ORIGINAL ARTICLE

# On the Role of Asymptomatic Infection in Transmission Dynamics of Infectious Diseases

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**Abstract** We propose a compartmental disease transmission model with an asymptomatic (or subclinical) infective class to study the role of asymptomatic infection in the transmission dynamics of infectious diseases with asymptomatic infectives, e.g., influenza. Analytical results are obtained using the respective ratios of susceptible, exposed (incubating), and asymptomatic classes to the clinical symptomatic infective class. Conditions are given for bistability of equilibria to occur, where trajectories with distinct initial values could result in either a major outbreak where the disease spreads to the whole population or a lesser outbreak where some members of the population remain uninfected. This dynamic behavior did not arise in a SARS model without asymptomatic infective class studied by Hsu and Hsieh (SIAM J. Appl. Math. 66(2), 627–647, 2006). Hence, this illustrates that depending on the initial states, control of a disease outbreak with asymptomatic infections may involve more than simply reducing the reproduction number. Moreover, the presence of asymptomatic infections could result in either a positive or negative impact on the outbreak, depending on different sets of conditions on the parameters, as illustrated with numerical simulations. Biological interpretations of the analytical and numerical results are also given.

**Keywords** Influenza · Asymptomatic infection · Basic reproduction number · Bistability · Threshold asymptomatic fraction

## 1. Introduction

The global threat of flu pandemic, either due to the potentially human-transmissible mutation of avian influenza (H5N1) or a new virulent strain of human influenza (e.g., Webster, 2004), has prompted numerous modeling studies of influenza in recent years. Many of the studies have focused on intervention measures with vaccine or antiviral drug prophylaxis to contain a pandemic outbreak (Longini et al., 2004, 2005; Ferguson et al., 2005)

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or on mitigating strategies to alleviate the severity of a global public health catastrophe (Germann et al., 2006; Ferguson et al., 2006). In some of these studies, namely, Longini et al. (2004, 2005) and Germann et al. (2006), the proposed models include 2 classes of infective persons, one is the symptomatic infectives with clinical symptoms and the other is the asymptomatic infectives with no or minor (subclinical) symptoms. The impact of asymptomatic cases on the severity of outbreak was explored using simulation studies. Stilianakis et al. (1998) first proposed to include the asymptomatic infectives in a standard SARS model to study treatment and chemoprophylaxis strategies and their effects on the spread of the infection. However, to our best knowledge, the role of asymptomatic infection on the overall transmission dynamics of influenza was never analytically explored.

It is widely believed that asymptomatic cases and asymptomatic infection of influenza, as well as, H5N1 do indeed occur regularly (e.g., Chan, 2002; Graat et al., 2003; Bell et al., 2006). Several earlier studies have indicated that subclinical infections account for about one-third of infections (Nafta et al., 1970; Oker-Blom et al., 1970; Monto et al., 1979; Pettersson et al., 1980; Quarles et al., 1981). Nonetheless, skepticism regarding asymptomatic spread of flu remains; some studies have suggested that virus shedding may sometimes occur before clinically significant symptoms or during subclinical symptoms, but virus shedding detected by nasal swabs cannot be equated to transmission of infection (Eccles, 2005). By its nature, asymptomatic or subclinical flu cases are difficult to diagnose. Hence, it is impossible to precisely define the number of asymptomatic cases, not to mention the demanding task of tracing the number of infections by those asymptomatic cases. Consequently, clinical evidence of asymptomatic infection is extremely scarce and the magnitude of its contribution to spread of flu is hard to ascertain. In Longini et al. (2004), it was assumed that the probability that a person will be symptomatic given that person has been infected is 0.67, based on population-level influenza cohort studies in the US. Moreover, they assumed that an asymptomatic infection is only 50% as infectious as a symptomatic infection. Intuitively, there might be a substantial (but poorly understood and inadequately quantified) difference in the respective transmission probabilities from asymptomatic person and symptomatic person to susceptible persons. Clearly, an infected person with clinical illness sheds more virus than does one with subclinical symptoms and also has illness manifestations (e.g., coughing) that contribute to the generation of infectious aerosols. On the other hand, infected persons with clinical symptoms may show reduced contacts if they are sufficiently ill to be confined to bed. For a lucid discussion, the readers are referred to Stilianakis et al. (1998).

The above-mentioned modeling studies with an asymptomatic infective class utilize complicated models and simulation studies to explore the role of asymptomatic infection in intervention strategies. It has been suggested that if a substantial proportion of disease transmission occurs through asymptomatic infection, the population impact of intervention measures such as health screening and case-patient isolation will be severely diminished (Bell et al., 2006). Moreover, a simulation study shows that, using 2003 Taiwan SARS outbreak as the hypothetical setting, if SARS patients in Taiwan had been infectious during incubation for a mere 2 days before onset of clinical symptoms, the number of cases would increase substantially (G. Webb et al., unpublished work). A recent study of an epidemic model which considers asymptomatic infection (Arino et al., 2006) suggested that many of the simulation results of the complicated simulation models can also be obtained from simple classical deterministic compartmental models. Therefore, in this work, we will make use of a simple compartmental model to study analytically the role

of asymptomatic infection on the transmission dynamics of influenza, by assuming that an asymptomatic infective is only half as infectious as a clinically ill infective. Similar to Stilianakis et al. (1998), we do not consider infections by flu patients during incubation. Moreover, we purposely do not consider interventions, for this direction of research could be carried out in future studies using more complicated models and computer simulations, if needed.

The article is organized as follows: Section 2 gives the proposed model with asymptomatic infection; in Section 3 we give some analytical results; Section 4 will be devoted to summarizing our results using numerical examples; finally, in Section 5, we provide biological interpretation of the impact of asymptomatic infection on the dynamical behavior of the system studied.

## 2. The model

We present a model which considers human transmission of infectious diseases such as influenza, possibly a new influenza strain or even human-transmissible strain of avian flu (H5N1), which might be more virulent than those strains in the past. We have the following assumptions:

1. Infective persons can be classified in two classes; one of which, $I(t)$, is with symptoms and the other, $A(t)$, is without any clinical presentation of symptoms, called asymptomatic or subclinical infectives. $A(t)$ is assumed to be less infective than $I(t)$, i.e., $0 < \delta < 1$, where $\delta$ is the reduction in infectivity.
2. As behavior change of people occurs due to public response to the outbreak (Hsu and Hsieh, 2006), contact rate (reflecting level of risky behaviors) decreases with the increasing cumulative numbers of hospitalized and removed persons.
3. A hospitalized person is removed from isolation either by death or discharged.
4. Homogeneous mixing population is assumed.
5. For convenience, we assume constant population size (including disease deaths) with negligible births and deaths during the course of the disease outbreak.

   The model variables are given as follows:

   S: susceptible population,
   E: exposed (incubating) population
   I: infective population,
   A: asymptomatic infective population
   H: hospitalized population
   R: removed population (both recovered and SARS deaths)

   A flow chart of the model is given in Fig. 1.
   The model parameters are given as follows:

$\mu$  is the progression rate of exposed to infective classes.
$\beta$  is the transmission probability per effective classes.
$a$  is the effect of behavior change in reduction of contact due to the cumulative numbers of hospitalized and removed cases. (For a detailed discussion, see Hsu and Hsieh, 2006).
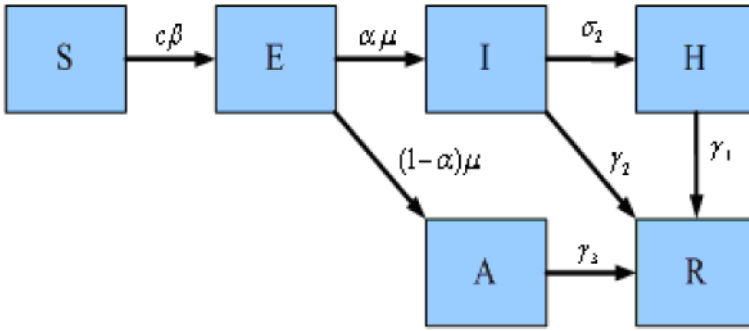
**Fig. 1** Flowchart of the proposed model.

$c$ is the contact rate in absence of an outbreak.

$\delta$ with $0 < \delta < 1$, is the reduction in infectiousness of asymptomatic infectives.

$\alpha$ with $0 < \alpha < 1$, is the fraction of exposed class $E$ progressing to class $I$, or proportion of symptomatic infections.

$\gamma_2$, $\gamma_3$ and $\gamma_1$ are the removal (recovered and disease death) rates of infective classes $I$, $A$, and hospitalized $H$, respectively.

$\sigma_2$ is the hospitalization rate of symptomatic infectives $I$.

Consequently, the model equations are:

$$S' = -\frac{\beta S(I + \delta A)}{S + E + I + A} \frac{c}{1 + a(H + R)},$$

$$E' = \frac{\beta S(I + \delta A)}{S + E + I + A} \frac{c}{1 + a(H + R)} - \mu E,$$

$$I' = \alpha \mu E - (\sigma_2 + \gamma_2)I,$$

$$A' = (1 - \alpha)\mu E - \gamma_3 A, \tag{1}$$

$$H' = \sigma_2 I - \gamma_1 H,$$

$$R' = \gamma_2 I + \gamma_3 A + \gamma_1 H,$$

$$S(0) = S_0 > 0, \qquad I(0) = I_0 > 0, \qquad A(0) = A_0 > 0,$$

$$E(0) = 0, \qquad H(0) = 0, \qquad R(0) = 0.$$

The system is similar to a SARS model without quarantine considered in Hsu and Hsieh (2006), but with the addition of an asymptomatic infective class. Note that the hospitalized class $H$ in this work is essentially the probable cases $P$ in that SARS model. The basic reproduction number $R_0$ of this system is:

$$R_0 = \frac{c\beta}{1 + aR_\infty}\left[\frac{\alpha}{\sigma_2 + \gamma_2} + \frac{\delta(1 - \alpha)}{\gamma_3}\right],$$

where the parameters are as described earlier and $R_\infty$ is the limiting removed population size, i.e., $R(t) \to R_\infty > 0$ as $t \to \infty$. Note that $R_\infty$ is also the total prevalence or the number of persons infected during the course of the outbreak.

## 3. Some analysis of model

We begin with some basic properties of the system.

**Lemma 1.** *If $f(t) \to constant$ at $t \to \infty$ and $|f''(t)| \le M$ for all $t$, then $f(t) \to 0$ as $t \to \infty$.*

The proof can be found in Coppell (1965, p. 139) and hence omitted.

**Theorem 1.** *We have the following results*: $S(t) \to S_\infty \ge 0$, $E(t) \to 0$, $I(t) \to 0$, $A(t) \to 0$, $H(t) \to 0$, and $R(t) \to R_\infty > 0$ as $t \to \infty$.

*Proof:* Since $S(t)$ is decreasing, $S(t) \downarrow S_\infty \ge 0$. Moreover, we know that $(S + E)' = -\mu E < 0$ and $E(t) + S(t) \downarrow E_\infty + S_\infty$, hence, $E(t) \to E_\infty$. We also have $S(t) + E(t) + I(t) + A(t) + H(t) + R(t) \equiv N = S_0 + I_0 + A_0$. With $R' \ge 0$, we have $R(t) \to R_\infty > 0$. Furthermore, $R'' = \gamma_2 I + \gamma_3 A' + \gamma_1 H'$ is bounded, therefore, by Lemma 1, $I(t) \to 0$, $A(t) \to 0$, and $H(t) \to 0$. It then follows that $E(t) \to E_\infty = 0$ since if $E_\infty > 0$, then from the third equation in (1) and $I(t) \to 0$, $I(t)$ becomes unbounded which is a contradiction.                                                                                        $\square$

Now we consider the limiting system of the model in (1) as follows, with $\hat{\beta}$ defined by $\hat{\beta} \doteq c\beta/(1 + aR_\infty) < c\beta$.

$$S' = -\frac{\hat{\beta} S(I + \delta A)}{S + E + I + A}, \quad 0 < \delta < 1,$$

$$E' = \frac{\hat{\beta} S(I + \delta A)}{S + E + I + A} - \mu E, \quad 0 < \alpha < 1, \tag{2}$$

$$I' = \alpha \mu E - (\sigma_2 + \gamma_2)I,$$

$$A' = (1 - \alpha)\mu E - \gamma_3 A.$$

Let $W_1 = S/I$, $W_2 = E/I$, and $W_3 = A/I$, then the above system in (2) can be reduced to

$$W_1' = -\hat{\beta} W_1 \frac{1 + \delta W_3}{1 + W_1 + W_2 + W_3} - W_1 \big[ \alpha \mu W_2 - (\sigma_2 + \gamma_2) \big],$$

$$W_2' = \hat{\beta} W_1 \frac{1 + \delta W_3}{1 + W_1 + W_2 + W_3} - \mu W_2 - W_2 \big[ \alpha \mu W_2 - (\sigma_2 + \gamma_2) \big], \tag{3}$$

$$W_3' = \big[ (1 - \alpha)\mu W_2 - \gamma_3 W_3 \big] - W_3 \big[ \alpha \mu W_2 - (\sigma_2 + \gamma_2) \big].$$

Now we discuss the equilibria of system (3).

(1) $E_0 = (0, 0, 0)$ which always exists.

The variation matrix of system (3) at $E_0$ is

$$M(E_0) = \begin{bmatrix} -\hat{\beta} + (\sigma_2 + \gamma_2) & 0 & 0 \\ \hat{\beta} & -\mu + (\sigma_2 + \gamma_2) & 0 \\ 0 & (1-\alpha)\mu & -\gamma_3 + (\sigma_2 + \gamma_2) \end{bmatrix}.$$

The eigenvalues of $M(E_0)$ are $-\hat{\beta} + \sigma_2 + \gamma_2$, $-\mu + \sigma_2 + \gamma_2$, $-\gamma_3 + \sigma_2 + \gamma_2$. Thus $E_0$ is locally stable if $\sigma_2 + \gamma_2 < \min\{\hat{\beta}, \mu, \gamma_3\}$.

(2) $E_{23} = (0, W_2^\star, W_3^\star)$, where $W_2^\star = \frac{-\mu + \sigma_2 + \gamma_2}{\alpha\mu} > 0$, $W_3^\star = \frac{(1-\alpha)\mu W_2^\star}{\gamma_3 - \mu} > 0$.

Clearly, $E_{23}$ exists $\Leftrightarrow \sigma + \gamma_2 > \mu$ and $\gamma_3 > \mu$. $E_{23}$ is locally stable if $\mu < \hat{\beta}\frac{1+\delta W_3^\star}{1+W_2^\star+W_3^\star} \Leftrightarrow \hat{\beta} > \frac{\alpha\mu(\gamma_3-\mu)+[(\sigma_2+\gamma_2)-\mu](\gamma_3-\alpha\mu)}{\alpha(\gamma_3-\mu)+\delta(1-\alpha)[(\sigma_2+\gamma_2)-\mu]}$. The variational matrix of system (3) at $E_{23}$ is

$$M(E_{23}) = \begin{bmatrix} -\hat{\beta}\frac{1+\delta W_3^\star}{1+W_2^\star+W_3^\star} - [\alpha\mu W_2^\star - (\sigma_2+\gamma_2)] & 0 & 0 \\ \hat{\beta}\frac{1+\delta W_3^\star}{1+W_2^\star+W_3^\star} & -\mu - 2\alpha\mu W_2^\star + (\sigma_2+\gamma_2) & 0 \\ 0 & (1-\alpha)\mu - \alpha\mu W_3^\star & -\gamma_3 - [\alpha\mu W_2^\star - (\sigma_2+\gamma_2)] \end{bmatrix}.$$

The eigenvalues of $M(E_{23})$ are $\lambda_1 = -\hat{\beta}\frac{1+\delta W_3^\star}{1+W_2^\star+W_3^\star} - [\alpha\mu W_2^\star - (\sigma_2 + \gamma_2)] = -\hat{\beta}\frac{1+\delta W_3^\star}{1+W_2^\star+W_3^\star} + \mu$, $\lambda_2 = -\mu - (\sigma_2 + \gamma_2) < 0$, $\lambda_3 = -\gamma_3 + \mu < 0$. Therefore, $E_{23}$ is locally stable $\Leftrightarrow \mu < \hat{\beta} > \frac{1+\delta W_3^\star}{1+W_2^\star+W_3^\star}$. Note that $E_0$ and $E_{23}$ are both equilibria at which the whole population becomes infected, i.e., $S_\infty = 0$.

(3) $E_\infty = (+\infty, \tilde{W}_2, \tilde{W}_3)$.

Result on the existence and stability of $E_\infty$ is given in the following theorem, with the proof given in the Appendix.

**Theorem 2.** *We have the equivalent relations below regarding the existence and stability of $E_\infty$:* $\frac{\alpha_2+\gamma_2}{\alpha}[\frac{1}{\hat{\beta}} - \frac{(1-\alpha)\delta}{\gamma_3}] > 1 \Leftrightarrow \hat{\beta} < \frac{1}{\frac{\delta(1-\alpha)}{\gamma_3} + \frac{\alpha}{\sigma_2+\gamma_2}} = \frac{\gamma_3(\sigma_2+\gamma_2)}{\delta(1-\alpha)(\sigma_2+\gamma_2)+\alpha\gamma_3} \Leftrightarrow E_\infty$ *is stable.*

To investigate in further details, we go back to limiting system in (3) and let $Z_1 = 1/W_1$, $Z_2 = W_2/W_1$, and $Z_3 = W_3/W_1$. That is, we let $Z_1 = I/S$, $Z_2 = E/S$, and $Z_3 = A/S$. It follows

$$Z_1' = -\hat{\beta}Z_1\frac{Z_1 + \delta Z_3}{1 + Z_1 + Z_2 + Z_3} - [\alpha\mu Z_2 - (\sigma_2 + \gamma_2)Z_1],$$

$$Z_2' = \hat{\beta}(Z_2 + 1)\frac{Z_1 + \delta Z_3}{1 + Z_1 + Z_2 + Z_3} - \mu Z_2, \tag{4}$$

$$Z_3' = (1-\alpha)\mu Z_2 - \gamma_3 Z_3 - \hat{\beta}Z_3\frac{Z_1 + \delta Z_3}{1 + Z_1 + Z_2 + Z_3}.$$

The stability of $\hat{E}_0 = (0, 0, 0)$ of system (4) is equivalent to that of $E_\infty = (+\infty, \tilde{W}_2, \tilde{W}_3)$ of system (3). We have the following theorem.

**Theorem 3.** *Let $B_2 = \frac{(\sigma_2+\gamma_2)\gamma_3\mu}{\alpha\mu\gamma_3+\delta(1-\alpha)\mu(\sigma_2+\gamma_2)} > \hat{\beta}$, we then have $\hat{E} = (0, 0, 0)$ is locally stable*

$\Leftrightarrow \hat{\beta} < B_2 \Leftrightarrow R_0 < 1 \Leftrightarrow \hat{\beta} < \frac{\gamma_3(\sigma_2+\gamma_2)}{\alpha\gamma_3+\delta(1-\alpha)(\sigma_2+\gamma_2)}$, *where $R_0$ is the basic reproduction number of system* (1) *given at the end of Section* 2.

*Remark 1.* The last inequality above is exactly the same as the second inequality in Theorem 2, thus verifying our local stability result of the system.

*Remark 2.* There are two other equilibria for system (3), namely $E_c = (W_{1c}, W_{2c}, W_{3c})$ and $E_{3\infty} = (0, 0, +\infty)$, for which we do not know their analytic properties. Their existence and stability will be discussed further using numerical examples.

## 4. Summary of stability analysis and numerical examples

We will summarize the resulting cases from our stability analysis in the last section. We first note that at $E_\infty$, we have $S_\infty > 0$, and hence, some members of the population remain uninfected throughout the course of the outbreak. On the other hand, at the other equilibria ($E_0$, $E_{23}$, $E_c$, and $E_{3\infty}$), $S_\infty = 0$, and thus, the whole population becomes infected. The distinction between a major outbreak where everyone gets infected and a lesser outbreak where some members remain uninfected is closely related to, but not the same as, the idea of "major outbreak" and "minor outbreak" as discussed in Diekmann and Heesterbeek (2000).

Case 1: $\sigma_2 + \gamma_2 < \min\{\mu, \gamma_3\}$.

Since $0 < \delta < 1$ and $\sigma_2 + \gamma_2 < \gamma_3$, let $C = \frac{\gamma_3(\sigma_2+\gamma_2)}{\alpha\gamma_3+\delta(1-\alpha)(\sigma_2+\gamma_2)} > \sigma_2 + \gamma_2$, we then have the following diagram in Fig. 2:
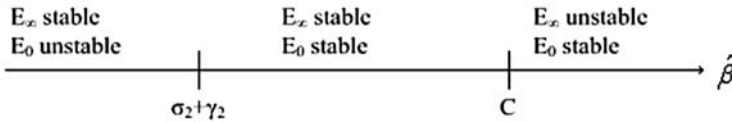


**Fig. 2**   Stability of $E_0$ and $E_\infty$ when $\sigma_2 + \gamma_2 < \mu$ and $\sigma_2 + \gamma_2 < \gamma_3$.

It follows that $\hat{\beta} > C \Longrightarrow \lim_{t\to\infty} S(t) = S_\infty = 0$ and $\hat{\beta} < \sigma_2 + \gamma_2 \Longrightarrow \lim_{t\to\infty} S(t) = S_\infty > 0$. Moreover, when $\sigma_2 + \gamma_2 < \hat{\beta} < C$ we have bistability of the equilibria $E_0$ and $E_\infty$, subsequently, the limiting behavior of the solution trajectories depends on initial populations. We now give some numerical examples in Figs. 3.1–3.3, with parameter values and initial population $X_0 = (S_0, E_0, I_0, A_0, H_0)$ as given in the figures, to illustrate our results. We let the proportion of symptomatic infections $\alpha$ equal to 0.7, to be in line with the proportions of 2/3 in Stilianakis et al. (1998) and of 0.67 in Longini et al. (2004). We also let the reduction of infectivity of asymptomatic infectives $\delta$ equal to 0.5, the same as in Longini et al. (2004). All other parameter values are chosen theoretically. In Fig. 3.1, we have $\sigma_2 + \gamma_2 > \hat{\beta}$ so that the populations approach $E_\infty$; Figs. 3.2(a) and 3.2(b) where $\sigma_2 + \gamma_2 < \hat{\beta} < C$, and we have bistability; and Fig. 3.3 where $\hat{\beta} > C$ and the solutions approaches $E_0$.

Case 2: $\sigma_2 + \gamma_2 > \mu$ and $\sigma_2 + \gamma_2 < \gamma_3$.

If in addition, we let $B = \frac{\alpha\mu(\gamma_3-\mu)+[(\sigma_2+\gamma_2)-\mu](\gamma_3-\alpha\mu)}{\alpha(\gamma_3-\mu)+\delta(1-\alpha)[(\sigma_2+\gamma_2)-\mu]}$. It is easy to verify that in this case, we have $B < C$. We thus obtain the stability relation below in Fig. 4.

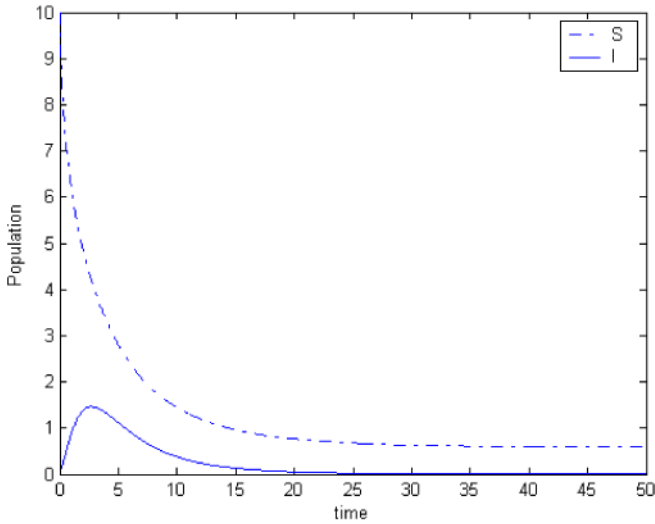**Fig. 3.1** Numerical simulation with $\sigma_2 + \gamma_2 > \hat{\beta}$, the population approaches $E_\infty$ where some members of the population remain uninfected.
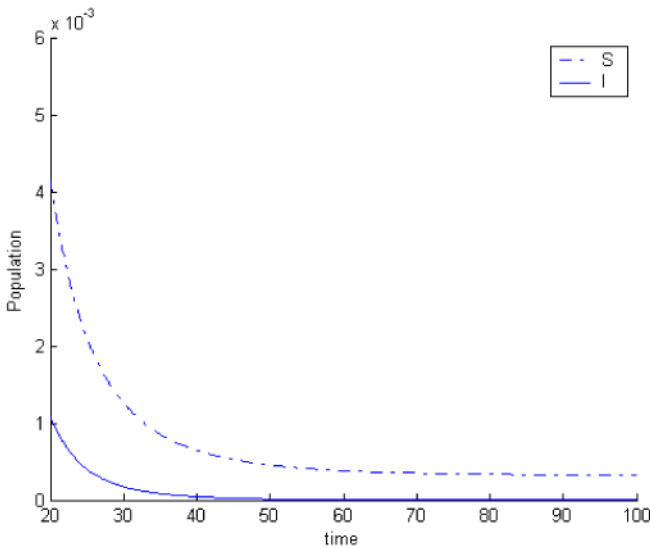


**Fig. 3.2(a)** Numerical simulation with $\sigma_2 + \gamma_2 < \hat{\beta} < C$, the population approaches $E_\infty$.

From Fig. 4, we know that $\hat{\beta} > C \implies \lim_{t\to\infty} S(t) = S_\infty = 0$ and $\hat{\beta} < B \implies \lim_{t\to\infty} S(t) = S_\infty > 0$. But when $B < \hat{\beta} < C$, we have bistable case as in case 1 before.

Case 3: $\sigma_2 + \gamma_2 > \mu$ and $\sigma_2 + \gamma_2 > \gamma_3$. We have two subcases to consider.
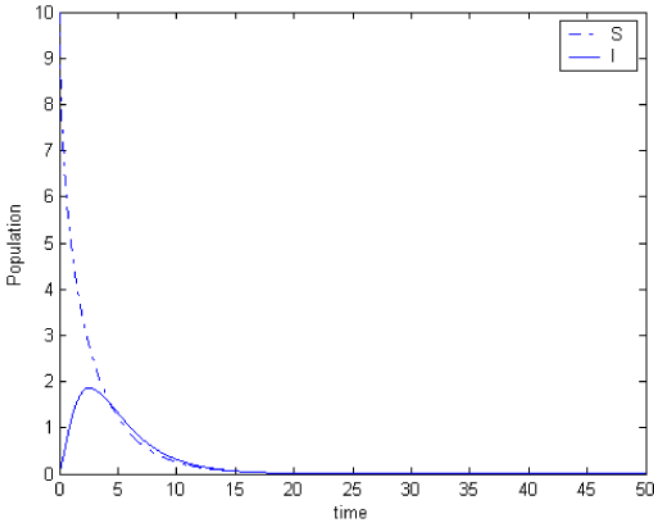
**Fig. 3.2(b)** Numerical simulation with $\sigma_2 + \gamma_2 < \hat{\beta} < C$, the population approaches $E_0$ where the whole population gets infected.
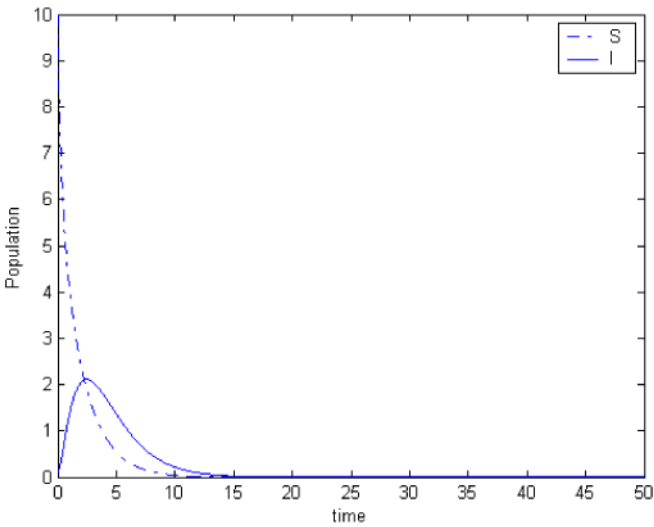


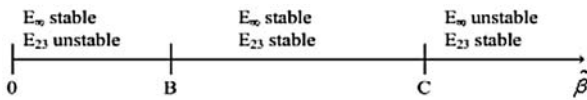**Fig. 3.3** Numerical simulation with $\hat{\beta} > C$, the population approaches $E_0$.



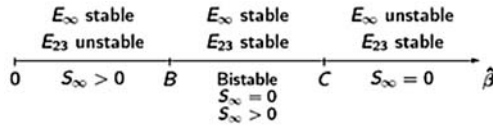**Fig. 4** Stability of $E_{23}$ and $E_\infty$ when $\sigma_2 + \gamma_2 > \mu$ and $\sigma_2 + \gamma_2 < \gamma_3$.

| $E_\infty$ stable | $E_\infty$ stable | $E_\infty$ unstable |
| $E_{23}$ unstable | $E_{23}$ stable | $E_{23}$ stable |

| 0 | $S_\infty > 0$ | B | Bistable $S_\infty = 0$ $S_\infty > 0$ | C | $S_\infty = 0$ | $\hat{\beta}$ |

**Fig. 5.1** Stability of $E_{23}$ and $E_\infty$ when $\sigma_2 + \gamma_2 > \mu$ and $\sigma_2 + \gamma_2 > \gamma_3$ with $\gamma_3 > \mu$ and $\delta(\sigma_2 + \gamma_2) > \gamma_3$.
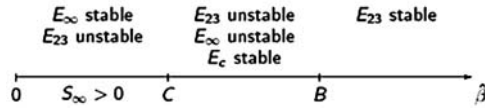
| $E_\infty$ stable | $E_{23}$ unstable | $E_{23}$ stable |
| $E_{23}$ unstable | $E_\infty$ unstable | |
| | $E_c$ stable | |

| 0 | $S_\infty > 0$ | C | | B | | $\hat{\beta}$ |

**Fig. 5.2** Stability of $E_{23}$, $E_c$, and $E_\infty$ when $\sigma_2 + \gamma_2 > \mu$ and $\sigma_2 + \gamma_2 > \gamma_3$ with $\gamma_3 > \mu$ and $\delta(\sigma_2 + \gamma_2) < \gamma_3 < \sigma_2 + \gamma_2$.
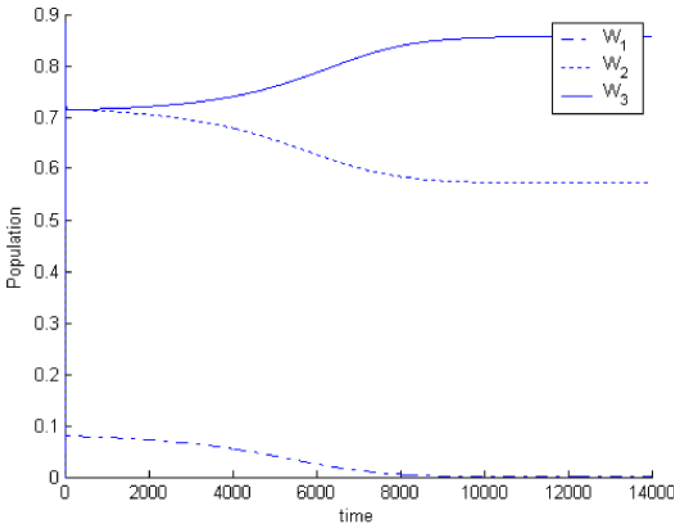


**Fig. 6(a)** Numerical simulation of the populations $W_1$, $W_2$, and $W_3$ when $\gamma_3 > \mu$, $\delta(\sigma_2 + \gamma_2) > \gamma_3$, $\sigma_2 + \gamma_2 > \mu$ and $\sigma_2 + \gamma_2 > \gamma_3$, the population approaches $E_\infty$.

Subcase 1: When $\gamma_3 > \mu$, $E_{23}$ exists. We note that in this case, $B < C \Leftrightarrow \gamma_3 < \sigma_2 + \gamma_2$.
(i) If $\delta(\sigma_2 + \gamma_2) > \gamma_3$ we have Fig. 5.1.
(ii) If $\delta(\sigma_2 + \gamma_2) < \gamma_3 < \sigma_2 + \gamma_2$ we have Fig. 5.2.
The bistable case in (i) is illustrated again with numerical examples in Figs. 6(a)–(b). However, for (ii), we only know that the equilibrium $E_c$ exists and is locally stable when $C < \hat{\beta} < B$, in which case $E_{23}$ and $E_\infty$ are both unstable.

Subcase 2: $\gamma_3 > \mu$, then $E_{23}$ does not exist but there is another equilibrium $E_{3\infty}$, and we have the diagram in Fig. 6 as follows:

Here we simply have $\hat{\beta} > C \Longrightarrow S_\infty = 0$ and $\hat{\beta} < C \Longrightarrow S_\infty > 0$. The existence of $E_{3\infty}$, which again is stable when $\hat{\beta} > C$, will be illustrated numerically in the next case.
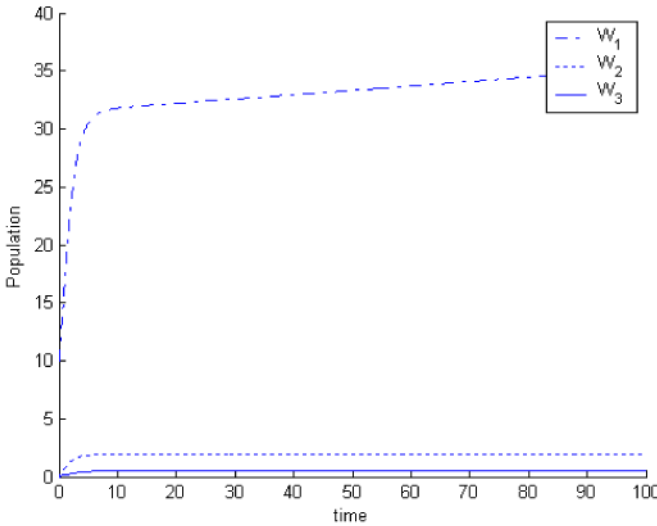
**Fig. 6(b)** Numerical simulation of the populations $W_1$, $W_2$, and $W_3$ when $\gamma_3 > \mu$, $\delta(\sigma_2 + \gamma_2) > \gamma_3$, $\sigma_2 + \gamma_2 > \mu$ and $\sigma_2 + \gamma_2 > \gamma_3$, the population approaches $E_{23}$ where everyone in the population gets infected.
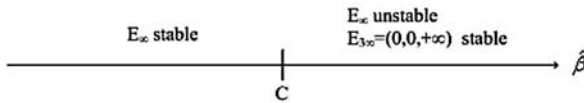


**Fig. 6** Stability of $E_{3\infty}$ and $E_\infty$ when $\sigma_2 + \gamma_2 > \mu$ and $\sigma_2 + \gamma_2 > \gamma_3$ with $\gamma_3 < \mu$.
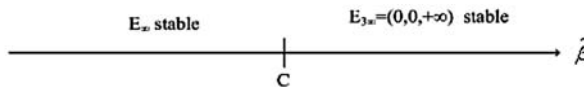


**Fig. 7** Stability of $E_{3\infty}$ and $E_\infty$ when $\sigma_2 + \gamma_2 < \mu$ and $\sigma_2 + \gamma_2 > \gamma_3$.

Case 4: $\sigma_2 + \gamma_2 < \mu$ and $\sigma_2 + \gamma_2 > \gamma_3$.

We have following result in Fig. 7.

It follows simply that $\hat{\beta} > C \Longrightarrow S_\infty = 0$ and $\hat{\beta} < C \Longrightarrow S_\infty > 0$. Due to our limited knowledge regarding the stability properties of this case, we again make use of numerical simulations. Figs. 8.1 and 8.2 illustrate the two possible scenarios, with Fig. 8.3 showing the convergence to $E_{3\infty}$ on $(W_1, W_2, W_3)$-space.

## 5. Discussions

The proposed model is similar to the SARS model without quarantine discussed in Section 3 of Hsu and Hsieh (2006) except for the addition of an asymptomatic infective class.
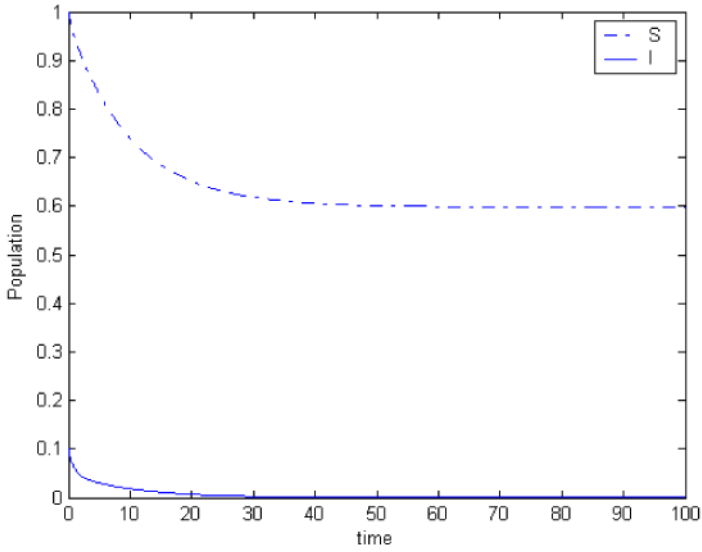
**Fig. 8.1** Numerical simulation with $\sigma_2 + \gamma_2 < \mu$, $\sigma_2 + \gamma_2 > \gamma_3$, and $\hat{\beta} < C$, the population approaches $E_\infty$.
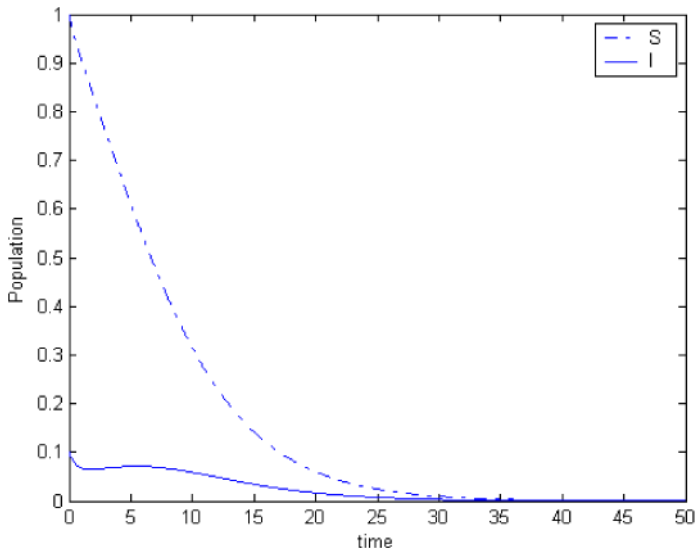


**Fig. 8.2** Numerical simulation with $\sigma_2 + \gamma_2 < \mu$, $\sigma_2 + \gamma_2 > \gamma_3$, and $\hat{\beta} > C$, the population approaches $E_{3\infty}$.

For that SARS model without quarantine, global analysis was carried out to show that if the basic reproduction number $R_0$ is less than 1, the disease-free equilibrium (DFE) is globally asymptotically stable. For this work, we showed that by considering asymp-
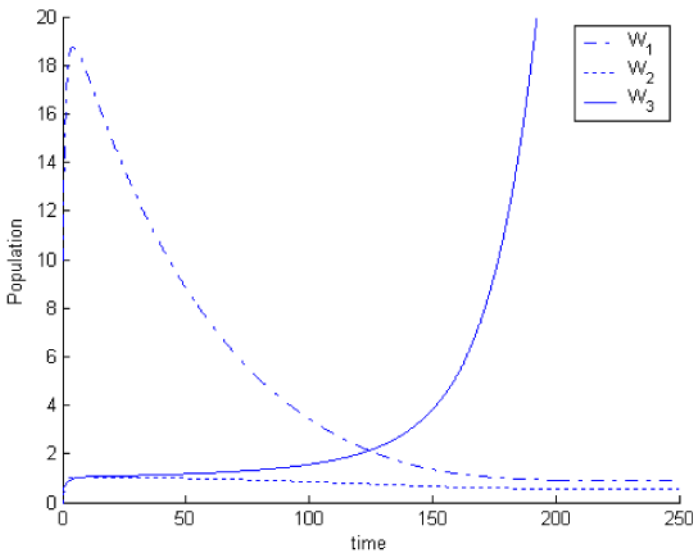
**Fig. 8.3** Numerical simulation with $\sigma_2 + \gamma_2 < \mu$, $\sigma_2 + \gamma_2 > \gamma_3$, and $\hat{\beta} > C$ in $(W_1, W_2, W_3)$-space, as the population approaches $E_{3\infty}$.

tomatic infection by subclinical infected individuals, bistability could occur. That is, even when $R_0$ is less than 1, the steady state where some members of the population remain uninfected, $E_\infty$, is only locally asymptotically stable with a locally stable endemic equilibrium, as illustrated in Figs. 3.2(a)–(b) and 6(a)–(b). Biologically, it demonstrates the possibility that even if the basic reproduction number is lower than 1, the disease could still persist in the community given appropriate parameter values and hypothetical initial population sizes. Moreover, in both cases where bistability occurs, we can conjecture the existence of an interior equilibrium which is a saddle point with a 2-dimensional stable manifold, although we are unable to prove it. Hence, depending on the initial states, control of a disease outbreak with asymptomatic infections may involve more than simply reducing the reproduction number, as was for a SARS model without asymptomatic infection studied in Hsu and Hsieh (2006).

Another way to ascertain the role of asymptomatic infection is to determine how the presence of asymptomatic cases, or a change in the asymptomatic proportion $1 - \alpha$, would impact the outbreak in a way which would cause the whole population being infected when some members would remain uninfected, where there was no asymptomatic infection, or vice versa. To do so, we note that $E_0$ is stable if $\hat{\beta} > \delta_2 + \gamma_2$, $E_{23}$ is stable if $\hat{\beta} > B = g(\alpha)$ and $E_\infty$ is stable if $\hat{\beta} < C = h(\alpha)$. Moreover, $g(\alpha)$ and $h(\alpha)$ satisfy the following: if $0 < \delta < \frac{\gamma_3}{\delta_2 + \gamma_2}$, then $g'(\alpha) < 0$ and $h'(\alpha) < 0$, and if $\delta > \frac{\gamma_3}{\delta_2 + \gamma_2}$, then $g'(\alpha) > 0$, and $h'(\alpha) > 0$. We note that when $\alpha = 1$, $g(1) = h(1) = \sigma_2 + \gamma_2$, and we have the case of no asymptomatic infection; when $\alpha = 0$, $g(0) = h(0) = \gamma_3/\delta$, and we have the extreme case of every infective is asymptomatic with reduced infectivity $\delta$. Moreover, the presence of asymptomatic cases ($1 - \alpha$ differing from 0) represents a decrease in $\alpha$ from 1. Subsequently, for Case 1 in Section 4, we have $h'(\alpha) < 0$, and hence, $\sigma_2 + \gamma_2 = h(1) < C = h(\alpha)$; that is, the stability region of $E_\infty$ becomes larger

due to presence of asymptomatic cases (Fig. 2), and for a given range of values of $\hat{\beta}$ and depending on the initial states, the presence of asymptomatic cases could keep some individuals uninfected when they would have been infected otherwise. For Case 2 in Section 4, we have $g(1) = h(1) = \sigma_2 + \gamma_2 < B = g(\alpha) < C = h(\alpha)$. Clearly, both the bistability region and the stability region of $E_\infty$ becomes larger due to presence of asymptomatic cases, or $\alpha$ decreasing (see Fig. 4). Therefore, the impact of asymptomatic infection could again be beneficial, for a range of values of $\hat{\beta}$. For Case 3, Subcase 1-(i), we have $0 < B = g(\alpha) < C = h(\alpha) < g(1) = h(1) = \sigma_2 + \gamma_2$. In this case, the asymptomatic population has a negative effect on the stability region of $E_\infty$, since we have the condition of $\delta > \gamma_3/(\delta_2 + \gamma_2)$ (see Fig. 5.1). For Case 3, Subcase 1-(ii), $0 < g(1) = h(1) = \sigma_2 + \gamma_2 < C = h(\alpha) < B = g(\alpha)$, and we have the same situation as Case 2 (Fig. 5.2). Case 3, Subcase 2 (Fig. 6) and Case 4 (Fig. 7) are similar to Case 1.

For a biological interpretation of the above conditions, it is interesting to note that $1/C = \alpha/(\sigma_2 + \gamma_2) + \delta(1 - \alpha)/\gamma_3$. Therefore, the condition for positive impact of asymptomatic infections to occur, $\sigma_2 + \gamma_2 < C$, is equivalent to the inequality $c\beta/C = c\beta\alpha/(\sigma_2 + \gamma_2) + c\beta\delta(1 - \alpha)/\gamma_3 < c\beta/(\sigma_2 + \gamma_2)$. The last term of this inequality is the infection rate per infective times the duration in the infective class, which is roughly the average number of infections by an infective, if there is no asymptomatic infection. The term on the left-hand side of the inequality is the average of the number of infections by an infective when there is asymptomatic infections, i.e., the number of infections by an symptomatic infective (I) times the probability that the person is symptomatic plus the number of infections by an asymptomatic infective (A) times the probability that the person is asymptomatic. It is intuitive that if the presence of asymptomatic infectives leads to a reduction in the average number of infections by an infective individual, then it is beneficial. Conversely, similar observation can be made for the case of negative impact, i.e., $C < \sigma_2 + \gamma_2$, where the condition implies that the presence of asymptomatic infectives leads to an increase in the average number of infections by an infective individual, and hence, has a negative effect on the outbreak. The expression for B is, however, more complicated to allow easy interpretation.

For illustration, we present additional numerical examples. In Fig. 9.1, the susceptible population $S(t)$ is given in the case where asymptomatic infection has a positive effect. Here, the susceptible population goes to 0 when $\alpha = 1$ (i.e., no asymptomatic infection) and remains at a high level when $\alpha = 0.3$. Moreover, Fig. 9.2 gives the final susceptible population size $S(\alpha)$ as decreasing function of $\alpha$. This numerical example indicates that, for this set of parameter values, the minimum threshold asymptomatic fraction $(1 - \alpha)$ which would prevent the whole population becoming infected is less than 0.1. The case of negative effect of asymptomatic infection is similarly illustrated in Fig. 10. Here, Fig. 10.2 indicates that for this numerical example, the minimum threshold asymptomatic fraction $(1 - \alpha)$ that would lead to everyone in the population becoming infected is around 0.2.

It is interesting to note that, in our analysis using ratios of $S$, $E$, and $A$ to the symptomatic infective class $I$, there are several equilibria with $S_\infty = 0$ (whole population becoming infected) which could exist in the 3-dimensional $W_1W_2W_3$-space. In the original $(S, E, I, A, H, R)$-system, they represent the same equilibrium $(0, 0, 0, 0, 0, R_\infty)$ (see Theorem 1). Biologically, these distinct equilibria in $W_1W_2W_3$-space signify the different ratio with which the trajectories could approach $(0, 0, 0, 0, 0, R_\infty)$ in $(S, E, I, A, H, R)$-space. For instance, $E_0 = (0, 0, 0)$, which always exists, is the case where $E$ and $A$ approaches 0 faster then $I$. This is made clear by its stability condition, $\sigma_2 + \gamma_2 <$
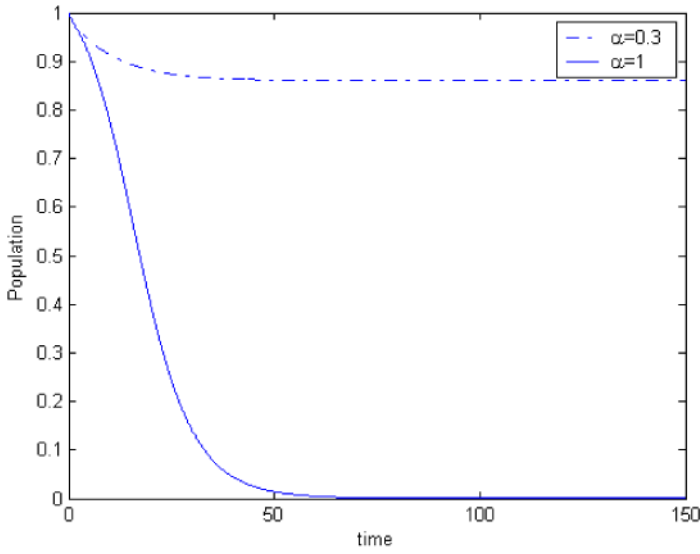
**Fig. 9.1** The susceptible population as function of time, $S(t)$, for the case $\sigma_2 + \gamma_2 = 0.7 < B = 0.9532 < C = 1.2233$.
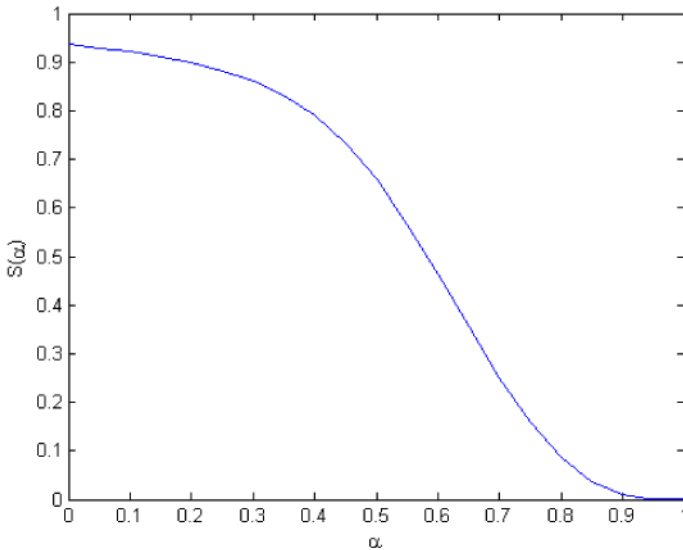


**Fig. 9.2** The final susceptible population size as a function of $\alpha$, $S(\alpha)$, for the case $\sigma_2 + \gamma_2 = 0.7 < B = 0.9532 < C = 1.2233$.

$\min\{\hat{\beta}, \mu, \gamma_3\}$, i.e., $\sigma_2 + \gamma_2$, the removal rate of $I$, must be smaller (slower) than either that of $E(\mu)$ or $A(\gamma_3)$, in addition to being small than $\hat{\beta}$ (see Section 3). The second equilibrium in $W_1 W_2 W_3$-space, $E_{23} = (0, W_2^\star, W_3^\star)$, is the instance where $E$, $A$, and $I$
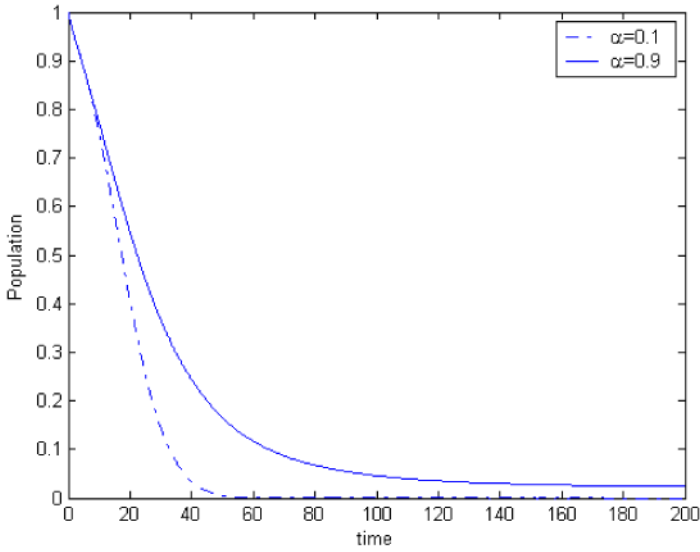
**Fig. 10.1** The susceptible population as function of time, $S(t)$, for $\sigma_2 + \gamma_2 = 0.7 > B = 0.5868 > C = 0.4736$.
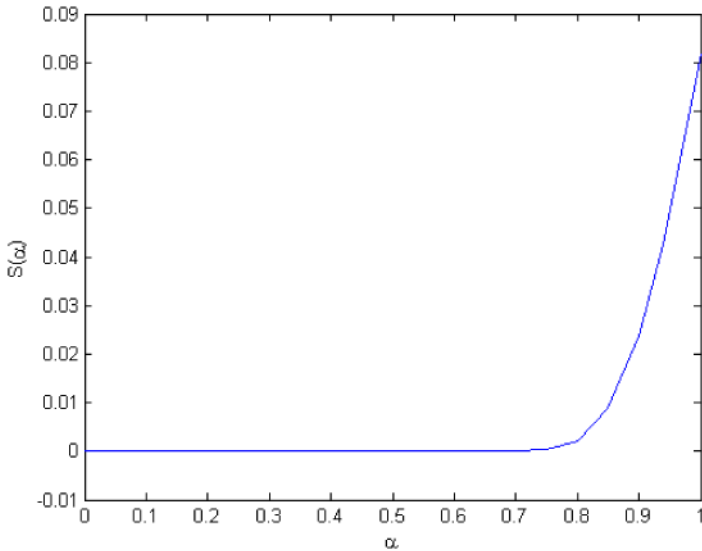


**Fig. 10.2** The final susceptible population size as a function of $\alpha$, $S(\alpha)$, for the case $\sigma_2 + \gamma_2 = 0.7 > B = 0.5868 > C = 0.4736$.

approach 0 at the same rate. Hence, it is intuitively reasonable that its existence and stability is predicated on the removal rate of $E$ being smaller than that of $A$ and $I$, as well

the infection rate $\hat{\beta}$ being sufficiently large, so that the flow into $A$ and $I$ would not end prematurely.

The equilibrium where some individuals remain uninfected, $E_\infty$, always exists and its local stability clearly depends on $R_0$. For the remaining equilibria in $W_1 W_2 W_3$-space, namely $E_c = (W_{1c}, W_{2c}, W_{3c})$ and $E_{3\infty} = (0, 0, +\infty)$, we only have partial results that they exist and is stable only when $E_0$ and $E_{23}$ either do not exist or are unstable.

For $E_c$, the equilibrium where $S$, $E$, $I$, and $A$ approach 0 at the same rate, the conditions are $\delta(\sigma_2 + \gamma_2) < \gamma_3 < (\sigma_2 + \gamma_2)$ and $C < \hat{\beta} < B$. The first condition says the removal of $A$ must be less than that of $I$, but sufficiently greater than the removal of $I$ multiplied by a factor of $\delta < 1$, and greater than that of $E$. The second condition is difficult to decipher, due to the complicated expressions of $B$ and $C$.

$E_{3\infty} = (0, 0, +\infty)$ denotes the situation where $S$ and $E$ approach 0 faster than $I$, which in turn goes to 0 faster than $A$. Here, the conditions $\gamma_3 < \sigma_2 + \gamma_2 < \mu$ and $C < \hat{\beta}$ seem to indicate that the removal of $A$ must be sufficiently small compared to that of $E$ and $I$ with a sufficiently large infection rate for the asymptomatic infectives to become asymptotically the largest and last group to go to 0. We note that in the SARS model with quarantine by Hsu and Hsieh (2006), similar scenarios of multiple endemic equilibria in ratios also occurred.

The theoretical parameter to measure public response to outbreak severity (a) occurs only in the denominator of $\hat{\beta} = c\beta/(1 + aR_\infty)$, but not anywhere else in the expressions for $B_1$, $B_2$, $B$, and $C$. Since $\hat{\beta}$ is the *adjusted* infection rate due to public response as quantified by $a$. We can, therefore, conclude that public response only serves to lower the magnitude of infections, as roughly measured by $\hat{\beta}$, but does not affect the basic dynamics of the system, as opposed to quarantine which could bring about bistability, as demonstrated in Hsu and Hsieh (2006).

As mentioned earlier, we purposely did not consider intervention measures such as quarantine, border control, vaccine, prophylaxis treatment, etc., which have been considered in many recent studies. Another direction for further exposition is adding spatial spread, perhaps in a multipatch framework (Hsieh et al., 2007). Clearly, adding those factors would make the analysis decidedly more challenging, but is a worthwhile topic for future studies. Another open problem for future work is to explore whether the role of asymptomatic infection also depends on the standard incidence term we have used in this work, which can be accomplished perhaps by using a more general expression for disease incidence (e.g., Hsieh et al., 2007).

As a final note, the aim of using limiting system (2) is to conduct qualitative analysis of the original system (1). Comparing the behavior of the solutions of systems (1) and (2), we know that when $S_\infty = 0$, the behavior of the solutions for the two systems are exactly the same. On the other hand, when $S_\infty > 0$, they are different but positive for both systems, albeit with different values. It is reasonable since the final size of the solution $S(t)$ depends only on the initial population $S_0$, $I_0$ and $A_0$. However, we note that, in all numerical examples given, system (1) is used for the simulations, and hence, all numerical results, including the minimum threshold asymptomatic fractions $(1 - \alpha)$ obtained from Figs. 9.2 and 10.2, are that of the original system (1).

## Acknowledgement

## Appendix

*Proof of Theorem 2*: We have

$$W_1' = -\hat{\beta} W_1 \frac{1 + \delta W_3}{1 + W_1 + W_2 + W_3} - W_1[\alpha\mu W_2 - (\sigma_2 + \gamma_2)].$$

Hence $\alpha\mu W_2 - (\sigma_2 + \gamma_2)$, i.e., $W_2 < (\sigma_2 + \gamma_2)/\alpha\mu$. Moreover,

$$W_2' = 0 \Leftrightarrow (1 + \delta W_3) \frac{\hat{\beta} W_1}{1 + W_1 + W_2 + W_3} = W_2[\mu + \alpha\mu W_2 - (\sigma_2 + \gamma_2)].$$

Note that $\frac{\hat{\beta} W_1}{1 + W_1 + W_2 + W_3} \to \hat{\beta}$ as $W_1 \to \infty$.

Hence $\hat{\beta}(1 + \delta W_3) = W_2[\mu - (\sigma_2 + \gamma_2) + \alpha\mu W_2]$.

Consider $W_3 = f_1(W_2) = \{\frac{1}{\hat{\beta}}[W_2(\mu - (\sigma_2 + \gamma_2) + \alpha\mu W_2] - 1\}/\delta$. We have the following two subcases in Fig. A.1:
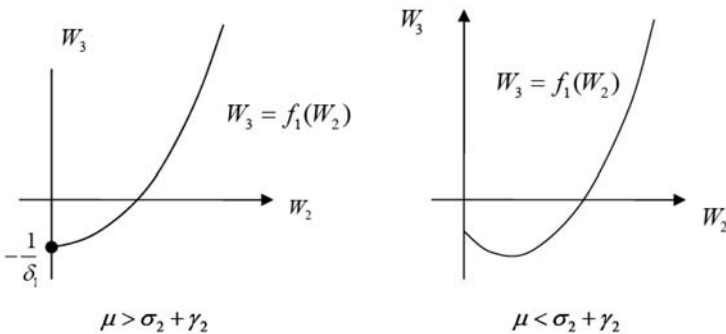


**Fig. A.1** Diagrams of $W_3 = f_1(W_2)$ for $\sigma_2 + \gamma_2 < \mu$ and $\sigma_2 + \gamma_2 > \mu$.

Furthermore, $W_3' = 0 \Leftrightarrow (1 - \alpha)\mu W_2 = [\gamma_3 - (\sigma_2 + \gamma_2) + \alpha\mu W_2]W_3$.

Let $W_3 = f_2(W_2) = \frac{(1-\alpha)\mu W_2}{\alpha\mu W_2 + [\gamma_3 - (\sigma_2 + \gamma_2)]}$ and considering whether $\sigma_2 + \gamma_2 < \gamma_3$, we again have two subcases in Fig. A.2.
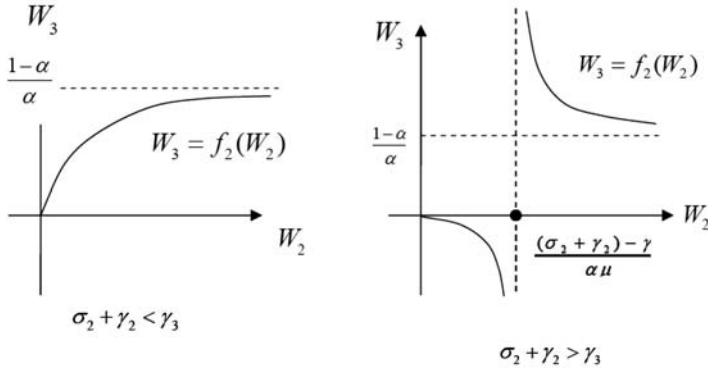
**Fig. A.2** Diagrams of $W_3 = f_2(W_2)$ for $\sigma_2 + \gamma_2 < \gamma_3$ and $\sigma_2 + \gamma_2 > \gamma_3$.

Hence, by considering the two conditions in Figs. A.1 and A.2 together, we have following four subcases in Fig. A.3.

Subsequently, we have

$$W_2 < \frac{\sigma_2 + \gamma_2}{\alpha\mu} \Leftrightarrow f_1\left(\frac{\sigma_2 + \gamma_2}{\alpha\mu}\right) > f_2\left(\frac{\sigma_2 + \gamma_2}{\alpha\mu}\right)$$

$$\Leftrightarrow \frac{1}{\delta}\left[\frac{\sigma_2 + \gamma_2}{\hat{\beta}\mu} - 1\right] > \frac{(1-\alpha)(\sigma_2 + \gamma_2)}{\alpha\gamma_3}$$

$$\Leftrightarrow \frac{\sigma_2 + \gamma_2}{\hat{\beta}\mu} - 1 > \frac{\delta(1-\alpha)(\sigma_2 + \gamma_2)}{\alpha\gamma_3}.$$

Or equivalently,

$$\frac{\sigma_2 + \gamma_2}{\alpha}\left[\frac{1}{\hat{\beta}}\frac{(1-\alpha)\delta}{\gamma_3}\right] > 1$$

$$\Leftrightarrow \hat{\beta} > \frac{1}{(\frac{\delta(1-\alpha)}{\gamma_3}) + (\frac{\alpha}{\sigma_2+\gamma_2})} = \frac{\gamma_3(\sigma_2 + \gamma_2)}{\delta(1-\alpha)(\sigma_2 + \gamma_2) + \alpha\gamma_3}$$

$$\Leftrightarrow E_\infty \text{ is stable.}$$

*Proof of Theorem 3*: The variational matrix of $\hat{E}_0$ is

$$M(\hat{E}_0) = \begin{bmatrix} -\sigma_2 + \gamma_2 & \alpha\mu & 0 \\ \hat{\beta} & -\mu & \hat{\beta}\delta \\ 0 & (1-\alpha)\mu & -\gamma_3 \end{bmatrix}.$$

The characteristic polynomial of $M(\hat{E}_0)$ is

$$\lambda^3 + \lambda^2\big[(\sigma_2 + \gamma_2) + (\mu + \gamma_3)\big]$$

$$+ \lambda\big[(\sigma_2 + \gamma_2)(\mu + \gamma_3) + \gamma_3\mu - \alpha\mu\hat{\beta} - \hat{\beta}\delta(1-\alpha)\mu\big]$$

$$+ \gamma_3\mu(\sigma_2 + \gamma_2) - \alpha\mu\hat{\beta}\gamma_3 - \hat{\beta}\delta(1-\alpha)\mu(\sigma_2 + \gamma_2) = 0.$$
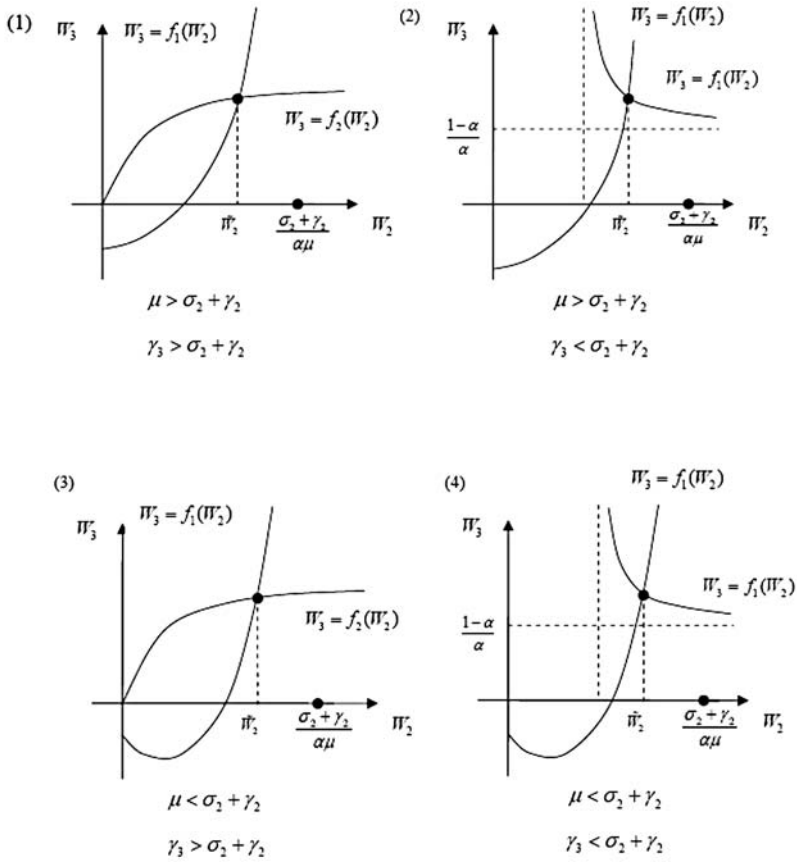
Fig. A.3 Diagrams of $W_3 = f_1(W_2)$ and $W_3 = f_2(W_2)$ by combining the two conditions in Figs. 2 and 3.

$\hat{E}_0 = (0, 0, 0)$ is stable if, by Routh–Hurwicz criterion,

$$(\sigma_2 + \gamma_2)(\mu + \gamma_3) + \gamma_3\mu - \alpha\mu\hat{\beta} - \hat{\beta}\delta(1 - \alpha)\mu > 0,$$
$$\gamma_3\mu(\sigma_2 + \gamma_2) - \hat{\beta}\big[\alpha\mu\gamma_3 - \delta(1 - \alpha)\mu(\sigma_2 + \gamma_2)\big] = 0,$$

and

$$(\sigma_2 + \gamma_2)(\mu + \gamma_3)\big[(\sigma_2 + \gamma_2)(\mu + \gamma_3) + \gamma_3\mu - \hat{\beta}\alpha\mu + \delta(1 - \alpha)\mu\big]$$
$$> \gamma_3\mu(\sigma_2 + \gamma_2) - \hat{\beta}\big[\alpha\mu\gamma_3 + \delta(1 - \alpha)\mu(\sigma_2 + \gamma_2)\big],$$

which together is equivalent to

$$B_1 = \frac{(\sigma_2 + \gamma_2)(\mu + \gamma_3) + \gamma_3\mu}{\alpha\mu + \delta(1 - \alpha)\mu} > \hat{\beta}, \tag{A.1}$$

$$B_2 = \frac{(\sigma_2 + \gamma_2)\gamma_3\mu}{\alpha\mu\gamma_3 - \delta(1-\alpha)\mu(\sigma_2 + \gamma_2)} > \hat{\beta}, \tag{A.2}$$

and

$$(\sigma_2 + \gamma_2)(\mu + \gamma_3)\big[(\sigma_2 + \gamma_2)(\mu + \gamma_3) + \gamma_3\mu\big] - \gamma_3\mu(\sigma_2 + \gamma_2)$$
$$> -\hat{\beta}\big\{\big[\alpha\mu + \delta(1-\alpha)\mu\big](\sigma_2 + \gamma_2)(\mu + \gamma_3)$$
$$- \big[\alpha\mu\gamma_3 + \delta(1-\alpha)\mu(\sigma_2 + \gamma_2)\big]\big\}. \tag{A.3}$$

Note that the last inequality is also equivalent to

$$B_3 = \frac{(\sigma_2 + \gamma_2)(\mu + \gamma_3)[(\sigma_2 + \gamma_2) + (\mu + \gamma_3)] + \gamma_3\mu(\mu + \gamma_3)}{\alpha\mu(\sigma_2 + \gamma_2 + \mu) + \delta(1-\alpha)\mu(\mu + \gamma_3)} > \hat{\beta}. \tag{A.4}$$

It is easy to check that $B_1 > B_2$ and $B_3 > B_2$, it then follows

$$\hat{E}_0 = (0, 0, 0) \text{ is locally stable}$$
$$\Leftrightarrow \hat{\beta} < B_2$$
$$\Leftrightarrow R_0 < 1$$
$$\Leftrightarrow \hat{\beta} < \frac{\gamma_3(\sigma_2 + \gamma_2)}{\alpha\gamma_3 + \delta(1-\alpha)(\sigma_2 + \gamma_2)}.$$

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