



Stochastic Model of Pneumonia and Meningitis Co-infection Using Continuous Time Markov Chain Approach

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Abstract: Pneumonia disease is a lung infection caused by *Streptococcus pneumoniae*. Meningitis is an infection of the meninges and cerebrospinal fluid caused by *Streptococcus pneumoniae*. Both diseases may occur at the same time. A mathematical model is needed to represent the spread of pneumonia and meningitis co-infection. This study aims to build the stochastic model of pneumonia and meningitis co-infection with CTMC, determine the transition and outbreak probability, and conduct simulations to assess the effect of increasing the contact rate on pneumonia (a) and meningitis (b). Based on the computer simulation undertaken, it can be concluded that if a was decreased while b was set to be fixed, the probability of disease outbreak decreased. If a was set to be fixed while b was decreased, the probability of disease outbreak decreased. However, the latter is smaller than the previous. Similarly, if a was increased while b was set to be fixed, the probability of disease outbreak increased. If a was set to be fixed while b was increased, the probability of disease outbreak increased. However, the latter is smaller than the previous. Moreover, if both a and b were decreased, the probability of disease outbreak was equal to zero.

Keywords: Co-infection; Markov chain; Meningitis; Pneumonia

Introduction

Pneumonia is an infection in the lungs that affects the alveolar space explicitly (Lim, 2022). The infection can be transmitted by breathing in pathogenic microorganisms or inhalin (Cilloniz et al., 2016). The disease can claim the lives of millions of people through inhalation of pathogenic organisms. In 2015, as many as 920,000 children under the age of five died from pneumonia worldwide, or two children every minute and approximately 99% of these child deaths took place in developing countries (Watkins et al., 2017). Bacteria, fungi, and viruses can cause pneumonia, but the most common cause is *Streptococcus pneumoniae* (Leach & McLuckie, 2009). Pneumonia is particularly dangerous in people with weakened immune systems, such as infants and the elderly, or when infected with other diseases, such as meningitis (Feldman & Anderson, 2019; Kotola & Mekonnen, 2022).

Meningitis is an infection of the meninges and cerebrospinal fluid surrounding the brain and the spinal cord (Howlett, 2012). The disease affects all age groups, and children under the age of 5 are particularly at risk. In 2017, 290 thousand meningitis-related deaths and 5 million new cases of meningitis were reported globally. (W.H.O., 2021). Bacteria or viruses can cause meningitis. One of the bacteria that commonly causes meningitis is *Streptococcus pneumoniae* (Tambunan, 2019).

The same bacteria can cause pneumonia and meningitis, so a person can get both diseases simultaneously (Zhang et al., 2018). Approximately 4% to 20% of patients infected with meningitis may develop pneumonia. In other words, both disorders occur at the same time. Based on age, 20% are elderly, while younger patients vary between 4% and 10%. When grouped by the pathogen causing the infection, patients infected with meningitis due to *S. pneumoniae* have the highest pneumonia infection rate, which is about 18% - 22% (Brueggemann et al., 2021; Figueiredo et al., 2020).

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Mathematical modelling is essential in representing the dynamics of infectious disease co-infection and its control. Mathematical models for infectious diseases are divided into two types, namely deterministic models and stochastic models (Dadlani et al., 2020; & Li, 2018). Research on the spread of disease co-infection using deterministic models has been widely conducted. However, there are still relatively few studies of infectious disease co-infection using stochastic models. Stochastic models are needed to account for variation and uncertainty in an epidemic (Nurlazuardini et al., 2016). In their study, Allen & Lahodny (2012) found that outbreak opportunity information is very useful in epidemic models, and the value of the disease-free opportunity obtained by the branching process is almost the same as in numerical studies. The disease-free probability can be used to determine the persistence or extinction of a disease (Maliyoni, 2021).

Therefore, a Continuous Time Markov Chain (CTMC) stochastic model is developed in this study, referencing the model introduced by (Tilahun, 2019a). This approach was chosen because infection can occur at any time. In addition, this study also modified the recovery compartment in the co-infection of pneumonia and meningitis.

Method

This research is a literature study with a mathematical approach regarding the co-infection of pneumonia and meningitis. The steps of this study are as follows: Modify (Nigmatulina, 2009; Tilahun (2019) deterministic model of pneumonia and meningitis co-infection into a stochastic model using the CTMC approach and change the pneumonia-cured and meningitis-cured compartments into pneumonia-cured but still infected with meningitis and meningitis-cured but still infected with pneumonia compartments; Determine the transition probability and the outbreak probability; Perform numerical simulations using *Mathematica* 11.3 and *R-Studio* software to determine the following: (a). The effect of changing the pneumonia contact rate (*a*) when the meningitis contact rate (*b*) is fixed; (b). The impact of changing the meningitis transition rate (*b*) when the pneumonia transition rate (*a*) is fixed (Asamoah et al., 2020).

Deterministic Model of Co-infection in Pneumonia and Meningitis

Tilahun (2019) introduced the SIRS model of co-infection in pneumonia and meningitis by dividing the population into seven compartments, namely *S* (susceptible), *I_p* (pneumonia only infectious), *I_M* (meningitis only infectious), *I_{pM}* (pneumonia and

meningitis co-infectious), *R_p* (pneumonia recovered), *R_M* (meningitis recovered), *R_{pM}* (pneumonia and meningitis co-infectious recovered).

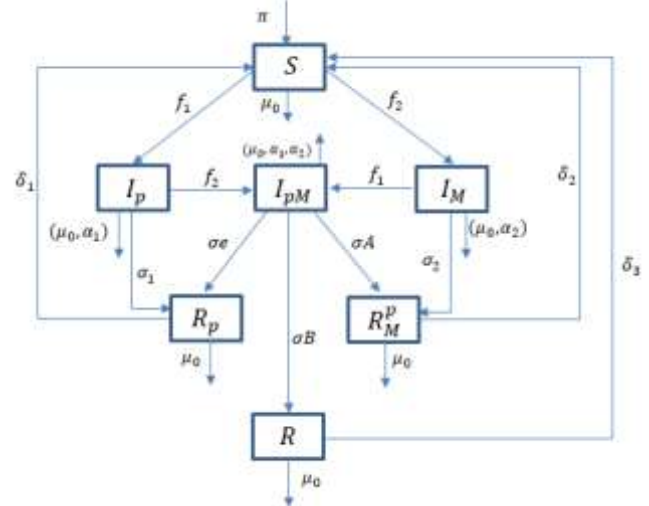


Figure 1. Flow diagram of Tilahun's model (Tilahun (2019))

The following differential system is obtained based on the assumptions and diagram:

$$\begin{aligned}
 \frac{dS}{dt} &= \pi + \delta_1 R_p + \delta_2 R_M + \delta_3 R_{pM} - (f_1 + f_2 + \mu_0)S, \\
 \frac{dI_p}{dt} &= f_1 S - (f_2 + \sigma_1 + \alpha_1 + \mu_0)I_p, \\
 \frac{dI_M}{dt} &= f_2 S - (f_1 + \sigma_2 + \alpha_2 + \mu_0)I_M, \\
 \frac{dI_{pM}}{dt} &= f_2 I_p + f_1 I_M - (\sigma + \alpha_1 + \alpha_2 + \mu_0)I_{pM}, \\
 \frac{dR_p}{dt} &= \sigma_1 I_p + \sigma e I_{pM} - (\delta_1 + \mu_0)R_p, \\
 \frac{dR_M}{dt} &= \sigma_2 I_M + \sigma A I_{pM} - (\delta_2 + \mu_0)R_M, \\
 \frac{dR_{pM}}{dt} &= \sigma B I_{pM} - (\delta_3 + \mu_0)R_{pM},
 \end{aligned}
 \tag{1}$$

with $A = g(1 - e), B = (1 - g)(1 - e)$.

Result and Discussion

Mathematical Modification Model

The modification of the pneumonia and meningitis co-infection model is done by changing the variables *R_M* and *R_p* to *R_M^p* and *R_p^M* as the subpopulation cured of meningitis and still infected with pneumonia and the subpopulation cured of pneumonia and still infected with meningitis, respectively (Tilahun, 2018). Therefore, this model has seven variables, namely *S(t)*, *I_p(t)*, *I_M(t)*, *I_{pM}(t)*, *R_p^M(t)*, *R_M^p(t)*, and *R(t)*.

The assumptions used in this study are as follows: Birth and death rates are equal in each subpopulation; there is no migration within each subpopulation; Individuals in the susceptible (*S*) subpopulation have two possibilities to become infected with the disease, namely to become infected with pneumonia with an

infection rate of k_1 (I_p) and to become infected with meningitis with an infection rate of k_2 (I_M), where $k_1 = \frac{a(I_p+I_{pM}+R_p^p)}{N}$ and $k_2 = \frac{b(I_M+I_{pM}+R_M^p)}{N}$; individuals in subpopulation I_p or I_M are still likely to be infected with both diseases (co-infection of pneumonia and meningitis (I_{pM})); individuals with co-infection of pneumonia and meningitis (I_{pM}) may recover from one of the infections, but there is still another infection to become R_p^p or R_M^p ; individuals in the R_p^p subpopulation can still infect the S and I_M subpopulations because there is still a pneumonia infection; individuals in the R_M^p subpopulation can still infect the S and I_p subpopulations because there is still a meningitis infection; and the parameter value $\sigma_1^* = d_1\sigma_1$ and $\sigma_2^* = d_2\sigma_2$. In this study, the value of $d_1 = d_2 = 1$.

Schematically, the following compartment diagram can illustrate the pneumonia and meningitis co-infection model.

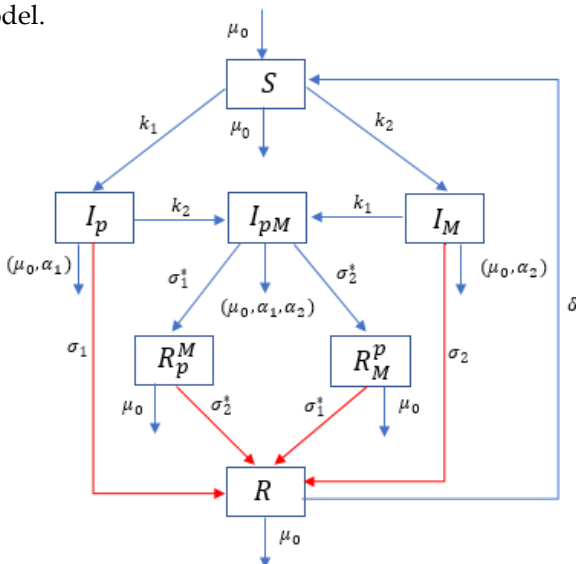


Figure 2. The modified model diagram (the red arrows were added to improve the original model)

The differential equation obtained from the above diagram is as follows:

$$\begin{aligned}
 \frac{dS}{dt} &= \mu_0 N + \delta R - (k_1 + k_2 + \mu_0)S, \\
 \frac{dI_p}{dt} &= k_1 S - (k_2 + \sigma_1 + \alpha_1 + \mu_0)I_p, \\
 \frac{dI_M}{dt} &= k_2 S - (k_1 + \sigma_2 + \alpha_2 + \mu_0)I_M, \\
 \frac{dI_{pM}}{dt} &= k_2 I_p + k_1 I_M - [\sigma_1 + \sigma_2 + \alpha_1 + \alpha_2 + \mu_0]I_{pM}, \\
 \frac{dR_p^p}{dt} &= \sigma_1 I_{pM} - (\sigma_2 + \mu_0)R_p^p, \\
 \frac{dR_M^p}{dt} &= \sigma_2 I_{pM} - (\sigma_1 + \mu_0)R_M^p, \\
 \frac{dR}{dt} &= \sigma_2 R_p^p + \sigma_1 R_M^p + \sigma_1 I_p + \sigma_2 I_M - (\delta + \mu_0)R,
 \end{aligned} \tag{2}$$

The description of the parameters is as follows

- μ_0 : Birth and natural death rate
- a : Pneumonia contact rate

- b : Meningitis contact rate
- α_1 : Mortality rate due to pneumonia infection
- α_2 : Mortality rate due to meningitis infection
- σ_1, σ_1^* : Treatment rate of pneumonia
- σ_2, σ_2^* : Treatment rate of meningitis
- δ : Transition rate of recovered individuals to re-susceptibility

The overall pneumonia and meningitis co-infection model was separated into several sub-models, namely the pneumonia-only model and the meningitis-only model. This is useful to gain a deeper understanding of the dynamics and interactions of pneumonia and meningitis (Tilahun, 2019b) & (Kotola et al., 2022).

Pneumonia Disease Model

Based on the system of differential equations in the modified model, the pneumonia model with $I_M = I_{pM} = R_p^p = R_M^p = 0$ and $\sigma_2 = k_2 = 0$ as follows:

$$\begin{aligned}
 \frac{dS}{dt} &= \mu_0 N + \delta R - \left(\frac{aI_p}{N} + \mu_0\right)S, \\
 \frac{dI_p}{dt} &= \frac{aI_p}{N}S - (\sigma_1 + \alpha_1 + \mu_0)I_p, \\
 \frac{dR}{dt} &= \sigma_1 I_p - (\delta + \mu_0)R,
 \end{aligned} \tag{3}$$

Disease-Free Fixed Point

The disease-free fixed point is obtained by solving the equation in the pneumonia-only model with $\frac{dS}{dt} = \frac{dI_p}{dt} = \frac{dR}{dt} = 0$ and $I_p = 0$, thus obtained as follows:

$$E_{0p} = (N, 0, 0)$$

Basic Reproduction Number

The basic reproduction number (\mathfrak{R}_0) is necessary to determine the potential spread of disease in the population. The calculation of the basic reproduction number from the equation is obtained by using the next-generation matrix, which is based on the subpopulations that cause infection only. \mathfrak{R}_0 is defined as the largest eigenvalue of the matrix K . The matrix K is the product of two matrices written $K = FV^{-1}$, where F is the infection rate increase matrix, while V is the rate at which infection moves evaluated at a fixed point (Diekmann et al., 2010) & (Delamater et al., 2019). The basic reproduction number for pneumonia (\mathfrak{R}_{0p}) to determine the potential spread of pneumonia in the population is obtained as follows (Adeniyi & Oluyo, 2018).

$$\mathfrak{R}_{0p} = \frac{a}{\sigma_1 + \alpha_1 + \mu_0} \tag{4}$$

Expected value of many infected individuals (m_p)

Stochastically, an outbreak occurs when the expected value of the number of infected individuals

(m) is greater than 1. The determination of the outbreak probability and disease-free probability can be obtained by using a branching process with a probability-generating function (pgf). Pgf for I_p with initial value $I_p(0) = 1$ is

$$f(u) = \frac{\alpha_1 + \sigma_1 + \mu_0}{a + \alpha_1 + \sigma_1 + \mu_0} + \frac{a}{a + \alpha_1 + \sigma_1 + \mu_0} u^2 \tag{5}$$

Furthermore, the expected value of the number of pneumonia-infected individuals is obtained

$$M = f'(1) = \frac{2a}{a + \alpha_1 + \sigma_1 + \mu_0}$$

$$m_p = \rho(M)_p = \frac{2a}{a + \alpha_1 + \sigma_1 + \mu_0} \tag{6}$$

Meningitis Only Model

Based on the system of equations, the meningitis model is obtained by assuming $I_p = I_{pM} = R_p^M = R_M^p = 0$ and $\sigma_1 = k_1 = 0$ as follows:

$$\frac{dS}{dt} = \mu_0 N + \delta R - \left(\frac{bI_M}{N} + \mu_0\right) S,$$

$$\frac{dI_M}{dt} = \frac{bI_M}{N} S - (\sigma_2 + \alpha_2 + \mu_0) I_M,$$

$$\frac{dR}{dt} = \sigma_2 I_M - (\delta + \mu_0) R, \tag{7}$$

Disease-Free Fixed Point

The disease-free fixed point is obtained by solving the equation in the meningitis only model with $\frac{dS}{dt} =$

$$\frac{dI_M}{dt} = \frac{dR}{dt} = 0 \text{ and } I_M = 0, \text{ thus obtained as follows:}$$

$$E_{0M} = (N, 0, 0)$$

Basic Reproduction Number

After obtaining the disease-free fixed point, the next step is to find the basic reproduction number of meningitis (\mathfrak{R}_{0M}) to determine the potential spread of meningitis in the population. The calculation of the basic reproduction number is obtained by using the next-generation matrix, so the value of \mathfrak{R}_{0M} is obtained as follows:

$$\mathfrak{R}_{0M} = \frac{b}{\sigma_2 + \alpha_2 + \mu_0} \tag{8}$$

Expected value of many infected individuals (m_M)

Pgf for I_p with initial value $I_M(0) = 1$ is

$$f(u) = \frac{\alpha_2 + \sigma_2 + \mu_0}{b + \alpha_2 + \sigma_2 + \mu_0} + \frac{b}{b + \alpha_2 + \sigma_2 + \mu_0} u^2 \tag{9}$$

Furthermore, the expected value of the number of meningitis-infected individuals is obtained

$$M = f'(1) = \frac{2b}{b + \alpha_2 + \sigma_2 + \mu_0}$$

$$m_M = \rho(M)_M = \frac{2b}{b + \alpha_2 + \sigma_2 + \mu_0} \tag{10}$$

Pneumonia and Meningitis Co-infection Model
Disease-Free Fixed Point

The disease-free fixed point is obtained by solving the system of equations of the overall co-infection model with $\frac{dS}{dt} = \frac{dI_p}{dt} = \frac{dI_M}{dt} = \frac{dI_{pM}}{dt} = \frac{dR_p^M}{dt} = \frac{dR_M^p}{dt} = \frac{dR}{dt} = 0$ and satisfying $I_p(t) = 0, I_M(t) = 0, I_{pM} = 0,$ so the following disease-free fixed point is obtained:

$$E_0 = (N, 0, 0, 0, 0, 0, 0) \tag{11}$$

Basic Reproduction Number

The basic reproduction number (\mathfrak{R}_0) is obtained using the next generation matrix based on the subpopulations that cause infection only, namely $I_p, I_M, I_{pM}, R_p^M,$ dan R_M^p . Therefore, the differential equation system used is as follows.

$$\frac{dI_p}{dt} = k_1 S - (k_2 + \sigma_1 + \alpha_1 + \mu_0) I_p,$$

$$\frac{dI_M}{dt} = k_2 S - (k_1 + \sigma_2 + \alpha_2 + \mu_0) I_M,$$

$$\frac{dI_{pM}}{dt} = k_2 I_p + k_1 I_M - [\sigma_1 + \sigma_2 + \alpha_1 + \alpha_2 + \mu_0] I_{pM},$$

$$\frac{dR_p^M}{dt} = \sigma_1 I_{pM} - (\sigma_2 + \mu_0) R_p^M,$$

$$\frac{dR_M^p}{dt} = \sigma_2 I_{pM} - (\sigma_1 + \mu_0) R_M^p,$$

The matrices F_i and V_i are defined as follows:

$$F_i = \begin{bmatrix} k_1 S \\ k_2 S \\ k_2 I_p + k_1 I_M \\ \sigma_1 I_{pM} \\ \sigma_2 I_{pM} \end{bmatrix}$$

$$= \begin{bmatrix} \frac{a(I_p + I_{pM} + R_M^p)}{N} S \\ \frac{b(I_M + I_{pM} + R_p^M)}{N} S \\ \frac{b(I_M + I_{pM} + R_p^M)}{N} I_p + \frac{a(I_p + I_{pM} + R_M^p)}{N} I_M \\ \sigma_1 I_{pM} \\ \sigma_2 I_{pM} \end{bmatrix}$$

$$V_i = \begin{bmatrix} (k_2 + \sigma_1 + \alpha_1 + \mu_0) I_p \\ (k_1 + \sigma_2 + \alpha_2 + \mu_0) I_M \\ [\sigma_1 + \sigma_2 + \alpha_1 + \alpha_2 + \mu_0] I_{pM} \\ (\sigma_2 + \mu_0) R_p^M \\ (\sigma_1 + \mu_0) R_M^p \end{bmatrix}$$

$$= \begin{bmatrix} \left(\frac{b(I_M + I_{pM} + R_p^M)}{N} + \sigma_1 + \alpha_1 + \mu_0 \right) I_p \\ \left(\frac{a(I_p + I_{pM} + R_M^p)}{N} + \sigma_2 + \alpha_2 + \mu_0 \right) I_M \\ [\sigma_1 + \sigma_2 + \alpha_1 + \alpha_2 + \mu_0] I_{pM} \\ (\sigma_2 + \mu_0) R_p^M \\ (\sigma_1 + \mu_0) R_M^p \end{bmatrix}$$

Next, the matrices F_i and V_i are derived concerning I_p, I_M, I_{pM}, R_p^M , and R_M^p into matrices F and V and then evaluated against the fixed point so that

$$F = \begin{bmatrix} a & 0 & a & 0 & 0 \\ 0 & b & b & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \sigma_1 & 0 & 0 \\ 0 & 0 & \sigma_2 & 0 & 0 \end{bmatrix}$$

$$V^{-1} = \begin{bmatrix} \frac{1}{\sigma_1 + \alpha_1 + \mu_0} & 0 & 0 & 0 & 0 \\ 0 & \frac{1}{\sigma_2 + \alpha_2 + \mu_0} & 0 & 0 & 0 \\ 0 & 0 & \frac{1}{\sigma_1 + \sigma_2 + \alpha_1 + \alpha_2 + \mu_0} & 0 & 0 \\ 0 & 0 & 0 & \frac{1}{\sigma_2 + \mu_0} & 0 \\ 0 & 0 & 0 & 0 & \frac{1}{\sigma_1 + \mu_0} \end{bmatrix}$$

The next generation matrix K is

$$K = FV^{-1} = \begin{bmatrix} \frac{a}{\sigma_1 + \alpha_1 + \mu_0} & 0 & 0 & 0 & 0 \\ 0 & \frac{b}{\sigma_2 + \alpha_2 + \mu_0} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

Based on the K matrix above, the eigenvalues are obtained as follows:

$$\lambda_1^* = \frac{a}{\sigma_1 + \alpha_1 + \mu_0} = \mathfrak{R}_{0p}, \lambda_2^* = \frac{b}{\sigma_2 + \alpha_2 + \mu_0} = \mathfrak{R}_{0M}, \lambda_3^* = \lambda_4^* = \lambda_5^* = 0$$

The basic reproduction number is determined from the dominant eigenvalue, thus obtained $\mathfrak{R}_0 = \max(\mathfrak{R}_{0p}, \mathfrak{R}_{0M})$.

Determination of Transition Probability

The modified model (equation 2) is assumed to fulfil Markov properties.

$$P\{S(t + \Delta t), I_p(t + \Delta t), I_M(t + \Delta t), I_{pM}(t + \Delta t), R_p^M(t + \Delta t), R_M^p(t + \Delta t), R(t + \Delta t) \mid (S(0), I_p(0), I_M(0), I_{pM}(0), R_p^M(0), R_M^p(0), R(0)), \dots, (S(t), I_p(t), I_M(t), I_{pM}(t), R_p^M(t), R_M^p(t), R(t))\} \\ = P\{S(t + \Delta t), I_p(t + \Delta t), I_M(t + \Delta t), I_{pM}(t + \Delta t), R_p^M(t + \Delta t), R_M^p(t + \Delta t), R(t + \Delta t) \mid S(t), I_p(t), I_M(t), I_{pM}(t), R_p^M(t), R_M^p(t), R(t)\}$$

The transition probability at time $(t + \Delta t)$ depends only on the process one-time step earlier, i.e. at time t . If suppose an ordered pair

$$(S(t), I_p(t), I_M(t), I_{pM}(t), R_p^M(t), R_M^p(t), R(t)) = (s, i_p, i_M, i_{pM}, r_p^M, r_M^p, r) \text{ and } (S(t + \Delta t), I_p(t + \Delta t), I_M(t + \Delta t), I_{pM}(t + \Delta t), R_p^M(t + \Delta t), R_M^p(t + \Delta t), R(t + \Delta t)) = (n, u, v, w, x, y, z)$$

with $s, i_p, i_M, i_{pM}, r_p^M, r_M^p, r, n, u, v, w, x, y, z = 0, 1, 2, \dots$, then the displacement from state $(s, i_p, i_M, i_{pM}, r_p^M, r_M^p, r)$ to state (n, u, v, w, x, y, z) can be expressed as follows:

$$P_{(n, u, v, w, x, y, z), (s, i_p, i_M, i_{pM}, r_p^M, r_M^p, r)}(t, t + \Delta t) = P\{S(t + \Delta t) = n, I_p(t + \Delta t) = u, I_M(t + \Delta t) = v, I_{pM}(t + \Delta t) = w, R_p^M(t + \Delta t) = x, R_M^p(t + \Delta t) = y, R(t + \Delta t) = z \mid (S(t) = s, I_p(t) = i_p, I_M(t) = i_M, I_{pM}(t) = i_{pM}, R_p^M(t) = r_p^M, R_M^p(t) = r_M^p, r(t) = r)\}$$

The following are the transition probabilities occurred for each component, for Δt period of time.

The probability of adding one susceptible individual (S):

$$P_{(s+1, i_p, i_M, i_{pM}, r_p^M, r_M^p, r), (s, i_p, i_M, i_{pM}, r_p^M, r_M^p, r)}(\Delta t) = (\mu N)\Delta t + o(\Delta t)$$

The probability of reducing one recovered individual (R), resulting in the addition of one susceptible individual (S):

$$P_{(s+1, i_p, i_M, i_{pM}, r_p^M, r_M^p, r-1), (s, i_p, i_M, i_{pM}, r_p^M, r_M^p, r)}(\Delta t) = (\delta R)\Delta t + o(\Delta t)$$

The probability of reducing one susceptible individual (S), resulting in the addition of one pneumonia-infected individual (I_p):

$$P_{(s-1, i_p+1, i_M, i_{pM}, r_p^M, r_M^p, r), (s, i_p, i_M, i_{pM}, r_p^M, r_M^p, r)}(\Delta t) = a \left(\frac{I_p + I_{pM} + R_p^M}{N} \right) S\Delta t + o(\Delta t)$$

The probability of reducing one susceptible individual (S), resulting in the addition of one meningitis-infected individual (I_M):

$$P_{(s-1, i_p, i_M+1, i_{pM}, r_p^M, r_M^p, r), (s, i_p, i_M, i_{pM}, r_p^M, r_M^p, r)}(\Delta t) = b \left(\frac{I_M + I_{pM} + R_p^M}{N} \right) S\Delta t + o(\Delta t)$$

The probability of reducing one pneumonia-infected individual (I_p), resulting in the addition of one pneumonia and meningitis co-infected individual (I_{pM}):

$$P_{(s, i_p-1, i_M, i_{pM}+1, r_p^M, r_M^p, r), (s, i_p, i_M, i_{pM}, r_p^M, r_M^p, r)}(\Delta t) = b \left(\frac{I_M + I_{pM} + R_p^M}{N} \right) I_p\Delta t + o(\Delta t)$$

The probability of reducing one meningitis-infected individual (I_M), resulting in the addition of one pneumonia and meningitis co-infected individual (I_{pM}):

$$P_{(s,i_p,i_m-1,i_{pm}+1,r_p^m,r_m^p),(s,i_p,i_m,i_{pm},r_p^m,r_m^p)}(\Delta t) = a \left(\frac{I_p + I_{pM} + R_M^p}{N} \right) I_M \Delta t + o(\Delta t)$$

The probability of reducing one pneumonia and meningitis co-infected individual (I_{pM}), resulting in the addition of one recovered individual of pneumonia but still infected with meningitis (R_p^M):

$$P_{(s,i_p,i_m,i_{pM}-1,r_p^M+1,r_M^p,r),(s,i_p,i_m,i_{pM},r_p^M,r_M^p)}(\Delta t) = \sigma_1 I_{pM} \Delta t + o(\Delta t)$$

The probability of reducing one pneumonia and meningitis co-infected individual (I_{pM}), resulting in the addition of one recovered individual of meningitis but still infected with pneumonia (R_M^p):

$$P_{(s,i_p,i_m,i_{pM}-1,r_p^M,r_p^p+1,r),(s,i_p,i_m,i_{pM},r_p^M,r_M^p)}(\Delta t) = \sigma_2 I_{pM} \Delta t + o(\Delta t)$$

The probability of reducing one susceptible individual (S):

$$P_{(s-1,i_p,i_m,i_{pM},r_p^M,r_M^p),(s,i_p,i_m,i_{pM},r_p^M,r_M^p)}(\Delta t) = \mu_0 S \Delta t + o(\Delta t)$$

The probability of reducing one pneumonia-infected individual (I_p):

$$P_{(s,i_p-1,i_m,i_{pM},r_p^M,r_M^p),(s,i_p,i_m,i_{pM},r_p^M,r_M^p)}(\Delta t) = (\alpha_1 + \mu_0) I_p \Delta t + o(\Delta t)$$

The probability of reducing one pneumonia-infected individual (I_p), resulting in the addition of one recovered individual (R):

$$P_{(s,i_p-1,i_m,i_{pM},r_p^M,r_p^p+1),(s,i_p,i_m,i_{pM},r_p^M,r_M^p)}(\Delta t) = (\sigma_1) I_p \Delta t + o(\Delta t)$$

The probability of reducing one meningitis-infected individual (I_M):

$$P_{(s,i_p,i_m-1,i_{pM},r_p^M,r_M^p),(s,i_p,i_m,i_{pM},r_p^M,r_M^p)}(\Delta t) = (\alpha_2 + \mu_0) I_M \Delta t + o(\Delta t)$$

The probability of reducing one meningitis-infected individual (I_M), resulting in the addition of one recovered individual (R):

$$P_{(s,i_p,i_m-1,i_{pM},r_p^M,r_p^p+1),(s,i_p,i_m,i_{pM},r_p^M,r_M^p)}(\Delta t) = (\sigma_2) I_M \Delta t + o(\Delta t)$$

The probability of reducing pneumonia and meningitis co-infected individual (I_{pM}):

$$P_{(s,i_p,i_m,i_{pM}-1,r_p^M,r_p^p),(s,i_p,i_m,i_{pM},r_p^M,r_M^p)}(\Delta t) = (\alpha_1 + \alpha_2 + \mu_0) I_{pM} \Delta t + o(\Delta t)$$

The probability of reducing one pneumonia recovered individual but still infected with meningitis (R_p^M):

$$P_{(s,i_p,i_m,i_{pM},r_p^M-1,r_M^p,r),(s,i_p,i_m,i_{pM},r_p^M,r_M^p)}(\Delta t) = (\mu_0) R_p^M \Delta t + o(\Delta t)$$

The probability of reducing one pneumonia recovered individual but still infected with meningitis (R_p^M) resulting in the addition of one recovered individual (R):

$$P_{(s,i_p,i_m,i_{pM},r_p^M-1,r_M^p,r+1),(s,i_p,i_m,i_{pM},r_p^M,r_M^p)}(\Delta t) = (\sigma_2) R_p^M \Delta t + o(\Delta t)$$

The probability of reducing one meningitis recovered individual but still infected with pneumonia (R_M^p):

$$P_{(s,i_p,i_m,i_{pM},r_p^M,r_p^p-1,r),(s,i_p,i_m,i_{pM},r_p^M,r_M^p)}(\Delta t) = (\mu_0) R_M^p \Delta t + o(\Delta t)$$

The probability of reducing one meningitis recovered individual but still infected with pneumonia (R_M^p), resulting in the addition of one recovered individual (R):

$$P_{(s,i_p,i_m,i_{pM},r_p^M,r_p^p-1,r+1),(s,i_p,i_m,i_{pM},r_p^M,r_M^p)}(\Delta t) = (\sigma_1) R_M^p \Delta t + o(\Delta t)$$

The probability of reducing one recovered individual (R):

$$P_{(s,i_p,i_m,i_{pM},r_p^M,r_M^p,r-1),(s,i_p,i_m,i_{pM},r_p^M,r_M^p)}(\Delta t) = (\mu_0) R \Delta t + o(\Delta t)$$

Transition probabilities other than probabilities number 1 to 19 are equal to $(1 - \varphi)\Delta t + o(\Delta t)$, where

$$\varphi = \mu_0 N + \delta R + a \left(\frac{I_p + I_{pM} + R_M^p}{N} \right) S + b \left(\frac{I_M + I_{pM} + R_p^M}{N} \right) S + b \left(\frac{I_M + I_{pM} + R_p^M}{N} \right) I_p + a \left(\frac{I_p + I_{pM} + R_M^p}{N} \right) I_M + \sigma_1 I_{pM} + \sigma_2 I_{pM} + \mu_0 S + (\alpha_1 + \mu_0 + \sigma_1) I_p + (\alpha_2 + \mu_0 + \sigma_2) I_M + (\alpha_1 + \alpha_2 + \mu_0) I_{pM} + (\mu_0 + \sigma_2) R_p^M + (\mu_0 + \sigma_1) R_M^p + \mu_0 R$$

The value of $o(\Delta t)$ represents a minimal probability value and cannot be expressed exactly, with $\lim_{t \rightarrow \infty} \frac{o(\Delta t)}{\Delta t} = 0$ (Allen & Lahodny, 2012).

Determination of Outbreak Probability

Disease outbreak occurs when the number of infected individuals increases over a long period. On the other hand, disease-free occurs when there are no more infected individuals. Stochastically, the disease outbreak occurs when the expected value of the number of infected individuals greater than one ($m > 1$) (Rizzo et al., 2014) & (Yan, 2008). The probability of disease outbreak and the probability of disease-free can be determined using a branching process with a probability generating function (PGF) (Maity & Mandal, 2022) & (Muhumuza et al., 2022). Based on the branching process, there is a certain fixed point for a pgf where $f_i(q_1, q_2, q_3, q_4, q_5) = q_i, 0 < q_i < 1$. This gives,

$$f_1(q_1, q_2, q_3, q_4, q_5) = q_1 = \frac{\alpha_1 + \sigma_1 + \mu_0 + \alpha q_1^2}{\alpha + \alpha_1 + \sigma_1 + \mu_0}$$

$$\begin{aligned}
 f_2(q_1, q_2, q_3, q_4, q_5) &= q_2 = \frac{\alpha_2 + \sigma_2 + \mu + bq_2^2}{b + \alpha_2 + \sigma_2 + \mu_0}, \\
 f_3(q_1, q_2, q_3, q_4, q_5) &= q_3 = \frac{\alpha_1 + \alpha_2 + \mu_0 + aq_1q_3 + bq_2q_3 + \sigma_1q_4 + \sigma_2q_5}{a + b + \alpha_1 + \alpha_2 + \sigma_1 + \sigma_2 + \mu_0}, \\
 f_4(q_1, q_2, q_3, q_4, q_5) &= q_4 = \frac{\sigma_2 + \mu_0 + bq_2q_4}{b + \sigma_2 + \mu_0}, \\
 f_5(q_1, q_2, q_3, q_4, q_5) &= q_5 = \frac{\sigma_1 + \mu_0 + aq_1q_5}{a + \sigma_1 + \mu_0}.
 \end{aligned}$$

By substituting $q_1, q_2, q_3, q_4,$ and q_5 the following results are obtained:

$$\left\{ \begin{aligned}
 &(q_1 = 1, q_2 = 1, q_3 = 1, q_4 = 1, q_5 = 1), \\
 &(q_1 = 1, q_2 = \frac{\alpha_2 + \mu_0 + \sigma_2}{b}, q_3 = -\frac{x}{y}, q_4 = \frac{\mu_0 + \sigma_2}{b - \alpha_2}, q_5 = 1), \\
 &(q_1 = \frac{\alpha_1 + \mu_0 + \sigma_1}{a}, q_2 = 1, q_3 = \frac{u}{v}, q_4 = 1, q_5 = \frac{\mu_0 + \sigma_1}{a - \alpha_1}), \\
 &(q_1 = \frac{\alpha_1 + \mu_0 + \sigma_1}{a}, q_2 = \frac{\alpha_2 + \mu_0 + \sigma_2}{b}, q_3 = \frac{r + s}{t}, q_4 = \frac{\mu_0 + \sigma_2}{b - \alpha_2}, q_5 = \frac{\mu_0 + \sigma_1}{a - \alpha_1})
 \end{aligned} \right\}$$

where

$$\begin{aligned}
 x &= \alpha_1\alpha_2 + \alpha_2^2 + \alpha_2\mu_0 - \mu_0\sigma_1 + \alpha_2\sigma_2 - \sigma_1\sigma_2 - b(\alpha_1 + \alpha_2 + \mu_0 + \sigma_2) \\
 y &= (b - \alpha_2)(b + \alpha_1 + \sigma_1) \\
 u &= (a - \alpha_1)(\alpha_1 + \alpha_2 + \mu_0 + \sigma_1) + (\mu_0 + \sigma_1)\sigma_2 \\
 v &= (a - \alpha_1)(a + \alpha_2 + \sigma_2) \\
 r &= (a - \alpha_1)((b - \alpha_2)(\alpha_1 + \alpha_2 + \mu_0) + \mu_0\sigma_1) \\
 s &= ((a - \alpha_1)\sigma_1 + b(\mu_0 + \sigma_1) - \alpha_2(\mu_0 + \sigma_1))\sigma_2 \\
 t &= (a - \alpha_1)(b - \alpha_2)(a + b - \mu_0)
 \end{aligned}$$

Suppose $J(t) = \{I_p(t), I_M(t), I_{pM}(t), R_p^M(t), R_M^p(t)\}$. If given the initial value, $J(0) = (\phi, \chi, \psi, \omega, \tau)$, then the disease-free probability is

$$P(J(t) = 0) = \begin{cases} 1, & m \leq 1 \\ q_1^\phi q_2^\chi q_3^\psi q_4^\omega q_5^\tau, & m > 1 \end{cases}$$

So that the probability of an outbreak is obtained, namely

$$1 - P(J(t) = 0) = \begin{cases} 0, & m \leq 1 \\ 1 - q_1^\phi q_2^\chi q_3^\psi q_4^\omega q_5^\tau, & m > 1 \end{cases}$$

Numerical Simulation

Simulations were conducted to see the effect of pneumonia contact rate (a) on pneumonia and meningitis co-infection and meningitis contact rate (b) on pneumonia and meningitis co-infection. The assumed initial values of the subpopulations

were $S(0) = 820, I_p = 100, I_M = 50, I_{pM} = 30, R_p^M = 0,$ and $R_M^p = 0$. The parameter values used include $\mu_0, \alpha_1, \alpha_1, \delta, a,$ and b obtained from Tilahun's research (2019), while the parameters σ_1 and σ_2 use assumptions as presented in Table 1.

Table 1. Parameter values

Parameter	Parameter Value
μ_0	0.01
α_1	0.025
α_2	0.037
σ_1	0.271
σ_2	0.2
δ	0.01
a	0.6
b	0.9

The value of m by determining the dominant eigenvalue of matrix M is defined as $\rho(M) = m$ below:

$$\begin{aligned}
 m &= \max\left(\frac{2a}{a + \alpha_1 + \sigma_1 + \mu_0}, \frac{2b}{b + \alpha_2 + \sigma_2 + \mu_0}\right) \\
 &= \max(m_p, m_M)
 \end{aligned}$$

Stochastically, an outbreak occurs when the value of $m > 1$ (Allen & Lahodny, 2012).

$$\frac{\partial f_i}{\partial u_j} = \begin{pmatrix} \frac{\partial f_1}{\partial u_1} & \frac{\partial f_2}{\partial u_1} & \frac{\partial f_3}{\partial u_1} & \frac{\partial f_4}{\partial u_1} & \frac{\partial f_5}{\partial u_1} \\ u_1 & u_1 & u_1 & u_1 & u_1 \\ \frac{\partial f_1}{\partial u_2} & \frac{\partial f_2}{\partial u_2} & \frac{\partial f_3}{\partial u_2} & \frac{\partial f_4}{\partial u_2} & \frac{\partial f_5}{\partial u_2} \\ u_2 & u_2 & u_2 & u_2 & u_2 \\ \frac{\partial f_1}{\partial u_3} & \frac{\partial f_2}{\partial u_3} & \frac{\partial f_3}{\partial u_3} & \frac{\partial f_4}{\partial u_3} & \frac{\partial f_5}{\partial u_3} \\ u_3 & u_3 & u_3 & u_3 & u_3 \\ \frac{\partial f_1}{\partial u_4} & \frac{\partial f_2}{\partial u_4} & \frac{\partial f_3}{\partial u_4} & \frac{\partial f_4}{\partial u_4} & \frac{\partial f_5}{\partial u_4} \\ u_4 & u_4 & u_4 & u_4 & u_4 \\ \frac{\partial f_1}{\partial u_5} & \frac{\partial f_2}{\partial u_5} & \frac{\partial f_3}{\partial u_5} & \frac{\partial f_4}{\partial u_5} & \frac{\partial f_5}{\partial u_5} \\ u_5 & u_5 & u_5 & u_5 & u_5 \end{pmatrix}$$

Furthermore, the expected number of infected individuals (m) is defined as the dominant eigenvalue of the matrix M , i.e., $m = \rho(M)$, where M is a nonnegative matrix whose elements are $\frac{\partial f_i}{\partial u_j} |_{u=1}$.

Below are simulation results with changes in the parameters a and b , including the value of \mathfrak{R}_0, m and the probability of an outbreak, as indicated in Table 2.

Table 2. Numerical simulation result

a	b	\mathfrak{R}_{0p}	\mathfrak{R}_{0M}	\mathfrak{R}_0	m_p	m_M	m	Chance of an outbreak
0.2	0.2	0.654	0.810	0.810	0.791	0.895	0.895	0
0.6	0.2	1.961	0.810	1.961	1.325	0.895	1.325	$1 - 1.74 \times 10^{-4}$
1.0	0.2	3.268	0.810	3.268	1.531	0.895	1.531	$1 - 2.45 \times 10^{-7}$
0.2	0.9	0.654	3.644	3.644	0.791	1.569	1.569	$1 - 3.51 \times 10^{-5}$
0.6	0.9	1.961	3.644	3.644	1.325	1.569	1.569	$1 - 7.34 \times 10^{-9}$
1.0	0.9	3.268	3.644	3.644	1.531	1.569	1.569	$1 - 1.24 \times 10^{-11}$
0.2	1.6	0.654	6.478	6.478	0.791	1.732	1.732	$1 - 3.77 \times 10^{-7}$
0.6	1.6	1.961	6.478	6.478	1.325	1.732	1.732	$1 - 8.71 \times 10^{-11}$
1.0	1.6	3.268	6.478	6.478	1.531	1.732	1.732	$1 - 1.66 \times 10^{-13}$

0.2	0	0.654	0	0.654	0.791	0	0.791	0
0.6	0	1.961	0	1.961	1.325	0	1.325	$1 - 1.74 \times 10^{-4}$
1.0	0	3.268	0	3.268	1.531	0	1.531	$1 - 2.45 \times 10^{-7}$
0	0.2	0	0.810	0.810	0	0.895	0.895	0
0	0.9	0	3.644	3.644	0	1.569	1.569	$1 - 3.51 \times 10^{-5}$
0	1.6	0	6.478	6.478	0	1.732	1.732	$1 - 3.77 \times 10^{-7}$

Table 2 shows a certain probability that an outbreak will occur when $\mathfrak{R}_0 > 1$ and $m > 1$. The higher the pneumonia contact rate (a) or meningitis contact rate (b), the higher the probability of an outbreak.

When the value of $a = 0.6$ and $b = 0.9$ results in a matter of $\mathfrak{R}_0 = 3.644$, $m = 1.569$, and the probability of an outbreak is $1 - 7.34 \times 10^{-9}$. The following is a sample path when the values of $a = 0.6$ and $b = 0.9$.

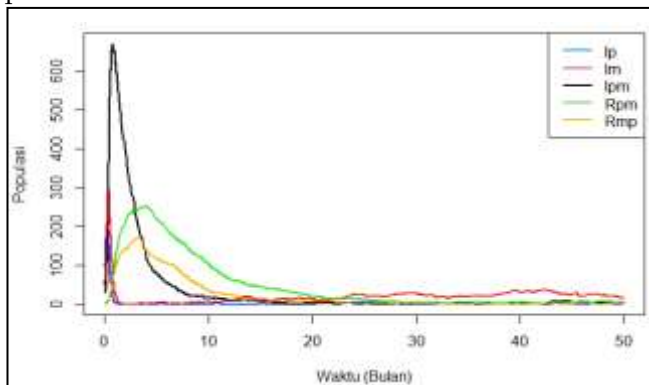


Figure 3. Human population dynamics with parameter values $a = 0.6$ and $b = 0.9$

Figure 3 shows that co-infection of pneumonia and meningitis is endemic. If the value of a was set to be fixed while the value of b was decreased, then $\mathfrak{R}_0 = 1.96$ and $m = 1.325$ were obtained. Probability of a disease outbreak was $1 - 1.74 \times 10^{-4}$. If the value of a was set to be fixed while the value of b was increased, then $\mathfrak{R}_0 = 6.478$ and $m = 1.732$ were obtained. Probability of disease outbreak was $1 - 8.71 \times 10^{-11}$. The following is a sample path when the value of a was set to be fixed, while the value of b was changed.

Figure 4 shows that when $b = 0$, co-infection (I_{pM}) will disappear from the population in about 15 months and the outbreak is due to the dominant pneumonia

infection. $b = 0.2$, I_{pM} will disappear in about 46 months and the outbreak is due to pneumonia infection. When $b = 1.6$, I_{pM} becomes endemic.

If the value of a was decreased while the value of b was set to be fixed, the value of $\mathfrak{R}_0 = 3.644$ and $m = 1.569$ was obtained and the probability of a disease outbreak was $1 - 3.51 \times 10^{-5}$. Similarly, if the value of a was increased while the value of b was set to be fixed, the same values of \mathfrak{R}_0 and m was obtained as previous. nevertheless, the probability of a disease outbreak was $1 - 1.24 \times 10^{-11}$. The following is a sample path when the value of a was changed and the value of b was set to be fixed.

Figure 5 shows that when $a = 0$, I_{pM} disappears from the population in approximately 13 months and the outbreak occurs due to the dominant meningitis infection. When $a = 0,2$ causes I_{pM} to disappear from the population in approximately 28 months and the outbreak occurs due to meningitis infection only. When $a = 1,0$, it causes I_{pM} to be endemic.

If both values of a and b were decreased to $a = b = 0.2$, then $\mathfrak{R}_0 = 0.810$, $m = 0.895$, and the probability of a disease outbreak was zero. In this case, pneumonia, meningitis and their co-infections would disappear from the population within a particular time. When both values of a and b were increased to $a = 1.0$ and $b = 1.6$, then $\mathfrak{R}_0 = 6.478$ and $m = 1.732$, and the probability of a disease outbreak was $1 - 1.66 \times 10^{-13}$.

Figure 6 shows that if the values of a and b were decreased to 0.2 , I_{pM} will disappear in the population in about 25 months and no outbreak will occur. If the values of a and b was increased to $a = 1.0$ and $b = 1.6$, then I_{pM} becomes endemic.

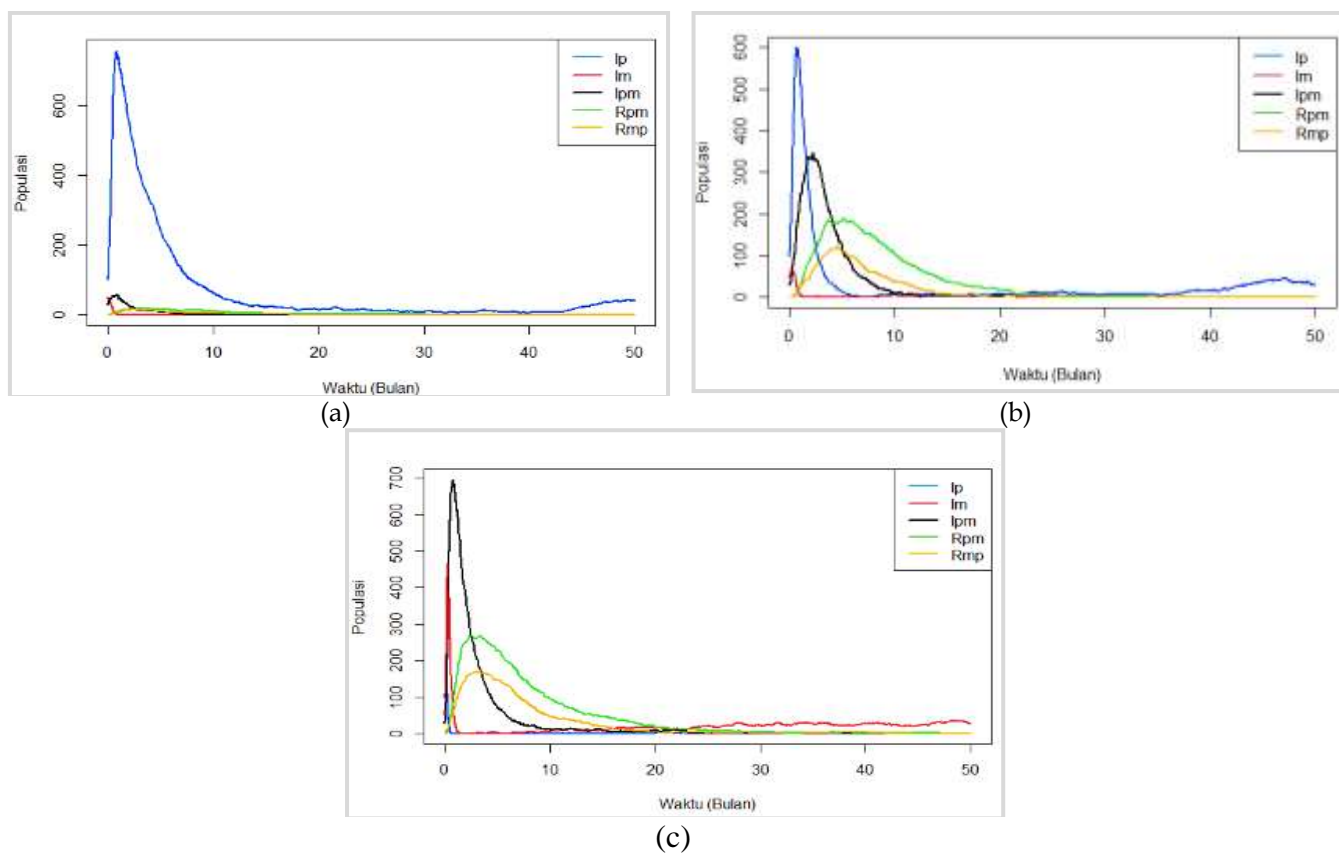


Figure 4. Human population dynamics with a fixed parameter value a and (A) $b = 0$; (B) $b = 0.2$; and (C) $b = 1.6$

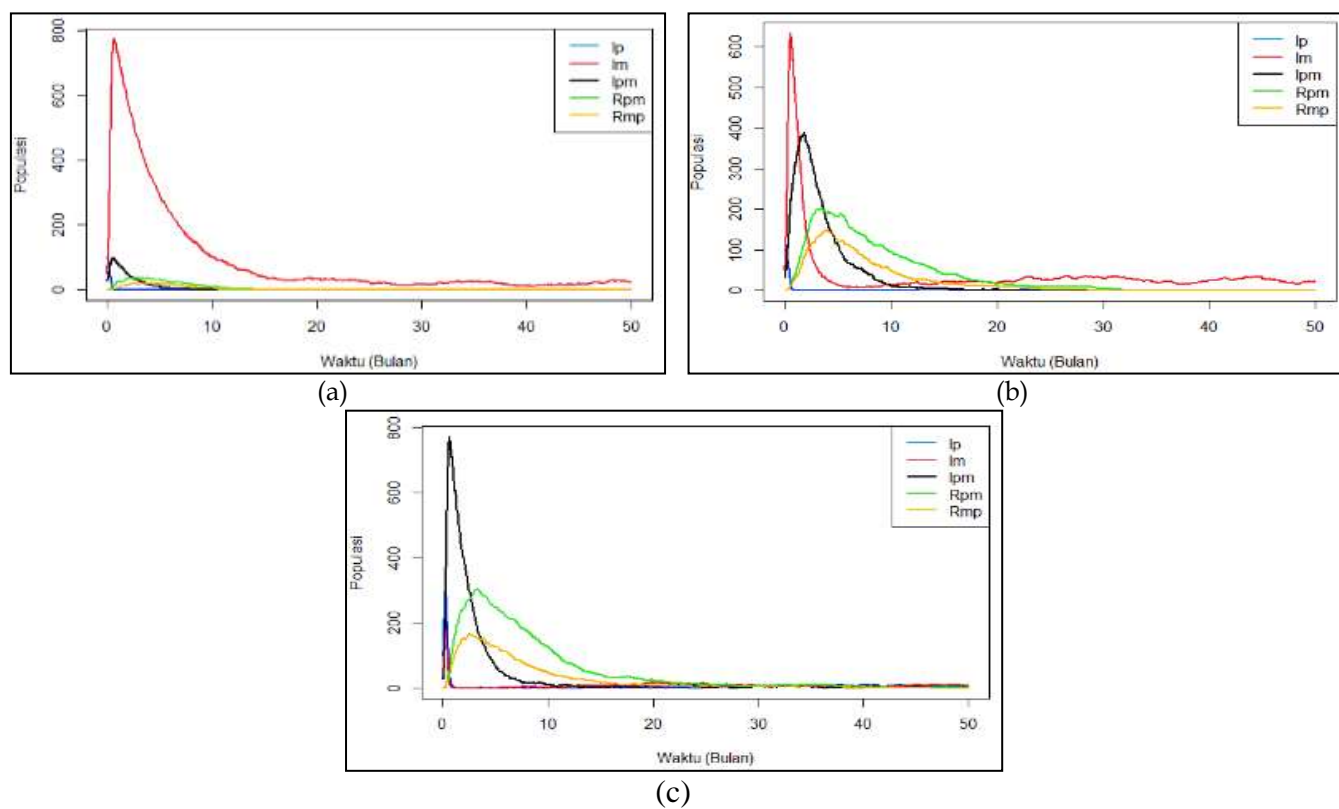
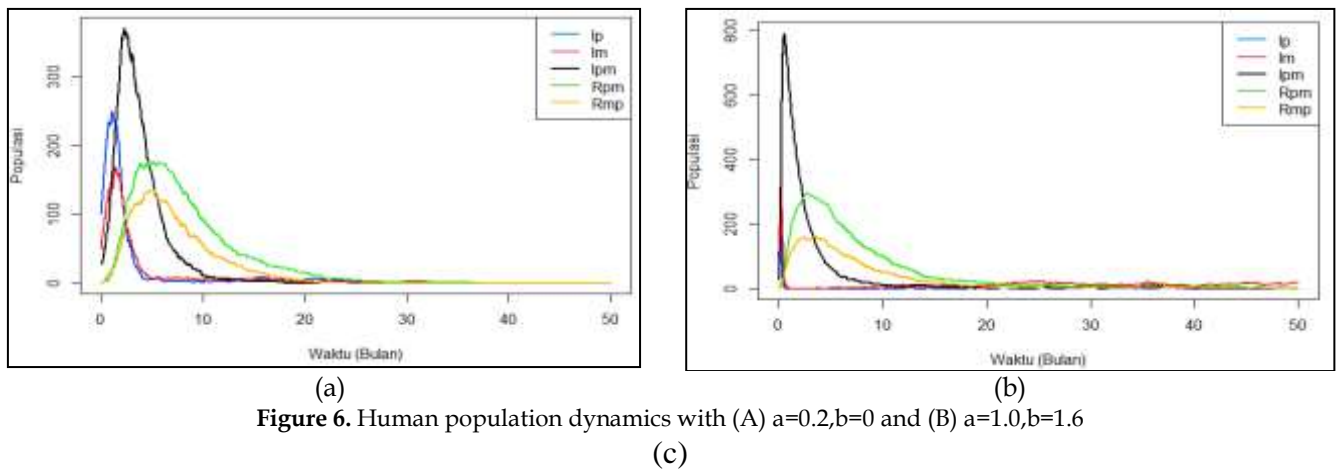


Figure 5. Human population dynamics with a fixed parameter value a and (A) $b=0$; (B) $b=0.2$; and (C) $b=1.6$.



Conclusion

In this study, a deterministic SIRS model of pneumonia and meningitis co-infection was developed into a stochastic CTMC model of pneumonia and meningitis co-infection. Based on this study, information on the expected value of the number of infected individuals and information on the probability of an outbreak can be obtained. Both the increasing of pneumonia contact rate (a) or meningitis contact rate (b), will increase the probability of disease outbreak. Based on the computer simulation undertaken, it can be concluded that if the value of a was decreased while the value of b was set to be fixed, the probability of disease outbreak decreased. If the value of a was set to be fixed while the value of b was decreased, the probability of disease outbreak decreased. However, the disease outbreak probability of the latter is smaller than the previous. Similarly, if the value of the value a was increased while b was set to be fixed, the probability of disease outbreak increased. If the value of a was set to be fixed while the value of b was increased, the probability of disease outbreak increased. Nevertheless, disease outbreak probability of the latter is smaller than the previous. Moreover, if both values of a and b were decreased, the probability of disease outbreak was equal to zero. In other words, the disease will disappear from the population within a certain period.

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