CHAPTER: 10

A MATHEMATICAL MODEL FOR ANALYZING SWINE FLU OUTBREAKS IN THE PRESENCE OF VACCINATION

SATYENDRA SINGH YADAV
Professor, Department of Mathematics, Narain (P.G.) College, Shikohabad,UP India

BED PRAKASH SINGH
Assistant Professor, Department of Mathematics, Govt. (P.G.) College Fatehabad, Agra UP India

Ch.Id:-RBS/NSP/EB/ RAASTTSE/2024/Ch-10
DOI: https://doi.org/10.52458/9788197112492.nsp.2024.eb.ch-10

ABSTRACT

The development and evaluation of efficient vaccination techniques are crucial in light of the reoccurring hazards posed by Swine flu (H1N1). This paper offers a novel compartmental mathematical model, abbreviated as SEIQVR, to completely investigate Swine flu transmission dynamics considering both vaccination interventions. By separating the population into those who are Vulnerable (S), Exposed (E), Infected (I), Quarantined (Q), Vaccinated (V), and Recovered (R), the model can accurately simulate the intricate dynamics of Swine Flu pandemics. The relationship between vaccination tactics and the spread of disease is studied by factoring in variables such as the prevalence of the disease, the vaccination rate, the rate at which immunity declines, and the length of time spent in quarantine. The findings of this research have important implications for the development and implementation of effective immunization programs to prevent further Swine Flu epidemics. Decisions on resource allocation, vaccination campaign planning, and general pandemic preparedness can all be informed by a deeper comprehension of the complex dynamics of SEIQVR. This mathematical model contributes to the arsenal of tools accessible to epidemiologists and policymakers, supporting the creation of preventative measures to defend world health against Swine flu and comparable infectious dangers.

Keywords: *Swine flu, Vaccination, Outbreak mitigation, Waning immunity, Transmission rates*

1. INTRODUCTION

The recurring occurrences of swine flu (H1N1) epidemics serve as a persistent indication of the challenges associated with safeguarding the well-being of the global populace. The utilization of vaccination has been empirically proven to be a crucial strategy in mitigating the intensity of outbreaks of infectious diseases and preventing the transmission of these diseases. The researchers in this study develop and employ a mathematical model to analyze the effects of vaccination techniques within the setting of Swine Flu outbreaks. In recent years, the reliance on mathematical models has increased for comprehending the intricacies of infectious diseases and assessing the effectiveness of various public health interventions. The objective of this study is to provide a novel mathematical model that incorporates the intricate dynamics of Swine Flu in the context of vaccination.The proposed model incorporates essential epidemiological factors, including transmission rates, vaccine efficacy, and vaccination coverage, in order to depict the complex interplay between the virus and the vaccinated population. The mathematical framework provides a systematic approach to analyze the dynamics of Swine Flu epidemics in different vaccination scenarios. This is achieved by representing the population as distinct compartments, each representing individuals in various states such as susceptibility, exposure, infection, and vaccination. The primary objective of this study is to evaluate the efficacy of various vaccination strategies through the utilization of modeling techniques, specifically in relation to the transmission and severity of Swine Flu outbreaks. The objective of the model is to offer valuable insights that can inform evidence-based decision making by public health authorities. This involves assessing several factors such as the optimal scheduling of vaccination campaigns, desired levels of coverage, and the potential occurrence of waning immunity.

Chowell et al. (2009) presented vaccination regimens for six discrete age cohorts, which were subsequently deployed in Mexico. Qiu and Feng (2010) developed a mathematical model to analyze the effects of antiviral and vaccination regimens on influenza, considering both drug-sensitive and drug-resistant strains. Tchuenche et al. (2011) developed a mathematical model encompassing three control functions, namely vaccination fading, vaccine efficacy, and treatment effectiveness controls, with the aim of discerning the pivotal drivers in disease transmission and prevalence. The study conducted by Al-Sheikh (2012) examined a pandemic model known as SEIR, which incorporates constrained medical resources. It is postulated that the rate of therapy is directly proportional to the quantity of patients, provided that this quantity remains below a predetermined capacity. Once this capacity is reached, the treatment rate is presumed to remain constant. Lee et al. (2013b) conducted an analysis employing a seasonal forcing model and an age-structured model to examine the optimal strategies for mitigating influenza pandemics. Reynolds et al. (2014) developed mathematical models that accurately replicate typical swine breeding and finishing operations, using real data as the basis for their research. The utilization of these models serves to analyze and elucidate the intricacies of influenza infection dynamics within agricultural settings, an area that currently lacks comprehensive comprehension. The study conducted by Imran et al. (2016) involved the development of a deterministic model to analyze the dynamics of swine flu transmission and assess the impact of antiviral drugs in controlling the 2009 pandemic. Kim et al. (2017) utilized the transmission rate derived from the fundamental reproductive number, R0, of the intervention-free model to assess the reduction in transmission rate resulting from government intervention programs. Kanyiri et al. (2018) created a mathematical model to investigate the dynamics of influenza A virus transmission, incorporating the influence of drug resistance. The mathematical epidemiological model proposed by Parolini et al. (2021) consists of seven compartments: susceptible uninfected individuals (S), undetected infected individuals (both asymptomatic and symptomatic) (U), isolated infected individuals (I), hospitalized individuals (H), threatened individuals (T), extinct individuals (E), and recovered individuals (R). Jonnalagadda (2022) conducted an analysis on a proposed novel mathematical model that incorporates several rate parameters pertaining to transmission, progression, recovery, and vaccination, with a specific focus on accounting for those who are affected. In their study, Khondaker (2022) proposed a theoretical framework to analyze the dynamics of influenza transmission. This model was subsequently employed to assess the effectiveness of two distinct control strategies: preventive measures encompassing an awareness campaign, hand hygiene practices (such as hand washing and hand sanitizer usage), and mask-wearing; and therapeutic interventions.

This work possesses the capacity to contribute to the existing discourse on pandemic preparedness by providing policymakers with additional evidence to enhance Swine Flu vaccine campaigns and mitigate their societal consequences. The mathematical model discussed in this study is a crucial instrument for enhancing global health resilience in light of potential future infectious threats. It signifies a notable progression in our understanding of the dynamics of Swine flu, particularly in relation to vaccination.

2. FORMALIZATION OF THE MATHEMATICS MODEL

Adding Quarantine (Q) and Vaccination (V) zones to the original Susceptible-Exposed-Infectious-Recovered (SEIR) model results in the more complex SEIQVR model. The SEIQVR model, which accounts for the impact of vaccination on swine flu epidemics, is described by the following set of differential equations.

$$\frac{dS}{dt} = \mathrm{A} - \beta SI - \rho SQ - \mu S \quad (1)$$

$$\frac{dE}{dt} = \beta SI + \rho SQ - (\sigma + \mu)E \quad (2)$$

$$\frac{dI}{dt} = \sigma E - (\gamma + \alpha + \mu)I \quad (3)$$

$$\frac{dQ}{dt} = \alpha I - (\delta + \mu)Q \quad (4)$$

$$\frac{dR}{dt} = \gamma I + \delta Q + \theta V - \mu R \quad (5)$$

$$\frac{dV}{dt} = \kappa S - (\theta + \mu)V \quad (6)$$

With the initial $S(0) \geq 0, E(0) \geq 0, I(0) \geq 0, Q(0) \geq 0, R(0) \geq 0, V(0) \geq 0$

Where

$$N = S + E + I + Q + V + R \quad (7)$$

Table 1: Input parameters of SEIVQR model

Parameter	Meaning	Numerical values
Δ	Recruitment rate	2
β	Transmission rate	0.3
ρ	Quarantine rate	0.1
σ	rate of progression from exposed to infectious	0.2
γ	recovery rate	0.1
α	rate of quarantine of infectious individuals	0.05
δ	recovery rate of quarantined individuals	0.1
κ	vaccination rate	0.05
θ	rate of waning immunity	0.01

Disease-Free Equilibrium: Numerous epidemiological models exhibit a disease-free equilibrium, when the population remains unaffected by the presence of disease. Typically, these models are equipped with a threshold parameter referred to as the fundamental reproduction number. In subsection (4), the calculation of the fundamental reproduction number for the system (1-6) will be performed. By utilizing the fundamental reproduction number, we establish adequate criteria for the local and global asymptotic stability of the disease-free equilibrium in sections (4) and (5) correspondingly.

Basic Reproduction Number: The Basic reproductive number is formally defined as the numerical value representing the quantity of newly infected individuals generated by a solitary infected individual upon introduction into a community of susceptible individuals, during the duration of the infected individual's effective period of contagiousness. The basic reproduction number of the system (1-6) is derived using the formulation of the next generation matrix approach.

The scheme (1-6) should be taken into consideration. The disease-free equilibrium of the system (1-6) is readily apparent.

$\epsilon_0 = (E_0, I_0, Q_0, S_0, R_0, V_0) = (0,0,0,S_0,0,V_0)$, where

$S_0 = \frac{\Lambda}{\mu}, V_0 = \frac{\kappa S_0}{\theta+\mu} = \frac{\kappa \Lambda}{\mu(\theta+\mu)}$

Let $x = (E, I, Q, S, R, V)^T$. Then, (1-6) can be written as

$\frac{dx}{dt} = \mathcal{F}(x) - \mathcal{V}(x)$

$$\mathcal{F}(x) = \begin{bmatrix} \beta SI \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}, \mathcal{V}(x) = \begin{bmatrix} -\rho SQ + (\sigma+\mu)E \\ -\sigma E + (\gamma+\alpha+\mu)I \\ -\alpha I + (\delta+\mu)Q \\ -\Delta + \beta SI + \rho SQ + \mu S \\ -\gamma I - \delta Q - \theta V + \mu R \\ -\kappa S + (\theta+\mu)V \end{bmatrix}$$

The Jacobian matrices of $\mathcal{F}(x)$ and $\mathcal{V}(x)$ at the disease free equilibrium ϵ_0 are given by, respectively

$$d\mathcal{F}(\epsilon_0) = F = \begin{bmatrix} 0 & \frac{\Lambda\beta}{\mu} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

$$d\mathcal{V}(\epsilon_0) = V = \begin{bmatrix} \sigma+\mu & 0 & -\frac{\Lambda\rho}{\mu} & 0 & 0 & 0 \\ -\sigma & \gamma+\alpha+\mu & 0 & 0 & 0 & 0 \\ 0 & -\alpha & \delta+\mu & 0 & 0 & 0 \\ 0 & \frac{\Lambda\beta}{\mu} & \frac{\Lambda\rho}{\mu} & \mu & 0 & 0 \\ 0 & -\gamma & -\delta & 0 & \mu & -\theta \\ 0 & 0 & 0 & -\kappa & 0 & \theta+\mu \end{bmatrix}$$

The subsequent iteration matrix is represented as FV^{-1}, where V^{-1} denotes the inverse of matrix V. The fundamental reproduction number, denoted as R_0, is equivalent to the spectral radius of FV^{-1}, which can be expressed as $R_0 = FV^{-1}$. The calculation yields the fundamental reproduction number as.

$$R_V = \frac{\Lambda\beta\sigma(\theta+\mu)}{\mu(\sigma+\mu)(\gamma+\alpha+\mu)(\mu+\kappa)} \qquad (8)$$

The disease-free equilibrium ϵ_0 of the system (1-6) exhibits local asymptotic stability when R_V is less than 1, whereas it becomes unstable when R_V exceeds 1.

5. Global Stability of the Disease-Free Equilibrium: The disease-free equilibrium ϵ_0 of the system (1-6) exhibits global asymptotic stability when R_V is less than 1. The given system, denoted as (1-6), can be expressed as

$Y = (E, I, Q)^T, Z = (S, R, V)^T$

$Y' = -(V - F)Y - F(Y, Z)$

$Z' = H(Y, Z)$

$F(Y, Z) = \begin{bmatrix} \beta SI \\ 0 \\ 0 \end{bmatrix}$

$H(Y, Z) = \begin{bmatrix} \mathrm{A} - \beta SI - \rho SQ - \mu S \\ \gamma I + \delta Q + \theta V - \mu R \\ \kappa S - (\theta + \mu)V \end{bmatrix}$

It is evident that the function $F(Y, Z)$ is non-negative in the set of real numbers, denoted as $\mathbb{R}$. Moreover, the matrix $(V - F)$ is a nonsingular M-matrix. The disease-free equilibrium ϵ_0 of the system (1-6) exhibits global asymptotic stability when R_V is less than 1.

The Impact of Vaccination: To analyze the system without the presence of vaccination, we can set the values of κ and V to zero in equations (1-6). In light of the aforementioned, it is necessary to deliberate upon the system. n:

$\frac{dS}{dt} = \mathrm{A} - \beta SI - \rho SQ - \mu S$ (9)

$\frac{dE}{dt} = \beta SI + \rho SQ - (\sigma + \mu)E$ (10)

$\frac{dI}{dt} = \sigma E - (\gamma + \alpha + \mu)I$ (11)

$\frac{dQ}{dt} = \alpha I - (\delta + \mu)Q$ (12)

$\frac{dR}{dt} = \gamma I + \delta Q - \mu R$ (13)

With the initial $S(0) \geq 0, E(0) \geq 0, I(0) \geq 0, Q(0) \geq 0, R(0) \geq 0$ (14)

In this study, we conduct an analysis of the system (9-10) within the biologically viable zone.

$\mathbb{R}_0 = \{(S, E, I, Q, R) \in \mathcal{R}_5^+ \ : S(0) \geq 0, E(0) \geq 0, I(0) \geq 0, Q(0) \geq 0, R(0) \geq 0\}$

It is evident that the area $\mathbb{R}_0$ exhibits positive invariance in relation to the system (9-13) when considering the beginning circumstances (14) within the positive orthant $\mathcal{R}_5^+$. The presence of a disease-free equilibrium $\acute{\epsilon}_0$ in the system (9-13) can be readily observed, where $\acute{\epsilon}_0$is defined as $(0,0,0, S_0, 0)$.

Where $S_0 = \frac{\mathrm{A}}{\mu}$

The basic reproductive number of the system, denoted by the range of values between (9) and (13), is provided as

$R_0 = \frac{\mathrm{A}\beta\sigma(\theta+\mu)}{\mu^2(\sigma+\mu)(\gamma+\alpha+\mu)}$ (15)

The disease-free equilibrium $\acute{\epsilon}_0$ of the system (9-13) exhibits both local and global asymptotic stability when R_0 is less than 1. However, it becomes unstable when R_0exceeds 1.

The Impact of Vaccination Rates on Dependency: In this subsection, we establish fixed values for the parameters $A, \mu, \beta, \kappa, \gamma, \rho, \sigma, \theta$ and proceed to conduct an analysis on the impact of the vaccinated class in influencing the progression of an epidemic wave, through the manipulation of the parameter κ. In this particular interpretation, the notation $R_V(\kappa)$ is employed to represent the fundamental reproduction number of the system, ranging from 1 to 6. The present study encompasses

$R_V(k) = \frac{\mathrm{A}\beta\sigma(\theta+\mu)}{\mu(\sigma+\mu)(\gamma+\alpha+\mu)(\mu+\kappa)}$ (16)

$\frac{dR_V}{d\kappa} = -\frac{\mathrm{A}\beta\sigma(\theta+\mu)}{\mu(\sigma+\mu)(\gamma+\alpha+\mu)(\mu+\kappa)^2}$ (17)

It is evident that the derivative of the variable $\frac{dR_V}{d\kappa}$ with respect to κ is less than or equal to zero. Therefore, the function $R_V(\kappa)$ has a diminishing trend as κ increases. This demonstrates the impact of vaccination on decreasing the vaccine-induced reproduction number. Furthermore, in the event of a lack of immunization, the basic reproduction number (R_0) of the system is denoted as (9-13). The collective entity known as we possesses

$$R_0 = \frac{A\beta\sigma(\theta+\mu)}{\mu^2(\sigma+\mu)(\gamma+\alpha+\mu)} \quad (18)$$

Based on the definitions of $R_V(\kappa)$and R_0, it is evident that the implementation of vaccination entails.

$$R_V(\kappa) \leq R_0 \quad (19)$$

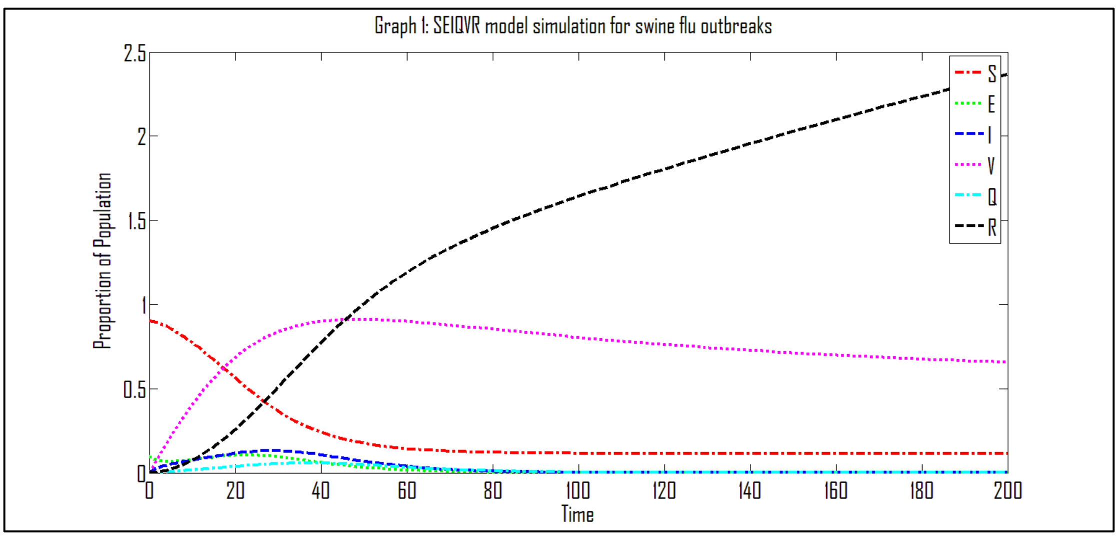
Consequently $R_V(\kappa) < 1$ if $R_0 < 1$

Therefore, the condition for local asymptotic stability of ϵ_0 is that $R_V(\kappa)$ must be less than 1.

$$\lim_{\kappa \to \infty} R_V(\kappa) = 0 < 1 \quad (20)$$

suggesting that the attainment of a sufficiently high vaccination rate κ within the population can lead to the potential suppression of the illness.

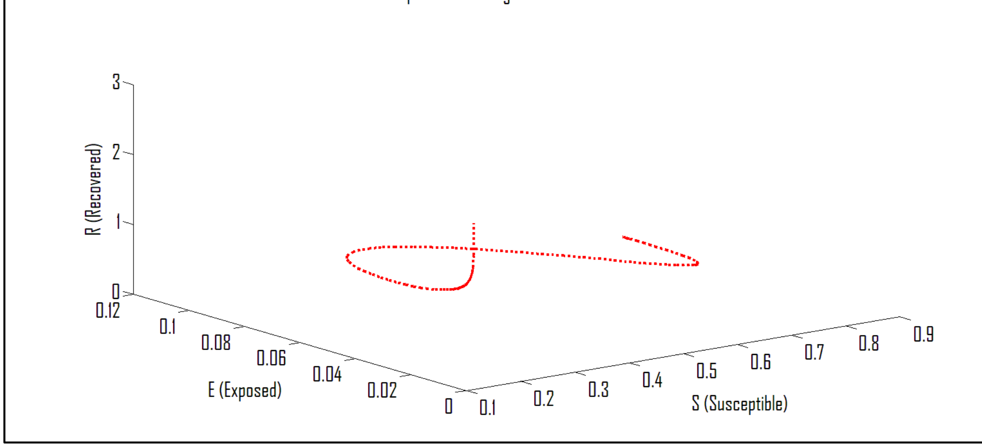
3. RESULTS AND DISCUSSION



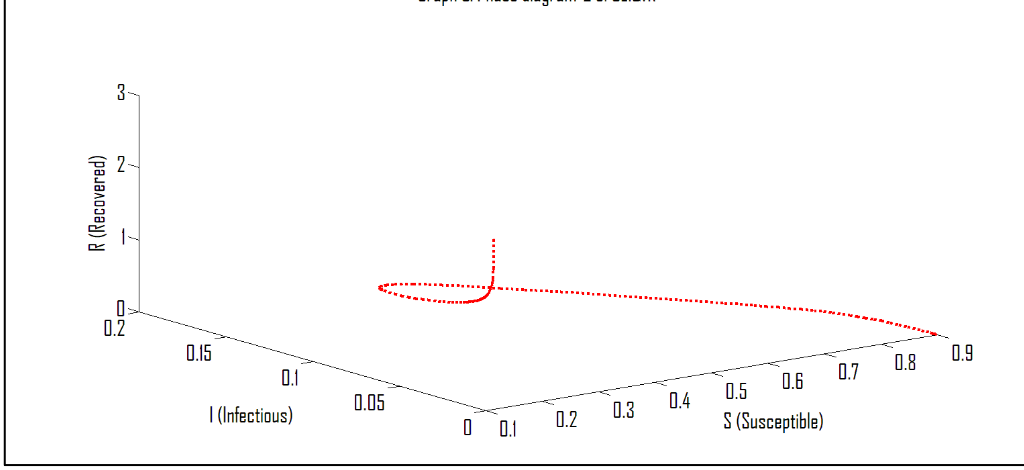
Graph 1: SEIQVR model simulation for swine flu outbreaks

Mathematical models are commonly employed to examine Swine flu outbreaks and the effects of vaccination. These models often employ graphical representations to facilitate the comprehension and analysis of disease dynamics and the efficacy of vaccination approaches. The graph (1) depicts the epidemic curves, which demonstrate the temporal variations in the population size inside each compartment. Peaks serve as indicators of the temporal occurrence and intensity of the outbreak. The graph additionally depicts the temporal evolution of vaccination campaigns, providing insights on the timing and extent of population-wide immunization efforts.

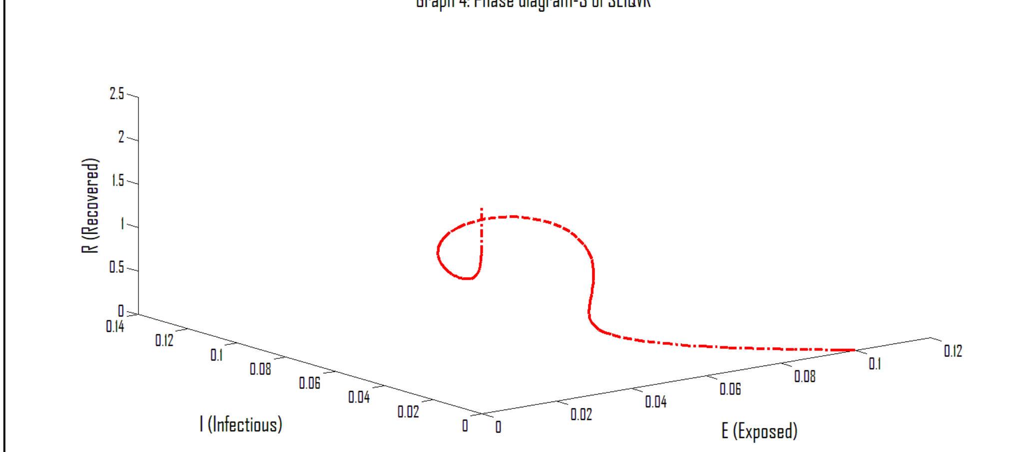
Graph 2: Phase diagram-I of SEIQVR model

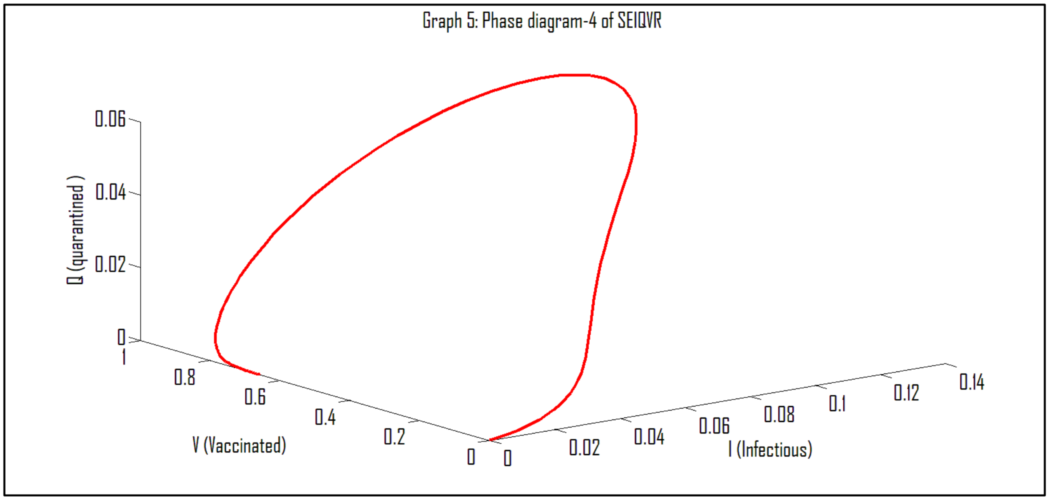


Graph 3: Phase diagram-2 of SEIQVR

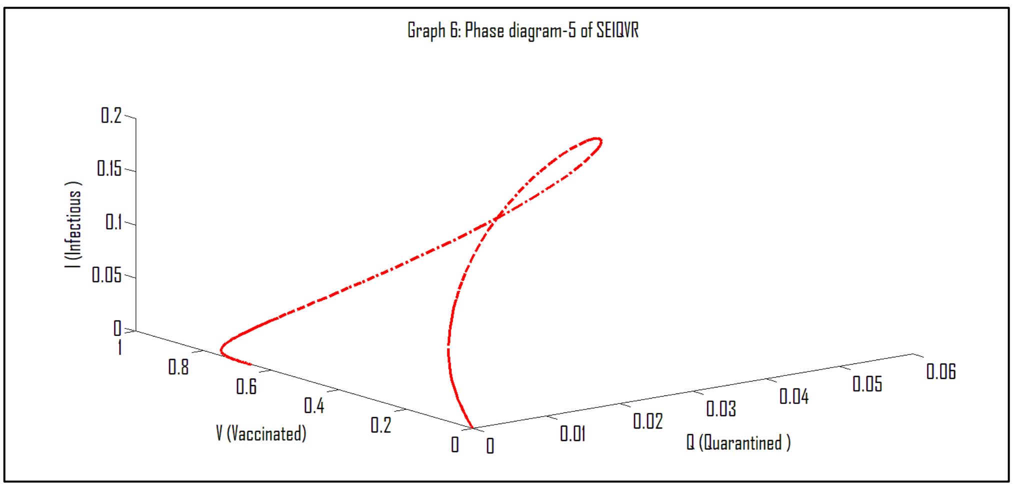


Graph 4: Phase diagram-3 of SEIQVR





Graph 5: Phase diagram-4 of SEIQVR



Graph 6: Phase diagram-5 of SEIQVR

The 3D phase diagram of the SEIQVR model offers a full representation of the dynamics of the Swine flu outbreak, encompassing the impacts of vaccination, exposure, and quarantine measures. The examination of this picture facilitates the ability of researchers and policymakers to make well-informed judgments regarding vaccination programs and other activities aimed at managing and reducing the consequences of the outbreak. The three-dimensional phase space, denoted as graph-2, is characterized by the three variables S, E, and R. Every point inside this spatial framework corresponds to a distinct configuration of susceptible, exposed, and recovered individuals. The trajectories within this spatial context depict the temporal progression of the system. In a three-dimensional phase diagram, the three axes commonly indicate the quantities of individuals within the compartments S, I, and R. The trajectories within this spatial domain depict the temporal progression of the system, taking into account the dynamics between individuals who are vulnerable, infectious, and recovered. The 3-dimensional phase space, represented by graph-4, serves as a visual representation of the system's state, specifically highlighting the values associated with the three principal compartments: E, I, and R. The trajectories observed within this spatial domain depict the temporal evolution of the system. The utilization of a three-dimensional phase space provides a more comprehensive comprehension of the dynamics, facilitating the examination of interactions among numerous compartments. The 3D phase diagram, also known as graph-5, entails the representation of three variables inside a three-dimensional spatial framework. The figure consists of three axes representing the number of infectious individuals (I), vaccinated individuals (V), and quarantined individuals (Q), respectively. The trajectories seen within this spatial context depict the temporal evolution of the system. The 3D phase diagram entails the representation of three fundamental divisions in a three-dimensional space by arranging them against each other. The graph illustrates the distribution of individuals categorized into three groups: quarantined (Q), vaccinated (V), and infectious (I). Each axis inside the coordinate system corresponds to one of the compartments, while the trajectories seen within the three-dimensional space depict the temporal evolution of the system. The trajectory exhibits variations or transitions towards distinct geographical areas, signifying diverse patterns of disease dissemination and management.

9. CONCLUDING REMARKS

In summary, the SEIQVR model offers a comprehensive framework for the analysis of Swine flu epidemics, encompassing crucial elements such as vaccination, quarantine measures, and the decline of immunity over time. The mathematical model presented in this study provides significant insights into the dynamics of the disease and the effects of different intervention tactics on the spread of outbreaks. In conclusion, our examination of the model yields some noteworthy observations. The model adopts a comprehensive approach by combining not just the conventional SEIR components, but also integrating the dynamics of vaccination and quarantine. This thorough depiction enables a more accurate comprehension of Swine flu epidemics and the potential impacts of vaccination campaigns. The incorporation of a vaccinated compartment within the model enables the examination of vaccination campaigns in a comprehensive manner, taking into account many elements such as the extent of vaccination coverage, the gradual decline of immunity over time, and the complex interactions between vaccinated individuals and those who are vulnerable to the disease. The evaluation of the long-term effects of vaccination on the epidemic curve is of utmost importance. The incorporation of a quarantined compartment within the model allows for the consideration of individuals who are currently under quarantine. This inclusion acknowledges the influence of public health interventions on the transmission of diseases. The significance of the Quarantine compartment is particularly notable within the framework of outbreak management and the mitigation of transmission rates. The inclusion of a diminishing immunity period within the Vaccinated group recognizes the transient nature of immunity conferred by vaccination. This characteristic improves the model's capacity to simulate and forecast the dynamic evolution of immunity across the population as time progresses. The results of the model have significant consequences for the formulation of public health policies and the process of decision-making. Through the examination of diverse situations, policymakers can get valuable knowledge regarding the efficacy of distinct vaccine and quarantine tactics, which in turn informs the allocation of resources and the planning of responses. The inherent design of the model permits versatility and adaptation in the face of evolving conditions and newly emerging data. The accuracy and applicability of the model can be enhanced through additional refinement and parameterization, which should be informed by real-world observations. Similar to other mathematical models, this particular model possesses inherent limits, and the accuracy of its predictions is contingent upon the precision of the input parameters. Potential future research could entail further enhancing the model by incorporating additional data, integrating spatial factors, and resolving uncertainty related to emerging virus strains. In brief, the model functions as a powerful instrument for comprehending and addressing Swine flu outbreaks in the context of vaccination. The comprehensive methodology employed by this approach offers a nuanced viewpoint on the intricate dynamics of infectious diseases, hence providing practical insights that may be utilized for the purpose of public health planning and response endeavors. As the refinement and adaptation of mathematical models persist, their indispensability in our collaborative endeavors to protect global health from rising dangers endures.

REFERENCES

1. Al-Sheikh S.A. (2012): “Modeling and analysis of an SEIR epidemic model with a limited resource for treatment”, Global Journal of Science Frontier Research Mathematics and Decision Sciences, 12(14):1-11.
2. Chowell, G., Viboud, C., Wang, X., Bertozzi S. M., Miller M. A. (2009): “Adaptive vaccination strategies to mitigate pandemic influenza: Mexico as a case study”, PLoS One 4 (12):e8164.
3. Imaran M., Malik T., Ansari A.R., Khan A. (2016): “Mathematical analysis of swine influenza epidemic model with optimal control”, Japan Journal of Industrial and Applied Mathematics, 33:269-296.
4. Jonnalagadda J.M. (2022): “Epidemic Analysis and Mathematical Modelling of H1N1 (A) with Vaccination”, Nonautonomous Dynamical Systems, 9:1-10.
5. Kanyiri C.W., Mark K., Luboobi L. (2018): “Mathematical analysis of influenza a dynamics in the emergence of drug resistance”, Computational and Mathematical Methods in Medicine, Article ID 2434560, 14 pages.
6. Khondaker F. (2022): “Optimal control analysis of influenza epidemic model”, Applied Mathematics, 13:845-857.
7. Kim S., Lee J., Jung E. (2018): “Mathematical model of transmission dynamics and optimal control strategies for 2009 A/H1N1 influenza in the Republic of Korea”, Journal of Theoretical Biology, 412: 74-85.
8. Lee J., Kim J., Kwon H.D. (2013b): “Optimal control of an influenza model with seasonal forcing and age-dependent transmission rates”, Journal of Theoretical Biology, 317(1): 310–320.
9. Parolini N., Dede L., Antonietti P.F., Ardenghi G., Manzoni A., Miglio E., Pugliese A., Verani M. , A. Quarteroni A. (2021): “SUIHTER: a new mathematical model for COVID-19. Application to the analysis of the second epidemic outbreak in Italy”, Proceeding Royal Society, 1-21.
10. Qiu Z., Feng Z. (2010): “Transmission dynamics of an influenza model with vaccination and antiviral treatment”, Bulletin of Mathematical Biology, 72 (1):1–33.
11. Reynolds J.J.H., Torremorell M., Craft M.E. (2014): “Mathematical modeling of influenza a virus dynamics within swine farms and the effects of vaccination”, PLOS ONE, 9(11):e111832.
12. Tchuenche J.M., Khamis S.A., Agusto F.B., Mpeshe S.C. (2011): “Optimal control and sensitivity analysis of an influenza model with treatment and vaccination”, Acta Biotheoretica, 59 (1):1–28.