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Mathematical Modeling And Simulation Study Of Influenza Diseases

Tadele Degefa Bedada[1], Mihretu Nigatu Lemma[2] and Purnachandra Rao Koya[3*]
[1]College of Natural & Computational Sciences, Aksum University, Aksum, Ethiopia, [2,3]School of Mathematical & Statistical Sciences, Hawassa University, Hawassa, Ethiopia
Email: tadedegu@gmail.com[1], legenigatu@gmail.com[2], and drkpraocecc@yahoo.co.in[3]
*Author for correspondence

***Abstract*—In this paper we have considered SEI_SI_NR mathematical model, as an extension of SEIR, to describe the propagation of Influenza disease among the population. Influenza has been a burning issue around the world. Mathematical analysis, descriptions, stability analysis and simulation studies of influenza epidemic are taken up and are included. The registered data of influenza epidemic collected from the main campus, University of Central Florida, is used for parameter estimation and simulation studies. It is hoped that the information and results provided here would encourage other researchers to use mathematical modeling in the study of evolution and transmission of epidemic diseases.**

Keywords—Influenza, Flu, Modeling, Simulation study, Infectious diseases.

1. Introduction

The interconnectedness among the people and places in the world has created the need to understand the present and predict the future dynamics of infectious diseases. Obviously, the infectious diseases suffering the people are caused due to pathogenic micro-organisms such as bacteria, viruses, fungi and parasites. The pathogenic micro-organisms could spread from person to person or from animals and birds to human beings in a direct or indirect ways and propagates diseases. These infectious diseases have a potential cause leading to deaths of people worldwide as the medical advancement is not up to the requirement level [1]. Also, the medical administer is not proper and costs involved are not reachable to a common man [2 – 3].

Influenza, commonly known as "flu" is one of the infectious diseases that transmits from birds and mammals to people and then propagates among the people. The flu disease has the symptoms such as common cold, chills, high fever, sore throat, muscle pains, severe headache, coughing, bleeding from nose, body weakness and other general discomforts. The disease flu is caused by three types of Reborn Nucleolus Acid (RNA) viruses called as Influenza types A, B and C of the family orthomyxoviridae. Influenza type – A affects all age groups of humans and other animals and the disease causes moderate to several illnesses. Influenza type – B is a milder disease in comparison with that of type – A, and affects only humans specially children. Influenza type – C is rarely reported causing illness among the infected people and has not been considered as an epidemic disease. The serious outcome of the flu infection can result in hospitalization or death [4 – 5].

The mathematical modeling of infectious diseases is used to study the means by which diseases spread, to forecast the future course of an outbreak and to evaluate strategies to control an epidemic [6]. The mathematical models do not offer comprehensive descriptions of how to control the diseases. But, they are elegant methods used for evaluating the possible influence and effectiveness of different strategies offered in public health intervention programs [7]. During the recent Influenza – A known as $H1N1$ type or Swine Flu pandemic mathematical modeling is used to investigate interventions of both social and medical and thus modeling has become popular.

The present work considers the effects of disease control measures applied on a Meningococcal Disease or meningitis outbreak. The data of the current influenza pandemic collected from a college campus as well as a broader reveals the effects of the disease on the defined population. Analysis of such data helps decision makers, clinical practitioners and allocation of health care resource [8 – 9].

Influenza type – A or $H1N1$ is one of the diseases that have a latent or exposed phase, during which the individuals are said to be infected but not infectious. Due to the characteristics of the disease the $SEIR$ model requires modifications. The infectious compartment I is replaced with (i) symptomatic I_S and (ii) non-symptomatic I_N compartments. Thus, the modified model is named as SEI_SI_NR and is used in the present work for further analysis and interpretations.

In other words, the total population size $N(t)$ is partitioned into five compartments namely, susceptible $S(t)$, infected with symptoms $I_S(t)$, infected without symptoms $I_N(t)$, an incubation period E, and removed $R(t)$. Thus, $N = S + E + I_S + I_N + R$ [16]

Many mathematical models describing the evolution and dynamics of infectious diseases including Ebola, Breast cancer, Malaria and Tuberculosis have been proposed in literature [10 - 14].

In the present paper we have introduced a new compartmental model called as SEI_SI_NR model**.** Here, we have presented mathematical analysis of

SEI_SI_NR model and conducted simulation study in case of the disease called Influenza A, $H1N1$. Also we have identified the equilibrium points and conducted the stability analysis of those points. The details are included in the body of the paper.

Here we now introduce some important terminology that is frequently used in this work. **Compartment is** a group of people with similar status for example with respect to a disease. **Susceptible** a person is said to be susceptible if she or he has not yet infected by the disease but likely to get the disease in future. **Exposed** a person is said to be exposed to a disease when the bacteria enters into the person's body. At this stage the effects of the disease cannot be identified with the person, because the effects are in sleeping state. **Infected** a person is said to be infected if she or he has the disease and is able to transfer it to other susceptible persons. **Infected with symptoms** this person exhibits symptoms of the disease. But, the disease will be confirmed after conducting proper tests only. **Infected without symptoms** this person does not exhibit symptoms of the disease. But, the disease will be confirmed only with conducting of proper tests. **Incubation period** the time duration between an individual gets exposed to an infection and he gets sickness or confirmation of the disease. The person may be tested positive of the infection after this period. This is the time taken by a person to shift from the compartment E to the compartment I_S or I_N. The incubation period is also known as Latent period. **Removed compartment** a person is said to be in the removed compartment if he will never again get infected or infect others. The persons of this compartment are completely immune against the disease or isolated from the population or simply dead. **Epidemic diseases** these are the diseases which migrate in from other areas. These diseases will come and go with time. **Endemic** diseases these diseases always present in a population. They may occur several times or may lead to immunity over a period of time. **Contagious disease** these are the diseases which spread by physical contact between susceptible and infected persons.

2. Mathematical Modeling using $SEIR$ compartments

In this section, we have considered $SEIR$ epidemic model as it is a base for the $\mathrm{SEI_SI_NR}$ model. The letters in the string $SEIR$ respectively stand for the Susceptible, Exposed, Infected, and Removed compartments. We also have discussed its mathematical analysis briefly [15 – 16]. The simple flow diagram of $SEIR$ model is as follows:

The mathematical equations describing the $SEIR$ model can be described by a system of ordinary differential equations as

$$dS/dt = -\beta\,(SI/N) \quad (1a)$$
$$dE/dt = \beta\,(SI/N) - \sigma E \quad (1b)$$
$$d\mathrm{I}/\mathrm{dt} = \sigma E - \gamma \mathrm{I} \quad (1c)$$
$$dR/\mathrm{dt} = \gamma \mathrm{I} \quad (1d)$$

In the $SEIR$ compartment model (1) the population is assumed to be closed. That is, births, deaths and migrations are considered to be negligible and omitted. Thus, the population size parameter $N = S(t) + E(t) + I(t) + R(t)$ is a constant. Here, $S(t)$ represents the number of individuals those are susceptible to the disease but not infected at time t. The parameter $E(t)$ denotes the number of individuals those are exposed to the virus or infected but not yet tested positive of the infection. The parameter $I(t)$ denotes the number of infected individuals who are able to spread the disease to other susceptible people, and $R(t)$ represents the number of individuals those have successfully gained immunity from the disease and/or removed by death.

After exposed by the virus the individuals from the susceptible compartment $S(t)$ enters the exposed compartment $E(t)$ before they become infectious individuals and later either recover or die. The parameter β represents the transmission rate of disease from susceptible to exposed. Similarly, $(1/\sigma)$ and $(1/\gamma)$ are the average durations of incubation and infectiousness periods respectively.

2.1 Analysis of $SEIR$ model

Using the biological interpretation of system defined by the ordinary differential equations (1), it can be easily understand that the feasible region for system (1) is R_+^4, the four dimensional space surrounded by only the positive axes.

Clearly, the addition of all the equations of the system (1) results in $(d/dt)(S + E + I + R) = 0$. It can be interpreted that this restriction on the variables S, E, I and R simplifies the 4 – dimensional world and the solution region can be represented by the simplex $\mathcal{E} = \{(S, E, I, R) \in R_+^4 : (S + E + I + R) = N\}$.

Further, it can be noted that the region $\mathcal{E}$ is positively invariant. The population size of the removed compartment satisfies the relation $R(t) = N - S(t) - E(t) - I(t)$ everywhere in the region $\mathcal{E}$. Also, it can be noticed that disease – free equilibrium state exists for the model (1). In the disease – free equilibrium state absence of infection occurs. Thus, all the compartments except the susceptible will be zero and the entire population will comprise of only infection free susceptible individuals.

Here in what follows equilibrium points of system (1) are found, analyzed and discussed. For this very purpose Jacobean stability approach is used and shown that the stability of the disease-free equilibrium state occurs. The disease free equilibrium (DFE) point of the model (1) which we have discussed above can be computed as

2.2 Analysis of $SEIR$ model

$$(dS/dt) = (dE/dt) = (dI/dt) = (dR/dt) = 0 \quad (2a)$$
$$-\beta(SI/N) = 0 \quad (2b)$$
$$\beta(SI/N) - \sigma E = 0 \quad (2c)$$
$$(\sigma E - \gamma \mathrm{I}) = 0 \quad (2d)$$

On solving the equations (2) we get the disease free equilibrium point as $E_0 = (N, 0, 0)$ and at this equilibrium point the basic reproductive number takes the value $R_0 = (\beta/\gamma) < 1$. This shows that the susceptible individuals are stable at the equilibrium point E_0 and it can be interpreted as the epidemic is died out. Note that at any equilibrium point if the reproductive number assumes the value $R_0 > 1$ then the equilibrium point is considered to be unstable and it means that the epidemic spread continuous. The relation $R_0 > 1$ means an infected individual will infect more than one i.e., R_0 number of susceptible individuals. In our present work, the basic $SEIR$ epidemic model (1) given in [17] was modified to include death rates occurring in the symptomatic infectious compartment due to the disease.

3. Formulation of the SEI_SI_NR model

In this study we have considered $SEIR$, Susceptible – Expose – Infected – Removed, epidemic model and classified the infected population I as those with symptoms I_S and without symptoms $\mathrm{I_N}$. We will also conduct a simulation study by assigning different valid values to the parameters of the model. The present model has a compartmental structure and is designed based on the assumptions described as follows:

The individuals in the susceptible compartment are subjected to get infection due to contact with infected population at a rate of β. The susceptible population on getting infection enters in to the exposed compartment. The virus in the exposed population multiplies for a period of time k. It is important to note here that for the present model (1) we do not consider mutation of the pathogens. From the exposed compartment a portion p of individuals enter into the infected with symptoms compartment I_S, while the remaining portion $(1-p)$ of individuals enter into the infected without symptoms compartment I_N. An infected person of the I_S compartment will either die with the disease or recover from the disease by some means and enter into the removed compartment. The population of the I_S compartment will enter into the removed compartment R at a rate of γ and die with influenza disease at a rate of μ. The population of the I_N compartment recovers from the disease and enters into the removed compartment R at a rate of η [18]. The compartmental structure and flow directions of populations of this model can be illustrated as shown in Figure 1.

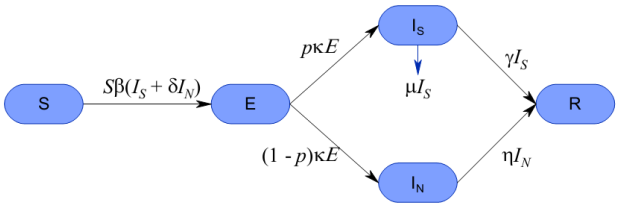

Figure 1 Flow Diagram of populations for Influenza disease

The mathematical formulation of $\mathrm{SEI_SI_NR}$ model can be expressed as systems of differential equation as follows:

$$dS/dt = -\beta S\ (\mathrm{I_S} + \delta\,\mathrm{I_N}) \quad (3a)$$
$$dE/dt = \beta S\ (\mathrm{I_S} + \delta \mathrm{I_N}) - K\,E \quad (3b)$$
$$d\mathrm{I_S}/\mathrm{dt} = \mathrm{P\,K\,E} - \gamma\,\mathrm{I_S} - \mu\,\mathrm{I_S} \quad (3c)$$
$$d\mathrm{I_N}/\mathrm{dt} = (1-\mathrm{P})\,\mathrm{K\,E} - \eta\,\mathrm{I_N} \quad (3d)$$
$$dR/dt = \gamma\,\mathrm{I_S} + \eta\,\mathrm{I_N} \quad (3e)$$

The notations and physical meanings of the parameters used in (3) are as follows: β is the contact rate of susceptible individuals with infection; k is the latency period in the exposed class; p is the fraction of exposed individuals that enter into I_S compartment; γ is the rate of recovery from the disease in I_S compartment; μ is death rate with influenza in I_S compartment; η is the rate of recovery from the disease in the I_N compartment and δ is the factor by which I_N have reduced infectivity.

4. Expression of the model in terms of scaling variables

Scaling of the variables in mathematical modeling has some advantages. Scaling removes unnecessary parameters and decreases the number of parameters. Also, scaling eliminates the physical units. Note that the physical units are not important for the dynamical analysis of a model [19]. For the purpose of constructing dimensionless or scaled system of model equations we now introduce a set of new variables as $u = (S/N)$, $z = (E/N)$, $v_s = (I_S/N)$, $v_n = (I_N/N)$, $w = (R/N)$ and $t = (\tau/\gamma)$. With the use of these scaling variables the system of model equations given in (3) will take the form

$$du/d\tau = -R_1\,u\,(v_s + \delta v_n) \quad (4a)$$
$$dz/d\tau = R_1 u\,(v_s + \delta v_n) - R_2\,z \quad (4b)$$
$$dv_s/d\tau = p\,R_2\,z - (1+R_3)\,v_s \quad (4c)$$
$$dv_n/d\tau = (1-P)\,R_2\,z - R_4 v_n \quad (4d)$$
$$w = 1 - u - z - v_s - v_n \quad (4e)$$

Here in (4) we have used the notations $R_1 = (\beta/\gamma)$, $R_2 = (k/\gamma)$, $R_3 = (\mu/\gamma)$ and $R_4 = (\eta/\gamma)$. The purpose of these notations is just to make the equations appear simple. The basic reproduction ratio **(R_0)**, which we have used in the present simulation study, was calculated using the formula given in [20] as $\mathrm{R_0} = [\beta/(\gamma + \mu + \eta)]$.

5. Mathematical analysis of the model

Here we consider mathematical analysis of the model (3) and draw some important observations. From the system of equations (3) it can be easily understood that the feasible region of system is R^5_+, the five dimensional space surrounded by only the positive axes.

On summing up all the individual equations of the system (3), it is straight forward in getting $(\mathrm{dS}/\mathrm{dt}) + (\mathrm{dE}/\mathrm{dt}) + (\mathrm{dI_S}/\mathrm{dt}) + (\mathrm{dI_N}/\mathrm{dt}) + (\mathrm{dR}/\mathrm{dt}) = 0$. This homogeneous equation can be integrated to obtain $(S + E + I_S + I_N + R) = N$ which is a constant. Here N can be interpreted as size of the total human population and is usually considered as a constant during the small interval of an epidemic.

Further, it can be interpreted that this restriction on the variables S, E, I_S, I_N and R simplifies the 5-dimensional world and can be represented by the simplex region $\mathcal{E} = \{(S,\ E,\ \mathrm{I_S},\ \mathrm{I_N},\ R) \epsilon\ \mathrm{R_+^5} :\ (S + E + I_S + I_N + R) = N\}$. Further, it can be noted that $\mathcal{E}$ is positively invariant and on which $R(t) = N - S(t) - E(t) - I_S\,(t) - I_N\,(t)$ is satisfied everywhere [8]. It can be noticed that disease-free equilibrium state for (3) exists. In the disease – free equilibrium state the infection is absent.

During the disease-free equilibrium state all the infected classes, except the susceptible class are empty, and as a result the entire population comprises of only infection free susceptible individuals. Here in what follows equilibrium points of system (3) are found, analyzed and discussed. For this very purpose here Jacobian stability approach is used and shown that the stability of the disease – free equilibrium state occurs. The disease free equilibrium point of the model which we have discussed above can be computed as

$(\mathrm{dS}/\mathrm{dt}) = (dE/\mathrm{dt}) = (\mathrm{dI_S}/\mathrm{dt}) = (\mathrm{dI_N}/\mathrm{dt}) = (\mathrm{dR}/\mathrm{dt}) = 0$ (5a)

$-S\,\beta\,(\mathrm{I_S} + \delta\,\mathrm{I_N}) = 0$ (5b)

$S\,\beta\,(\mathrm{I_S} + \delta\,\mathrm{I_N}) - K\,E = 0$ (5c)

$\mathrm{P\,K\,E} - \gamma\,\mathrm{I_S} - \mu\,\mathrm{I_S} = 0$ (5d)

$(1 - \mathrm{P})\,\mathrm{K\,E} - \eta\,\mathrm{I_N} = 0$ (5e)

$\gamma\,\mathrm{I_S} + \eta\,\mathrm{I_N} = 0$ (5f)

The basic reproduction ratio R_0 quantifies the transmission potential of a disease. If the basic reproduction ratio falls below one ($R_0 < 1$), i.e. the infective may not pass the infection on during the infectious period, the infection dies out. If the basic reproduction ratio is greater than 1, ($R_0 > 1$) then the equilibrium point is considered to be unstable and there is an epidemic in the population. In case where $R_0 = 1$, the disease becomes endemic, meaning the disease remains in the population at a consistent rate, as one infected individual transmits the disease to one susceptible [20].

On solving the equations (5) we get the disease free equilibrium point $E_0 = (N, 0,0,0)$ and at this equilibrium point the basic reproductive number takes the value $R_0 = [\beta/(\gamma + \mu + \eta)] < 1$. This shows that the susceptible individuals are stable at the equilibrium point and it can be interpreted as the epidemic is died out [20 – 22].

6. Simulation study of the model

Here we consider simulation study of the model (3) and draw some important observations. This simulation study is based on the given data of University of Central Florida (UCF) main campus. To facilitate the simulation study, we arranged the system of ODE in (4) as follows:

$du/d\tau = -a\,R_0 u\,(v_s + \delta v_n)$ (6a)

$dz/d\tau = aR_0 u\,(v_s + \delta v_n) - R_2\,z$ (6b)

$dv_s/d\tau = p\,R_2\,z - (1 + R_3)\,v_s$ (6c)

$dv_n/d\tau = (1 - P)\,R_2\,z - R_4 v_n$ (6d)

$w = 1 - u - z - v_s - v_n$ (6e)

Here $\mathrm{R_0}$ is as described before and $a = [(\gamma + \mu + \eta)/\gamma]$.

Calculations of parameters From the given data, we have that $N = 50{,}000$ people, $A = 5.726$ sq. kms., $q = 10\% = 0.1$ (where q is the probability of an infective transmitting the infection), $\mu = 0.0002$, $\gamma = \eta = 0.244$, $R = 1cm = 0.00001km$, (where *R* is the radius within which an infected individual must encounter a susceptible person in order to transmit the disease), v = (4.39km/hr)(24hr/day) = 105.36 km/day (where v is the population average speed). Then, contact rate, β, was determined for the specified campus area using the following equation derived in [16] $\beta = (8Rqv\rho/\pi) = 2.343/day$. This formula considers a moving population where the transmission rate of the disease is a factor of the density of the individuals within the specified area. Here $\rho = (N/A)$ and is considered to be 8732 people per one square kilometer. Here A is the area in which the population is constrained and N is the total population size. Hence, one can determine the values of R_0, R_1, R_2, R_3 and R_4 based on these values which have been calculated based on the collected data of Influenza on the UCF campus. The results of the simulation study are pictorially represented and described in what follows.

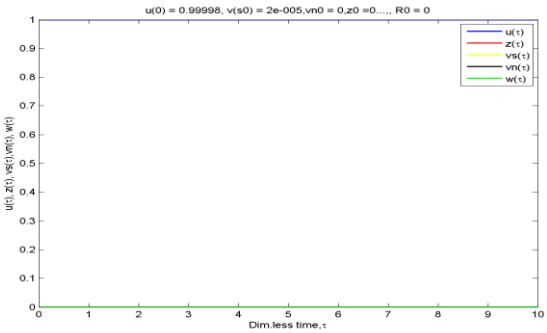

Figure 2: For $\mathrm{R_0} = 0$, the population size of susceptible decreases smoothly, whereas the exposed and infected compartments decreases to asymptotically zero, but the removed compartment size increases smoothly. The complete population sizes of these compartments are the multiples of the respective fractions and the total population N.

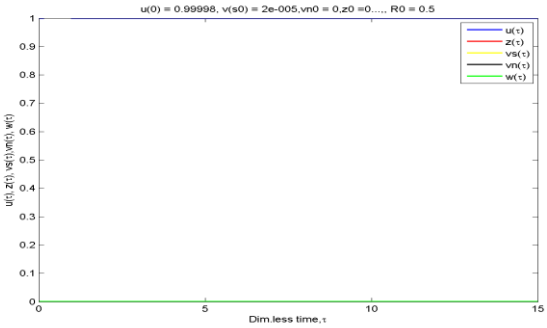

Figure 3 population dynamics of SEI_SI_NR - epidemic compartmental model when $\mathrm{R_0} = 0.5$. The susceptible fraction decreases smoothly, whereas the Exposed, infective with both symptoms and without symptoms and removed compartments decrease asymptotically to zero. Finally the epidemic dies out.

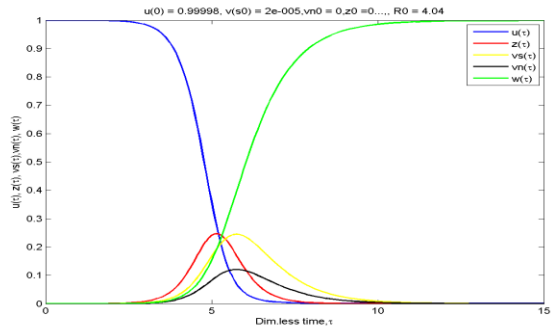

Figure 4 Population dynamics of SEI_SI_NR – epidemic compartmental model when $R_0 = 4.04$. The susceptible fraction decreases steadily, whereas the exposed and infective both with symptoms and without symptoms compartments are increasing to a maximum and then decreases to zero. But removed compartment increases steadily. Finally the epidemic seems dies out.

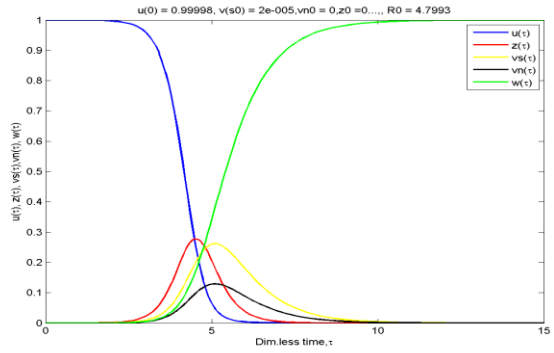

Figure 5 population dynamics of SEI_SI_NR – epidemic when $R_0 = 4.7993$ together with the progression of time. The susceptible population decreases steadily, whereas the exposed population, and infected population with both symptoms and without symptoms are initially increasing. All these populations are decreasing after reaching a maximum. But the removed population increases steadily. Finally the epidemic seems dies out.

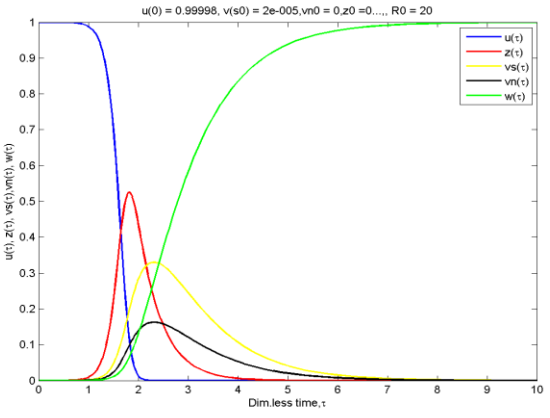

Figure 6 population dynamics of a SEI_SI_NR - epidemic compartmental model when $R_0 = 20$. The susceptible fraction decreases steadily, whereas the exposed and infective both with symptoms and without symptoms compartments are increasing to a maximum and then decreases to vanish. But removed compartment increases steadily. Finally the epidemic seems dies out.

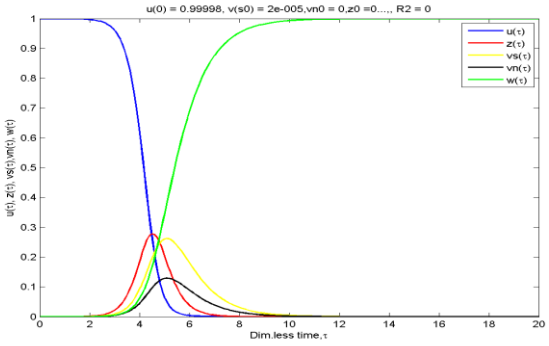

Figure 7 population dynamics of a SEI_SI_NR - epidemic compartmental model when $R_2 = 0$. The susceptible fraction decreases steadily, whereas the exposed and infective both with symptoms and without symptoms compartments are increasing to a maximum and then decreases to zero. But removed compartment increases steadily. Finally the epidemic dies out.

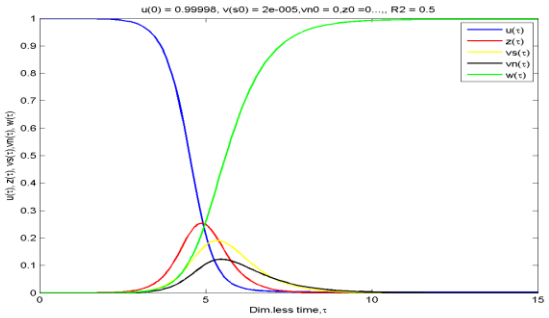

Figure 8 population dynamics of a SEI_SI_NR - epidemic compartmental model when $R_2 = 0.5$. The susceptible fraction decreases steadily, whereas the exposed and infective both with symptoms and without symptoms compartments are increasing to a maximum and then decreases to vanish. But removed compartment increases steadily. Finally the epidemic dies out.

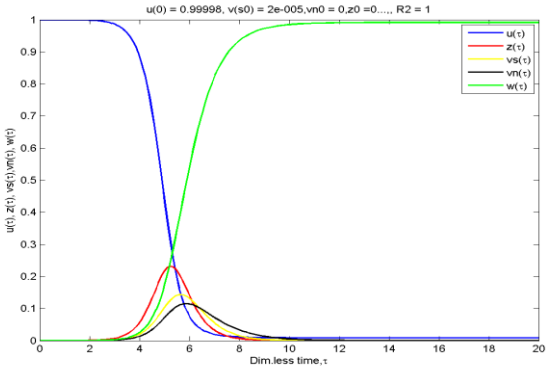

Figure 9 population dynamics of SEI_SI_NR - epidemic compartmental model when $R_2 = 1$. The susceptible fraction decreases to approximately steadily, whereas

the Exposed, and infective both with symptoms and without symptoms compartments are increases and then decreases, but removed compartments increases. Finally the epidemic dies out.

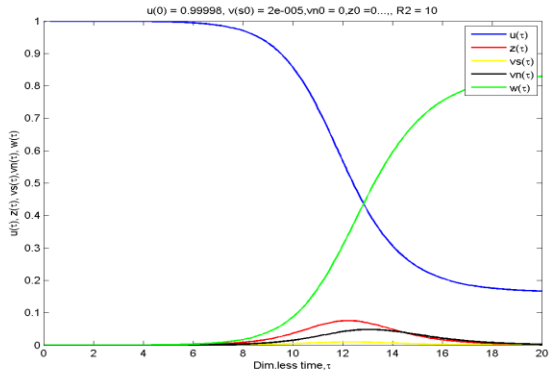

Figure 10: For $R_2 = 10$ the figure shows that the population size of susceptible compartment decreases steadily up to approximately 0.2 and then decreases smoothly. The population size of exposed and infected compartments increase and then decrease. But the removed compartment increases steadily up to approximately 0.8 and then the increment is smoothly. Finally the epidemic seems to be dies out.

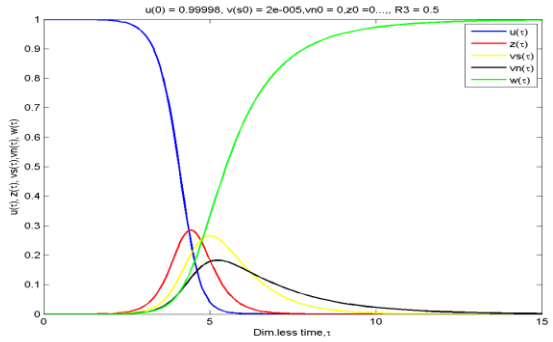

Figure 11 population dynamics of a SEI_SI_NR - epidemic compartmental model when $R_3 = 0.5$. The susceptible fraction decreases steadily, whereas the exposed and infective both with symptoms and without symptoms compartments are increasing to a maximum and then decreases to zero. But removed compartment increases steadily. Finally the epidemic dies out.

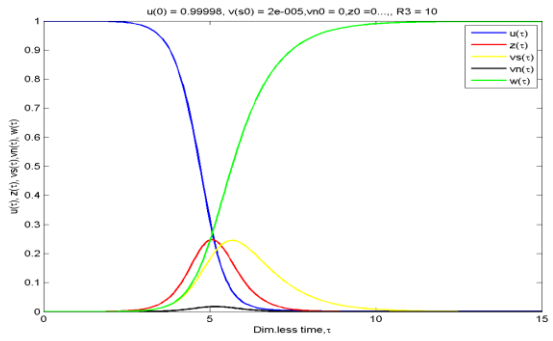

Figure 12 population dynamics of a SEI_SI_NR - epidemic compartmental model when $R_3 = 10$. The susceptible fraction decreases steadily, whereas the exposed and infective both with symptoms and without symptoms compartments are increasing to a maximum and then decreases to zero. But removed compartment increases steadily. Finally the epidemic seems dies out.

7. Conclusions

Mathematical modeling has provided the ability to choose the most effective and economical intervention activities for preventing and treating disease. In this study we have modeled influenza A (H1N1) disease. In order to describe about long and short durations of time and many or few for the populations, we need scales for all variables in the model equations. As a result, we can understand how to scale the system of ordinary differential equations of a model.

As we have seen from the simulation study, time development of a SEI_SI_NR -epidemic when $R_0 = 4.7993$ shows the susceptible fraction and a latent or exposed phase decreases steadily whereas the infective fraction increases to a maximum value and then decreases. Again when $R_0 = 10$, the susceptible fraction decreases steadily to zero whereas a latent or exposed phase and the infective fraction increase to a maximum value and then decrease to zero. Finally, in both cases the infectious dies out.

Furthermore, one can understand from the simulation study that relatively the variability is very sensitive to the basic reproduction ratio (R_0) than any other parameters which are considered in our study.

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