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Optimal Control of an Influenza Model with Multiple Control Strategies

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Abstract:- Effective control of influenza pandemic is an important public health goal. Number of recent studies, have shown that how different intervention measures allow to control the number of clinical cases of influenza. Here we introduce optimal control strategies and their impact on disease control and also investigate the necessary conditions for the control of disease. Further we try to evolve optimal control policies to reduce the susceptible that are at risk and clinically ill and infectious cases by introducing four control strategies at a minimal cost. We use Pontryagin's Maximum Principle of optimal control theory. Simulations are carried out using fourth order Runge-Kutta forward-backward scheme. We evaluated the potential effect of control measures such as non-pharmaceutical intervention, antiviral treatment and vaccination effect on the disease dynamics.

Keywords: *Optimal control; Influenza model; non-pharmaceutical intervention; Treatment; Vaccination.*

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I. Introduction

Emerging influenza is a seasonal viral disease caused by influenza A virus (H1N1). It spreads rapidly and costs society a considerable amount in terms of health care expenses, reduction in productivity as well as loss of life. The World Health Organization (WHO) has declared the outbreak to be a pandemic because of growing worldwide cases [1]. It cost the society a huge amount in terms of morbidity and mortality and monetary cost as well with a typical flu pandemic. The existence of influenza virus among human population in many countries of the world including India has emphasized public health care organizations to take effective preventive measure.

However, there are situations where, in spite of the medical care available to infected cases, diseases may spread sporadically in no time and situation may go beyond our control of medical care. Such situations can be perfectly controlled by introducing initial preventive measure such as Non Pharmaceutical Interventions (NPIs) specifically by keeping all mediating agencies away from contact [2]. NPIs include social distancing, quarantine, school closure, mask wearing etc. These measures may play an important role when effective vaccine and anti-viral drugs may not be available for the general population at the start of the pandemic disease. The use of such NPIs were applied during the 1918 pandemic and for Severe Acute Respiratory Syndrome (SARS) and also recently during 2009-10 H1N1 pandemic.

In India there were 31,924 laboratory-confirmed cases and 1,525 deaths were reported, i.e. 4.78% of the cases tested positive for H1N1 influenza virus [3]. In this situation vaccination is the most effective means of pandemic mitigation. In the last decade, various studies have been carried out concerning the pandemic influenza [4]; their study explores the impact of immunization with a partially effective vaccine on the transmission dynamics of influenza infection. In many situations such vaccine programs do well to stop the spread of infection and determines the minimal vaccine efficacy and vaccination rate required to control or eradicate infection in a population. Recently, an economic analysis of influenza vaccination and anti-retroviral treatment for healthy working adults has been carried out and found that the controls: Vaccination and treatment are two elements of the international strategy to prevent a pandemic [5]. Also it has been shown to be most effective as a public health measures to curtail the disease outbreak. Such models are suitable for developed countries as they capable to adapt vaccination programs as they can meet the cost, material and manpower. But for developing countries are concerned very few people may get vaccinated and very few may be accessible to the medical care as they unable to afford the cost. Further, it may be difficult also if they may not have access to treatment and health services because of poor resource settings. In view of these problems, it is better to introduce the combination of these vaccination and treatment strategies along with non pharmaceutical intervention control to curtail the spread of epidemic, where the social distancing, household quarantine and mask wearing can be offered and can be hoped for the control of spread of a disease to extinct.

In this paper we introduce appropriate optimal control measures and their impact on disease control and also investigate the necessary conditions for the control of disease. After introduction in Section-1, we try to evolve an optimal disease control policy to reduce the susceptible that are at risk and clinically ill and infectious cases by introducing four control strategies in Section -2 and derive a control model consisting of non-linear differential equations which describe the dynamics of influenza model. Section 3 deals with derivation of optimal control policies using Pontryagin's Maximum principle and determines the necessary conditions for the optimal of the disease. In section 4 we discussed the theorem on existence of optimal control policy. In section 5 we discuss the results of numerical simulations and the final section give summary and conclusions of the paper.

II. Optimal Control Model

The optimal control of influenza model with four control strategies is given by the following nonlinear differential equations[6].

$$\dot{S}(t) = \omega V(t) + \rho R(t) - \frac{\beta\big(1-\varepsilon_1 u_1(t)\big)S(t)[I(t)+T(t)]}{N(t)} - \big(\phi + \varepsilon_2 u_2(t)\big)S(t)$$

$$\dot{E}(t) = \frac{\beta\big(1-\varepsilon_1 u_1(t)\big)S(t)[I(t)+T(t)]}{N(t)} - kE(t)$$

$$\dot{V}(t) = \big(\phi + \varepsilon_2 u_2(t)\big)S(t) - \omega V(t) \quad (1)$$

$$\dot{I}(t) = \kappa E(t) - \big(\gamma_1 + \alpha + \delta + \varepsilon_3 u_3(t)\big)I(t)$$

$$\dot{T}(t) = \alpha I(t) - \big(\gamma_2 + (1-\theta)\delta + \varepsilon_4 u_4(t)\big)T(t)$$

$$\dot{R}(t) = \gamma_1 I(t) + \gamma_2 T(t) + \varepsilon_3 u_3(t) I(t) + \varepsilon_4 u_4(t) T(t) - \rho R(t)$$

$$\dot{D}(t) = \delta I(t) + (1-\theta)\delta T(t)$$

with initial conditions,

$S(0) = S_0$, $V(0) = V_0$, $E(0) = E_0$, $I(0) = I_0$, $T(0) = T_0$, $R(0) = R_0$, $D(0) = D_0$ and

$N(t) = S(t) + E(t) + V(t) + I(t) + T(t) + R(t) + D(t)$ where $N(t)$ is the total population at time t.

Variables and Parameters

Variable/parameter	explanation
S	Susceptible Individuals
E	Exposed Individuals
V	Vaccinated individuals
I	Infected and Infectious Individuals
T	Treated Individuals
R	Recovered Individuals
D	Disease Induced Deaths
N $N = S + E + V + I + T + R + D$	Total population
ϕ	Rate at which susceptible are vaccinated
β	Per capita transmission rate
k	Rate of progression from exposed class to infectious class
γ_1	Rate of recovery of infectious individuals
γ_2	Recovery rate due to treatment
δ	Disease induced death rate
ρ	Rate of immunity loss of recovered individuals
α	Rate at which clinically infectious individuals hospitalized for treatment
θ	Effectiveness of the drug as a reduction factor in disease induced death of infectious individuals ($0 < \theta \leq 1$).
ω	Vaccine based immunity wanes.

III. Analysis of optimal control

Optimal control theory has been used successfully in many situations to make decisions involving biological or medical models. In developing response plans for disease outbreaks, decision makers seek optimal responses that can minimize the incidence cases and disease related deaths along with the cost of each mitigation strategy. Here the control theory is used to explore the impact of both non pharmaceutical intervention and vaccination control for the susceptible that are at risk and also antiviral treatment control for clinically infectious and hospitalized individuals. The control theoretic approach assigns costs to both interventions and infection and looks for a policy that can minimize the total combined cost. The control strategies are modeled by the functions $u_i(t)$ $(i = 1,2,3,4)$ that externally control the number of susceptible, clinically infectious and hospitalized individuals over a finite time interval.

We use the following Controls variables:

Control $u_1(t)$ as a successful practice of non-pharmaceutical interventions to susceptible $(\varepsilon_1 S(t))$ to protect themselves from attack of the disease; ε_1 measures the effectiveness of $u_1(t)$, $\varepsilon_1 \epsilon\ (0,1)$). Control $u_2(t)$

represents the controlling effort that alters the fraction of susceptible individuals ($\varepsilon_2 S(t)$) receiving vaccination per unit of time, and hence limiting the rate of infection; ε_2 measures the effectiveness of $u_2(t)(\varepsilon_2 \in (0,1))$. The Control $u_3(t)$ alters the fraction of clinically infectious cases ($\varepsilon_3 I(t)$) receiving anti-virals per unit time; ε_3 measures the effectiveness of $u_3(t)(\varepsilon_3 \in (0,1))$ and the Control $u_4(t)$ alters the fraction of hospitalized individuals ($\varepsilon_4 T(t)$) gettting antiviral treatment per unit of time; ε_4 measures the effectiveness of $u_4(t)(\varepsilon_4 \in (0,1))$.

The control problem involves an objective functional J that formulates the optimization problem of interest, namely that of identifying the most effective strategies. Our objective involves minimizing the number of individuals with flu as well as the costs for applying non pharmaceutical intervention and vaccination controls for the susceptible that are at risk and also antiviral treatment control for clinically ill, infectious and hospitalized individuals. The controls $u_1(t)$, $u_2(t)$, $u_3(t)$ and $u_4(t)$ are minimized subject to differential equations (1) which are nonlinear and complex, unable to find an analytical solution.

The objective functional J is given by

$$J(u_1, u_2, u_3, u_4) = \int_0^{t_f} [AI(t) + BT(t) + \frac{W_1}{2}u_1^2(t) + \frac{W_2}{2}u_2^2(t) + \frac{W_3}{2}u_3^2(t) + \frac{W_4}{2}u_4^2(t)]dt \quad (2)$$

where t_f is the final time and the co-efficient $A, B, C, W_1, W_2, W_3, W_4$ are balancing cost factors. A quadratic function is implemented for measuring the control cost. Optimal control problem is to find an optimal functions u_1^*, u_2^*, u_3^* and u_4^* such that

$$J(u_1^*, u_2^*, u_3^*, u_4^*) = \min_U J(u_1(t), u_2(t), u_3(t), u_4(t)) \quad (3)$$

Subject to system (1), where the control set is defined as

$$U = \{(u_1(t), u_2(t), u_3(t), u_4(t)) \text{ are measurable}, 0 \leq ((u_1(t), u_2(t), u_3(t), u_4(t)) \leq 1\}$$

IV. Existence of control problem

In this section, we consider the control system (1) with initial conditions to show the existence of the control problem. Note that for the bounded lebesgue measurable controls and non-negative initial conditions, non-negative bounded solutions to the state system exists [7]. In order to find an optimal solution, first we should find the Lagrangian and Hamiltonian for the optimal control problem. The minimal value of the Lagragian is given by

$$L = AI(t) + BT(t) + \frac{1}{2}(W_1u_1^2 + W_2u_2^2 + W_3u_3^2 + W_4u_4^2)$$

We define the Hamiltonian H for the control problem, where $\lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5,$ and λ_6 are adjoint variables:

$$H = AI(t) + BT(t) + \frac{W_1}{2}u_1^2(t)\ \frac{W_2}{2}u_2^2(t) + \frac{W_3}{2}u_3^2(t) + \frac{W_4}{2}u_4^2(t) + \lambda_1\left[\omega V(t) + \rho R(t) - \frac{\beta(1-\varepsilon_1 u_1(t))S(t)[I(t)+T(t)]}{N(t)} - (\phi + \varepsilon_2 u_2(t))S(t)\right] + \lambda_2\left[\frac{\beta(1-\varepsilon_1 u_1(t))S(t)[I(t)+T(t)]}{N(t)} - kE(t)\right]$$

$$+\lambda_3[(\phi + \varepsilon_2 u_2(t))S(t) - \omega V(t) + \lambda_4[\kappa E(t) - (\gamma_1 + \alpha + \delta + \varepsilon_3 u_3(t))I(t)] + \lambda_5[\alpha I(t) - (\gamma_2 + (1-\theta)\delta + \varepsilon_4 u_4(t))T(t)] + \lambda_6[\gamma_1 I(t) + \gamma_2 T(t) + \varepsilon_3 u_3(t)I(t) + \varepsilon_4 u_4(t)T(t) - \rho R(t)] \quad (4)$$

For the existence of our control system (1), we state and prove the following theorem.

Theorem 4.1 *There exists an optimal control* $u^* = (u_1^*, u_2^*, u_3^*, u_4^*) \in U$ *such that*

$$J(u_1^*, u_2^*, u_3^*, u_4^*) = \min_U J(u_1(t), u_2(t), u_3(t), u_4(t))$$

Subject to the control system (1) with the initial conditions.

Proof: *to prove the existence of an optimal control we use the result in [8] [9]. Here the control and state variables are non-negative values. In this minimizing problem, the necessary convexity of the objective functional in* u_1, u_2, u_3 and u_4 *are satisfied. The set of all the control variables* $(u_1, u_2, u_3, u_4) \in U$ *is also convex and closed by definition. The optimal system is bounded which determines the compactness needed for the existence of an optimal control. In addition the integrand in the functional (2),* $AI(t) + BT(t)\frac{1}{2}(W_1u_1^2(t) + W_2u_2^2(t) + W_3u_3^2(t) + W_4u_4^2(t))$ *is convex on the control set U. Also we can see that, there exists a constant* $\rho > 1$ *and positive numbers* ω_1, ω_2 *such that*

$$J(u_1, u_2, u_3, u_4) \geq c_1(|u_1|^2 + |u_2|^2 + |u_3|^2 + |u_4|^2)^{\rho/2} - \omega_2$$

Because, the state variables are bounded, this completes the existence of optimal control.

In order to derive the necessary conditions, we use Pontryagin's Maximum Principle as follows. If (x,u) is an optimal solution of an optimal control problem, then there exists a non trivial vector function $\lambda = (\lambda_1, \lambda_2, \dots, \lambda_3)$ satisfying the following equations:

$$\frac{dx}{dt} = \frac{\partial H(t,x,u,\lambda)}{\partial \lambda},$$

$$0 = \frac{\partial H(t,x,u,\lambda)}{\partial u}, \qquad (5)$$

$$\frac{d\lambda}{dt} = \frac{\partial H(t,x,u,\lambda)}{\partial x}.$$

We now derive the necessary conditions that optimal control functions and corresponding states must satisfy.The following theorem , we present the adjoin system and control characterization.

Theorem 4.2 *Let S^*, E^*, V^*, I^*, T^* and R^* be optimal state with associated optimal control variables $(u_1^*(t), u_2^*(t), u_3^*(t), u_4^*(t))$ respectively for the optimal control problem. Then there exist adjoint variables $\lambda_i(t)(i = 1,2,3,4,5,6)$ satisfying*

$$\dot{\lambda}_1(t) = (\lambda_1(t) - \lambda_2(t))\frac{\beta(1-\varepsilon_1 u_1(t))S(t)\,[I(t)+T(t)]}{N(t)} + (\lambda_1(t) - \lambda_3(t))(\phi + \varepsilon_2 u_2(t))$$

$$\dot{\lambda}_2(t) = ((\lambda_2(t) - \lambda_4(t))k$$

$$\dot{\lambda}_3(t) = (\lambda_1(t) - \lambda_3(t))\,\omega$$

$$\dot{\lambda}_4(t) = -A + (\lambda_1(t) - \lambda_2(t))\frac{\beta(1-\varepsilon_1 u_1(t))S(t)}{N(t)} + \lambda_4(t)(\gamma_1 + \alpha + \delta + \varepsilon_3 u_3(t)) - \lambda_5\alpha - \lambda_6(\gamma_1 + \varepsilon_3 u_3(t))$$

$$\dot{\lambda}_5(t) = (\lambda_1(t) - \lambda_2(t))\frac{\beta(1-\varepsilon_1 u_1(t))S(t)}{N(t)} + \lambda_5(t)(\gamma_2 + (1-\theta)\delta + \varepsilon_4 u_4(t)) - \lambda_6(t)(\gamma_2 + \varepsilon_4 u_4(t)$$

$$\dot{\lambda}_6(t) = (\lambda_1(t) - \lambda_6(t))\rho \qquad (6)$$

With transversality conditions,

$$\lambda_1(t_f) = \lambda_2(t_f) = \lambda_3(t_f) = \lambda_4(t_f) = \lambda_5(t_f) = \lambda_6(t_f) = 0 \qquad (7)$$

Furthermore the control functions $u_1^*(t), u_2^*(t), u_3^*(t)$, and $u_4^*(t)$ are given by,

$$u_1^*(t) = \min\left\{\max\left\{0, \frac{(\lambda_2(t) - \lambda_1(t))\beta\varepsilon_1 S(t)[I(t)+T(t)]}{W_1 N(t)}\right\}, 1\right\}$$

$$u_2^*(t) = \min\left\{\max\left\{0, \frac{((\lambda_1(t) - \lambda_3(t))\varepsilon_2 S(t))}{W_2}\right\}, 1\right\}$$

$$u_3^*(t) = \left\{\max\left\{0, \frac{(\lambda_4(t) - \lambda_6(t))\varepsilon_3 I(t)}{W_3}\right\}, 1\right\} \qquad (8)$$

$$u_4^*(t) = \min\left\{\max\left\{0, \frac{((\lambda_5(t) - \lambda_6(t))\varepsilon_4 T(t))}{W_4}\right\}, 1\right\}$$

Proof: *To determine the ad joint equations and the transversality conditions, we use the Hamiltonian H in equation (4). The form of the adjoint equations and transversality conditions are standard results from Pontryagin's Maximum Principle. We differentiate the Hamiltonian with respect to each state (respectively as stated above), then the adjoint system can be written as:*

$$\dot{\lambda}_1(t) = -\frac{\partial H}{\partial S}, \quad \dot{\lambda}_2(t) = -\frac{\partial H}{\partial E}, \quad \dot{\lambda}_3(t) = -\frac{\partial H}{\partial V},$$
$$\dot{\lambda}_4(t) = -\frac{\partial H}{\partial I}, \quad \dot{\lambda}_5(t) = -\frac{\partial H}{\partial T},$$

$$\dot{\lambda}_6(t) = -\frac{\partial H}{\partial R}$$

With transversality conditions,

$$\lambda_1(t_f) = \lambda_2(t_f) = \lambda_3(t_f) = \lambda_4(t_f) = \lambda_5(t_f) = \lambda_6(t_f) = 0$$

To get the characterization of the optimal control we have to solve the equations,

$$\frac{\partial H}{\partial u_1(t)} = 0, \quad \frac{\partial H}{\partial u_2(t)} = 0, \quad \frac{\partial H}{\partial u_3(t)} = 0 \;\&\; \frac{\partial H}{\partial u_4(t)} = 0$$

for $u_1^*(t), u_2^*(t), u_3^*(t)$ & $u_4^*(t)$ subject to the constraints, the characterization (8) can be derived and we have

$$\frac{\partial H}{\partial u_1(t)} = W_1 u_1(t) - \frac{(\lambda_2(t) - \lambda_1(t))\beta\varepsilon_1 S(t)[I(t)+T(t)]}{N(t)} = 0$$

$$\frac{\partial H}{\partial u_2(t)} = W_2 u_2(t) - (\lambda_1(t) - \lambda_3(t))\varepsilon_3 S(t) = 0$$

$$\frac{\partial H}{\partial u_3(t)} = W_3 u_3(t) - (\lambda_4(t) - \lambda_6(t))\varepsilon_3 I(t) = 0$$

$$\frac{\partial H}{\partial u_4(t)} = W_4 u_4(t) - \left(\lambda_5(t) - \lambda_6(t)\right)\varepsilon_4 T(t) = 0$$

Then by standard variation arguments with the control bounds, we obtain the properties (8)

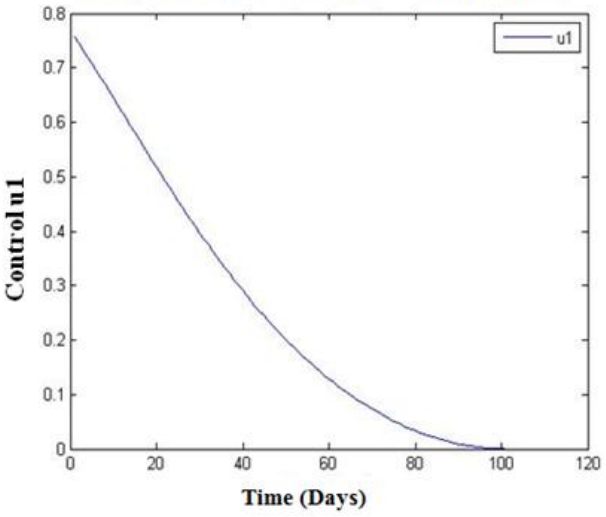
Table 1. Description of parameter values in the optimal control simulation

Parameter	Baseline value	Reference
δ	0.01	Assumed
β	1.5	Chowell et al. (2010)
k	1.75	Assumed
γ_1	0.34	Chowell et al. (2010)
γ_2	0.34	Assumed
ρ	0.02	Chowell et al. (2010)
α	0.54	Assumed
ϵ_1	0.5	Chowell et al. (2010)
ϵ_2	0.5	Assumed
ϵ_3	0.5	Assumed
ϵ_4	0.5	Assumed
θ	0.5	Assumed
$\emptyset$	1	Assumed

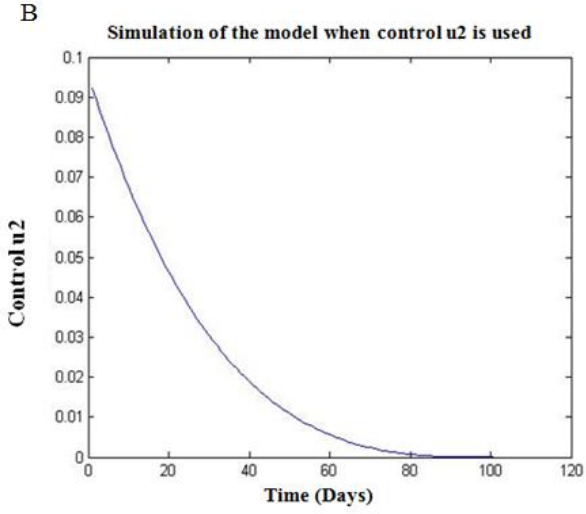
V. Numerical Illustrations:

Numerical solutions to the optimality system comprising of the state Eq.(1) and adjoint Eq.(6) are carried out using Mat Lab using parameters from the above Table together with the following weight factors and initial conditions: $A = 1, B = 1, W_1 = 25, W_2 = 25, W_3 = 25, W_4 = 25,\ S(0) = 1{,}00{,}000,$ $E(0) = V(0) = I(0) = 100,\ T(0) = 10, R(0) = D(0) = 0$. The algorithm is the forward-backward scheme; starting with an initial guess for the optimal controls. The state variables are then solved forward in time using a Runge-Kutta method of the fourth order. Then, those state variables and initial guess for the controls are used to solve the adjoint Equation backward in time with given final conditions (8), again employing a fourth order Runge-Kutta method. The controls are updated and used to solve the state and then the adjoint system. This iterative process terminates when current state, adjoint, and control values converge sufficiently [10][11]. Figure.1 shows the optimal control functions as a function of time computed for strategies using only single control functions respectively.

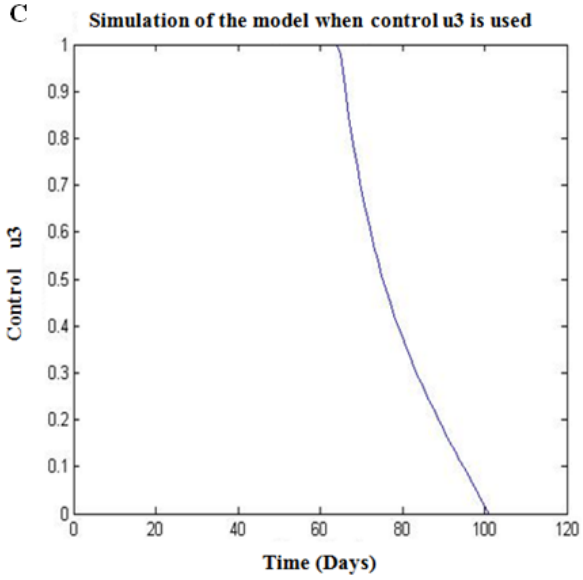
A



B



C



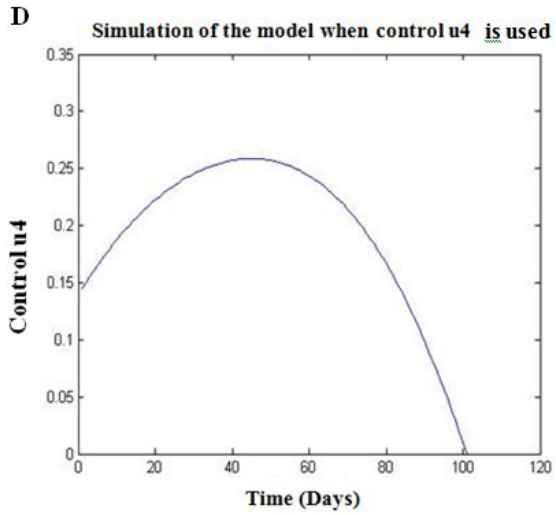


Figure.1 A, B, C & D show the time dependent optimal control functions computed for all strategies using the controls $u_1, u_2, u_3,$ & u_4 respectively.

For the figures presented below, Figure 2. Show the optimal vaccinated, treatment and non-pharmaceutical intervention control laws. The controls are plotted as a function of time. The optimal control u_1 is at its upper bound for 30 days and then is steadily decreasing its lower bound value; it means that the non-pharmaceutical intervention control safeguards the susceptible individuals from the possible infection. The optimal control u_2 stays at its upper bound for a short time about four days, and then steadily decreases to its lower bound. While the optimal control u_3 stays at its upper bound for 57 days & steadily decreases to the lower bound. The control u_3 increases gradually at its upper bound from 0.3 and decreases to its lower bound over the rest of the simulated time. In fact, at the beginning of the simulated time the controls are staying at their upper bound in order to minimize as many as susceptible individuals that are at risk and also to prevent the increasing of the number of infected individuals.

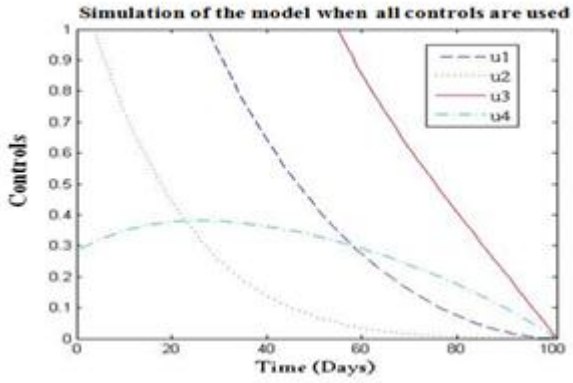


Figure. 2 Four optimal control functions implemented for all strategies as a function of time.

In order to illustrate the overall picture of the epidemic, simulations for the infectious and treated are shown in Figure 3. The treatment control is more effective in reducing the number of infected individuals. The graph show the effectiveness of the treatment control in reducing the spread of disease.

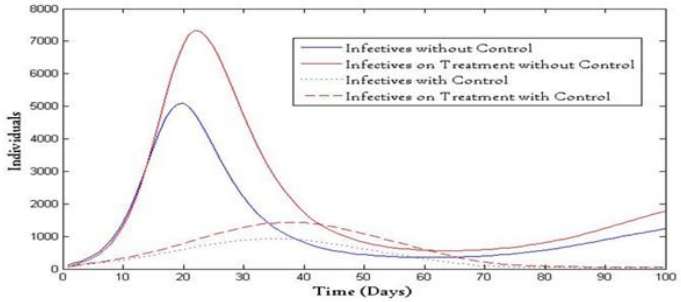


Figure.3 Infectious and treated individuals with and without control

The infectious individuals without control increases rapidly to 7, 0000 in first 30 days and it decreases to 5,000 with control. The treated individual also decreases with control.

VI. Conclusion

In our present study, an optimal control model of the transmission dynamics of the pandemic influenza is performed using four control strategies. Using Pontryagin's Maximum Principle, the control system is analyzed to determine the necessary conditions for the existence of an optimal control. The control plots we developed indicate that the number of suceptibles and infectious individuals decreased in the optimality system. The simultaneous use of multiple control policies is more effective at reducing the number of secondary infections than the use of single-control policies. The results show the importance in minimizing the spread rate of infection at the initial time when medical control measures are not available or inadequate in preventing the spread of a disease.

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