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Modelling Influenza Dynamics with Drug Resistance Aspect

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Authors' contributions

This work was carried out in collaboration between the all authors. Author CWK designed the study, carried out the model analysis and wrote the first draft of the manuscript. Author MK managed the numerical simulation of the study and assisted to fine tune the model. Author LSL gave insightful comments on all sections of the draft manuscript. All authors read and approved the final manuscript.

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Abstract

Despite improvement in medical and public health standards, influenza continues to plague humankind causing high morbidity,mortality and socio-economic cost. Efforts to effectively combat the spread of influenza can be put in place if its dynamics are well understood. Numerous challenges have been faced in the event of controlling the spread and eradicating this contagious disease, a major impediment being the rise of drug resistance. In light of this, a deterministic model is formulated and used to analyze the transmission dynamics of influenza having incorporated the aspect of drug resistance. A system of differential equations that models

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the transmission dynamics of influenza is developed. The effective reproduction number (R_e) and the basic reproduction number (R_0) are calculated.For this model,there exists at least four equilibrium points. The stability of the disease free equilibrium point and endemic equilibrium point is analyzed. Results of the analysis show that there exists a locally stable disease free equilibrium point, E_0 when $R_e < 1$ and a unique endemic equilibrium E^*, when $R_e > 1$. Sensitivity analysis is carried out to determine parameters that should be targeted by intervention strategies. The effect of drug resistance and transmission rate of the resistant strain on the infected and the recovered is discussed.Results show that development of drug resistance and transmission of the resistant strain result in widespread of the resistant strain. A decrease in either of these two factors leads to a significant reduction in the number of infected individuals,hence, social distancing can be used as an intervention mechanism to curb the spread of the resistant strain.

Keywords: Effective reproduction number; drug resistance; stability.

2010 Mathematics Subject Classification: 53C25, 83C05, 57N16.

1 Introduction

Influenza also called flu is a contagious respiratory illness caused by influenza viruses. The viruses infect the nose, throat, and lungs. They usually are spread through the air when the infected people cough, sneeze or talk making the surrounding air and surfaces to be temporarily contaminated with infected droplets [1], [2]. A person gets infected when they inhale the infected droplets. A person might also get flu by touching the surface or object that has flu virus on it and then touching their own mouth, eyes or possibly their nose [2].

Influenza can be prevented by getting vaccination each year. However, given that the virus evolves rapidly, a vaccine made for one year may not be useful in the following year. According to [3] other preventive actions include staying away from people who are sick, covering coughs and sneezes and frequent hand washing.

Influenza has afflicted the human population for centuries. For instance,the 1918 influenza pandemic infected nearly one quarter of the world's population and resulted in the deaths of about 100 million people [4]. Studies show that this pandemic is specially responsible for the high morbidity and mortality among vulnerable groups such as children,the elderly and patients with underlying health conditions [5]. There is an outbreak of influenza every year around the world which results to about three to five million cases of severe illness and about 250,000 to 500,000 deaths [6]. According to [7], the mortality rates due to this respiratory disease are much higher in Africa than anywhere else in the world. Poor nutritional status, poor access to healthcare including vaccination and antibiotics and the presence of other, less measurable factors related to poverty in Africa may be additional risk factors for higher mortality rates. The death toll from the disease is unacceptably high given that influenza is preventable. Efforts to combat it must therefore be accelerated.

In view of the catastrophic effects of influenza globally, several models have been proposed and analyzed with the aim of shedding more light in the transmission dynamics of influenza,among them are; [8], [9], [10], [11], [12], [13], [14], [15]. Among the pioneer mathematical models to describe influenza dynamics is one developed by [12].

Drug resistance refers to reduction in the effectiveness of a drug in curing a disease. It occurs when microorganisms such as bacteria, viruses, fungi and parasites change in ways that render the medications used to cure the infections they cause ineffective [16], [17]. The microorganisms are therefore able to survive the treatment.

According to [18] epidemics with drug resistant strains and those with drug sensitive strains are fundamentally different in their growth and dynamics. Drug-sensitive epidemics are fuelled by only one process i.e. transmission, however, drug-resistant epidemics are fuelled by two processes: transmission and the conversion of treated drug sensitive infections to drug-resistant infections (acquired resistance). Therefore the rate of increase in drug-resistant infections can be much faster than the rate of increase in drug-sensitive infections. Studies from [19] show that drug resistance is a function of time and treatment rate.With the development of drug resistant influenza viruses, various models have also been formulated in order to understand this phenomena better. Among them are [20], [21], [22], [23], [24].

In this paper, a mathematical model that illustrates the transmission dynamics of a wild type influenza virus and the development and transmission of drug resistant influenza virus is formulated and analyzed.

2 Model Description and Formulation

The model subdivides the total population into five compartments; Susceptible(S), Vaccinated(V), Infected with Wild type strain(I_w), Infected with Resistant strain(I_R) and Recovered(RC). Individuals in a given compartment are assumed to have similar characteristics. Parameters vary from compartment to compartment but are identical for all individuals in a given compartment. Individuals enter the population at the rate of π,all recruited individuals are assumed to be susceptible. The susceptible get infected after effective contact with either the Infected with wild type strain or the Infected with resistant strain.The force of infection is given by either $\lambda_1 = \beta_w I_w$ or $\lambda_2 = \beta_r I_R$.(λ_1 is the force of infection of the wild type strain while λ_2 is the force of infection of the resistant strain).β_w and β_r refer to the transmission rate of wild type strain and resistant strain respectively. The susceptible can only be infected by one strain at a time. While in the population, the susceptible get vaccinated at the rate of ϕ.The vaccinated can however become infected with either the wild type strain or the resistant strain. This depends on the vaccine efficacy. When the vaccine efficacy is 100 percent,the vaccinated cannot become infected.Individuals who are infected with the wild type strain are treated and recover at the rate of α while those who are infected with the resistant strain recover at the rate of α_r. The wild type strain is assumed to mutate to resistant strain and hence those infected with the wild type join those infected with the resistant strain at the rate of b.Individuals with wild type strain and those with resistant strain suffer disease induced death at the rates a_w and a_r, respectively. The recovered lose immunity at the rate of ϑ and join the susceptible class. Individuals in all the epidemiological compartments suffer natural death at the rate of μ.

The model considered in this study is illustrated by the population flow diagram in Fig. 1 and the associated system of differential equations (1)-(5).

Model Equations

From Fig. 1, we deduce the model equations;

$$\frac{dS}{dt} = \pi + \vartheta RC - (\phi + \mu + \lambda_1 + \lambda_2)S(t) \tag{1}$$

$$\frac{dV}{dt} = \phi S(t) - ((1-\epsilon)\lambda_1 + (1-\epsilon)\lambda_2 + \mu)V(t) \tag{2}$$

$$\frac{dI_w}{dt} = \lambda_1 S(t) + (1-\epsilon)\lambda_1 V(t) - (b + \mu + a_w + \alpha)I_w(t) \tag{3}$$

$$\frac{dI_R}{dt} = \lambda_2 S(t) + (1-\epsilon)\lambda_2 V(t) + bI_w - (\mu + \alpha_r + a_r)I_R(t) \tag{4}$$

$$\frac{dRC}{dt} = \alpha I_w(t) + \alpha_r I_R(t) - (\vartheta + \mu)RC(t) \tag{5}$$

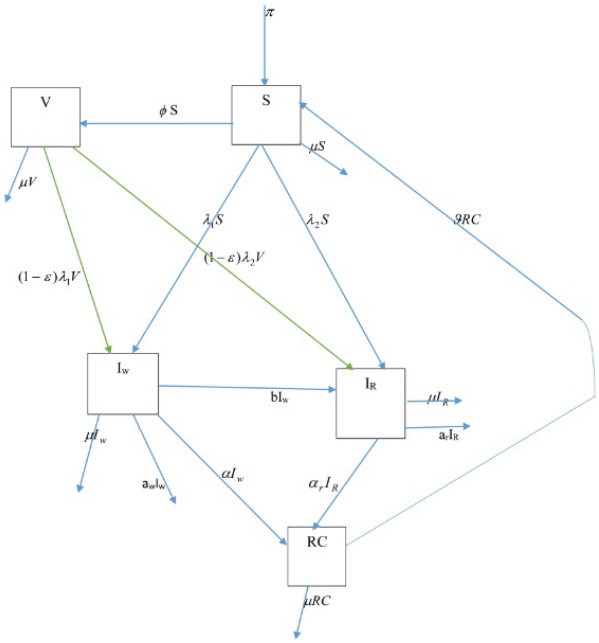

Fig. 1. Flow diagram showing population flows between different compartments

Table 1 gives the description of the various parameters used in the model along with reasonable estimates of their values.

Table 1. Description and values of Parameters used

Parameter Symbol	Description	Value	Reference.
$\frac{1}{\mu}$	Average human lifespan	$70 * 365$ days	estimated.
π	Recruitment rate	$1000/70 * 365$	estimated.
ϵ	vaccine efficacy	0.6	[25]
ϕ	Vaccination rate	0.00109589	[26]
β_1	Transmission rate of wild type strain	0.0008	estimated
β_2	Transmission rate of resistant strain	0.0006	estimated
b	Rate of developing drug resistance	0.04	estimated.
α	Recovery rate for individuals in I_w class	0.1428	[2].
α_r	Recovery rate for individuals in I_R class	0.0714	estimated
ϑ	Rate of losing immunity	0.00833	[27].
a_w	Death rate due to infection with wild type virus	0.01	[13].
a_r	Death rate due to infection with resistant virus	0.01	estimated

3 Model Analysis

In this section, essential properties of the model system (1)-(5) are derived.

3.1 Positivity of the solutions

Theorem 1: *The state variables of the model system (1)-(5) are non-negative and solutions remain positive for all time $t \geq 0$ provided that the initial conditions are non-negative.*

Proof
Let $\{S(t), V(t), I_w(t), I_R(t), RC(t)\}$ be any solutions of the system for all $t \geq 0$ with non-negative initial conditions $\{S(0) \geq 0, V(0) \geq 0, I_w(0) \geq 0, I_R(0) \geq 0, RC(0) \geq 0\}$. Considering equation(1), it follows that

$$\frac{dS(t)}{dt} \geq -(\phi + \mu + \lambda_1 + \lambda_2)S(t)$$

Using separation of variables to integrate yields;
$lnS \geq -(\phi + \mu + \lambda_1 + \lambda_2)t + C$, where C is the constant of integration.
$S(t) \geq S_0 e^{-(\phi+\mu+\lambda_1+\lambda_2)t} \geq 0$, hence $S(t) \geq 0$
Considering equation (2),

$$\frac{dV}{dt} \geq ((1-\epsilon)\lambda_1 + (1-\epsilon)\lambda_2 + \mu)V$$

$$\int \frac{dV}{V} \geq \int ((1-\epsilon)\lambda_1 + (1-\epsilon)\lambda_2 + \mu)dt$$

$$V(t) \geq V_0 e^{((1-\epsilon)\lambda_1+(1-\epsilon)\lambda_2+\mu)t} \geq 0$$

Hence,$V(t) \geq 0$,
The positivity of $V(t), I_w(t), I_R(t), RC(t)$ is proved along the same lines to yield;
$I_w(t) \geq I_{w0} e^{-(b+\alpha+a_w+\mu)t} \geq 0$,
$I_R(t) \geq I_{R0} e^{-(\alpha_r+a_r+\mu)t} \geq 0$,
$RC(t) \geq RC_0 e^{-(\vartheta+\mu)t} \geq 0$.
The solutions to the model remain positive given positive initial conditions. This shows that the model is biologically relevant.

3.2 Boundedness of the solutions

Theorem 2: *The solutions of the system are bounded in a region Q given by;*
$Q = \{S(t), V(t), I_w(t), I_R(t), RC(t) \epsilon R_+^5 : N(t) \leq \frac{\pi}{\mu}\}$ *for all time* $t \geq 0$.
Proof
The total population $N(t) = S(t) + V(t) + I_w(t) + I_R(t) + RC(t)$.

$$\frac{dN(t)}{dt} = \frac{dS(t)}{dt} + \frac{dV(t)}{dt} + \frac{dI_w(t)}{dt} + \frac{dI_R(t)}{dt} + \frac{dT(t)}{dt} + \frac{dR(t)}{dt}$$

$$\frac{dN(t)}{dt} = \pi - \mu N - a_w I_w - a_r I_R$$

In the absence of influenza infection, it follows that, $\frac{dN(t)}{dt} \leq \pi - \mu N$

$$\frac{dN(t)}{dt} + \mu N \leq \pi$$

Using integrating factor: $e^{\int \mu dt}$ yields;
$Ne^{\mu t} \leq \frac{\pi e^{\mu t}}{\mu} + C$, where C is a constant of integration.
Dividing through by $e^{\mu t}$ yields,
$N(t) \leq \frac{\pi}{\mu} + Ce^{-\mu t}$,at $t = 0, C = N_0 - \frac{\pi}{\mu}$,hence
$N(t) \leq N_0 e^{-\mu t} + \frac{\pi}{\mu}(1 - e^{-\mu t})$,where N_0 is the initial population size. Therefore,
$N(t) \leq \frac{\pi}{\mu}$ for $N_0 \leq \frac{\pi}{\mu}$ or
$N(t) \leq N_0$ for $N_0 \geq \frac{\pi}{\mu}$
Thus, $N(t) \leq max\{N_0, \frac{\pi}{\mu}\}$,therefore bounded above.

4 Equilibrium Points and Stability Analysis

At the equilibrium points the populations are unchanging and hence the rate of change for each population is zero. With this model,it can be shown that there exists four equilibria:-

- When both influenza strains are extinct from the population (E_0)
- When the resistant strain is extinct but the wild type persists(E_1)
- When the wild type is extinct but the resistant strain persists(E_2)
- When both strains persists (EE)

The equilibrium points are analyzed in order to understand what behavior is predicted by the differential equations in the neighbourhood of the points.

Since the model system is nonlinear, Jacobian linearization and the Hartman-Grobman Theorem will be used to unify the local behavior of the linear and nonlinear systems, [28].According to Hartman-Grobman Theorem,the asymptotic behavior of a non-linear system in the neighbourhood of an equilibrium point is equivalent to that of the linear system near this equilibrium point [29].

4.1 Disease Free Equilibrium point (DFE)

To obtain the DFE of the model system (1)-(5),the derivatives with respect to time are set to zero.DFE describes the model in the absence of disease or infection, hence all the infectious classes(I_w and I_R) and the recovered class (RC) are also set to zero. This yields;

$$\pi - (\phi + \mu)S^0 = 0 \tag{6}$$

$$\phi S^0 - \mu V^0 = 0 \tag{7}$$

Using equation (6), S^0 is obtained as $S^0 = \frac{\pi}{\phi+\mu}$. Substituting S^0 in equation (7), V^0 is obtained as $V^0 = \frac{\phi\pi}{\mu(\phi+\mu)}$.
The DFE point of the system is hence given by;

$$E_0 = \left(S^0, V^0, I_w^0, I_R^0, RC^0\right) = \left(\frac{\pi}{\phi+\mu}, \frac{\phi\pi}{\mu(\phi+\mu)}, 0, 0, 0\right)$$

The DFE point of the model system (1)-(5), indicates that in the absence of influenza, the system will consist of only two compartments, the susceptible and the vaccinated. If E_0 is stable, both strains, i.e the wild type strain and the resistant strain will vanish.

The stability of each equilibrium point depends on the threshold parameter that governs the spread of the disease,in the case of this model; the effective reproduction number.Theorems that demonstrate the relationship between the effective reproduction number and the local asymptotic stability of equilibria are proved. These results imply that it is possible to examine the value of this threshold parameter and determine whether the disease persists or the disease dies out as $t \to \infty$.

4.1.1 Threshold for disease spread

A major concern regarding any infectious disease is its ability to invade the population. It is hence paramount to obtain the threshold parameter which determines whether the disease will persist or die out. This is one of the most important parameters in epidemiology and is known as the basic reproduction number(R_0).This quantity gives the average number of secondary infections generated when one infected individual is introduced in a fully susceptible population [30]. If $R_0 < 1$,on average an infected individual produces less than one new infected individual in the course of the infectious period and hence the disease dies out of the population. However, if $R_0 > 1$, each

infected individual produces,on average, more than one new infection and spread of the disease is possible [31]. In the case of this model, the effective reproduction number (R_e) is calculated since the population consists of both the susceptibles and non susceptible(the vaccinated).The effective reproduction number may be calculated the same way as the basic reproduction number is calculated using the next generation matrix approach as illustrated in [31] . Using the model system (1)-(5),the effective reproduction number is obtained as shown in the following subsection.

4.1.2 Effective reproduction number

From the model, the infected compartments are I_w and I_R. Using the notation f for the new infections and v for the transition terms, the following matrices are obtained;

$$f = \begin{bmatrix} \lambda_1 S(t) + (1-\epsilon)\lambda_1 V(t) \\ \lambda_2 S(t) + (1-\epsilon)\lambda_2 V(t) \end{bmatrix}, \qquad v = \begin{bmatrix} K_1 I_w(t) \\ K_2 I_R(t) - bI(t) \end{bmatrix}$$

where $\lambda_1 = \beta_w I_w, \quad \lambda_2 = \beta_r I_R, \quad K_1 = \alpha + b + a_w + \mu$ and $K_2 = \alpha_r + a_r + \mu$.
The partial derivatives of f with respect to the infected classes, evaluated at E_0 is denoted by F and obtained as;

$$F = \begin{bmatrix} \beta_w S^0 + (1-\epsilon)\beta_w V^0 & 0 \\ 0 & \beta_r S^0 + (1-\epsilon)\beta_r V^0 \end{bmatrix}$$

Next, the partial derivative of v with respect to the infected classes,evaluated at E_0, is obtained and denoted by V given as;

$$V = \begin{bmatrix} K_1 & 0 \\ -b & K_2 \end{bmatrix}$$

The inverse of V is computed and obtained as;

$$V^{-1} = \begin{bmatrix} \frac{1}{K_1} & 0 \\ \frac{b}{K_1 K_2} & \frac{1}{K_2} \end{bmatrix}$$

Multiplying matrices F and V^{-1} yields;

$$FV^{-1} = \begin{bmatrix} \beta_w S^0 + (1-\epsilon)\beta_w V & 0 \\ \frac{\beta_r S^0 + (1-\epsilon)\beta_r V b}{K_1 K_2} & \frac{\beta_r S^0 + (1-\epsilon)\beta_r V}{K_2} \end{bmatrix}$$

The effective reproduction number is given by the spectral radius of FV^{-1}. The eigenvalues of the matrix FV^{-1} are $\frac{\beta_w S^0 + (1-\epsilon)\beta_w V^0}{K_1}$ and $\frac{\beta_r S^0 + (1-\epsilon)\beta_r V^0}{K_2}$. Therefore the effective reproduction number is given by;

$$R_e = max\{\frac{\beta_w S^0 + (1-\epsilon)\beta_w V^0}{K_1}, \frac{\beta_r S^0 + (1-\epsilon)\beta_r V^0}{K_2}\}$$

Substituting S^0,V^0,K_1 and K_2 gives;

$$R_e = max\{\frac{\beta_w \pi(\mu + \phi(1-\epsilon))}{\mu(\phi+\mu)(a+b+a_w+\mu)}, \frac{\beta_r \pi(\mu + (1-\epsilon)\phi)}{\mu(\phi+\mu)(\alpha_r + a_r + \mu)}\}$$

Denoting $R_{ew} = \frac{\beta_w \pi(\mu+\phi(1-\epsilon))}{\mu(\phi+\mu)(a+b+a_w+\mu)}$ and $R_{er} = \frac{\beta_r \pi(\mu+(1-\epsilon)\phi)}{\mu(\phi+\mu)(\alpha_r+a_r+\mu)}$, it follows that $R_e = max\{R_{ew}, R_{er}\}$. R_{ew} is a measure of the average number of secondary wild type influenza infections caused by a single infected individual introduced into the model population. Similarly,R_{er}, gives the average number of secondary resistant-influenza infections caused by one infected individual introduced into the model population.

The basic reproduction number can then be obtained from the effective reproduction number already calculated. This is done by setting the vaccination rate ϕ to zero. Thus the basic reproduction number R_0 is given by:

$$R_0 = max\{\frac{\beta_w \pi \mu}{\mu^2(\alpha + b + a_w + \mu)}, \frac{\beta_r \pi \mu}{\mu^2(\alpha_r + a_r + \mu)}\}.$$

4.1.3 Effect of vaccination on basic reproduction number

Fig. 2 illustrates the effect of vaccination on the basic reproduction number.

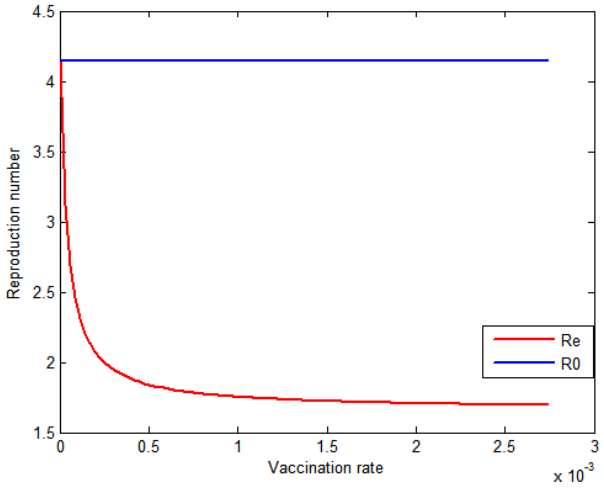

Fig. 2. Effect of vaccination on R0

It can be observed that vaccination reduces the basic reproduction number. This implies that vaccination should be put into consideration in order to control the spread of influenza.

A necessary condition for the establishment of a given strain is that its reproduction number should be greater than one [32]. In this model, there is no cross immunity. The wild type influenza strain and the resistant influenza strain compete for susceptible individuals. Fig. 3 depicts the outcome of this competition.

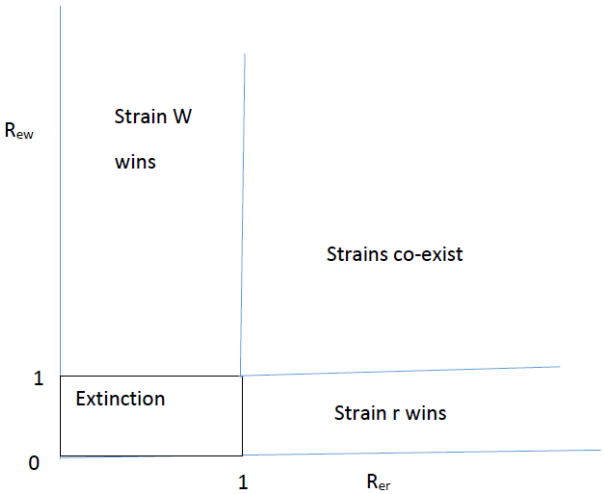

Fig. 3. Outcome of competition between the two strains with no cross immunity

4.2 Existence of endemic equilibruim (E_1)

There exists an endemic state when the resistant strain dies out but the wild type strain persists.
Theorem 3: *For $R_{ew} > 1$ a unique endemic equilibrium E_1 exists.*
Proof
To obtain the steady state E_1 of the model system (1)-(5), the derivatives with respect to time are set to zero. In this case, the infectious class (I_w) and the recovered class (RC) are not set to zero. This yields:

$$S^* = \frac{\pi\vartheta + \pi\mu + \vartheta\alpha I_w^*}{\phi + \mu + \beta_w I_w^*}$$

$$V^* = \frac{\phi(\pi\vartheta + \pi\mu + \vartheta\alpha I_w^*)}{((1-\epsilon)\beta_w I_w^* + \mu)(\phi + \mu + \beta_w I_w^*)}$$

$$I_w^* = \frac{\beta_w I_w^* S^* + (1-\epsilon)\beta_w I_w^* V^*}{b + \mu + a_w + \alpha}$$

$$RC^* = \frac{\alpha I_w^*}{\vartheta + \mu}$$

The wild type influenza strain endemic equilibrium satisfies the following polynomial.

$$P(I_w^*) = I_w^*(AI_w^{*2} + BI_w^* + C) = 0$$

Either $I_w^* = 0$, corresponding to the disease free equilibrium, or the roots of the quadratic $AI_w^{*2} + BI_w^* + C = 0$, give the endemic equilibrium,where;

$$A = \beta_w^2\vartheta\alpha((1-\epsilon) + \mu(1-\epsilon) + \phi(1-\epsilon)),$$

$$B = \beta_w^2\pi((1-\epsilon)(\vartheta + \vartheta\mu + \mu + \phi\mu + \phi\vartheta + \mu^2)) + \beta_w\vartheta\alpha((1-\epsilon)(2\mu\phi + \mu^2 + \phi^2)),$$

$$C = \mu(\phi+\mu)(\phi+\mu)(b+\mu+a_w+\alpha)[\beta_w\pi\mu^2((1-\epsilon)(2\phi+\mu) - \vartheta\epsilon) + \beta_w\pi\mu(\phi((1-\epsilon)+\vartheta\epsilon)) + \vartheta(1-R_{ew})]$$

All the variables are positive and ϵ is the vacccine efficacy where $0 < \epsilon < 1$. The existence of endemic equilibria is determined by the presence of positive real solutions of the quadratic equation $AI_w^{*2} + BI_w^* + C$.For positive real roots,$B^2 > 4AC$. $A > 0$ and for $R_{ew} > 1$,$C = \mu(\phi+\mu)(\phi+\mu)(b+\mu+a_w+\alpha)[\beta_w\pi\mu^2((1-\epsilon)(2\phi+\mu) - \vartheta\epsilon) + \beta_w\pi\mu(\phi((1-\epsilon)+\vartheta\epsilon)) + \vartheta(1-R_{ew})] < 0$, hence there exists at least one positive root.This implies that the system has a unique endemic equilibrium E_1.

4.3 Existence of endemic equilibrium (E_2)

There exists an endemic state when the wild type strain dies out but the resistant strain persists.
Theorem 4: *For $R_{er} > 1$ a unique endemic equilibrium E_2 exists.*

Proof To obtain the steady state E_2 of the model system (1)-(5), the derivatives with respect to time are set to zero. In this case, the infectious class (I_R) and the recovered class (RC) are not set to zero. This yields:

$$S^* = \frac{\pi + \vartheta RC^*}{\phi + \mu + \beta_r I_R^*}$$

$$V^* = \frac{\phi(\pi\vartheta + \pi\mu + \vartheta\alpha_r I_R^*)}{((1-\epsilon)\beta_r I_R^* + \mu)(\phi + \mu + \beta_r I_R^*)}$$

$$I_R^* = \frac{\beta_r I_R^* S^* + (1-\epsilon)\beta_r I_R^* V^*}{\mu + a_r + \alpha_r}$$

$$RC^* = \frac{\alpha_r I_R^*}{\vartheta + \mu}$$

The resistant influenza strain endemic equilibrium satisfies the following polynomial.

$$q(I_R^*) = I_R^*(G_1 I_R^{*2} + G_2 I_R^* + G_3) = 0$$

$I_R^* = 0$, corresponds to the disease free equilibrium.The roots of the quadratic $G_1 I_R^{*2} + G_2 I_R^* + G_3 = 0$, give the endemic equilibrium,where;

$$G_1 = \beta_r^2 \vartheta \alpha_r((1-\epsilon) + \mu(1-\epsilon) + \phi(1-\epsilon)),$$

$$G_2 = \beta_r^2 \pi((1-\epsilon)(\vartheta + \vartheta\mu + \mu + \phi\mu + \phi\vartheta + \mu^2)) + \beta_r \vartheta \alpha_r((1-\epsilon)(2\mu\phi + \mu^2 + \phi^2)),$$

$$G_3 = (a_r\mu + a_r\phi + \mu^2 + \mu\phi + \mu\alpha_r + \phi\alpha_r)[\beta_r \pi \mu^2((1-\epsilon)(2\phi+\mu) - \vartheta\epsilon) + \beta_r \pi \mu(\phi((1-\epsilon) + \vartheta\epsilon)) + \vartheta(1-R_{er})]\mu(\mu+\phi)$$

For positive real solutions in the quadratic equation $G_1 I_R^{*2} + G_2 I_R^* + G_3 = 0$, $G_2^2 > 4G_1G_3$. $G_1 > 0$ and for $R_{er} > 1$,$G_3 < 0$,this shows that there exists at least one positive root;implying that the system has a unique endemic equilibrium E_2.

4.4 Local stability analysis of the disease free equilibrium point

The local stability of the DFE is established using Jacobian of the model evaluated at E_0. The stability of this equilibrium point, is then determined based on the sign of the real part of the eigenvalues of the corresponding Jacobian.

Theorem 5: *The disease free equilibrium point* (E_0) *of the system of differential equations(1)-(5) is locally asymptotically stable whenever* $R_{ew} < 1$ *and* $R_{er} < 1$.*That is whenever* $R_e < 1$ *since* $R_e = max\{R_{ew}, R_{er}\}$

Proof

The Jacobian matrix evaluated at E_0 is obtained as;

$$J(E^0) = \begin{bmatrix} -\phi-\mu & 0 & -\beta_w S^0 & -\beta_r S^0 & \vartheta \\ \phi & -\mu & -(1-\epsilon)\beta_w V^0 & -(1-\epsilon)\beta_r V^0 & 0 \\ 0 & 0 & \beta_w S^0 + (1-\epsilon)\beta_w V^0 - K1 & 0 & 0 \\ 0 & 0 & b & \beta_r S^0 + (1-\epsilon)\beta_r V^0 - K2 & 0 \\ 0 & 0 & \alpha & \alpha_r & -\vartheta-\mu \end{bmatrix}$$

where $K1 = \alpha + b + a_w + \mu$ and $K2 = \alpha_r + a_r + \mu$,

The following eigenvalues are obtained:

$$\lambda_1 = -\mu,$$

$$\lambda_2 = -\phi - \mu,$$

$$\lambda_3 = -\vartheta - \mu,$$

$$\lambda_4 = \beta_w(S^0 + (1-\epsilon)V^0) - K1,$$

$$\lambda_5 = \beta_r(S^0 + (1-\epsilon)V^0) - K2.$$

$\lambda_1, \lambda_2, \lambda_3$ have negative real part,the condition necessary and sufficient for λ_4 and $\lambda_5$is;

$$\lambda_4 : \quad \beta_w(S^0 + (1-\epsilon)V^0) - K1 < 0$$

$$\beta_w(S^0 + (1-\epsilon)V^0) < K1$$

$$\frac{\beta_w(S^0 + (1-\epsilon)V^0)}{K1} < 1$$

That is,

$$R_{ew} < 1$$

Similarly from λ_5, it can be shown that;

$$\frac{\beta_r(S^0 + (1-\epsilon)V^0)}{K2} < 1$$

That is,

$$R_{er} < 1$$

Under the condition that all the eigenvalues have negative real part, then E_0 is locally asymptotically stable, otherwise it is unstable.

4.5 Local stability analysis of the endemic equilibrium

Theorem 6: *For $R_{ew} > 1$ and $R_{er} > 1$ there exists an Endemic Equilibrium (EE) of the model system which is locally asymptotically stable.*

The system (1)-(5) is linearized about EE and the characteristic polynomial examined. The Jacobian matrix at the Endemic Equilibrium is as follows:-

$$J(EE) = \begin{bmatrix} -\phi - \mu - \bar{\lambda_1} - \bar{\lambda_2} & 0 & 0 & 0 & \vartheta \\ \phi & -\mu - (1-\epsilon)\bar{\lambda_1} - (1-\epsilon)\bar{\lambda_2} & 0 & 0 & 0 \\ \bar{\lambda_1} & (1-\epsilon)\bar{\lambda_1} & -K1 & 0 & 0 \\ \bar{\lambda_2} & (1-\epsilon)\bar{\lambda_2} & b & -K2 & 0 \\ 0 & 0 & \alpha & \alpha_r & -\vartheta - \mu \end{bmatrix}$$

where $K1 = \alpha + b + a_w + \mu$ and $K2 = \alpha_r + a_r + \mu$. $\bar{\lambda_1}$ and $\bar{\lambda_2}$ is the force of infection of the wild type strain and resistant strain respectively,at the endemic equilibrium.

The characteristic polynomial obtained is;

$$P_5(\lambda) = \lambda^5 + a_1\lambda^4 + a_2\lambda^3 + a_3\lambda^2 + a_4\lambda + a_5$$

where;

$$\begin{aligned} a_1 &= \mu + \vartheta + K1 + K2 + J2 + J1, \\ a_2 &= J1J2 + K1 + K2 + \mu + \vartheta(J1 + J2) + K1K2 + K1\mu + K1\vartheta + K2\mu + K2\vartheta, \\ a_3 &= J1J2(K1 + K2 + \mu + \vartheta) + MJ1 + MJ2 - \bar{\lambda_1}\alpha\vartheta - J3\alpha_r\vartheta + K1K2\mu + K1K2\vartheta, \\ a_4 &= MJ1J2 + J1(K1K2\mu + K1K2\vartheta) + J2(K1K2\mu + K1K2\vartheta - J3\alpha_r\vartheta - \bar{\lambda_1}\alpha\vartheta) \\ &\quad -\bar{\lambda_1}K2\alpha\vartheta - \bar{\lambda_1}b\alpha_r\vartheta - \bar{\lambda_2}\alpha\phi\vartheta - J3K1\alpha_r\vartheta - J4\phi\alpha_r\vartheta, \\ a_5 &= K2K1J2J1\mu + K1K2J2J1\vartheta - \bar{\lambda_1}J2K2\alpha\vartheta - \bar{\lambda_1}J2b\alpha_r\vartheta - J2J3K1\alpha_r\vartheta \\ &\quad -\bar{\lambda_2}K2\alpha\phi\vartheta - \bar{\lambda_2}b\phi\alpha_r\vartheta - J4K1\phi\alpha_r\vartheta. \end{aligned}$$

and;

$$\begin{aligned} K1 &= \alpha + b + a_w + \mu, \qquad K2 = \alpha_r + a_r + \mu \\ J1 &= \phi + \mu + \bar{\lambda_1} + \bar{\lambda_2}, \qquad J2 = (1-\epsilon)\bar{\lambda_1} + (1-\epsilon)\bar{\lambda_2} + \mu \\ J3 &= (1-\epsilon)\bar{\lambda_1}, \qquad J4 = (1-\epsilon)\bar{\lambda_2} \\ M &= K1K2 + K1\mu + K1\vartheta + K2\mu + K2\vartheta \end{aligned}$$

Using Routh-Hurwitz criterion, the following matrix is obtained;

$$\begin{bmatrix} 1 & a_2 & a_4 & 0 & \lambda^5 \\ a_1 & a_3 & a_5 & 0 & \lambda^4 \\ a_2 - \frac{a_3}{a_1} & a_4 - \frac{a_5}{a_1} & 0 & 0 & \lambda^3 \\ a_3 - \frac{a_4 - a_5}{a_2 - \frac{a_3}{a_1}} & a_5 & 0 & 0 & \lambda^2 \\ a_4 - \frac{a_5}{a_1} - a_5\left(\frac{(b_1)^2}{a_3(a_4 - a_5)}\right) & 0 & 0 & 0 & \lambda \\ a_5 & 0 & 0 & 0 & 1 \end{bmatrix} \tag{8}$$

where $b_1 = a_2 - \frac{a_3}{a_1}$. According to Routh-Hurwitz criterion [33], [34], for $R_{ew} > 1$ and $R_{er} > 1$, the endemic equilibrium is locally asymptotically stable if $a_1, a_2, a_3, a_4, a_5 > 0$ and all the elements of the first column of matrix (8) are positive,i.e, $a_1 > 0$, $a_2 - \frac{a_3}{a_1} > 0$, $a_3 - \frac{a_4 - a_5}{a_2 - \frac{a_3}{a_1}} > 0$,$a_4 - \frac{a_5}{a_1} - a_5\left(\frac{(b_1)^2}{a_3(a_4 - a_5)}\right)$ and $a_5 > 0$. This implies that all the eigenvalues of $J(EE)$ have negative real parts.

5 Sensitivity Analysis

The sensitivity analysis of the reproduction number R_e is used to quantify the relative importance of the different parameters to disease control. It is used to discover the parameters that have a high impact on R_e and should be targeted by intervention strategies [35]. Sensitivity indices of the model reproduction number to the parameters in the model are calculated. The normalized sensitivity index which measures the relative change in a parameter k, with respect to the reproduction number R_e is given by $P_q = \frac{k}{R_e}\frac{\partial R_e}{\partial k}$.The sign of P_q determines the direction of changes,increasing (for positiveP_q) and decreasing (for negativeP_q) [36]. Table 2 gives the sensitivity indices obtained using the parameter values given in Table 1.

Table 3. Sensitivity Indices of R_{ew} and R_{er}

Parameter Symbol	Description	Sensitivity Index
β_w	transmission rate of wild type	1
β_r	transmission rate of resistant strain	1
π	Recruitment rate	1
ϕ	Vaccination rate	-0.9408538762
α_r	Recovery rate for resistant strain	-0.8767287461
α	Recovery rate for wild type strain	-0.7405137236
b	Development of drug resistance rate**	-0.2074268133
a_r	Death rate due to infection with resistant strain	-0.1227911409
aw	Death rate due to infection with wild type strain	-0.05185670333
μ	Natural death rate	-0.03421955424
ϵ	vaccine efficacy	-0.01884699679

The parameters are ordered from the most sensitive to the least .It can be observed that the most sensitive parameters are transmission rates and recruitment rate. A positive sensitivity index indicates that R_e is an increasing function of the corresponding parameter and hence an increase in the parameter while other factors are held constant leads to disease spread [36]. On the other hand, a negative sensitivity index shows that an increase in the parameter while other factors are held constant leads to disease control.

6 Numerical Simulation

In this section simulations of the model system (1)-(5) are carried out using parameter values in Table 1.

Simulation of model population depicted by system (1)-(5)

Fig. 4 shows the relationship between susceptible, Infected with wild type strain,infected with resistant strain and the recovered.

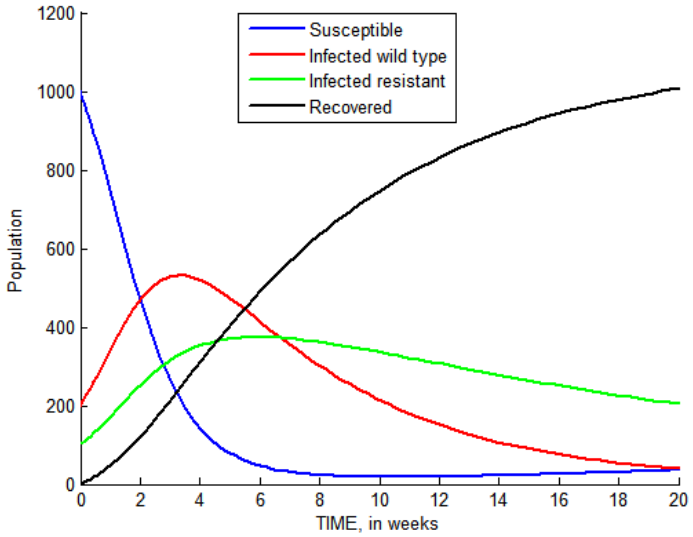

Fig. 4. Model population of system (1)-(5)

It can be observed that in the first about three weeks,there is a sharp decrease in the susceptible and a sharp increase in those infected with wild type strain and those infected with resistant strain.The sharp increase in the infected could be attributed to the fact that influenza is highly contagious.The recovered gradually increases from zero. From week four,the infected decreases as the recovered increase. This decrease in the infected could be as a result of disease induced deaths and recovery.

6.1 Effect of drug resistance and transmission rate of the resistant strain

A major challenge in controlling the spread of diseases is the development of drug resistance. The challenge becomes even harder in case the drug resistant virus can be transmitted. This section focuses on the effect of drug resistance and transmission rate of the resistant virus on individuals infected with the resistant virus and on the recovered individuals.

6.1.1 Resistant strain is not transmissible while rate of developing drug resistance is varied

The rate of developing drug resistance b, is varied while the rate of transmitting the resistant virus is set as zero and all the other factors are held constant.

Fig. 5 shows that when there is no development of drug resistance and the resistant strain is not being transmitted, the number of infected individuals decrease gradually to zero. An increase in b leads to a sharp increase in the number of infected individuals followed by a gradual decrease. The decrease could be attributed to disease induced deaths and recovery. From Fig. 6, it can be observed that the number of recovered individuals decrease with increase in b.

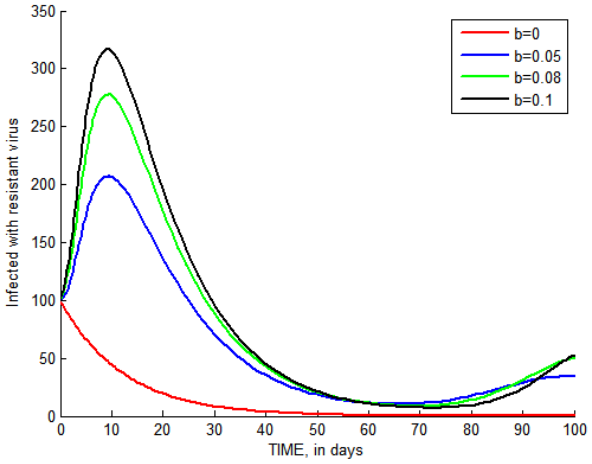

Fig. 5. Infected with resistant strain

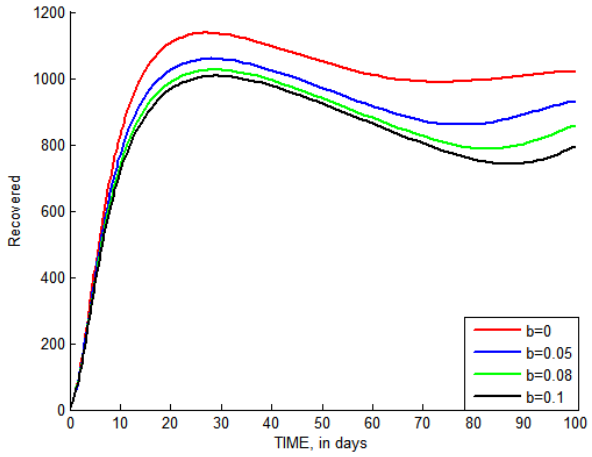

Fig. 6. Recovered individuals

6.1.2 Resistant strain is transmissible and rate of developing drug resistance is varied

The resistant strain is assumed to be transmitted at a rate lower than that of transmitting the wild type strain, b is varied and all the other factors are held constant.

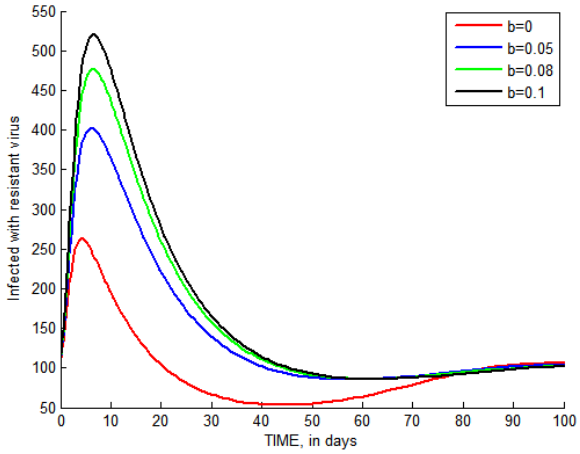

Fig. 7. Infected with resistant strain

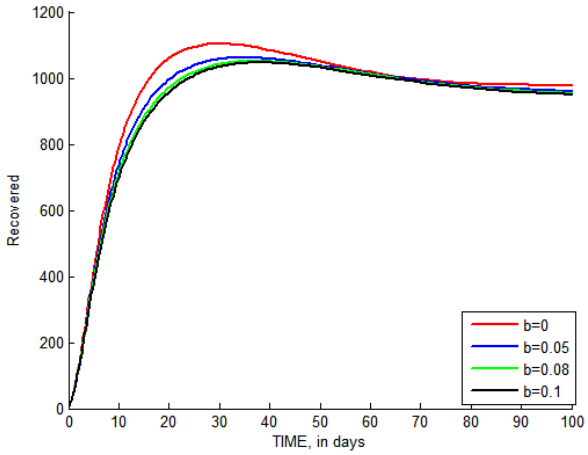

Fig. 8. Recovered individuals

Fig. 7 shows that when the resistant strain is being transmitted and there is no development of drug resistant, there is an initial sharp increase in the number of the infected followed by a drastic decrease to about fifty percent of the initial number infected. An increase in the rate of developing drug resistance results to a high number of the infected in the first about ten days. Later,this high number decreases gradually to about the initial number of the infected. The recovered, from Figure 8, decrease with increase in b and the resistant strain being transmitted.

6.1.3 Rate of transmitting resistant strain varied while rate of developing drug resistance is constant

The rate of developing drug resistance b is taken to be a constant, while the rate of transmitting the drug resistance strain is varied and all other factors held constant.

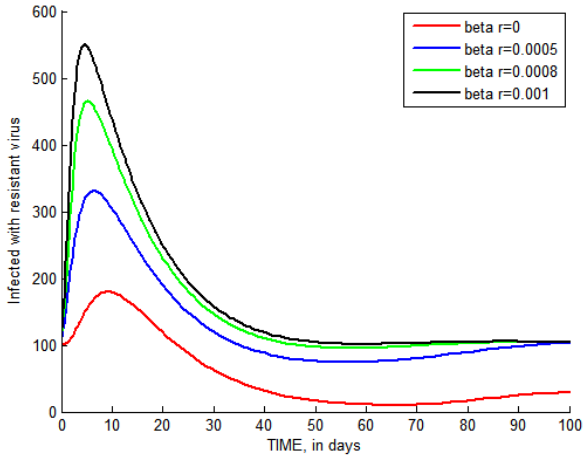

Fig. 9. Infected with resistant strain

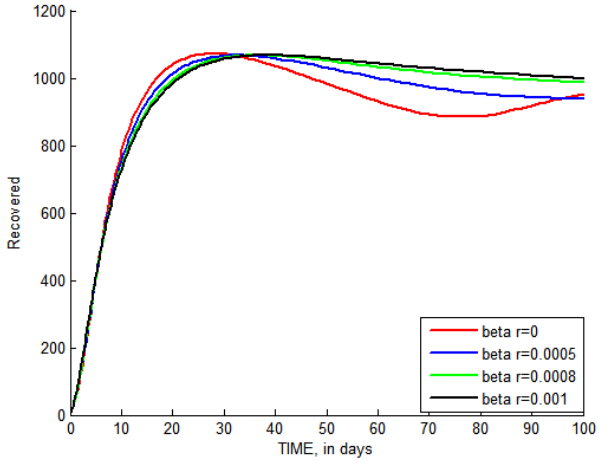

Fig. 10. Recovered individuals

Fig. 9 shows that when the resistant strain is not being transmitted and the development of drug resistance is a constant, the infected increase slightly in the first about ten days and then drastically decrease to about ten percent of the initial number infected. Increase in the transmission rate results to a increase in the infected and followed by a gradual decrease.

The recovered, from Fig. 10, are observed to decrease with increase in the transmission rate in the first about thirty days. After about the thirty days,the recovered increase. The increase could be attributed to the constant rate of developing resistance and hence many recover.

7 Conclusion

From analysis of the model system (1)-(5), it has been shown that given positive initial conditions, solutions to the system remain positive for all time.In the absence of influenza,the population size approaches the carrying capacity. The stability analysis shows that whenever $R_e < 1$ the disease free equilibrium point is locally asymptotically stable and whenever $R_e > 1$ there is a locally asymptotically stable endemic equilibrium. From the sensitivity analysis, it has been shown that a major factor that should be targeted in order to control the spread of influenza is vaccination.Results from the numerical simulation done indicate that in order to eradicate influenza in a population especially in the case where drug resistance sets in, it is paramount to consider with great precision the influence of various parameters. Of great importance would be the parameters that fuel the spread of resistant strain. Among other parameters, the rate of developing drug resistant strain and the transmission of this strain have great impact on the spread or control of influenza.

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Competing Interests

Authors have declared that no competing interests exist.

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