BAREKENG: Journal of Mathematics and Its Applications
March 2024 Volume 18 Issue 1 Page 0467–0474
P-ISSN: 1978-7227 E-ISSN: 2615-3017
https://doi.org/10.30598/barekengvol18iss1pp0467-0474

SPREADING PATTERN OF INFECTIOUS DISEASES: SUSCEPTIBLE INFECTED RECOVERED MODEL WITH VACCINATION AND DRUG-RESISTANT CASES (APPLICATION ON TB DATA IN INDONESIA)

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Article History:

Received: 12th October 2023
Revised: 22nd December 2023
Accepted: 16th January 2024

Keywords:

Drug-resistant;
MAPE;
Relapse;
SVITR;
TB.

ABSTRACT

Mycobacterium tuberculosis is the causative agent of the infectious illness tuberculosis (TB). Indonesia has the third-highest number of TB sufferers in the world. TB transmission is prevented by the BCG vaccination. A directly observed treatment short-course (DOTS) approach can cure TB illness. Recurrent TB may occur due to either relapse or reinfection with drug-resistant bacteria. The goals of this article are to formulate the SVITR model with relapse and drug-resistant cases, apply the model to the TB data in Indonesia, determine the model accuracy, determine the spreading pattern and interpret the result, and simulate the parameters. Literature study and application methods are used in this research. The SVITR model with relapse and drug-resistant cases is a first-order nonlinear differential equation system. The model is applied to TB in Indonesia based on annual data from Indonesian Health Profile, World Bank, and WHO. The model is solved by the fourth-order Runge-Kutta method. The model is accurate enough to explain the spread of TB in Indonesia with a MAPE value of 15,5%. The spreading pattern of tuberculosis infection is upward from 2010 to 2050. In 2050, there are still 8.115.976 TB cases in Indonesia. Hence in 2050, Indonesia's free of TB target has yet to be achieved. Simulation is conducted by increasing BCG vaccination to 95%, reducing contact with TB patients to 5%, increasing treatment to 95%, and lowering relapses and drug-resistant cases to 0.00005%, so the Indonesia free of TB target in 2050 can be achieved from 2042.

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How to cite this article:

P. Widyaningsih, S. R. Yumaroh and D.R.S. Saputro, "SPREADING PATTERN OF INFECTIOUS DISEASES: SUSCEPTIBLE INFECTED RECOVERED MODEL WITH VACCINATION AND DRUG-RESISTANT CASES (APPLICATION ON TB DATA IN INDONESIA)," *BAREKENG: J. Math. & App.*, vol. 18, iss. 1, pp. 0467-0474, March, 2024.

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Journal homepage: *https://ojs3.unpatti.ac.id/index.php/barekeng/*
Journal e-mail: *barekeng.math@yahoo.com; barekeng.journal@mail.unpatti.ac.id*

Research Article · Open Access

1. INTRODUCTION

A communicable disease is an infectious disease caused by microorganisms such as bacteria, viruses, fungi, or parasites that spread to people. The symptoms of infectious disease include fever, chills, sweats, sore throat, shortness of breath, and many more. The communicable disease is transmitted through direct or indirect contact through air [1]. Transmission of communicable diseases can be prevented by vaccination [2]. Vaccine effectiveness lasts for a certain period. The communicable disease may be cured by treatment. The recurrent infectious disease may occur in a cured individual and can return to its previous state or evolve drug resistance. The drug-resistant state is when the relapse individual is resistant to specific drugs used before [3].

Tuberculosis (TB) is a widespread contagious disease caused by Mycobacterium tuberculosis. TB is the world's second leading cause of death. According to the World Tuberculosis Report 2022, Indonesia has the third-highest number of TB sufferers in the world [4]. TB is disseminated through air polluted by TB germs when persons with TB diseases sneeze, cough, or spit. The BCG immunization program for 0-2 month(s)-old neonates prevents TB transmission. In its best condition, the BCG vaccine's effectiveness can last up to 15 years [5]. TB disease is treated with a brief course of directly observed treatment short-course (DOTS). A standard six-month course of TB treatment includes at least four antibiotics. The treatment of TB is supervised and supported by a health worker or trained volunteer. Relapse TB or drug-resistant TB can occur in recovered TB patients due to evolution of the bacteria to deal with the antibiotic compounds [6].

The spread of infectious disease is represented in a first-order nonlinear differential equation system. The susceptible infected recovered (SIR) model is introduced by Kermack and McKendrick [7] and studied by Hethcote [8]. The SIR model is applied to many infectious disease transmissions, including measles by Utari [9] and monkeypox by Al-Temimi and Al-Shammrty [10]. The susceptible vaccinated infected recovered (SVIR) model is formulated by Liu et al. [11], Islam [12], and Harianto and Suprawati [13]. Then susceptible vaccinated infected recovered (SVIR) model with relapse cases is formulated and applied to TB disease in Indonesia by Widyaningsih et al. [14]. The susceptible infected treatment recovered (SITR) model is developed by considering the treatment process and applied to hepatitis B by Sacrifice [15], TB by Side et al. [16], COVID-19 by Bezabih et al. [17], and other diseases. Thus, the susceptible vaccinated infected treatment recovered (SVITR) model with relapse cases was formulated by Lestari et al. [18] and applied to TB cases in Indonesia in 2021.

Different than SVITR model formulated by Lestari et al. [18], the cured individual who develops drug resistance is considered in this paper. So, the SVITR model with relapse and drug resistance cases is obtained. Afterward, the model is applied to TB transmission cases in Indonesia, determining the transmission pattern of TB. The Indonesian Government issued Presidential Regulation No. 67 of 2021 on Tuberculosis Management. The regulation manages national strategy and the goal of ending TB epidemics by 2050. Therefore, Indonesian achievements will be considered in this paper, and numerical simulation will be conducted.

2. RESEARCH METHODS

The literature review and application method are used in this study. Books, journal articles, and internet sources are used as literature. Infectious disease characteristics are identified and previous research is studied. Assumptions and parameters from the previous models are changed and added so the SVITR model with relapse and drug-resistant cases is obtained. The model is then applied to TB transmission in Indonesia, using secondary data from the Indonesian Health Profile [19], the World Bank [20], and the WHO [4]. The 2010 data are used as the initial value, whereas the 2011–2020 data are used to estimate the parameters, and 2021 data are used to calculate mean absolute percentage error (MAPE) to determine the model accuracy. The fourth-order Runge-Kutta method is used to solve the model. Then the spreading pattern is defined and interpreted for Indonesia’s free of TB target in 2050. Simulations are conducted to achieve Indonesia’s free of TB target in 2050.

3. RESULTS AND DISCUSSION

3.1 SVITR Model with Relapse and Drug-Resistant Cases

The model used in this study is based on the basic SIR model by Hethcote [8]. A constant population and no migration assumptions in the SIR model are changed to a non-constant population and no migration assumptions resulted in differing birth and death rates. Birth rate notation μ in SIR model is transformed into θ, so the number of births is θN. All births are assumed as susceptible. Because of that assumption, the number of births θN is added to S individual group. Hence, the number of S is increased by θN. In this paper, death due to disease is considered. If δ states the death rate due to disease, the number of deaths of I individuals are reduced by δI.

Vaccination prevents the spread of infectious disease, allowing the body develops immunity. In this research, vaccinated individuals are classified as V individuals. Same as Liu et al. [11], a vaccine is provided for the S individual, and the SVIR model is formulated. If the vaccination rate is α then the number of vaccinated individuals is αS. Hence, the number of S is decreased, and the number of V is increased by αS. The vaccine gives temporary immunity and its effectiveness decreases over time. If the vaccine effectiveness decreasing rate is λ, then the number of V that becomes susceptible again is λV. So, the number of V is reduced and the number of S is increased by λV.

In this model, infected individuals should go through treatment and be classified into treatment (T) individuals, so the SVITR model is attained. If η states the treatment rate, the I individuals who go through treatment is as much as ηI. Hence, the number of I is reduced and the number of T is increased by ηI. If the recovery rate is γ, so the number of recovered persons after treatment is γR. Then, the number of T is decreased and R is increased by γR. Same as Lestari et al. [18], the recovered individual can relapse. If ξ is the relapse rate, the number of R individuals who relapse is ξR. Hence, the number of T is reduced and the number of R is added by γR. Unlike Lestari et al. [18], R can develop a drug-resistant state. Drug-resistant states occur where R individuals relapse and become I with a resistance condition to specific drugs. If the drug-resistant rate is ϵ, the number of R that relapse with drug-resistant is ϵR. So, the number of R is reduced and the number of I is added by ϵR. Hence, the SVITR model with relapse and drug-resistant cases of spreading of infectious diseases is

$$\begin{aligned}
\frac{dS}{dt} &= \theta N - \beta \frac{SI}{N} - (\alpha + \mu)S + \lambda V \\
\frac{dV}{dt} &= \alpha S - (\lambda + \mu)V \\
\frac{dI}{dt} &= \beta \frac{SI}{N} + (\xi + \epsilon)R - (\eta + \delta + \mu)I \\
\frac{dT}{dt} &= \eta I - (\gamma + \mu)T \\
\frac{dR}{dt} &= \gamma T - (\xi + \mu + \epsilon)R
\end{aligned} \tag{1}$$

with $S(0) \geq 0$, $V(0) \geq 0$, $I(0) > 0$, $T(0) \geq 0$, $R(0) \geq 0$ and $\theta, \mu, \beta, \delta, \alpha, \lambda, \eta, \gamma, \xi, \epsilon > 0$. The ten parameters are birth rate, natural death rate, contact rate, death due to infectious disease rate, vaccination rate, vaccine effectiveness decreasing rate, treatment rate, recovery rate, relapse rate, and drug-resistance rate. The SVITR model with relapse and drug-resistant cases (1) is a first-order nonlinear differential equations system with independent variable t and dependent variables S, V, I, T, and R.

3.2 Application

The SVITR model with relapses and drug-resistant cases (1) is applied to TB data in Indonesia. Parameter estimations are calculated based on 2011-2020 data from the Indonesian Health Profile [19], the World Bank [20], and WHO [4].

Table 1. Estimated Values of Ten Parameters

Parameters	Notations	Estimated Value
Birth rate	θ	0,018353
Natural death rate	μ	0,007601
Contact rate	β	0,505503
Death due to infectious disease rate	δ	0,010695

Vaccination rate	α	0,019268
Vaccine effectiveness decreasing rate	λ	0,066667
Treatment rate	η	0,339866
Recovery rate	γ	0,787718
Relapse rate	ξ	0,008843
Drug-resistant rate	ϵ	0,002017

Vaccination rate, 0.019268 or ≈ 0.02, is estimated as the average number of individuals vaccinated divided by the number of susceptible on 2011-2020. It means that about 2 out of 1000 susceptible individuals are vaccinated. Parameter relapse rate, ξ, is the average of the number of individuals who relapse is divided by the number of individuals who recover on 2011-2020. We find the estimated relapse rate is 0.008843 ≈ 0,01 which means that about 1 individual who relapses out of 1000 individuals who recover.

Thus, the SVITR model with relapse and drug-resistant cases for the spread of TB is

$$\begin{aligned}
\frac{dS}{dt} &= 0.018353N - 0{,}505503\frac{SI}{N} - 0.026753S + 0.066667V \\
\frac{dV}{dt} &= 0.019301S + 0.074119V \\
\frac{dI}{dt} &= 0.486051\frac{SI}{N} + 0.011563R - 0.368108I \\
\frac{dT}{dt} &= 0.348816I - 0.833386T \\
\frac{dR}{dt} &= 0.825934T - 0.019015R
\end{aligned} \qquad (2)$$

with S(0)≥ 0, V(0) ≥ 0, I(0) > 0, T(0) ≥ 0, R(0) ≥ 0.

Referred 2010 data as initial values are

$$\begin{aligned}
&S(0) = 238.704.834, \quad V(0) = 4.687.234, \\
&I(0) = 300.592, \quad T(0) = 169.219, \\
&R(0) = 154.294
\end{aligned} \qquad (3)$$

The solutions of initial value problem (2)-(3) are the number of S, V, I, T, and R individuals at *t*. Based on 2021 data, the MAPE value is obtained at 15,5%, or the model is accurate to explain the spread of TB in Indonesia. The number of S, V, I, T, and R individuals in the next 30 years is shown in **Figure 1**.

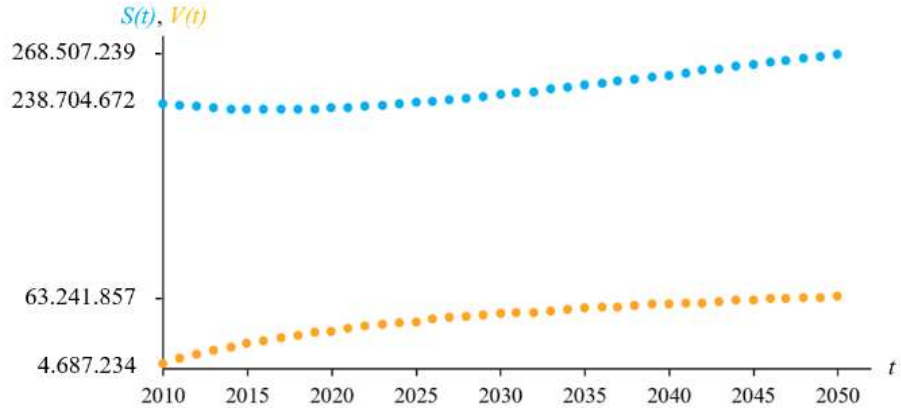

Figure 1. Scatter plot of the number of S and V individuals at 2010-2050

From **Figure 1**, the number of S and V are increasing over time. The number of S is increasing from 238.704.672 to 268.507.239 in 2050. The escalation of the number S is affecting the number of V due to increasing number of susceptible individuals to be vaccinated. The number of V increases over time, eventually reaching 63.241.857 in 2050. Hence, the number of S and V are linear upward trends. The number of I and T are shown in the **Figure 2**.

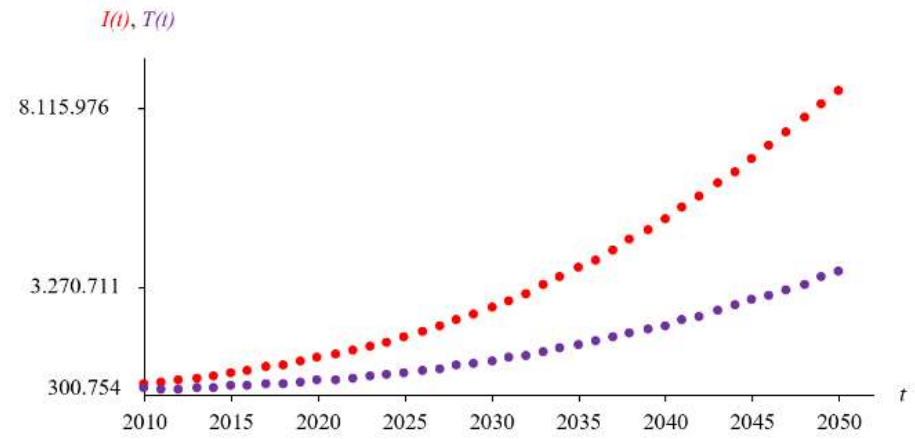

Figure 2. Scatter plot of the number of I and T individuals at 2010-2050

Based on **Figure 2**, the number of I is exponential upward trend for the next 30 years. The number of I are expected to expand from 300.754 to 8.115.976. The number of T will be 3.270.711 in 2050. The number of T is also an exponential upward trend. Afterward, the number of R is shown by the **Figure 3**.

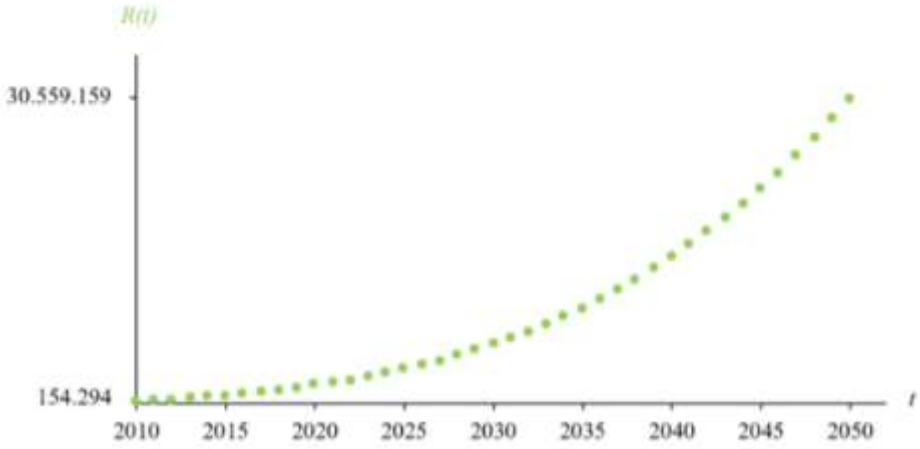

Figure 3. Scatter plot of the number of R individuals at 2010-2050

Based on **Figure 3**, the number of R is moving upward from 154.294 to 30.559.159. Same as the number of I and T, the number of R is also an exponential upward trend. Based on **Figure 1**, **Figure 2**, and **Figure 3**, the spreading pattern can be obtained. The number of susceptible and vaccinated individuals are linear upward trends, whereas the number of infected, treatment, and recovered individuals are exponential upward trends. Still, it is expected to be 8.115.976 TB cases in Indonesia in 2050, which means the Indonesia free of TB target in 2050 has not been achieved.

3.3 Simulation

Due to the application of SVITR with relapse and drug-resistant cases of TB transmission in Indonesia (2)-(3), Indonesia's target of being free of TB has not been achieved in 2050. The goal can be reached by expanding BCG vaccination, reducing contact with TB patients, increasing treatment, and lowering relapses and drug-resistant cases. The system (2)-(3) is simulated for various sets of parameter values. The number of I individuals is affected by vaccination rate (α), contacts rate (β), treatment rate (η), relapse rate (ξ), and drug-resistant rate (ϵ). The first simulation is done by increasing the vaccination rate (α) while other parameters don't change. Increasing α means increasing the number of vaccinated people. The simulation is shown in **Table 2**.

Table 2. Number of I individuals based on α Simulations

t	A			
	0,019268	0,1	0,5	0,95
2021	1.070.104	344.420	60.876	39.988
2030	2.321.805	227.585	32.005	23.512

2040	4.701.605	199.500	29.136	21.536
2050	8.115.976	205.440	27.578	20.149

From **Table 2** in columns 3 and 4, it can be seen the simulation of α value is increased to 0,1 and 0,5. There are still 205.440 TB cases in 2050 after the simulation of α = 0,1. The number of I in 2050 is reduced 400 times when α=0,5 compared to the number of I when α=0,019268.

The simulation is continued by increasing the α up to 0,95, and the number 20.149 of TB cases is obtained in 2050. This simulation is related to the Indonesian Government's Program of BCG Vaccination, which should be a must for up to 95% of births in Indonesia. The second simulation is conducted by reducing the contact rate (β). The number of I based on the simulation is shown in **Table 3**.

Table 3. Number of I Individuals Based on β Simulations

t	β			
	0,505503	0.3	0.2	0.05
2021	1.070.104	176.141	82.235	30.776
2030	2.321.805	137.050	50.705	19.597
2040	4.701.605	134.241	46.445	17.981
2050	8.115.976	143.608	45.846	16.806

Based on **Table 3**, we can see the simulation of lowering β to 0,3, 0,2, and 0,05. T number of I individuals is still more than 16 thousand TB cases in 2050 when β = 0,05. So, Indonesia's free of TB target has not been achieved in 2050 by lowering β itself while other parameters don't change. The third simulation is conducted by reducing the treatment rate (η) while other parameters don't change. The number of I based on the simulation is shown in **Table 4**.

Table 4. Number of I individuals based on η simulations

t	η			
	0,339866	0,5	0,7	0,95
2021	1.070.104	238.179	56.310	18.921
2030	2.321.805	224.414	42.999	17.200
2040	4.701.605	251.931	43.901	16.982
2050	8.115.976	302.206	45.986	16.897

From **Table 4** in column 4, it can be seen the simulation of η value is increased to 0,5 and get the result of the number of I in 2050 is about 27 times lower than the number of I when the η = 0,339866. The simulation is continued by increasing η to 0,7 and 0,95 as shown in Table 4, column 4 and 5. The number of I individuals is 45.986 and 16.897. There are still more than 16 thousand TB cases in 2050 after the simulation of η = 0,95. So, Indonesia's free of TB target has not been achieved in 2050 by either increasing α, lowering β, or expanding η. Then, the simulation is conducted with constant values of α = 0,95, β = 0,05, η = 0,95 and changed relapse rate (ξ) and drug-resistant rate (ϵ).

Table 5. Number of I individuals based on ξ and ϵ simulations

	ξ, ϵ		
	0.00001	0.000001	0.0000005
2020	33	22	16
2030	11	1	1
2042	10	1	0
2050	10	1	0

Based on the simulation in **Table 5**, column 4, it can be seen that the number of I individuals is 0 when ξ and ϵ are 0,0000005. Concluded if the BCG vaccination is expanded to 95%, contact with TB patients is reduced to 5%, treatment is increased to 95%, and relapses and drug-resistant cases are reduced until 0.00005%, Indonesia's free of TB target in 2050 can be achieved from 2042.

4. CONCLUSIONS

Based on the study and application above, the conclusions are as follows

1. The SVITR model with relapse and drug-resistant cases for the spread of infectious disease is a first order nonlinear differential equation system (1).
2. The SVITR model with relapse and drug-resistant cases for the spread of TB in Indonesia is written in the system (2) and accurate enough to explain the spread of TB in Indonesia with a MAPE value of 15,5%.
3. The number of susceptible, vaccinated, infected, treatment, and recovered individuals of TB in Indonesia are upward trends in 2010-2050.
4. There are expected to be still 8.115.976 TB cases in Indonesia, so Indonesia's free of TB target has yet to be achieved in 2050.

Indonesia may achieve its free of TB target by boosting BCG vaccination to 95%, reducing contact with TB patients to 5%, increasing treatment to 95%, and lowering relapses and drug-resistant cases to 0.00005%, achieving the target in 2042.

ACKNOWLEDGMENT

Thank you to the Softcomputing Mathematics Research Group for their moral support and constructive comments in improving this paper. We also express our gratitude to the Institute for Research and Community Service (LPPM) Universitas Sebelas Maret (UNS) for the research group grant through the letter of approval for research implementation of non-APBN funds No. 228/UN27.22 /PT.01.03/2023.

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