

DETERMINISTIC MODEL FOR THE ROLE OF ANTIVIRALS IN CONTROLLING THE SPREAD OF THE H1N1 INFLUENZA PANDEMIC

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ABSTRACT. A deterministic model is designed and used to theoretically assess the impact of antiviral drugs in controlling the spread of the 2009 swine influenza pandemic. In particular, the model considers the administration of the antivirals both as a preventive as well as a therapeutic agent. Rigorous analysis of the model reveals that its disease-free equilibrium is globally-asymptotically stable under certain conditions involving having the associated reproduction number less than unity. Furthermore, the model has a unique endemic equilibrium if the reproduction threshold exceeds unity. The model provides a reasonable fit to the observed H1N1 pandemic data for the Canadian province of Manitoba. Numerical simulations of the model suggest that the singular use of antivirals as preventive agents only makes a limited population-level impact in reducing the burden of the disease in the population (except if the effectiveness level of this “prevention-only” strategy is high). On the other hand, the combined use of the antivirals (both as preventive and therapeutic agents) resulted in a dramatic reduction in disease burden. Based on the parameter values used in these simulations, even a moderately-effective combined treatment-prevention antiviral strategy will be sufficient to eliminate the H1N1 pandemic from the province.

1. INTRODUCTION

Since its emergence in the Spring of 2009, the H1N1 Influenza A pandemic (also known as the Swine Influenza) continues to pose significant challenges to public health around the world [11, 15, 17, 41, 42, 43]. For instance, the H1N1 pandemic has accounted for 33,494 cases [31] (8,669 hospitalized cases including 1,472 admitted to ICU) and 429 deaths in Canada (over 16,000 people have died globally [45]). The H1N1 pandemic is believed to have resulted from a genetic reassortment involving swine influenza virus lineages [30]. Several chronic conditions and behavioral and other factors have been associated with increased risk of disease severity among H1N1-infected individuals. Infants and pregnant women (especially in the third trimester) are at increased risk of hospitalization and intensive care unit (ICU) admission [10, 23, 37, 44]. Furthermore, some studies have shown that people with pre-existing chronic conditions (such as asthma and other chronic lung diseases,

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chronic kidney and heart diseases, obesity and conditions associated with immune suppression) are prone to increased risk of death and ICU admission [25, 38]. In the Canadian province of Manitoba, Aborigines and people residing in remote and isolated communities are at increased risk of severe illness due to the pandemic H1N1 infection [40].

Like in the case of seasonal flu, the H1N1 pandemic is believed to be spreading mainly through coughs and sneezes of people who are infected with the pandemic and touching of contaminated objects. H1N1 infection has been reported to cause a wide range of flu-like symptoms, including fever, cough, sore throat, body aches, headache, chills and fatigue. Additionally, many have reported nausea, vomiting and/or diarrhea [9]. The second wave of H1N1 started around early October 2009 in Canada [7] and data [27] suggests that it has diminished by the end of January 2010 (after peaking in November 2009).

The pandemic H1N1 is being controlled using various measures including social exclusion (e.g., closure of schools, banning large public gatherings, etc.), mass vaccination (the limited supply of the H1N1 vaccine, in the early stage of the second wave, has forced its prioritization to high-risk groups, such as children under the age of six, pregnant women, people with weakened immune systems, etc.) and the use of antiviral drugs (notably, *oseltamivir* (Tamiflu) and *zanamivir* (Relenza)). It should be mentioned that a rare occurrence of antiviral resistance (specifically to the use of Tamiflu) has been reported [8].

Some mathematical modeling studies have been carried out, aimed at gaining insight into the transmission dynamics and control of the H1N1 pandemic (see, for instance, [3, 18, 30, 1, 4, 12, 22, 32]). In particular, Sharomi *et al.* [32] presented a model for the spread of H1N1 that incorporates an imperfect vaccine and antiviral drugs administered to infected individuals with disease symptoms (the model in [32] stratifies the infected population in terms of their risk of developing severe illness). The purpose of the current study is to complement the aforementioned studies by designing a new model for assessing the impact of singular use of the antiviral drugs, administered as a preventive agents only (i.e., given to susceptible individuals) or, as a therapeutic agent (i.e., given to individuals with symptoms of the pandemic H1N1 infection in the early stage of illness), in curtailing or mitigating the burden of the H1N1 pandemic in a population. An additional special feature of the model to be designed is that it stratifies the susceptible population according to risk of infection. The model is used to theoretically compare the potential impact of the targeted administration of the available antivirals (as a preventive agent alone, or their combined use as both preventive and therapeutic agent combined) in combatting the spread of the H1N1 pandemic in the Canadian province of Manitoba.

The paper is organized as follows. The model is formulated in Section 2 and rigorously analysed in Section 3. Numerical simulations are reported in Section 4.

2. MODEL FORMULATION

The total human population at time t , denoted by $N(t)$, is sub-divided into ten mutually-exclusive sub-populations of low-risk susceptible individuals ($S_L(t)$), high-risk susceptible individuals ($S_H(t)$), susceptible individuals who were given antiviral drugs ($P(t)$), latent individuals ($L(t)$), infectious individuals who show no

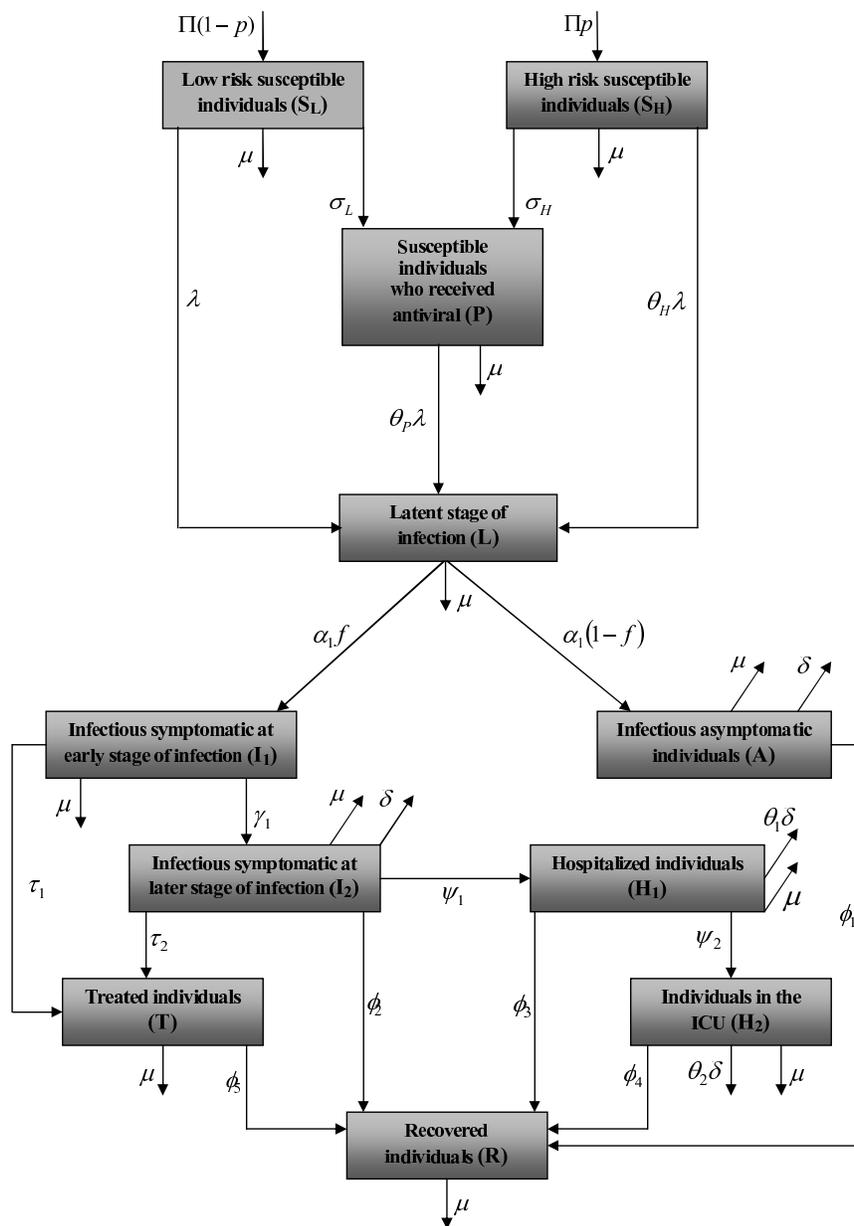


FIGURE 1. Schematic diagram of the model (2.1)

disease symptoms ($A(t)$), symptomatic individuals at early stage ($I_1(t)$), symptomatic individuals at later stage ($I_2(t)$), hospitalized individuals ($H_1(t)$), hospitalized individuals at ICU ($H_2(t)$), treated individuals ($T(t)$) and recovered individuals ($R(t)$), so that

$$N(t) = S_L(t) + S_H(t) + P(t) + L(t) + A(t) + I_1(t) + I_2(t) + H_1(t) + H_2(t) + T(t) + R(t).$$

The high-risk susceptible population includes pregnant women, children, health-care workers and providers (including all front-line workers), the elderly and other immuno-compromised individuals. The rest of the susceptible population is considered to be of low-risk of acquiring H1N1 infection. The model to be considered in this study is given by the following deterministic system of non-linear differential equations (a schematic diagram of the model is given in Figure 1, and the associated variables and parameters are described in Table 1):

$$\begin{aligned}
\frac{dS_L}{dt} &= \Pi(1-p) - \lambda S_L - \sigma_L S_L - \mu S_L, \\
\frac{dS_H}{dt} &= \Pi p - \theta_H \lambda S_H - \sigma_H S_H - \mu S_H, \\
\frac{dP}{dt} &= \sigma_L S_L + \sigma_H S_H - \theta_P \lambda P - \mu P, \\
\frac{dL}{dt} &= \lambda(S_L + \theta_H S_H + \theta_P P) - (\alpha_1 + \mu)L, \\
\frac{dA}{dt} &= \alpha_1(1-f)L - (\phi_1 + \mu - \delta)A, \\
\frac{dI_1}{dt} &= \alpha_1 f L - (\tau_1 + \gamma_1 + \mu)I_1, \\
\frac{dI_2}{dt} &= \gamma_1 I_1 - (\tau_2 + \psi_1 + \phi_2 + \mu + \delta)I_2, \\
\frac{dH_1}{dt} &= \psi_1 I_2 - (\psi_2 + \phi_3 + \mu + \theta_1 \delta)H_1, \\
\frac{dH_2}{dt} &= \psi_2 H_1 - (\phi_4 + \mu + \theta_2 \delta)H_2, \\
\frac{dT}{dt} &= \tau_1 I_1 + \tau_2 I_2 - (\phi_5 + \mu)T, \\
\frac{dR}{dt} &= \phi_1 A + \phi_2 I_2 + \phi_3 H_1 + \phi_4 H_2 + \phi_5 T - \mu R.
\end{aligned} \tag{2.1}$$

Here, the parameter Π represents the recruitment rate into the population (all recruited individuals are assumed to be susceptible) and p is the fraction of recruited individuals who are at high-risk of acquiring infection. low-risk susceptible individuals acquire infection at a rate λ , given by

$$\lambda = \frac{\beta(\eta_1 L + \eta_2 A + I_1 + \eta_3 I_2 + \eta_4 H_1 + \eta_5 H_2 + \eta_6 T)}{N},$$

where β is the effective contact rate, η_i ($i = 1, \dots, 6$) are the modification parameters accounting for relative infectiousness of individuals in the L, A, I_2, H_1, H_2 and T classes in comparison with those in the I_1 class. high-risk susceptible individuals acquire infection at a rate $\theta_H \lambda$, where $\theta_H > 1$ accounts for the assumption that high-risk susceptible individuals are more likely to get infected in comparison to low-risk susceptible individuals. Low (high) risk susceptible individuals receive antivirals at a rate σ_L (σ_H), and individuals in all epidemiological classes suffer natural death at a rate μ (it is assumed, in this study, that individuals in the latent class can transit infection).

Susceptible individuals who received prophylaxis (P) can become infected at a reduced rate $\theta_P \lambda$, where $1 - \theta_P$ (with $0 < \theta_P < 1$) is the efficacy of the antiviral drugs in preventing infection. Individuals in the latent class become infectious at a

TABLE 1. Description and nominal values of the model parameters

	Description	Value	Ref
Π	birth rate	1119583/80*365	
$1/\mu$	average human lifespan	80*365	
β	probability for transmitting swine flu	0.9	assumed
σ_L	antiviral coverage rate for low-risk susceptible individuals	1/25	assumed
σ_H	antiviral coverage rate for high-risk susceptible individuals	1/25	assumed
α_1	rate at which latent individuals become infectious	0.35	assumed
f	fraction of latent individuals that progress to the symptomatic class	0.2	[28]
τ_1	treatment rate for individuals in the early stage of infection	0.5	assumed
τ_2	treatment rate for individuals in the later stage of infection	0.5	assumed
ϕ_1	recovery rate for asymptomatic infectious individuals	1/5	[28]
ϕ_2	recovery rate for symptomatic infectious individuals in the later stage	1/5	[28]
ϕ_3	recovery rate for hospitalized individuals	1/5	[28]
ϕ_4	recovery rate for individuals in ICU	1/7	assumed
ϕ_5	recovery rate treated individuals	1/7	assumed
η_1	modification parameter (see text)	0.1	[28]
η_2	modification parameter (see text)	1/2	[28]
η_3	modification parameter (see text)	1.2	[28]
η_4	modification parameter (see text)	1	[28]
η_5	modification parameter (see text)	0.01	[28]
η_6	modification parameter (see text)	0.2	[28]
θ_H	modification parameter for infection rate of high-risk susceptible individuals	≥ 1	assumed
$1 - \theta_P$	drug efficacy in preventing infection	[0,1]	assumed
ψ_1	hospitalization rate of individuals in I_2 class	0.5	[28]
ψ_2	rate of ICU admission of hospitalized individuals	0.8	[28]
γ_1	progression rate from I_1 to I_2 classes	0.06	[28]
δ	disease-induced death rate of individuals in I_2 class	1/100	[28]
$\theta_1 \delta$	disease-induced death rate for hospitalized individuals	1/100	[28]
$\theta_2 \delta$	disease-induced death rate for individuals in ICU	1/100	[28]

rate α_1 . A fraction, f , of these individuals display clinical symptoms of the disease and the remaining fraction, $1 - f$, does not show disease symptoms (and are moved to the class A). Infectious individuals that show no disease symptoms recover at a rate ϕ_1 and die due to the disease at a rate δ . Individuals in the I_1 class receive antiviral treatment at a rate τ_1 . These individuals progress to the later infectious class (I_2) at a rate γ_1 . Similarly, individuals in the I_2 class are treated (at a rate τ_2), hospitalized (at a rate ψ_1), recover (at a rate ϕ_2) and suffer disease induced death (at a rate δ). Hospitalized individuals (not currently in ICU) are admitted into ICU (at a rate ψ_2). Hospitalized individuals recover (at a rate ϕ_3) and suffer disease-induced death (at a reduced rate $\theta_1 \delta$, where $0 < \theta_1 < 1$ accounts for the assumption that hospitalized individuals, in the H_1 class, are less likely to die than unhospitalized infectious individuals in the I_2 class).

Individuals in ICU recover (at a rate ϕ_4) and die due to the H1N1 pandemic (at an increased rate $\theta_2 \delta$, where $\theta_2 > 1$ accounts for the assumption that those in ICU are more likely to die than those in the I_2 class). Finally, treated individuals recover (at a rate ϕ_5). It is assumed that recovery confers permanent immunity against re-infection with H1N1.

The model (2.1) is an extension of the model presented by Sharomi *et al.* [32] by:

- (i) administering antivirals to susceptible individuals (only individuals with clinical symptoms of the disease are given antivirals in [32]);
- (ii) stratifying the susceptible population based on their risk of acquiring infection.

The basic qualitative properties of the model (2.1) will now be analyzed.

2.1. Basic properties of the model.

Theorem 2.1. *The variables of the model (2.1) are non-negative for all time $t > 0$. In other words, the solutions of the model (2.1) with positive initial data will remain positive for all $t > 0$.*

Proof. Let,

$$t_1 = \sup \left\{ t > 0 : S_L > 0, S_H > 0, P > 0, L > 0, A > 0, \right. \\ \left. I_1 > 0, I_2 > 0, H_1 > 0, H_2 > 0, T > 0, R > 0 \right\}.$$

Thus, $t_1 > 0$. The first equation of the model (2.1) can be rewritten as

$$\frac{d}{dt} \left\{ S_L(t) \exp \left[(\sigma + \mu)t + \int_0^t \lambda(\psi) d\psi \right] \right\} = \Pi(1-p) \exp \left[(\sigma + \mu)t + \int_0^t \lambda(\psi) d\psi \right],$$

so that

$$S_L(t_1) \exp \left[(\sigma + \mu)t_1 + \int_0^{t_1} \lambda(\psi) d\psi \right] - S_L(0) \\ = \int_0^{t_1} \left[\Pi(1-p) \exp \left((\sigma + \mu)y + \int_0^y \lambda d\psi \right) \right] dy.$$

Therefore,

$$S_L(t_1) \geq S_L(0) \exp \left[-(\sigma + \mu)t_1 - \int_0^{t_1} \lambda d\psi \right] + \exp \left[-(\sigma + \mu)t_1 - \int_0^{t_1} \lambda d\psi \right] \\ \times \int_0^{t_1} \left\{ \Pi(1-p) \exp \left[(\sigma + \mu)y + \int_0^y \lambda d\psi \right] \right\} dy > 0.$$

Similarly, it can be shown that $S_H(t) > 0$, $P(t) > 0$, $L(t) > 0$, $A(t) > 0$, $I_1(t) > 0$, $I_2(t) > 0$, $H_1(t) > 0$, $H_2(t) > 0$, $T(t) > 0$, $R(t) > 0$ for all $t > 0$. \square

Theorem 2.1 can also be proven by applying a result from Appendix A of [36]. Adding all the equations in the system (2.1) gives

$$\frac{dN}{dt} = \Pi - \mu N - \delta(I_2 + \theta_1 H_1 + \theta_2 H_2), \quad (2.2)$$

so that,

$$\frac{dN}{dt} \leq \Pi - \mu N. \quad (2.3)$$

Since $N(t) \geq 0$, it follows, using Gronwall inequality, that

$$N(t) \leq N(0)e^{-\mu t} + \frac{\Pi}{\mu}(1 - e^{-\mu t}).$$

Hence,

$$N(t) \leq \Pi/\mu \quad \text{if } N(0) \leq \Pi/\mu. \quad (2.4)$$

This result is summarized below.

Lemma 2.2. *The following biologically-feasible region of model (2.1) is positively-invariant:*

$$\mathcal{D} = \left\{ (S_L, S_H, P, L, A, I_1, I_2, H_1, H_2, T, R) \in \mathbb{R}_+^{11} : \right. \\ \left. S_L + S_H + P + L + A + I_1 + I_2 + H_1 + H_2 + T + R \leq \frac{\Pi}{\mu} \right\}.$$

Thus, in the region \mathcal{D} , the model is well-posed epidemiologically and mathematically [21]. Hence, it is sufficient to study the qualitative dynamics of the model (2.1) in \mathcal{D} .

3. EXISTENCE AND STABILITY OF EQUILIBRIA

3.1. **Local stability of disease-free equilibrium (DFE).** The model (2.1) has a DFE, given by

$$\begin{aligned} \mathcal{E}_0 &= (S_L^*, S_H^*, P^*, L^*, A^*, I_1^*, I_2^*, H_1^*, H_2^*, T^*, R^*) \\ &= \left(S_L^*, S_H^*, \frac{\sigma_L S_L^* + \sigma_H S_H^*}{\mu}, 0, 0, 0, 0, 0, 0, 0, 0 \right), \end{aligned}$$

with

$$S_L^* = \frac{\Pi(1-p)}{\sigma_L + \mu}, \quad S_H^* = \frac{\Pi p}{\sigma_H + \mu}.$$

Following [13], the linear stability of \mathcal{E}_0 can be established using the next generation operator method on system (2.1). The matrices F (for the new infection terms) and V (of the transition terms) are given, respectively, by

$$F = \begin{bmatrix} \beta\eta_1\Omega & \beta\eta_2\Omega & \beta\Omega & \beta\eta_3\Omega & \beta\eta_4\Omega & \beta\eta_5\Omega & \beta\eta_6\Omega \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix},$$

$$V = \begin{bmatrix} K_1 & 0 & 0 & 0 & 0 & 0 & 0 \\ -\alpha_1(1-f) & K_2 & 0 & 0 & 0 & 0 & 0 \\ -\alpha_1 f & 0 & K_3 & 0 & 0 & 0 & 0 \\ 0 & 0 & -\gamma_1 & K_4 & 0 & 0 & 0 \\ 0 & 0 & 0 & -\psi_1 & K_5 & 0 & 0 \\ 0 & 0 & 0 & 0 & -\psi_2 & K_6 & 0 \\ 0 & 0 & -\tau_1 & -\tau_2 & 0 & 0 & K_7 \end{bmatrix},$$

where, $\Omega = (S_L^* + \theta_H S_H^* + \theta_P P^*)/N^*$, $K_1 = \alpha_1 + \mu$, $K_2 = \phi_1 + \mu + \delta$, $K_3 = \tau_1 + \gamma_1 + \mu$, $K_4 = \tau_2 + \psi_1 + \phi_2 + \mu + \delta$, $K_5 = \psi_2 + \phi_3 + \mu + \theta_1 \delta$, $K_6 = \phi_4 + \mu + \theta_2 \delta$, $K_7 = \phi_5 + \mu$ and $N^* = \frac{\Pi}{\mu}$.

It follows then that the *control reproduction number*, denoted by \mathcal{R}_c , is given by

$$\begin{aligned} \mathcal{R}_c &= \rho(FV^{-1}) \\ &= \frac{\beta\Omega}{K_1} \left\{ \eta_1 + \left\{ \frac{\alpha_1 \eta_2 (1-f)}{K_2} + \frac{\alpha_1 f}{K_3 K_4} [K_4 + \eta_3 \gamma_1 + \frac{\eta_6}{K_7} (\tau_1 K_4 + \tau_2 \gamma_1) + Q] \right\} \right\}, \end{aligned} \tag{3.1}$$

where, $Q = (\psi_1 \gamma_1 (K_6 \eta_4 + \psi_2 \eta_5)) / (K_5 K_6)$ and ρ is the spectral radius (dominant eigenvalue in magnitude) of the next generation matrix FV^{-1} . Hence, using [13, Theorem 2], the following result is established.

Lemma 3.1. *The DFE, \mathcal{E}_0 , of the model (2.1), is locally asymptotically stable (LAS) if $\mathcal{R}_c < 1$, and unstable if $\mathcal{R}_c > 1$.*

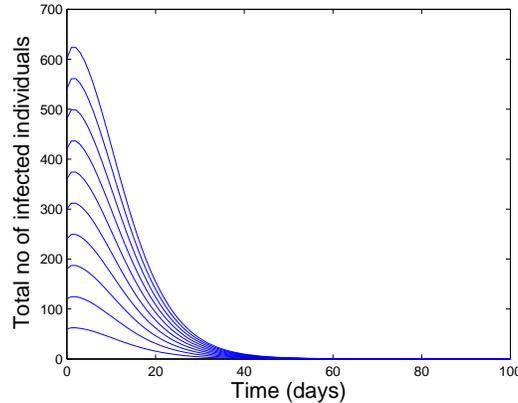


FIGURE 2. Simulations of the model (2.1) showing the total number of infected individuals as a function of time, using various initial conditions. Parameter values used are as in Table 1 with $p = 0.5$, $\theta_H = 1$, $\theta_P = 0$, $f = 0.5$, $\phi_4 = 1/7$, $\phi_5 = 1/7$, $c = 1$, $\beta = 0.4$, $\eta_1 = 0.1$ (so that, $\mathcal{R}_c = 0.004 < 1$)

The epidemiological significance of the *control reproduction number*, \mathcal{R}_c , which represents the average number of new cases generated by a primary infectious individual in a population where some susceptible individuals receive antiviral prophylaxis, is that the H1N1 pandemic can be effectively controlled if the use of antiviral can bring the threshold quantity (\mathcal{R}_c) to a value less than unity. Biologically-speaking, Lemma 3.1 implies that the H1N1 pandemic can be eliminated from the population (when $\mathcal{R}_c < 1$) if the initial sizes of the sub-populations in various compartments of the model are in the basin of attraction of the DFE (\mathcal{E}_0). To ensure that disease elimination is independent of the initial sizes of the sub-populations of the model, it is necessary to show that the DFE is globally asymptotically stable (GAS). This is considered below, for a special case.

It is convenient to define the following quantities

$$\begin{aligned} \mathcal{R}_P &= \mathcal{R}_c|_{\tau_1=\tau_2=0} = \frac{\beta\Omega}{K_1} \left\{ \eta_1 + \left\{ \frac{\alpha_1\eta_2(1-f)}{K_2} + \frac{\alpha_1f}{K_3K_4} [K_4 + \eta_3\gamma_1 + Q] \right\} \right\}, \\ \mathcal{R}_T &= \mathcal{R}_c|_{\sigma_L=\sigma_H=0} \\ &= \frac{\beta\omega}{N^*K_1} \left\{ \eta_1 + \left\{ \frac{\alpha_1\eta_2(1-f)}{K_2} + \frac{\alpha_1f}{K_3K_4} [K_4 + \eta_3\gamma_1 + \frac{\eta_6}{K_7} (\tau_1K_4 + \tau_2\gamma_1) + Q] \right\} \right\}. \end{aligned} \quad (3.2)$$

The quantities, \mathcal{R}_P and \mathcal{R}_T , represent the control reproduction numbers associated with the singular prophylactic (\mathcal{R}_P) or therapeutic (\mathcal{R}_T) use of antivirals in the community, respectively.

3.2. Global stability of DFE. The GAS property of the DFE (\mathcal{E}_0) of the model is considered for the special case where all the susceptible individuals (i.e., there is no stratification of the susceptible individuals based on risk of infection) are equally likely to acquire infection (i.e., $\theta_H = 1$) and the susceptible individuals

who received antivirals are fully protected against infection (i.e., $\theta_P = 0$). Define $\tilde{\mathcal{R}}_c = \mathcal{R}_c|_{\theta_H=1, \theta_P=0}$. We claim the following result.

Theorem 3.2. *The DFE, \mathcal{E}_0 , of the model (2.1) with $\theta_H = 1$ and $\theta_P = 0$, is GAS in \mathcal{D} if $\tilde{\mathcal{R}}_c \leq 1$.*

Proof. Consider the model (2.1) with $\theta_H = 1$ and $\theta_P = 0$. Further, consider the Lyapunov function

$$\mathcal{F} = g_1L + g_2A + g_3I_1 + g_4I_2 + g_5H_1 + g_6H_2 + g_7T,$$

where

$$\begin{aligned} g_1 &= \eta_1 K_2 K_3 K_4 K_5 K_6 K_7 + \eta_2 \alpha_1 K_3 K_4 K_5 K_6 K_7 (1-f) + \alpha_1 f K_2 K_4 K_5 K_6 K_7 \\ &\quad + \eta_3 \gamma_1 \alpha_1 f K_2 K_5 K_6 K_7 + \eta_4 \gamma_1 \psi_1 \alpha_1 f K_2 K_6 K_7 + \eta_5 \psi_1 \psi_2 \gamma_1 \alpha_1 f K_2 K_7 \\ &\quad + \eta_6 \alpha_1 \tau_1 f K_2 K_4 K_5 K_6 + \eta_6 \alpha_1 \tau_2 \gamma_1 f K_2 K_5 K_6, \\ g_2 &= \eta_2 K_1 K_3 K_4 K_5 K_6 K_7, \\ g_3 &= K_1 K_2 (K_4 K_5 K_6 K_7 + \eta_3 \gamma_1 K_5 K_6 K_7 + \eta_4 \psi_1 \gamma_1 K_6 K_7 + \eta_5 \psi_1 \psi_2 \gamma_1 K_7 \\ &\quad + \eta_6 \tau_1 K_4 K_5 K_6 + \eta_6 \tau_2 \gamma_1 K_5 K_6), \\ g_4 &= K_1 K_2 K_3 (\eta_3 K_5 K_6 K_7 + \eta_4 \psi_1 K_6 K_7 + \eta_5 \psi_1 \psi_2 K_7 + \eta_6 \tau_2 K_5 K_6), \\ g_5 &= K_1 K_2 K_3 K_4 K_7 (\eta_4 K_6 + \eta_5 \psi_2), \\ g_6 &= \eta_5 K_1 K_2 K_3 K_4 K_5 K_7, \\ g_7 &= \eta_6 K_1 K_2 K_3 K_4 K_5 K_6. \end{aligned}$$

The Lyapunov derivative is given by (where a dot represents differentiation with respect to t)

$$\begin{aligned} \dot{\mathcal{F}} &= g_1 \dot{L} + g_2 \dot{A} + g_3 \dot{I}_1 + g_4 \dot{I}_2 + g_5 \dot{H}_1 + g_6 \dot{H}_2 + g_7 \dot{T} \\ &= g_1 [\lambda(S_L + S_H + \theta_P P) - (\alpha_1 + \mu)L] + g_2 [\alpha_1(1-f)L - (\phi_1 + \mu)A] \\ &\quad + g_3 [\alpha_1 f L - (\tau_1 + \gamma_1 + \mu)I_1] + g_4 [\gamma_1 I_1 - (\tau_2 + \psi_1 + \phi_2 + \mu + \delta)I_2] \\ &\quad + g_5 [\psi_1 I_2 - (\psi_2 + \phi_3 + \mu + \theta_1 \delta)H_1] + g_6 [\psi_2 H_1 - (\phi_4 + \mu + \theta_2 \delta)H_2] \\ &\quad + g_7 [\tau_1 I_1 + \tau_2 I_2 - (\phi_5 + \mu)T], \end{aligned}$$

so that

$$\begin{aligned} \dot{\mathcal{F}} &= g_1 \lambda [S_L(t) + S_H(t)] - K_1 K_2 K_3 K_4 K_5 K_6 K_7 (\eta_1 L + \eta_2 A + I_1 + \eta_3 I_2 \\ &\quad + \eta_4 H_1 + \eta_5 H_2) \\ &= g_1 \lambda [S_L(t) + S_H(t)] - K_1 K_2 K_3 K_4 K_5 K_6 K_7 \frac{\lambda N}{\beta} \\ &\leq g_1 \lambda N - K_1 K_2 K_3 K_4 K_5 K_6 K_7 \frac{\lambda N}{\beta}, \end{aligned}$$

since $S_L(t) + S_H(t) \leq N(t)$ in \mathcal{D} .

It can be shown that $g_1 = \frac{\beta}{K_1} K_2 K_3 K_4 K_5 K_6 K_7$. Hence,

$$\begin{aligned} \dot{\mathcal{F}} &\leq \frac{\tilde{\mathcal{R}}_c}{\beta} K_1 K_2 K_3 K_4 K_5 K_6 K_7 \lambda N - K_1 K_2 K_3 K_4 K_5 K_6 K_7 \frac{\lambda N}{\beta} \\ &= K_1 K_2 K_3 K_4 K_5 K_6 K_7 \frac{\lambda N}{\beta} (\tilde{\mathcal{R}}_c - 1). \end{aligned}$$

Thus, $\dot{\mathcal{F}} \leq 0$ if $\tilde{\mathcal{R}}_c \leq 1$ with $\dot{\mathcal{F}} = 0$ if and only if $L = A = I_1 = I_2 = H_1 = H_2 = T = 0$. Further, the largest compact invariant set in $\{(S_L, S_H, P, L, A, I_1, I_2, H_1, H_2, T, R) \in \mathcal{D} : \dot{\mathcal{F}} = 0\}$ is the singleton $\{\mathcal{E}_0\}$. It follows from the LaSalle Invariance Principle ([26, Chapter 2, Theorem 6.4]) that every solution to the equations in (2.1) with $\theta_H = 1$ and $\theta_P = 0$ and with initial conditions in \mathcal{D} converge to DFE, \mathcal{E}_0 , as $t \rightarrow \infty$. That is, $[L(t), A(t), I_1(t), I_2(t), H_1(t), H_2(t), T(t)] \rightarrow (0, 0, 0, 0, 0, 0, 0)$ as $t \rightarrow \infty$. Substituting $L = A = I_1 = I_2 = H_1 = H_2 = T = 0$ into the first three equations of the model (2.1) gives $S_L(t) \rightarrow S_L^*$, $S_H(t) \rightarrow S_H^*$ and $P(t) \rightarrow P^*$ as $t \rightarrow \infty$. Thus, $[S_L(t), S_H(t), P(t), L(t), A(t), I_1(t), I_2(t), H_1(t), H_2(t), T(t), R(t)] \rightarrow (S_L^*, S_H^*, P^*, 0, 0, 0, 0, 0, 0, 0, 0)$ as $t \rightarrow \infty$ for $\tilde{\mathcal{R}}_c \leq 1$, so that the DFE, \mathcal{E}_0 , is GAS in \mathcal{D} if $\tilde{\mathcal{R}}_c \leq 1$. \square

Theorem 3.2 shows that the H1N1 pandemic can be eliminated from the community if the use of antivirals can lead to $\tilde{\mathcal{R}}_c \leq 1$ for the case when $\theta_H = 1$ and $\theta_P = 0$. This result is illustrated in Figure 2.

3.3. Existence and stability of an endemic equilibrium point (EEP). In order to find endemic equilibria of the basic model (2.1) (that is, equilibria where the infected components of the model (2.1) are non-zero), the following steps are taken. Let

$$E_1 = (S_L^{**}, S_H^{**}, P^{**}, L^{**}, A^{**}, I_1^{**}, I_2^{**}, H_1^{**}, H_2^{**}, T^{**}, R^{**})$$

represents an arbitrary endemic equilibrium of the model (2.1). Further, let

$$\lambda^{**} = \frac{\beta(\eta_1 L^{**} + \eta_2 A^{**} + I_1^{**} + \eta_3 I_2^{**} + \eta_4 H_1^{**} + \eta_5 H_2^{**} + \eta_6 T^{**})}{N^{**}},$$

be the associated force of infection at steady-state. Solving the equations of the model at steady-state gives

$$\begin{aligned} S_L^{**} &= \frac{\Pi(1-p)}{\lambda^{**} + \sigma_L + \mu}, & S_H^{**} &= \frac{\Pi p}{\lambda^{**} + \sigma_H + \mu}, \\ P^{**} &= \frac{\Pi\{\sigma_L(1-p) + \sigma_H p\}(\lambda^{**} + \mu) + \sigma_L \sigma_H}{(\lambda^{**} + \sigma_H + \mu)(\lambda^{**} + \sigma_L + \mu)\mu}, \\ L^{**} &= \frac{\lambda^{**} \Pi[\sigma_H(1-p) + \sigma_L + \lambda^{**} + \mu]}{K_1(\lambda^{**} + \sigma_H + \mu)(\lambda^{**} + \sigma_L + \mu)}, \\ A^{**} &= \frac{\lambda^{**} \Pi \alpha_1 (1-f)[\sigma_H(1-p) + \sigma_L + \lambda^{**} + \mu]}{K_1 K_2 (\lambda^{**} + \sigma_H + \mu)(\lambda^{**} + \sigma_L + \mu)}, \\ I_1^{**} &= \frac{\lambda^{**} \Pi \alpha_1 f [\sigma_H(1-p) + \sigma_L + \lambda^{**} + \mu]}{K_1 K_3 (\lambda^{**} + \sigma_H + \mu)(\lambda^{**} + \sigma_L + \mu)}, \\ I_2^{**} &= \frac{\lambda^{**} \Pi \alpha_1 f \gamma_1 [\sigma_H(1-p) + \sigma_L + \lambda^{**} + \mu]}{K_1 K_3 K_4 (\lambda^{**} + \sigma_H + \mu)(\lambda^{**} + \sigma_L + \mu)}, \\ H_1^{**} &= \frac{\lambda^{**} \Pi \alpha_1 f \gamma_1 \psi_1 [\sigma_H(1-p) + \sigma_L + \lambda^{**} + \mu]}{K_1 K_3 K_4 K_5 (\lambda^{**} + \sigma_H + \mu)(\lambda^{**} + \sigma_L + \mu)}, \\ H_2^{**} &= \frac{\lambda^{**} \Pi \alpha_1 f \gamma_1 \psi_1 \psi_2 [\sigma_H(1-p) + \sigma_L + \lambda^{**} + \mu]}{K_1 K_3 K_4 K_5 K_6 (\lambda^{**} + \sigma_H + \mu)(\lambda^{**} + \sigma_L + \mu)}, \\ T^{**} &= \frac{\lambda^{**} \Pi \alpha_1 f (K_4 \tau_1 + \gamma_1 \tau_2) [\sigma_H(1-p) + \sigma_L + \lambda^{**} + \mu]}{K_1 K_3 K_4 K_7 (\lambda^{**} + \sigma_H + \mu)(\lambda^{**} + \sigma_L + \mu)}, \end{aligned}$$

$$R^{**} = \frac{\lambda^{**} \Pi \alpha_1 [\sigma_H (1-p) + \sigma_L + \lambda^{**} + \mu] X}{\mu K_1 K_2 K_3 K_4 K_5 K_6 K_7 (\lambda^{**} + \sigma_H + \mu) (\lambda^{**} + \sigma_L + \mu)}, \quad (3.3)$$

where

$$X = K_5 K_6 [K_7 K_3 K_4 \phi_1 (1-f) + K_2 \phi_5 f (K_4 \tau_1 + \gamma_1 \tau_2)] \\ - f k_2 \gamma_1 K_7 (\psi_2 \phi_4 \psi_1 + K_6 \phi_3 \psi_1 + K_6 \phi_2 K_5).$$

It can be shown that the non-zero equilibria of the model satisfy the following quadratic (in terms of λ^{**}):

$$a_0 (\lambda^{**})^2 + b_0 \lambda^{**} + c_0 = 0, \quad (3.4)$$

where,

$$a_0 = \mu K_2 K_6 K_5 K_4 K_3 K_7 + \alpha_1 (1-f) K_7 K_3 K_4 K_5 K_6 \mu + \alpha_1 K_7 \psi_1 \gamma_1 f k_2 K_6 \phi_3 \\ + \psi_1 \gamma_1 \alpha_1 f k_7 K_6 K_2 \mu + \alpha_1 K_5 K_6 K_2 \phi_5 K_4 \tau_1 f + \alpha_1 f k_5 K_6 K_2 \mu \gamma_1 \tau_2 \\ + \alpha_1 f k_7 K_4 K_5 K_6 K_2 \mu + \alpha_1 K_7 K_3 K_4 K_5 K_6 \phi_1 (1-f) + \psi_2 \psi_1 \gamma_1 \alpha_1 f k_7 K_2 \mu \\ + \alpha_1 K_5 K_6 K_2 \phi_5 f \gamma_1 \tau_2 + \alpha_1 K_7 \psi_1 \gamma_1 f k_2 \phi_4 \psi_2 + \gamma_1 \alpha_1 f k_7 K_5 K_6 K_2 \mu \\ + \alpha_1 K_7 \gamma_1 f k_2 K_6 \phi_2 K_5 + \alpha_1 f k_5 K_6 K_2 \mu K_4 \tau_1,$$

$$b_0 = K_6 K_7 K_5 K_4 K_3 K_1 K_2 \mu - \mu \beta \eta_1 K_2 K_3 K_4 K_5 K_6 K_7 \\ - \mu \beta \eta_2 \alpha_1 (1-f) K_3 K_4 K_5 K_6 K_7 - \mu \beta \alpha_1 f K_2 K_4 K_5 K_6 K_7 \\ - \mu \beta \eta_3 \gamma_1 \alpha_1 f K_2 K_5 K_6 K_7 - \mu \beta \eta_4 \psi_1 \gamma_1 \alpha_1 f K_2 K_6 K_7 - \mu \beta \eta_5 \psi_2 \psi_1 \gamma_1 \alpha_1 f K_2 K_7 \\ - \mu \beta \eta_6 \alpha_1 f K_2 K_5 K_6 \tau_2 \gamma_1 + \mu K_2 K_3 K_4 K_5 K_7 K_6 \sigma_l p - \mu \beta \eta_6 \alpha_1 f K_2 K_5 K_6 \tau_1 K_4 \\ + K_2 K_1 K_3 K_4 K_5 K_7 K_6 \sigma_l + K_6 K_7 K_5 K_4 K_3 K_2 \mu^2 \\ + K_2 K_1 K_3 K_4 K_5 K_7 K_6 \sigma_h p - K_2 K_1 K_3 K_4 K_5 K_7 K_6 \sigma_l p \\ - \alpha_1 (1-f) \mu K_3 K_4 K_5 K_7 K_6 \sigma_h p - \mu K_2 K_3 K_4 K_5 K_7 K_6 \sigma_h p \\ + \mu K_2 K_3 K_4 K_5 K_7 K_6 \sigma_h + \alpha_1 (1-f) \mu K_3 K_4 K_5 K_7 K_6 \sigma_l p \\ + \alpha_1 (1-f) \mu K_3 K_4 K_5 K_7 K_6 \sigma_h + \alpha_1 f \mu K_2 K_4 K_5 K_7 K_6 \sigma_l p \\ + \psi_2 \psi_1 \gamma_1 \alpha_1 f \mu K_2 K_7 \sigma_h + \alpha_1 (1-f) \mu^2 K_3 K_4 K_5 K_7 K_6 + \gamma_1 \alpha_1 f \mu K_2 K_5 K_7 K_6 \sigma_h \\ - \gamma_1 \alpha_1 f \mu K_2 K_5 K_7 K_6 \sigma_h p + \alpha_1 f \mu K_2 K_4 K_5 K_7 K_6 \sigma_h - \alpha_1 f \mu K_2 K_4 K_5 K_7 K_6 \sigma_h p \\ + \alpha_1 f \mu^2 K_2 K_4 K_5 K_7 K_6 + \alpha_1 \phi_4 K_2 K_7 \psi_2 \psi_1 \gamma_1 f \sigma_h - \alpha_1 \phi_5 K_2 K_5 f \tau_2 \gamma_1 \sigma_h p K_6 \\ - \psi_2 \psi_1 \gamma_1 \alpha_1 f \mu K_2 K_7 \sigma_h p + \psi_2 \psi_1 \gamma_1 \alpha_1 f \mu^2 K_2 K_7 + \gamma_1 \alpha_1 f \mu^2 K_2 K_5 K_7 K_6 \\ + \gamma_1 \alpha_1 f \mu K_2 K_5 K_7 K_6 \sigma_l p + \psi_1 \gamma_1 \alpha_1 f \mu K_2 K_7 K_6 \sigma_h - \psi_1 \gamma_1 \alpha_1 f \mu K_2 K_7 K_6 \sigma_h p \\ + \psi_1 \gamma_1 \alpha_1 f \mu^2 K_2 K_7 K_6 + \psi_1 \gamma_1 \alpha_1 f \mu K_2 K_7 K_6 \sigma_l p + \alpha_1 \phi_2 K_2 \gamma_1 f \mu K_5 K_7 K_6 \\ + \alpha_1 \phi_2 K_2 \gamma_1 f \sigma_h K_5 K_7 K_6 + \alpha_1 \phi_2 K_2 \gamma_1 f \sigma_l p K_5 K_7 K_6 + \alpha_1 \phi_5 K_2 K_5 f \tau_2 \gamma_1 \sigma_h K_6 \\ + \alpha_1 \phi_4 K_2 K_7 \psi_2 \psi_1 \gamma_1 f \mu + \alpha_1 \phi_4 K_2 K_7 \psi_2 \psi_1 \gamma_1 f \sigma_l p + \psi_2 \psi_1 \gamma_1 \alpha_1 f \mu K_2 K_7 \sigma_l p \\ + \alpha_1 f \mu K_2 K_5 K_6 \tau_2 \gamma_1 \sigma_h - \alpha_1 f \mu K_2 K_5 K_6 \tau_2 \gamma_1 \sigma_h p + \alpha_1 f \mu^2 K_2 K_5 K_6 \tau_2 \gamma_1 \\ + \alpha_1 f \mu K_2 K_5 K_6 \tau_2 \gamma_1 \sigma_l p + \alpha_1 f \mu K_2 K_5 K_6 \tau_1 \sigma_h K_4 - \alpha_1 f \mu K_2 K_5 K_6 \tau_1 \sigma_h p K_4 \\ + \alpha_1 f \mu^2 K_2 K_5 K_6 \tau_1 K_4 + \alpha_1 f \mu K_2 K_5 K_6 \tau_1 \sigma_l p K_4 + \alpha_1 \phi_5 K_2 K_5 f \tau_1 \sigma_l p K_4 K_6 \\ + \alpha_1 \phi_5 K_2 K_5 f \tau_2 \gamma_1 \mu K_6 + \alpha_1 \phi_5 K_2 K_5 f \tau_2 \gamma_1 \sigma_l p K_6 \\ + \alpha_1 \phi_1 (1-f) \mu K_3 K_4 K_5 K_7 K_6 - \alpha_1 \phi_1 (1-f) \sigma_h p K_3 K_4 K_5 K_7 K_6 \\ - \alpha_1 \phi_2 K_2 \gamma_1 f \sigma_h p K_5 K_7 K_6 + \alpha_1 \phi_1 (1-f) \sigma_h K_3 K_4 K_5 K_7 K_6$$

$$\begin{aligned}
& + \alpha_1 \phi_3 K_2 \psi_1 \gamma_1 f \sigma_h K_7 K_6 - \alpha_1 \phi_3 K_2 \psi_1 \gamma_1 f \sigma_h p K_7 K_6 \\
& + \alpha_1 \phi_3 K_2 \psi_1 \gamma_1 f \mu K_7 K_6 + \alpha_1 \phi_5 K_2 K_5 f \tau_1 \sigma_h K_4 K_6 \\
& - \alpha_1 \phi_5 K_2 K_5 f \tau_1 \sigma_h p K_4 K_6 + \alpha_1 \phi_5 K_2 K_5 f \tau_1 \mu K_4 K_6 \\
& + \alpha_1 \phi_3 K_2 \psi_1 \gamma_1 f \sigma_l p K_7 K_6 + \alpha_1 \phi_1 (1 - f) \sigma_l p K_3 K_4 K_5 K_7 K_6 \\
& - \alpha_1 \phi_4 K_2 K_7 \psi_2 \psi_1 \gamma_1 f \sigma_h p,
\end{aligned}$$

$$c_0 = K_1 K_2 K_3 K_4 K_5 K_6 K_7 (\mu + \sigma_l)(\mu + \sigma_h)(1 - \mathcal{R}_c).$$

The positive endemic equilibria of the model (2.1) are then obtained by solving for λ^{**} from the quadratic (3.4) and substituting the results (positive values of λ^{**}) into (3.3). The coefficient a_0 , of (3.4), is always positive, and c_0 is positive (negative) if \mathcal{R}_c is less than (greater than) unity, respectively. Thus, the following result is established.

Theorem 3.3. *The model (2.1) has:*

- (i) a unique endemic equilibrium if $c_0 < 0 \Leftrightarrow \mathcal{R}_c > 1$;
- (ii) a unique endemic equilibrium if $b_0 < 0$, and $c_0 = 0$ or $b_0^2 - 4a_0c_0 = 0$;
- (iii) two endemic equilibrium if $c_0 > 0$, $b_0 < 0$ and $b_0^2 - 4a_0c_0 > 0$;
- (iv) no endemic equilibrium otherwise.

It is clear from Theorem 3.3 (Case (i)) that the model has a unique endemic equilibrium whenever $\mathcal{R}_c > 1$. Case (iii) of Theorem 3.3 suggests the possibility of backward bifurcation in the model (2.1) (where a stable DFE co-exists with a stable EEP when $\mathcal{R}_c < 1$). This phenomenon is not considered in detail in the current study (the reader may refer to [2, 5, 6, 14, 16, 19, 24, 29, 32, 33, 34, 35, 39], and some of the references therein for discussions on backward bifurcation).

Global Stability of EEP: Special Case ($\theta_H = 1$ and $\theta_P = 0$). Consider, again, the model (2.1) subject to the special case where all the susceptible individuals (from both risk groups) are equally likely to acquire infection (so that, $\theta_H = 1$) and the use of antiviral prophylaxis gives perfect protection against infection (i.e., $\theta_P = 0$). Further, let

$$\begin{aligned}
\text{sign}(S_L - S_L^{**}) &= \text{sign}(S_H - S_H^{**}) = \text{sign}(P - P^{**}) \\
&= \text{sign}(L - L^{**}) = \text{sign}(A - A^{**}) = \text{sign}(I_1 - I_1^{**}) \\
&= \text{sign}(I_2 - I_2^{**}) = \text{sign}(H_1 - H_1^{**}) = \text{sign}(H_2 - H_2^{**}) \\
&= \text{sign}(T - T^{**}) = \text{sign}(R - R^{**}) \}.
\end{aligned} \tag{3.5}$$

It is convenient to define the region:

$$\begin{aligned}
\mathcal{D}_0 &= \{(S_L, S_H, P, L, A, I_1, I_2, H_1, H_2, T, R) \in \mathcal{D} : \\
&L = A = I_1 = I_2 = H_1 = H_2 = T = R = 0\}.
\end{aligned}$$

We claim the following result.

Theorem 3.4. *The associated unique endemic equilibrium of the model (2.1), with $\theta_H = 1$ and $\theta_P = 0$, is GAS in $\mathcal{D} \setminus \mathcal{D}_0$ whenever $\tilde{\mathcal{R}}_c > 1$ and equation (3.5) holds.*

Proof. Consider the model (2.1) with $\theta_H = 1$ and $\theta_P = 0$. Further, let $\tilde{\mathcal{R}}_c > 1$ (so that the model (2.1) has a unique EEP, as guaranteed by Theorem 3.3). Furthermore, let the relations in equation (3.5) hold. Consider the Lyapunov function (Lyapunov functions of this type have been used in the literature, such as in [46])

$$\mathcal{F} = |S_L - S_L^{**}| + |S_H - S_H^{**}| + |P - P^{**}| + |L - L^{**}| + |A - A^{**}| + |I_1 - I_1^{**}|$$

$$+ |I_2 - I_2^{**}| + |H_1 - H_1^{**}| + |H_2 - H_2^{**}| + |T - T^{**}| + |R - R^{**}|.$$

It follows that the right derivative, $D^+\mathcal{F}$, of \mathcal{F} , along the solutions of (2.1) with $\theta_H = 1$ and $\theta_P = 0$, is given by:

$$\begin{aligned} & D^+\mathcal{F} \\ &= \text{sign}(S_L - S_L^{**})\{(1-p)\Pi - \lambda S_L - \sigma_L S_L - \mu S_L - [(1-p)\Pi - \lambda^{**} S_L^{**} \\ &\quad - \sigma_L S_L^{**} - \mu S_L^{**}]\} + \text{sign}(S_H - S_H^{**})\{p\Pi - \lambda S_H - \sigma_H S_H - \mu S_H \\ &\quad - [p\Pi - \lambda^{**} S_H^{**} - \sigma_H S_H^{**} - \mu S_H^{**}]\} \\ &\quad + \text{sign}(P - P^{**})[\sigma_L S_L + \sigma_H S_H - \mu P - (\sigma_L S_L^{**} + \sigma_H S_H^{**} - \mu P^{**})] \\ &\quad + \text{sign}(L - L^{**})\{[\lambda(S_L + S_H) - (\alpha_1 + \mu)L] - [\lambda^{**}(S_L^{**} + S_H^{**}) \\ &\quad - (\alpha_1 + \mu)L^{**}]\} \\ &\quad + \text{sign}(A - A^{**})\{\alpha_1(1-f)L - (\phi_1 + \mu)A - [\alpha_1(1-f)L^{**} - (\phi_1 + \mu)A^{**}]\} \\ &\quad + \text{sign}(I_1 - I_1^{**})\{\alpha_1 fL - (\tau_1 + \gamma_1 + \mu)I_1 - [\alpha_1 fL^{**} - (\tau_1 + \gamma_1 + \mu)I_1^{**}]\} \\ &\quad + \text{sign}(I_2 - I_2^{**})\{\gamma_1 I_1 - (\tau_2 + \psi_1 + \phi_2 + \mu + \delta)I_2 \\ &\quad - [\gamma_1 I_1^{**} - (\tau_2 + \psi_1 + \phi_2 + \mu + \delta)I_2^{**}]\} \\ &\quad + \text{sign}(H_1 - H_1^{**})\{\psi_1 I_2 - (\psi_2 + \phi_3 + \mu + \theta_1 \delta)H_1 \\ &\quad - [\psi_1 I_2^{**} - (\psi_2 + \phi_3 + \mu + \theta_1 \delta)H_1^{**}]\} \\ &\quad + \text{sign}(H_2 - H_2^{**})\{\psi_2 H_1 - (\phi_4 + \mu + \theta_2 \delta)H_2 \\ &\quad - [\psi_2 H_1^{**} - (\phi_4 + \mu + \theta_2 \delta)H_2^{**}]\} \\ &\quad + \text{sign}(T - T^{**})\{\tau_1 I_1 + \tau_2 I_2 - (\phi_5 + \mu)T - [\tau_1 I_1^{**} + \tau_2 I_2^{**} - (\phi_5 + \mu)T^{**}]\} \\ &\quad + \text{sign}(R - R^{**})\{\phi_1 A + \phi_2 I_2 + \phi_3 H_1 + \phi_4 H_2 + \phi_5 T - \mu R \\ &\quad - (\phi_1 A^{**} + \phi_2 I_2^{**} + \phi_3 H_1^{**} + \phi_4 H_2^{**} + \phi_5 T^{**} - \mu R^{**})\} \\ &= \text{sign}(S_L - S_L^{**})\{(1-p)\Pi - \lambda^{**}(S_L - S_L^{**}) - \sigma_L(S_L - S_L^{**}) - \mu(S_L - S_L^{**})\} \\ &\quad + \text{sign}(S_H - S_H^{**})\{p\Pi - \lambda^{**}(S_H - S_H^{**}) - \sigma_H(S_H - S_H^{**}) - \mu(S_H - S_H^{**})\} \\ &\quad + \text{sign}(P - P^{**})\{\sigma_L(S_L - S_L^{**}) + \sigma_H(S_H - S_H^{**}) - \mu(P - P^{**})\} \\ &\quad + \text{sign}(L - L^{**})\{\lambda^{**}[(S_L - S_L^{**}) + (S_H - S_H^{**})] - (\alpha_1 + \mu)(L - L^{**})\} \\ &\quad + \text{sign}(A - A^{**})\{\alpha_1(1-f)(L - L^{**}) - (\phi_1 + \mu)(A - A^{**})\} \\ &\quad + \text{sign}(I_1 - I_1^{**})\{\alpha_1 f(L - L^{**}) - (\tau_1 + \gamma_1 + \mu)(I_1 - I_1^{**})\} \\ &\quad + \text{sign}(I_2 - I_2^{**})\{\gamma_1(I_1 - I_1^{**}) - (\tau_2 + \psi_1 + \phi_2 + \mu + \delta)(I_2 - I_2^{**})\} \\ &\quad + \text{sign}(H_1 - H_1^{**})\{\psi_1(I_2 - I_2^{**}) - (\psi_2 + \phi_3 + \mu + \theta_1 \delta)(H_1 - H_1^{**})\} \\ &\quad + \text{sign}(H_2 - H_2^{**})\{\psi_2(H_1 - H_1^{**}) - (\phi_4 + \mu + \theta_2 \delta)(H_2 - H_2^{**})\} \\ &\quad + \text{sign}(T - T^{**})\{\tau_1(I_1 - I_1^{**}) + \tau_2(I_2 - I_2^{**}) - (\phi_5 + \mu)(T - T^{**})\} \\ &\quad + \text{sign}(R - R^{**})\{\phi_1(A - A^{**}) + \phi_2(I_2 - I_2^{**}) + \phi_3(H_1 - H_1^{**}) \\ &\quad + \phi_4(H_2 - H_2^{**}) + \phi_5(T - T^{**}) - \mu(R - R^{**})\}, \\ &= -\mu|S_L - S_L^{**}| - \mu|S_H - S_H^{**}| - \mu|P - P^{**}| - \mu|L - L^{**}| - \mu|I_1 - I_1^{**}| \\ &\quad - (\mu + \delta)|I_2 - I_2^{**}| - (\mu + \theta_1 \delta)|H_1 - H_1^{**}| - (\mu + \theta_2 \delta)|H_2 - H_2^{**}| \\ &\quad - \mu|R - R^{**}| \\ &\leq -\mu|S_L - S_L^{**}| - \mu|S_H - S_H^{**}| - \mu|P - P^{**}| - \mu|L - L^{**}| - \mu|I_1 - I_1^{**}| \end{aligned}$$

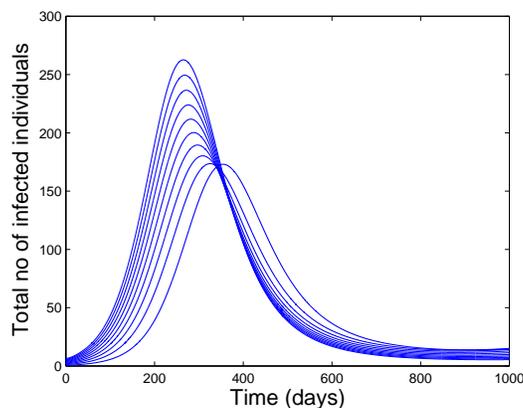


FIGURE 3. Simulations of (2.1) showing the total number of infected individuals as a function of time, using various initial conditions. Parameter values used are as in Table 1 with $p = 0.5$, $\theta_H = 1.2$, $\theta_P = 0.9$, $\alpha_1 = 0.3$, $f = 0.5$, $\phi_4 = \phi_5 = 1/7$, $c = 1$, $\beta = 0.4$, $\eta_1 = 0.1$ (so that $\mathcal{R}_c = 1.15 > 1$)

$$\begin{aligned}
 & -\mu|I_2 - I_2^{**}| - \mu|H_1 - H_1^{**}| - \mu|H_2 - H_2^{**}| - \mu|R - R^{**}| \\
 & = -\mu\mathcal{F}.
 \end{aligned}$$

Thus, $D^+\mathcal{F} \leq 0$. Hence, \mathcal{F} is a Lyapunov function on $\mathcal{D} \setminus \mathcal{D}_0$. It follows, by the LaSalle's Invariance Principle [20], that every solution in $\mathcal{D} \setminus \mathcal{D}_0$ approaches the model (2.1), with $\theta_H = 1$ and $\theta_P = 0$, with initial conditions in $\mathcal{D} \setminus \mathcal{D}_0$ approaches the associated unique endemic equilibrium of the model (2.1), with $\theta_P = 0$ and $\theta_H = 1$, as $t \rightarrow \infty$ if $\mathcal{R}_c > 1$ and equation (3.5) holds. \square

The sensitivity analysis of variables of the model (2) using the sensitivity functions, $\partial X/\partial q$, (where X represents a variable, and q represents a parameter), with respect to selective parameters (given the size of the parameter space) was carried out. The sensitivity analysis reveals that the sensitivity function of low risk susceptible individuals, S_L , decreases (taking negative values) with $\beta, \sigma_L, \alpha_1$, and f initially, attaining a minimum value in around 10 days. It then increases, and finally becomes insensitive to the respective parameter. On the other hand, S_L increases with τ_1 first, with a peak within first 10 days. It then decreases, and finally becomes insensitive to τ_1 . Similarly, the number of infectious symptomatic individuals at early stage of infection (I_1) is insensitive to π, η_i, β , and σ_L . However I_1 increases initially with α_1 , and f , attaining a peak in less than 10 days, then decreases before becoming insensitive asymptotically. On the other hand, it first decreases (taking negative values), then increases with τ_1 and γ_1 , and then becomes insensitive to the corresponding parameter. It should be noted that the sensitivity functions of state variables take the maximum magnitudes during transient time interval. However, they become insensitive asymptotically. It should be mentioned that this univariate approach does not account for a possible influence of correlation between parameter estimates.

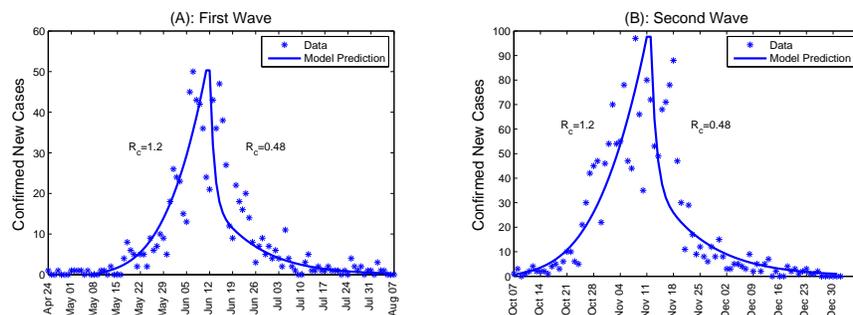


FIGURE 4. Simulations of model (2.1) showing the time series for the number of infected cases per day and its fit with the actual confirmed new daily cases in Manitoba. (A): First Wave. The first wave was assumed to begin in April and end in early August. Here, we used $\theta_P = 0.6$, $\alpha_1 = 5$ and $\beta = .609$ in the beginning and it is assumed that the combined use of antivirals (prophylaxis and therapeutic) takes effect around the middle of June, (with $\theta_P = 0.7$, $\alpha_1 = 0.4$, $\beta = 0.2$). Other parameter values are as in Table 1. (B): Second Wave. The second wave began in early October and ended at the end of December. Here, $\theta_P = 0.6$, $\alpha_1 = 3$, $\beta = 0.6061$ in the beginning of the wave

Figure 3 depicts the numerical simulation results obtained for the case when $\tilde{R}_c > 1$, from which it is clear that all initial solutions converged to the unique endemic equilibrium (in line with Theorem 3.4).

4. NUMERICAL SIMULATIONS

The model (2.1) is further simulated using the parameter values in Table 1 (unless otherwise stated) to quantitatively assess the role of antivirals in curtailing the spread of the H1N1 pandemic. First of all, the model's output is compared with the pandemic H1N1 data obtained from the province of Manitoba. The results obtained, depicted in Figure 4, show that the model fits the observed data (for both the first and second waves of the pandemic) reasonably well. It should be mentioned that the model simulations for the first wave (Figure 4A) were based on the assumptions that 30% of Manitobans are in the high-risk (of infection) category, and that the antivirals are available at the beginning of the pandemic. For the second wave plot (Figure 4B), it is additionally assumed that 20% of the Manitoban population have pre-existing immunity against the H1N1 infection (due to their assumed H1N1 infection during the first wave). We also point out that insufficient H1N1 data at this point hinders the definition of realistic ranges for the parameters, and a thorough sensitivity analysis is not feasible.

The model is further simulated to assess the targeted use of the antivirals as a preventive agent only (i.e., the drugs are only given to susceptible individuals, and not to infected individuals with disease symptoms), under the assumptions that all susceptible individuals are equally likely to acquire the H1N1 infection ($\theta_H = 1$) and that all those who received prophylaxis are completely protected against infection

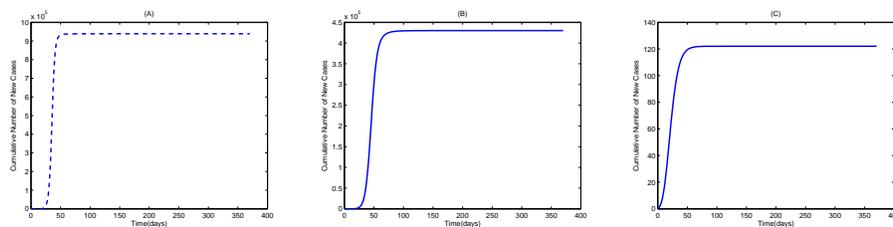


FIGURE 5. Simulations of model (2.1) in the absence of antiviral treatment ($\tau_1 = \tau_2 = 0$) showing the cumulative number of new cases of infection for different effectiveness levels of the prevention-only strategy. (A) Low effectiveness level: $\sigma_L = \sigma_H = 0.005$, $\beta = 0.9$, $\theta_P = 0$, $\theta_H = 1$, $f = 0.5$, $\alpha_1 = 0.9$ (so that $\mathcal{R}_P = 0.0741$); (B) Moderate effectiveness level: $\sigma_L = \sigma_H = 0.02$, $\beta = 0.9$, $\theta_P = 0$, $\theta_H = 1$, $f = 0.5$, $\alpha_1 = 0.9$ (so that $\mathcal{R}_P = 0.0186$), (C) High effectiveness level: $\sigma_L = \sigma_H = 0.08$, $\beta = 0.9$, $\theta_P = 0$, $\theta_H = 1$, $f = 0.5$, $\alpha_1 = 0.9$ (so tha, $\mathcal{R}_P = 0.0047$). Other parameter values are as in Table 1

($\theta_P = 0$). It should be recalled that, in such a case, Theorem 3.2 guarantees that the disease will be eliminated if $\tilde{\mathcal{R}}_c \leq 1$.

We consider three different levels of effectiveness for this prevention-only targeted strategy, namely:

- (i) Low effectiveness level of the prevention-only strategy ($\sigma_L = \sigma_H = 0.005$, $\tau_1 = \tau_2 = 0$, $\theta_H = 1$, $\theta_P = 0$; so that $\mathcal{R}_P = \tilde{\mathcal{R}}_c|_{\tau_1=\tau_2=0} = 0.0741$);
- (ii) Moderate effectiveness level of the prevention-only strategy ($\sigma_L = \sigma_H = 0.02$, $\tau_1 = \tau_2 = 0$, $\theta_H = 1$, $\theta_P = 0$; so that $\mathcal{R}_P = \tilde{\mathcal{R}}_c|_{\tau_1=\tau_2=0} = 0.0186$);
- (iii) High effectiveness level of the prevention-only strategy ($\sigma_L = \sigma_H = 0.08$, $\tau_1 = \tau_2 = 0$, $\theta_H = 1$, $\theta_P = 0$; so that $\mathcal{R}_P = \tilde{\mathcal{R}}_c|_{\tau_1=\tau_2=0} = 0.0047$).

In other words, the moderate effectiveness level of the prevention-only strategy is assumed to be four times more effective than the low effectiveness prevention-only strategy. Similarly, the high effectiveness prevention-only strategy is assumed to be four times more effective than the moderate effectiveness prevention-only strategy. These effectiveness levels are chosen arbitrarily. The total cumulative number of new cases of infection is computed over a span of one year. The results obtained, depicted in Figure 5, show a decrease in the cumulative number of new cases of infection with increasing effectiveness level of the prevention-only strategy. While the low effectiveness strategy resulted in close to a million cumulative cases over one year (Figure 5A), the moderate effectiveness level resulted in a decrease to about 425,000 cases (Figure 5B). Furthermore, the high effectiveness level strategy, which is assumed to be sixteen times more effective than the low effectiveness strategy, resulted in only about 120 new cases over the same time period (Figure 5C). Thus, these simulations suggest that the singular use of antivirals as prophylaxis would have limited population-level impact (in reducing disease burden) except if its effectiveness level is very high.

Additional simulations are carried out to assess the effect of the combined use of the antivirals (both as prophylaxis and therapeutic agents), under the assumptions

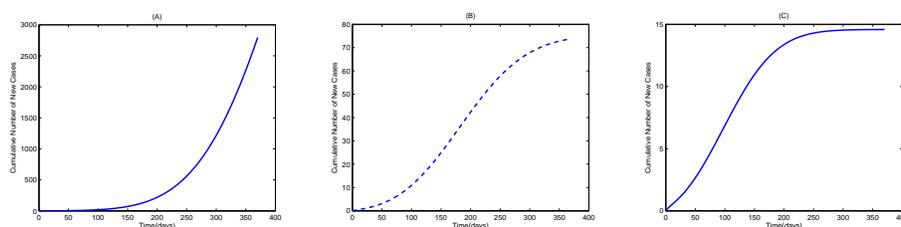


FIGURE 6. Simulations of model (2.1) showing the cumulative number of new cases of infection for different effectiveness levels of the prevention-treatment combined strategy. (A) Low effectiveness level: $\sigma_L = \sigma_H = 0.001$, $\tau_1 = \tau_2 = 0.005$, $\beta = 0.14$, $\theta_P = 0$, $\theta_H = 1$, $f = 0.5$, $\alpha_1 = 0.9$ (so that $\tilde{\mathcal{R}}_c = 0.0522$); (B) Moderate effectiveness level: $\sigma_L = \sigma_H = 0.002$, $\tau_1 = \tau_2 = 0.01$, $\beta = 0.14$, $\theta_P = 0$, $\theta_H = 1$, $f = 0.5$, $\alpha_1 = 0.9$ (so that $\tilde{\mathcal{R}}_c = 0.0248$), (C) High effectiveness level: $\sigma_L = \sigma_H = 0.003$, $\tau_1 = \tau_2 = 0.015$, $\beta = 0.14$, $\theta_P = 0$, $\theta_H = 1$, $f = 0.5$, $\alpha_1 = 0.9$ (so that $\tilde{\mathcal{R}}_c = 0.0157$). Other parameter values used are as given in Table 1

that all susceptible individuals are equally likely to acquire the H1N1 infection and that all those who received prophylaxis are completely protected against infection. Here, too, three effectiveness levels (of the universal strategy) are considered as below:

- (i) Low effectiveness level of the universal strategy ($\sigma_L = \sigma_H = 0.001$, $\tau_1 = \tau_2 = 0.005$, $\theta_H = 1$, $\theta_P = 0$; so that $\tilde{\mathcal{R}}_c = 0.0522$);
- (ii) Moderate effectiveness level of the universal strategy ($\sigma_L = \sigma_H = 0.002$, $\tau_1 = \tau_2 = 0.01$, $\theta_H = 1$, $\theta_P = 0$; so that $\tilde{\mathcal{R}}_c = 0.0248$);
- (iii) High effectiveness level of the universal strategy ($\sigma_L = \sigma_H = 0.003$, $\tau_1 = \tau_2 = 0.015$, $\theta_H = 1$, $\theta_P = 0$; so that $\tilde{\mathcal{R}}_c = 0.0157$).

The moderate effectiveness level of the universal strategy is assumed to be twice more effective than the low effectiveness level. Similarly, the high effectiveness level is assumed to be three times more effective than the low effectiveness level (it should be noted that, in all these cases of the universal strategy, the associated reproduction number $\tilde{\mathcal{R}}_c < 1$ (so that, by Theorem 3.2, the disease will be eliminated from the community). The simulations show that while the low effectiveness level results in about 2800 cases (Figures 6A), the moderate and high effectiveness levels of the universal strategy resulted in about 75 and 15 cases, respectively (Figures 6B, C). Thus, even the moderate effectiveness level of the universal strategy will be extremely effective in curtailing the spread of the disease. Figure 7 shows the time to disease elimination using the three effectiveness levels of the universal strategy. As depicted in Figure 7A, the disease can be eliminated in about 150 days using the high effectiveness level of the universal strategy. The time to eliminate the disease increases with decreasing effectiveness level of the universal strategy (Figures 7B, C).

In summary, this study suggests that the use of antivirals as both prophylaxis and therapeutic agents is more effective than their targeted use as prophylaxis only.

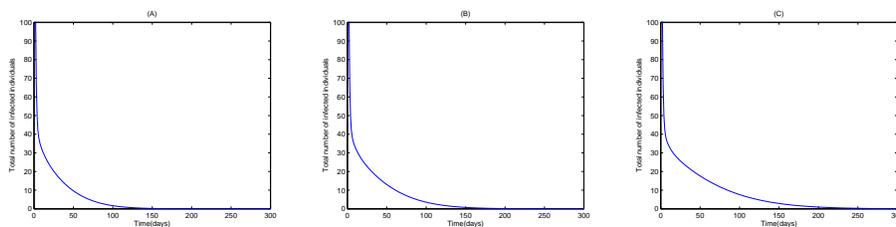


FIGURE 7. Simulations of model (2.1) showing the time needed to eliminate the disease for different effectiveness levels of the prevention-treatment combined strategy. (A) High effectiveness level: $\sigma_L = \sigma_H = 0.003$, $\tau_1 = \tau_2 = 0.015$, $\beta = 0.14$, $\theta_P = 0$, $\theta_H = 1$, $f = 0.2$ (so that $\tilde{\mathcal{R}}_c = 0.0087$). (B) Moderate effectiveness level: $\sigma_L = \sigma_H = 0.002$, $\tau_1 = \tau_2 = 0.01$, $\beta = 0.14$, $\theta_P = 0$, $\theta_H = 1$, $f = 0.2$ (so that $\tilde{\mathcal{R}}_c = 0.0136$), (C) Low effectiveness level: $\sigma_L = \sigma_H = 0.001$, $\tau_1 = \tau_2 = 0.005$, $\beta = 0.14$, $\theta_P = 0$, $\theta_H = 1$, $f = 0.2$ (so that $\tilde{\mathcal{R}}_c = 0.0281$); Other parameter values used are as given in Table 1

In other words, the prospect of disease elimination from the community is greatly enhanced if the universal strategy is used.

Conclusions. A deterministic model is designed and rigorously analyzed to assess the impact of antiviral drugs in curtailing the spread of disease of the 2009 swine influenza pandemic. The analysis of the model, which consists of eleven mutually-exclusive epidemiological compartments, shows the following:

- (i) The disease-free equilibrium of the model is shown to be globally-asymptotically stable under the following conditions:
 - (a) the associated reproduction number $\tilde{\mathcal{R}}_c \leq 1$;
 - (b) all susceptible individuals are equally likely to acquire infection (so that, $\theta_H = 1$);
 - (c) susceptible individuals who received antivirals are fully protected (so that, $\theta_P = 0$).
- (ii) The model has a unique endemic equilibrium when the associated reproduction threshold (\mathcal{R}_c) exceeds unity. The unique endemic equilibrium is shown to be globally-asymptotically stable for the special case where all susceptible individuals are equally likely to acquire infection and the use of antiviral prophylaxis gives perfect protection against infection.

Numerical simulations of the model, suggest the following:

- (a) The singular use of antivirals, as a preventive agent, has limited population-level impact in reducing disease burden, except if its effectiveness level is very high;
- (b) The combined use of the antivirals, as preventive and therapeutic agents, offers great reduction in disease burden, and will result in disease elimination.

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