Modeling and Simulation of Susceptible - Exposed – Infected – Recovered – Vaccinated - Susceptible Model of Influenza

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Abstract **– Influenza, surpassing all other respiratory diseases in both morbidity and mortality, annually triggers seasonal epidemics responsible for approximately 500,000 global deaths. Mathematical epidemic models serve as valuable tools for forecasting potential outbreaks and predicting the trajectory of the disease. This paper represents a comprehensive SEIRVS model tailored to the context of Influenza transmission dynamics in North Macedonia. In this paper the classical Susceptible- Exposed- Infectious-Recovered (SEIR) model is enhanced by incorporating vaccination and a death compartment while examining their impact on the spread of Influenza through the population. Simulations are conducted using data from the 2022/2023 season, focusing on a case study of North Macedonia. The simulations were conducted utilizing both the actual vaccination rate in N. Macedonia for that season and an increased vaccination rate to observe the influence of vaccination. The simulation results emphasize the need to increase the vaccination rate. The findings contribute valuable insights for public health planning and policy making.**

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1. Introduction

Influenza, commonly referred to as the flu, is a highly communicable respiratory illness caused by influenza viruses. It impacts the respiratory system and spreads primarily through respiratory droplets released during coughing or sneezing by an infected person. These droplets can either land in the mouths or noses of individuals in close proximity (typically within a 6-foot range) or potentially be breathed into the lungs. Infrequently, one might contract influenza by coming into contact with a contaminated surface or object and subsequently touching their mouth, nose, or even eyes.

Influenza manifests across a spectrum of severity, ranging from mild to severe illness. For individuals with compromised immunity or underlying health conditions, it can be particularly dangerous, potentially resulting in fatal outcomes [1].

Influenza commonly manifests with symptoms including high fever, headaches, muscle aches, fatigue, sore throat, and nasal congestion or a runny nose, accompanied by a cough. These symptoms persist for several days to a couple of weeks. Typically, they emerge around two days after the influenza virus infects the respiratory tract, although the onset can extend up to four days. Importantly, there is a theoretical possibility that an infected individual may transmit influenza to others before exhibiting symptoms. Some individuals may carry the virus without showing symptoms, known as asymptomatic cases, yet still have the potential to spread the infection to close contacts [2].

Influenza viruses are classified in several groups depending on their surface proteins hemagglutinin (H) and neuraminidase (N).

There are three basic types of influenza viruses: A, B, and C. Influenza B and C viruses only affect humans, so novel antigens are not introduced from other species. Only influenza A viruses infect nonhuman hosts and a reassortment of genes can occur between those subtypes that typically infect animals which can infect humans resulting in antigenic shift that can lead to potential pandemic. The subtypes of influenza A that can cause significant epidemic or possible pandemic are H1N1, H2N2, H3N, and H5N1 (avian influenza), [3], [4].

An influenza pandemic occurs when a new influenza A virus, distinct from the current and recently circulating human seasonal influenza A viruses, spreads globally. The constant evolution of influenza A viruses creates the rare potential for nonhuman influenza viruses to undergo changes, enabling them to infect individuals easily and transmit efficiently from one person to another [2].

In the 20th century, three global influenza pandemics occurred in 1918, 1957, and 1968 [4], [5]. The latter two took place during the era of modern virology and were extensively studied. Informally labeled as Spanish, Asian, and Hong Kong influenza, respectively, these pandemics were associated with presumed sites of origin. A more recent H1N1 pandemic, commonly known as swine flu, occurred during the 2009/2010 season. In contrast to the earlier pandemics, this event had a relatively low mortality rate but still resulted in hundreds of thousands of deaths worldwide.

Effective prevention is crucial for managing the spread of any infectious disease. Vaccination plays a pivotal role by activating the immune system to generate antibodies targeted against specific influenza viruses, thereby mitigating the severity of illness in the event of infection. Due to the capacity of influenza viruses to mutate within each subtype, resulting in distinct strains, the composition of influenza vaccines is revised annually. The influenza vaccine is designed to be quadrivalent, offering protection against four different influenza viruses, encompassing influenza A and two influenza B viruses [2].

Comparable epidemiological models are under consideration for various infectious diseases, including but not limited to COVID-19 [9], [10], [11], measles [12], [13], [14], and tuberculosis [8].

2. Model Description

In this paper SEIRVS+D model has been analysed in order to understand the transmission dynamics of Influenza. SEIRVS+D model is an extension of classical SEIR model that includes an additional compartment of vaccinated and death.

The total population size at any given time t is denoted as $N(t)$ and is dived into six compartments: susceptible $S(t)$, exposed $E(t)$, infected $I(t)$, recovered $R(t)$, vaccinated $V(t)$ and death $D(t)$. Hence the total population at time t is:

$$N(t) = S(t) + E(t) + I(t) + R(t) + V(t) + D(t) \quad (1)$$

Each element in the SEIRVS+D model represents a distinct stage of individuals in the disease progression. The susceptible compartment encompasses all individuals who are vulnerable to the disease and could potentially get infected through contact with an individual carrying the infection. The exposed compartment represents individuals who recently have been exposed to influenza but are not yet infectious. During the latent period, individuals are incubating the virus and are not yet showing symptoms and are not able to transmit the disease to other individuals in the population. The infected compartment signifies individuals presently carrying the virus and capable of transmitting it to others. These individuals may exhibit symptoms or may be asymptomatic carriers. The infectious period typically lasts for a certain period ranging from one to seven days after developing symptoms. The vaccinated compartment represents individuals who have been vaccinated against influenza. Vaccination provides a level of immunity to the virus reducing the likelihood of infection, severity of symptoms and the risk of transmission. The recovered compartment represents individuals who have recovered from Influenza and have gained a level of immunity. These individuals after immunity lost can be infected again and thereby can contribute to spread of Influenza. The death compartment represents individuals who have died from Influenza. The implemented model with progression from one compartment to another is given on Figure 1.

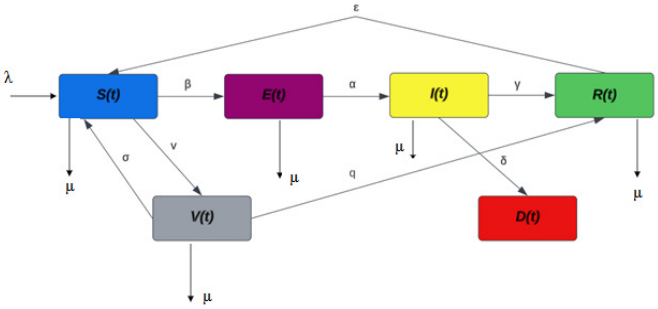

Figure 1. Flow chart of Influenza

The susceptible compartment decreases with transmission rate β as the population gets exposed and vaccination rate ν when the proportion of susceptible individuals gets vaccinated.

This compartment increases with birth rate λ, immunity loss rate ε when recovered individuals do not develop permanent immunity and unsuccessful vaccination rate σ. The exposed compartment is decreased by exposure rate α when exposed individuals get infected and is increased by transmission rate β. Infected compartment is decreased at recovery rate γ when infected individuals recover and mortality rate δ when individuals die due to influenza. This compartment is increased by exposure rate α. The recovery compartment is decreased by immunity loss rate ε and increased by rate q when susceptible individuals are vaccinated and gain immunity. Also, this compartment is increased by recovery rate γ when individuals recover from influenza. The vaccination compartment is increased by vaccination rate ν and decreased by unsuccessful vaccination rate σ and vaccination immunity gain q. All compartments except death compartment are decreased by natural mortality rate μ. Based on the aforementioned explanation the SEIRVS+D model for influenza can be delineated through the following set of ordinary differential equations:

$$\begin{aligned}
\frac{dS}{dt} &= \lambda - \frac{\beta SI}{N} + \varepsilon R + \sigma V - \upsilon S - \mu S \\
\frac{dE}{dt} &= \frac{\beta SI}{N} - \alpha E - \mu E \\
\frac{dI}{dt} &= \alpha E - \gamma I - \delta I - \mu I \\
\frac{dR}{dt} &= \gamma I + qV - \varepsilon R - \mu R \\
\frac{dV}{dt} &= \upsilon S - \sigma V - qV - \mu V \\
\frac{dD}{dt} &= \delta I
\end{aligned} \tag{2}$$

The initial conditions of model (2) are assumed to be nonnegative given as: $S(0) = S_0 \geq 0, E(0) = E_0 \geq 0, I(0) = I_0 \geq 0, R(0) = R_0 \geq 0, V(0) = V_0 \geq 0, D(0) = D_0 \geq 0$.

Theorem 1. The solution region of model (2) which is positively invariant set is given by:

$$\Omega = \left\{ \left(S, E, I, R, V, D\right) \in \mathbb{R}_+^6 : 0 \leq N(t) \leq \frac{\lambda}{\mu} \right\}$$

Proof: Summation of all differential equations of model (2) gives:

$$\frac{dN}{dt} = \frac{dS}{dt} + \frac{dE}{dt} + \frac{dI}{dt} + \frac{dR}{dt} + \frac{dV}{dt} + \frac{dD}{dt}$$

$$\frac{dN}{dt} = \lambda - \mu N - \delta I$$

From where:

$$\frac{dN}{dt} \leq \lambda - \mu N \tag{3}$$

By integration Equation (3) and taking the limit as t approaches infinity on both sides, the resulting equation is:

$$N(t) \leq \frac{\lambda}{\mu}$$

From where:

$$\Omega = \left\{ \left(S, E, I, R, V, D\right) \in \mathbb{R}_+^6 : 0 \leq N(t) \leq \frac{\lambda}{\mu} \right\} \tag{4}$$

Theorem 2. Let the initial values $\{\left(S(0), E(0), I(0), R(0), V(0), D(0)\right) \geq 0\} \in \Omega$, then the solution set $\{S(t), E(t), I(t), R(t), V(t), D(t)\}$ of the model (2) is non-negative for all $t \geq 0$.

Proof: From the first equation of model (2) follows:

$$\begin{aligned}
&\frac{dS}{dt} = \lambda - \frac{\beta SI}{N} + \varepsilon R + \sigma V - \upsilon S - \mu S, \\
&\frac{dS}{dt} \geq -\left(\frac{\beta I}{N} + \upsilon + \mu \right) S, \\
&\frac{dS}{S} \geq -\left(\frac{\beta I}{N} + \upsilon + \mu \right) dt, \\
&\int \frac{dS}{S} \geq \int -\left(\frac{\beta I}{N} + \upsilon + \mu \right) dt, \\
&\ln S \geq -\left(\frac{\beta I}{N} + \upsilon + \mu \right) t, \\
&S\left(t\right) \geq S\left(0\right) e^{-\left(\frac{\beta I}{N} + \upsilon + \mu \right) t}, \\
&S\left(t\right) \geq 0.
\end{aligned}$$

Similar, can be shown that all compartments of model (2) are positive for all $t \geq 0$.

From the second equation of the model (2):

$$\frac{dE}{dt} = \frac{\beta SI}{N} - \alpha E - \mu E,$$
$$\frac{dE}{dt} \geq -(\alpha + \mu)E,$$
$$E(t) \geq E(0)e^{-(\alpha+\mu)t},$$
$$E(t) \geq 0.$$

From the third equation within the system presented in Equation (2), follows:

$$\frac{dI}{dt} = \alpha E - \gamma I - \delta I - \mu I,$$
$$\frac{dI}{dt} \geq -(\gamma + \delta + \mu)I,$$
$$I(t) \geq I(0)e^{-(\gamma+\delta+\mu)t},$$
$$I(t) \geq 0.$$

Similarly, the solutions for the others two compartments are:

$$V(t) \geq V(0)e^{-(\sigma+q+\mu)t} \geq 0,$$
$$R(t) \geq R(0)e^{-(\mu+\varepsilon)t} \geq 0.$$

In the theorem it was assumed that $D(0) \geq 0$. At time instant $t = t_1$, $I(t_1) \geq 0$ since:

$$\frac{dD(t_1)}{dt} = \delta I(t_1) \geq 0$$

from where it can be concluded that $dD(t_1^+) \geq 0$, so that $D(t) \geq 0$ for all $t \geq 0$.

The feasible solution represents region where the solution of the system of differential equations are epidemiologically meaningful. Since the region given by Equation (4) is a positively invariant for the model (2) it can be concluded that the model is mathematically and epidemiologically feasible.

Corollary 1. The total population $N(t)$ is nonnegative wherever the initial conditions of the Influenza model represented with (2) are nonnegative since $N(t) = S(t) + E(t) + I(t) + R(t) + V(t) + D(t)$ and from Theorem 2, $S(t) \geq 0$, $E(t) \geq 0$, $I(t) \geq 0$ $R(t) \geq 0$, $V(t) \geq 0$ and $D(t) \geq 0$.

Theorem 3. The population has equilibrium point:

$$X^* = (S^*, E^*, I^*, R^*, V^*, D^*)$$

Proof: The equilibrium point is obtained when all equations of model (2) are equal to zero:

$$\frac{dS}{dt} = \frac{dE}{dt} = \frac{dI}{dt} = \frac{dR}{dt} = \frac{dV}{dt} = \frac{dD}{dt} = 0$$

An infection-free population implies that both the number of infected and exposed individuals is zero. Setting the right side of the equation in model (2) to zero:

$$\lambda - \frac{\beta SI}{N} + \varepsilon R + \sigma V - \upsilon S - \mu S = 0$$
$$\frac{\beta SI}{N} - \alpha E - \mu E = 0$$
$$\alpha E - \gamma I - \delta I - \mu I = 0$$
$$\gamma I + qV - \varepsilon R - \mu R = 0$$
$$\upsilon S - \sigma V - qV - \mu V = 0$$
$$\delta I = 0$$

Solving the system, the equilibrium point is obtained:

$$S^* = \frac{\lambda(\sigma + q + \mu)(\varepsilon + \mu)}{(\varepsilon + \mu)[(\upsilon + \mu)(\sigma + q + \mu) - \sigma\upsilon] - \varepsilon q\nu}$$
$$I^* = 0$$
$$E^* = 0$$
$$R^* = \frac{q\lambda\nu}{(\varepsilon + \mu)[(\upsilon + \mu)(\sigma + q + \mu) - \sigma\upsilon] - \varepsilon q\nu}$$
$$V^* = \frac{\lambda\nu(\varepsilon + \mu)}{(\varepsilon + \mu)[(\upsilon + \mu)(\sigma + q + \mu) - \sigma\upsilon] - \varepsilon q\nu}$$
$$D^* = 0$$

The basic reproduction number is a crucial factor in mathematical models, providing the count of secondary infections resulting from a single infected individual within the entire population. The reproduction number for the model defined by Equation (2) is:

$$\Re_0 = \frac{\alpha\beta\mu}{(\alpha + \mu)(\gamma + \delta + \mu)} \cdot \frac{(\sigma + q + \mu)(\varepsilon + \mu)}{(\varepsilon + \mu)[(\upsilon + \mu)(\sigma + q + \mu) - \sigma\upsilon] - \varepsilon q\nu}$$

The reproduction number is obtained using next generation matrix that is a square matrix where each element represents the rate of transmission from one compartment to another This matrix is derived from two matrices: matrix $\Im(x)$ that gives the rate of appearance of new infection in the population and matrix $\Upsilon(x)$ that gives the rate of progression in and out of the compartments for the individuals in the population. Let $X=(S,E,I,R,V,D)^T$ then model (2) is:

$$\frac{dX}{dt}=\Im(x)-\Upsilon(x)$$

Where:

$$\Im(X)=\begin{bmatrix}0\\ \frac{\beta SI}{N}\\ 0\\ 0\\ 0\\ 0\end{bmatrix}$$

and

$$\Upsilon(X)=\begin{bmatrix}\frac{\beta SI}{N}+\nu S-\varepsilon R+\mu S-\sigma V-\lambda\\ (\alpha+\mu)E\\ (\gamma+\delta+\mu)I-\alpha E\\ \mu R+\varepsilon R-\gamma I-qV\\ (\sigma+q+\mu)V-qS\\ -\delta I\end{bmatrix}$$

The infectious compartments in this model are infected and exposed compartments. If F is matrix that represents infection transmission in exposed and V is the matrix that presents infected compartments, then the matrixes F and V are the Jacobian matrix of order 2 × 2. These two matrixes at equilibrium point (DFEP) transform as:

$$F(X^*)=\begin{pmatrix}0 & \frac{\beta S}{N}\\ 0 & 0\end{pmatrix}$$

And

$$V(X^*)=\begin{pmatrix}\alpha+\mu & 0\\ -\alpha & \sigma+\gamma+\mu\end{pmatrix}$$

With Theorem 1 it was proven that the total population is $N\le\frac{\lambda}{\mu}$, so that:

$$F(X^*)=\begin{pmatrix}0 & \frac{\beta\mu S}{\lambda}\\ 0 & 0\end{pmatrix}$$

The next generation matrix is:

$$FV^{-1}=\begin{pmatrix}0 & \frac{\beta\mu S^*}{\lambda}\\ 0 & 0\end{pmatrix}\begin{pmatrix}\frac{1}{\alpha+\mu} & 0\\ \frac{\alpha}{(\alpha+\mu)(\gamma+\mu+\delta)} & -\frac{1}{\gamma+\mu+\delta}\end{pmatrix} \tag{13}$$

Hence, the reproduction number is:

$$\Re_0=\frac{\beta\mu(\sigma+q+\mu)}{(\alpha+\mu)(\gamma+\delta+\mu)}\cdot\frac{(\varepsilon+\mu)}{(\upsilon+\mu)(\sigma+\mu+q)-\sigma\nu(\varepsilon+\mu)-\varepsilon q\upsilon} \tag{14}$$

3. Results

The parameters of Influenza SEIRVS+D model were obtained from Institute of Public Health of North Macedonia for season 2022/2023 [7]. This season a total of 10216 cases of Influenza had been reported, which means that the incidence is 556.2 per 100000 individuals. During Influenza that season, five deaths have been reported. According to [7] a total of 57375 individuals have been vaccinated.

Simulation scenarios of Influenza were performed in software AnyLogic® [6]. AnyLogic® is a powerful simulation tool that allows creation of dynamic simulation model for various fields including epidemic spread. The first simulation was performed with the set of parameters' values given in Table 1.

Table 1. Description and values of parameters

Parameter	Description	Value
β	Transmission rate	0.6
α	Exposure rate	0.5
γ	Recovery rate	0.071
δ	Mortality rate	0.03
ν	Vaccination rate	0.027
q	Immunity development rate	0.9
μ	Natural mortality rate	0.013
λ	Natural birth rate	0.00932
ε	Immunity lost rate	0.001

The simulation results shown in Figure 2 illustrate that the count of infected individuals reaches a peak at 13,000 and subsequently undergoes a substantial decline. Also, the results show that the number of deceased individuals from Influenza is very low due to low mortality rate. The number of exposed individuals also rises to a maximum value and then starts to decrease.

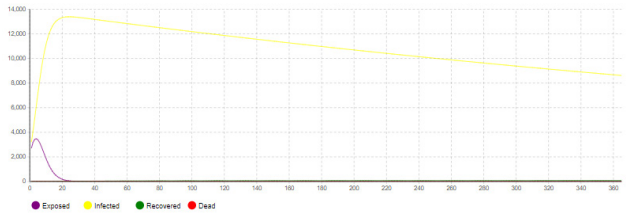

Figure 2. Simulation with parameter from Table 1

In the second simulation the vaccination rate significantly increased up to value of 0.75. Additionally, the transmission rate of influenza has been reduced to a value of 0.285. The values of the remaining parameters are specified in Table 1, and the simulation results are presented in Figure 3.

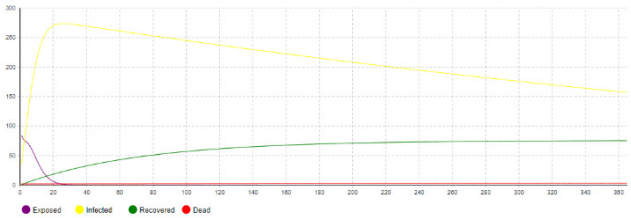

Figure 3. Simulation results for vaccination rate 0.75 and transmission rate 0.285

The simulation outcomes shown in Figure 3 indicate that the count of infected individuals rises to a maximum of 260 and subsequently declines. The number of deceased individuals is notably low. A higher vaccination rate has resulted in a substantial reduction in the number of infected individuals.

4. Conclusion

In this paper an enhanced SEIR model of Influenza was analyzed. In addition, a compartment of vaccination individuals was introduced. The vaccination is a preventive measure in which an individual is administered a vaccine to stimulate their immune system to develop immunity against Influenza. When vaccinated individual is exposed to Influenza the immune system recognizes the pathogen of Influenza and can quickly and effectively respond to the virus. SEIRVS+D model have played a pivotal role in this regard, providing insights into transmission dynamics that will lead to public health interventions and vaccination campaigns.

The simulation results of Influenza using different vaccination rates emphasize the need of higher vaccination rate. Higher vaccination rate of the population helps to control and prevent the spread of Influenza. Also, when a significant portion of the population is vaccinated the transmission of pathogen is interrupted reducing the likelihood of Influenza outbreak.

It is important to note that despite the positive trends observed, Influenza remains a threat and potential future pandemics may occur. Continuous monitoring, evaluation of management strategies, and adaptation of evolving nature of Influenza are crucial. The study of Influenza modeling and transmission dynamics will continue to play a vital role in guiding public health responses and mitigating the impact of Influenza outbreak.

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