



## Mathematical Model on Optimal Combination of Vaccination and Antiviral Therapy to Curb Influenza in Kenya

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### Authors' contributions

This work was carried out in collaboration between both authors. Author JKG designed the study and wrote the first draft of the manuscript. Both authors managed literature searches. Author DMN performed the Mathematical analysis of the study and the simulations. Both authors read and approved the final manuscript.

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## Abstract

Human influenza is a contagious disease which, if proper precautions are not taken to control the disease, can lead to massive mortality rates and high costs will be incurred to control the disease in case of an outbreak. As a result, we investigate how the cost of implementing both vaccination and antiviral therapy can be minimized and at the same time minimize the number of infected individuals. We have developed a system of ordinary differential equations from our formulated SVIR model and used vaccination and antiviral therapy to study influenza dynamics. We have the basic reproductive number determined using the next generation matrix. The equilibria and stability of the model has also been determined and analyzed. We have used the maximization theory of Pontryagin to define the optimal control rates and then used MATLAB program to do the numerical simulations. The numerical simulations done indicate that an ideal combination of vaccination and antiviral therapy decreases the number of infected individuals which in turn reduces the cost of applying the two control measures.

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## 1 Introduction

Influenza is an infectious respirational disease initiated by the RNA influenza virus of the Orthomyxoviridae family, Earn [1] and lamb [2]. The infected person has symptoms such as fever, sore throat, muscle pain, severe headache, coughing, nausea and fatigue. Influenza at times is associated with common cold since both have similar symptoms only that influenza causes high mortality and morbidity. Various strains of influenza virus exist, that is, influenza A,B,C and D.

According to WHO, influenza A and B viruses are of epidemiological interest to humans because of their different strains. In Kenya, distinct influenza outbreaks occur in a year and their pandemic existence is of varying extent. This is because of the changing antigenic properties of the virus whose spread depends on the ability of transmission of the virus and exposure of the population to the virus. The most recent outbreak of influenza in Kenya was reported in June 2009 and also in 2012. In 2009, the first case was reported at Kisumu in June when a British student tested positive of influenza A(H1N1) and by September many cases of H1N1 had been reported in Kenya, Oria [3]. In 2012, cases of H1N1 influenza pandemic were confirmed to have declined. Out of 745 samples collected from January to May 2012, 92 of the samples tested positive of influenza virus: with 80 of the samples having influenza A and the rest had influenza B. Also, of these 80 samples, 91% were of H3N2 seasonal influenza and 9% were of H1N1, Achilla [4]. Recent studies have still shown that seasonal influenza H3N2 circulates in Kenya even to date.

Outbreak of influenza has severe economic impacts like decreasing work force productivity, loss of life and strained health services. With the current population growth and urbanization, influenza is expected to become increasingly wide spread (Gasparani [5] and Molinari [6]) and will need to be controlled. In our case, the best prevention technique is a combination of vaccination and antiviral therapy. However, the imposition of these two strategies is very costly and, therefore, the need for an ideal combination of these two methods which is cost-effective and will eliminate the disease within a limited time frame. This has prompted us, just like other mathematicians, to take a step in increasing the understanding of the disease dynamics. Mathematical modeling has proved to be a good tool for understanding the dynamics of transmission and disease management by assessing their effectiveness and impact on disease prevention and control.

Optimal control theory is an area of mathematics, derived from variations calculus, which can be used extensively to control the spread of infectious diseases by assisting scientists make choices involving complicated biological problems, Lenhart [7]. The concept of optimal control is used in most cases to control the spread of most diseases that can be controlled either through vaccination or therapy eg. ([8], [9], [10], [11], [12]). Various methods can be used to calculate optimal control, but in our case we will use the maximum principle of Pontryagin's which allows the computation of optimal control for a system of ordinary differential equations with a given limitation. This technique will provide great insight by providing the best way to reduce the burden of disease. For instance, to get the best vaccination schedule that balances the vaccination cost and cost of disease burden, Herbert [13].

Our work is an extension of works done by Tchuenche [14], Muhammed [15], Saiful [16] and recent work by Joko and Titik [17].

The rest of the work is organized as follows : in section 2, we present and describe the influenza model. In section 3, we discuss the model analysis, which involves examining the equilibrium

and stability states of our model, and finally identifying and analyzing the optimal control problem using the Pontryagin Maximization Principle. Section 4 is the numerical simulation of our optimized problem, and in section 5 we are engaged in discussions and conclusions.

## 2 Description and Formulation of the Model

Kermack and Mckendrick [18] in the 20th century developed the first generic model describing epidemic influenza. They simulated influenza epidemic using a Susceptible-Infectious- Recovered (SIR). We find in this analysis a generalized model of SVIR with a bilinear incidence and a robust total population.

In our model, recruitment into susceptible class (S) is by birth  $b$  from which the class can be exited by natural death  $\delta$ , vaccination  $\omega$  into the vaccination compartment  $V$  or through influenza infection  $\beta$  into the infected compartment  $I$ . Those in the vaccination compartment may lose immunity at the rate of  $(1 - \sigma)\beta$  into the infected compartment while those who do not lose immunity move to the recovered compartment  $R$  or even exit the vaccination compartment by natural death. People in the infected compartment are treated and recover at a rate  $\gamma$  and move to the recovered class while others in the compartment die due to illness  $\mu$  or natural death  $\delta$ . Since there is no re-infection upon successful treatment and vaccination, those in the recovered class can only exit by natural death  $\delta$ .

Based on the above description we have the following assumptions and flow chart;

### Assumptions:

- i. Recruitment into the vulnerable class is only by childbirth.
- ii. Recovered individuals receive permanent immunity from reinfection.
- iii. A flexible total population.
- iv. Antiviral therapy is administered to all infected individuals.
- v. No drug intolerant and resilient influenza strains.

From Fig. 1, we obtain the following differential equations of the model with  $S(0) \geq 0$ ,  $V(0) \geq 0$ ,  $I(0) \geq 0$  and  $R(0) \geq 0$ , non-negative initial conditions.

$$\begin{aligned} \frac{dS}{dt} &= b - \beta SI - (\delta + \omega)S, \\ \frac{dV}{dt} &= \omega S - \delta V - (1 - \sigma)\beta VI - rV, \\ \frac{dI}{dt} &= \beta SI + (1 - \sigma)\beta VI - (\mu + \gamma + \delta)I, \\ \frac{dR}{dt} &= \gamma I + rV - \delta R. \end{aligned} \tag{2.1}$$

Letting  $N(t)$  denote the total population such that:

$$N(t) = S(t) + V(t) + I(t) + R(t),$$

it follows that:

$$\begin{aligned} \frac{dN}{dt} &= \frac{dS}{dt} + \frac{dV}{dt} + \frac{dI}{dt} + \frac{dR}{dt}, \\ \frac{dN}{dt} &= b - \delta N - \mu I. \end{aligned} \tag{2.2}$$

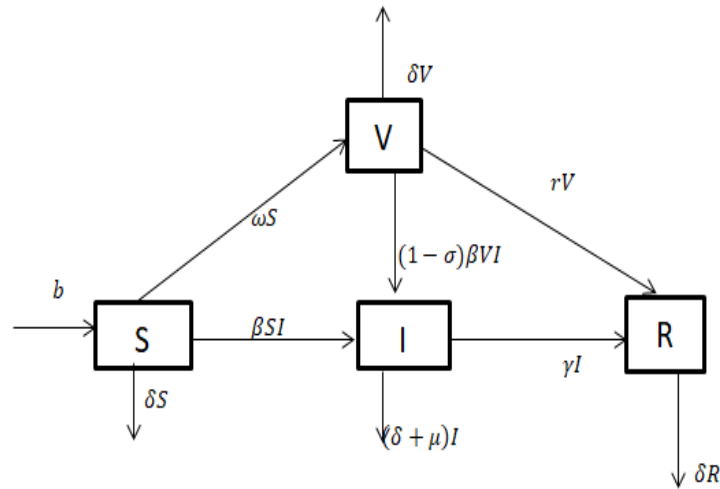


Fig. 1. Flow chart

At time  $t = 0$ , the total population  $N(t)$  is 1 such that  $1 = S(0) + V(0) + I(0) + R(0)$ .

### 3 Model Analysis

**Lemma 1.** All solutions  $(S(t), V(t), I(t), R(t))$  of equation (2.2) are bounded.

*Proof.* We derive, from the total human population in equation (2.2), that:

$$\frac{dN}{dt} = b - \delta N(t) - \mu I \leq b - \delta N(t).$$

Integrating the above equation and taking the suprimum limit as  $t \rightarrow \infty$  to get

$\limsup_{t \rightarrow \infty} N(t) \leq \frac{b}{\mu}$ , hence all system solutions of (2.2) are bounded. The area that is feasible to the total population becomes  $\Omega = \{(S, V, I, R) \in \mathbb{R}_+^4; S + V + I + R \leq \frac{b}{\mu}, S(t) \geq 0, V(t) \geq 0, I(t) \geq 0, R(t) \geq 0\}$ . Therefore the region  $\Omega \subset \mathbb{R}_+^4$  is positively invariant for our model with non negative initial conditions in  $\mathbb{R}_+^4$ .  $\square$

#### 3.1 Disease-free Equilibrium(DFE) point

In the absence of disease, the disease free equilibrium point denoted by  $E^0$  is the model's stable state solution.

Letting the left hand side of equations (2.1) be equal to zero and that  $S = S^0, V = V^0, I = I^0$  and  $R = R^0$ , we get:

$$\begin{aligned} 0 &= b - (\delta + \omega)S, \\ 0 &= \omega S - \delta V - rV, \\ 0 &= I, \\ 0 &= rV - \delta R. \end{aligned}$$

Thus the disease free equilibrium  $E^0$  point of our model is:

$$E^0 = \left( \frac{b}{\delta + \omega}, \frac{\omega b}{(\delta + \omega)(\delta + r)}, 0, \frac{r\omega b}{\delta(\delta + \omega)(\delta + r)} \right)$$

### 3.2 The basic reproduction number ( $R_0$ )

$R_0$  refers to the number of secondary infections produced by one single infectious organism in a fully infectious population. To evaluate  $R_0$ , we use the next generation matrix method, [19], such that  $\rho(F_0V_0^{-1})$  where  $F_0$  is the Jacobian of  $f_i$  at  $E^0$ . The pace at which new infections appear in compartment  $i$  is  $f_i$  and the Jacobian of  $v_i$  (the transfer rate of persons to and from the  $i$  container) at disease free equilibrium  $E^0$  is  $V_0$ .

Take  $x = (I, V)$ , from system equation(2.1) to have that:

$$\frac{dx}{dt} = f_i - v_i$$

where  $f_i = \begin{bmatrix} \beta SI + (1 - \sigma)\beta VI \\ 0 \end{bmatrix}$  and  $v_i = \begin{bmatrix} \mu + \delta + \gamma \\ \omega S - (\delta + r)V \end{bmatrix}$

$$F_0 = \text{jacobian of } f \text{ at } E^0 = \begin{bmatrix} \beta S^0 + (1 - \sigma)\beta V^0 & 0 \\ 0 & 0 \end{bmatrix}$$

$$V_0 = \text{jacobian of } v \text{ at } E^0 = \begin{bmatrix} \mu + \delta + \gamma & 0 \\ 0 & \delta + r \end{bmatrix}.$$

The next generation matrix of system of equations (2.1) becomes

$$F_0V_0^{-1} = \begin{bmatrix} \frac{\beta S^0 + (1 - \sigma)\beta V^0}{\mu + \delta + \gamma} & 0 \\ 0 & \delta + r \end{bmatrix}$$

The  $R_0$  spectral radius of the  $F_0V_0^{-1}$  matrix is given by:

$$\begin{aligned} R_0 &= \rho(F_0V_0^{-1}) \\ &= \frac{\beta b}{\delta + \omega} + \frac{(1 - \sigma)\beta \omega b}{(\delta + \omega)(\delta + r)} \\ &= \frac{\beta b}{(\delta + \omega)(\mu + \delta + \gamma)} + \frac{(1 - \sigma)\beta \omega b}{(\delta + \omega)(\delta + r)(\mu + \delta + \gamma)} \\ &= \frac{\beta b(\delta + r) + (1 - \sigma)\beta \omega b}{(\delta + \omega)(\mu + \delta + \gamma)(\delta + r)} \end{aligned}$$

which is the required basic reproductive number  $R_0$  of system of equations (2.1)

### 3.3 Endemic Equilibrium point

This refers to the disease spreading point within the population. Let  $E^* = (S^*, V^*, I^*, R^*)$  be the endemic equilibrium point, where  $S^*, V^*, I^*, R^* > 0$ .

Consider

$$\begin{aligned} 0 &= b - \beta S^* I^* - (\delta + \omega)S^*, \\ 0 &= \omega S^* - \delta V^* - (1 - \sigma)\beta V^* I^* - rV^*, \\ 0 &= \beta S^* I^* + (1 - \sigma)\beta V^* I^* - (\mu + \delta + \gamma)I^*, \\ 0 &= \gamma I^* + rV^* - \delta R^*. \end{aligned} \tag{3.1}$$

We get, from the first equation of (3.1)

$$S^* = \frac{b}{\beta I^* + (\delta + \omega)},$$

from the second equation of (3.1)

$$V^* = \frac{\omega b}{(\delta + (1 - \sigma)\beta I^* + r)(\beta I^* + \delta + \omega)}$$

and from the fourth equation of (3.1)

$$R^* = \frac{\gamma I^* + rV^*}{\delta}.$$

Thus  $E^* = (S^*, V^*, I^*, R^*)$  of our system (3.1) becomes:

$$E^* = \left( \frac{b}{\beta I^* + (\delta + \omega)}, \frac{\omega b}{(\delta + (1 - \sigma)\beta I^* + r)(\beta I^* + \delta + \omega)}, I^*, \frac{\gamma I^* + rV^*}{\delta} \right)$$

### 3.4 Local stability of the disease free Equilibrium point

From system of equations (2.1) we can consider

$$\begin{aligned} \frac{dS}{dt} &= b - \beta SI - (\delta + \omega)S, \\ \frac{dV}{dt} &= \omega S - \delta V - (1 - \sigma)\beta VI - rV, \\ \frac{dI}{dt} &= \beta SI + (1 - \sigma)\beta VI - (\mu + \delta + \gamma)I, \end{aligned} \tag{3.2}$$

since the fourth equation of system of equations (3.2) is independent of the rest. Now, we investigate local stability of DFE of system (3.2)

**Theorem 2.** *At  $E^0$ , system of equations (3.2) is stable locally asymptotically and  $R_0 < 1$ .*

*Proof.* The jacobian matrix of the system is:

$$J = \begin{bmatrix} -\beta I - (\delta + \omega) & 0 & -\beta S & 0 \\ \omega & -(\delta + r) - (1 - \sigma)\beta I & -(1 - \sigma)\beta V & 0 \\ \beta I & (1 - \sigma)\beta I & \beta S + (1 - \sigma)\beta V - (\mu + \delta + \gamma) & 0 \\ 0 & r & \gamma & -\delta \end{bmatrix}$$

At DFE

$$E^0 = \left( \frac{b}{\delta + \omega}, \frac{\omega b}{(\delta + \omega)(\delta + r)}, 0, \frac{r\omega b}{\delta(\delta + \omega)(\delta + r)} \right)$$

the jacobian of our matrix at  $E^0$  becomes

$$J_0 = \begin{bmatrix} -(\delta + \omega) & 0 & -\beta S & 0 \\ \omega & -(\delta + r) & -(1 - \sigma)\beta V & 0 \\ 0 & 0 & \beta S + (1 - \sigma)\beta V - (\mu + \delta + \gamma) & 0 \\ 0 & r & \gamma & -\delta \end{bmatrix}$$

By using the relation  $|J_0 - \lambda I| = 0$  we get the eigen values of our matrix as:

$$\lambda_1 = -(\delta + \omega),$$

$$\lambda_2 = -\delta,$$

$$\begin{aligned} \lambda_3 &= -(\delta + r), \\ \lambda_4 &= -(\mu + \delta + \gamma) + \beta S + (1 - \sigma)\beta V \\ &= -(\mu + \delta + \gamma) + \frac{\beta b}{\delta + \omega} + \frac{(1 - \sigma)\beta \omega b}{(\delta + \omega)(\delta + r)}. \end{aligned}$$

since for positive parameter  $\lambda_1, \lambda_2$  and  $\lambda_3$  are negative, the only condition for stability of the DFE is  $\lambda_4 < 0$ .

$$\begin{aligned} \text{i.e } & -(\mu + \delta + \gamma) + \frac{\beta b}{\delta + \omega} + \frac{(1 - \sigma)\beta \omega b}{(\delta + \omega)(\delta + r)} < 0 \\ \frac{\beta b}{\delta + \omega} + \frac{(1 - \sigma)\beta \omega b}{(\delta + \omega)(\delta + r)} & < (\mu + \delta + \gamma) \\ \frac{\beta b(\delta + r) + (1 - \sigma)\beta \omega b}{(\delta + \omega)(\mu + \delta + \gamma)(\delta + r)} & < 1 \end{aligned}$$

which is the vaccine reproductive number  $R_0$  and that DFE locally asymptotically stable iff  $R_0 < 1$ . □

### 3.5 Global stability of the disease free Equilibrium point

**Lemma 3.** *The model's disease-free equilibrium is asymptotically stable globally if  $R_0 < 1$ .*

*Proof.* We construct a Lyapunov [20] function:

$$L = U_1(S - S^0) + U_2(V - V^0) + U_3I \tag{3.3}$$

where  $U_1, U_2, U_3$  are positive constants.

Differentiating equation (3.3) with respect to time  $t$ , we get:

$$L' = U_1(b - \beta SI - (\delta + \omega)S) + U_2(\omega S - \delta V - (1 - \sigma)\beta VI - rV) + U_3(\beta SI + (1 - \sigma)\beta VI - (\delta + \mu + \gamma)I).$$

Rearranging we get:

$$L' = b + \beta SI(U_3 - U_1) - (1 - \sigma)\beta VI(U_2 - U_3) - \delta U_1 S - \omega S(U_1 - U_2) - \delta U_2 V - rV U_2 - \delta U_3 I - \mu U_3 I - \gamma U_3 I.$$

We choose the constants  $U_1 = U_2 = U_3 = 1$ , and the above equation reduces to:

$$L' = b - \delta(S + V + I) - rV - \gamma I < 0$$

Thus the device equation disease-free equilibrium point (2.1) is globally asymptotically stable if  $R_0 < 1$ . □

### 3.6 Local stability of the Endemic Equilibrium point

**Theorem 4.** *The endemic equilibrium state of the system of equations (2.1) is locally asymptotically stable if  $R_0 > 1$  otherwise unstable.*

*Proof.* The jacobian matrix of the system is:

$$J = \begin{bmatrix} -\beta I - (\delta + \omega) & 0 & -\beta S & 0 \\ \omega & -(\delta + r) - (1 - \sigma)\beta I & -(1 - \sigma)\beta V & 0 \\ \beta I & (1 - \sigma)\beta I & \beta S + (1 - \sigma)\beta V - (\mu + \delta + \gamma) & 0 \\ 0 & r & \gamma & -\delta \end{bmatrix}$$

Taking  $I = 0$ , the above matrix becomes:

$$J_E = \begin{bmatrix} -(\delta + \omega) & 0 & -\beta S & 0 \\ \omega & -(\delta + r) & -(1 - \sigma)\beta V & 0 \\ 0 & 0 & \beta S + (1 - \sigma)\beta V - (\mu + \delta + \gamma) & 0 \\ 0 & r & \gamma & -\delta \end{bmatrix}$$

By using the relation  $|J_E - \lambda I| = 0$  we get the result:

$$\begin{aligned} \lambda_1 &= -(\delta + \omega) < 0, \\ \lambda_2 &= -\delta < 0, \\ \lambda_3 &= -(\delta + r) < 0, \\ \lambda_4 &= -(\mu + \delta + \gamma) + \beta S + (1 - \sigma)\beta V \\ &= -(\mu + \delta + \gamma) + \frac{\beta b}{\delta + \omega} + \frac{(1 - \sigma)\beta \omega b}{(\delta + \omega)(\delta + r)} < 0. \end{aligned}$$

Thus, all the true  $\lambda$  values are negative and so our endemic equilibrium state is asymptotically stable locally.  $\square$

### 3.7 Global stability of the Endemic Equilibrium point

**Theorem 5.** *If  $R_0 > 1$ , then an endemic equilibrium point exists, and it is stable globally.*

*Proof.* Consider the Lyapunov [20] function:

$$Y(SVI) = \frac{1}{2}(S - S^*)^2 + \frac{1}{2}(V - V^*)^2 + \epsilon \left( I - I^* - I^* \ln \frac{I}{I^*} \right) \text{ where } \epsilon \geq 0$$

The  $Y$  derivative along the System of equation solution curve (2.1) yields:

$$Y' = (S - S^*)S' + (V - V^*)V' + \epsilon \left( 1 - \frac{I^*}{I} \right) I' \tag{3.4}$$

Substituting equations (2.1) for equation (3.4) we obtain this:

$$\begin{aligned} Y' &= (S - S^*)(b - \beta SI - (\delta + \omega)S) + (V - V^*)(\omega S - \delta V - (1 - \sigma)\beta VI - rV) \\ &\quad + \epsilon \left( 1 - \frac{I^*}{I} \right) (\beta SI + (1 - \sigma)\beta VI - (\mu + \delta + \gamma)I) \end{aligned} \tag{3.5}$$

We have at endemic equilibrium from system equation (3.1):

$$\begin{aligned} b &= \beta S^* I^* + (\delta + \omega)S^*, \\ (1 - \sigma)\beta V^* I^* &= \omega S^* - \delta V^* - rV^*, \\ \beta S^* I^* &= -(1 - \sigma)\beta V^* I^* + (\mu + \gamma + \delta)I^*. \end{aligned} \tag{3.6}$$

From the second equation of system of equations (3.6), the first and the third equation of system of equations (3.6) becomes;

$$\begin{aligned} b &= (\mu + \delta + \gamma)I^* + \delta S^* + (\delta + r)V^*, \\ (1 - \sigma)\beta V^* I^* &= \omega S^* - \delta V^* - rV^*, \\ \beta S^* I^* &= (\mu + \delta + \gamma)I^* - \omega S^* + (\delta + r)V^*. \end{aligned} \tag{3.7}$$

Thus

$$\begin{aligned} (b - \beta SI - (\delta + \omega)S) &= (\mu + \delta + \gamma)I^* + \delta S^* + (\delta + r)V^* - (\mu + \delta + \gamma)I^* + \delta S^* \\ &\quad + (\delta + r)V^* - (\delta + \omega)S \\ &= (\delta + \omega)S^* - (\delta + \omega)S \\ &= (\delta + \omega)(S^* - S) \end{aligned} \tag{3.8}$$



and

$$\begin{aligned} \omega S - \delta V - (1 - \sigma)\beta VI - rV &= \omega S - (\delta + r)V - \omega S^* + (\delta + r)V^* \\ &= \omega(S - S^*) - (\delta + r)(V - V^*) \end{aligned} \tag{3.9}$$

and also

$$\begin{aligned} \beta SI + (1 - \sigma)\beta VI - (\mu + \delta + \gamma)I &= (\mu + \gamma + \delta)I^* - \omega S^* + (\delta + r)V^* + \omega S^* - \delta V^* \\ &\quad - rV^* - (\mu + \gamma + \delta)I \\ &= -(\mu + \gamma + \delta)(I - I^*) \end{aligned} \tag{3.10}$$

Substituting (3.8), (3.9) and (3.10) into equation (3.5), We get:

$$\begin{aligned} Y' &= (S - S^*)(\delta + \omega) + (V - V^*)(S - S^*)\omega - (\delta + r)(V - V^*)^2 \\ &\quad - \in (I - I^*)(\mu + \delta + \omega)(I - I^*) \end{aligned} \tag{3.11}$$

Setting  $S \leq S^*$ ,  $V \leq V^*$  and  $I \leq I^*$ ,

thus  
 $Y' \leq 0$ .

We note that  $Y' = 0$  holds. By Lassalle Invariant principle (Lassalle [21]), every solution to system of equations (2.1) approaches endemic equilibrium as  $t \rightarrow \infty$ , if  $R_0 > 1$  and therefore the endemic equilibrium is asymptotically stable globally.  $\square$

### 3.8 Optimal control analysis

In this section, we find the best control strategy that can reduce the epidemic level by formulating an optimal control problem for our influenza model. Consider:

$$\begin{aligned} \frac{dS}{dt} &= b - \beta SI - (u_1 + \delta)S, \\ \frac{dV}{dt} &= u_1 S - \delta V - (1 - \sigma)\beta VI - rV, \\ \frac{dI}{dt} &= \beta SI + (1 - \sigma)\beta VI - (\mu + \delta + u_2)I, \\ \frac{dR}{dt} &= u_2 I + rV - \delta R. \end{aligned} \tag{3.12}$$

The above system of equations (3.12) represents the dynamics of vaccination and treatment rate. The control variable  $u_1(t)$  measures the effectiveness of vaccination and  $u_2(t)$  is the effectiveness of treatment. The effectiveness of vaccination will depend on how early or late the vaccine will be administered. A finite time interval can be specified at which the vaccination and treatment will be performed.

We find the optimal values of  $u_1(t)$  and  $u_2(t)$  that maximize the efficiency of the vaccine and in turn minimize the cost of administration and the total number of infected population within Kenya. We note that the effectiveness of administering a vaccine is determined by how prompt it's administered relative to how suitable the season is for influenza outbreak. Additionally, the target group of choice could help cut costs, Bowman and Gumel [22]. After a positive diagnosis, therapy should begin immediately, since it's crucial to ensure the efficacy of therapy and the efficacy of drugs, ([23], [24], [25]).

Our control issue includes a model that minimizes the number of people with influenza and the cost of vaccines and controls of treatment,  $u_1(t)$  and  $u_2(t)$  respectively, subject to the system of equations (3.12).

Our objective function becomes:

$$J = \min_{u_1, u_2} \int_0^T [A_1S + A_2V + A_3I + B_1u_1^2 + B_2u_2^2]dt \quad (3.13)$$

where  $T$  is the end time and the coefficients  $A_1, A_2, A_3$  are the per capita loss due to presence of susceptible, vaccinated and infected individuals at any given time.  $B_1$  and  $B_2$  are the cost factors incurred in vaccinating the susceptible and treating the infected and it covers the requisite funds for care, hospitalization and the hours lost due to illness and thus the optimum regulation of  $u_1^*$  and  $u_2^*$  occurs using the findings of Lukes [26] such that:

$$J(u_1^*(t), u_2^*(t)) = \min J(u_1(t), u_2(t) | u_1(t), u_2(t) \in \mathbb{U}) \quad (3.14)$$

where  $\mathbb{U} = \{u_1(t), u_2(t) | u_1(t), u_2(t) \text{ is measurable on } [0,1], 0 \leq (u_1(t), u_2(t)) \leq 1, t \in [0, T] \}$  is the control set.

The necessary condition to satisfy an optimal question of control comes from the maximum theory of Pontryagin [27]. The theory transforms system equations (3.12) and (3.13) into a problem of minimizing point-wise, a Hamiltonian,  $H$  in relation to  $u_1(t)$  and  $u_2(t)$ .

The Lagrangian of problem (3.13) is given by;  $L = A_1S + A_2V + A_3I + B_1u_1^2 + B_2u_2^2$  from where we use the governing dynamics (3.12) to formulate the Hamiltonian to achieve optimal conditions.

$$\begin{aligned} H = & A_1S + A_2V + A_3I + B_1u_1^2 + B_2u_2^2 + \lambda_S(b - \beta SI - (u_1 + \delta)S) + \lambda_V(u_1S - \delta V \\ & - (1 - \sigma)\beta VI - rV) + \lambda_I(\beta SI + (1 - \sigma)\beta VI - (\delta + \mu + u_2)I) + \lambda_R(u_2I \\ & + rV - \delta R) \end{aligned} \quad (3.15)$$

where  $\lambda_S, \lambda_V, \lambda_I$  and  $\lambda_R$  are the associated adjoints for taking the necessary Hamiltonian (3.15) partial derivatives in respect of the corresponding state variable.

**Lemma 6.** *Given the optimal control  $u_1^*, u_2^*$  and the solutions  $S^*, V^*, I^*, R^*$  of the corresponding state system (3.12) which minimizes  $J(u_1, u_2)$  over  $\mathbb{U}$ , there are adjunct variables  $\lambda_S, \lambda_V, \lambda_I, \lambda_R$ , satisfying*

$$\frac{-d\lambda_i}{dt} = \frac{\partial H}{\partial i} \quad (3.16)$$

with transversity condition

$$\lambda_S(T) = \lambda_V(T) = \lambda_I(T) = \lambda_R(T) = 0 \quad (3.17)$$

*Proof.* Using the Maximization Theory of Pontryagin [27], the differential equations regulating the adjunct factors are obtained by differentiating the Hamiltonian function and determining the optimum control pair such that;

$$\begin{aligned} \frac{d\lambda_S}{dt} &= \frac{-\partial H}{\partial S}, \\ \frac{d\lambda_V}{dt} &= \frac{-\partial H}{\partial V}, \\ \frac{d\lambda_I}{dt} &= \frac{-\partial H}{\partial I}, \\ \frac{d\lambda_R}{dt} &= \frac{-\partial H}{\partial R}. \end{aligned} \quad (3.18)$$

We can write the Adjoint System as;

$$\begin{aligned} \frac{d\lambda_S}{dt} &= -A_1 + \lambda_S(\beta I + u_1 + \delta) - \lambda_V(u_1) - \lambda_I(\beta I), \\ \frac{d\lambda_V}{dt} &= -A_2 + \lambda_V(\delta + (1 - \sigma)\beta I + r) - \lambda_I((1 - \sigma)\beta I) - r\lambda_R, \\ \frac{d\lambda_I}{dt} &= -A_3 + \lambda_S(\beta S) + \lambda_V(1 - \sigma)\beta V - \lambda_I(\beta S + (1 - \sigma)\beta V - \delta - \mu - u_2) - u_2\lambda_R, \\ \frac{d\lambda_R}{dt} &= \delta\lambda_R. \end{aligned} \tag{3.19}$$

with transversality condition;

$$\lambda_S(T) = 0 \quad \lambda_V(T) = 0 \quad \lambda_I(T) = 0 \quad \lambda_R(T) = 0 \tag{3.20}$$

By considering the optimality conditions  $\frac{\partial H}{\partial u_1} = 0$  and  $\frac{\partial H}{\partial u_2} = 0$ . Solving  $u_1$  and  $u_2$  subject to the constrains we have:

$$\begin{aligned} \frac{\partial H}{\partial u_1} &= 2B_1u_1 - \lambda_S S + \lambda_V S = 2B_1u_1 - S(\lambda_S - \lambda_V) \\ \frac{\partial H}{\partial u_2} &= 2B_2u_2 - \lambda_I I + \lambda_R I = 2B_2u_2 - I(\lambda_I - \lambda_R) \end{aligned} \tag{3.21}$$

We establish (Lenhart and Workman [7]) that the optimal concern is minimal at  $u_1^*$  and  $u_2^*$  where  $u_1^* = \max\left\{0, \min\left\{\frac{S^*(\lambda_S^* - \lambda_V^*)}{2B_1}, 1\right\}\right\}$  and  $u_2^* = \max\left\{0, \min\left\{\frac{I^*(\lambda_I^* - \lambda_R^*)}{2B_2}, 1\right\}\right\}$  where  $S^*, V^*, I^*, R^*$  are the the optimal values of  $S, V, I, R$  respectively and  $\lambda_S^*, \lambda_V^*, \lambda_I^*, \lambda_R^*$  are the solutions of system (3.19) with conditions (3.20).  $\square$

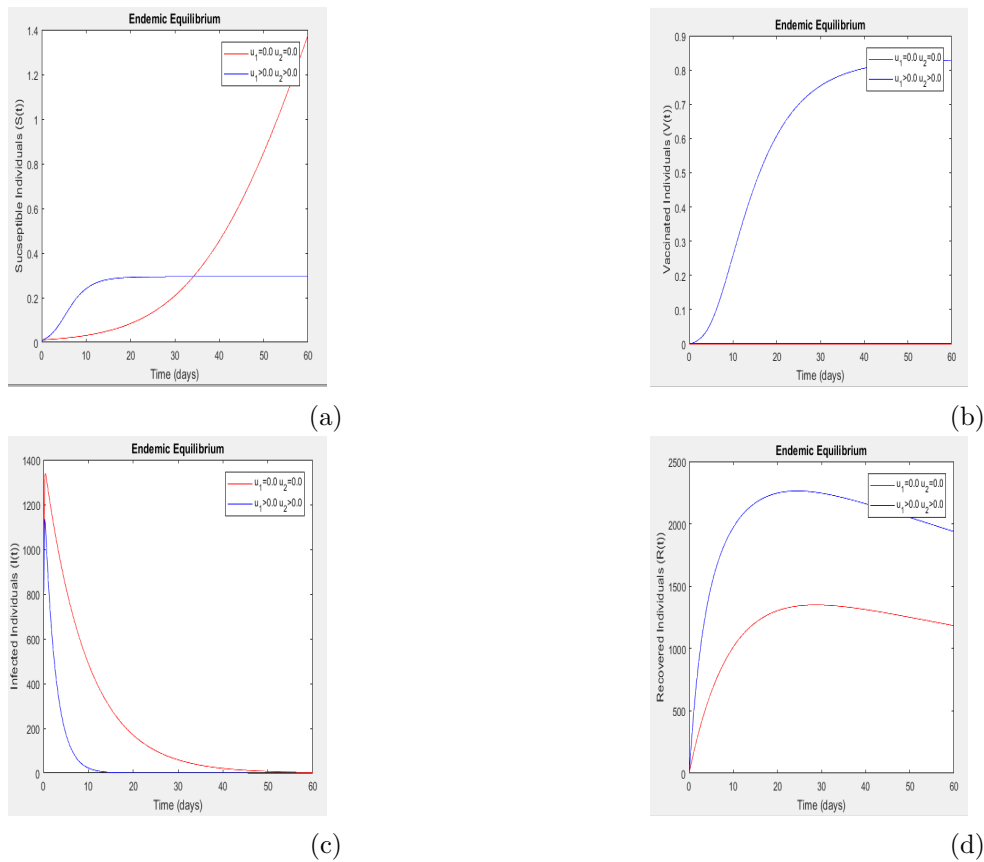
## 4 Numerical Simulation

Using MATLAB, we simulate the system of equations (3.12) to examine the role of optimal combination of vaccination and antiviral therapy in influenza control. Parameters used in our simulation are set out in Table 1 and the results displayed in Fig. 2.

**Table 1. Parameter values of the model**

Parameters	Values/day	Reference
b	0.09	Assumed
$\beta$	0.01	[28]
$\delta$	0.006	Assumed
$\mu$	0.1	[28]
$\gamma$	0.3 or 0.6 or 0.9	Assumed
$\sigma$	1 or 0	Assumed
r	0.1	[28]
$\omega$	0.3,0.6,0.9	Assumed

When optimal control is applied to our model, it is visible from Fig. (2a), without control, the susceptible population tends to increase but is controlled, the susceptible population increases slightly and remains constant. From Fig. 2(b), when control is applied to the population, the vaccinated population increases but, without control, there are no vaccinated individuals. From Fig. 2(c), the number of infected individuals is lower when there is control compared to when there is no control and from Fig. 2(d) the number of recovered individuals increases when control is applied to the population compared to when no control is imposed in the population. Generally, from Fig. 2 we observe that optimal controls due to vaccination and antiviral therapy are very efficient in controlling the disease.



**Fig. 2.** The impact of optimal combination of vaccination and antiviral therapy on (a) susceptible individuals, (b) vaccinated individuals, (c) infected individuals and (d) recovered individuals

## 5 Discussion and Conclusion

In this paper we have established an SVIR model with vaccination and antiviral therapy as control strategies to determine the optimal combination of implementing the two strategies. In our work we calculated the basic reproductive number  $R_0$ , using the next generation matrix, which enabled us to investigate the disease-free stability and endemic equilibrium points from which we proved that the disease-free equilibrium point is asymptotically stable locally and globally if  $R_0 < 1$  and the endemic point is stable locally and globally if  $R_0 > 1$ .

We also formulated an optimal control problem and then characterized the controls,  $u_1^*$  and  $u_2^*$ , using Pontryagin maximization principle. We also modified our optimal problem to compare a system with control and a system without control. Numerical simulations have shown the impact of optimal control on the four compartments and noted that application of optimal control has significant impact in reducing the number of infected individuals as compared to a system without control. The control functions  $u_1^*$  and  $u_2^*$ , associated with vaccination and antiviral therapy respectively, played an important role in reducing the number of infected individuals making it an assured strategy of controlling influenza disease in Kenya.

Further research on this work should focus on the effects of drug-resistant strains on the model, the recurrence of the model disease, the effect of age-dependent infection on the model as well as the effect of saturated incidence on the model.

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## Competing Interest

We declare that we do not have significant competing interests that may have affected the quality or delivery of the work mentioned in this manuscript.

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