Dynamics of an "SAIQR" Influenza Model

Ana Vivas-Barber[1], Carlos Castillo-Chavez[2], Ernest Barany[3]

[1]Norfolk State University, Department of Mathematics, Norfolk,VA,USA
Email:alvivasbarber@nsu.edu

[2]Arizona State University, Math., Comp., and Model. Sciences Ctr., Tempe, AZ,USA
Email: cccchavez@asu.edu

[3]New Mexico State University, Department of Mathematics, Las Cruces, NM, USA
Email: ebarany@nmsu.edu

Abstract—Modifications or extensions of the classical Susceptible-Infected-Recovered (SIR) model that account for a Quarantine (Q) class have shown to be capable of supporting recurrent, that is, periodic disease outbreaks. The fact that in such outbreaks a significant proportion of individuals are asymptomatic or experience mild infections has not been explored extensively. Motivated by our interests on the transmission dynamics and evolution of influenza A in human populations, we proceed to explore the role of an asymptomatic class (A) of individuals on the long-term transmission dynamics of influenza. We focus on a Susceptible-Asymptomatic-Infectious-Quarantine-Recovered (SAIQR) model that limits the interactions of Q-individuals and assumes that A-individuals are infectious, possibly not as infectious as those with clear symptoms. The analysis is carried out taking advantage of the significant time scale differences provided by the demographic and epidemic processes involved. It is shown that SAIQR-models with vital dynamics (births and deaths) support recurrent outbreaks under reasonable disease or intervention periods. Further, we show that recurrence is possible within regions of parameter space that are consistent with influenza A transmission in human populations.

Keywords-epidemics, periodic, damped oscillations, multiple time scales, influenza, infectious diseases, quarantine-isolation, recurrent outbreaks, asymptomatic class.

I. INTRODUCTION

For centuries policies that limit or eliminate contacts between susceptible and symptomatic infectious individuals have been put in place under voluntary or mandatory intervention models. In the case of diseases like Ebola or SARS, drastic measures are put in place once we become aware that an outbreak is imminent or even possible. The response is due to the tremendous risk that such diseases pose to others due to their link to high mortality rates. Typically, we would start with a clear definition of each epidemiological class, particularly the Quarantine or Q-class, see ([9], [13]). However, rather than proceeding in such a direction, we make use of the term quarantine in an inclusive fashion (not the norm of epidemiology) since the goal is not to explore the role of the Q-class, done by several researchers in the past ([13], [15], [20], [21], [28], [40], [41]), but rather to investigate the impact of the Asymptomatic or A-class on transmission.

The practice of putting individuals under some model of quarantine (an Italian word, *quaranta*,

since the original period of quarantine was forty days) probably became an established form of intervention in the fight against tuberculosis in Europe and later in the US at the end of the nineteenth century. The concepts of I & Q [Isolation and Quarantine] have plastic meanings and uses. An epidemiological dictionary ... defines at least seven forms of isolation and two classes of quarantine – one restrictive and the other broad enough to include many possibilities. The selection of which definition to use depends on the disease, form of transmission, and infectious agent. One of the problems associated with the implementation of I & Q strategies is that nobody is really sure how effective they are at the "population level".

The program on the use of dynamical systems to describe and study transmission dynamics and control of infectious communicable diseases has been in place for nearly a century, following the introduction of the celebrated Susceptible-Infectious-Recovered or SIR framework of Kermack and McKendrick ([29], [30]). SIR-models are now routinely used as platforms for the study of the spread and control of communicable diseases like measles, tuberculosis, rubella, chicken pox and influenza ([4], [8], [14], [24], [31], [34], [44], [45], [46], [47], [48]). The recent SARS emergency has reinforced the need to understand the role of the concepts of I & Q as systematic methods of disease control over global scales and to better understand multiple-outbreak epidemiological models ([4], [13], [15]). SIR epidemiological models have been modified to account for epidemiological factors like permanent or partial immunity after recovery as well as intervention/control measures through the inclusion of I & Q treated or vaccinated classes. The most modern version of I & Q is now referred to as "social distancing", which gained momentum under the 2009 A/H1N1 influenza pandemic ([18], [22], [23], [25], [35], [38]). The inclusion of a class of individuals that are isolated (quarantined) after infection gained increased mathematical attention ([9], [21], [28], [34]), after the incorporation of such a class provided SIQR epidemiological models the ability

to support recurrent outbreaks ([20], [27], [36], [39], [48]).

Influenza is one of the most common human diseases with the uncanny ability to re-invent itself through minor changes known as point mutations (nucleotide substitutions in the HA molecule) or through dramatic transformations (shifts) known to have led to major pandemic with the 1918 A/H1N1 influenza, possibly the most memorable, pandemic in recorded history ([2], [16]).

The dynamics of influenza type A lives in a global landscape shaped by the history of past outbreaks that alters the immunological profile over large geographical scales every year ([6], [17], [32], [34], [37], [44], [45], [46], [50]). The adaptive immunological global landscape fosters competing and coexisting strains of three subtypes: A/H1N1, A/H2N2 and A/H3N2. It is believed that exposure to a subtype does not provide any type of protection or cross-immunity against strains of a different subtype, a problem under a system that generates new strains year after year within subtypes ([40], [41], [42]).

Novel strains of influenza A emerge, possibly within each subtype, regularly, as a result of the accumulation of point mutations (or replacement of key nucleotides) within the influenza HA molecule, while the emergence of new subtypes is rare as it demands major genetic shifts. The dangers posed this by changing pathogen means that treatment or vaccines may not be available that can prevent or ameliorate an epidemic outbreak. As a result, isolation or quarantine or social distancing are routinely factored in as key to effective influenza control; policies that must account for disease evolution (cross-immunity), vaccine-treatment supply, mobility, connectivity (mass transportation) and behavioral dynamics from the individual to the population to the community level ([1], [3], [7], [8], [12], [22], [33], [34], [36], [39], [40], [41], [42]).

In this work, an extension (motivated from our ongoing work on influenza) of the SIQR modeling framework that deliberately includes a class *A* of asymptomatic individuals ([9], [49]). We

are aware that this is a rather restrictive model for influenza as it does not account for shifts in population-levels of susceptibility ignoring the role of cross-immunity. We have carried out work under models that allow for shifting profiles of susceptibility ([1], [11], [33], [34], [36], [40], [41], [42]), and naturally, the work here fits within such a framework. However, we do not proceed to study the long-term dynamics of influenza under such a level of generality as the goal here is simply to address the impact of, possibly, a large proportion of asymptomatic individuals on the transmission of communicable diseases that live under the same temporal scales as influenza. We are mainly interested in the relatively short term dynamics of influenza at population level. The time scale we study is one year to few years. As we shall see, through this analysis we not only manage to set the stage for a more comprehensive study but we identify the role of the A-class in capturing the qualitative *recurrent* disease dynamics within acceptable parameter ranges, a situation that has not always been considered.

Here, it will be assumed that A-individuals may be less infectious than those in the I class. The well-posedness of the model, existence of equilibria, and the conditions for the existence of damped solutions are studied in the next sections. The focus of the analysis exploits the dramatic differences in epidemiological and demographic time scales as was done in ([1], [10], [18], [20], [26], [28], [38], [40], [42]). The inclusion of A and Q classes can support sustained oscillations, this qualitative behavior (damped oscillations) has not been seen in SIQR models that do not include the A- class as in ([8], [36]). Furthermore, Heathcote, Zhien, and Shengbing [28] found that the SIQR model with quarantine-adjusted incidence $\beta SI/(N-Q)$, can have an endemic equilibria that is stable or unstable spiral, so that periodic solutions can occur. The research in this manuscript is a part of the PhD dissertation of the main author [49]. The most valuable contributions of this work are that we obtain an analytic expression for the endemic equilibrium point; for some specific

parameters values for influenza, we found damped oscillations approaching the endemic equilibrium for the model SAIQR with quarantine-adjusted incidence $\beta S(I+\sigma A)/(N-Q)$, due to the inclusion of the A-class. The dynamics of the model SAIQR changed compared with the dynamics of the model SIQR; and an inequality for the final relation size was found, following the techniques as in [5].

II. THE SAIQR MODEL WITH QUARANTINE-ADJUSTED INCIDENCE

As noted, we will be dealing with the dynamics of a single strain that provides permanent immunity after recovery. The susceptible pool will be replenished by a continuous flow of newborns who are assumed to be susceptible to the circulating strain. It is further assumed that the population is not experiencing measurable long term growth, that is, it is assumed that the population is constant asymptotically in time. Hence, the population is divided into five disjoint classes: $S(t)$, susceptible; $A(t)$, asymptomatic ; $I(t)$, infectious; $Q(t)$, isolated (quarantined), and $R(t)$, recovered individuals. The transmission coefficient, that is the average number of effective contacts that lead to new infectious per-susceptible and per-infected is denoted by β, but this contacts would occur within the population of size $N-Q$, the incidence given by $\beta S(I + \sigma A)/(N - Q)$ is called the quarantine-adjusted incidence. We assume that individuals from the A-class are infectious but with a possibly reduced per-capita transmission rate, $\beta\sigma$, $\sigma \in [0, 1]$. The proportion of individuals moving from the S-class into the I-class per unit of time is denoted by p while the proportion transferred from the S-class into the A-class is given by $1 - p$. The per-capita isolation or quarantine rate is θ. Further, it is assumed that isolated (quarantined) individuals have a negligible number of contacts with members of the overall population; that is, they play no role in the transmission process. Therefore, if the per-capita recovery rates for asymptomatic, infectious and isolated individuals are γ_1, γ_2 and γ_3, respectively, then the use of above definitions and assumptions leads to the following system of

nonlinear ordinary differential equations:

$$
\begin{aligned}
S' &= \Lambda - \beta S \frac{(I + \sigma A)}{N - Q} - \mu S \\
A' &= (1-p)\beta S \frac{(I + \sigma A)}{N - Q} - (\gamma_1 + \mu)A \\
I' &= p\beta S \frac{(I + \sigma A)}{N - Q} - (\gamma_2 + \theta + \mu)I \\
Q' &= \theta I - (\gamma_3 + \mu)Q \\
R' &= \gamma_1 A + \gamma_2 I + \gamma_3 Q - \mu R,
\end{aligned}
\tag{1}
$$

with initial conditions

$$
S(0) = S_0, A(0) = A_0, I(0) = I_0, Q(0) = 0,
$$
$$
R(0) = 0.
$$

TABLE I: Definition of symbols and parameter values

Symb.	Definition	Value(Range)
$S(t)$	Susceptible individ. at time t	
$A(t)$	Asymptom. individ. at time t	
$I(t)$	Infectious individ. at time t	
$Q(t)$	Isolated individ. at time t	
$R(t)$	Recovered individ. at time t	
Λ	Birth rate	$1/(80 * 365)$
μ	Mortality rate	$1/(80 * 365)$
β	Transmiss. rate	0.6
σ	Transmiss. rate from class A	$[0, 1]$
θ	Isolation rate	$1/\theta \in [1, 7]$
γ_1	Recovery rate from class A	$1/\gamma_1 \in [3, 7]$
γ_2	Recovery rate from class I	$1/\gamma_2 \in [3, 7]$
γ_3	Recovery rate from class Q	$1/\gamma_3 \in [3, 7]$

Since $N = S + A + I + Q + R$ we conclude that

$$
\frac{dN}{dt} = \Lambda - \mu N,
$$

and, therefore, that $N(t) \to \Lambda/\mu$ as $t \to \infty$. That is the total population is asymptotically constant. The well-posedness of the model follows from a straightforward application of the classical theory:

Result 2.1: Let $S_0, A_0, I_0, Q_0, R_0 \geq 0$, $S_0 + A_0 + I_0 + Q_0 + R_0 = N_0$. Then there exist solutions $S(t), A(t), I(t), Q(t), R(t)$ to System (1) with initial data S_0, A_0, I_0, Q_0, R_0 that are defined for all time $t \geq 0$ such that S, A, I, Q, R are nonnegative for all t. Note that if $A_0 = 0, I_0 = 0, Q_0 = 0$ then $A(t) \equiv 0$ and $I(t) \equiv 0$, and if $I_0 > 0$ and $A_0 > 0$ then $S(t), A(t), I(t), Q(t), R(t)$ are strictly positive for all $t > 0$ and Q is bounded by $\hat{Q} = max\{Q_0, \theta/(\gamma_3 + \mu)\}$. An outline of the proof is in the Appendix.

Since the total population is asymptotically constant the results in [10], guarantee that System (1) can be reduced to the qualitatively equivalent System

$$
\begin{aligned}
S' &= \Lambda - \beta S \frac{(I + \sigma A)}{N - Q} - \mu S \\
A' &= (1-p)\beta S \frac{(I + \sigma A)}{N - Q} - (\gamma_1 + \mu)A \\
I' &= p\beta S \frac{(I + \sigma A)}{N - Q} - (\gamma_2 + \theta + \mu)I \\
Q' &= \theta I - (\gamma_3 + \mu)Q,
\end{aligned}
\tag{2}
$$

with $N = \dfrac{\Lambda}{\mu}$.

If we define the state vector $E = (S, A, I, Q)$, then System (2) supports at most two equilibria: the disease free equilibrium $E_0 = (\Lambda/\mu, 0, 0, 0)$ and, an unique endemic equilibrium $E^*(S_\infty(\Re_0), A_\infty(\Re_0), I_\infty(\Re_0), Q_\infty(\Re_0))$, where the quantities $S_\infty(\Re_0), A_\infty(\Re_0), I_\infty(\Re_0), Q_\infty(\Re_0)$ are the unique nonzero equilibrium solutions to System (2) that exist if the *basic reproduction number*, $\Re_0$, is greater than one, as will be discussed in the next section.

III. BASIC REPRODUCTION NUMBER AND THE ENDEMIC EQUILIBRIUM

To see how the basic reproduction number arises, we linearize System (2) around E_0 yielding the jacobian matrix

$$
\begin{bmatrix}
-\mu & -\beta\sigma & -\beta & 0 \\
0 & \begin{array}{c}-(\gamma_1+\mu)\\ +(1-p)\beta\sigma\end{array} & (1-p)\beta & 0 \\
0 & p\beta\sigma & \begin{array}{c}-(\gamma_2+\theta+\mu)\\ +p\beta\end{array} & 0 \\
0 & 0 & \theta & -(\gamma_3+\mu)
\end{bmatrix}
$$

Therefore, the eigenvalues of the above jacobian are $\lambda = -\mu$; $\lambda = -(\gamma_3 + \mu)$ and, the two eigenvalues of the sub matrix $J_1(E_0)$ given by

$$
\begin{bmatrix}
-(\gamma_1+\mu)+(1-p)\beta\sigma & (1-p)\beta \\
p\beta\sigma & -(\gamma_2+\theta+\mu)+p\beta
\end{bmatrix}
$$

Conditions $trace(J_1(E_0)) < 0$ and $det(J_1(E_0)) > 0$ are equivalent to $\Re_0 < 1$, where

$$
\Re_0 = \frac{p\beta}{\gamma_2+\theta+\mu} + \frac{(1-p)\beta\sigma}{\gamma_1+\mu}, \tag{3}
$$

so that the disease-free state is locally asymptotically stable as long as $\Re_0 < 1$. $\Re_0$ is called the *basic reproduction number* and is the sum of the additive contributions of the A- and I-classes to the generation of secondary infections when $S(0) \approx \Lambda/\mu$.

The SAIQR model can be thought of as a family of models parameterized by σ and p, that is $\mathcal{M}(\sigma, p)$. The asymptomatic class is not present when $p = 1$ and $\sigma = 0$ so that $\mathcal{M}(0, 1)$ corresponds to the classical SIQR model with
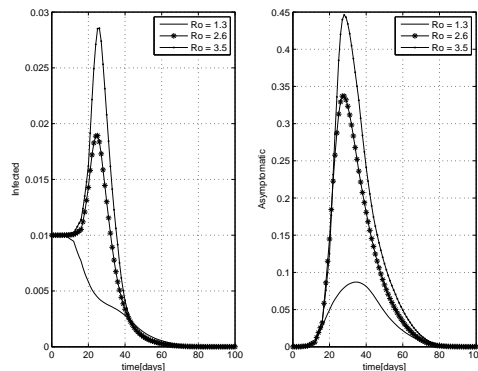
$$
\Re_0 = \frac{\beta}{\gamma_2+\theta+\mu}.
$$

Fig. 1: Infectious and asymptomatic individuals for $p = 0.3$. When $\Re_0 = 2.6$ and $\Re_0 = 3.5$ we can observe that the number of asymptomatic individuals has a peak around day 30 of the spread of the disease. For all values of $\Re_0$ the number of infectious individuals is increasing at the beginning of the spread of the disease.

The importance of $\Re_0$ in the control of disease dynamics is evident from the extensive efforts to estimate its value for various diseases and its role in the study of the dynamics of infections diseases ([19], [26]).

The simulation of the solutions for System (1), for different $\Re_0$ values, shows for example, that at the beginning of an outbreak, the population of the infectious class actually increases (Figure 1) due to the inclusion of the A-class, this last simulation highlights the effect of the inclusion of an asymptomatic class.

We collect our stability results below:

Result 3.1: If $\Re_0 < 1$ the disease free equilibrium point $E_0 = (\Lambda/\mu, 0, 0, 0)$ for System (2), is locally asymptotically stable. If $\Re_0 > 1$ then E_0 is unstable. An outline of the proof is in the Appendix.

Result 3.2: If $\Re_0 \leq 1$, then

$$
\Omega = \{(S, A, I, R)|0 \leq S + A + I + R \leq \Lambda/\mu\},
$$

with $S \geq 0, A \geq 0, I \geq 0, R \geq 0$ is an asymptotic stability region for the disease free equilibrium E_0.

The Liapunov function

$$L(x) = \sigma(\gamma_2 + \theta + \mu)A + (\gamma_1 + \mu)I,$$

is used to prove that all solutions for System (2) starting in Ω approach E_0. An outline of the proof is in the Appendix.

The endemic equilibrium

$$E^*(S_\infty(\Re_0), A_\infty(\Re_0), I_\infty(\Re_0), Q_\infty(\Re_0)),$$

of System (2) is obtained when $\Re_0 > 1$, and is given by

$$
\begin{aligned}
S_\infty(\Re_0) &= \frac{\Lambda}{\mu} \frac{(c-ab)}{(c-ab\Re_0)} \\
A_\infty(\Re_0) &= (1-p)\Lambda \frac{ab}{d} \frac{(1-\Re_0)}{(c-ab\Re_0)} \\
I_\infty(\Re_0) &= p\Lambda b \frac{(1-\Re_0)}{(c-ab\Re_0)} \\
Q_\infty(\Re_0) &= p\Lambda\theta \frac{(1-\Re_0)}{(c-ab\Re_0)},
\end{aligned}
\tag{4}
$$

where $a = \gamma_2 + \theta + \mu$, $b = \gamma_3 + \mu$, $c = p\mu\theta$ and $d = \gamma_1 + \mu$.

The endemic equilibrium obeys the property that $S_\infty(\Re_0) + A_\infty(\Re_0) + I_\infty(\Re_0) + Q_\infty(\Re_0) < \Lambda/\mu$ if and only if $\Re_0 > 1$. The infected population approaches to zero for any value of $\Re_0$. When $\Re_0 > 1$, the endemic equilibrium is positive and the values of $A_\infty(\Re_0)$, $I_\infty(\Re_0)$, in Figure 1, which seem to be approaching to zero but are actually approaching small positive values. However, we like to highlight that under different parameter values (still satisfying $\Re_0 > 1$), different dynamics are observed such as the ones in Figure 1 and damped oscillations in Figure 2.

The stability of the endemic equilibrium is tied to the roots of the characteristic polynomial associated with $J(E^*)$. It is at this point that we make the decision to explore a region of parameter space that is relevant to the study of the dynamics of influenza. Specifically we observe that the average life-expectancy $1/\mu$ is on the order of decades while $1/\gamma_1$, $1/\gamma_2$ $1/\gamma_3$ and $1/\theta$ are on the order of days. Hence, we can safely assume that μ is much smaller than $\gamma_1, \gamma_2, \gamma_3$ and θ. Taking into account these differences in time scales (longevity versus the infectious period), we proceed to generate a series expansion for the coefficients of the characteristic polynomial near μ, the following result was obtained

Result 3.3: The expansion of the characteristic polynomial for $J(E^*)$ about μ is

$$P(\lambda; \xi) = \lambda^4 + p_3(\xi)\lambda^3 + p_2(\xi)\lambda^2 + p_1(\xi)\lambda + p_0(\xi), \tag{5}$$

where ξ is the set of parameters for the model, when $\mu = 0$, Polynomial (5) reduces to

$$P(\lambda; \xi) = \lambda^4 + p_3(\xi)\lambda^3 + p_2(\xi)\lambda^2, \tag{6}$$

where

$$
\begin{aligned}
p_3(\xi) &= \Gamma - \frac{r}{\Re_0^0} \\
p_2(\xi) &= \gamma_3 \left[\gamma_1 + \gamma_2 + \theta - \frac{r}{\Re_0^0}\right] \\
p_1(\xi) &= 0 \\
p_0(\xi) &= 0,
\end{aligned}
$$

and

$$
\begin{aligned}
\Gamma &= \gamma_1 + \gamma_2 + \gamma_3 + \theta \\
\Re_0^0 &= \frac{(1-p)\sigma\beta}{\gamma_1} + \frac{p\beta}{\gamma_2 + \theta} \\
r &= (1-p)\sigma\beta + p\beta.
\end{aligned}
$$

Polynomial (6) has two zero eigenvalues, and two eigenvalues given by

$$\lambda_{1,2} = \frac{\left[\frac{r}{\Re_0^0} - (\gamma_1 + \gamma_2 + \gamma_3 + \theta)\right] \pm \sqrt{D}}{2}, \tag{7}$$

where

$$D = \left[\gamma_1 + \gamma_2 + \gamma_3 + \theta - \frac{r}{\Re_0^0}\right]^2 - 4\gamma_3\left[\gamma_1 + \gamma_2 + \theta - \frac{r}{\Re_0^0}\right].$$

An outline of the proof is in the Appendix.

IV. AN EXAMPLE.

We set $\gamma = \gamma_1 = \gamma_2 = \gamma_3$ and $\theta = k\gamma$ where $k \geq 3$.

The exact algebraic expressions for the roots are extremely complex and therefore we proceed to postulate specific relations between the recovery and the isolation rates. Specifically, we let $\gamma = \gamma_1 = \gamma_2 = \gamma_3$, and let the isolation rate
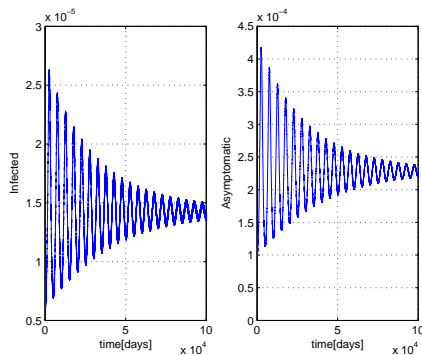
Fig. 2: Damped oscillations approaching the endemic equilibrium, $\gamma = \gamma_1 = \gamma_2 = \gamma_3$, $1/\gamma \in (3, 7)$, $\Re_0 = 1.7$, $p = 0.2$, $\sigma = 0.2$, $\beta = 0.6$, and $k \geq 3$.

Fig. 3: Sustained oscillations, can be observed for $\gamma = \gamma_1 = \gamma_2 = \gamma_3$, $1/\gamma \in (3, 7)$, $\Re_0 = 1.7$ and $k \geq 3$, $p = 0.2$, $\sigma = 0.2$.

be proportional to the recovery rate, $\theta = k\gamma$. A reasonable quarantine period for influenza is a week since infected people normally stay isolated between 1 and 7 days, then $1/\theta \in [1, 7]$, and the recovery rate is minimum 3 days, then $1/\gamma \geq 3$ therefore $k \geq 3$. Under these assumptions the discriminant and the real part for $\lambda_{1,2}$ reduce to

$$D = \left[\gamma(3 + k) - \frac{r}{\Re_0^0} \right]^2 - 4\gamma \left[\gamma(2 + k) - \frac{r}{\Re_0^0} \right],$$

and

$$Re(\lambda_{1,2}) = \frac{1}{2} \left[\frac{r}{\Re_0^0} - \gamma(3 + k) \right],$$

Recurring epidemic is shown through simulations with typical parameters for influenza. Figures 3 and 4 show damped oscillations for the solutions to the SAIQR model with particular values of $\Re_0$.

The inclusion of A and Q classes can support sustained oscillations, this qualitative behavior (damped oscillations) can be observed in Figure 2, this has not been seen in SIQR models that do not include the A- class as in ([8], [36]). Furthermore, Heathcote, Zhien, and Shengbing [28] found that the SIQR model with quarantine-adjusted incidence can have an endemic equilibria that is stable or unstable spiral, so that periodic solutions can occur.
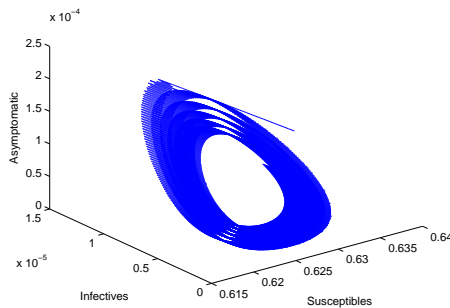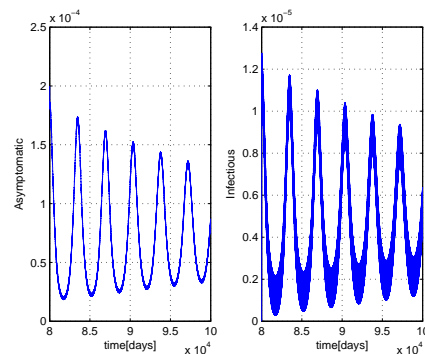

Fig. 4: The inclusion of A and Q can support sustained oscillations, $\gamma = \gamma_1 = \gamma_2 = \gamma_3$, $1/\gamma \in (3, 7)$, $\Re_0 = 1.7$ and $k \geq 3$, $p = 0.2$, $\sigma = 0.2$.

V. FINAL SIZE RELATION

In epidemiology models, the final size relation is a fundamental equation relating the final size of the epidemic to the basic reproduction number. The final size relation is an important tool for analyzing the behavior of an epidemic model. Kermack and McKendrick [29], derived this equation for a general age-of-infection model, without writing the equation directly related with the basic reproduction number, recent work [5], show the final size relation for a general epidemiological model, depending on the basic reproduction number, in a new simpler form if the total population size remains constant.

In order to find the final size relation, we start with the reduced SAIR, which corresponds to the SAIQR model where Q is not included; $\Lambda = 0$; and $\mu = 0$, then System (1) becomes

$$
\begin{aligned}
S' &= -\beta S \frac{(I + \sigma A)}{N}, \\
A' &= (1 - p)\beta S \frac{(I + \sigma A)}{N} - \gamma_1 A, \\
I' &= p\beta S \frac{(I + \sigma A)}{N} - \gamma_2 I, \\
R' &= \gamma_1 A + \gamma_2 I,
\end{aligned}
\tag{8}
$$

where

$$
\Re_0 = \frac{p\beta}{\gamma_2} + \frac{\sigma(1-p)\beta}{\gamma_1}.
\tag{9}
$$

Define $\varphi(t)$ as the total infectivity at time t, $B(\tau)$ as the fraction of infected members remaining infected at infection age τ, and $\pi(\tau)$ as the mean infectivity per individual at the infection age τ, where $0 < \pi(\tau) \le 1$, see [5] for more details.

For System (8), two infective classes are involved, for the I-class, we have

$$
\pi_I(\tau) = 1,
$$

and

$$
B_I(\tau) = p \exp^{-\gamma_2 \tau},
$$

for the A-class, we have

$$
\pi_A(\tau) = \sigma,
$$

and

$$
B_A(\tau) = (1 - p) \exp^{-\gamma_1 \tau}.
\tag{10}
$$

The mean infectivity per individual for members of the population with infection age τ, denoted by $M(\tau)$ is

$$
\begin{aligned}
M(\tau) &= \pi_I(\tau)B_I(\tau) + \pi_A(\tau)B_A(\tau), \\
&= pe^{-\gamma_2 \tau} + \sigma(1-p)e^{-\gamma_1 \tau}.
\end{aligned}
$$

In order to find the final size relation for System (8), we follow the method used in [5]. The total infectivity at time t is

$$
\varphi(t) = I(t) + \sigma A(t),
$$

then

$$
S' = -\frac{\beta}{N}S(t)\varphi(t),
$$

$$
\varphi(t) = \varphi_0(t) + \int_0^t -S'(t - \tau)\left[pe^{-\gamma_2 \tau} + \sigma(1 - p)e^{-\gamma_1 \tau}\right]d\tau
\tag{11}
$$

since $\varphi(t) = I(t) + \sigma A(t)$, then

$$
\begin{aligned}
-\frac{S'}{S} &= \frac{\beta}{N}\varphi_0(t) \\
&- \frac{\beta}{N}\int_0^t S'(t - \tau)\left[pe^{-\gamma_2 \tau} + \sigma(1 - p)e^{-\gamma_1 \tau}\right]d\tau.
\end{aligned}
\tag{12}
$$

Integrating Equation (12) with respect to t from 0 to infinity gives the general final size relation for SAIR model,

$$
\ln\left(\frac{S_0}{S_\infty}\right) = \Re_0\left(1 - \frac{S_\infty}{N}\right).
\tag{13}
$$

where the basic reproduction number is

$$
\begin{aligned}
\Re_0 &= \beta \int_0^\infty A(\tau)d\tau, \\
&= \beta \int_0^\infty pe^{-\gamma_2 \tau} + \sigma(1 - p)e^{-\gamma_1 \tau}d\tau, \\
&= \frac{p\beta}{\gamma_2} + \frac{\sigma(1-p)\beta}{\gamma_1}.
\end{aligned}
\tag{14}
$$

Using the previous method, we proceed to find the final size relation for one outbreak ($\Lambda = 0$ and $\mu = 0$), for the SAIQR model, under these conditions the model SAIQR becomes

$$
\begin{aligned}
S' &= -\beta S \frac{(I + \sigma A)}{N - Q}, \\
A' &= (1 - p)\beta S \frac{(I + \sigma A)}{N - Q} - \gamma_1 A, \\
I' &= p\beta S \frac{(I + \sigma A)}{N - Q} - (\gamma_2 + \theta)I, \\
Q' &= \theta I - \gamma_3 Q, \\
R' &= \gamma_1 A + \gamma_2 I + \gamma_3 Q.
\end{aligned}
\tag{15}
$$

Denote

$$\hat{A} = \int_0^\infty A(t)dt, \qquad \hat{I} = \int_0^\infty I(t)dt,$$

from System (15), integration of the equation for S' gives

$$\ln\left(\frac{S_0}{S_\infty}\right) = \beta \int_0^\infty \frac{I + \sigma A}{N - Q}dt.$$

From Result 2.1, we have that

$$Q(t) < \hat{Q} = max\{Q_0, \theta/(\gamma_3 + \mu)\},$$

since demographic is not taken into account, then $\mu = 0$; also, $Q_0 = 0$; furthermore $\hat{Q} < N$ and $\hat{Q} = \theta/\gamma_3$, then it holds that

$$Q(t) \leq \frac{\theta}{\gamma_3} < N,$$

then

$$\frac{\beta}{N}\left[\hat{I} + \sigma\hat{A}\right] \leq \ln\left(\frac{S_0}{S_\infty}\right) < \frac{\beta}{N - \theta/\gamma_3}\left[\hat{I} + \sigma\hat{A}\right],$$

furthermore

$$\beta\left[\hat{I} + \sigma\hat{A}\right] = \beta\left[\frac{I_0}{\gamma_2 + \theta} + \frac{\sigma A_0}{\gamma_1}\right] + (S_0 - S_\infty)\Re_0,$$

assuming $A_0 = I_0 = 0$, the following inequalities represent the final size relation for the SAIQR model

$$\frac{1}{N}\left[(S_0 - S_\infty)\Re_0\right] \leq \ln\left(\frac{S_0}{S_\infty}\right)$$
$$\leq \frac{1}{N - \theta/\gamma_3}\left[(S_0 - S_\infty)\Re_0\right], \tag{16}$$

with

$$\Re_0 = \frac{p\beta}{\gamma_2 + \theta} + \frac{(1 - p)\beta\sigma}{\gamma_1}.$$

The final size relation is a measure of the total number of infected individuals after an outbreak of the disease during certain period of time. In order to find the final size relation the initial number of infected individuals can be approximated to zero, so, $A_0 = I_0 = Q_0 = R_0 = 0$, since $S_0 + A_0 + I_0 + Q_0 + R_0 = N$, then $N = S_0$, from where the final size relation (16) becomes

$$\left(1 - \frac{S_\infty}{N}\right)\Re_0 \leq \ln\left(\frac{N}{S_\infty}\right)$$
$$\leq \frac{1}{N - \theta/\gamma_3}\left[(N - S_\infty)\Re_0\right]. \tag{17}$$

More details about final size relation and final epidemic size for different epidemiological models can be found in [5].

APPENDIX

Proof of Result 2.1: The right hand side of System (1) is continuously differentiable and hence it is locally Lipschitz, and therefore there exits a unique solution $S(t), A(t), I(t), Q(t), R(t)$ to System (1) with the initial data S_0, A_0, I_0, Q_0, R_0 that is defined on a maximal forward interval of existence [43]. Consider the set $\Omega \subset R^5$ defined by

$$\Omega = \{(S, A, I, R, Q) : 0 \leq S + A + I + Q + R \leq \frac{\Lambda}{\mu}\}$$

we show that

i) Since $I(0) \geq 0$ and $A(0) \geq 0$ from System (1) we have that

$$I(t) \geq I_0 \exp\int_0^\infty \left(p\beta S\frac{1}{N - Q}\right)dt$$
$$- I_0 \exp\int_0^\infty ((\gamma_2 + \theta + \mu))dt$$
$$A(t) \geq A_0 \exp\int_0^\infty \left((1 - p)\beta\sigma\frac{S}{N - Q}\right)dt$$
$$- A_0 \exp\int_0^\infty ((\gamma_1 + \mu))dt$$
$$Q(t) = Q_0 e^{(\gamma_3 + \mu)(t_0 - t)}$$
$$+ \left(\int_0^t \theta I(\zeta)e^{(\gamma_3 + \mu)(\zeta - t_0)}d\zeta\right)e^{(\gamma_3 + \mu)(t_0 - t)}$$
$$R(t) = R_0 e^{\mu(t_0 - t)}$$
$$+ \left(\int_0^t (\gamma_1 A(\zeta) + \gamma_2 I(\zeta) + d\zeta\right)e^{\mu(t_0 - t)}$$
$$+ \left(\int_0^t \gamma_3 Q(\zeta)e^{\mu(\zeta - t_0)}\right)e^{\mu(t_0 - t)}.$$

then $S(t) \geq 0$, $A(t) \geq 0$, $I(t) \geq 0$, $Q(t) \geq 0$, $R(t) \geq 0$ for all $t > 0$.

ii) Q is bounded by $\hat{Q} = max\left\{Q_0, \dfrac{\theta}{\gamma_3 + \mu}\right\}$. The last statement will be established if we show that $Q(t) \leq \kappa$ for all $t \geq 0$ and that $\kappa \geq \frac{\theta}{\gamma_3+\mu}$ if $Q_0 \leq \kappa$. Suppose that the above inequalities do not hold then there exists a time t_1 with $Q'(t_1) > 0$ and $Q(t_1) > \kappa$. From the Q-equation in System (1) we have

$$\frac{dQ(t_1)}{dt} = \theta I(t_1) - (\gamma_3 + \mu)Q(t_1)$$
$$\leq \theta(I(t_1) - 1) \leq 0,$$

since $(I(t_1) - 1) < 0$ and $\theta > 0$, $Q'(t_1) > 0$, this contradiction implies that $Q(t) \leq \kappa$ for all $t \geq 0$. Suppose now that $Q(0) > \kappa \geq \frac{\theta}{\gamma_3+\mu}$. In order to show that $Q(t) \leq Q(0)$ for all $t \geq 0$ we assume that the last inequality does not hold. Hence there exists a time $t_2 > 0$ such that $Q(t_2) \geq Q(0)$ and $Q'(t_2) > 0$. However since $Q(t_2) > \theta/(\gamma_3 + \mu)$, then

$$Q'(t_2) = \theta I(t_2) - (\gamma_3 + \mu)Q(t_2)$$
$$\leq \theta(I(t_2) - 1) \leq 0,$$

but $Q'(t_2) > 0$. Hence we have reach a contradiction and $Q(t)$ is bounded from above by $\hat{Q}$, where $\hat{Q} = max\{Q_0, \theta/(\gamma_3 + \mu)\}$.

Proof of Result 3.1: The stability of the disease free equilibrium point depends on the signs of the real parts of the eigenvalues of the Jacobian matrix $J(E_0)$, $-\mu$ and $-(\gamma_3 + \mu)$ are two eigenvalues of $J(E_0)$. Conditions

$$trace(J_1(E_0)) < 0,$$

and

$$det(J_1(E_0)) > 0,$$

are equivalent to $\Re_0 < 1$, hence this guarantee the asymptotic stability of the disease-free equilibrium. If $\Re_0 > 1$ implies that E_0 is unstable. see [43] for more mathematical details.

Proof of Result 3.2: For $S \geq 0, A \geq 0, I \geq 0, Q \geq 0$, Define the region

$$\Omega = \{(S, A, I, R)|0 \leq S + A + I + Q \leq \Lambda/\mu\}.$$

Define a Liapunov function L over $\Omega_0 \in \Omega$ as follows, for $\mathbf{x} \in \Omega_0$,

$$L(\mathbf{x}) = \sigma(\gamma_2 + \theta + \mu)A + (\gamma_1 + \mu)I,$$

hence L satisfies

i) $L \in C^1(\Omega_0)$, $L(\Lambda/\mu, 0, 0, 0) = 0$ and $L(\mathbf{x}) > 0$ if $\mathbf{x} \neq E_0$.

ii) If $\Re_0 < 1$, for all $\mathbf{x} \in \Omega_0$, $\mathbf{x} \neq E_0$, then $\dfrac{dL}{dt} < (\gamma_1 + \mu)(\gamma_2 + \theta + \mu)(I + \sigma A)[\Re_0 - 1] < 0$,

then all solutions of System (2) starting in Ω approach E_0.

Proof of Result 3.3: The characteristic polynomial for $J(E^*)$, has the form

$$P(\lambda; \xi) = \lambda^4 + p_3(\xi)\lambda^3 + p_2(\xi)\lambda^2 + p_1(\xi)\lambda + p_0(\xi), \tag{18}$$

the expansion of the characteristic polynomial for $J(E^*)$ to first order in μ can be obtained as follow, define

$$\begin{aligned}
\Re_0^0 &= \frac{(1-p)\sigma\beta}{\gamma_1} + \frac{p\beta}{\gamma_2 + \theta} \\
\Re_0^1 &= \frac{(1-p)\sigma\beta}{\gamma_1^2} + \frac{p\beta}{(\gamma_2 + \theta)^2}, \\
\Gamma &= \gamma_1 + \gamma_2 + \gamma_3 + \theta \\
r &= (1-p)\sigma\beta + p\beta,
\end{aligned}$$

then $\Re_0 = R_0^0 - R_0^1\mu + \mathcal{O}(\mu^2)$. The coefficients for the characteristic polynomial are given by

$$\begin{aligned}
p_3(\xi) &= -Tr(J(E^*)) \\
p_2(\xi) &= \frac{1}{2}\{[Tr(J(E^*))]^2 - Tr[J(E^*)^2]\} \\
p_1(\xi) &= -\frac{1}{6}\{[Tr(J(E^*))]^3 \\
&\quad - 3Tr[J(E^*)^2]Tr(J(E^*))\} \\
&\quad + 2Tr[(J(E*))^3] \\
p_0(\xi) &= Det(J(E^*)),
\end{aligned}$$

after some calculations, we have

$$p_3(\xi) = \left(\Gamma - \frac{r}{\Re_0^0}\right)$$
$$+ \left(3 + \Re_0^0 - \frac{\Re_0^1}{(\Re_0^0)^2}r\right)\mu + \mathcal{O}(\mu^2)$$

$$p_2(\xi) = \gamma_3 \left(\gamma_1 + \gamma_2 + \theta - \frac{r}{\Re_0^0} \right)$$
$$+ \left(\frac{p\theta - 3r - \gamma_1(\gamma_2 + \theta)\Re_0^1}{\Re_0^0} \right) \mu$$
$$+ \left(\Gamma(2 + \Re_0^0) - p\theta - \frac{\gamma_3 r \Re_0^1}{(\Re_0^0)^2} \right) \mu + \mathcal{O}(\mu^2)$$

$$p_1(\xi) = - \left(\frac{2r\gamma_3 - p\theta\gamma_1}{\Re_0^0} - \frac{\gamma_1(\gamma_2 + \theta)\gamma_3 \Re_0^1}{\Re_0^0} \right) \mu$$
$$+ \left(((\gamma_1 + \gamma_3)(\gamma_2 + \theta) + \gamma_1\gamma_3)(1 + \Re_0^0) \right) \mu$$
$$- \gamma_1 \left(p\theta + 2(\gamma_2 + \theta) \right) \mu + \mathcal{O}(\mu^2)$$

$$p_0(\xi) = (\gamma_2 + \theta) \left((1-p)\sigma\beta - \gamma_1 \right) \mu$$
$$+ (\gamma_1\gamma_3 p\beta) \mu + \mathcal{O}(\mu^2).$$

Note that, if $\mu = 0$ then $p_1(\xi) = p_0(\xi) = 0$, so the characteristic polynomial has two zero eigenvalues.

VI. CONCLUSION

In this work, we look at the simplest epidemiological model that incorporates the dynamics of an asymptomatic class. We focus on parameter values appropriate for a model of an influenza epidemic, and look specifically for evidence that models that include A and Q classes can exhibit sustained oscillations. We have carried out the standard analysis of an SAIQR model, and shown that when $\Re_0 < 1$, the free disease equilibrium point is globally asymptotically stable, and when $\Re_0 > 1$, we found an analytic expression for the unique endemic equilibrium in terms of $\Re_0$ and the other parameters. Through simulations with typical parameters for influenza, we observe damped oscillations that describes recurring epidemics, this has not been seen in SIQR models that do not include the A- class as in ([8], [36]). A final size relation for the SAIQR model is then established. The utility of a final size relation is that it gives an implicit determination for the final size of the epidemic, and it can be used to estimate the effects of changes in the parameters on the epidemic size. This is something that cannot be obtained from numerical simulations. Numerical simulations are used if we have a specific set of parameters and we want to predict a quantitative outcome, but qualitative results cannot be proved to exist persistently using only numerical methods.

REFERENCES

[1] V. Andreasen, J. Lin and S.A. Levin, *The dynamics of co-circulating influenza strains conferring partial cross-immunity*, J. Math. Biol., 35: 825-842, 1997.

[2] L.A. Angelova *Long-term immunity to influenza A (H1N1) in humans*, In Annales de L'Institut Pasteur. Virologie, Elsevier, 133 (3): 267–272, 1982.

[3] J. Arino, F.Brauer,P. van den Driessche, J. Watmouugh, and J. Wu, *A model for influenza with vaccination and antiviral treatment*, Journal of Theoritical Biology, 253 (1):118-130, 2008.

[4] F. Brauer and C. Castillo-Chavez "Mathematical Models in Population Biology and Epidemiology," Texts in Applied Mathematics, 40, Springer-Verlag, New York, 2001.

[5] F. Brauer, *Age of Infection and the final size realtion*, Mathematical Biosciences and Engineering 5, 2008.

[6] R.M. Bush, C.A. Bender, K. Subbarao, N.J. Cox and W.M. Fitch, *Predicting the evolution of Human Influenza A*, Science, 286 (5446):1921, 1999.

[7] Castillo-Chavez, C., Hethcote, H. W., Andreasen, V. Levin, S. A. and Liu, W. M., *Cross-Immunity in the dynamics of homogeneous and heterogeneous populations*, Mathematical ecology, Trieste, World Sci. Publishing, NJ, 303–316, 1988.

[8] C. Castillo-Chavez, H.W. Hethcote, V. Andreasen, S.A. Levin and W.M. Liu, *Epidemiological models with age structure, proportionate mixing, and cross-immunity*, Journal of Mathematical Biology, Springer, 40: 233–258, 1989.

[9] C. Castillo-Chavez, C. Castillo-Garsow and A.A. Yakubu, *Mathematical models of isolation and quarantine*, JAMA, American Medical Association, 290: 2876–2877, 2003.

[10] C. Castillo-Chavez and H.R. Thieme, *Asymptotically authonomous epidemic models, mathematical pulation dynamics: Analysis of heterogeneity*, O. Orino, D. Axelrod, M. Kimmel, M. Langlais, Eds. 1: 33–50, 1995.

[11] C. Castillo-Chavez and G. Chowell, *Mathematical models, challenges, and lessons learned from the 2009 A/H1N1 Influenza pandemic*, Mathematical Biosciences and Engineering, 8(1): 246 pages, 2011. http://aimsciences.org/journals/displayPapers1.jsppubID=411

[12] P. Caley, D. J. Philp and K. McCracken, *Quantifying social distancing arising from pandemic influenza*, Journal of The Royal Society Interface, 5(23):631, 2008.

[13] G.Chowell, P.W.Fenimore, M.A. Castillo-Garsow and C. Castillo-Chavez, *SARS outbreaks in Ontario, Hong Kong and Singapore: the role of diagnosis and isolation as a control mechanism*, Journal of Theoritical Biology, 224 (1): 1-8, 2003.

[14] G.Chowell, Hiroshi Nishiura, Luis M.A.Bettencourt, *Comparitive estimation of the reproduction number for pandemic influenza from daily case notification data*, Journal of the Royal Society Interface, 4 (12):154-166, 2007.

[15] G. Chowell, S.M. Bertozzi, M.A. Colchero, H. Lopez-Gatell, C. Alpuche-Aranda, M. Hernandez and M.A. Miller, *Severe respiratory disease concurrent with the circulation of H1N1 influenza*, The New England journal of medicine, 361(7):674, 2009.

[16] N.J. Cox and Subbarao, *Global epidemiology of influenza: Past and present*, Annu. Rev. Med. 51: 407-421, 2000.

[17] R.B.Couch and J.A.Kasal, *Inmmunity to influenza in man*, Annual Reviews in Microbiology, 37 (1): 529-549, 1983.

[18] M. Cruz-Aponte, E. McKiernan, and M.A. Herrera-Valdez, *Mitigating effects of vaccination on influenza outbreaks given constraints in stockpile size and daily administration capacity*, BMC Infectious Diseases, (11), 2011.

[19] P. Van den Driessche and J. Watmough, *Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission*, Mathematical Biosciences 180:29-48, 2002.

[20] Z. Feng, "A Mathematical Model for the Dynamics of Childhood Diseases Under the Impact of Isolation," Ph.D thesis, Arizona State University, 1994.

[21] Z. Feng and H. Thieme, *Recurrent outbreaks of childhood diseases revisited: The impact of isolation*, Math. Biosc. and Eng. 129: 93-130, 1995.

[22] E.Fenichel, C. Castillo-Chavez, M.Ceddia, G. Chowell, P. Gonzalez-Parra and others, *Adaptative human behaviour in epidemiological models*, National Acad Sciences, 108(15):6306-6311, 2011.

[23] A. Flahault, X. De Lamballerie, T. Hanslik and N. Salez, *Symptomatic infections less frequent with H1N1pdm than with seasonal strains*, URL http://knol.google.com/k/symptomatic-infections-less-frequent-with-h1n1pdm-than-with-seasonal-strains PLoS Curr Influenza 28, 2009.

[24] R. Gani, H. Hugues, D. Fleming, T. Griffin, J. Medlock and S. Leach, *Potential impact of antivirial drug use influenza pandemic*, Emerging Infecious Diseases, 11(9):1355-1362, 2005.

[25] M.A. Herrera-Valdez, M. Cruz-Aponte and C. Castillo-Chavez, *Multiple outbreaks for the same pandemic: Local transportation and socila distancing explain the diferent "waves" of A-H1N1pdm cases observed in Mexico during 2009*, Mathematical Biosciences and Engineering, 8 (1):21-48, 2011.

[26] H. W. Hethcote, *The mathematic of infectious diseases*, SIAM review, 42:599-653, 2000.

[27] H.W. Hethcote and S.A. Levin, *Periodicity in epidemiological models*, Levin, Hallman, gross (Eds), Springer-Verlag. Applied Mathematical Ecology. 18: 193–211, 1989.

[28] H. W. Hethcote, M. Zhien and L.Shengbing, *Effects of quarantine in six endemic models for infectious diseases*, John A. Jacquez memorial volume. Math. Biosci. 180:141-160, 2002.

[29] W. O. Kermack and A.G. McKendrick, *Contributions to the mathematical theory of epidemics*, Proc. Royal Soc. London, 115:700-721, 1927.

[30] W. O. Kermack and A.G. McKendrick, *Contributions to the mathematical theory of epidemics, part II*, Proc. Royal Soc. London, 138: 55-83, 1932.

[31] V.J. Lee , G.G. Frenandez, M.I. Chen, D. Lye and Y.S. Leo (2006). *Influenza and the pandemic threat*, Singapur Medical Journal, 47 (6): 463-470, 2006.

[32] J. B. Plotkin, J.B., Dushoff, J., Levin, S.A., *Hemagglutinin sequence clusters and the antigenic evolution of influenza A virus*, PNAS, 99: 62636268, 2002.

[33] Lin, J., Andreasen, V., Casagrandi, R., Levin, S. A., *Traveling waves in a model of influenza a drift,* Journal of Theoretical Biology 222: 437-445, 2003.

[34] S. A. Levin , J. Dushoff and J. B. Plotkin, *Evolution and persistence of influenza A and other diseases*, Math. Biosc. and Eng. 188: 17-28, 2004.

[35] MBE Influenza Special Issue, 8(1), 2011.

[36] E. Mustafa, "Epidemic in Structured Populations with Isolation and Cross-immunity," Ph.D thesis, Arizona State University, 2007.

[37] M.I.Nelson and E.C.Holmes, *The evolution of epidemic influenza*, Nature Review Genetics, 8(3):196-205, 2007.

[38] H. Nishiura, C.Castillo-Chavez, M. Safan and G. Chowell, *Transmission potential of the new influenza A (H1N1) virus and its age-specificity in Japan*, Euro Surveill, 14 (22):19227, 2009.

[39] M. Nuno, "A Mathematical Model for the Dynamics of Influenza at the Population and Host Level," Ph.D thesis, Cornell University, 2005.

[40] Nuño, M., Feng, Z., Martcheva, M. and Castillo-Chavez, C. *Dynamics of Two-Strain Influenza with Isolation and Cross-protection*, SIAM J. Appl. Math. 65(3): 964-982, 2005.

[41] Nuño, M., Castillo-Chavez, C., Feng, Z. and M. Martcheva, *Mathematical Model of Influenza: The Role of cross-immunity, quarantine and age-structure*, In: Mathematical Epidemiology, P. van den Driessche, J Wu and F Brauer, Springer-Verlag (Eds.), 2008.

[42] Nuño, M., Martcheva, M. and Castillo-Chavez, C. *Immune Level Structure Model for Influenza Strains*, Journal of Biological Systems, 17(4): 713-737, 2009.

[43] L. Perko, "Differential Equations and Dynamical Systems," Springer, 2000.

[44] L.A. Rvachez and I.M. Jr Longini, *A mathematical model for the global spread of influenza*, Mathematical Biosciences, 1985.

[45] L. Sattenspiel and D.A. Herring, *structured epidemic models and the spread of influenza in the central canadian subarctic*, Human Biology, An international record of Research, 70 (1): 91, 1998.

[46] A.N.Slepushkin, E.I.Bourtseva, A.L.Belyaev, L.N.Vlassova and E.L.Feodoritova, *Influenza morbidity and some peculiarities of antiinfluenza immunity and prevention during influenza pandemics*, International Congress Series, 1263:787-790, 2004.

[47] C.Sun and Y.H. Hsieh, *Global analysis of an SEIR model with varing population size and vaccination*, Applied Mathematical Modeling, 2009.

[48] H. Thieme, "Mathematics in Population Biology," Princeton series in Theoritical and Computational Biology, Princeton University Press, Princeton, NJ, 2003.

[49] Vivas, A. L., *Dynamics of a "SAIQR" Influenza Model* Ph.D thesis, New Mexico State University, 2011.

[50] R. J. Webby, *Are we ready for pandemic influenza*, Science, 302:1519-1522, 2003.