Int. J. Nonlinear Anal. Appl. 14 (2023) 1, 903–917
ISSN: 2008-6822 (electronic)
http://dx.doi.org/10.22075/ijnaa.2022.26746.3402

Optimal control strategies and cost effectiveness analysis of Pneumonia disease with drug resistance

Fikru Shiferaw Tessema, Boka Kumsa Bole*, Purnachandra Rao Koya*

Department of Mathematics, Faculty of Natural Science, Wollega University, Nekemt, Ethiopia

(Communicated by Saman Babaie-Kafaki)

Abstract

Pneumonia is a very serious infectious disease that affects one or two sides of the human lungs. The disease is caused by infectious agents such as bacteria, viruses and fungi. In general, pneumonia is caused by Streptococcus bacteria. In present paper, we developed and analyzed the optimal control and cost-effectiveness strategies for pneumonia with the inclusion of a drug resistance compartment. The basic reproduction number that governs disease transmission has been obtained as the largest eigenvalue of the next-generation matrix. Both local and global stabilities of the disease-free equilibrium and endemic equilibrium points of the model equations were established using basic reproduction numbers. It is found in this research that the control strategies work well and thus the infective population sizes of both asymptomatic and symptomatic classes reduce drastically within a short period of time. Also, the analysis of cost-effectiveness is depicted. Finally, based upon the simulation values of optimal controls, the combination of Prevention, Treatment and Screening of infectious humans is the most efficient and less costly strategy to eradicate pneumonia diseases from the community.

Keywords: Pneumonia diseases, $SPI_aI_sR_sR$ model, optimal control, cost-effectiveness analysis
2020 MSC: 92-10, 93-10

1 Introduction

Pneumonia is one of the very serious infectious diseases that affect one or both sides of the human lungs. The disease occurs due to a variety of infectious agents such as fungi, viruses and bacteria. However, the common bacteria that causes pneumonia is Streptococcus. Though people of all age groups are affected by pneumonia, the most vulnerable include adults over 65 years and children under 5 years. Further, humans with weak immune systems, irrespective of age, are too affected the most [6]. It is estimated that the upper respiratory system of about 20-40 percent of children and 10 percent of adults are permanently colonized by Streptococcus pneumonia [8]. Pneumonia is mostly caused by the result of exposure to sneezes and coughs of infected humans i.e., by inhaling small droplets containing the bacteria. An infected person through his coughs or sneezes spreads small droplets containing pneumonia bacteria into the air [12]. Symptoms of Pneumonia infection include coughing, rise in body temperatures, unusual sounds in lungs, loosing of appetite, deficiency in oxygen levels and rapid heartbeats [15].

*Corresponding author
Email addresses: fikmaths@gmail.com (Fikru Shiferaw Tessema), abitb2012@gmail.com (Boka Kumsa Bole), drkpraophd@gmail.com (Purnachandra Rao Koya)

Received: April 2022 *Accepted:* October 2022

However, Pneumonia disease is preventable through proper medication viz., diagnosis, screening, vaccination, environmental control measures, and appropriate treatment of other diseases [5]. Vaccination is the most effective prevention mechanism to prevent pneumonia in both children and adults. Various types of vaccines are now available to fight against Pneumonia. The pneumococcal conjugate vaccine (PCV) is used for children and the pneumococcal polysaccharide vaccine (PPV) is for adults [3], [7].

Pneumonia is an endemic infectious disease and has been a major public health concern in developing countries. UNICEF reported in 2013 that half of the deaths of under-five-year-old children in the world were occurring in only five countries: Nigeria, India, Congo, Pakistan, and China. Most deaths are due to infectious but preventable diseases. Malaria, Diarrhea and Pneumonia together killed about 2.2 million under-five children in 2012, accounting for share one-third of all under-five deaths [4]. In Ethiopia, Pneumonia, Diarrhea, and Malaria have been the major causes of death among under-five children. However, Pneumonia is the leading cause of mortality among under-five children in the country, contributing 28 percent of deaths [1]. Humans with poor nutrition, pre-existing lung diseases, difficulty in swallowing, problems with their immunity system and other chronic health problems are at higher risk of being attacked by pneumonia. Other higher risk factors that can cause pneumonia are smoking, sustaining injuries that interfere with swallowing or coughing or alcoholism and also neurological problems [11].

So far, various studies have been conducted and mathematical models have been developed so as to study the transmission dynamics of pneumonia. These studies and models have varying objectives and different procedures. In [14] a nonlinear mathematical model has presented the cost effectiveness of various control strategies is analyzed. In [9] a deterministic compartmental model with treatment and screening as intervention strategies is presented and their impact on controlling the disease is studied. A deterministic compartmental model presented by [8] discussed various aspects like inoculation of Pneumonia, the strength of immunity and fighting capacity against the infection. In the model developed by [5], sensitivity analysis on the effective reproduction number was conducted and showed that vaccination and treatment could eradicate pneumonia infection.

All the above studies have developed a deterministic as well as the stochastic mathematical model of pneumonia dynamics by subdividing the population into sub-classes of Susceptible, infectious, vaccinated, treated, carrier and recovered. But none of them considered optimal control and cost effectiveness strategies of pneumonia with the inclusion of drug resistance compartments and also no study has been undertaken by applying optimal control. This, therefore, motivated us to undertake this study to fulfill this gap. In the present model, the control strategies of Prevention, Treatment and Screening have been incorporated. Descriptions of further sections of the paper are as follows: In Section 2, a system of model equations is formulated and transmission dynamics of pneumonia are described, the model is proved to be mathematically well-posed and is biological meaningful by showing the model equations are both positive and bounded. Further, it is shown that the solution exists and is unique. The basic reproduction number is formulated. Equilibrium including disease free and endemic are identified and their local and global stability are analyzed. In Section 3, the optimal control problem is presented and analyzed. In Section 4, numerical simulations are carried out. In Section 4, the analysis of cost-effectiveness is depicted. The paper ends in Section 5, by deriving some conclusions depending on the importance of control variables.

2 Description and formulation of modified model

2.1 Model Assumption

The total human population of the model at any time t is divided into six compartments with respect to their disease status. The names, notations and description of these compartments are as follows: (i) Susceptible compartment $S(t)$:These people are at a risk of infected by Pneumonia disease, (ii) Protected compartment $P(t)$: This class of people which are protected against the disease over a period of time. (iii) Asymptomatic infected compartment $I_a(t)$: These people are already infected by the disease. They are potential source of infection and can transfer to other individuals, but they do not show any symptoms of the disease, (iv) Symptomatic infected compartment $I_s(t)$: These people are already infected by the disease. They are potential source of infection and can transfer to other individuals. Also, they show symptoms of the disease, (v) Drug resistance compartment $R_s(t)$: denotes the number of individual who have been infected with the disease and are treated, and (vi) Recovered compartment $R(t)$: This class includes all the individuals that are recovered from the disease and got temporal immunity. However, a fraction of these people may become susceptible in due course. New population is recruited in to the model with a constant rate of Λ per capita. This population is divided into two groups depending on their immunity capacity viz., susceptible and protected. A fraction $\rho\Lambda$ of the people with more immunity power will go to protected compartment $P(t)$ and the remaining fraction $(1-\rho)\Lambda$ with less immunity will go to susceptible compartment $S(t)$. Protected populations are recruited into the population at per capita rate $\rho\Lambda$. The Protected population groups are assumed to lose protection

and they will join susceptible class with rate of α. Susceptible individuals are recruited into the population at per capita rate $(1-\rho)\Lambda$. Susceptible class is increased by birth or emigration at rate of $(1-\rho)\Lambda$ and also from recovered class by losing temporary immunity with ω rate and from Immune class by imperfect vaccine with α rate. Susceptible individual acquire the disease through ingestion of contaminated foods and water at per capita rate λ. The force of infection for this model given by $\lambda = \frac{\beta(I_s+\gamma I_a)}{N}$, where $\beta = \kappa\sigma$, κ is contact rate, σ is the probability that a contact is effective to cause Pneumonia infection and γ is transmission coefficient for the Asymptomatic infective individual. Susceptible individuals by the force of infection become either Asymptomatic infective individual with the probability of π to join the Asymptomatic infective class I_a or move to the Symptomatic infective class I_s with the probability of $(1-\pi)$.The Asymptomatic infective individual can develop disease symptom and join the infected class with the rate of δ or recovered by against natural immunity at ψ rate. Those individuals in the infected class can get drug and join drug resistance class with the rate θ or recovered class at ϕ rate. Individuals in the drug resistance class move to recovered class at a per capita rate of τ by drug efficacy of q proportion of individuals join the recovered class or join the infected class with $(1-q)$ proportion by adapting the drug. In all compartments μ is the natural death rate of individual, but d_1 and d_2 are the disease induced death rate of the Asymptomatic infective individual and infected class respectively. Also the model assumes that all parameters are positive.

2.2 Description of parameters

The parameters used in this model are introduced in Table 1 Their notations and descriptions are also included.

Table 1: Description of Parameters used in the model equations

Parameters	*Description*
Λ	Recruitment rate
ρ	fraction of newly protected individuals who become susceptible
ω	Rate at which recovered individuals lose immunity
κ	Contact rate
μ	Natural mortality for all individuals
ϕ	Recovery rate for symptomatic infections individuals
q	Probability of drug resistance individuals joining recovery individuals
δ	Rate at which Asymptomatic infections develop symptoms
π	Probability of susceptible individuals joining Asymptomatic infections individuals
ψ	Recovery rate for Asymptomatic infections individuals
ω	Rate at which recovered individuals lose immunity
θ	Rate of drug therapy for symptomatic infections individuals
d_1	ADisease-induced mortality rate of Asymptomatic infections individuals
d_2	Disease-induced mortality rate of symptomatic infections individuals
τ	Capita rate of drug resistance individuals
ε	Assumed
γ	Transmission rate for Asymptomatic infections individuals

Considering the definitions, assumptions, and inter-relations between the variables and the parameters,the basic dynamics of Pneumonia is illustrated as a flow diagram in 1 blow: Based on the model assumption and the Schematic diagram the model equation is formulated with initial condition: $P(0) = P_0, S(0) = S_0, Ia(0) = Ia_0, Is(0) = Is_0, Rs(0) = Rs_0, R(0) = R_0$ and given as follows:

$$\begin{cases} \frac{dP(t)}{dt} = & \rho\Lambda - (\mu+\alpha)P(t), \\ \frac{dS(t)}{dt} = & (1-\rho).\Lambda + \alpha P(t) + \omega R(t) - (\lambda+\mu)S(t), \\ \frac{dI_a(t)}{dt} = & \pi\lambda S(t) - (\psi+\delta+\mu+d_1).I_a(t), \\ \frac{dI_s(t)}{dt} = & (1-\pi)\lambda S(t) + \delta I_a(t) + (1-q)\tau R_s(t) - (\theta+\phi+\mu+d_2)I_s(t), \\ \frac{dR_s(t)}{dt} = & \theta I_s(t) - (\tau+\mu)dR_s(t), \\ \frac{dR(t)}{dt} = & \psi I_a(t) + \phi I_s(t) + \tau q R_s(t) - (\omega+\mu)R(t). \end{cases} \tag{2.1}$$

2.3 Invariant Region

In this subsection, we obtain a region in which the solution of Eq. 2.1 is bounded.

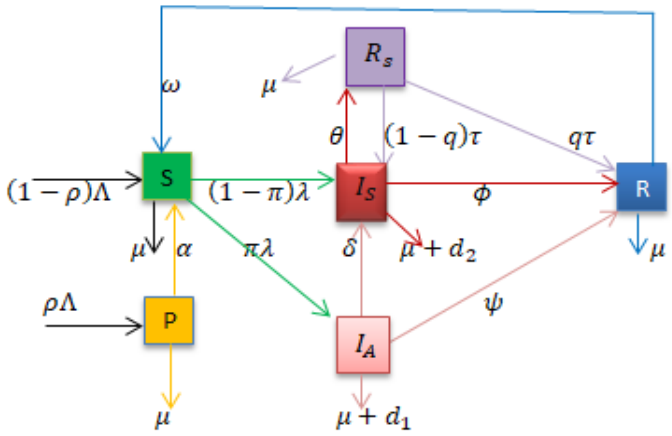


Figure 1: schematic diagram of the model

Theorem 2.1. The feasible solution set P, S, I_a, I_s, R_s, R of the system equation of the model enter and bounded in the region $\Omega = \{(P, S, I_a, I_s, R_s, R) \in R_+^6 : 0 \leq N \leq \frac{\Lambda}{N}\}$.

Proof . for this model the total human population is $N = P + S + I_a + I_s + R_s + R$ differentiating N with respect to time and substituting the expression for $\frac{dP}{dt}, \frac{dS}{dt}, \frac{I_a}{dt}, \frac{I_s}{dt}, \frac{R_s}{dt}$ and from Eq. 2.1 after simplification and also by applying initial condition $N(0) = N_0$, we obtained $N \leq \frac{\Lambda}{N} - (\Lambda - \frac{\mu.N}{\mu}).e^{-\mu.t}$. Further, it can be observed that $N(t)$ tends to $\frac{\Lambda}{\mu}$ as t tends to ∞.
Thus, it can be concluded that $N(t)$ is bounded as $0 \leq N(t) \leq \frac{\Lambda}{\mu}$. Hence, the feasible solution set of the system equation of the model enters and remains in the region:

$$\Omega = \{(P, S, I_a, I_s, R_s, R) \in R_+^6 : 0 \leq N \leq \tfrac{\Lambda}{N}\}.$$

Therefore, the model system of equations given in 2.1 is well posed biologically and meaningful mathematically. Hence, it is appropriate and sufficient to study the dynamics of the model variables in the invariant region Ω. □

2.4 Positivity of the solution

The solution of the system remains positive at any point in time t, if the initial values of all the variables are positive.

Theorem 2.2. Let the initial data be $((P_0, S_0, Ia_0, Is_0, Rs_0, R_0) > 0) \in \Omega$. Then, the solution set $\{P(t), S(t), I_a(t), I_s(t), R_s(t), R(t)\}$ of system 2.1 is positive for all $t \geq 0$.

Proof . From the first equation of model system 2.1:

$$\begin{aligned} \tfrac{dP}{dt} &= \rho\Lambda - (\mu + \alpha)P, \\ \tfrac{dP}{dt} &\geq -(\mu + \alpha)P, \\ \tfrac{dP}{P} &\geq -(\mu + \alpha)dt. \end{aligned}$$

Now, by using variable separable method and applying on integration, solution of foregoing differential inequality is found as:

$$P(t) \geq P_0 e^{(\alpha+\mu)t} \geq 0.$$

Hence it can conclude that $P(t) \geq 0$ Similarly, we obtained:

$$\begin{aligned} S(t) &\geq S_0 e^{-(\lambda+\mu)t} \geq 0, \\ I_a(t) &\geq Ia_0 e^{-(\psi+\delta+\mu+d_1)t} \geq 0, \\ I_s(t) &\geq Is_0 e^{-(\theta+\phi+\mu+d_2)t} \geq 0, \\ R_s(t) &\geq Rs_0 e^{-(\tau+\mu)t} \geq 0, \\ R(t) &\geq R_0 e^{-(\omega+\mu)t} \geq 0. \end{aligned}$$

Thus, this can be show that the model equations of system 2.1 are positive for all $t \geq 0$. Hence, the model is meaning full and well posed in Ω. $\square$

2.5 The Disease Free Equilibrium (DFE)

In order to find the disease free equilibrium (DFE) point of the model, the right hand sides of the system of equations given in 2.1 are equated to zero, evaluating the resultant equations at $I_a = I_s = R_s = R = 0$ and solving for non-infected and non-carrier state variables. Thus, disease free equilibrium is identified as :

$$E_0 = (P^0, S^0, I_a^0, I_s^0, R_s^0, R^0) = (\tfrac{\rho.\Lambda}{(\alpha+\mu)}, \tfrac{(\Lambda(\alpha+\mu-\mu.\rho))}{\mu.(\alpha+\mu)}, 0, 0, 0, 0).$$

2.6 The Basic Reproduction Number (R_0)

Here, the threshold parameter that governs the spread of disease known as the basic reproduction number is obtained. It is nothing but the spectral radius of the next-generation matrix. For the purpose the system of model equations 2.1 is rearranged starting with those representing newly infective classes.

$$\begin{array}{rcl} \frac{dI_a(t)}{dt} = & \pi\lambda S(t) - (\psi + \delta + \mu + d_1)I_a(t), \\ \frac{dI_s(t)}{dt} = & (1-\pi)\lambda S(t) + \delta I_a(t) + (1-q)\tau R_s(t) - (\theta + \phi + \mu + d_2)I_s(t), \\ \frac{dR_s(t)}{dt} = & \theta I_s(t) - (\tau + \mu)dR_s(t). \end{array} \tag{2.2}$$

Then by the principle of next-generation matrix, we obtained:

$$f_i = \begin{bmatrix} \pi\beta(\frac{I_s+\gamma I_a}{N})S \\ (1-\pi)\beta(\frac{I_s+\gamma.I_a}{N})S \\ 0 \end{bmatrix} \text{ and } v_i = \begin{bmatrix} (\psi+\delta+\mu+d_1)I_a(t) \\ (\theta+\phi+\mu+d_2)I_s(t) - (1-q)\tau R_s(t) \\ (\tau+\mu)dR_s(t) - \theta I_s(t) \end{bmatrix}.$$

Now partially differentiating the variables I_a, I_s and R_s with respect to time and evaluating at the disease free equilibrium point reduces the Jacobian matrices to:

$$F = \begin{bmatrix} \frac{\pi\beta\gamma K_4}{K_6} & \frac{\beta\gamma K_4}{K_6} & 0 \\ \frac{(1-\pi)\beta\gamma K_4}{K_6} & \frac{(1-\pi)\beta K_4}{K_6} & 0 \\ 0 & 0 & 0 \end{bmatrix} \text{ and } V = \begin{bmatrix} k_1 & 0 & 0 \\ -\delta & k_2 & -(1-q)\tau \\ 0 & -\theta & k_3 \end{bmatrix}.$$

Thus, the basic reproduction number, $R_0 = \rho(FV^{-1})$, where ρ is the largest eigenvalue of the product FV^{-1} and R_0 at disease free equilibrium point is as follows:

$$R_0 = \frac{\pi\beta K_4(\gamma K_5 + \delta K_3)}{K_3 K_5 K_6}. \tag{2.3}$$

Where $\begin{array}{llll} K_1 = & \psi+\delta+\mu+d_1, & K_4 = & \mu+\alpha-\mu\rho, \\ K_2 = & \theta+\phi+\mu+d_2, & K_5 = & k_2k_2+\tau\theta(1-q), \\ K_3 = & \tau+\mu, & K_6 = & \alpha+\mu. \end{array}$,

2.7 Local Stability of Disease Free Equilibrium

Theorem 2.3. Disease free equilibrium E_0 of system of equations given in 2.1 is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.

Proof . Now, the Jacobian matrix of the model equations given in (1) at the disease free equilibrium E_0 reduces the form as follows:

$$J(E_0) = \begin{pmatrix} K_6 & 0 & 0 & 0 & 0 & 0 \\ \alpha & -\mu & -\frac{\beta\gamma S}{N} & -\frac{\beta S}{N} & 0 & \omega \\ 0 & 0 & \frac{\pi\beta\gamma S}{N} - k_1 & \frac{\beta\pi S}{N} & 0 & 0 \\ 0 & 0 & \frac{(1-\pi)\beta\gamma S}{N} + \delta & \frac{(1-\pi)\beta S}{N} - k_2 & (1-q)\tau & 0 \\ 0 & 0 & 0 & \theta & -k_3 & 0 \\ 0 & 0 & \psi & \phi & \tau q & -k_7 \end{pmatrix}. \tag{2.4}$$

From the Jacobian matrix of 2.4, we obtained a characteristic polynomial:

$$(-k_6-\lambda)(-k_7-\lambda)(\lambda^3+L_1\lambda^2+L_2\lambda+L_3)=0. \tag{2.5}$$

where

$$\begin{aligned}
L_1 = &\ \tfrac{1}{k_6}\left[\beta(K_6-\mu\rho)((1-\pi)-\pi\gamma)+(K_1-K_2-K_3)K_6\right],\\
L_2 = &\ \tfrac{1}{k_6}[(\beta\pi\gamma(K_6-\mu\rho)-K_1K_6)(K_3K_6-\beta(1-\pi)(K_6-\mu\rho)-K_2K_6)+\\
&(K_2K_3K_6+\theta(1-q)\tau K_6-K_3\beta(1-\pi)(K_6-\mu\rho))-\pi\beta(K_6-\mu\rho)(\beta\gamma(K_6-\mu\rho)+\delta k_6)],\\
L_3 = &\ \tfrac{1}{k_6}[[\beta\pi(K_6-\mu\rho)(k_3(1-\pi)\beta\gamma)(K_6-\mu\rho)]+\\
&[(\beta\pi\gamma(K_6-\mu\rho)-K_1K_6)(K_2K_3K_6+\theta(1-q)\tau K_6-K_3\beta(1-\pi)(K_6-\mu\rho))]].
\end{aligned}$$

In 2.5, clearly it is observable that $\lambda_1=-k_6, \lambda_2=-\mu, \lambda_3=-k_7$.
For the last expression, that is:

$$\lambda^3+L_1\lambda^2+L_2\lambda+L_3=0. \tag{2.6}$$

As required by the principle of Routh-Hurwitz criteria, equation 2.6 will have negative real roots if and only if the following conditions hold true:

$$L_1>0, L_2>0, L_3>0, L_1L_2-L_3>0, L_1L_2L_3-L_3^2>0.$$

Therefore, it can be concluded that by Routh-Hurwitz criteria all the roots have negative real parts. Thus, DFE E_0 of the system of the differential equations given in 2.1 is locally asymptotically stable if $R_0<1$ and unstable if $R_0>1$. □

2.8 Global Stability of Disease Free Equilibrium

The global stability of disease free equilibrium was implemented by [2] technique.

Theorem 2.4. if $R_0<1$, then the disease free equilibrium $E_0=(X^*,0)$ of system of equations given in 2.1 is globally asymptotically stable in Ω and there is no unique endemic steady state.

Proof . Let $X=(P,S,R)\in R^3$ stands for the uninfected population and $Z=(I_A,I_s,R_s)\in R^3$ also stands for the infected population then the model equation 2.1 can be re-written as;

$$\begin{cases} \frac{dX}{dt}=F(X,Z), \\ \frac{dZ}{dt}=G(X,Z), G(X,0)=0. \end{cases}$$

where

$$F(X,Z)=\begin{bmatrix} \rho\Lambda-(\alpha+\mu)P \\ (1-\rho)\Lambda+\alpha P+\omega R-(\lambda+\mu)S \\ \psi I_a+\phi I_s+\tau q R_s-(\omega+\mu)R_s \end{bmatrix} \text{ and } G(X,Z)=\begin{bmatrix} \pi\lambda S-(\delta+\psi+\mu+d_1) \\ (1-\pi)\lambda S+\delta I_a+(1-q)\tau R_s-(\theta+\phi+\mu+d_1)I_s \\ \theta I_s-(\tau+\mu) \end{bmatrix}. \tag{2.7}$$

Consider the reduced system

$$\frac{dX}{dt}|_{Z=0}=\begin{bmatrix} \rho\Lambda-(\alpha+\mu)P \\ (1-\rho)\Lambda+\alpha P+\omega R-(\lambda+\mu)S \\ 0 \end{bmatrix}. \tag{2.8}$$

This implies from equation 2.8 it is obvious that $X^*=(\frac{\rho\Lambda}{(\alpha+\mu)}, \frac{(\Lambda(\alpha+\mu-\mu.\rho))}{\mu.(\alpha+\mu)}, 0)$ is globally asymptotically stable steady state. This can be verified that from the solution of expression 2.8 gives $P=\frac{\rho\Lambda}{(\alpha+\mu)}+[P(0)-\frac{\rho.\Lambda}{(\alpha+\mu)}]e^{-\mu t}$ and $S=\frac{(\Lambda(\alpha+\mu-\mu\rho))}{\mu.(\alpha+\mu)}+[S(0)-\frac{(\Lambda(\alpha+\mu-\mu\rho))}{\mu.(\alpha+\mu)}]e^{-\mu t}$.which converges X^* As $t\to\infty$ this implying that the global convergence of 2.8 is in Ω. We re-write the following two conditions as H_2 in 2.8 that guarantee for globally asymptotically stable equilibrium.

i. $\frac{dX}{dt}=G(X,Z), X^*$,
ii. $G(X,Z)=AZ-\tilde{G}(X,Z), \tilde{G}(X,Z)\geq 0$ for $(X,Z)\in\Omega$.

Where: $A = D_Z G(X^*, 0)$ is an Metzler matrix (the off diagonal elements of A are non-negative and G is the region where the model makes biologically sense). If system 2.8 satisfies condition (i) and (ii) then Theorem 2.4 holds.
From the equation for infected compartments in Eq. (2.7) the linearizion of G(X,Z) is:

$$A = \begin{bmatrix} -(k_1 - \frac{\pi\beta\gamma S}{N}) & \frac{\pi\beta S}{N} & 0 \\ \delta + \frac{(1-\pi)\beta\gamma S}{N} & -\left[k_1 - \frac{(1-\pi)\beta\gamma S}{N}\right] & (1-q)\tau \\ 0 & \theta & -(\tau+\mu) \end{bmatrix}.$$

Hence, G(X,Z) can be written as $G(XZ) = AZ - \tilde{G}(X,Z)$, where

$$\tilde{G}(X,Z) = \begin{bmatrix} \tilde{G}_1(X,Z) \\ \tilde{G}_2(X,Z) \\ \tilde{G}_3(X,Z) \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 0 \end{bmatrix}.$$

Thus the condition H_1 and H_2 are satisfied and we conclude that E_0 is globally asymptotically stable for the infection free steady state for $R_0 < 1$. □

2.9 Endemic Equilibrium Points

Here, the endemic equilibrium is denoted by $E^* = (P^*, S^*, I_a^*, R_s^*, I_s^*, R^*)$ and it occurs whenever the disease persists in the population. It is obtain by setting left hand sides of the equations of the system 2.1 to zero and solving the resultants. Thus, obtained the following:

$$\begin{aligned}
P^* &= \tfrac{(\alpha+\mu)}{\rho\Lambda}, \\
S^* &= \tfrac{\rho\Lambda(1-\rho)\Lambda+\alpha(\alpha+\mu)+\omega\rho\Lambda R^*}{(\lambda^*+\mu)}, \\
I_a^* &= \tfrac{\pi\lambda^*[\rho\Lambda(1-\rho)+\alpha(\alpha+\mu)+\omega\rho\Lambda R^*]}{(\lambda^*+\mu)(\delta+\Phi+\mu+d_1)}, \\
I_s^* &= \tfrac{(\tau+\mu)R_s^*}{\theta}, \\
R_s^* &= \left(\tfrac{\theta k_2}{k_2k_3-(1-q)\tau\theta}\right)\left(\tfrac{[\rho\Lambda(1-\rho)\Lambda+\alpha(\alpha+\mu)+\omega\Lambda R^*]}{(\lambda^*+\mu)(\theta+\delta+\mu+d_1)}\left(\tfrac{(1-\pi)\lambda^*k_1+\delta\pi\lambda^*}{k_1}\right)\right), \\
R^* &= \tfrac{[\rho\Lambda(1-\Lambda)\Lambda+\alpha(\alpha+\mu)]G}{(\omega+\mu)(\lambda^*+\mu)(\theta k_1(k_2k_3-(1-q)\tau\theta)-\omega\rho\Lambda G)}.
\end{aligned}$$

where $G = \theta\psi\pi\lambda^*[k_2k_3 - (1-q)\tau\theta] + k_1[k_2k_3 - (1-q)\tau\theta][\phi k_3\theta\tau q] + \theta[\theta(1-\pi)\lambda^*k_1 + \delta\pi\lambda^*\theta]$.

3 Extension of the Model into an Optimal Control

This section is dedicated to find the optimal control strategies of the model [10]. This helps to identify the best intervention strategies in order to eradicate the disease within a specified time. These control strategies are (i) prevention u_1, representing prevention effort for the susceptible population (ii) Treatment u_2, representing treatment of individuals showing symptoms of the disease (iii) screening u_3, representing screening of asymptomatic infective individuals which helps them to get proper treatment if they are aware of their status.
After incorporating u_1, u_2 and u_3 in 2.1, optimal control model of pneumonia is obtained as follows:

$$\begin{cases}
\frac{dP(t)}{dt} = & \rho\Lambda - (1-u_1)\alpha P(t) - \mu P(t), \\
\frac{dS(t)}{dt} = & (1-\rho)\Lambda + (1-u_1)\alpha P(t) + \omega R(t) - (1-u_1)\lambda S(t) - \mu)S(t), \\
\frac{dI_a(t)}{dt} = & (1-u_1)\pi\lambda S(t) - (\delta+u_3)I_a(t) - (\psi+u_2)I_a(t) - (\mu+d_1)I_a(t), \\
\frac{dI_s(t)}{dt} = & (1-u_1)(1-\pi)\lambda S(t) + (\delta+u_3)I_a(t) + (1-q)\tau R_s(t) - (u_2+\phi)I_s(t) - (\theta+\mu+d_2)I_s(t), \\
\frac{dR_s(t)}{dt} = & \theta I_s(t) - (\tau+\mu)R_s(t), \\
\frac{dR(t)}{dt} = & (\psi+u_2)I_a(t) + (u_2+\phi)I_s(t) + \tau q R_s(t) - (\omega+\mu)R(t).
\end{cases}$$

where $\lambda = \beta\frac{(I_s(t)+\gamma I_a(t))}{N}$. Now, the optimal levels of the control set U are Lebesgue measurable. It is defined as $U = (u_1(t), u_2(t), u_3(t)) : 0 \le u_1, u_2, u_3 < 1, 0 \le t \le T$. It is aimed to identify U P, S, I_a, I_s, R_s and R which are supposed to minimize the proposed objective function J. Here, the objective function is considered in line with literature on epidemic models [13] and given by:

$$J = \min_{u_1,u_2,u_3} \int_0^{t_f} \left(b_1 I_s + b_2 I_a + \frac{1}{2}\sum_{i=1}^{3} w_i u_i^2\right) dt. \tag{3.1}$$

Here in J, b_1, b_2 and w_i are positive quantities. The expression $1/2w_iu_i^2$ represents cost which depends on the controls u_i. The form of J is quadratic because it is assumed that the costs are not linear in nature. This research is aimed in minimizing the number of exposed and infective humans as well as the costs involved. Thus, it is sought to find an optimal triple controls (u_1^*, u_2^*, u_3^*) such that $J(u_1^*, u_2^*, u_3^*) = \min\{J(u_1, u_2, u_3); u_i \in U\}$ Where $U = \{(u_1, u_2, u_3)$ for each u_i is measurable with $0 \le u_i \le 1$for $0 \le t \le t_f\}$ for the control. Again, Hamiltonian (H) is constructed by following the methods given in [10] as presented hence forth:

$$H = \frac{dJ}{dt} + \lambda_1\frac{dP}{dt} + \lambda_2\frac{dS}{dt} + \lambda_3\frac{dI_a}{dt} + \lambda_4\frac{dI_s}{dt} + \lambda_5\frac{R_s}{dt} + \lambda_6\frac{dR}{dt}. \tag{3.2}$$

That is:

$$H(P, S, I_a, I_s, R_s, R) = L(I_a, I_s, u_1, u_2) + \lambda_1\frac{dP}{dt} + \lambda_2\frac{dS}{dt} + \lambda_3\frac{dI_a}{dt} + \lambda_4\frac{dI_s}{dt} + \lambda_5\frac{R_s}{dt} + \lambda_6\frac{dR}{dt}.$$

where $L(I_a, I_s, u_1, u_2) = b_1I_a + b_2I_2 + \frac{1}{2}\sum_{i=1}^{3} w_iu_i^2$ Here, $\lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5$ and λ_6 are known as adjoint variable functions. To obtain adjoint variable functions, the classical results given in [10] are adapted and are implemented as shown in the following theorem.

Theorem 3.1. Given an optimal control (u_1, u_2, u_3) and corresponding state solution P, S, I_a, I_s, R_s, R of corresponding system on (15) which minimize the objective function $J(u_1, u_2, u_3)$ over U, there exist adjoint variables $\lambda_i, i = 1, \ldots, 6$ satisfying the following equations.

$$\begin{cases}
\frac{d\lambda_1}{dt} = & (\lambda_1 - \lambda_2)(1-u_1)\alpha + \lambda_1\mu, \\
\frac{d\lambda_2}{dt} = & \lambda_1\left[\frac{(1-u_1)\beta(I_s+\gamma I_a)}{N} + \mu\right] - \lambda_3\left[\frac{(1-u_1)\pi\beta(I_s+\gamma I_a)}{N}\right] - \lambda_4\left[\frac{(1-\pi)(1-u_1)\beta(I_s+\gamma I_a)}{N}\right], \\
\frac{d\lambda_3}{dt} = & -b_1 + \lambda_2\left[\frac{(1-u_1)\beta\gamma S}{N}\right] - \lambda_3\left[\frac{(1-u_1)\pi\beta\gamma S}{N}\right] + \lambda_4\left[\frac{(1-\pi)(1-u_1)\beta\gamma S}{N} + \delta + u_3\right] + \\
& \lambda_3(\delta + u_3 + \psi + u_2\mu + d_1) - \lambda_6(u_2 + \psi), \\
\frac{d\lambda_4}{dt} = & -b_2 + \lambda_2\left[\frac{(1-u_1)\beta S}{N}\right] - \lambda_3\left[\frac{(1-u_1)\pi\beta S}{N}\right] - \lambda_4\left[\frac{(1-\pi)(1-u_1)\beta S}{N}\right] - \lambda_6(u_2 + \phi) - \\
& \lambda_4\left[u_2 + \phi + \theta + \mu + d_2\right] - \lambda_5(\theta), \\
\frac{d\lambda_5}{dt} = & \lambda_5(\tau + \mu) - \lambda_4(1-q)\tau - \lambda_6\tau q, \\
\frac{d\lambda_6}{dt} = & -\lambda_2\omega + \lambda_6(\omega + \mu).
\end{cases}$$

Together with the transversality conditions $\lambda_i(t_f) = 0, i = 1, \ldots, 6$. Furthermore, the optimal controls u_1, u_2 and u_3 are given as below:
$u_1^* = min\left\{1, max\left\{0, \frac{(\lambda_2-\lambda_1)\alpha P + (\pi\lambda_3 + (1-\pi)\lambda_4\lambda_2)(I_s^* + \gamma I_a^*)\beta S_*}{Nw_1}\right\}\right\}$, $u_2^* = min\left\{1, max\left\{0, \frac{(\lambda_3-\lambda_6)I_a^* + (\lambda_4-\lambda_6)I_s^*}{w_2}\right\}\right\}$ and $u_3^* = min\left\{1, max\left\{0, \frac{(\lambda_3-\lambda_4)I_a^*}{w_3}\right\}\right\}$.

Proof . Adjoint equations as well as transversality conditions are obtained from the Pontryagin's Maximum Principle, such that:

$$\begin{cases}
\frac{d\lambda_1}{dt} = -\frac{\partial H}{dP} = & (\lambda_1 - \lambda_2)(1-u_1)\alpha + \lambda_1\mu, \\
\frac{d\lambda_2}{dt} = -\frac{\partial H}{dS} = & \lambda_1\left[\frac{(1-u_1)\beta(I_s+\gamma I_a)}{N} + \mu\right] - \lambda_3\left[\frac{(1-u_1)\pi\beta(I_s+\gamma I_a)}{N}\right] - \lambda_4\left[\frac{(1-\pi)(1-u_1)\beta(I_s+\gamma I_a)}{N}\right], \\
\frac{d\lambda_3}{dt} = -\frac{\partial H}{dI_a} = & -b_1 + \lambda_2\left[\frac{(1-u_1)\beta\gamma S}{N}\right] - \lambda_3\left[\frac{(1-u_1)\pi\beta\gamma S}{N}\right] + \lambda_4\left[\frac{(1-\pi)(1-u_1)\beta\gamma S}{N} + \delta + u_3\right] + \\
& \lambda_3(\delta + u_3 + \psi + u_2\mu + d_1) - \lambda_6(u_2 + \psi), \\
\frac{d\lambda_4}{dt} = -\frac{\partial H}{dI_s} = & -b_2 + \lambda_2\left[\frac{(1-u_1)\beta S}{N}\right] - \lambda_3\left[\frac{(1-u_1)\pi\beta S}{N}\right] - \lambda_4\left[\frac{(1-\pi)(1-u_1)\beta S}{N}\right] - \lambda_6(u_2 + \phi) - \\
& \lambda_4\left[u_2 + \phi + \theta + \mu + d_2\right] - \lambda_5(\theta), \\
\frac{d\lambda_5}{dt} = -\frac{\partial H}{dR_s} = & \lambda_5(\tau + \mu) - \lambda_4(1-q)\tau - \lambda_6\tau q, \\
\frac{d\lambda_6}{dt} = -\frac{\partial H}{dR} = & -\lambda_2\omega + \lambda_6(\omega + \mu).
\end{cases}$$

Again the optimal control u_1, u_2 andu_3 can be solved from the optimality conditions using the method in [10] we obtain; Again the optimal control u_1, u_2 and u_3 can be solved from the optimality conditions using the method in [10] we obtain:
$\frac{\partial H}{du_1}$ = i.e. $u_1w_1 = (\lambda_2 - \lambda_2)\alpha P + (\pi\lambda_3 + (1-\pi)\lambda_4 - \lambda_2)\left(\frac{I_s+\gamma I_a}{N}\right)\beta S$
$\Rightarrow u_1 = \frac{(\lambda_2-\lambda_1)\alpha P + (\pi\lambda_3 + (1-\pi)\lambda_4 - \lambda_2)(I_s+\gamma I_a)\beta S}{Nw_1}$. By applying the same method for u_2 and u_3 we found:
$u_2 = \frac{(\lambda_3-\lambda_6)I_a + (\lambda_4-\lambda_6)I_s}{w_2}$ and $u_3 = \frac{(\lambda_3-\lambda_4)I_a}{w_3}$

Putting $u_1 = u_1^*, u_2 = u_2^*$ and $u_3 = u_3^*$ and $S = S^*, I_a = I_a^*, I_s = I_s^*$, we get:

$$\begin{aligned} u_1^* &= \frac{(\lambda_2-\lambda_1)\alpha P+(\pi\lambda_3+(1-\pi)\lambda_4-\lambda_2)(I_s^*+\gamma I_a^*)\beta S^*}{Nw_1} \\ u_2^* &= \frac{(\lambda_3-\lambda_6)I_a^*+(\lambda_4-\lambda_6)I_s^*}{Nw_2} \\ u_3^* &= \frac{(\lambda_3-\lambda_4)I_a^*}{Nw_3} \end{aligned}$$

Since the bounds of u_1, u_2 and u_3 are $0 \leq u_1, u_2, u_3 < 1$. Hence, optimum control has the following form:

$$u_1^* = \begin{cases} \frac{(\lambda_2-\lambda_1)\alpha P+(\pi\lambda_3+(1-\pi)\lambda_4-\lambda_2)(I_s^*+\gamma I_a^*)\beta S^*}{Nw_1}, & \text{If } 0 < u_1^* < 1 \\ 0, \quad \text{If } u_1^* \leq 1 \\ 1; \quad \text{If } u_1^* \geq \end{cases}$$

$$u_2^* = \begin{cases} \frac{(\lambda_3-\lambda_6)I_a^*+(\lambda_4-\lambda_6)I_s^*}{Nw_2}, & \text{If } 0 < u_2^* < 1, \\ 0, \quad \text{If } u_2^* \leq 10 \\ 1; \quad \text{If } u_2^* \geq \end{cases} \quad \text{and}$$

$$u_3^* = \begin{cases} \frac{(\lambda_3-\lambda_4)I_a^*}{Nw_3} \quad \text{If } 0 < u_1^* < 1 \\ 0, \quad \text{If } u_3^* \leq 10 \\ 1, \quad \text{If } u_3^* \geq 1 \end{cases}$$

□

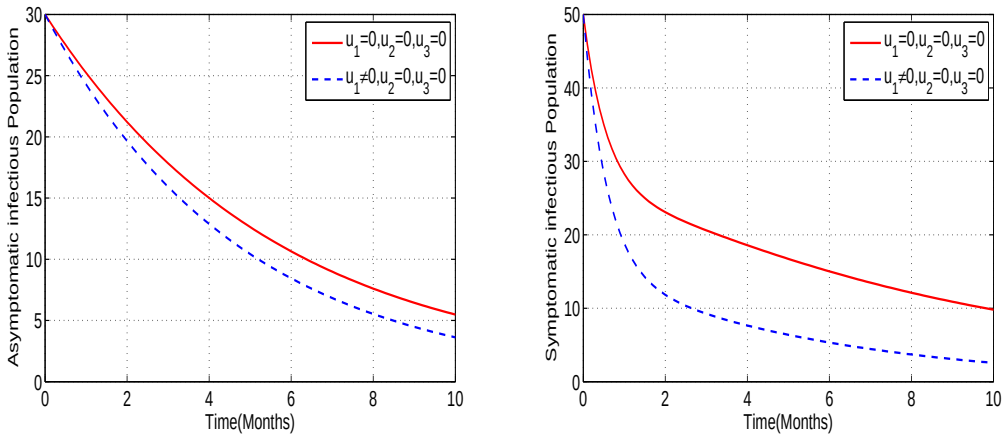
4 Numerical Simulation

The numerical simulations were carried out using the parametric values given in Table 2. Optimality of the system is achieved by using available iterative schemes. Solutions of the state equations given in (1) are initiated by assigning guessed values for the controls and simulated using fourth order Runge–Kutta scheme. It is followed by using current iterated solutions of the state equations to solve the adjoint equations by backward fourth order Runge–Kutta scheme.

Table 2: Parameter Values for Pneumonia Model

Parameters	*Value*	*Source*
ρ	20	Assumed
Λ	0.73	Assumed
α	0.87	Assumed
μ	0.01	Assumed
ψ	0.84	Assumed
q	0.03	Assumed
δ	0.2	Assumed
π	0.05	[14]
ψ	0.001	Assumed
ω	0.1	[14]
θ	0.68	Assumed
d_1	0.00057	Assumed
d_2	0.057	[14]
τ	0.5	Assumed
ε	0.45	Assumed
γ	1.5	Assumed

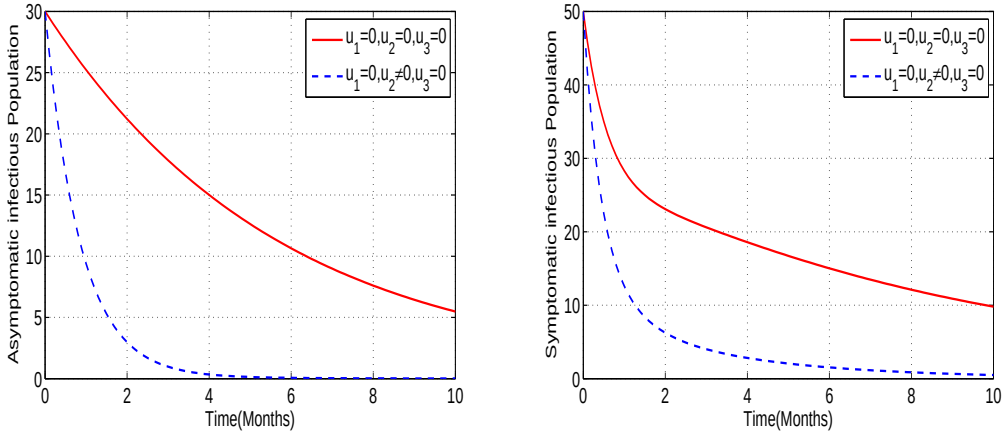
I. **Control with prevention alone**: Here, optimality system is simulated by incorporating prevention intervention alone. Figure 2 shows a decrease of asymptomatic infection and symptomatic infectious population within a specified time period. Hence, it is concluded that the intervention strategy prevention plays an important role in reducing infection of pneumonia from population.



(a) **(b)**

Figure 2: Impact of 'prevention' on asymptomatic and symptomatic Infectious population.

II. **Control with treatment alone**: We applied treatment only as intervention that is treating individuals who develop disease symptom. From figure 3 we understand that the number of Asymptomatic and symptomatic infectious population decreased when treatment intervention is applied. Therefore, we conclude that, applying optimized treatment only as control intervention decrease the burden of the disease and eradicate pneumonia disease in the community.



(a) **(b)**

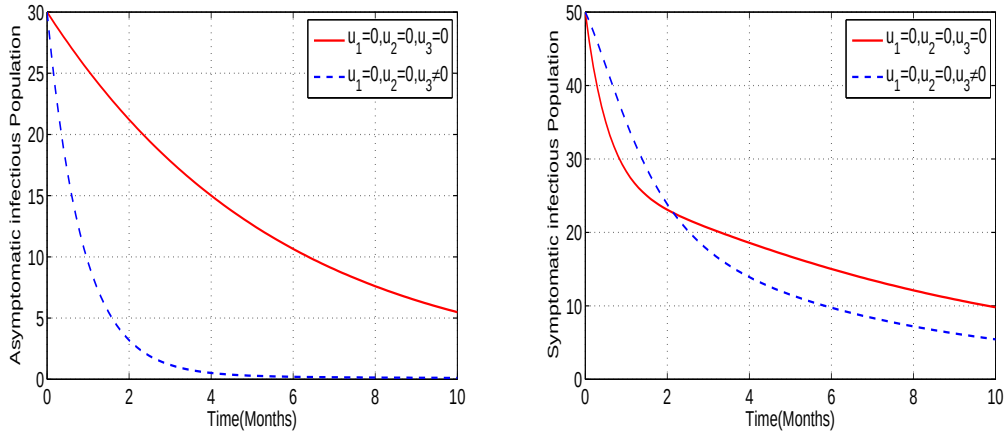
Figure 3: Impact of 'treatment' on asymptomatic and symptomatic Infectious population.

III. **Control with screening alone**:We applied screening only as intervention that is screening individuals who didn't show the disease symptom. Figure 4 clearly show that both asymptomatic and symptomatic population has gone to zero at the end of the implementation period. Therefore, we conclude that, these strategies are effective in eradicating the disease from the community in a specified period of time.

IV. **Control with prevention and screening only**: We simulate the model using a combination of prevention and screening as intervention strategy for control of Pneumonia disease in the community. Figure 5 shows that the number of infectious as well as asymptomatic infected population reduces considerably to minimum in the specified time period. Therefore, these strategies too work effectively in eradicating the disease from human population.

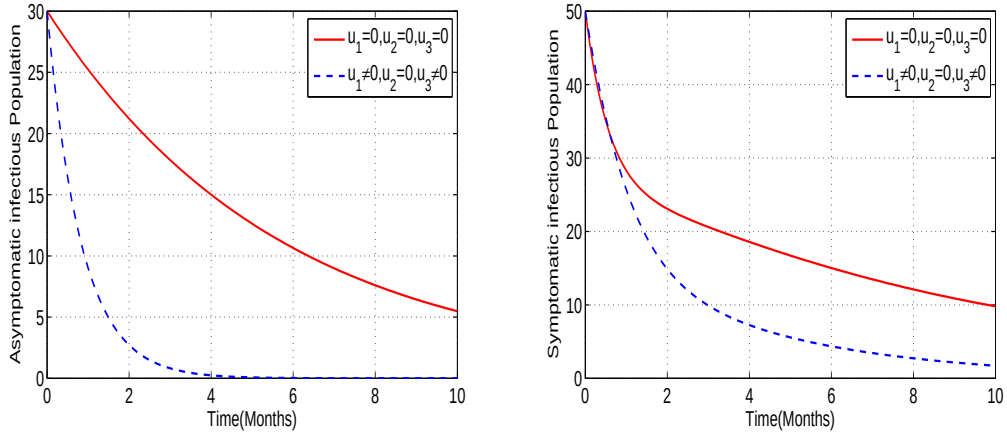
V. **Control with prevention and treatment only** : We used prevention and treatment as intervention strategy, and figure 6 show that, the number of symptomatic infectious and also asymptomatic infected population goes down in the specified time. Thus, these strategies are effective in reducing the disease from the community in a specified period of time.

VI. **Control with treatment and screening only**: We used treatment and screening controls as intervention.



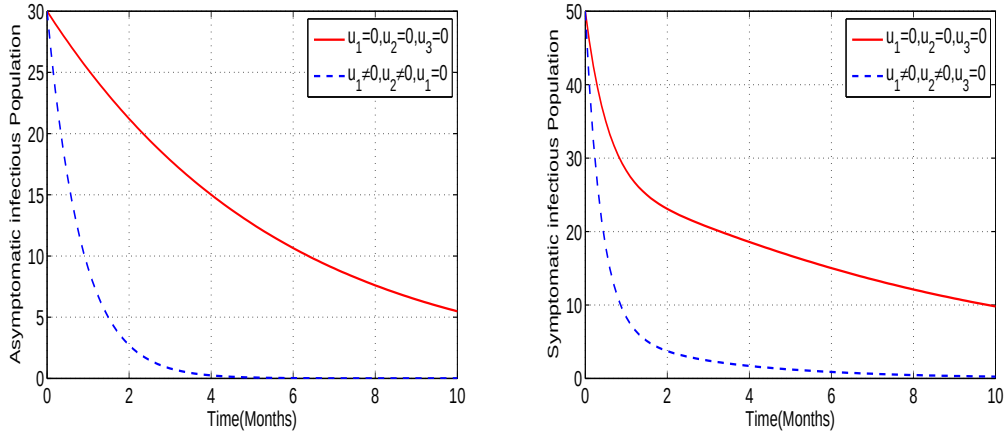
(a) **(b)**

Figure 4: Impact of screening on asymptomatic and symptomatic Infectious population.



(a) **(b)**

Figure 5: Impact of 'prevention and screening' on asymptomatic and symptomatic Infectious population.



(a) **(b)**

Figure 6: impact of 'prevention and treatment' on asymptomatic and symptomatic Infectious population.

From figures 7 we observe that optimal control of the combination of treatment and screening helps to bring down both the infectious and asymptomatic infected population which helps to eradicate the disease in the community.

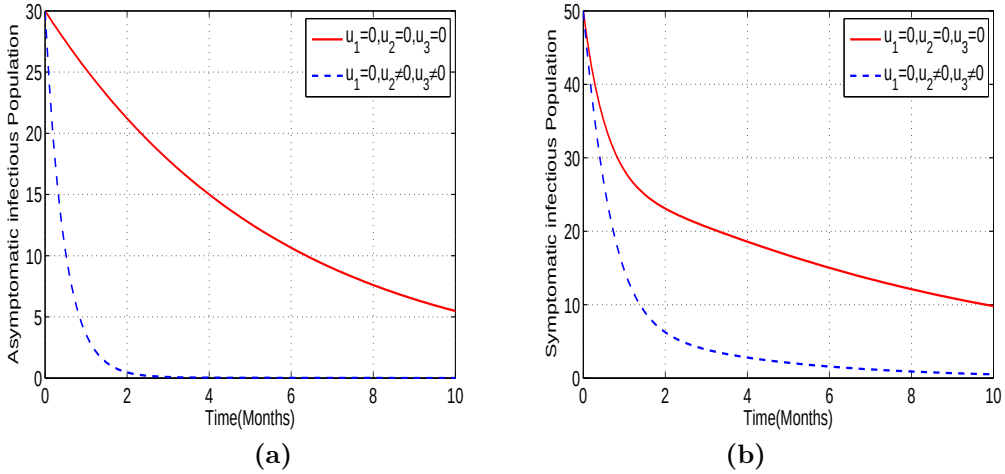


Figure 7: Impact of 'treatment and screening' on asymptomatic and symptomatic Infectious population.

VII. **Control with prevention, treatment and screening**: We implement all control the three controls interventions that helps to minimize the objective function. From figure 8 we observe that the number of the infectious and asymptomatic infected populations decrease at the specified time due to the intervention strategies. Therefore, applying this strategy helps to eradicate pneumonia disease in specified period of time.

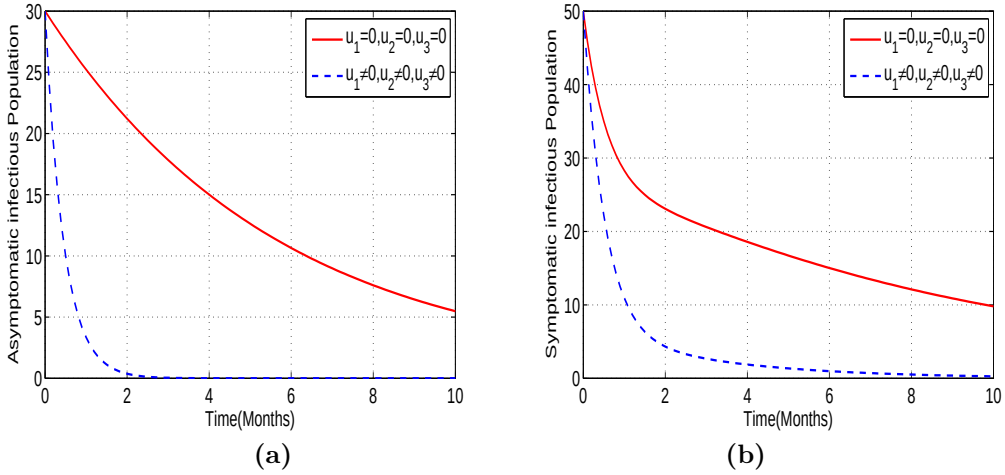


Figure 8: Impact of 'prevention, treatment and screening' on asymptomatic and symptomatic Infectious population.

5 Cost effectiveness analysis

In this section, we identified a strategy which is cost effective compared to other strategies. To obtain this strategy, we used the method of incremental cost-effectiveness ratio ($ICER$), which is done by dividing the difference of costs between two strategies to the difference of the total number of their infectious averted. This approach was defined as [16]:

$$"ICER = \frac{\text{Difference in costs between strategies}}{\text{Difference in infections averted between strategies}}"$$

The total number of infectious averted for each strategy is obtained by subtracting the total infectious with control from without control while the cost averted of each strategy was obtained by using the cost function represented by the

function $\frac{1}{2}w_1u_1^2$, $\frac{1}{2}w_2u_2^2$ and $\frac{1}{2}w_2u_2^2$ over the time [16]. We did not consider strategies that implement one intervention only, the reason that one intervention only is not guaranteed to eradicate the disease totally from the community. Those strategies which incorporate more than one intervention are ordered below to be compared pairwise. We used parameter values in table 2 to estimate the total cost and total infectious averted in table 3.

Table 3: Total amount of infection averted and total cost for all strategies

Strategies	Total cost (dollar)	Description	Total infectious averted
A	Prevention and Treatment	1493.86	6929.3
D	Prevention, Treatment and Screening	1434.83	9404.05
B	Treatment and Screening	1314.88	6434.35
C	Prevention and Screening	866.15	5444.45

After obtaining the total amount of people averted and total cost of each strategy as given in Table 3 to compare two intervention strategies, the incremental cost effectiveness ratio ($ICER$) for each competing strategy is estimated as:

$$\begin{aligned} ICER(A) &= \tfrac{6929.3}{1493.86} = 4.64 \\ ICER(D) &= \tfrac{9404.05-6929.3}{1434.83-1493.86} = -15.56 \\ ICER(B) &= \tfrac{6434.35-9404.05}{1314.88-1434.83} = 24.76 \\ ICER(C) &= \tfrac{5444.45-6434.35}{866.15-1314.88} = 2.2 \end{aligned}$$

The number of people averted in strategy C, B, D and A in an increasing rank is given in Table 4.

Table 4: Total amount of the infection averted and total cost with their $ICER$

Strategies	Total infections averted	Total cost (Dollar)	$TICER$
A	1493.86	6929.3	4.64
D	1434.83	9404.05	-15.56
B	1314.88	6434.35	24.76
C	866.15	5444.45	2.2

We can observe that from the strategies A and D in Table 4, the $ICER(D)$ is less than $ICER(A)$. This implies that strategy D is dominated by Strategy A. It means that strategy A more expensive than strategy D. Thus, we have deleted A from the strategies. Then re-calculate the $ICER$ for the remaining competing strategies D, B and C as given in Table 5.

Table 5: Total amount of the infection averted and total cost with their $ICER$

Strategies	Total infections averted	Total cost (Dollar)	$TICER$
D	1434.83	9404.05	6.55
B	1314.88	6434.35	24.76
C	866.15	5444.45	2.2

Here the competition between interventions D and B were shown in Table 5. It is observed that the $ICER(B)$ is greater than $ICER(D)$. This shows that strategy B is dominated by strategy D. Hence, strategy D is more efficient and less cheap than strategy B. Thus, we omitted strategy B from the list of competing and re-calculate the $ICER$ as given in Table 6.

Table 6: Total amount of the infection averted and total cost with their $ICER$

Strategies	Total infections averted	Total cost (Dollar)	$TICER$
D	1434.83	9404.05	6.56
C	866.15	5444.45	6.69

In Table 6 comparison between intervention strategies D and C indicates that $ICER(C)$ is greater than $ICER(D)$. This shows that strategy D is more dominates C. So that the strategy D provided the least total cost and the most effective. From the result of the analysis, therefore, we recommend that intervention D that is a combination of Prevention, Treatment and Screening of infectious human is the best effective and less costly strategy to minimize the spread of pneumonia diseases from the community.

6 Discussions and Conclusions

Here in this paper, a new deterministic model on pneumonia endemic is proposed. Fundamental properties of the model including the feasible region, the positivity of solutions and boundedness are discussed. A basic reproduction number is computed and multiple equilibrium points of the model are calculated and their stability analysis is conducted. Accordingly, if $R_0 < 1$, the disease-free-equilibrium point of the developed model is locally asymptotically stable while if $R_0 > 1$, the disease-free-equilibrium is unstable and the endemic equilibrium point is stable. For the basic pneumonia model, the control function is formulated by incorporating three control variables viz., Prevention, Treatment and Screening. Also, the optimality of the control function is evaluated. The Hamiltonian, adjoint variables, and characteristic equations of control variables are constructed. Optimum control strategies of the system are derived by solving the optimal control problem. The solutions of model equations are simulated by considering a single control strategy and pair of control strategies one at a time. The impacts of the proposed strategies are investigated numerically and their results are displayed graphically. The results displayed in the graphs suggest that the disease can be reduced by applying control strategies. Then also the analysis of cost-effectiveness is investigated with all the different combinations of controls. Hence, based on the simulation result of the optimality system and analysis of cost-effectiveness, we suggested that the combination of all control strategies such as prevention, treatment and screening of infectious humans is the best effective and less costly strategy to minimize the spread of pneumonia diseases from the community.

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