clinically diagnosed cases), the number of patients under care, and treatment outcomes (including the number of patients still on treatment, they who have died, and those who have recovered), as well as the number of TBrelated deaths.

Modeling will be conducted using a discrete time Markov chain with five states: Suspect (0), Infected (1), Treatment (2), Recovery (3) and Death (4). A discrete-time stochastic process X_n is a Markov Chain if it satisfies equation (1)

 $P(X_n = j \mid X_0 = x_0, X_1 = x_1, ..., X_{n-1} = i)$ (1) $P(X_n = j | X_{n-1} = i) = p_{ij}.$

For all $n \geq 1$ and $x_0, x_1, ..., i, j \in S$. Then, the transition probability for $i, j = 0,1,2$ is denoted in matrix shown in equation (2)

$$
P_{ij} = \begin{pmatrix} P_{00} & P_{01} & P_{02} & P_{03} & P_{04} \\ P_{10} & P_{11} & P_{12} & P_{13} & P_{14} \\ P_{20} & P_{21} & P_{22} & P_{23} & P_{24} \\ P_{30} & P_{31} & P_{32} & P_{33} & P_{34} \\ 0 & 0 & 0 & 0 & 1 \end{pmatrix}.
$$
 (2)

where $\sum_{j=0}^{4} P_{ij} = 1$, $i = 0, 1, 2, 3, 4$. P_{ii} is probability of remaining in state i. P_{ij} is ransition probability from state i to state $i, i \neq j$. Death is an absorbing state since the probability of becoming susceptible, infected, treated, or recovering is zero. The time step unit to ensure the transition from one state to another is measured on a yearly basis.

Definition of state in SITRD Model is as follows

- Suspected state (S) : It consists of individuals with symptoms or signs suggestive of TB who have never been infected with TB
- Infected state (I) : It consists of infected individuals, both new cases (extra pulmonary, pulmonary

bacteriologically, and pulmonary clinical diagnosed) and relapse cases (extra pulmonary, pulmonary bacteriologically, and pulmonary clinical diagnosed).

- Treatment state (T) : It consists of infected individuals who gets treatment at the first time and previously treated patient.
- Recovery (R) : It consists of treated patient who gets complete and success treatment
- Dead (D) : It consists of individuals who died due TB, both suspected, infected, or on treatment

There are several assumptions used in this study:

- The current state of an individual depends only on the state of the individual at the previous time step.
- The transition probability is independent of time and is assumed to be constant throughout time period.
- Individuals who have recovered can be infected with TB again (Relapse).
- Individuals who have been infected with TB cannot become suspects again.
- Individuals entering recovery status can only enter the infected status or remain in recovery. Death after recovery is not included in the study criteria.

Patients in treatment who were lost to follow-up and not evaluated were not included in the study criteria

Maximum likelihood estimation (MLE) was used to estimate transition probabilities for each disease with their respective standard errors. Transition events are independent of each other (as defined by the Markov principle); possible transition probability, P_{ij} follows the binomial model in equation (3)

$$
L(P_{ij}|N,x) = {N_i \choose x_{ij}} P_{ij}^{x_{ij}} (1 - P_{ij})^{N_i - x_{ij}}.
$$
 (3)

Where N_{ij} is the number of observed transition that starts from state i to j and

$$
\sum_{j} P_{ij} = 1. \tag{4}
$$

From equation (3) and the assumption of constant transition probability over the period, the transition probability matrix is estimated as a multinomial distribution given in equation (5)

$$
\hat{P}_{ij} = \frac{x_{ij}}{\sum_j x_{ij}} = \frac{x_{ij}}{N_i}.
$$
 (5)

For $i, j = 0, 1, 2, 3, 4$, with standard errors from the sampling distribution of the Maximum-Likelihood estimation given in equation (6) (Serfozo, 2009)

$$
\hat{s} \cdot e(P_{ij}) = \sqrt{\frac{\hat{P}_{ij}(1-\hat{P}_{ij})}{N_i}}.
$$
 (6)

The method for estimating the *th*step transition probability matrix for each disease uses the eigenvalue and eigenvector approach. The P_{ij}^n , $i, j =$ 0,1,2,3,4 transition probability matrix is estimated using a decomposition method that requires eigenvalues and the corresponding eigenvectors. Hence, it can be estimated using the decomposition as equation (7)

$$
P^n = Q\Lambda^n Q^{-1}.\tag{7}
$$

where Q is 5×5 nonsingular matrix and Λ^n is diagonal matrix corresponding to the eigenvalues λ_j , $j = 0,1,2,3,4$. Thus, matrix Λ^n shown in equation (8)

$$
\Lambda^{n} = \begin{pmatrix} \lambda_{0}^{n} & 0 & 0 & 0 & 0 \\ 0 & \lambda_{1}^{n} & 0 & 0 & 0 \\ 0 & 0 & \lambda_{2}^{n} & 0 & 0 \\ 0 & 0 & 0 & \lambda_{3}^{n} & 0 \\ 0 & 0 & 0 & 0 & \lambda_{4}^{n} \end{pmatrix}.
$$
 (8)

In many cases, Markov analysis will lead to a state of equilibrium (Steady State), which is a state where after the markov process runs for some period, then a value will be obtained for the probability that the state will remain constant. The vector π is said to be the stationary distribution of the chain if $\pi =$ $(\pi_j, j \in S)$ fulfil equation (9) and (10)

$$
\pi_j \ge 0, \forall j \in S \text{ and } \sum_j \pi_j = 1 \tag{9}
$$

$$
\pi = \pi P \text{ or } \pi(P, l) = 0 \tag{10}
$$

$$
\pi = \pi P \text{ or } \pi (P - I) = 0.
$$
 (10)

The probability that an individual at state i moves to state j for the first time between $m - 1$ and m time steps for states $i, j = 0,1,2,3,4$ from the transition probability matrix (S-I-T-R-D) is given as equation (11)

$$
f_{ij}^{m} = P(X_{n+m} = j, X_{n+m-1} = i, \cdots, X_{n+1} = i | X_n = i
$$

= $P_{ii}^{m-1} P_{ij}$. (11)

The probability of first infection for a suspected individual is given as f_{01}^m , the probability of first treatment for an infected individual is given as f_{12}^m , the probability of first recovery for a treated individual is given as f_{23}^m , and probability first relapse given as f_{31}^m .

The expected time for infection and recovery has a closed-form solution calculated as equation (12)

$$
E(\tau_{ij}^1) = \frac{\sum_{m=1}^{\infty} m f_{ij}^m}{P_r(i \to j)}.
$$
 (12)

for $i, j = 0,1,2,3,4, i \neq j$, where the numerator, $\sum_{m=1}^{\infty} m f_{ij}^m$, is the expected value of first passage time from state i to state i and the denominator shown in equation (13) is the overall probability or lifetime probability of transitioning from state i to state i

$$
P_r(i \to j) = \frac{P_{ij}}{1 - P_{ii}}.\tag{13}
$$

Life expectancy $(W_i, i = 0,1,2,3)$ for suspected, infected, treated, and recovery individuals can also be estimated using equation (14)

$$
W = (I - Q)^{-1} \times \begin{pmatrix} 1 \\ 1 \\ 1 \\ 1 \end{pmatrix}.
$$
 (14)

where I is a 4×4 identity matrix and Q is 4×4 matrix shown in equation (15)

$$
Q = \begin{pmatrix} P_{00} & P_{01} & P_{02} & P_{03} \\ P_{10} & P_{11} & P_{12} & P_{13} \\ P_{20} & P_{21} & P_{22} & P_{23} \\ P_{30} & P_{31} & P_{32} & P_{33} \end{pmatrix}.
$$
 (15)

RESULTS AND DISCUSSION

Suppose that the discrete states of the Markov chain model for TB are suspected (state 0), infected (state 1), treatment (state 2), recovered (state 3) and dead (state 4). Let $X_{ij} = 0.1, 2.3, 4$ represent the

number of individuals at any state at any time t that satisfy the first-order homogeneous time Markov dependence of the equation. Clearly, X_i satisfies the Markov chain model with state space $S =$

{0,1,2,3,4}. Figure 2 shows a multistate model of TB transmission. Table 1 shows the number of individuals in the population in states 0,1,2,3, and 4.

Figure 2. Multiple States Model of Tuberculosis

Table 1. Number of individuals at any state at the end of the period

State				3		Total
0	525.765	419.861	$\overline{}$			23.374 969.000
1	\sim 10 \pm	236.392 59.211		\blacksquare	124.258 419.861	
2	\blacksquare		-10.658	40.264	2.368	53.290
3	\blacksquare	12.716	~ 100 km s $^{-1}$	27.548	٠	40.264

Estimation of transition probabilities is an important aspect in understanding the dynamics of Markov chain models, especially in the context of the development of diseases such as Tuberculosis (TB). In our study, we used the maximum likelihood estimation (MLE) method to calculate the transition

probability matrix. The results of the MLE process are presented in Table 2, where both estimates and standard errors of transition probabilities are provided. The transition probability matrix for TB is presented as equation (16).

$$
P = \begin{pmatrix} 0.54258 & 0.43329 & 0 & 0 & 0.02412 \\ 0 & 0.56302 & 0.14103 & 0 & 0.29595 \\ 0 & 0 & 0.2 & 0.75556 & 0.04444 \\ 0 & 0.31582 & 0 & 0.68418 & 0 \\ 0 & 0 & 0 & 0 & 1 \end{pmatrix} . \tag{16}
$$

Desimal, 7 (2), 2024 - 401 Andini Setyo Anggraeni, Faradiba Jabnabillah

Looking at the estimates in Table 2, some noteworthy observations can be made. For example, the transition probability P_{00} (suspect to suspect) is estimated to be 0.54258 with a standard error of 0.0005061. This indicates that there is a relatively high probability of remaining in the suspected state in one time step. Similarly, the transition probability of P_11 (infected to infected) is estimated to be 0.56302 with a standard error of 0.0007655. This implies a high chance of the individual remaining infected in the next step. In contrast, P_14 (infected to dead) has an estimate of

0.29595 with a standard error of 0.0007045, indicating a relatively high probability of individuals transitioning from an infected state to a dead state.

The transition probability matrix, denoted as P^n , serves as a key tool for predicting state transitions and understanding disease progression across different states. The transition probability matrix P^n is estimated from equation (7). The transition probability matrix P^n predicts the transition probability at any time step. The transition probability matrix P^n is estimated as equation (17)

Clearly for $n = 1$ from the estimated $Pⁿ$ transition matrix gives the actual first transition matrix P_{ij} .

The steady-state probabilities, denoted as π_0 , π_1 , π_2 , π_3 , and π_4 , correspond to the proportions of individuals in the suspect, infected, treatment, recovery, and dead states, respectively. These probabilities represent the long-term distribution of individuals within each state, offering insight into the prevalence of TB cases in various stages of the disease. Using equations (7) and (8) TB case transmission reaches a steady state

condition at step 78 and is obtained π_0 = 3.88620×10^{-22} , $\pi_1 = 2.53567 \times$ 10^{-6} , $\pi_2 = 5.436534 \times 10^{-7}$, $\pi_3 =$ 2.366398×10^{-6} , and $\pi_4 = 0.9999946$.

From our analysis, we found that in the steady state, the majority of individuals, about 99.99946%, are in the dead state (π_4) . This suggests that the TB transmission model reaches an equilibrium state where most individuals have progressed to the fatal outcome of the disease. The remaining probabilities π_0 , π_1 , π_2 , and π_3 are very small, indicating that very few individuals are in the suspect, infected, treatment, and recovery states, respectively. The achievement of a steady state at step 78 highlights the balance achieved in the distribution of individuals across different disease states. This analysis sheds light on the long-term prevalence of TB cases at various levels, offering important insights for public health policy and interventions aimed at curbing the impact of Tuberculosis.

The probability that a susceptible individual becomes infected first, the probability that an infected individual receives the first treatment, the probability that a patient in treatment recovers for the first time, and the first probability are estimated using equation (11). Figure 2 shows a plot of the first transition probability across various time steps from 1 to 80.

Based on Figure 3, it can be observed that the probability of the first recovery is

the highest, and the probability of the first infection is higher than the first relapse and the first treatment. Moreover, the probability of first recovery from tuberculosis is very high at lower time steps but decreases sharply across increasing time steps. Therefore, it only suggests that if a patient is diagnosed with TB at an early or latent stage, lasting control measures can be implemented to start recovering from the disease. This is because most people with active TB after receiving appropriate treatment for at least two years are no longer contagious. However, if a TB patient is infected for a long period of time, then there is a relatively small probability of recovery from the disease in some time steps in the future.

Figure 3. First Transition Probability

Estimates of the expected time for various disease-related events play an important role in understanding the dynamics of Tuberculosis (TB) development and its impact on individual health outcomes. The expected time for individuals suspected to be infected with TB, infected individuals receiving treatment, infected individuals recovering

after treatment, and the expected time for recurrence is estimated from equation (12) and shown in Figure 4. The expected time for infection by susceptible individuals is found to be 2.1862 years. This suggests that individuals exposed to TB may, on average, begin to develop infection after this period. It is important to note that this expected time can vary

Desimal, 7 (2), 2024 - 403 Andini Setyo Anggraeni, Faradiba Jabnabillah

widely among individuals due to factors such as immune response, level of exposure and overall health. It was found that infected individuals on average will start receiving treatment after about 7.058 years after infection. These findings highlight the delayed initiation of treatment for infected individuals and emphasize the need for timely diagnosis and intervention to improve patient outcomes and prevent further transmission. On the other hand, the expected time to recover after treatment is 7.011 years. This means that a TB patient who undergoes treatment on average will recover after 7.011 years. These findings emphasize the importance of a consistent and effective treatment protocol in achieving successful recovery and managing the effects of the disease. Then, the expected time to repeat is 8.375 years. This means that an infected individual who recovers from TB will on average become infected with TB again is 8.375 years. This suggests that there is a significant period of time between recovery and the potential for relapse. Proper follow-up and monitoring of recovered patients is essential to detect and manage the potential for relapse.

Figure 4. Expected Time Each Transition

Figure 5. Life Expectancy

Life expectancy, shown in Figure 5, which is a statistical measure of the average time an individual is expected to live or survive, was estimated using equation (14) for suspected, infected and individuals on TB treatment. Life expectancy for suspected individuals is estimated at 7.1694 years. The results of this estimate show that a person suspected of having TB has a relatively low life expectancy. Life expectancy for infected individuals was estimated as 5.2606 years indicating a reduced life expectancy compared to suspected individuals. This is probably because many individuals infected with TB do not receive treatment. On the other hand, the life expectancy of patients in treatment is 9.2088 years. This suggests that individuals who undergo proper TB treatment have improved health outcomes and longevity compared to those who remain infected or in suspected conditions.

Based on the results of this study, the transmission of tuberculosis cases in Indonesia can be described more clearly than in previous studies. In previous studies, relapse and treatment were ignored (Twumasi et al., 2019), while based on the results of the study, patients who received treatment had a high chance of recovery if treated before 4 years since being exposed to TB. However, this is inversely proportional to the low probability of seeking treatment. While patients who receive treatment will have the highest life expectancy.

CONCLUSIONS AND SUGGESTIONS

Attainment of steady state at step 78 highlights that the majority of individuals are in a state of death. The first recovery probability is consistently the highest among all early transition probabilities. These findings emphasize the importance of effective treatment protocols in assisting individuals on their path to recovery. The probability of the first infection is higher than the first relapse and the first treatment. It suggests that once an individual is infected with TB, there is a higher chance of progressing to a re-infected state than receiving treatment or relapsing to infection after initial recovery. In contrast, TB patients under treatment had the highest life expectancy (9.2 years) compared to suspected (7.2 years) and infected (5.3 years) individuals. However, the expected time for an infected individual to receive treatment is after 7,058 years. It can make TB infection worse and harder to treat. The probability of an individual relapsing is also high, 31.582%, and an infected individual who recovers from TB will, on average, become infected with TB again in 8.375 years. It suggests that individuals who undergo proper TB treatment have improved health outcomes and longevity compared to those who remain infected or in suspected conditions.

These findings emphasize the importance of timely diagnosis, initiation of treatment, and adherence to treatment protocols in achieving successful recovery and increasing overall life expectancy. These results can guide healthcare strategies and interventions to effectively manage and reduce the impact of Tuberculosis. Further research can be conducted focusing on tuberculosis risk reduction and area-based modeling. In addition, considering the importance of early treatment, further studies can be conducted to measure the level of understanding and concern of the community about tuberculosis.

ACKNOWLEDGMENTS

We would like to express our sincere gratitude to the Ministry of Research, Technology, and Higher Education of the Republic of Indonesia for their financial support through the Penelitian Dosen Pemula (PDP) research grant program. This research was made possible by the grant with contract number 186/E5/PG.02.00.PL/2023.

REFERENCES

- Alim, K., Listiani, A., Anggraeni, A. S., & Effendie, A. R. (2019). Critical illness insurance pricing with stochastic interest rates model. *Journal of Physics: Conference Series*, *1341*(6). https://doi.org/10.1088/1742- 6596/1341/6/062026
- Anggraeni, A. S., Listiani, A., Alim, K., & Effendie, A. R. (2019). Morbiditymortality table construction for eleven chronical diseases (ECD) using constant force assumption. *Journal of Physics: Conference Series*, *1341*(6). https://doi.org/10.1088/1742- 6596/1341/6/062030
- Atsilah Hasibuan, N., Jaya, I., Husein, I., & Sumatera Utara, U. (2022). Factors that affect the healing rate for patiens with tuberculosis of the lung use bayesian mixture survival. *Journal of Analytical Research*, *1*(1), 51–63. https://doi.org/https://doi.org/10.4 590/jarsic.v1i3.3
- Bhardwaj, A. K., Kumar, D., Raina, S. K., Sharma, S., & Chander, V. (2015). Assessment of extra pulmonary tuberculosis (EPTB) cases from selected tuberculosis units (TUs) of Himachal Pradesh, India. *International Journal of Health*, *3*(2), 29–33. https://doi.org/10.14419/ijh.v3i2.4

567

Debanne, S. M., Bielefeld, R. A., Cauthen, G. M., Daniel, T. M., & Rowland, D. Y. (2000). Multivariate markovian modeling of tuberculosis: forecast for the united states. *Emerging Infectious Diseases*, *6*(2), 148–157. https://doi.org/10.3201/eid0602.00 0207

- Dubos, R. J. (1939). Bactericidal effect of an extract of a soil bacillus on gram positive cocci. *Proceedings of the Society for Experimental Biology and Medicine*, *40*(2), 311–312. https://doi.org/https://doi.org/10.3 181/00379727-40-10395P
- Dubos R.J ., D. J. (1987). *The white plague:tuberculosis, man, and society*. Rutgers University Press.
- Feldman, W. H., & Hinshaw, H. C. (1944). Effects of streptomycin on experimental tuberculosis in guinea pigs: Preliminary report. *Proceedings of Staff Meetings of the Mayo Clinic*, *19*, 593–600.
- Feldman, W. H., Hinshaw, H. C., & Mann, F. C. (1945). Streptomycin in experimental tuberculosis. *American Review of Tuberculosis*, *52*(4), 269– 298.
- Hinshaw, C., Feldman, W. H., & Pfuetze, K. H. (1946). Treatment of tuberculosis with streptomycin: a summary of observations on one hundred cases. *Journal of the American Medical Association*, *132*(13), 778–782.
- Hoad, K. A., Hoog, A. H. va. t., Rosen, D., Marston, B., Nyabiage, L., Williams, B. G., Dye, C., & Cheng, R. C. H. (2009). Modelling local and global effects on the risk of contracting Tuberculosis using stochastic Markov-chain models. *Mathematical Biosciences*, *218*(2), 98–104. https://doi.org/10.1016/j.mbs.2009. 01.002
- Houghton, L., Maher-Loughnan, G., Leslie, W., Perry, D. N. L., Beatty, D., & Sandiford, B. (1950). Treatment of pulmonary tuberculosis with streptomycin and paraaminosalicylic acid. *Br. Med. J*, *1073*.
- Kementerian Kesehatan RI. (2022).

Tuberculosis Control in Indonesia 2022. *The Acceptance of Islamic Hotel Concept in Malaysia: A Conceptual Paper*, *3*(July), 1–48. https://erenggar.kemkes.go.id/file_performan ce/1-465827-06-4tahunan-710.pdf

Lestari, B. W., McAllister, S., Hadisoemarto, P. F., Afifah, N., Jani, I. D., Murray, M., van Crevel, R., Hill, P. C., & Alisjahbana, B. (2020). Patient pathways and delays to diagnosis and treatment of tuberculosis in an urban setting in Indonesia. *The Lancet Regional Health - Western Pacific*, *5*, 100059.

> https://doi.org/10.1016/j.lanwpc.20 20.100059

- Long, E. R., & Ferebee, S. H. (1950). A controlled investigation of streptomycin treatment in pulmonary tuberculosis. *Public Health Reports (1896-1970)*, 1421– 1451.
- Makaju, R., Mohammad, A., & Thakur, N. K. (2010). Scenario of extrapulmonary tuberculosis in a tertiary care center. *Journal of Nepal Health Research Council*, *8*(1), 48–50.
- Masnarivan, Y., & Haq, A. (2022). Pemodelan faktor risiko tuberkulosis paru di Sumatera Barat. *Jambi Medical Journal "Jurnal Kedokteran Dan Kesehatan," 10*(1), 68–80.
- Natarajan, A., Beena, P. M., Devnikar, A. V., & Mali, S. (2020). A systemic review on tuberculosis. *Indian Journal of Tuberculosis*, *67*(3), 295–311. https://doi.org/10.1016/j.ijtb.2020. 02.005
- Noorcintanami, S., Widyaningsih, Y., & Abdullah, S. (2021). Geographically weighted models for modelling the prevalence of tuberculosis in Java. *Journal of Physics: Conference Series*, *1722*(1), 0–8. https://doi.org/10.1088/1742- 6596/1722/1/012089
- Peter R. Donald & Paul D. van Helden. (2012). Antituberculosis

chemotherapy (progress in respiratory research). *British Journal of Clinical Pharmacology*, *74*(3), 549– 550. https://doi.org/10.1111/j.1365-

2125.2012.04251.x

- Serfozo, R. (2009). *Basic of applied stochastic processes*. Springer.
- Sharma, S. K., & Mohan, A. (2013). Tuberculosis: From an incurable scourge to a curable disease - journey over a millennium. *The Indian Journal of Medical Research*, *137*(3), 455–493.
- Twumasi, C., Asiedu, L., & Nortey, E. N. N. (2019). Markov Chain modeling of hiv, tuberculosis, and hepatitis b transmission in Ghana. *Interdisciplinary Perspectives on Infectious Diseases*, *2019*. https://doi.org/10.1155/2019/9362 492

World Health Organization. (2022). *Global tuberculosis report 2022*. World Health Organization. https://www.who.int/teams/globaltuberculosis-programme/tbreports/global-tuberculosis-report-2022

Zhang, W. (2022). Disease clearance of tuberculosis infection: An in-host continuous-time Markov chain model. *Applied Mathematics and Computation*, *413*, 126614. https://doi.org/10.1016/j.amc.2021. 126614