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Transmission Dynamics of Avian Influenza Among Poultry With and Without Vaccination

Qiao Liang

THE UNIVERSITY OF NEW MEXICO
ALBUQUERQUE, NEW MEXICO 87131

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Qiao Liang
Candidate

Mathematics and Statistics
Department

This thesis is approved, and it is acceptable in quality and form for publication on microfilm:

Approved by the Thesis Committee:

Deborah Silsby, Chairperson

Pedro T Embid

Stanly Steinberg

Accepted:

Dean, Graduate School

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Date

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BY

Qiao Liang

B.S., Applied Mathematics, University of New Mexico, 2005

THESIS

Submitted in Partial Fulfillment of the
Requirements for the Degree of

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Albuquerque, New Mexico

July, 2007

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ABSTRACT OF THESIS

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ABSTRACT

The continuing avian influenza (AI) out break that began in late 2003 and early 2004 has been disastrous for the poultry industry worldwide. It has resulted in severe socio-economic damage, and it has raised serious concerns for general public health. In this research, we use mathematics to analyze transmission dynamics of AI among poultry. We use a status-based approach to construct systems of differential equations to describe virus transmission dynamics. We develop theoretical means to eradicate the spread of the disease, and we calculate the size of healthy and infected populations during an AI outbreak, and the final population size when the disease is eliminated. We study the dynamics when vaccination is absent, and when vaccination is used. For the latter case, we investigate different scenarios, including when the circulating virus consists of only one strain, and when multiple strains are present. Finally, we assume there exists a mutation which can create a non-existing strain from an existing strain and we analyze such dynamics using numerical simulation. The measures and information provided by this research can be used as references to develop disease control strategies.

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May 1, 2007

0.1 Introduction of Avian Influenza

There are three known types of influenza viruses. Type A virus can infect birds and mammals, including humans, and type B and C viruses can only be passed among humans. Type A flu virus has many subtypes, due to the two main surface proteins, hemagglutinin [HA] and neuraminidase [NA]. There are 16 subtypes of flu A virus with HA proteins and 9 with NA. Each possible combination of the HA and NA proteins makes up a different subtype [3]. Avian influenza (AI) is a type A influenza virus, and it was first discovered in Italy in the early 1900's [7]. Avian influenza is highly contagious, it can survive at low or moderate temperatures, but it can be destroyed by heat [4].

Wild birds, especially wild waterfowl, are believed to be the original source and natural reservoir of all subtypes of influenza A virus [1]. Wild birds carry the virus in their intestines, and circulate the virus worldwide. Although they are usually resistant to infections of AI, a particular AI subtype, namely H5N1 virus, can cause mortality in bird populations. Birds that survive the infection can shed virus through their saliva, nasal secretions, and feces. Susceptible birds can become infected during contact with the contaminated excretions or environments [6].

One of the most vulnerable populations to AI virus is poultry. Susceptible poultry may become infected with AI virus by inhaling virus polluted air, or making contact with infected wild birds (especially wild waterfowl). Live bird markets and movements of bird waste products are also responsible for causing an AI outbreak. As high as 90 to 100 percent of poultry, particularly chickens, infected with a high pathogenic form of AI virus die

within 48 hours [6].

0.1.1 Possible Virus Mutations

Influenza A viruses can mutate unpredictably. They can change in two ways, antigenic drift and antigenic shift. Antigenic drift refers to small, gradual and random point mutations in the two genes that contain the genetic materials to produce the two main surface proteins, hemagglutinin and neuraminidase. Antigenic drift happens all the time, and it causes minor changes to the main surface proteins. Therefore, antibodies that work against the older strain of virus may not be able to recognize the newer strains of virus, and new infections can occur. On the other hand, antigenic shift refers to sudden, major changes that happen only occasionally. These changes can create new influenza A virus subtypes. Antigenic shift can occur through a process called genetic reassortment, which occurs when genetic materials of human and avian viruses are exchanged. Genetic reassortment may generate a new virus that might be able to infect and spread among humans easily [3].

0.1.2 Thesis Objectives and Model Descriptions

The continuing avian influenza outbreaks that began in late 2003 and early 2004 have been disastrous for the poultry industry worldwide. By mid-2005, more than 140 million birds have been killed by the disease, or been put to death for disease control. The losses to the poultry industry are estimated in the excess of 10 billion US dollars. Avian flu has resulted in severe socio-economic damage, and it has raised serious concerns for general

public health.

My thesis uses mathematics to analyze transmission dynamics of avian influenza among domestic poultry. We use a status-based approach to construct systems of differential equations to describe virus transmission dynamics. We develop theoretical measures to control and eradicate the spread of disease, and we calculate size of healthy and infected populations during an AI outbreak, and the final population size when the disease is eliminated. We study the dynamics when vaccination is absent, and when vaccination is used. For the latter case, we investigate different scenarios, including when the circulating virus consists of only one strain, and when multiple strains are present. Finally, we assume there exists a mutation which can create a non-existing strain from an existing strain, and we analyze such dynamics using numerical simulation. The measures and information provided by this research can be used as references to develop disease control strategies.

0.2 Background study

0.2.1 The Basic Kermack-McKendrick Model

In Murray's book *Mathematical Biology* [15], the author analyzes a basic SIR model, the Kermack-McKendrick model, which has had a major influence on the development of mathematical models in population dynamics. The model considers a homogenous population with a constant size, N. It assumes the incubation period of the infectious agent is instantaneous, and the duration of infectivity is same as the length of the disease. The model uses a system of differential equations to describe the number of individuals infected with a contagious disease over time,

$$\begin{cases} \frac{dS}{dt} &= -\delta IS \\ \frac{dI}{dt} &= \delta IS - \eta I \;=\; (\delta S - \eta)I \\ \frac{dR}{dt} &= \eta I. \end{cases} \tag{0.2.1.1}$$

Notation	Description
S	Susceptible population
I	Infected population
R	Recovered population
δ	Probability acquiring infection in a susceptible individual from a random chosen contact with an infected individual per unit time
η	Total death count per unit time

Tab. 0.1: Notation Definitions

All of the model parameters are nonnegative for biological reasons. A question we want to ask is for constant δ and η, and given an initial number of susceptible, S_0, and infective, I_0, will the infection spread? If it does, how does the infected population vary in time? When will it start to decline? As a matter of fact, there exists a threshold, ρ, such that for $S_0 > \rho$, the infected population increases, and an epidemic will occur. If $S_0 < \rho$, the infected population decreases. This threshold phenomenon can be calculated explicitly. From the equation

$$\left[\frac{dI}{dt}\right]_{t=0} = I_0(\delta S_0 - \eta) = 0,$$

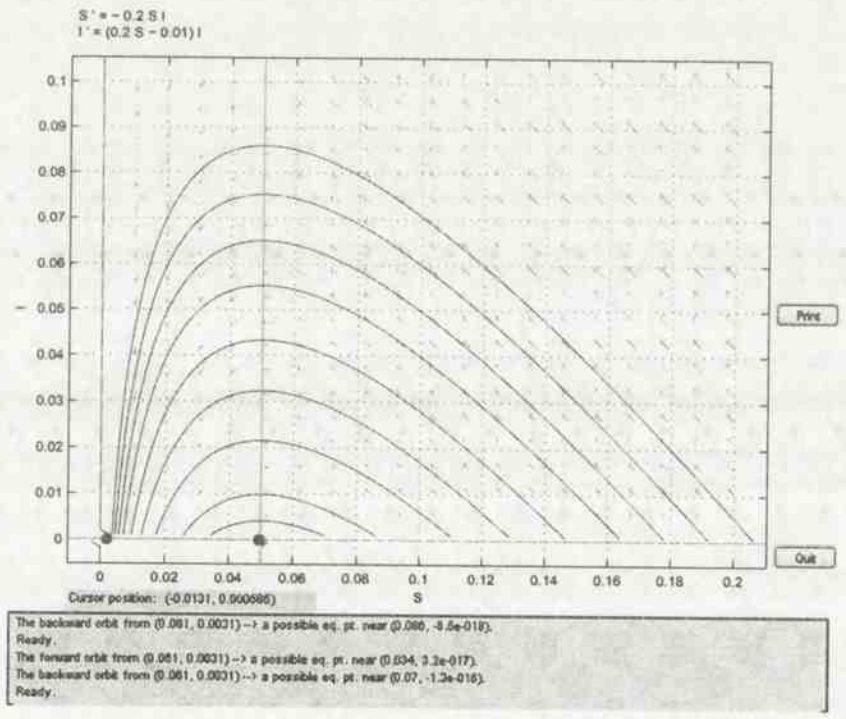
the threshold is

$$S_0 = \frac{\eta}{\delta} = \rho.$$

Since $\frac{dS}{dt} \leq 0$ for all t, we know $S \leq S_0$. Thus, if $S_0 < \rho$,

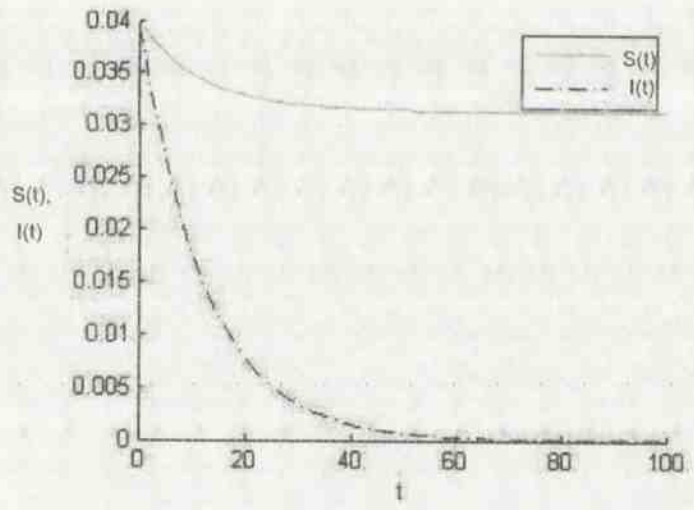
$$\frac{dI}{dt} = I(\delta S - \eta) \leq 0 \quad \text{for all} \quad t \geq 0.$$

In this case, as soon as the infection is introduced, it will decrease and die out. On the other hand, if $S_0 > \rho$, for any giving constant I_0, the infection will initially increase before starting to decrease and eventually die out. This threshold phenomenon can be observed from the phase trajectories in the susceptible (S)- infective (I) phase plane, or from population - time graphs of the SIR model 0.2.1.1.



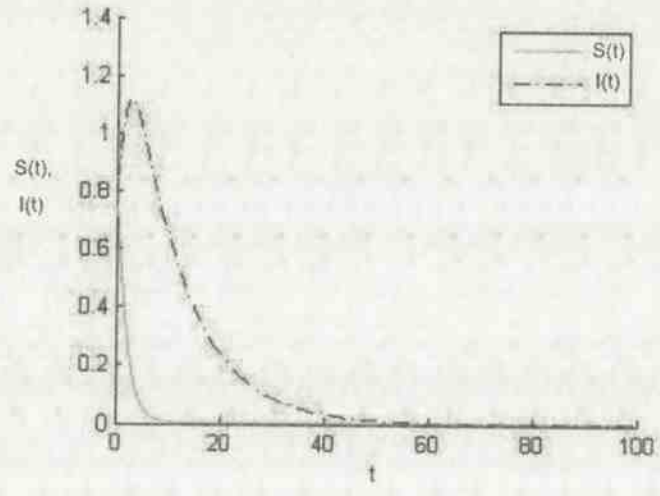
(0.2.1.2)

Fig.0.2.1.2. Phases trajectories in the susceptible (S)-infective(I) phase plane for the SIR model epidemic system 0.2.1.1. The curves are determined by initial conditions, S_0 and I_0, with $R_0 = 0$.



(0.2.1.3)

Fig.0.2.1.3. When the initial number of susceptible individuals is less than the threshold, the infective population is observed to go toward extinction in time, while the susceptible population decreases to a positive constant.



(0.2.1.4)

fig.0.2.1.4. When the initial number of susceptible individuals is greater than the threshold, the number of infective increases before it peaks and goes extinct in time.

It is traditional to define

$$r_0 = \frac{S_0}{\rho} = \frac{\delta S_0}{\eta}$$

as the basic reproductive rate of the infection, which represents the average number of secondary cases produced by an infectious individual in a wholly susceptible population. When $r_0 > 1$, an epidemic will ensue.

We can also obtain the maximum number of infected individuals, I_{max}, and the total number of infected individuals, I_{total}, from model 0.2.1.1. Integrate

$$\frac{dI}{dS} = -\frac{(\delta S - \eta)I}{\delta SI} = -1 + \frac{\rho}{S}, \quad I \neq 0,$$

we obtain

$$I + S - \rho \ln S = I_0 + S_0 - \rho \ln S_0 = constant.$$

The maximum occurs when $\frac{dI}{dt} = 0$, or S is at the threshold value ρ.

$$\begin{aligned} I_{max} &= \rho \ln \rho - \rho + I_0 + S_0 - \rho \ln S_0 \\ &= I_0 + S_0 - \rho + \rho \ln \left(\frac{\rho}{S_0} \right) \\ &= N - \rho + \rho \ln \left(\frac{\rho}{S_0} \right). \end{aligned} \tag{0.2.1.5}$$

We can also obtain the total infected population, I_{total}. Note that the total population is a constant $N = I_0 + S_0$, since $R(0) = 0$. Therefore $\frac{dN}{dt} = 0$, and for all $t > 0$, $0 \leq S + I \leq N$. From the SIR model 0.2.1.1, we have

$$\frac{dS}{dR} = -\frac{S}{\rho}.$$

Integrate both sides, we have

$$\Rightarrow S = S_0 \exp\left(-\frac{R}{\rho}\right) \geq S_0 \exp\left(-\frac{N}{\rho}\right) > 0 \tag{0.2.1.6}$$

$$\Rightarrow S(\infty) = S_0 \exp\left[-\frac{R(\infty)}{\rho}\right] = S_0 \exp\left[-\frac{N - S(\infty)}{\rho}\right].$$

Since $0 < S(\infty) < \rho$, and $I(\infty) = 0$. Therefore, $S(\infty)$ is the positive root $0 < z < \rho$ of the transcendental equation

$$z = S_0 \exp\left[-\frac{N - z}{\rho}\right],$$

and we obtain $I_{total} = I_0 + S_0 - S(\infty)$.

0.2.2 Non-Vaccinated SI model

Poultry infected by AI usually die a short time after the infection. They either die from the fatal disease, or they are put to death for disease control. We focus the dynamics of the spread of the disease within the susceptible and infected population, since the infected population does not become susceptible again, and we give the following SI model:

$$\begin{cases} \frac{dS}{dt} &= h - \delta SI - \mu S \\ \frac{dI}{dt} &= \delta SI - \eta I, \end{cases} \tag{0.2.2.1}$$

where h is the rate of population recruitment, which is assumed to be susceptible, and μ is the rate of susceptible population loss. The SI model 0.2.2.1 has a disease-free equilibrium (DFE) at

$$E_0 = \left(\frac{h}{\mu}, 0\right),$$

with corresponding Jacobian

$$J_0 = \begin{bmatrix} -\mu & -\frac{h\delta}{\mu} \\ 0 & \frac{h\delta}{\mu} - \eta \end{bmatrix},$$

and eigenvalues

$$\lambda_1 = -\mu, \qquad \lambda_2 = \frac{h\delta}{\mu} - \eta. \tag{0.2.2.2}$$

Clearly, the DFE E_0 is locally asymptotically stable, if and only if $\lambda_2 < 0$, which means $\frac{h\delta}{\mu\eta} < 1$. Define $r_0 = \frac{h\delta}{\mu\eta}$ as the basic reproductive number, which is the number of new infections in a disease-free population produced by one infected individual. Note $\lambda_2 < 0$, if and only if $r_0 < 1$. Thus, we give the following lemma.

Lemma 0.2.2.1. *The DFE (E_0) of the SI model 0.2.2.1 is locally asymptotically stable if $r_0 < 1$ and unstable if $r_0 > 1$.*

From another point of view, a successful disease invasion requires a sufficiently large transmissibility. In particularly, we will see that the infection will die out, if $\delta < \frac{\mu\eta}{h}$. For a strain with a sufficiently large transmission rate, $\delta > \frac{\mu\eta}{h}$, the poultry population will sustain an epidemic. A transcritical bifurcation occurs as the value of r_0 grows and becomes larger than 1. The DFE (E_0) is destabilized, and it coexists with an unique endemic equilibrium (EE) at

$$E_1 = \left(\frac{\eta}{\delta}, \frac{h}{\eta} - \frac{\mu}{\delta}\right),$$

which exists provided $r_0 = \frac{h\delta}{\mu\eta} > 1$. The Jacobian of the SI model 0.2.2.1 evaluated at the EE is:

$$J_1 = \begin{bmatrix} -\frac{h\delta}{\eta} & -\eta \\ \frac{h\delta}{\eta} - \mu & 0 \end{bmatrix},$$

and the corresponding eigenvalues are:

$$\lambda_{1,2} = \frac{-h\delta \pm \sqrt{h^2\delta^2 - 4\eta^2(h\delta - \mu\eta)}}{2\eta}. \qquad (0.2.2.3)$$

If

$$h^2\delta^2 - 4\eta^2(h\delta - \mu\eta) < 0, \qquad Re(\lambda_{1,2}) > 0.$$

If

$$h^2\delta^2 - 4\eta^2(h\delta - \mu\eta) > 0, \qquad Re(\lambda_{1,2}) < 0.$$

Since the existence condition for the EE (E_1) implies $h\delta - \mu\eta > 0$, it follows that $Re(\lambda_{1,2}) < 0$. Thus we give the following lemma.

Lemma 0.2.2.2. *The EE(E_1) of the SI model 0.2.2.1 is always locally asymptotically stable.*

Note that the size of the infected population at the EE depends on the transmissibility of the circulating virus strain. A high transmission rate can result in a large infected population limited by $\frac{h}{\eta}$. Furthermore, if the virus strain has an intermediate transmission rate, $\frac{2\eta(\eta-\sqrt{\eta(\eta-\mu)})}{h} < \delta < \frac{2\eta(\eta+\sqrt{\eta(\eta-\mu)})}{h}$, the population tends to the EE (E_1) with damped oscillation. For a transmission rate outside of this range, the population tends to the EE directly.

Knowing the local stability of the equilibrium states, we will now investigate the global behavior of model 0.2.2.1, using **Dulac's Criterion** [18].

Remark 0.2.2.3. **Dulac's Criterion:** Let $\dot{\mathrm{x}} = \mathrm{f}(\mathrm{x})$ be a continuously differentiable vector field defined on a simply connected subset R of the plane. If there exists a continuously differentiable, real-valued function $g(\mathrm{x})$ such that $\nabla \cdot (g\dot{\mathrm{x}})$ has one sign throughout R, then there are no closed orbits lying entirely in R.

Therefore, we obtain the following lemma.

Lemma 0.2.2.4. *The SI model 0.2.2.1 has no closed orbits in the positive quadrant, $S, I > 0$.*

Proof. Let us pick $g = \frac{1}{SI}$, where $S, I > 0$, then

$$\frac{\partial}{\partial S}\left(g\dot{S}\right) + \frac{\partial}{\partial I}\left(g\dot{I}\right)$$

$$= \frac{\partial}{\partial S}\left[\frac{1}{SI}(h - \delta SI - \mu S)\right] + \frac{\partial}{\partial I}\left[\frac{1}{SI}(\delta SI - \eta I)\right]$$

$$= \frac{\partial}{\partial S}\left(\frac{h}{I}\cdot\frac{1}{S} - \delta - \frac{\mu}{I}\right) + \frac{\partial}{\partial I}\left(\delta - \frac{\eta}{S}\right)$$

$$= -\frac{h}{IS^2} < 0.$$

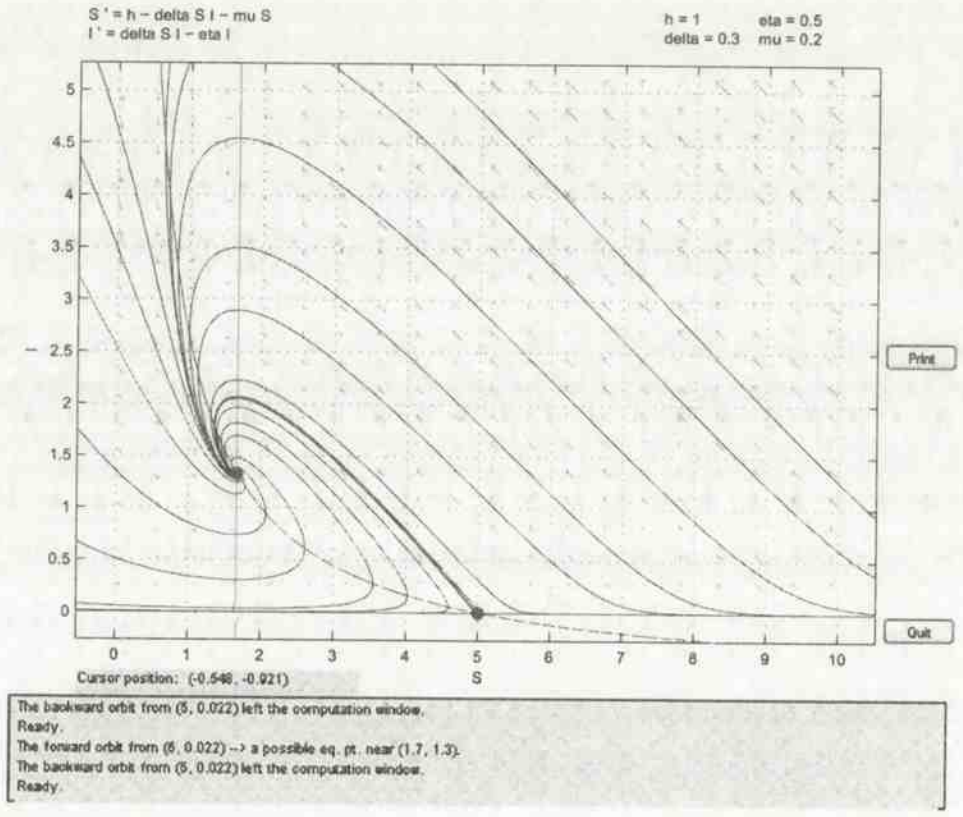
□

We also establish the following theorem.

Theorem 0.2.2.5. *(a) If $r_0 < 1$, the unique DFE (E_0) of the SI model is globally asymptotically stable.*
(b) If $r_0 > 1$, then the unique EE (E_1) is globally asymptotically stable outside of the basin of attraction of the DFE (E_0), which is the entire positive quadrant, $S(t)$, $I(t) > 0$.

Note an eigenvector of λ_1 from equations 0.2.2.2 is found to be $v_1 = (1, 0)^T$. Consequently, when $r_0 > 1$, the DFE (E_0) only attracts the trajectory along the axis $I(t) = 0$. Figure 0.2.2.4 shows a phase plane plot for the SI model 0.2.2.1 when the DFE (E_0) coexists with the EE (E_1), and the trajectories in the positive quadrant tends to E_1 with a damped oscillation.

Theoretically, the infection can be eliminated when the value of $r_0 = \frac{h\delta}{\mu\eta}$ is lowered below 1. The actual process to control the spread of disease may require a massive killing program, and disease eradication is realized through a significant loss of population. Thus, vaccination programs are carried out for disease control, in order to reduce the cost and damage caused by infection.

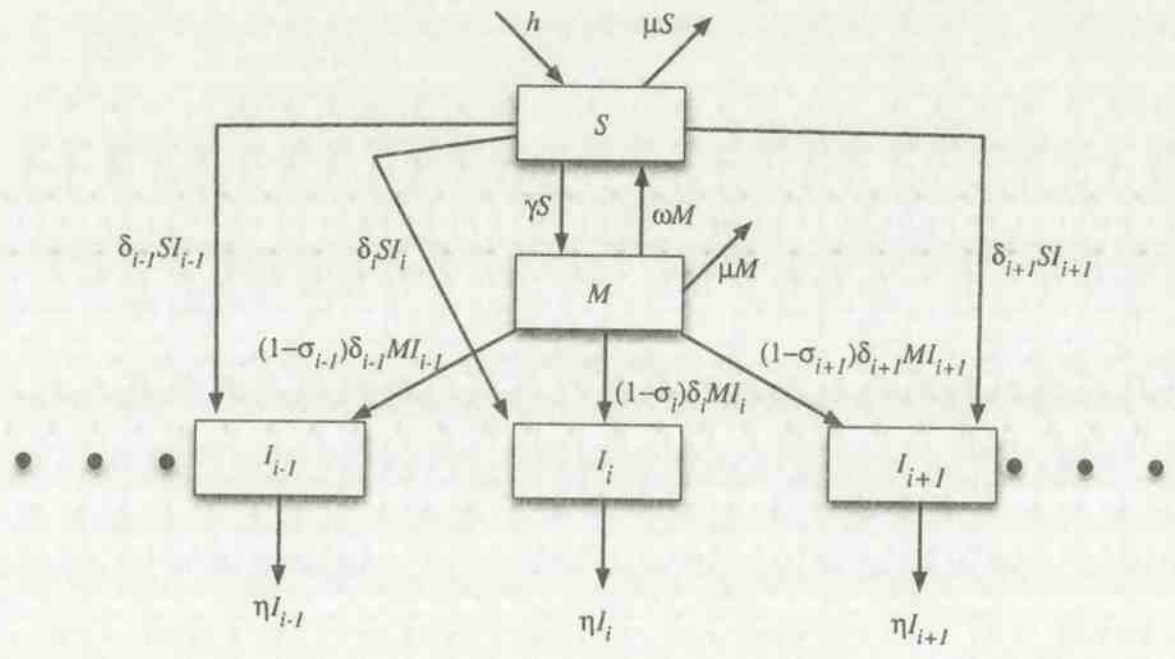


(0.2.2.4)

fig.0.2.2.4. parameter values $h = 1$, $\delta = 0.3$, $\eta = 0.5$ and $\mu = 0.2$, and $r_0 = 3 > 1$

0.3 Population Dynamics Under the Effect of Vaccination

Multiple strains of the AI virus are observed to circulate among poultry, and each of the strains is characterized by a particular antigen on the surface of the virus. Since the majority of infected poultry die within a short time period, our model uses a status-based approach to focus on the current transmission dynamics of the AI virus, and the model assumes individuals infected by one virus strain can not be infected again by another strain. We also assume a poultry population with homogenous susceptibility. Newly recruited populations are solely susceptible. The incubation period of the infectious agent is instantaneous. The model can be extended to incorporate as many strains as one wishes, and the complexity of the model only scales up linearly. We assume one vaccine is used for multiple strains, but the vaccination efficiency varies from strain to strain. This assumption is reasonable since it is impossible to develop a vaccine which can de-activate all virus antigens, and typical vaccination programs use one vaccine against multiple strains of the virus. For example, in Asia, vaccines of H5N2 virus are also used for vaccination against an H5N1 epidemic [14]. Diagram 0.3.0.5 describes the change of population at any time among all population groups.



(0.3.0.5)

Fig.0.3.0.5. Diagram of transmission dynamics among the susceptible (S), vaccinated (M) and infected (I_i) population groups.

Let us assume there exist n strains of the virus. We give the following SMI_i model:

$$\begin{cases} \frac{dS}{dt} &= h + \omega M - \sum_1^n \delta_i S I_i - (\mu + \gamma)S \\ \frac{dM}{dt} &= \gamma S - \sum_1^n (1-\sigma_i)\delta_i M I_i - (\mu + \omega)M \\ \frac{dI_i}{dt} &= \delta_i S I_i + (1-\sigma_i)\delta_i M I_i - \eta I_i, \end{cases} \tag{0.3.0.6}$$

for $i = 1, 2, ..., n$, and all parameters are assumed positive. Table 0.2 defines the notation in the system of equations 0.3.0.6.

The susceptible population, S, is increased by a constant recruitment of susceptible individuals (by birth or immigration), and by the loss of immunity acquired through previous vaccination. This population is reduced via vaccination, infection, and non-disease induced mortality or em-

Notation	Description
S	susceptible population
M	vaccinated population
I_i	population infected with strain i
h	total recruitment rate of individuals
δ_i	transmission rate for the ith strain
μ	rate of susceptible and vaccinated population loss
η	rate of infected population loss
σ_i	vaccine efficacy against the ith strain, $0 < \sigma_i < 1$
ω	rate at which vaccine-based immunity wanes
γ	vaccination rate
$(1-\sigma_i)\delta_i$	effective transmission rate for the ith strain

Tab. 0.2: Notation Definitions

igration. The vaccinated population M, is increased through vaccination of susceptible individuals, and it is decreased by vaccine-based immunity wane, non-disease induced mortality, as well as infection (though vaccinated individuals may be infected at a lower rate compared to susceptible individuals). The infected population, I_i, is increased by infecting susceptible individuals and those who are vaccinated but still remain susceptible. This population decreases as a result of disease induced mortality or via an eradication program.

The Equilibrium States of the SMI_i Model 0.3.0.6

Disease-free equilibrium

The SMI_i model 0.3.0.6 has a DFE,

$$E_{0/n} = (S_0^*, M_0^*, 0) = \left(\frac{h(\mu+\omega)}{\mu(\mu+\omega+\gamma)}, \frac{h\gamma}{\mu(\mu+\gamma+\omega)}, 0 \right).$$

The Jacobian of the SMI_i model evaluated at the DFE is

$$J_0 = \begin{bmatrix} -\mu-\gamma & \omega & -\delta_1 S_0^* & -\delta_2 S_0^* & \dots & \dots & -\delta_n S_0^* \\ \gamma & -\mu-\omega & -(1-\sigma_1)\delta_1 M_0^* & -(1-\sigma_2)\delta_2 M_0^* & \dots & \dots & -(1-\sigma_n)\delta_n M_0^* \\ 0 & 0 & \delta_1 S_0^* + (1-\sigma_1)\delta_1 M_0^* - \eta & 0 & \dots & \dots & 0 \\ 0 & 0 & 0 & \delta_2 S_0^* + (1-\sigma_2)\delta_2 M_0^* - \eta & 0 & \dots & 0 \\ . & . & . & . & \dots & \dots & . \\ . & . & . & . & \dots & \dots & . \\ 0 & 0 & 0 & 0 & \dots & \dots & \delta_n S_0^* + (1-\sigma_n)\delta_n M_0^* - \eta \end{bmatrix}.$$

and the corresponding eigenvalues are:

$$\lambda_1 = -\mu, \quad \lambda_2 = -(\mu+\gamma+\omega), \quad \lambda_{3\dots n+2} = \delta_i S_0^* + (1-\sigma_i)\delta_i M_0^* - \eta, \quad i = 1\dots n.$$

It is obvious that λ_1 and λ_2 are negative since all parameters are assumed positive. Local stability of the DFE ($E_{0/n}$) is guaranteed if and only if

$$\max_i [\delta_i S_0^* + (1-\sigma_i)\delta_i M_0^* - \eta]$$

$$= \max_i \left[\frac{h(\mu+\omega)}{\mu(\mu+\omega+\gamma)}\delta_i + \frac{h(1-\sigma_i)\gamma}{\mu(\mu+\omega+\gamma)}\delta_i - \eta \right] < 0,$$

which is equivalent to

$$\begin{aligned} R_{0/n} &= \frac{h}{\mu\eta} \max_i \delta_i \left[\frac{\mu+\omega+(1-\sigma_i)\gamma}{\mu+\omega+\gamma} \right] \\ &= \frac{S_0^*}{\eta} \max_i \left\{ \delta_i \left[1 + \frac{(1-\sigma_i)\gamma}{\mu+\omega} \right] \right\} \\ &< 1. \end{aligned} \qquad (0.3.0.7)$$

We call $R_{0/n}$ the reproductive number of the infection in the presence of vaccination, which can be interpreted as the number of secondary cases of infection produced by one infected poultry in a susceptible and vaccinated population. Note

$$\left[\frac{\mu+\omega+(1-\sigma_i)\gamma}{\mu+\omega+\gamma}\right]<1.$$

It is sufficient for $R_{0/n}<1$, if $\frac{h}{\mu\eta}\max_i\delta_i<1$. Otherwise, the value of the reproductive number can be brought below 1 via a combination of vaccination and additional measures such as slaughtering infected individuals. If $R_{0/n}<1$, the DFE $(E_{0/n})$ is locally asymptotically stable, which implies the disease can be eradicated if the initial subpopulations are in the basin of attraction of $E_{0/n}$. However, local stability of $E_{0/n}$ does not guarantee global disease eradication for arbitrary initial subpopulations.

The reproductive number $R_{0/n}$ has a lower bound,

$$\tilde{R}_{0/n}=\frac{h}{\mu\eta}\max_i[(1-\sigma_i)\delta_i]. \tag{0.3.0.8}$$

This means that if there are some strains which have sufficiently large effective transmission rate, $(1-\sigma)\delta$, such that $\tilde{R}_{0/n}>1$, no amount of vaccination can eradicate the disease. However, even for the most vaccine-resistant case with $\sigma=0$, we define the basic reproductive number of the infection, $r_{0/n}$,

$$r_{0/n}=\frac{h}{\mu\eta}\max_i\delta_i. \tag{0.3.0.9}$$

If $r_{0/n}<1$, disease invasion fails even without the presence of vaccination. To have $r_{0/n}<1$ may require slaughtering infected poultry on a large scale, and the spread of the disease is eventually controlled when the population size becomes too small to sustain an epidemic.

Therefore, a vaccination program should be accompanied with strategies such as elimination of infected poultry (or poultry under the suspicion of infection) in order to control the spread of the disease. We will now further the discussion of the model 0.3.0.6 by first considering the case that only one virus strain is present.

The Single Strain Case

I. Disease-Free Equilibrium

If the virus circulating among poultry only consists of one strain, then we can slim down the SMI_i model 0.3.0.6 to the following SMI model,

$$\begin{cases} \frac{dS}{dt} &= h + \omega M - \delta SI - (\mu + \gamma)S \\ \frac{dM}{dt} &= \gamma S - (1-\sigma)\delta MI - (\mu + \omega)M \\ \frac{dI}{dt} &= \delta SI + (1-\sigma)\delta MI - \eta I. \end{cases} \tag{0.3.0.10}$$

The corresponding eigenvalues of the DFE $E_0 = (S_0^*, M_0^*, 0)$ are

$$\lambda_1 = -\mu, \quad \lambda_2 = -(\mu+\gamma+\omega), \quad \lambda_3 = \frac{h(\mu+\omega)}{\mu(\mu+\omega+\gamma)}\delta + \frac{h(1-\sigma)\gamma}{\mu(\mu+\omega+\gamma)}\delta - \eta.$$

Thus, the local stability of E_0 depends on the sign of λ_3, and E_0 is locally asymptotically stable if $\lambda_3 < 0$. As before, we obtain the corresponding reproductive number, $R_{0/1}$, the lower bound of the reproductive number, $\tilde{R}_{0/1}$, and the basic reproductive number, $r_{0/1}$.

$$R_{0/1} = \frac{h\delta}{\mu\eta}\left[\frac{\mu+\omega+(1-\sigma)\gamma}{\mu+\omega+\gamma}\right], \tag{0.3.0.11}$$

$$\tilde{R}_{0/1} = \frac{h}{\mu\eta}[(1-\sigma)\delta], \tag{0.3.0.12}$$

$$r_{0/1} = \frac{h\delta}{\mu\eta}. \tag{0.3.0.13}$$

If $r_{0/1} < 1$, the disease invasion fails even without the presence of vaccination; but if $\tilde{R}_{0/1} > 1$, no amount of vaccination can eradicate the disease. If $R_{0/1} < 1$, the DFE is locally asymptotically stable, and the condition $R_{0/1} < 1$ gives three important threshold values, γ_c, σ_c, and δ_c. Provided $\tilde{R}_{0/1} < 1$, the DFE is locally asymptotically stable if and only if

$$\gamma > \gamma_c = \frac{r_{0/1} - 1}{1 - \tilde{R}_{0/1}}(\mu + \omega) = -\frac{h\delta - \mu\eta}{(1-\sigma)h\delta - \mu\eta}(\mu + \omega),$$

or

$$\sigma > \sigma_c = \frac{1}{\gamma} \cdot (1 - \frac{1}{r_{0/1}}) \cdot (\mu + \omega + \gamma) = \frac{h\delta - \mu\eta}{\gamma h\delta}(\mu + \omega + \gamma),$$

or

$$\delta < \delta_c = \frac{\mu\eta}{h} \cdot \frac{\mu + \omega + \gamma}{\mu + \omega + (1-\sigma)\gamma}.$$

The disease becomes endemic when the vaccination rate is below the threshold, γ_c, or if the vaccination efficacy is below the threshold, σ_c. In particular, if

$$\gamma < \min \gamma_c = (r_{0/1} - 1)(\mu + \omega),$$

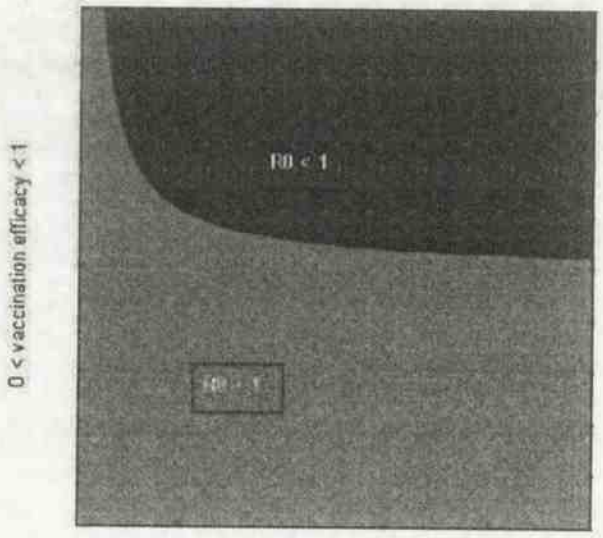
or if

$$\sigma < \min \sigma_c = 1 - \frac{1}{r_{0/1}},$$

no perfect vaccine, or any amount of vaccination can bring $R_{0/1} < 1$, and therefore the spread of disease cannot be stopped. Figure 0.3.0.14 shows the combined effect of the vaccination rate γ and the vaccination efficacy σ in bringing the value of reproductive number below 1. The figure illustrates that beyond the minimum vaccination rate, the higher the vaccination efficacy, the lower the vaccination rate that is needed to bring the reproductive number less than one. Since most vaccination is done through injection,

which is a slow process, using an effective vaccination can be crucial for disease control.

From another point of view, if the transmission rate of the strain is sufficiently high, such that $\delta > \delta_c$, then an epidemic is inevitable.



(0.3.0.14)

Fig.0.3.0.14. The combined effect of γ and σ to bring R_0 less than 1.

According to our model, it is easy to see that

$$R_{0/n} \geq R_{0/n-1} \geq \cdots, \geq R_{0/2} \geq R_{0/1},$$

$$\tilde{R}_{0/n} \geq \tilde{R}_{0/n-1} \geq, \cdots, \geq \tilde{R}_{0/2} \geq \tilde{R}_{0/1},$$

$$r_{0/n} \geq r_{0/n-1} \geq \cdots, \geq r_{0/2} \geq r_{0/1}.$$

Consequently, the more strains that circulate among poultry, the easier it is for the disease to grow out of control, and thus disease eradication becomes harder to realize.

II. Endemic Equilibrium

In order to analyze the endemic equilibria (EE) of the SMI model 0.3.0.10, we express the variables S and M in terms of I when $I \neq 0$, and we study a polynomial in I to determine the existence conditions for the EE.

From the first two equations of system 0.3.0.10, we obtain S and M in terms of I at the EE:

$$S^* = \frac{\eta}{\delta} \cdot \frac{(1-\sigma)\delta I^* + \mu + \omega}{(1-\sigma)\delta I^* + (1-\sigma)\gamma + \mu + \omega}, \tag{0.3.0.15}$$

$$M^* = \frac{\eta}{\delta} \cdot \frac{\gamma}{(1-\sigma)\delta I^* + (1-\sigma)\gamma + \mu + \omega}. \tag{0.3.0.16}$$

The third equation at the EE gives

$$\frac{\delta S^* + (1-\sigma)\delta M^*}{\eta} = 1, \tag{0.3.0.17}$$

and the first equation at the EE gives

$$\frac{\delta S^* I^* + (\mu+\gamma)S^* - \omega M^*}{h} = 1. \tag{0.3.0.18}$$

Substitute equation 0.3.0.17 in to equation 0.3.0.18, to obtain a homogeneous equation in S^* and M^*,

$$\left[\eta\delta I^* + \eta(\mu+\gamma) - h\delta\right] S^* - \left[h(1-\sigma)\delta + \eta\omega\right] M^* = 0,$$

which is a quadratic equation in I^*:

$$P(I^*) = a_2 I^{*2} + a_1 I^* + a_0 = 0, \tag{0.3.0.19}$$

where

$$\begin{aligned} a_2 &= \eta\delta^2(1-\sigma) \geq 0, \\ a_1 &= \left[\eta(\mu+\gamma) - h\delta\right](1-\sigma)\delta + (\mu+\omega)\eta\delta, \\ a_0 &= \left[\eta(\mu+\gamma) - h\delta\right](\mu+\omega) - \left[h(1-\sigma)\delta + \eta\omega\right]\gamma. \end{aligned} \tag{0.3.0.20}$$

The roots of $P(I^*)$ are given by the quadratic formula:

$$I^*_{1,2} = \frac{-a_1 \pm \sqrt{a_1^2 - 4a_2a_0}}{2a_2}.$$

Note $a_0 \geq 0$ implies

$$\eta(\mu+\gamma) - h\delta \geq \frac{[h(1-\sigma)\delta + \eta\omega]\gamma}{\mu+\omega} \geq 0,$$

so $a_1 \geq 0$. Since $a_2 \geq 0$, the roots $I^*_{1,2}$ are complex if $a_1^2 - 4a_2a_0 < 0$, and negative if $a_1^2 - 4a_2a_0 \geq 0$. Thus the polynomial $P(I^*)$ does not have a positive real root if $a_0 \geq 0$.

On the other hand, when $a_0 < 0$, $\sqrt{a_1^2 - 4a_2a_0} \geq |a_1|$, since $a_2 \geq 0$. In particular, if $a_2 = 0$, $\sqrt{a_1^2 - 4a_2a_0} = |a_1|$, and $P(I^*)$ has no real positive root. When $a_2 > 0$, $\sqrt{a_1^2 - 4a_2a_0} > |a_1|$. Consequently, $P(I^*)$ has one unique positive root at

$$I^* = \frac{-a_1 + \sqrt{a_1^2 - 4a_2a_0}}{2a_2}. \tag{0.3.0.21}$$

Since all parameters are assumed positive, $a_2 = 0$ implies $\sigma = 1$, and $a_2 > 0$ implies $0 \leq \sigma < 1$. Therefore, we give the following lemma.

Lemma 0.3.0.6. *i) If the vaccine is perfectly effective against the virus strain, $\sigma = 1$, there exists no endemic equilibrium. ii) If the vaccine is only partially effective, or completely ineffective, $0 \leq \sigma < 1$, then there exists one unique endemic equilibrium when $a_0 < 0$. The infected population at the endemic equilibrium is given by 0.3.0.21*

Proof. If $\sigma = 1$, then $a_2 = 0$ and there is no EE. If $0 \leq \sigma < 1$, then $a_2 > 0$ and there exists a unique EE when $a_0 < 0$.

□

In fact, the sign of a_0 is connected with the reproductive number, $R_{0/1}$. From 0.3.0.20, we see

$$a_0 < 0, \qquad \text{if and only if} \qquad [\eta(\mu+\gamma) - h\delta](\mu+\omega) - [h(1-\sigma)\delta + \eta\omega]\gamma < 0,$$

which means

$$a_0 < 0, \qquad \text{if and only if} \qquad R_{0/1} > 1.$$

Thus, under the effect of a partially effective vaccine or no vaccine, we have the following theorem given by Professor Hiromi Seno.

Theorem 0.3.0.7. *The endemic equilibrium of the SMI model 0.3.0.10 exists under the following necessary and sufficient condition:*

$$(1 - \tilde{R}_{0/1})\gamma < (r_{0/1} - 1)(\mu + \omega). \tag{0.3.0.22}$$

Furthermore, it is sufficient for

$$a_0 < 0, \qquad \text{if} \qquad \eta(\mu+\gamma) - h\delta < 0,$$

which means

$$\gamma < \mu(r_{0/1} - 1). \tag{0.3.0.23}$$

From another point of view, we can rewrite condition 0.3.0.22 and 0.3.0.23, so that it is evident that an epidemic occurs when the virus strain has a sufficiently large transmission rate. That is, an epidemic occurs when either one of the following two conditions is met:

$$\begin{aligned} &1) \quad \delta > \tfrac{\eta}{h}(\mu+\gamma), \quad \text{or} \\ &2) \quad \delta < \tfrac{\eta}{h}(\mu+\gamma), \quad \text{and} \quad \delta > \tfrac{\mu\eta}{h}\tfrac{\mu+\omega+\gamma}{\mu+\omega+(1-\sigma)\gamma}. \end{aligned} \tag{0.3.0.24}$$

We have shown that when the endemic equilibrium exists, the reproductive number is greater than 1. Therefore, the DFE (E_0) becomes unstable, and we establish the following theorem.

Theorem 0.3.0.8. *For the SMI model 0.3.0.10, when the EE (E_1) exists, a (transcritical) bifurcation always occurs to destabilize the DFE (E_0).*

In fact, when $R_{0/1} > 1$, the DFE (E_0) only attracts trajectories on the SM-plane. This means if the reproductive number is greater than 1, the disease free state can not be realized for any positive initial size of the infected population.

Knowing the existence conditions for the endemic equilibrium, we will now investigate its local stability. First, we find the Jacobian of the SMI system 0.3.0.10 evaluated at the EE (E_1),

$$J_1 = \begin{bmatrix} -(\gamma+\mu+\delta I^*) & \omega & -\delta S^* \\ \gamma & -[(\mu+\omega+(1-\sigma)\delta I^*] & -(1-\sigma)\delta M^* \\ \delta I^* & (1-\sigma)\delta I^* & 0 \end{bmatrix}.$$

We obtain its corresponding characteristic equation $P(\lambda)$, where λ is an eigenvalue.

$$P(\lambda) = a_3\lambda^3 + a_2\lambda^2 + a_1\lambda + a_0,$$

where

$$a_3 = 1,$$

$$a_2 = Y + (1-\sigma)C + X + C,$$

$$a_1 = (1-\sigma)^2BC + (1-\sigma)XC + (1-\sigma)C^2 + XY + YC + AC - \gamma\omega,$$

$$a_0 = (1-\sigma)\omega BC + (1-\sigma)\gamma AC + YAC + (1-\sigma)AC^2 + (1-\sigma)^2 XBC + (1-\sigma)^2 BC^2,$$

and

$$A = \delta S^*, \quad B = \delta M^*, \quad C = \delta I^*, \quad X = \gamma + \mu, \quad Y = \omega + \mu.$$

It is clear that a_3, a_2 and a_0 are positive, and it can be verified that a_1 is also positive since $XY > \gamma\omega$. We use the **Routh-Hurwitz Criterion** [2] to analyze the characteristic polynomial $P(\lambda)$, and to determine the local stability of the endemic equilibrium.

Remark 0.3.0.9. For a characteristic equation written in its general form:

$$a_n\lambda^n + a_{n-1}\lambda^{n-1} + \ldots + a_1\lambda + a_0 = 0, \qquad a_i > 0, \text{ for } i = 0, 1, 2, \ldots, n$$

the Routh Array can be constructed as follow

$$\begin{array}{c|cccc} \lambda^n & a_n & a_{n-2} & a_{n-4} & \cdots & 0 \\ \lambda^{n-1} & a_{n-1} & a_{n-3} & a_{n-5} & \cdots & 0 \\ \lambda^{n-2} & b_{n-2} & b_{n-4} & \cdots & & \\ \lambda^{n-3} & c_{n-3} & c_{n-5} & \cdots & & \\ \vdots & \vdots & & & & \\ \lambda^0 & \cdots & & & & \end{array} \tag{0.3.0.25}$$

The array has $n+1$ rows, and the first two rows of λ^n and λ^{n-1} are filled with the coefficients from the characteristic equation. The final columns for each row should contain zeros. We now construct appropriate terms to fill the rows λ^{n-2} and λ^{n-3}:

$$b_{n-i} = \frac{a_{n-1}a_{n-i} - a_n a_{n-i-1}}{a_{n-1}}, \qquad i = 2, 4, 6, \ldots$$

$$c_{n-j} = \frac{b_{n-2}a_{n-j} - a_{n-1}b_{n-j-1}}{b_{n-2}}, \qquad j = 3, 5, 7, ...$$

Fillers for the rest of the rows can be constructed in an analogous manner, until we reach the bottom of the array.

The **Routh-Hurwitz Criterion** states that for a characteristic polynomial in its general form, the number of unstable roots is the number of changes in sign in the first column of the Routh Array:

$$\begin{array}{c} a_n \\ a_{n-1} \\ b_{n-2} \\ c_{n-3} \\ \vdots \end{array} \tag{0.3.0.26}$$

Using this technique, we find the first column of Routh Array for the characteristic polynomial $P(\lambda)$,

$$\begin{array}{c} a_3 \\ a_2 \\ b_1 \\ c_0 \end{array} \tag{0.3.0.27}$$

where $b_1 = \frac{a_2a_1 - a_3a_0}{a_2} = \frac{a_2a_1 - a_0}{a_2}$, and $c_0 = \frac{b_1a_0}{b_1} = a_0$. The coefficients a_3, a_2 and c_0 are obviously positive, and we show that $b_1 > 0$ in appendix 1. Since there is no sign change in the first column of the Routh Array, no zero of $P(\lambda)$ has positive real part, thus we establish the following lemma.

Lemma 0.3.0.10. *The endemic equilibrium of the SMI model 0.3.0.10 is always locally asymptotically stable.*

Next, we will determine the condition for which the population tends to the EE(E_1) with damped oscillation. We have learned from the Routh-Hurwitz Criterion that all eigenvalues have negative real parts, and we will now determine when the eigenvalues have imaginary parts. If the eigenvalues have imaginary parts, the discriminant of the characteristic polynomial $P(\lambda)$ must be negative.

Let

$$D = 27a_0^2 + (4a_2^3 - 18a_2a_1)a_0 + 4a_1^3 - a_2^2a_1^2$$

be the discriminant of the cubic polynomial $P(\lambda)$. Note D is quadratic in terms of a_0, and we know $a_0 > 0$. If the population tends to the equilibrium E_1 with damped oscillation, there must exist a positive range of a_0, such that $D < 0$. We denote this range,

$$max\{0, a_{0-}\} < a_0 < a_{0+},$$

where

$$a_{0-} = \frac{-(4a_2^3 - 18a_2a_1) - \sqrt{(4a_2^3 - 18a_2a_1)^2 - 108(4a_1^3 - a_2^2a_1^2)}}{54},$$

and

$$a_{0+} = \frac{-(4a_2^3 - 18a_2a_1) + \sqrt{(4a_2^3 - 18a_2a_1)^2 - 108(4a_1^3 - a_2^2a_1^2)}}{54}.$$

If there exists such positive range for a_0, one of the two following two conditions must be satisfied:

$$\begin{cases} 1)\ \ 4a_1^3 - a_2^2a_1^2 < 0; \\ or \\ 2)\ \ 4a_1^3 - a_2^2a_1^2 \geq 0,\ \ 4a_2^3 - 18a_2a_1 < 0,\ \text{and} \\ \quad (4a_2^3 - 18a_2a_1)^2 \geq 108(4a_1^3 - a_2^2a_1^2). \end{cases} \tag{0.3.0.28}$$

Particularly, if condition 1) is true, $a_{0-} < 0$, so $D < 0$ when $0 < a_0 < a_{0+}$. If condition 2) is true, $a_{0-} > 0$, thus $D < 0$ when $a_{0-} < a_0 < a_{0+}$. Note

$$4a_1^3 - a_2^2 a_1^2 \lessgtr 0 \iff a_1^2(4a_1 - a_2^2) \lessgtr 0 \iff a_2^2 \gtrless 4a_1;$$

$$4a_2^3 - 18a_2a_1 < 0 \iff 2a_2(2a_2^2 - 9a_1) < 0 \iff a_2^2 < \frac{9}{2}a_1;$$

$$(4a_2^3 - 18a_2a_1)^2 \geq 108(4a_1^3 - a_2^2a_1^2) \iff a_2^6 - 9a_1a_2^4 + 27a_1^2a_2^2 - 27a_1^3 \geq 0$$

$$\iff a_2^2 \geq 3a_1.$$

Therefore, the conditions in 0.3.0.28 become

$$\begin{cases} 1)\ a_2^2 > 4a_1, \\ or \\ 2)\ 3a_1 \leq a_2^2 \leq 4a_1, \end{cases} \tag{0.3.0.29}$$

and they imply the trajectories tend to E_1 with damped oscillation when

$$a_2^2 - 3a_1 \geq 0. \tag{0.3.0.30}$$

In conclusion, when there is no perfectly effective vaccine to target the virus strain, and if the strain has a sufficiently large transmission rate so that the conditions in 0.3.0.24 are satisfied, an epidemic will occur, and the virus can persist if the initial size of the subpopulations is in the basin of attraction of the endemic equilibrium. Moreover, the population can tend to the EE with damped oscillation under proper conditions.

Endemic Equilibria of the SMI_i Model 0.3.0.6

Consider the case where the initial virus consists of multiple strains, and assume all model parameters are positive. We will show that the full SMI_i model 0.3.0.6 has an EE where there exists a maximum of two distinct strains with distinguished transmission rate and vaccination efficacy. We will first discuss the EE where only one virus strain exists.

I. EE with One Surviving Strain

In this section, we investigate an endemic equilibrium state where only one strain exists, and we determine the stability of this equilibrium. Mathematically speaking, we investigate the existence and stability of an equilibrium, $E_j = (S_j^*, M_j^*, I_1^*, I_2^*, ..., I_n^*)$, where S_j^*, M_j^*, and I_i^*, for $i = 1, 2, ..., n$ are respectively the population of susceptible, vaccinated and infected poultry at the EE E_j, and $I_j^* \neq 0$, while $I_i^* = 0$ for $i \neq j$. As in the simple SMI model, we write S_j^* and M_j^* in terms of I_j^*, and then consider a polynomial in I_j^* to derive existence conditions for the EE E_j.

$$S_j^* = \frac{\eta}{\delta_j} \cdot \frac{(1-\sigma_j)\delta_j I_j^* + \mu + \omega}{(1-\sigma_j)\delta_j I_j^* + (1-\sigma_j)\gamma + \mu + \omega},$$

$$M_j^* = \frac{\eta}{\delta_j} \cdot \frac{\gamma}{(1-\sigma_j)\delta_j I_j^* + (1-\sigma_j)\gamma + \mu + \omega},$$

and the polynomial in I_j^* is

$$P(I_j^*) = \tilde{a}_2 I_j^{*2} + \tilde{a}_1 I_j^* + \tilde{a}_0 = 0,$$

where

$$\tilde{a}_2 = \eta\delta_j^2(1-\sigma_j) \geq 0,$$

$$\tilde{a}_1 = [\eta(\mu+\gamma) - h\delta_j](1-\sigma_j)\delta_j + (\mu+\omega)\eta\delta_j,$$

$$\tilde{a}_0 = [\eta(\mu+\gamma) - h\delta_j](\mu+\omega) - [h(1-\sigma_j)\delta_j + \eta\omega]\gamma.$$

At the EE E_j, the size of the susceptible, vaccinated and infected populations given by strain j is the same as if the initial virus only consisted of strain j. Similarly, if $0 < \sigma_j < 1$, strain j becomes the only persisting strain if and only if $\tilde{a}_0 < 0$. As we verified in the previous section, $\tilde{a}_0 < 0$ if and only if $R_{0/j} > 1$, and we obtain the following Theorem.

Theorem 0.3.0.11. *When the vaccination against strain j is only partially effective or ineffective, strain j uniquely survives at the EE (E_j) under the following necessary and sufficient condition:*

$$(1-\tilde{R}_{0/j})\gamma < (r_{0/j}-1)(\mu+\omega). \tag{0.3.0.31}$$

Furthermore, it is sufficient for $\tilde{a}_0 < 0$, if

$$\gamma < \mu(r_{0/j}-1).$$

Note $R_{0/j} \leq R_{0/n}$, thus $R_{0/j} > 1$ implies $R_{0/n} > 1$. Therefore, we have the following theorem.

Theorem 0.3.0.12. *When the EE (E_j) exists, a (transcritical) bifurcation always occurs to destabilize the DFE of the SMI_i model 0.3.0.6.*

We have learned from the previous section that the endemic equilibrium E_1 of the SMI model is always locally asymptotically stable. Using this fact, we can show that under the right conditions, E_j of the SMI_i model, can also be locally asymptotically stable.

By exchanging the third and the j^{th} row of the n by n identity matrix, we obtain the permutation matrix below,

$$P = \begin{bmatrix} 1 & 0 & 0 & 0 & \cdots & \cdots & 0 & \cdots & \cdots & 0 \\ 0 & 1 & 0 & 0 & \cdots & \cdots & 0 & \cdots & \cdots & 0 \\ 0 & 0 & 0 & 0 & \cdots & \cdots & 1 & \cdots & \cdots & 0 \\ 0 & 0 & 0 & 1 & \cdots & \cdots & 0 & \cdots & \cdots & 0 \\ \vdots & & & & \ddots & & \vdots & & & \vdots \\ \vdots & & & & & \ddots & \vdots & & & \vdots \\ 0 & 0 & 1 & 0 & \cdots & \cdots & 0 & \cdots & \cdots & 0 \\ \vdots & & & & & & 0 & \ddots & & \vdots \\ \vdots & & & & & & 0 & & \ddots & \vdots \\ 0 & 0 & 0 & 0 & \cdots & \cdots & 0 & \cdots & \cdots & 1 \end{bmatrix}$$

(jth column; jth row)

Denote by J_j the Jacobian of the SMI_i model evaluated at E_j, with λ an eigenvalue. The matrices $P^{-1}(J_j - \lambda I)P$ and $(J_j - \lambda I)$ are similar matrices, thus

$$\det\left\{(P^{-1})(J_j - \lambda I)(P)\right\} = \det(P^{-1}P)\det(J_j - \lambda I) = \det(J_j - \lambda I) =$$

$$\begin{vmatrix} -\delta_j I_j^* - \mu - \gamma - \lambda & \omega & -\delta_j S_j^* & -\delta_2 S_j^* & \cdots & -\delta_n S_j^* \\ \gamma & -(1-\sigma_j)\delta_j I_j^* - \mu - \omega - \lambda & -(1-\sigma_j)\delta_j M_j^* & -(1-\sigma_2)\delta_2 M_j^* & \cdots & -(1-\sigma_n)\delta_n M_j^* \\ \delta_j I_j^* & (1-\sigma_j)\delta_j I_j^* & -\lambda & 0 & \cdots & 0 \\ 0 & 0 & 0 & \Phi_2 - \lambda & 0 & 0 \\ \vdots & & & & \ddots & \vdots \\ 0 & 0 & 0 & 0 & \cdots & \Phi_n - \lambda \end{vmatrix},$$

where $\Phi_i = \delta_i S_j^* + (1-\sigma_i)\delta_i M_j^* - \eta$, and $i = 1, 2, 3, ..., n$, and $i \neq j$. Consequently, E_j is locally asymptotically stable if and only if

$$\max_i \Phi_i = \max_i [\delta_i S_j^* + (1-\sigma_i)\delta_i M_j^* - \eta] < 0, \qquad (0.3.0.32)$$

where $i = 1, 2, 3, ..., n$ and $i \neq j$. The above stability condition 0.3.0.32 implies

$$\max_i \left\{ \frac{\delta_i \eta[(1-\sigma_j)\delta_j I_j^* + \mu + \omega] + (1-\sigma_i)\delta_i \eta\gamma}{\delta_j[(1-\sigma_j)\delta_j I_j^* + (1-\sigma_j)\gamma + \mu + \omega]} - \eta \right\} < 0, \qquad (0.3.0.33)$$

Below, we summarize the conditions for the locally stability of E_j.

Theorem 0.3.0.13. *When strain j uniquely exists at the $EE(E_j)$, E_j is locally asymptotically stable if and only if*

$$\frac{\max_i \left\{\delta_i[(1-\sigma_j)\delta_j I_j^* + (1-\sigma_i)\gamma + \mu + \omega]\right\}}{\delta_j[(1-\sigma_j)\delta_j I_j^* + (1-\sigma_j)\gamma + \mu + \omega]} < 1,$$

where $i = 1, 2, 3, ...n$ and $i \neq j$.

A sufficient condition for local asymptotic stability of EE (E_j) is

$$\delta_i < \delta_j, \text{ and } \sigma_i > \sigma_j.$$

That is, strain j has a higher transmission rate and the vaccine has lower efficacy than for any other strain.

II. EE with Two Distinct Strains

In this section, we answer the question of how many strains can exist simultaneously at an endemic equilibrium. Professor Hiromi Seno proved that if each strain is characterized by its own distinguished transmission rate and efficacy, a maximum of only two strains can coexist at the equilibrium, and he determined the characteristics of the two strains, as well as the co-existence conditions for the two strains at the EE.

Theorem 0.3.0.14. *No more than two distinct strains of virus can coexist at an endemic state of the SMI_i model 0.3.0.6.*

Proof. If the values of δ_i and σ_i are distinct, the last set of equations of the SMI_i model 0.3.0.6 at an endemic equilibrium is an inconsistent set for S^* and M^* if there are more than 2 virus strains. □

Note, in appendix 2 and 3, we will briefly discuss some special endemic equilibria where n strains exist simultaneously,under the assumption that model parameters can be zero.

To derive the existence conditions of an equilibrium consisting of two distinct virus strains, we first let

$$\begin{aligned} A(\{I_i^*\}) &= \textstyle\sum_{i=1}^n \delta_i I_i^* + \mu + \gamma, \\ B(\{I_i^*\}) &= \textstyle\sum_{i=1}^n (1-\sigma_i)\delta_i I_i^* + \mu + \omega. \end{aligned} \tag{0.3.0.34}$$

The SMI_i system 0.3.0.6 at its endemic equilibrium state $(S^*, M^*, \{I_i^*\})$ can be written as

$$\begin{cases} h + \omega M^* - A(\{I_i^*\})S^* = 0 \\ \gamma S^* - B(\{I_i^*\})M^* = 0 \\ \delta_i S^* + (1-\sigma_i)\delta_i M^* - \eta = 0, \quad for \ \ i \in E. \end{cases} \tag{0.3.0.35}$$

The first and second equations of 0.3.0.35 gives

$$S^* = \frac{hB(\{I_i^*\})}{A(\{I_i^*\})B(\{I_i^*\}) - \gamma\omega} > 0,$$

$$M^* = \frac{\gamma h}{A(\{I_i^*\})B(\{I_i^*\}) - \gamma\omega} > 0.$$

Substitute S^* and M^* into the last set of equations 0.3.0.35, and we have

$$\delta_i hB(\{I_i^*\}) + (1-\sigma_i)\delta_i\gamma h - \eta[A(\{I_i^*\})B(\{I_i^*\}) - \gamma\omega] = 0. \qquad (0.3.0.36)$$

If the endemic equilibrium consists of two strains, I_j and I_k, equation 0.3.0.36 gives

$$\begin{aligned} A(\{I_i^*\}) &= \tfrac{\delta_j h}{\eta} + \tfrac{(1-\sigma_j)\delta_j h/\eta + \omega}{B(\{I_i^*\})/\gamma} \\ &= \tfrac{1}{B(\{I_i^*\})/\gamma}\left[\tfrac{h}{\eta}\tfrac{\delta_j\delta_k}{\delta_j-\delta_k}(\sigma_j-\sigma_k) + \omega\right], \qquad (0.3.0.37) \\ B(\{I_i^*\}) &= \tfrac{(1-\sigma_j)\delta_j - (1-\sigma_k)\delta_k}{\delta_k-\delta_j}\gamma. \end{aligned}$$

Since, from equation 0.3.0.34, $A(\{I_i^*\}$ and $B(\{I_i^*\})$ both must be positive, we obtain the following lemma.

Lemma 0.3.0.15. *For the existence of the endemic equilibrium state with two distinct strains, the condition below is necessary.*

$$[(1-\sigma_j)\delta_j - (1-\sigma_k)\delta_k](\delta_j - \delta_k) < 0. \qquad (0.3.0.38)$$

Therefore, the following conditions must be satisfied simultaneously.

Lemma 0.3.0.16. *If two distinct virus strains coexist at the endemic equilibrium state, they necessarily have $\delta_j > \delta_k$ and $\sigma_j > \sigma_k$, or vice versa.*

This means that for two distinct strains to coexist at the endemic equilibrium state, the strain with greater transmission rate, must also be the one for which the vaccine is more effective.

Furthermore, from equation 0.3.0.34 and 0.3.0.37, we obtain a system of equations in terms of I_j^* and I_k^*,

$$\begin{cases} \delta_j I_j^* + \delta_k I_k^* + \mu + \gamma = \frac{1}{B(\{I_i^*\})/\gamma} \left[\frac{h}{\eta} \frac{\delta_j \delta_k}{\delta_j - \delta_k} (\sigma_j - \sigma_k) + \omega \right] \\ (1-\sigma_j)\delta_j I_j^* + (1-\sigma_k)\delta_k I_k^* + \mu + \omega = B(\{I_i^*\}). \end{cases} \tag{0.3.0.39}$$

The endemic equilibrium state with two coexisting strains exists if and only if equation 0.3.0.39 has a positive real root (I_j^*, I_k^*) under the condition 0.3.0.38.

Suppose there exist two strains I_j and I_k with characteristics $0 < \delta_k < \delta_j$, and $0 < \sigma_k < \sigma_j < 1$. Let

$$C_1 = \delta_j I_j^* + \delta_k I_k^*,$$

$$C_2 = (1-\sigma_j)\delta_j I_j^* + (1-\sigma_k)\delta_k I_k^*.$$

From equations 0.3.0.38 and 0.3.0.39, we give the following conditions for the existence of the positive real root (I_j^*, I_k^*),

$$\begin{cases} C_1 = \frac{1}{B(\{I_i^*\})/\gamma} \left[\frac{h}{\eta} \frac{\delta_j \delta_k}{\delta_j - \delta_k} (\sigma_j - \sigma_k) + \omega \right] - (\mu + \gamma) > 0, \\ C_2 = B(\{I_i^*\}) - (\mu + \omega) > 0, \\ (C_1 - \frac{C_2}{1-\sigma_j})(C_1 - \frac{C_2}{1-\sigma_k}) < 0. \end{cases} \tag{0.3.0.40}$$

Since $\sigma_k < \sigma_j < 1$, the third inequality from the above system of equations 0.3.0.40, is equivalent to

$$\begin{cases} (1-\sigma_j)C_1 - C_2 < 0, \\ (1-\sigma_k)C_1 - C_2 > 0. \end{cases} \tag{0.3.0.41}$$

We will solve the inequality above for γ, in order to determine if there exists a positive range of vaccination rate, such that two virus strains coexist at the endemic equilibrium state. We have

$$\begin{cases} \gamma < \frac{1}{B(\{I_i^*\})/\gamma}\left[\frac{h}{\eta}\frac{\delta_j\delta_k}{\delta_j-\delta_k}(\sigma_j-\sigma_k)+\omega\right]-\mu, \\ \gamma > \frac{\mu+\omega}{B(\{I_i^*\})/\gamma}, \\ \gamma > \frac{\delta_j-\delta_k}{(\sigma_j-\sigma_k)\delta_k}\left\{\frac{1-\sigma_j}{B(\{I_i^*\})/\gamma}\left[\frac{h}{\eta}\frac{\delta_j\delta_k}{\delta_j-\delta_k}(\sigma_j-\sigma_k)+\omega\right]+\sigma_j\mu+\omega\right\}, \\ \gamma < \frac{\delta_j-\delta_k}{(\sigma_j-\sigma_k)\delta_j}\left\{\frac{1-\sigma_k}{B(\{I_i^*\})/\gamma}\left[\frac{h}{\eta}\frac{\delta_j\delta_k}{\delta_j-\delta_k}(\sigma_j-\sigma_k)+\omega\right]+\sigma_k\mu+\omega\right\}, \end{cases} \tag{0.3.0.42}$$

$$\Downarrow$$

$$\begin{cases} \gamma < \frac{(\sigma_j-\sigma_k)\delta_j\delta_k}{(1-\sigma_k)\delta_k-(1-\sigma_j)\delta_j}\frac{h}{\eta}+\frac{\delta_j-\delta_k}{(1-\sigma_k)\delta_k-(1-\sigma_j)\delta_j}\omega-\mu, \\ \gamma > \frac{\delta_j-\delta_k}{(1-\sigma_k)\delta_k-(1-\sigma_j)\delta_j}(\mu+\omega), \\ \gamma > \frac{\delta_j-\delta_k}{(\sigma_j-\sigma_k)\delta_k}\left\{\frac{(1-\sigma_j)(\sigma_j-\sigma_k)\delta_j\delta_k}{(1-\sigma_k)\delta_k-(1-\sigma_j)\delta_j}\frac{h}{\eta}+\frac{(\sigma_j-\sigma_k)\delta_k}{(1-\sigma_k)\delta_k-(1-\sigma_j)\delta_j}\omega+\sigma_j\mu\right\}, \\ \gamma < \frac{\delta_j-\delta_k}{(\sigma_j-\sigma_k)\delta_j}\left\{\frac{(1-\sigma_k)(\sigma_j-\sigma_k)\delta_j\delta_k}{(1-\sigma_k)\delta_k-(1-\sigma_j)\delta_j}\frac{h}{\eta}+\frac{(\sigma_j-\sigma_k)\delta_j}{(1-\sigma_k)\delta_k-(1-\sigma_j)\delta_j}\omega+\sigma_k\mu\right\}, \end{cases} \tag{0.3.0.43}$$

$$\Downarrow$$

$$\begin{cases} \gamma < \frac{(\sigma_j-\sigma_k)\delta_j\delta_k}{(1-\sigma_k)\delta_k-(1-\sigma_j)\delta_j}\frac{h}{\eta}+\frac{\delta_j-\delta_k}{(1-\sigma_k)\delta_k-(1-\sigma_j)\delta_j}\omega-\mu, \\ \gamma > \frac{\delta_j-\delta_k}{(1-\sigma_k)\delta_k-(1-\sigma_j)\delta_j}(\mu+\omega), \\ \gamma > \frac{\delta_j-\delta_k}{(1-\sigma_k)\delta_k-(1-\sigma_j)\delta_j}\left\{(1-\sigma_j)\delta_j\frac{h}{\eta}+\frac{\sigma_j[(1-\sigma_k)\delta_k-(1-\sigma_j)\delta_j]}{(\sigma_j-\sigma_k)\delta_k}\mu+\omega\right\}, \\ \gamma < \frac{\delta_j-\delta_k}{(1-\sigma_k)\delta_k-(1-\sigma_j)\delta_j}\left\{(1-\sigma_k)\delta_k\frac{h}{\eta}+\frac{\sigma_k[(1-\sigma_k)\delta_k-(1-\sigma_j)\delta_j]}{(\sigma_j-\sigma_k)\delta_j}\mu+\omega\right\}, \end{cases} \tag{0.3.0.44}$$

$$\Downarrow$$

$$\begin{cases} \gamma < \widehat{\gamma_c}+\frac{(\sigma_j-\sigma_k)\delta_k\mu}{(1-\sigma_k)\delta_k-(1-\sigma_j)\delta_j}\left[r_{0/2}-\frac{\sigma_j\delta_j-\sigma_k\delta_k}{(\sigma_j-\sigma_k)\delta_k}\right], \\ \gamma > \widehat{\gamma_c}, \\ \gamma > \widehat{\gamma_c}+\frac{(1-\sigma_j)(\delta_j-\delta_k)\mu}{(1-\sigma_k)\delta_k-(1-\sigma_j)\delta_j}\left[r_{0/2}-\frac{\sigma_j\delta_j-\sigma_k\delta_k}{(\sigma_j-\sigma_k)\delta_k}\right], \\ \gamma < \widehat{\gamma_c}+\frac{(1-\sigma_k)(\delta_j-\delta_k)\mu\delta_k/\delta_j}{(1-\sigma_k)\delta_k-(1-\sigma_j)\delta_j}\left[r_{0/2}-\frac{\sigma_j\delta_j-\sigma_k\delta_k}{(\sigma_j-\sigma_k)\delta_k}\right], \end{cases} \tag{0.3.0.45}$$

where

$$\widehat{\gamma_c} = \frac{\delta_j - \delta_k}{(1-\sigma_k)\delta_k - (1-\sigma_j)\delta_j}(\mu+\omega);$$

$$r_{0/2} = \frac{h\delta_j}{\mu\eta}.$$

Eventually, the consistency between these inequalities gives the following necessary condition,

$$r_{0/2} > \frac{\sigma_j\delta_j - \sigma_k\delta_k}{(\sigma_j-\sigma_k)\delta_k} > 1. \tag{0.3.0.46}$$

Only if 0.3.0.46 is satisfied, does there exist a positive range of vaccination rate γ, that satisfies the inequalities of 0.3.0.45, which gives a positive root for (I_j^*, I_k^*). We summarize the existence conditions for two virus strains to coexist at the endemic equilibrium in the following theorem.

Theorem 0.3.0.17. *Let $E_{j,k}$ be the equilibrium state with two distinct surviving strains. $E_{j,k}$ exists if and only if the following four conditions are simultaneously satisfied:*

i) $\delta_j > \delta_k$ and $\sigma_j > \sigma_k$;

ii) The condition 0.3.0.38;

iii) The condition 0.3.0.46;

iv)

$$\begin{cases} \gamma > \widehat{\gamma_c} + \frac{(1-\sigma_j)(\delta_j-\delta_k)\mu}{(1-\sigma_k)\delta_k-(1-\sigma_j)\delta_j}\left[r_{0/2} - \frac{\sigma_j\delta_j-\sigma_k\delta_k}{(\sigma_j-\sigma_k)\delta_k}\right], \\ \gamma < \widehat{\gamma_c} + \frac{(1-\sigma_k)(\delta_j-\delta_k)\mu\delta_k/\delta_j}{(1-\sigma_k)\delta_k-(1-\sigma_j)\delta_j}\left[r_{0/2} - \frac{\sigma_j\delta_j-\sigma_k\delta_k}{(\sigma_j-\sigma_k)\delta_k}\right]. \end{cases} \tag{0.3.0.47}$$

The last condition in the above theorem indicates that such an endemic state with two surviving strains can exist for an intermediate range of the vaccination rate γ. We will next investigate if $E_{j,k}$ is locally asymptotically

stable.

Local Stability of $E_{j,k}$

Once again, we use eigenvalue analysis to study the local stability of $E_{j,k}$. Let $\nu_j = 1-\sigma_j$ be the effective transmission rate for strain j, and $\nu_k = 1-\sigma_k$ be the effective transmission rate for strain k. Since $\sigma_k < \sigma_j$, $\nu_k > \nu_j$. Then, let

$$x = \delta_j S^*,$$

$$X = \delta_k S^*,$$

$$y = \nu_j \delta_j M^*,$$

$$Y = \nu_k \delta_k M^*,$$

$$z = \delta_j I_j^*,$$

$$Z = \delta_k I_k^*.$$

We first suppose that the existing viruses are strains j and k, and we explore the corresponding stability criteria. Thus the Jacobian of the SMI_i system 0.3.0.6 evaluated at the equilibrium with two coexisting strains, $\bar{E}_{j,k}$ is:

$$\bar{J}_{j,k} = \begin{bmatrix} -A\{I_j^* + I_k^*\} & \omega & -x & -X \\ \gamma & -B\{I_j^* + I_k^*\} & -y & -Y \\ z & \nu_j z & 0 & 0 \\ Z & \nu_k Z & 0 & 0 \end{bmatrix},$$

and the characteristic polynomial of $\bar{J}_{j,k}$ is

$$P(\lambda) = a_4\lambda^4 + a_3\lambda^3 + a_2\lambda^2 + a_1\lambda + a_0,$$

where

$$a_4 = 1,$$

$$a_3 = A + B,$$

$$a_2 = XZ + \nu_k YZ + xz + \nu_j yz + AB - \gamma\omega,$$

$$a_1 = \omega(yz + YZ) + \gamma(\nu_j xz + \nu_k XZ) + A(\nu_j yz + \nu_k YZ) + B(xz + XZ),$$

$$a_0 = [\nu_j(Xy - xY) + \nu_k(xY - Xy)]Zz.$$

All coefficients of $P(\lambda)$ are positive since S^*, M^*, I_j^* and I_k^* are all positive at the equilibrium $\bar{E}_{j,k}$.

To determine if $P(\lambda)$ has unstable roots, we first construct the Routh Array:

$$\begin{array}{c|ccc} \lambda^4 & a_4 & a_2 & a_0 \\ \lambda^3 & a_3 & a_1 & 0 \\ \lambda^2 & b_2 & b_0 & \\ \lambda^1 & c_1 & 0 & \\ \lambda^0 & d_0, & & \end{array} \qquad (0.3.0.48)$$

where

$$b_2 = \frac{a_3 a_2 - a_1}{a_3},$$
$$b_0 = \frac{a_3 a_0 - a_4 \cdot 0}{a_3} = a_0,$$
$$c_1 = \frac{b_2 a_1 - a_3 b_0}{b_2} = a_1 - \frac{a_3^2 a_0}{a_3 a_2 - a1},$$
$$d_0 = \frac{c_1 b_0 - b_2 \cdot 0}{c_1} = b_0 = a_0.$$

The signs of b_2 and c_1 determine if the characteristic polynomial $P(\lambda)$ has any unstable root. If both b_2 and c_1 are positive, there is no sign

change in the first column of the Routh Array, and therefore, $\bar{E}_{j,k}$ is locally asymptotically stable. In contrast, if either b_2 or c_1 is negative, which results in a sign change in the first column of the Routh Array, $\bar{E}_{j,k}$ is unstable.

If $\bar{E}_{j,k}$ is stable, we can derive the criterion for stability of $E_{j,k}$ using the same technique done in the previous section when we determined the stability of E_j.

Apply the permutation matrix,

$$A = \begin{bmatrix}
1 & 0 & 0 & 0 & 0 & \cdots & 0 & \cdots & 0 & \cdots & 0 \\
0 & 1 & 0 & 0 & 0 & \cdots & 0 & \cdots & 0 & \cdots & 0 \\
0 & 0 & 0 & 0 & 0 & \cdots & 1 & \cdots & 0 & \cdots & 0 \\
0 & 0 & 0 & 0 & 0 & \cdots & 0 & \cdots & 1 & \cdots & 0 \\
0 & 0 & 0 & 0 & 1 & \cdots & 0 & \cdots & 0 & \cdots & 0 \\
\vdots & & & & & & \vdots & & \vdots & & \\
0 & 0 & 1 & 0 & 0 & \cdots & 0 & \cdots & 0 & \cdots & 0 \\
\vdots & & & & & & \vdots & & \vdots & & \\
0 & 0 & 0 & 1 & 0 & \cdots & 0 & \cdots & 0 & \cdots & 0 \\
\vdots & & & & & & \vdots & & \vdots & & \\
0 & 0 & 0 & 0 & 0 & \cdots & 0 & \cdots & 0 & \cdots & 1
\end{bmatrix}$$

jth row

kth row

jth column

kth column

to $J_{j,k}$, the Jacobian evaluated at $E_{j,k}$. The matrix $J_{j,k} - \lambda I$ is similar to the matrix $\mathbb{J}_{j,k} - \lambda I = A(J_{j,k} - \lambda I)A^{-1}$, where

$$\mathbb{J}_{j,k} - \lambda I =$$

$$\begin{bmatrix}
-A-\lambda & \omega & -\delta_j S^* & -\delta_k S^* & -\delta_3 S^* & \cdots & -\delta_1 S^* & \cdots & -\delta_2 S^* & \cdots & -\delta_n S^* \\
\gamma & -B-\lambda & -(1-\sigma_j)\delta_j M^* & -(1-\sigma_k)\delta_k M^* & -(1-\sigma_3)\delta_3 M^* & \cdots & -(1-\sigma_1)\delta_1 M^* & \cdots & -(1-\sigma_2)\delta_2 M^* & \cdots & -(1-\sigma_n)\delta_n M^* \\
\delta_j I_j^* & (1-\sigma_j)\delta_j I_j^* & -\lambda & 0 & 0 & \cdots & 0 & \cdots & 0 & \cdots & 0 \\
\delta_k I_k^* & (1-\sigma_k)\delta_k I_k^* & 0 & -\lambda & 0 & \cdots & 0 & \cdots & 0 & \cdots & 0 \\
0 & 0 & 0 & 0 & \Phi_3-\lambda & \cdots & 0 & \cdots & 0 & \cdots & 0 \\
\vdots & & & & & \vdots & & \vdots & & \vdots & \\
0 & 0 & 0 & 0 & 0 & \cdots & \Phi_1-\lambda & \cdots & 0 & \cdots & 0 \\
\vdots & & & & & \vdots & & \vdots & & \vdots & \\
0 & 0 & 0 & 0 & 0 & \cdots & 0 & \cdots & \Phi_2-\lambda & \cdots & 0 \\
\vdots & & & & & \vdots & & \vdots & & \vdots & \\
0 & 0 & 0 & 0 & 0 & \cdots & 0 & \cdots & 0 & \cdots & \Phi_n-\lambda
\end{bmatrix}$$

and $\Phi_i = \delta_i S^* + (1-\sigma_i)\delta_i M^* - \eta$, for $i \in \{1,2,3,...,n\} \setminus \{j,k\}$. Thus we conclude the stability conditions for $E_{j,k}$ as below.

Theorem 0.3.0.18. *If there only exist two initial virus strains, j and k, and they coexist at the EE($E_{j,k}$). $E_{j,k}$ is locally asymptotically stable if and only if*

$$b_2 > 0 \quad \textit{and} \quad c_1 > 0.$$

If there exist more than two initial virus strains, and strains j and k coexist at $E_{j,k}$, $E_{j,k}$ is locally asymptotically stable if and only if the above two conditions are satisfied, and

$$\frac{h \max_i \left\{\delta_i [B\{I_j^* + I_k^*\} + (1-\sigma_i)\gamma]\right\}}{\eta[A\{I_j^* + I_k^*\}B\{I_j^* + I_k^*\} - \gamma\omega]} < 1,$$

where $i \in \{1,2,3,...n\} \setminus \{j,k\}$.

Summary

Assume all model parameters are positive, the table below summarizes the equilibria of the SMI_i model 0.3.0.6.

Type of Equilibrium	Equilibrium State	Number of Equilibria
disease-free equilibrium	$E_{0/n} = (S_0^*, M_0^*, 0)$	1
endemic equilibrium consists of a single strain, j	$E_j = (S_j^*, M_j^*, I_1^*, I_2^*, ..., I_n^*)$, for $i = 1, 2, ..., n$, and $I_j^* \neq 0$, while $I_i^* = 0$ for $i \neq j$	n
endemic equilibrium consists of two distinct strains, j and k	$E_{j,k} = (S_{j,k}^*, M_{j,k}^*, I_1^*, I_2^*, ..., I_n^*)$, for $i = 1, 2, ..., n$, and $I_j^* \neq 0$, $I_k^* \neq 0$, while $I_i^* = 0$ for $i \in \{1, 2, 3, ...n\} \setminus \{j, k\}$	$\binom{n}{2}$

Tab. 0.3: Equilibria of the SMI_i model 0.3.0.6

0.4 Disease Invasion Analysis

Suppose two virus strains, j and k, are introduced into a poultry population. Let $\delta_j > \delta_k$ and $\sigma_j > \sigma_k$, such that the EE, E_j and E_k, both exist, and E_j is the only locally asymptotically stable equilibrium state. We use numerical calculation to observe if the increase of δ_k can effect the stability of all equilibrium states, and we want to see if strain k can successfully invade the poultry population by becoming the only persisting strain at an stable EE.

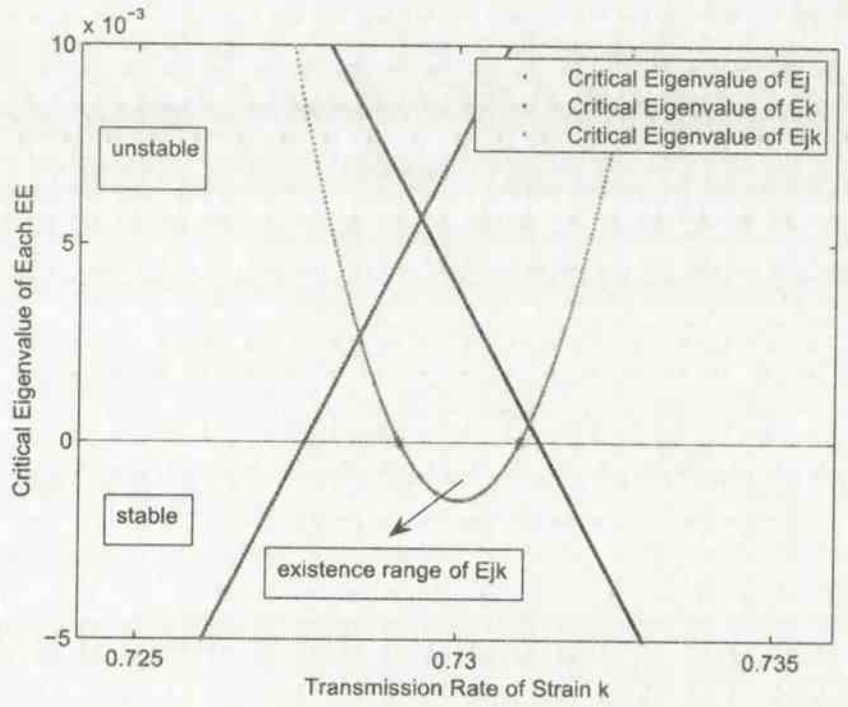
Note the EE E_j exists for the initial value of δ_k. Thus the reproductive number

$$R_{0/2} = \frac{h}{\mu\eta} \max_i \delta_i \left[\frac{\mu + \omega + (1 - \sigma_i)\gamma}{\mu + \omega + \gamma} \right] > 1,$$

for $i = j, k$. By increasing δ_k, the value of $R_{0/2}$ is always greater than 1. Therefore, the DFE is always unstable as δ_k increases.

We define the critical eigenvalue as the eigenvalue that determines the stability of an equilibrium state. Figure 0.4.0.49 graphs the changes of the critical eigenvalue of all three endemic equilibria, E_j, E_k, and $E_{j,k}$, as a function of δ_k. The figure shows by increasing the transmissibility of strain k, the critical eigenvalue of E_j is increased linearly and eventually becomes positive, thus E_j becomes unstable. Outside the range in between the two asterisk signs indicated in figure 0.4.0.49, there exist two intermediate ranges of δ_k such that all equilibrium states of the dynamic system are unstable. When δ_k is between the two asterisk signs indicated in figure 0.4.0.49, both strains can coexist at the EE $E_{j,k}$, which is shown to be stable.

As δ_k increases, the critical eigenvalue of the EE E_k decreases linearly, and it becomes negative when δ_k is sufficiently large. thus, E_k becomes the only stable equilibrium state in the dynamic system, and strain k successfully invades the poultry population.

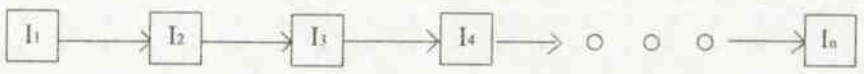


(0.4.0.49)

Fig.0.2.1.2. Parameter values: $h = 4$, $\mu = 1$, $\eta = 2.3$, $\gamma = 0.073$, $\omega = 0.01$, $\delta_j = 0.75$, $\sigma_j = 0.6$, $\sigma_k = 0.15$. The EE $E_{j,k}$ exists when $0.7291 < \delta_k < 0.7310$.

0.5 Virus Mutation

New AI virus strains can be created through virus mutation. To consider this possibility, we construct a linear strain space such that one virus strain can give rise to an immediately adjacent strain by mutation. Specifically, let strain 1 be the wild type, and it can mutate to become strain 2, and strain 2 can mutate to become strain 3, and so forth until reaching the nth strain, which can not mutate to become a new strain. Figure 0.5.0.50 describes the mutation in the linear strain space.



(0.5.0.50)

Fig.0.5.0.50. Step-wise mutation.

Considering this step-wise mutation, we augment the SMI_i model 0.3.0.6, and obtain the following dynamics:

$$\begin{cases} \frac{dS}{dt} &= h + \omega M - \sum_1^n \delta_i S I_i - (\mu + \gamma) S, \\ \frac{dM}{dt} &= \gamma S - \sum_1^n (1 - \sigma_i) \delta_i M I_i - (\mu + \omega) M, \\ \frac{dI_1}{dt} &= \delta_1 S I_1 + (1 - \sigma_1) \delta_1 M I_1 - \eta I_1 - m I_1, \\ \frac{dI_i}{dt} &= \delta_i S I_i + (1 - \sigma_i) \delta_i M I_i - \eta I_i + m(I_{i-1} - I_i), \\ \frac{dI_n}{dt} &= \delta_n S I_n + (1 - \sigma_n) \delta_n M I_n - \eta I_n + m I_{n-1}, \end{cases} \tag{0.5.0.51}$$

where $i = 2, 3, ..., n-1$, and m is the mutation rate. Let

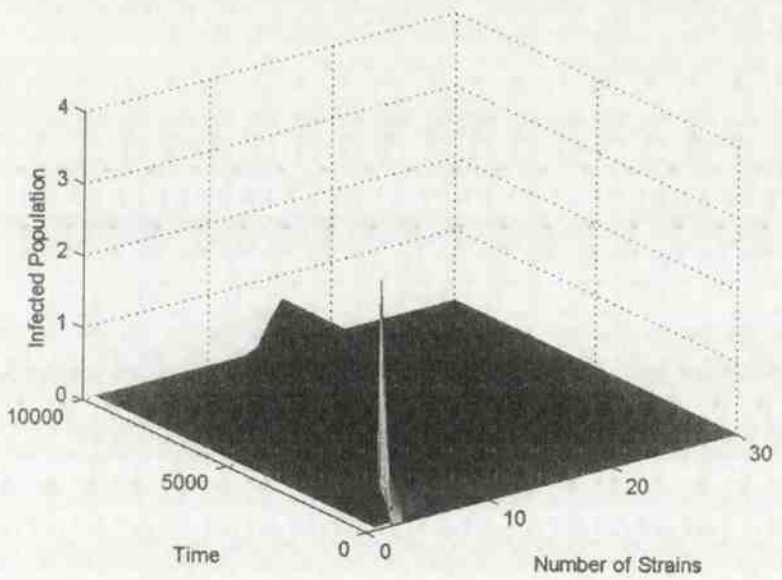
$$\delta_i = \frac{2}{1 + e^{|d_\delta (1-i)|}},$$

$$\sigma_i = \frac{2}{1 + e^{|d_\sigma (1-i)|}},$$

where d_δ and d_σ are constant. We assume the vaccination efficacy is perfect against strain 1, and it exponentially decays as the mutated strain becomes distant from strain 1.

From the system of equations 0.5.0.51, it is easy to find the disease-free equilibrium at $(S_m^*, M_m^*, 0) = \left(\frac{h(\mu+\omega)}{\mu(\mu+\omega+\gamma)}, \frac{h\gamma}{\mu(\mu+\gamma+\omega)}, 0\right)$. Using numerical calculation, we want to see if there exists an endemic equilibrium such that only mutated strains persist. If such an equilibrium exists, how is the increase of vaccination rate related to the number of infected individuals? How is the vaccination rate related to the genetic distance between the persisting mutant strains and the wild type strain?

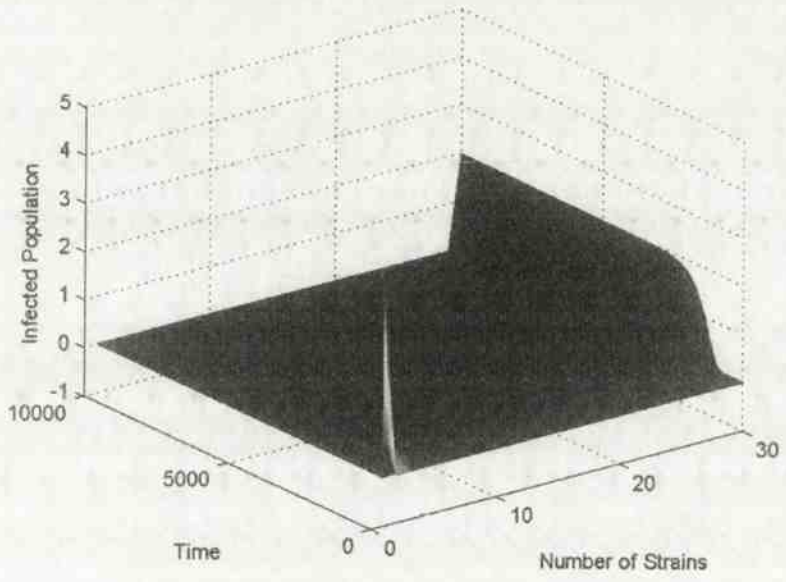
Solving the system 0.5.0.51 numerically using 30 virus strains, it is found that at most one cluster of virus strains is observed to persist in an endemic state, and the cluster can consist of mutant strains that are genetically distant from the wild-type. Figure 0.5.0.52 illustrates when the transmissibility of mutant strains decays exponentially as the mutant strains become more genetically distant to strain 1, strain 1 can be eliminated with a perfect vaccine. However, a cluster of mutated strains eventually rises and persists.



(0.5.0.52)

Fig.0.5.0.52. Parameter values: $h = 1$, $\gamma = 0.5$, $\omega = 0.001$, $\mu = 0.05$, $\eta = 0.5$, $m = 0.001$, $d_\delta = 0.025$, $d_\sigma = 0.05$.

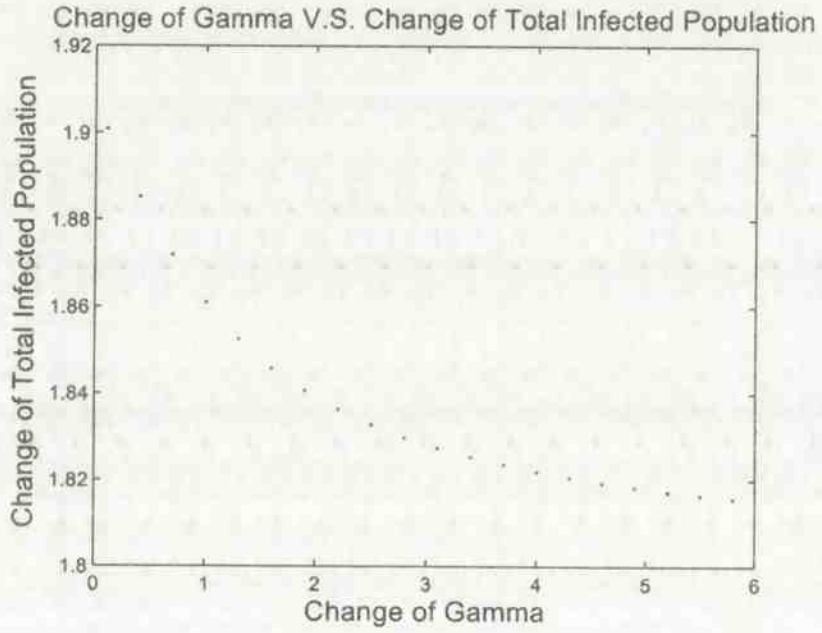
When the mutant strains are equally or even more transmissible than strain 1, the surviving strains at the endemic state are the most genetically distant to the wild type, which are the most resistent to the vaccine. In figure 0.5.0.53 we see strain 1 is quickly eliminated, but a cluster of persisting strains at the end of the simulated strain space become endemic and persist.



(0.5.0.53)

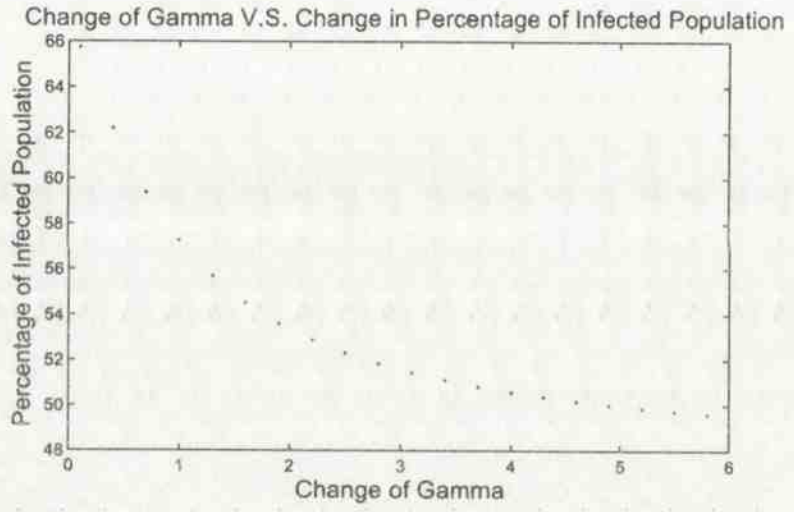
Fig.0.5.0.52. Parameter values: $h = 1$, $\gamma = 0.5$, $\omega = 0.001$, $\mu = 0.05$, $\eta = 0.5$, $m = 0.001$, $d_\delta = -0.2$, $d_\sigma = 0.05$.

In addition, by increasing the vaccination rate, γ, the total number of infected individuals and the percentage of the infected population are both observed to decrease exponentially. See figures 0.5.0.54 and 0.5.0.55.



(0.5.0.54)

Fig.0.5.0.54. Parameter values: $h = 1$, $\omega = 0.001$, $\mu = 0.05$, $\eta = 0.5$, $m = 0.001$, $d_\delta = 0.05$, $d_\sigma = 0.05$.

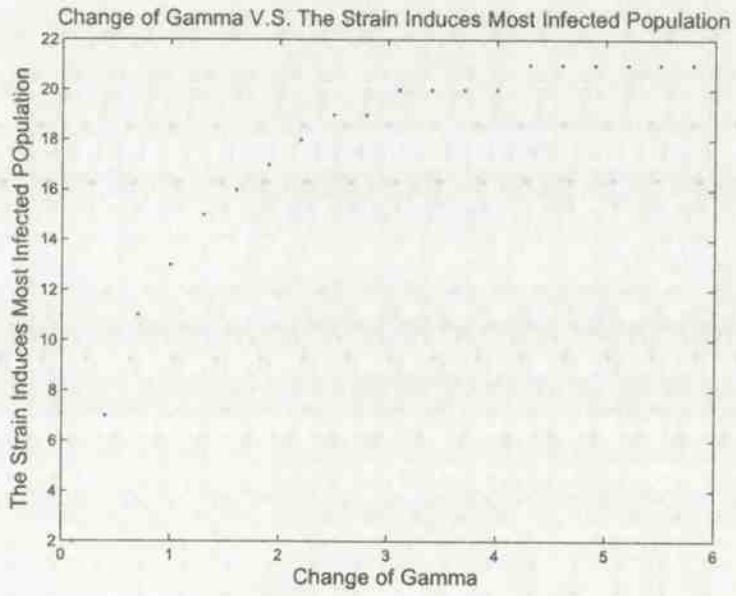


(0.5.0.55)

Fig.0.5.0.56. Parameter values: $h = 1$, $\omega = 0.001$, $\mu = 0.05$, $\eta = 0.5$, $m = 0.001$, $d_\delta = 0.05$, $d_\sigma = 0.05$.

We also observe when γ increases, the genetic distance increases logarithmically between the wild type and the persisting mutated strains, as

shown in 0.5.0.56.



(0.5.0.56)

Fig.0.5.0.56. Parameter values: $h = 1$, $\omega = 0.001$, $\mu = 0.05$, $\eta = 0.5$, $m = 0.001$, $d_\delta = 0.05$, $d_\sigma = 0.05$.

0.6 Future Work

Future research can include a global stability analysis of the SMI_i model 0.3.0.6. Several susceptible classes can be incorporated into model 0.5.0.51 to observe if multiple clusters of mutated virus strains can persist.

0.7 Acknowledgements

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0.8 Appendices

0.8.1 Appendix 1: Partial Proof of the Local Stability of the EE E_1

Using the Routh-Hurwitz Criterion, we have determined the local stability of the EE (E_1) depends on the sign of b_1. In this section, we will show b_1 is positive.

$$\begin{aligned} b_1 &= (a_2a_1 - a_3a_0)(a_2)^{-1} \\ &= T\{C(1-\sigma)+\mu+\omega+(1-\sigma)\gamma)(2\mu+\omega+C(1-\sigma)+\gamma+C\}^{-1}, \end{aligned}$$

where $C = \delta I^*$. Since $I^* > 0$, C is positive. Note b_1 is positive if and only if $T > 0$, and T is a cubic function in γ,

$$T(\gamma) = d_3\gamma^3 + d_2\gamma^2 + d_1\gamma + d_0,$$

where

$$\begin{aligned} d_3 &= \mu(1-\sigma) + C(1-\sigma)^2, \\ d_2 &= 2\omega\mu(1-\sigma) + 2C(1-\sigma)\omega + 4\mu C(1-\sigma)^2 + C^2(1-\sigma)^3 \\ &\quad +\omega C(1-\sigma)^2 + 3C^2(1-\sigma)^2 + \mu\omega + 3\mu^2(1-\sigma) + \mu^2 \\ &\quad +4C1-\sigma)\mu, \\ d_1 &= C\omega^2 - C\eta(1-\sigma)\mu + \mu C\eta(1-\sigma)^2 + \omega C\eta(1-\sigma)^2 \\ &\quad +11\mu C(1-\sigma)\omega + 2\omega C(1-\sigma)^2\mu - 2C\eta(1-\sigma)\omega + 3\mu^2\omega(1-\sigma) \\ &\quad +9\mu C^2(1-\sigma)^2 + 4\omega C^2(1-\sigma) + 4\omega C^2(1-\sigma)^2 + \mu\omega^2(1-\sigma) \\ &\quad +C^2(1-\sigma)^3\mu + C^2(1-\sigma)^3\eta + 5\mu C^2(1-\sigma) + 3\mu^3 + C^2\eta(1-\sigma) \\ &\quad +C\eta\mu + C\eta\omega + 2C(1-\sigma)\omega^2 - C^2\eta(1-\sigma)^2 + 10C(1-\sigma)\mu^2 \\ &\quad +3C(1-\sigma)^2\mu^2 + 2C^3(1-\sigma)^3 + 5\mu^2\omega + 3C^3(1-\sigma)^2 + 2C\mu^2 \\ &\quad +2\mu\omega^2 + 2\mu^3(1-\sigma) + 3\mu C\omega, \end{aligned}$$

$$
\begin{aligned}
d_0 \;=\;& 2\mu C^2\omega + 7\mu^2C^2(1-\sigma) + 2\omega C^3(1-\sigma) + 5\mu C^3(1-\sigma)^2 \\
&+C^3\eta(1-\sigma) + C^3(1-\sigma)^3\mu + C\eta\mu^2 + 4C^2(1-\sigma)^2\mu^2 \\
&+2\mu C^3(1-\sigma) + 3\omega C^3(1-\sigma)^2 + 3\omega^2C^2(1-\sigma) + 7\mu^2C\omega \\
&+C^2\eta\omega + C^2\eta\mu + 3\omega^2C(1-\sigma)\mu + 10\mu\omega C^2(1-\sigma) \\
&+5\mu^3\omega + 3\omega C^2(1-\sigma)^2\mu + 3C\mu^3 + \mu C\eta\omega + 8\omega C(1-\sigma)\mu^2 \\
&+C^4(1-\sigma)^2 + C^4(1-\sigma)^3 + C^2\omega^2 + \mu\omega^3 + C\omega^3 + 4\mu^2\omega^2 \\
&+2\mu^4 + \mu C^2\eta(1-\sigma) + 5C(1-\sigma)\mu^3 + 5\mu C\omega^2 + C^2\mu^2.
\end{aligned}
$$

It is easy to see that d_3, d_2 and d_0 are positive. We will now investigate the sign of d_1, which is a linear function in η:

$$d_1(\eta) = g_1\eta + g_0,$$

where

$$
\begin{aligned}
g_1 \;=\;& C\mu + C\omega + \mu C(1-\sigma)^2 + C^2(1-\sigma) - C(1-\sigma)\mu \\
&-2C(1-\sigma)\omega - C^2(1-\sigma)^2 + C^2(1-\sigma)^3 + \omega C(1-\sigma)^2, \\
g_0 \;=\;& C\omega^2 + 11\mu C(1-\sigma)\omega + 2C^3(1-\sigma)^3 + 4\omega C^2(1-\sigma)^2 \\
&+4\omega C^2(1-\sigma) + 3\mu C\omega + 5\mu C^2(1-\sigma) + 2\omega C(1-\sigma)^2\mu \\
&+3C^3(1-\sigma)^2 + 3\mu^3 + 3C(1-\sigma)^2\mu^2 + 5\mu^2\omega + 2\mu\omega^2 \\
&+2C(1-\sigma)\omega^2 + 9\mu C^2(1-\sigma)^2 + 2C\mu^2 + 3\mu^2\omega(1-\sigma) \\
&+10C(1-\sigma)\mu^2 + 2\mu^3(1-\sigma) + C^2(1-\sigma)^3\mu + \mu\omega^2(1-\sigma).
\end{aligned}
$$

Clearly g_0 is positive. We can represent g_1 as a linear function in μ,

$$g_1(\mu) = l_1\mu + l_0,$$

and

$$
\begin{aligned}
l_1 \;=\;& C\left[1-\sigma(1-\sigma)\right] > 0, \\
l_0 \;=\;& C\left\{\omega\sigma^2 + C\left[(1-\sigma)^2 + (1-\sigma)\sigma^2\right]\right\} > 0.
\end{aligned}
$$

Since all model paramters are assumed positive, g_1 positive, so d_1 is positive, and T is positive. This means b_1 is positive.

0.8.2 Appendix 2: A Special Endemic Equilibrium when $\delta_i = \delta$

In this section, we study the EE states when $\delta_i = \delta$, for $i = 1, 2, ..., n$, but $\sigma_i \neq \sigma_j$, for $i \neq j$. We will show that the endemic equilibrium, $\bar{E}$, can consist of up to n virus strains. The vaccinated population at $\bar{E}$ is depleted, $\bar{M}^* = 0$, and the last set of equations in 0.3.0.6 gives the susceptible population at $\bar{E}$,

$$\bar{S}^* = \frac{\eta}{\delta}.$$

From the second equation of 0.3.0.6, we get

$$\gamma \bar{S}^* = \gamma \frac{\eta}{\delta} = 0.$$

Assume $\gamma = 0$ and $\eta > 0$. Solving from the first equation of 0.3.0.6, n strains of virus can exist at $\bar{E}$, and the total number of infected individuals at $\bar{E}$ is found to be,

$$\sum_{i=1}^{n} \{\bar{I}_i\}^* = \frac{h}{\eta} - \frac{\mu}{\delta},$$

provided that $h\delta > \mu\eta$. In this case, there exists an upper bound for the susceptible population,

$$\bar{S}^* = \eta/\delta < h/\mu.$$

Moreover,

$$\sum_{i=1}^{n} \bar{I}^* = \frac{1}{\eta}(h - \mu)\bar{S}^* > 0,$$

thus

$$h > \mu.$$

Let $\bar{E} = (\bar{S}^*, 0, \bar{I_1}^*, \bar{I_2}^*, ...\bar{I_n}^*)$, such that $\sum_{i=1}^{n} \bar{I_i}^* = \frac{h}{\eta} - \frac{\mu}{\delta}$. The Jacobian of 0.3.0.6 when $\delta_i = \delta$, and $\gamma = 0$, evaluated at $\bar{E}$ is

$$\bar{J} = \begin{bmatrix} -\delta\sum_{i=1}^{n} \bar{I}_i^* - \mu & \omega & -\eta & -\eta & -\eta & \dots \\ 0 & -\mu-\omega-\delta\sum_{i=1}^{n}(1-\sigma_i)\bar{I}_i^* & 0 & 0 & 0 & \dots \\ \delta\bar{I}_1^* & (1-\sigma_1)\delta\bar{I}_1^* & 0 & 0 & 0 & \dots \\ \delta\bar{I}_2^* & (1-\sigma_2)\delta\bar{I}_2^* & 0 & 0 & 0 & \dots \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ \delta\bar{I}_n^* & (1-\sigma_n)\delta\bar{I}_n^* & 0 & 0 & 0 & \dots \end{bmatrix}.$$

The eigenvalues of $\bar{J}$ are

$$\begin{aligned} \lambda_1 &= -\mu-\omega-\delta\textstyle\sum_{i=1}^{n}(1-\sigma_i)\bar{I}_i^*, \\ \lambda_2 &= -\tfrac{1}{2}(\delta\textstyle\sum_{i=1}^{n}\bar{I}_i^*+\mu)+\tfrac{1}{2}\sqrt{(\delta\sum_{i=1}^{n}\bar{I}_i^*+\mu)^2-4\delta\eta\sum_{i=1}^{n}\bar{I}_i^*} \\ &= \tfrac{-h\delta+\sqrt{h^2\delta^2-4\eta^2h\delta+4\mu\eta^3}}{2\eta} \\ \lambda_3 &= -\tfrac{1}{2}(\delta\textstyle\sum_{i=1}^{n}\bar{I}_i^*+\mu)-\tfrac{1}{2}\sqrt{(\delta\sum_{i=1}^{n}\bar{I}_i^*+\mu)^2-4\delta\eta\sum_{i=1}^{n}\bar{I}_i^*} \\ &= \tfrac{-h\delta-\sqrt{h^2\delta^2-4\eta^2h\delta+4\mu\eta^3}}{2\eta}, \\ \lambda_{4,\dots,n+2} &= 0. \end{aligned} \tag{0.8.2.1}$$

Note $\lambda_1 < 0$, and since $4\delta\eta\sum_{i=1}^{n}\bar{I}_i^* > 0$, $(\delta\sum_{i=1}^{n}\bar{I}_i^*+\mu)^2-4\delta\eta\sum_{i=1}^{n}\bar{I}_i^* < \delta\sum_{i=1}^{n}\bar{I}_i^*+\mu$. Thus, $Re(\lambda_2) < 0$ and $Re(\lambda_3) < 0$. If the system 0.3.0.6 only has one non-zero virus population, then the three eigenvalues have negative real parts, and the endemic equilibrium is therefore locally asymptotically stable. If $n > 1$ strains of virus are present, there are $n-1$ zero eigenvalues. We use the Center Manifold Theorem [16] to study the stability of $\bar{E}$.

Theorem 0.8.2.1. *(The Center Manifold Theorem). Consider an n-dimensional nonlinear system*

$$\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x}). \tag{0.8.2.2}$$

Let

$$\dot{x} = Ax \tag{0.8.2.3}$$

be the corresponding linearized system, where $A = Df(x_0)$, *and* x_0 *is a fixed point. Let* $f \in C^r(E)$ *where* E *is an open subset of* R^n *containing* x_0 *and* $r \geq 1$. *Suppose that* $f(x_0) = 0$ *and that* $Df(x_0)$ *has* k *eigenvalues with negative real part,* j *eigenvalues with positive real part, and* $m = n - k - j$ *eigenvalues with zero real part. Then there exists an* m*-dimensional center manifold* $W^c(x_0)$ *of class* C^r *tangent to the center subspace* E^c *of equation 0.8.2.3 at* x_0, *there exists a* k*-dimensional stable manifold* $W^s(x_0)$ *of class* C^r *tangent to the stable subspace* E^s *of 0.8.2.3 at* x_0 *and there exists a* j*-dimensional unstable manifold* $W^u(x_0)$ *of class* C^r *tangent to the unstable subspace* E^u *of* 0.8.2.3 *at* x_0*; furthermore,* $W^c(x_0)$, $W^s(x_0)$ *and* $W^u(x_0)$ *are invariant under the flow of 0.8.2.2.*

In our $n + 2$ dimensional system, we have $n - 1$ zero eigenvalues and 3 eigenvalues with negative real part. There exists an invariant center manifold and an invariant stable manifold, and the center manifold is locally exponentially attractive. In summary we give the following theorem.

Theorem 0.8.2.2. *The EE* $\bar{E}$ *can consist of* n *virus strains, if the following conditions are met simultaneously:*

$$\begin{aligned} &1)\ \delta_i = \delta, \quad \sigma_i \neq \sigma_j, \quad \text{for } i \neq j; \\ &2)\ \gamma = 0; \\ &3)\ h > \mu; \\ &4)\ h\delta > \mu\eta. \end{aligned} \tag{0.8.2.4}$$

The EE $\bar{E}$ is always locally asymptotically stable.

In addition, for an intermediate range of δ,

$$\frac{2\eta(\eta - \sqrt{\eta(\eta-\mu)})}{h} < \delta < \frac{2\eta(\eta + \sqrt{\eta(\eta-\mu)})}{h},$$

provided that $\eta > \mu$, trajectories go toward $\bar{E}$ with damped oscillation. Otherwise, trajectories tend to $\bar{E}$ directly. However, as soon as a vaccination program is turned back on, the EE $\bar{E}$ can no longer exist. Thus it is unlikely that more than two virus strains can exist at an endemic state.

The disease-free equilibrium $E_{0/n}$ can coexist with the endemic equilibrium $\bar{E}$, and

$$E_{0/n} = (\frac{h}{\mu}, 0, 0).$$

When EE $\bar{E}$ exists, $R_{0/n} = \frac{h\delta}{\mu\eta} > 1$, thus $E_{0/n}$ becomes unstable.

0.8.3 *Appendix 3: A Special Endemic Equilibrium when $\sigma_i = \sigma$*

Though AI is very deadly to infected domestic poultry, many wild birds, such as waterfowl, are usually resistent to the virus. Domestic poultry may also eventually develop immunity against the virus, and no longer suffer from disease induced mortality. Under this hypothesis, if a vaccine is invariant against all virus strains, there exists an endemic equilibrium state that consists of multiple virus strains. We first consider the case when the vaccine is only partially effective.

When $0 < \sigma < 1$, denote by $\tilde{S}_1^*$, and $\tilde{M}_1^*$ the susceptible and vaccinated population at the EE $\tilde{E}_1$. If $\eta = 0$, From the last set of equations in 0.3.0.6, we find

$$\tilde{S}_1^* = -(1-\sigma)\tilde{M}_1^* = 0.$$

Since $0 < \sigma < 1$,

$$\tilde{S}_1^* = \tilde{M}_1^* = 0.$$

Thus we also get

$$h = 0$$

from the first equation of 0.3.0.6. Let $\tilde{I}_{i/1}^*$ be the infected population at the EE $\tilde{E}_1$ for strain i. The EE $\tilde{E}_1 = (\tilde{S}_1^*, \tilde{M}_1^*, \tilde{I}_{1/1}^*, \tilde{I}_{2/1}^*, ..., \tilde{I}_{n/1}^*) = (0, 0, \tilde{I}_{1/1}^*, \tilde{I}_{2/1}^*, ..., \tilde{I}_{n/1}^*)$, for $i = 1, 2, ..., n$, and $\tilde{I}_{i/1}^*$ can be any nonnegative constants. To determine the local stability of $\tilde{E}_1$, we first find the Jacobian evaluated at $\tilde{E}_1$,

$$\tilde{J}_1 = \begin{bmatrix} -\sum_{i=1}^n \delta_i \tilde{I}_{i/1}^* - \mu - \gamma & \omega & 0 & 0 & 0 & \dots \\ \gamma & -(1-\sigma)\sum_{i=1}^n \delta_i \tilde{I}_{i/1}^* - \mu - \omega & 0 & 0 & 0 & \dots \\ \delta_1 \tilde{I}_{1/1}^* & (1-\sigma)\delta_1 \tilde{I}_{1/1}^* & 0 & 0 & 0 & \dots \\ \delta_2 \tilde{I}_{2/1}^* & (1-\sigma)\delta_2 \tilde{I}_{2/1}^* & 0 & 0 & 0 & \dots \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ \delta_n \tilde{I}_{n/1}^* & (1-\sigma)\delta_n \tilde{I}_{n/1}^* & 0 & 0 & 0 & \dots \end{bmatrix}.$$

The eigenvalues of $\tilde{J}_1$ are:

$$\begin{aligned} \lambda_1 &= \tfrac{1}{2}(P+Q) + \tfrac{1}{2}\sqrt{(P+Q)^2 - 4(PQ-\omega\gamma)}, \\ \lambda_2 &= \tfrac{1}{2}(P+Q) - \tfrac{1}{2}\sqrt{(P+Q)^2 - 4(PQ-\omega\gamma)}, \\ \lambda_{3,\ldots,n+2} &= 0, \end{aligned} \tag{0.8.3.1}$$

where

$$P = -\sum_{i=1}^{n} \delta_i \tilde{I}^*_{i/1} - \mu - \gamma,$$

$$Q = -(1-\sigma)\sum_{i=1}^{n} \delta_i \tilde{I}^*_{i/1} - \mu - \omega.$$

Since P and Q are both negative, and $PQ - \omega\gamma > 0$, $Re(\lambda_1) = Re(\lambda_2) < 0$. The rest of the eigenvalues are identically 0. We use the Center Manifold Theorem 0.8.2.1 defined in appendix 2, and conclude the EE $\tilde{E}_1$ is always locally asymptotically stable. In summary,

Theorem 0.8.3.1. *The EE $\tilde{E}_1$ can consist of n virus strains, if the following conditions are met simultaneously:*

$$\begin{aligned} &1)\ \ \sigma_i = \sigma \text{ and } 0 < \sigma < 1; \\ &2)\ \ \delta_i \neq \delta_j, \text{ for } i \neq j; \\ &3)\ \ h = 0. \\ &4)\ \ \eta = 0. \end{aligned} \tag{0.8.3.2}$$

The EE $\tilde{E}_1$ is always locally asymptotically stable.

In addition, the radicand in 0.8.3.1 is $(P+Q)^2 - 4(PQ-\omega\gamma) = (P-Q)^2 + 4\omega\gamma > 0$, thus populations always tend to $\tilde{E}_1$ directly without oscillation.

On the other hand, if $\sigma = 1$, and if $h = \mu = \omega = 0$, multiple virus strains can exist at an EE $\tilde{E}_2 = (\tilde{S}_2^*, \tilde{M}_2^*, \tilde{I}_{1/2}^*, \tilde{I}_{2/2}^*, ..., \tilde{I}_{n/2}^*) = (0, \tilde{M}_2^*, \tilde{I}_{1/2}^*, \tilde{I}_{2/2}^*, ..., \tilde{I}_{n/2}^*)$, where $\tilde{M}_2^*$ and $\tilde{I}_{i/2}^*$ are any nonnegative constants. In this case, the Jacobian of the system is

$$\tilde{J}_2 = \begin{bmatrix} -\sum_{i=1}^{n} \delta_i I_{i/2}^* - \gamma & 0 & 0 & 0 & 0 & \dots \\ \gamma & 0 & 0 & 0 & 0 & \dots \\ \delta_1 I_{1/2}^* & 0 & 0 & 0 & 0 & \dots \\ \delta_2 I_{2/2}^* & 0 & 0 & 0 & 0 & \dots \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ \delta_n I_{n/2}^* & 0 & 0 & 0 & 0 & \dots \end{bmatrix},$$

and the eigenvalues are

$$\begin{aligned} \lambda_1 &= -\sum_{i=1}^{n} \delta_i \tilde{I}_{i/2}^* - \gamma, \\ \lambda_{2,\dots,n+2} &= 0. \end{aligned} \tag{0.8.3.3}$$

Analogously, $\tilde{E}_2$ is always locally asymptotically stable, and the population always tends to $\tilde{E}_2$ directly. We summarize the following:

Theorem 0.8.3.2. *The EE $\tilde{E}_2$ can consist of n virus strains, if the following conditions are met simultaneously:*

$$\begin{aligned} &1)\ \ \sigma_i = \sigma \text{ and } \sigma = 1; \\ &2)\ \ \delta_i \neq \delta_j, \text{ for } i \neq j; \\ &3)\ \ h = 0; \\ &4)\ \ \mu = 0; \\ &5)\ \ \omega = 0. \\ &6)\ \ \eta = 0. \end{aligned} \tag{0.8.3.4}$$

The EE $\tilde{E}_2$ is always locally asymptotically stable.

BIBLIOGRAPHY

[1] Avian influenza/bird flu. *National Irish Safety Organization.* http://www.niso.ie/documents/AvianInfluenza.pdf .

[2] C91 fundamentals of control systems using Routh-Hurwitz. http://lims.mech.northwestern.edu/~lynch/courses/ME391/2005/routh.pdf .

[3] Influenza viruses. *Center for Disease Control and Prevention*, 2005. http://www.cdc.gov/flu/avian/gen-info/flu-viruses.htm .

[4] Avian influenza (" bird flu") - fact sheet. *World Health Organization*, 2006. http://www.who.int/mediacentre/factsheets/avian_influenza/en/ .

[5] Avian influenza: significance of mutations in the H5N1 virus. *World Health Organization*, 2006. http://www.who.int/csr/2006_02_ 20/en/index.html .

[6] Key facts about avian influenza (bird flu) and avian influenza A (H5N1) virus. *Center for Disease Control and Prevention*, 2006. http://www.cdc.gov/flu/avian/gen-info/facts.htm .

[7] Special feature: Frequently asked questions on avian influenza. *The Wildlife Rehabilitator*, 6(1), 2006.

[8] Maciej. F. Boni, Julia R. Gog, Viggo Andreasen, and Freddy B. Christiansen. Influenza drift and epidemic size: the race between generating and escaping immunity. *Theoretical Population Biology*, 65:179–191, 2004.

[9] Fred Brauer and Carlos Castillo-Chávez. *Mathematical models in population biology and epidemiology*. Springer, 2000.

[10] D. Chowell-Puente, P. Delgado, D. Pérez, C. H. Sánchez Tapia, F. Sánchez, and D. Murillo. The impact of mosquito-bird interaction on the spread of west nile virus to human populations. 2004. http://math.lanl.gov/SummerPrograms/Reports2004/ch_de_pe_ta_sa_mu.pdf.

[11] Leah Edelstein-Keshet. *Mathematical models in biology*. McGraw-Hill Companies, 1988.

[12] J. Gjorgjieva, K. Smith, G. Chowell, F. Sánchez, J. Snyder, and C. Castillo-Chávez. The role of vaccination in the control of SARS. *Mathematical Biosciences and Engineering*, 2(4), 2005.

[13] Julia R. Gog and Bryan T. Crenfell. Dynamics and selection of many-strain pathogens. *PNAS*, 99, 2002.

[14] Thomas C Mettenleiter. Questions on vaccination against highly pathogenic avian influenza (HPAI, fowl plague, 'bird flu'). *Friedrich-Loeffler-Institut*, 2005.

[15] J. D. Murray. *Mathematical biology*. New York: Springer, 2002. Edition 3.

[16] Lawrence Perko. *Differential equations and dynamical systems.* Springer, 2000. Third edition.

[17] H. Seno and N. Sato. Mathematical models for epidemic dynamics with adult vaccination against waning immunity. 2005.

[18] S. H. Strogatz. *Nonlinear dynamics and chaos.* Westview Press, 2000.