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Optimal control for pandemic influenza: The role of limited antiviral treatment and isolation

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ABSTRACT

The implementation of optimal control strategies involving antiviral treatment and/or isolation measures can reduce significantly the number of clinical cases of influenza. Pandemic-level control measures must be carefully assessed specially in resource-limited situations. A model for the transmission dynamics of influenza is used to evaluate the impact of isolation and/or antiviral drug delivery measures during an influenza pandemic. Five pre-selected control strategies involving antiviral treatment and isolation are tested under the "unlimited" resource assumption followed by an exploration of the impact of these "optimal" policies when resources are limited in the context of a 1918-type influenza pandemic scenario. The implementation of antiviral treatment at the start of a pandemic tends to reduce the magnitude of epidemic peaks, spreading the maximal impact of an outbreak over an extended window in time. Hence, the controls' timing and intensity can reduce the pressures placed on the health care infrastructure by a pandemic reducing the stress put on the system during epidemic peaks. The role of isolation strategies is highlighted in this study particularly when access to antiviral resources is limited.

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1. Introduction

The innate ability of the influenza virus to generate secondary cases of infection over short windows in time mean that the timely implementation of pandemic containment strategies is critical (Colizza et al., 2007; Ferguson et al., 2005, 2006; Germann et al., 2006; Longini et al., 2004, 2005). The identification, evaluation, and implementation of effective regional, national or global pandemic mitigation plans can be enhanced with the assistance of mathematical frameworks and the extensive simulations and/or analysis of appropriate submodels. Preparedness plans dealing with the allocation of antiviral medications must account for a multitude of factors including the pathogens' virulence (defined in terms of case fatality rates in the population) which plays a central role in the assessment of the size of the antiviral medication stockpile for a community (Lipsitch et al., 2009). These levels of assessment take on a new meaning when the antiviral drug supplies are insufficient (Bar et al., 2009; Merler et al., 2009) and consequently, the use of non-pharmaceutical interventions or treatment measures that include the distribution of face masks and/or the availability of ventilators must also be factored in any preparedness plan (Ferguson et al., 2006; Merler et al., 2009; Tracht et al., 2010).

The world's insufficient capacity to produce antiviral drugs and vaccines (specially the new 2009 H1N1pdm influenza vaccine) during *an emergency* such as the one posed by the 2009 H1N1pdm influenza virus raises concerns at multiple levels (Fedson, 2003; Gostin and Berkman, 2007; Kotalik, 2005; Ulmer and Liu, 2002). The stockpiles of antiviral drugs (and H1N1pdm influenza vaccine) during a pandemic event are expected to be in the hands of the industrialized nations. Countries with high population densities and limited access to quality health care like Mexico and/or India do not have the infrastructure to produce antiviral drugs to meet their needs during this type of emergencies. Poor nations did not get timely access to what one would consider minimally adequate drug stockpiles, equipment or vaccine supplies. In fact, without the efforts of the World Health Organization (WHO) a large number of nations would have had no access to the most basic pandemic medical supplies at all. The unusual levels of morbidity and mortality among young adults have raised additional concerns (e.g., Chowell et al., 2009a; Nishiura et al., 2009; Reichert et al., 2010). Who should be vaccinated first? The young, the elderly, expecting women, or emergency personnel? The usefulness of the World Health Organization's (WHO) definition of pandemic is now being questioned since it appears that the severity of this pandemic

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appears to be lower than that associated with past influenza pandemics.

The task of identifying "optimal" control strategies that minimize the impact of influenza pandemics through the *judicious* use of a limited antiviral drug supplies in combination with measures like isolation, is the focus of this manuscript. The parameters used in our dynamical systems model are initially calibrated using influenza pandemic data of the 1918 influenza pandemic (Chowell et al., 2006), our severe pandemic baseline scenario. The usefulness of intervention alternatives that involve the distribution of antiviral drugs and/or the isolation of hospitalized patients are explored. Optimal control theory (Fleming and Rishel, 1975; Lenhart and Workman, 2007; Pontryagin et al., 1962), with a history of successful applications in biological, medical and industrial problems (Behncke, 2000; Blayneh et al., 2009; Jung et al., 2002; Rowthorn et al., 2009), is the primary tool used in our analysis.

This paper is organized as follows: Section 2 describes the model including several control functions and defines the objective functionals used in the optimal control framework. We present and compare the results of numerical simulations for five scenarios in Section 3, and our thoughts and conclusions are summarized in Section 4.

2. Influenza pandemic model with controls

Optimal control theory is used to explore the impact of antiviral treatment and isolation strategies in situations that mimic 1918-like influenza pandemic scenarios (Chowell et al., 2006). We calibrate our model using parameter estimates that correspond to the worst influenza pandemic in record (Andreasen et al., 2008; Chowell et al., 2006; Mills et al., 2004). Intervention strategies (policies) are modeled by the functions $u_i(t)$ $(i=1,2,3)$ that externally control the number of clinical cases and hospitalizations over a prescribed finite time horizon. The underlying dynamic model classifies individuals as susceptible (S), exposed (E), clinically ill and infectious (I), asymptomatic (A), hospitalized (J), recovered (R), and death (D). The disease dynamics are modeled by the following set of nonlinear differential equations (Chowell et al., 2006):

$$\begin{cases} \dot{S}(t) = -\beta S(t)[I(t)+(1-\varepsilon_3 u_3(t))J(t)+qA(t)]/N(t) \\ \dot{E}(t) = \beta S(t)[I(t)+(1-\varepsilon_3 u_3(t))J(t)+qA(t)]/N(t)-kE(t) \\ \dot{A}(t) = k(1-\rho)E(t)-\gamma_1 A(t) \\ \dot{I}(t) = k\rho E(t)-(\alpha+\gamma_1+\varepsilon_1 u_1(t))I(t) \\ \dot{J}(t) = \alpha I(t)-(\gamma_2+\delta+\varepsilon_2 u_2(t))J(t) \\ \dot{R}(t) = \gamma_1(A(t)+I(t))+\gamma_2 J(t)+\varepsilon_1 u_1(t)I(t)+\varepsilon_2 u_2(t)J(t) \\ \dot{D}(t) = \delta J(t) \end{cases} \quad (1)$$

Susceptible individuals become infected at the rate $\beta S(t)(I(t)+(1-\varepsilon_3 u_3(t))J(t)+qA(t))/N(t)$ where β is the per capita transmission rate while q $(0<q\le 1)$ accounts for the "average" reduction in transmissibility among individuals in the asymptomatic class (A). The total population size at time t is $N(t)=S(t)+E(t)+I(t)+A(t)+J(t)+R(t)$ and therefore, homogeneous mixing between individuals means that the fraction $(I(t)+(1-\varepsilon_3 u_3(t))J(t)+qA(t))/N(t)$ denotes the "probability" of interacting with an infectious individual. The constant per-capita rate k models progression from the E class to the either the A or I infectious classes; the constant ρ $(0<\rho<1)$ budgets the rate of "progress" of individuals who move to either the I class or to the asymptomatic partially-infectious class A at the per-capita rate k. Asymptomatic cases progress to the recovered class at the per-capita rate γ_1 while clinically infectious individuals (class I) are hospitalized (reported) at the per-capita rate α or do recover without being diagnosed at the per-capita rate γ_1. Hospitalized individuals recover at the per-capita rate γ_2 or die at the per-capita rate δ. In other words, exponentially waiting times within each epidemic logical state are most often assumed. The controlling effort $u_1(t)$ alters the fraction of clinically infectious cases $(\varepsilon_1 I(t))$ receiving antivirals *per unit of time* while the control $u_2(t)$ alters the fraction of hospitalized individuals $(\varepsilon_2 J(t))$ getting antiviral treatment *per unit of time. It is assumed that both controls* achieve maximal per-capita efficacy antiviral rates when the controls equal to 1.

The isolation rate-modifying control factor, $(1-\varepsilon_3 u_3(t))$ quantifies the external effort put in preventing or limiting the rate of interaction between J and S individuals. Hence, in $\beta(1-\varepsilon_3 u_3(t))S(t)J(t)$, the parameter β denotes the maximal transmission rate per hospitalized and per susceptible individuals with $(1-\varepsilon_3 u_3(t))$ denoting the reduction in β generated by the external isolation control; ε_3 measures the effectiveness of $u_3(t)$ $(\varepsilon_3 \in (0,1)$ and $u_3(t)\in[0,1])$. The case when $\varepsilon_3 u_3(t)\approx 1$ corresponds to the most desirable scenario, that is, the situation when contacts between susceptible and hospitalized individuals are nearly "perfectly" avoided (prevented through effective isolation) reducing the total transmission rate effectively to zero. We assume the same baseline contact rates for both community members and hospitalized individuals while reductions in contact rates among hospitalized individuals is achieved via parameter ε_3 which models the efficacy of isolation strategies for hospitalized individuals. Hospitalization and effective isolation measures are not standard because the effective isolation of infectious individuals is rather costly and requires special facilities. As the number of cases increases, the availability of such specialized facilities would be limited and rare in resource limited nations. When it comes down to the I-class, one would expect some form of social distancing, which in turn may affect transmission. Large-scale social distancing measures like those put in place in Mexico are effective while in place but so costly for relatively low levels of pandemic severity. Hence, here we focus on the cost of recognized isolation strategies in hospital settings and do not assume that every hospital has the resources and the facilities to isolate a large number of hospitalized individuals.

The dynamics of Model (1) in the absence of control strategies is determined by the basic reproduction number $\mathcal{R}_0$, an average measure of the number of secondary cases generated by a primary infectious case during the infectious period in a completely susceptible population (Anderson and May, 1991; Brauer and Castillo-Chavez, 2000; Diekmann and Heesterbeek, 2000). Under the absence of control measures $(u_i(t)=0,\ i=1,2,3)$, the basic reproduction number of Model (1) is given by the expression

$$\mathcal{R}_0 = \beta\left\{\rho\left(\frac{1}{\gamma_1+\alpha}+\frac{\alpha}{(\gamma_1+\alpha)(\gamma_2+\delta)}\right)+(1-\rho)\left(\frac{q}{\gamma_1}\right)\right\} \quad (2)$$

This dimensionless quantity accounts for the number of secondary cases generated by three groups: the infectious (I), hospitalized (J), and asymptomatic (A), respectively (Chowell et al., 2006).

Parameter definitions and assumptions lead to Model (1) which involves a system of coupled nonlinear differential equations and three controls. The impact of the controls is explored via simulations of Model (1) parameterized in the context of the transmission dynamics of the 1918 influenza pandemic. The objective functional $\mathcal{F}$ formulates the optimization problem of interest, namely, that of identifying the most effective strategies. The overall pre-selected objective involves the minimization of the number of clinically infectious and hospitalized individuals at a minimal cost over a finite time interval $[0,T]$.

The objective functional $\mathcal{F}$ is given

$$\mathcal{F}(u_1(t),u_2(t),u_3(t)) = \int_0^T \left[C_1 I(t) + C_2 J(t) + \frac{W_1}{2}u_1^2(t) + \frac{W_2}{2}u_2^2(t) + \frac{W_3}{2}u_3^2(t)\right] dt \quad (3)$$

We choose (as it is customary) to model the control efforts via a linear combination of quadratic terms, $u_i^2(t)$ $(i=1,2,3)$. The constants C_1, C_2, and W_i $(i=1, 2, 3)$ are a measure of the relative cost of the interventions over $[0,T]$. The optimal control problem is that of finding optimal functions $(u_1^*(t), u_2^*(t), u_3^*(t))$ such that

$$\mathcal{F}(u_1^*(t),u_2^*(t),u_3^*(t)) = \min_{\Omega} \mathcal{F}(u_1(t),u_2(t),u_3(t)) \quad (4)$$

where
$\Omega = \{(u_1(t),u_2(t),u_3(t)) \in (L^2(0,T))^3 \| 0 \le u_1(t),u_2(t),u_3(t) \le 1,\ t \in [0,T]\}$
subject to the state equations (1) and appropriate initial conditions. Pontryagin's Maximum Principle is used to solve this optimal control problem and the derivation of the necessary conditions for its application are provided in Appendix A.

Five different control strategies are explored. This approach can be used to test various options. Here, however, we only look at the following five alternatives:

- Strategy 1: Antiviral treatment control on clinically infectious cases (control $u_1(t)$ alone).
- Strategy 2: Antiviral treatment control on hospitalizations (control $u_2(t)$ alone).
- Strategy 3: Isolation control on hospitalizations ($u_3(t)$ alone).
- Strategy 4: Two antiviral treatment controls on clinical cases and hospitalizations (controls $u_1(t)$ and $u_2(t)$).
- Strategy 5: Two antiviral treatment controls on clinical cases and hospitalizations together with isolation control (controls $u_1(t)$, $u_2(t)$, and $u_3(t)$).

The results of a single policy or multiple policies that combine antiviral and isolation controls are computed numerically. Strategies are implemented from the solutions of the associated optimality system which consists of a system of nonlinear ordinary differential equations involving state and adjoint equations (1) and (8). An iterative process used to solve each system. The state equations are solved using a forward method with given initial conditions for the state variables (1). The corresponding adjoint system is solved using a backward scheme with the Transversality Conditions (8) and (9). A convex combination of previously and currently computed controls is used to generate updated controls using the Optimality Equations (10) and lastly, the process is repeated until a pre-specified convergence criterion (10^{-5}) is satisfied. The default values for the initial conditions and model parameters are given in Table 1. Units are per day for all rates and baseline values are used throughout the manuscript unless otherwise indicated.

3. Numerical results

In this section we present the results of selected simulations generated by the numerical implementation of the intervention strategies described in Section 2 under unlimited and finite resource scenarios. Results of the sensitivity analyses on some of the model parameters in System (1) are given in Section 3.2. In this section we only report the sensitivity analyses associated with the unlimited antiviral resources scenarios.

3.1. Implications of treatments and interventions

We evaluate the impact of optimal antiviral treatments and isolation strategies for the dynamics of pandemic influenza under distinct degrees of transmissibility as measured by the basic reproduction number $\mathcal{R}_0$; first under the assumption that we have access to an unlimited supply of antiviral drugs. Estimates of the basic reproduction number $\mathcal{R}_0$ for pandemic influenza lie in the reasonable range 1.5–4 (Andreasen et al., 2008; Chowell et al., 2006; Chowell and Nishiura, 2008; Mills et al., 2004). The graphs of the four computed optimal controls under strategies 1, 2, 3, and 5 are shown in Fig. 1 (the parameter values used are provided in Table 1 with $\mathcal{R}_0 = 3.5$). The controls $u_1(t)$ and $u_2(t)$ model antiviral treatment efforts aimed at clinically infectious and hospitalized individuals, respectively. The control $u_3(t)$ manages the reduction in the generation of secondary cases resulting from hospitalized cases. The top left three graphs (A, B, and C) in Fig. 1 display the optimal control functions computed for Strategies 1, 2, and 3 (single control strategies). The results of implementing three control efforts simultaneously, Strategy 5, are illustrated in three graphs (D, E, and F).

In general, high reproduction numbers ($\mathcal{R}_0 > 2.5$) generate epidemics characterized by high epidemic peaks. The graphs (G, H, and I) in Fig. 1, compare the impact of each strategy on the epidemic state variables in the absence of controls when $\mathcal{R}_0 = 3.5$. These graphs show the daily number of clinical cases, hospitalizations, and deaths under no controls and under Strategies 1, 3, and 5 (Strategy 2 is omitted from the graph because it generates almost the same result as that under Strategy 1). Black

Table 1
Parameter definitions and baseline values (and their corresponding sources) used in numerical simulations.

Parameter	Description	Value	References
β	Transmission rate (days^{-1})	1.03–2.75	Chowell et al. (2006)
ρ	Proportion of clinical infections	0.5	Chowell et al. (2006)
q	Relative infectiousness of the asymptomatic class	0.003	Chowell et al. (2006)
k	Rate of progression to infectious (days^{-1})	0.53	Mills et al. (2004)
δ	Mortality rate (days^{-1})	0.01	Gani et al. (2005)
γ_1	Recovery rate (days^{-1}) for infectious class (days^{-1})	0.34	Chowell et al. (2006)
γ_2	Recovery rate for hospitalized class (days^{-1})	0.34	–
α	Diagnostic rate (days^{-1})	0.51	Chowell et al. (2006)
ε_1	Efficacy of antiviral treatment on clinically infectious individuals	0.5	Longini et al. (2004)
ε_2	Efficacy of antiviral treatment on hospitalized individuals	0.5	Longini et al. (2004)
ε_3	Efficacy of isolation	0.5	–
$S(0)$	Initial number of susceptible individuals	174 673	Chowell et al. (2006)
$E(0)$	Initial number of exposed individuals	207	Chowell et al. (2006)
$I(0)$	Initial number of infectious individuals	132	Chowell et al. (2006)
T	Total simulation duration (days)	200	–
C_i	Weight constants on I and J classes $(i=1,2)$	1	–
W_i	Weight constants on controls $(i=1,2,3)$	50	–

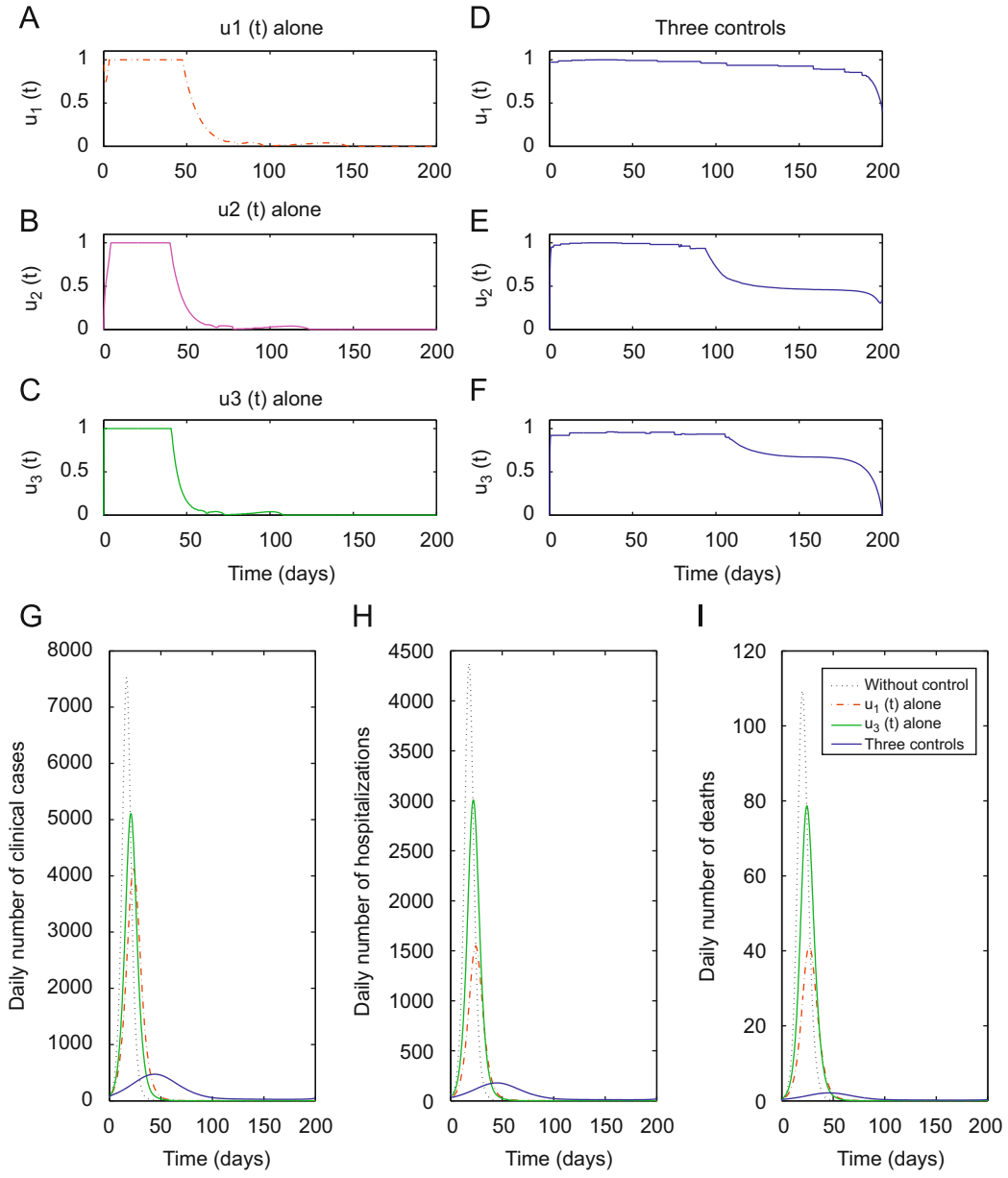

Fig. 1. A, B, and C show the optimal control functions as a function of time computed for Strategies 1, 2, and 3 using only *one* control function, respectively. Three optimal control functions implemented for Strategy 5 as a function of time are shown in D, E, and F. The bottom three graphs (G, H, and I) show the comparisons of the corresponding daily incidence in clinical, hospitalized, and disease-induced deaths under no controls with those generated with Strategies 1, 3, and 5. Optimal Strategy 5 (blue solid curves in G, H, I) shows significant reductions in all state solutions. Parameter values are given in Table 1 when $\mathcal{R}_0 = 3.5$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

dotted epidemic curves (under no interventions) are shown to highlight the difference from those generated via the implementation of optimal strategies. Strategy 5 (blue solid curve) shows significant reductions (about 90% reduction when compared to the no interventions scenario) in all three epidemics while Strategy 1 (red dashed-dotted curve) and Strategy 3 (green curve) generate reductions around the 30% level (when compared with the no intervention scenario). Strategy 1 does slightly better than Strategy 3 since hospitalization delays result in postponed isolations. Optimal strategies based on single controls (Strategies 1–3) demand the implementation of intensive efforts at the beginning of an outbreak (A, B, and C) followed by sudden reductions (most likely the result of high depletion in the levels of susceptibility of the population). The use of integrated control strategies (4 or 5) require a high level effort at the beginning that must be maintained for sustained periods of time, that is, longer than it would be required for policies based on Strategy 1 or 3. These intense efforts (Strategies 4 or 5) are followed by smooth reductions throughout the rest of the epidemic outbreak (D, E, and F).

Naturally, the optimal strategy is an implicit function of $\mathcal{R}_0$. Values of $\mathcal{R}_0 > 2.5$ generate outbreaks for which the optimal control requires the immediate implementation of full efforts (never effective enough). Efforts must be maintained for a short period of time in the case of Strategies 1, 2 and 3 *because* large $\mathcal{R}_0's$ quickly deplete the susceptible population. The use of a single optimal control does not have a significant impact comparatively speaking, that is, the use of integrated multi-strategies is more efficient. In the case of Strategy 5 (integrated control policy), the temporal profile of the optimal controls differ *because* the

simultaneous implementation of multiple controls while incapable of eliminating the possibility of an outbreak still manages to reduce the magnitude of the influenza epidemic peak by distributing the cases of infection and hospitalization over a broader window in time. Distributing the influenza case burden over long windows in time is highly desirable when the hospital resources (bed capacity and personnel) are limited.

The case of low $\mathcal{R}_0$'s ($\mathcal{R}_0 < 2.5$) can be handled optimally through the implementation of an initial full effort followed by a smooth effort reduction over the remaining epidemic duration (compare Fig. 1 for $\mathcal{R}_0 = 3.5$ with Fig. 2 for $\mathcal{R}_0 = 1.7$). The usefulness of controls over longer windows in time comes from the fact that for "low" values of $\mathcal{R}_0$ ($\mathcal{R}_0 < 2.5$ in this context) enough susceptible individuals remain available for the controls to make a difference (reduction in the generation of secondary cases).

Strategy 5 can effectively control influenza epidemics (no outbreak takes place) for low but realistic $\mathcal{R}_0$ pandemic values (for example, $\mathcal{R}_0 = 1.7$ in Fig. 2). The panels in Fig. 1 (G, H, and I) show that, nevertheless, the use of optimal controls will not prevent epidemic outbreaks (see the rise in the number of cases for $\mathcal{R}_0 = 3.5$) even under Strategy 5. The generation of reliable $\mathcal{R}_0$ estimates as early as possible helps assess the degree of effectiveness of optimal control policies. Knowledge of $\mathcal{R}_0$

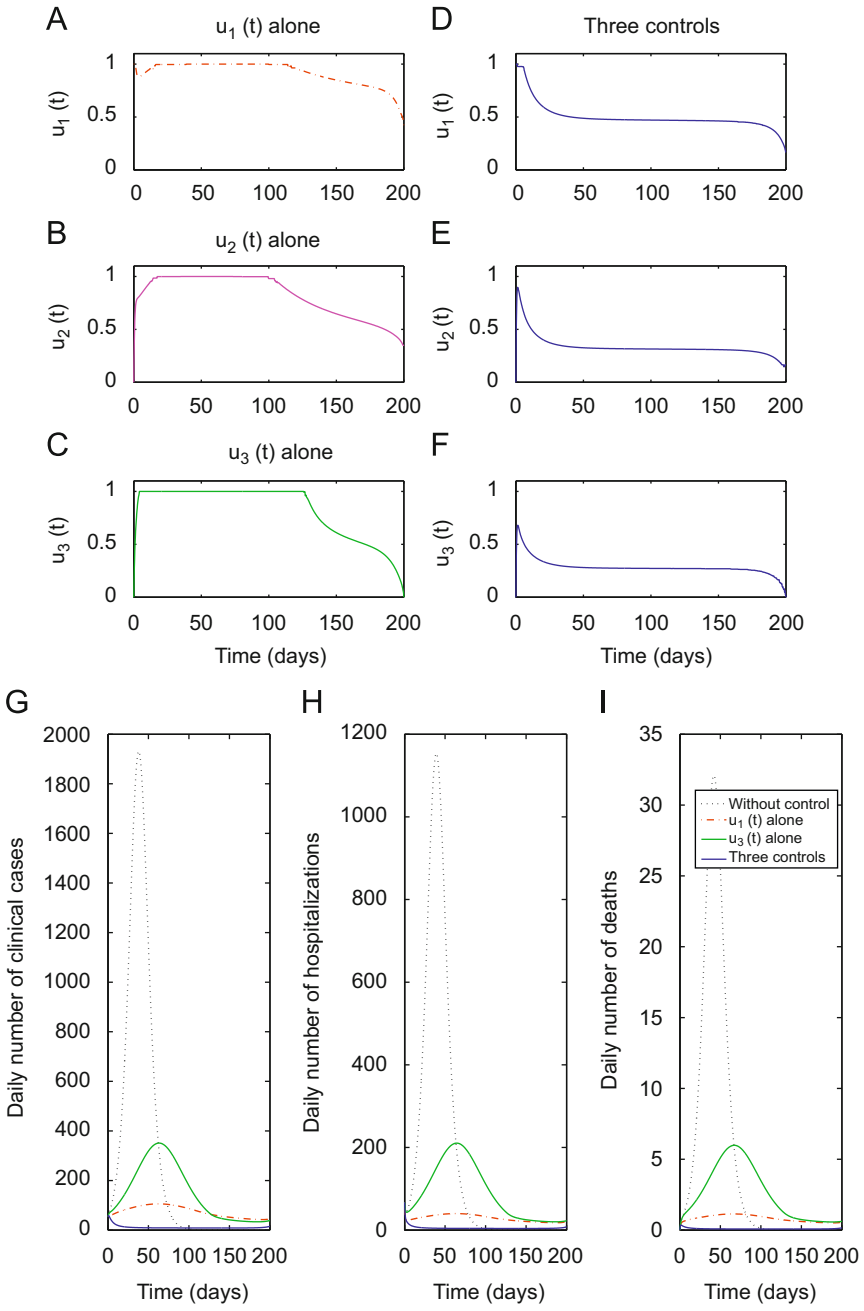

Fig. 2. A, B, and C show the optimal control functions as a function of time computed for Strategies 1, 2, and 3 using only *one* control function, respectively. Three optimal control functions implemented for Strategy 5 as a function of time are plotted in D, E, and F. The bottom three graphs (G, H, and I) show the comparisons of the corresponding daily incidence of clinical, hospitalized, and influenza related deaths under no controls with those generated with Strategies 1, 3, and 5. Optimal Strategy 5 (blue solid curves in G, H, I) shows significant reductions case incidence. Parameter values are given in Table 1 when $\mathcal{R}_0 = 1.7$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

estimates help assess the limitations of *optimal policies* in the presence of fast transmissible communicable diseases like influenza.

The impact of optimal Strategies 1–5 in terms of the cumulative number of clinical cases as a function of $\mathcal{R}_0$ is presented in Fig. 3. In Fig. 3A comparisons between the cumulative number of clinical cases (without interventions) and those generated under Strategies 1–5 as a function of $\mathcal{R}_0$ are shown; the black dot curve corresponds to the no interventions case; Strategy 3 corresponds to the red square curve. Strategy 1 (blue circle curve) generates slightly higher reductions than Strategy 2 (green triangle curve), that is, the use antiviral treatments for clinically infectious individuals can be more effective than their use in diagnosed cases in the unlimited resources case. Combined control strategies (Strategies 4 and 5) generate significant reductions in clinically infectious cases when compared to those generated via the use of single controls.

The total number of antiviral treatments used for each of the strategies was calculated and used as a measure of efficiency. Strategies 4 and 5 turned out to be quite efficient for values of $\mathcal{R}_0$ between 1.5 and 2.5 (low to moderate pandemic level) but hardly efficient for values of $\mathcal{R}_0$ in the range 2.5–4 (high pandemic level). Fig. 3B displays the cumulative number of antiviral treatments for Strategies 1, 2, 4, and 5. Strategy 1 (blue circled curve) uses about the same amount of antiviral treatments as Strategy 2 (green triangle curve) for the selected ranges of $\mathcal{R}_0$. A sudden increase takes place in the context of Strategy 4 (x curve) for $\mathcal{R}_0 > 2.5$. The joint implementation of isolation and antiviral treatment can significantly reduce the number of antiviral resources needed to execute the optimal strategy and therefore, as expected, Strategy 5 (diamond curve, antiviral treatments in combination with the isolation strategy) uses considerably less antiviral resources for the entire range of $\mathcal{R}_0$ values. This last result highlights the role of effective isolation strategies in regions with limited antiviral stockpiles.

The effectiveness of each strategy is also assessed via the percentage reduction (%) in the cumulative number of clinically infectious cases *relative* to the no intervention scenario. It is computed as the relative difference between the outcome without interventions versus the outcomes under Strategies 1–5. Fig. 3C illustrates this reduction (%) as a function of $\mathcal{R}_0$. It shows high reductions for low reproduction numbers regardless of the strategy. All five strategies generate more reductions of 75% or more at $\mathcal{R}_0 = 1.5$ but as $\mathcal{R}_0$ increases the benefits decrease under all strategies but not equally. For example, Strategies 4 and 5 generate improvements over the entire range of $\mathcal{R}_0$ values. Strategy 5 generates a reduction of about 90% for $\mathcal{R}_0$ values up to 3 while sustaining 50% reductions for $\mathcal{R}_0$ values in the range of 3–4.

The timing of the start of antiviral treatment, relative to the timing of the pandemic onset, is naturally quite important. The effect of time delays is evaluated as a function of the cumulative number of clinical cases at the end of the pandemic wave. The optimal control for each time delay case is recalculated under four different antiviral treatment starting times (0, 10, 20, 30 days after the epidemic onset). These scenarios are used to asses the impact of delayed intervention strategies relative to the start of a pandemic. Fig. 4 displays the cumulative number of clinical cases as a function of $\mathcal{R}_0$ for Strategies 1, 2, 4, and 5. Antiviral treatment starts in these simulations at time t, where $t=0$, 10, 20, 30 days after the pandemic onset, respectively (optimal controls under all strategies are recalculated for each time delay). All strategies are most effective if implemented earlier (at $t=0$ days). Delays in the availability of antiviral treatment leads to significant increases in the number of clinically infectious cases under all strategies (relative to the scenario of no interventions). Strategy 5 outperforms all selected strategies and it is highly efficient for the range $\mathcal{R}_0 = 1.5-3$ if implemented immediately ($t=0$ days). The range of $\mathcal{R}_0$ where optimal controls are effective, gets smaller as the start-time of antiviral treatment increases. For example, there is no efficient control strategy, if the start date for the use of antiviral treatment is $t=30$ days after the pandemic onset. This last observation highlights the importance of global surveillance in *real time* (Bettencourt et al., 2007) and increases the value and importance of the open approach used by the Mexican public health officials in the handling of the 2009 H1N1pdm influenza.

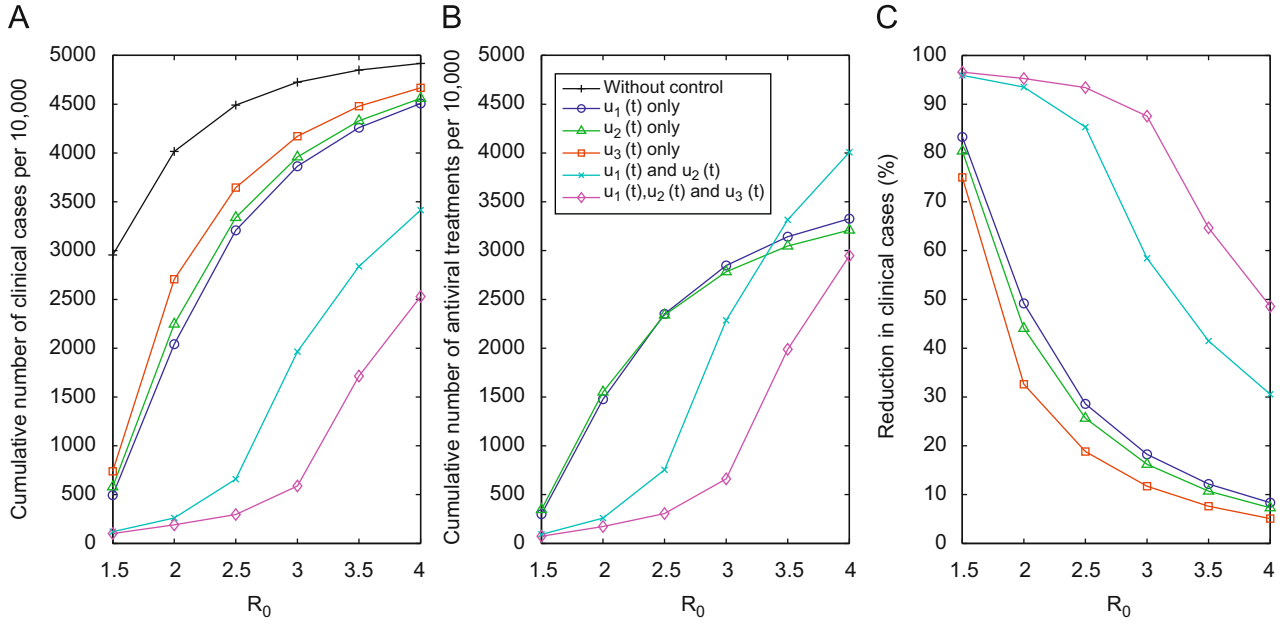

Fig. 3. A: the cumulative number of clinical cases under no control and the cumulative number of clinical cases under Strategies 1–5 as a function of $\mathcal{R}_0$. B: the cumulative number of antiviral treatment used for Strategies 1, 2, 4, and 5. C: the reduction in terms of the relative difference of the clinical cases with respect to the baseline scenario without interventions. Strategy 5 shows almost 90% reduction up to about $\mathcal{R}_0 = 3$, maintaining 50% reductions at a higher $\mathcal{R}_0 = 3-4$.

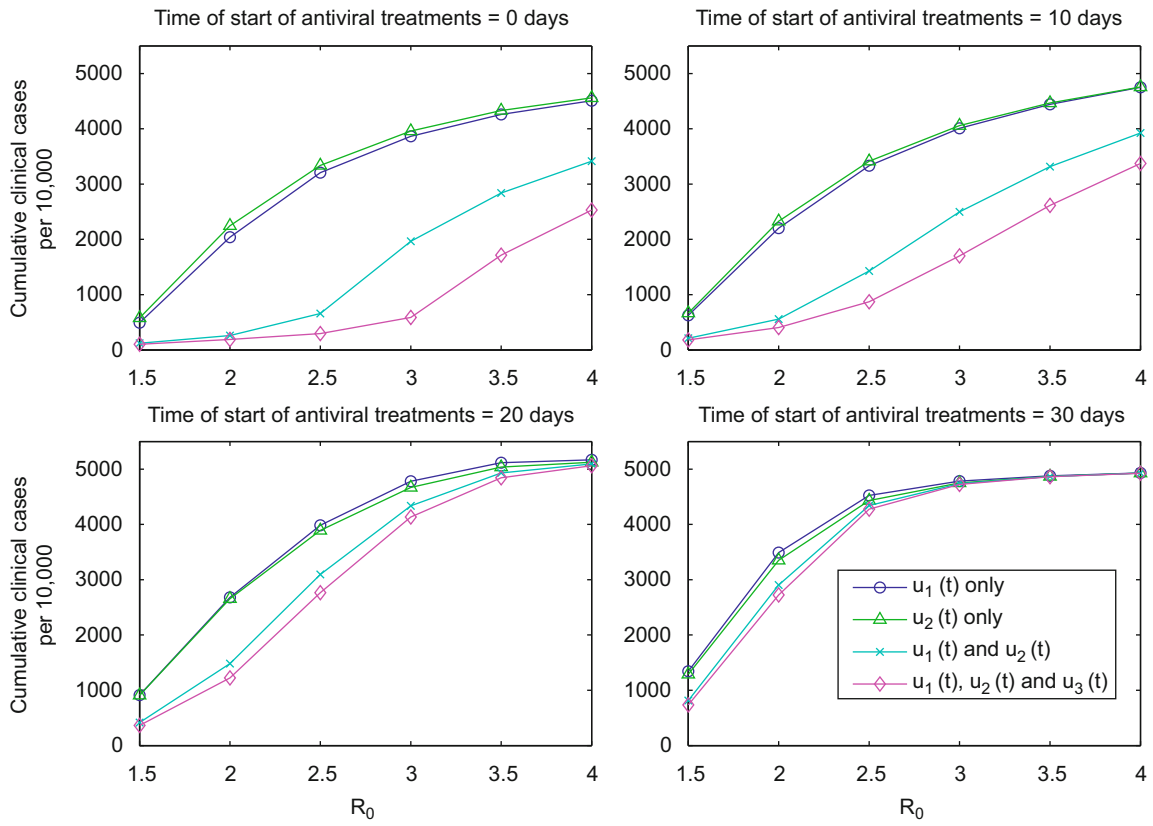

Fig. 4. The cumulative number of clinical cases are shown as a function of $\mathcal{R}_0$ for Strategies 1, 2, 4, and 5. Antiviral treatment starts at 0, 10, 20, 30 days after the pandemic onset. As expected all strategies are most effective when they are applied at 0 days of epidemic onset.

On the other hand, the initial handling of the SARS outbreak of 2003 (see Chowell et al., 2003 and references therein) left a lot to be desired.

3.2. Sensitivity analyses

The role of changes in model parameters is investigated by assessing their quantitative impact on the cumulative number of clinical cases via sensitivity analyses. The sensitivity of the weight constants on controls (parameters W_1, W_2, W_3), the proportion of clinical infections (parameter ρ), the relative infectiousness of the asymptomatic class (parameter q), and the efficacy of antiviral treatments and isolation strategies (parameters ε_1, ε_2, ε_3) has been assessed via extensive simulations. Figs. 5–8 provide a glance at the impact of varying these parameters in terms of the cumulative number of clinically infectious cases. The case of no interventions versus the scenarios generated when controls are in place are contrasted.

Effect of weight constants on controls: The five selected strategies are compared using distinct objective functionals (given in Appendix B). The role of weight constants for all five strategies is explored but the details of the analyses are not included since the outcome turned out not to be too sensitive to large variations in these weights. Instead, this lack of sensitivity to weight changes is illustrated via selected cases. The focus in this paper is on the role of relative costs as the exact costs are not always known.

Comparative results with the implementation of Strategy 1 under different weight constants on the control $u_1(t)$ are shown in Fig. 5 ($W_1=0.1$, 1, 50, 100, 1000 and no control for $R_0=2.0$). The value $W_1=1$ (or 0.1) results in an optimal solution that requires the use of maximum controls almost throughout the entire epidemic duration (see the blue solid curve and compare with the black dotted curve with $W_1=1000$). Fig. 6 shows the cumulative clinical cases (under all strategies and no interventions) as functions of $\mathcal{R}_0$ using three different weight constants, $W_1=W_2=W_3=10$, $W_1=W_2=W_3=50$, and $W_1=W_2=W_3=100$, respectively. The general shapes of the curves are similar with *slight* changes in magnitude. As we increase the weight constants, increasing the cost of treatments and isolation efforts, the overall number of clinical cases increases due to reductions in the intensity in the implementation of interventions.

We carried out a sensitivity analysis on W_3 fixing $W_1=W_2=50$ for Strategy 5 and obtained similar results. Initially, it was assumed that the cost of antiviral treatment in the I- and J- classes was the same (fixing $W_1=W_2=50$ from the previous simulations) but naturally as W_3 increases, the cost of the control u_3 increases resulting in a larger number of I- and J- infected individuals (from left to right). Differences in the cumulative number of the I- and J-individuals are not significant when W_3 varies in the range of 1–100. A sensitivity analysis on the weights (C_1 and C_2) for Strategy 5 was also carried out varying the costs (C_2) on the J-class while keeping the cost on the I-class fixed at $C_1=1$. We found that the effects of these changes on the cumulative number of individuals in the I- and J- classes were not very significant when C_2 was between 1 and 100.

Effect of the proportion of clinical infections: Three values for the clinical infections budgeting parameter ($\rho=0.25$, $\rho=0.5$, and $\rho=0.75$) are used to illustrate its impact on the cumulative number of clinical cases as functions of $\mathcal{R}_0$. A larger value of ρ indicates a stronger effort on the clinically infectious individuals for all strategies. Fig. 7 shows that the overall profiles of the graphs are very similar but *significant* changes in magnitude are

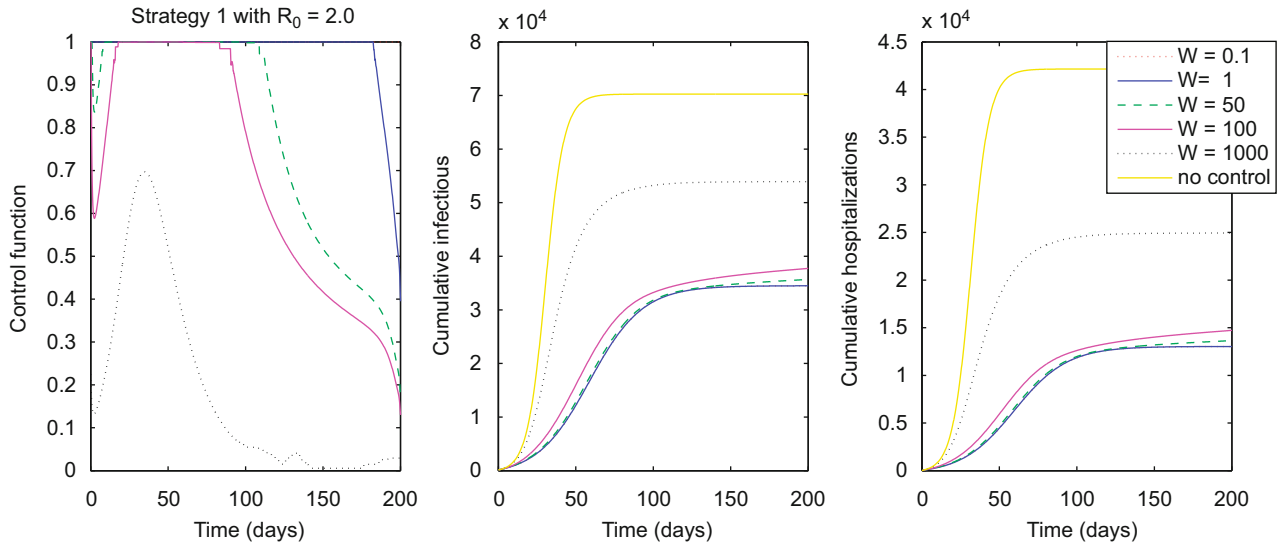

Fig. 5. Comparative results under Strategy 1 using different weight constants on the control ($W_1=0.1$, 1, 50, 100, 1000 and no control when $R_0=2.0$). The optimal control functions and, the corresponding cumulative number of clinical and hospitalized cases are shown.

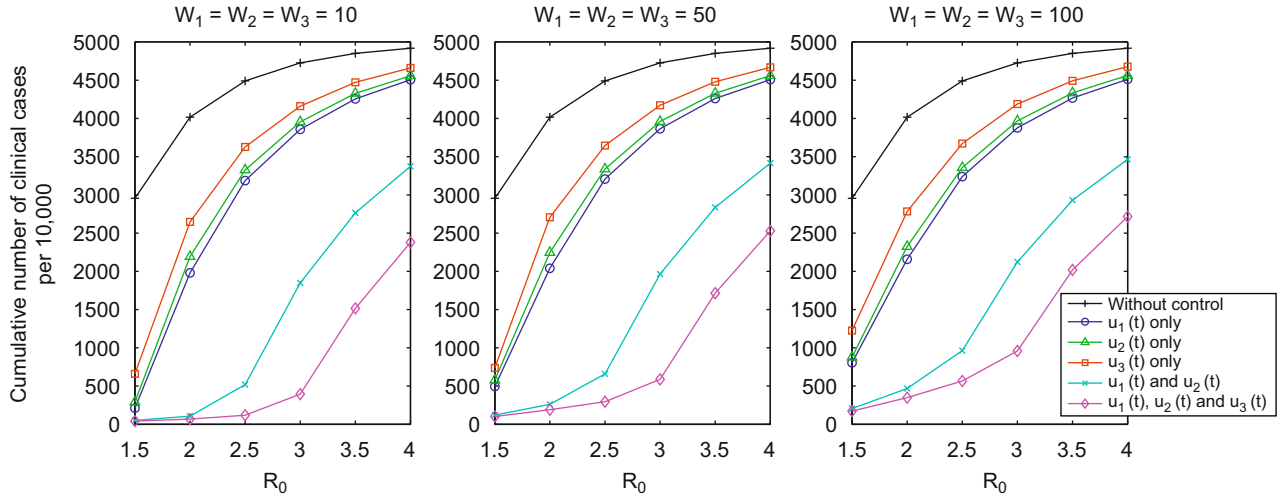

Fig. 6. The cumulative number of clinical cases are plotted as functions of $\mathcal{R}_0$ for three different values of weight constants, $W_1=W_2=W_3=10$, $W_1=W_2=W_3=50$, and $W_1=W_2=W_3=100$. The general shapes of the curves are very similar with slight changes in magnitude. As weight constants increase, costs of efforts increase and optimal controls decrease leading to higher morbidity.

expected. Larger values of ρ (closer to 1) generate larger cumulative numbers of clinical cases as displayed in the three graphs, from left to right. The cumulative number of clinical cases using $\rho=0.5$ is twice the number of those generated using $\rho=0.25$. At the value of $\rho=0.75$ twice the cumulative number of clinical cases than those generated when $\rho=0.5$ are obtained.

Effect of the relative infectiousness of the asymptomatic class: The relative infectiousness of the asymptomatic class, q, is varied from 0.003 to 0.3. Fig. 8 shows the cumulative number of clinical cases as functions of $\mathcal{R}_0$. The value $q=0.003$ (low transmissibility) is contrasted with the value $q=0.3$ (asymptomatic cases are 30% as effective at transmitting influenza as the clinical cases). A low value of $q=0.003$ leads to better controls on the cumulative number of clinical cases while $q=0.3$ makes the force of infection uncontrollably large rather quickly leaving not enough time to implement the controls (a large number of clinical cases are generated). At $q=0.3$, for example, there is a sudden increase for values of $\mathcal{R}_0>2$ for all strategies including Strategy 5 (diamond curve).

Effect of control efficacy: The effectiveness of antiviral treatment and isolation is explored in the range 0.25–0.75. The parameters (ε_1, ε_2) quantify the relative efficacy of antiviral treatment for clinical and hospitalized cases while ε_3 quantifies the relative efficacy of isolation strategies in hospitals. Fig. 9 illustrates the results of simulations for varying measures of efficacy. The larger the efficacy, the stronger the impact of control strategies in minimizing the number of clinical cases (three graphs from left and right). For $\varepsilon_1=\varepsilon_2=\varepsilon_3=0.75$, Strategies 1–5 generate significant reductions up to $\mathcal{R}_0=2$. Strategy 5 (diamond curve) supports dramatic reductions even for higher $\mathcal{R}_0$ levels. The performance of Strategies 1–5 with respect to each other varies as antiviral and isolation efficacious change (Fig. 9). The strategy of isolating infectious individuals in hospitals outperforms the strategy that focuses on antiviral treatment of hospitalized individuals at high isolation efficacy levels.

3.3. Suboptimal strategies with limited antiviral stockpiles

The expected number of antiviral courses available for pandemic control is limited everywhere particularly in developing

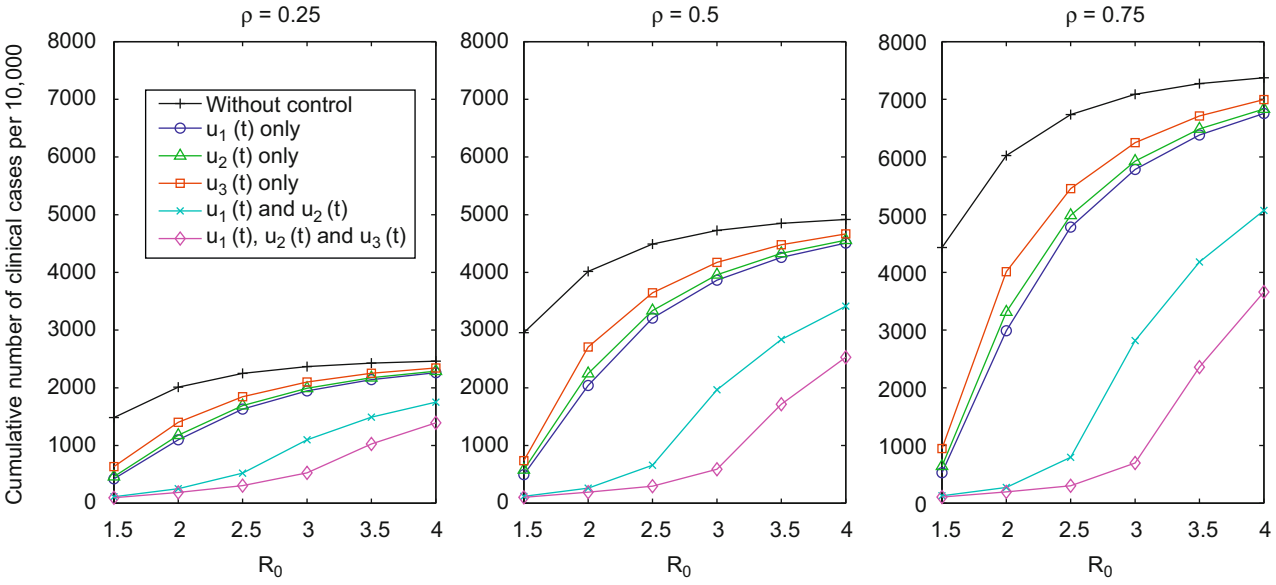

Fig. 7. The cumulative clinical cases are shown as a function of $\mathcal{R}_0$ for three different values of the proportion of clinical infections, $\rho = 0.25$, 0.5, and 0.75. The overall profile of the graphs are very similar with significant changes in magnitude. Larger values of ρ lead to larger numbers of clinical cases (three graphs from left to right). For example, the cumulative number of clinical cases using $\rho = 0.5$ is twice the number of that using $\rho = 0.25$ and similarly, $\rho = 0.75$ gives almost twice the number of clinical cases as the scenario using $\rho = 0.5$.

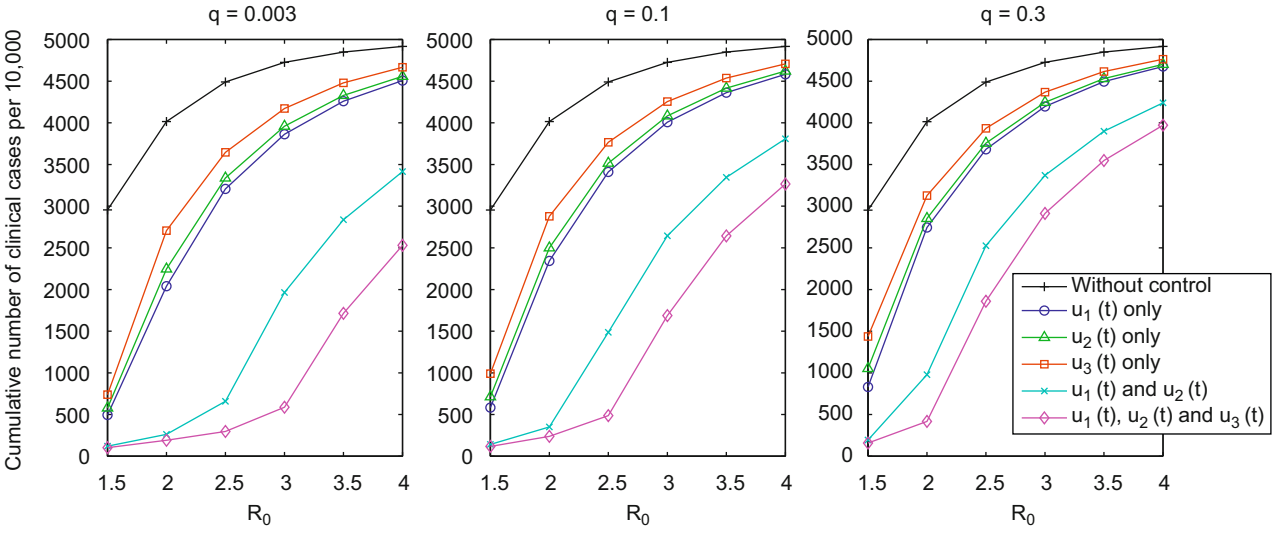

Fig. 8. The cumulative clinical cases are shown as a function of $\mathcal{R}_0$ for three different values of the relative infectiousness of asymptomatic cases, $q = 0.003$, 0.1, and 0.3. Clearly, using the low value of $q = 0.003$ gives us better control on the cumulative number of clinical cases. On the other hand using $q = 0.3$, the force of infection becomes large quickly leading to a larger number of clinical cases.

nations. They are almost not available in the poorest nations. Experimenting with scenarios that account for access to limited stockpiles of antiviral resources can be carried out in the framework introduced in this paper. The rest of this section focuses on scenarios of limited amount of antiviral resources; enough to provide antiviral coverage levels in the range of 5–30%. Two *suboptimal* strategies involving the exclusive use of antiviral treatment on the clinically infectious class are considered. These *suboptimal* strategies are defined in terms of the optimal control solution generated in the absence of restrictions (Section 3.1). Suboptimal Strategy 1 or SS1 (maximal effort) is constructed from the optimal solution in a subinterval $[0,T^*]$ where T^* is less than or equal to T, jumping to zero at T^*, the time when antiviral drugs are depleted. We set the controls equal to zero (in this limited resources case) and solve the state system forward in time for the remaining of the duration of the epidemic (when $t > T^*$). Suboptimal Strategy 2 or SS2 (uniformly distributed) uses a preselected fixed fraction of the antiviral treatment profile from the implementation of the full optimal control policy. The limited resources scenario can also be approached from a constrained optimization problem perspective which will be discussed elsewhere.

Fig. 10 presents the results generated under the full optimal control and under the two suboptimal approaches (SS1 and SS2) for Strategy 1. The full optimal strategy uses 28% antiviral coverage when $\mathcal{R}_0 = 3$. Fig. 10A compares the number of daily clinical cases using the full optimal (solid curve), SS1 (dotted curve) and SS2 (dashed-dotted curve). Fig. 10B plots each antiviral

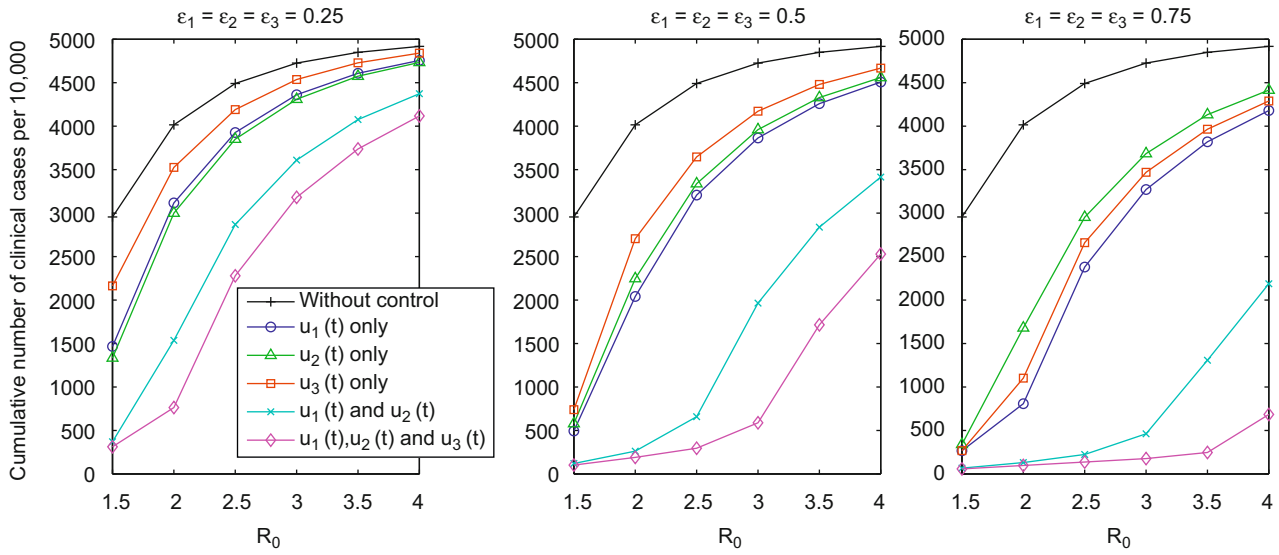

Fig. 9. The cumulative number of clinical cases are displayed as a function of $\mathcal{R}_0$ for three different values of efficacy, $\varepsilon_1=\varepsilon_2=\varepsilon_3=0.25$, $\varepsilon_1=\varepsilon_2=\varepsilon_3=0.5$, and $\varepsilon_1=\varepsilon_2=\varepsilon_3=0.75$. Note that using $\varepsilon_1=\varepsilon_2=\varepsilon_3=0.75$, Strategy 5 (diamond curve) gives a dramatic reduction even at high $\mathcal{R}_0$ values.

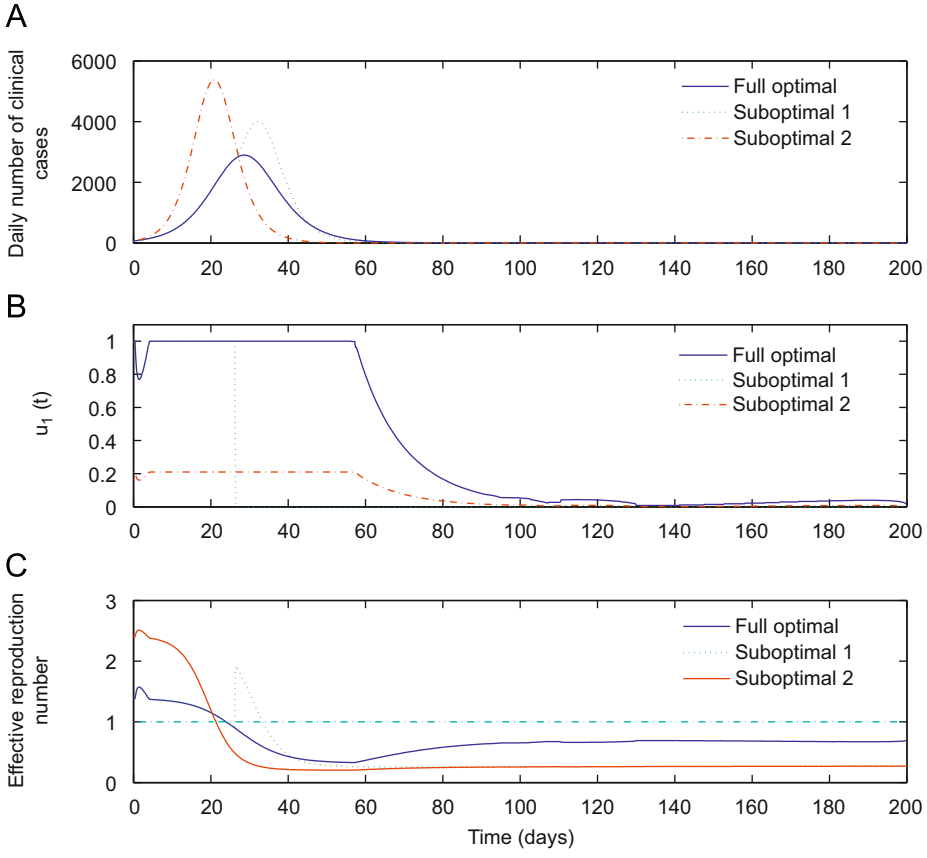

Fig. 10. A: The number of daily clinical cases are compared using Strategy 1 for the full optimal and corresponding two suboptimal solutions. B: antiviral controls as a function of time are plotted for the full optimal and corresponding two suboptimal approaches. The full optimal and two suboptimal controls use 28% and 15% of antiviral coverage of total population size, respectively; the suboptimal control 1 (SS1) is taking its maximum effort at the beginning of epidemics while the suboptimal control 2 (SS2) uses 22% of the full optimal control for the entire epidemic duration. C: the effective reproduction numbers as a function of time are shown for the full optimal and two suboptimal strategies.

treatment schedule as a function of time. The suboptimal control profiles of antiviral treatment are limited to 15% antiviral coverage of the total population size; SS1 (a maximal effort) takes maximum usage at the beginning of epidemics while SS2 (a distributed effort) uses 22% of the full optimal control effort. The effective reproduction number given by the following expression

$$\mathcal{R}(t)=\frac{S(t)}{N(t)}\beta\left\{\rho\left(\frac{1}{\gamma_1+\alpha}+\frac{\alpha}{(\gamma_1+\alpha)(\gamma_2+\delta)}\right)+(1-\rho)\left(\frac{q}{\gamma_1}\right)\right\} \tag{5}$$

captures the role of the time-dependent fraction of susceptible individuals in the population, $S(t)/N(t)$. In order to keep track of the impact of the controls, we evaluate the effective reproduction number over time in the presence of controls. The curves exhibiting the changes in the effective reproduction numbers as a function of time are plotted in Fig. 10C under the optimal (unlimited antiviral coverage) and the two suboptimal strategies (limited antiviral coverage). Interestingly, after antiviral resources have ran out, a secondary increase in the daily number of clinical cases (reflected in the effective reproduction number under SS1) is observed. This jump is consistent with other reports (Handel et al., 2007). However, as pointed out in McCaw et al. (2008), under a limited antiviral stockpile, SS1 reduces the epidemic peak size and delaying the timing of its occurrence; not the same result under SS2. Naturally, the implementation of intense antiviral treatments (maximal efforts) as early as possible reduces the overall pandemic impact.

The impact of varying the antiviral coverage on the cumulative number of clinically infectious individuals is investigated. Results obtained using SS1 are given in Figs. 11 and 12. Fig. 11 presents the cumulative number of clinical cases as a function of $\mathcal{R}_0$ for three different antiviral coverage levels, 10%, 20% and 30%. The overall results are similar to those obtained using unlimited antiviral resources when $\mathcal{R}_0 < 2.5$. Fig. 11A and B with antiviral coverages (10%, 20%) show significant increases in number of clinically infectious individuals using Strategy 4 ($u_1(t)$ and $u_2(t)$) when $\mathcal{R}_0 > 2.5$. Strategy 3 (isolation) is slightly more efficient than Strategies, 1 2, and 4, (antiviral treatments) for higher reproduction numbers (limited antiviral resources A, B). Fig. 11C (high antiviral coverage of 30%) shows almost the same results as those obtained under the scenario assuming unlimited antiviral resources. The importance of implementing an effective isolation strategy in the face of limited or absent medical resources is critical.

The reduction in the number of clinical cases under different strategies with respect to the baseline scenario of no interventions using a limited antiviral stockpile is quantified. Fig. 12 summarizes the relative reduction as a function of $\mathcal{R}_0$ for various levels of antiviral coverage. Higher relative reductions are observed for lower reproduction numbers in the presence of high levels of antiviral coverage (all strategies show more than 80% reductions in the number of clinical cases at $\mathcal{R}_0 = 1.5$). As $\mathcal{R}_0$ increases (or as antiviral coverage decreases), smaller reductions are observed for all strategies. However, Strategies 4 and 5 still generate excellent reductions (90%) for $\mathcal{R}_0$ values in the range of 1.5–2.5.

4. Discussion

Mitigating the impact and spread of the ongoing influenza A (H1N1) pandemic was on the minds of every newscaster, government official, aspiring politician, public health officials and literally billions of individuals around the world just a couple of months ago. The rate of growth/spread of influenza A(H1N1) news reports even surpassed the rate of growth of this new strain of influenza A around the world (Ginsberg et al., 2009). The rather unusual age-dependent patterns of spread, morbidity and mortality observed around the world added to the levels of uncertainty that are inherently common in health emergencies (Chowell et al., 2009a, b; Nishiura et al., 2009, 2010).

Issues being confronted in the face of health emergencies include the fact that not all clinical cases are diagnosed during an outbreak. A detailed analysis of missing data shows that a confident assessment of the magnitude and severity of a pandemic in real time poses serious challenges (Bettencourt et al., 2007). Further even when effective diagnostic tools are available, it is not possible to mount an appropriate response fast enough to stop the global spread of influenza. Medical services, even in the wealthiest of nations, do not have the capability of responding with high degree of effectiveness to influenza pandemics in the time scales of interest which is a serious national security concern (Banks and Castillo-Chavez, 2003). Public health policies must factor in the negative impact of time delays that are generated at multiple levels (lags between symptoms onset and diagnosis; delays in reporting; limited capacity of emergency facilities and availability of antiviral medications and delays in access to the vaccine delivery system). Mathematical models provide viable quick, cheap and effective ways of evaluating the consequences of local decisions, in the presence of multiple limiting factors, on disease dynamics at multiple levels of organization. Mathematical models can be used to build an array of model-ranked responses to questions like: what is the impact of the timing of start of interventions on

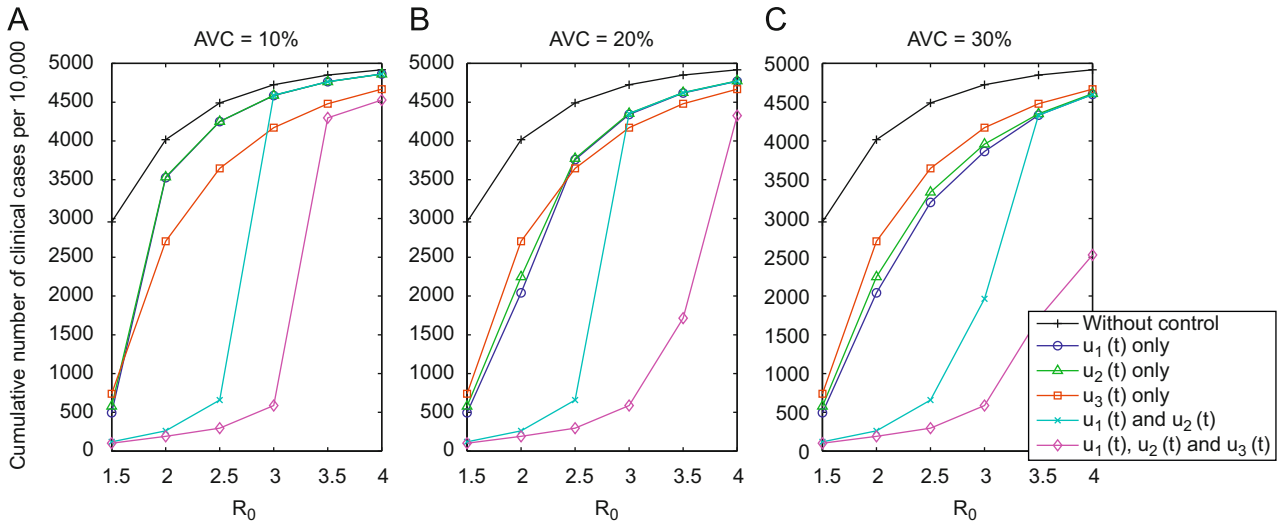

Fig. 11. The cumulative number of clinical cases are compared as a function of $\mathcal{R}_0$ for three different antiviral coverages, 10%, 20% and 30%. The overall results are similar to those obtained assuming an unlimited antiviral stockpile when $\mathcal{R}_0 < 2.5$. A and B with less antiviral coverage show significant increases in the number of clinically infectious individuals using Strategy 4 ($u_1(t)$ and $u_2(t)$) when higher $\mathcal{R}_0 > 2.5$. Note that Strategy 3 (isolation interventions) is more efficient than Strategies, 1 2, and 4, (antiviral treatments) in the range of higher reproduction numbers due to limited antiviral resources (A, B).

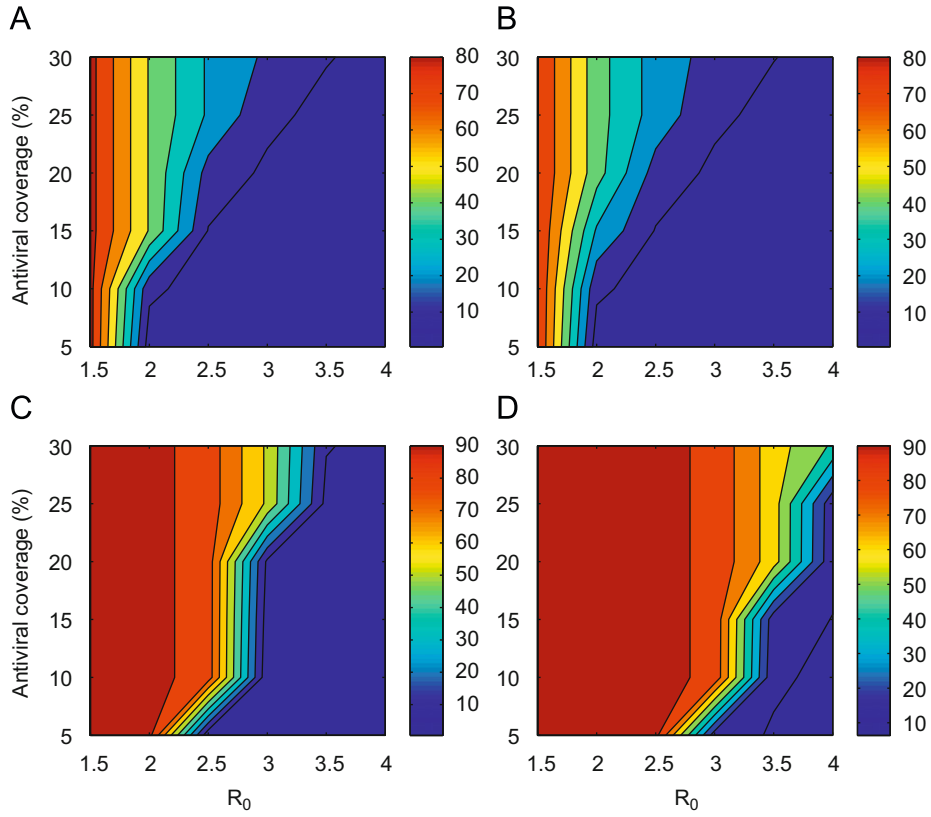

Fig. 12. The relative difference of cumulative clinical cases (%) between the baseline scenario (no interventions) and Strategies 1, 2, 4, and 5 (using SS1) as a function of $\mathcal{R}_0$ and antiviral coverage (5–30%). As $\mathcal{R}_0$ increases (or as antiviral coverage decreases), smaller reductions are observed for all strategies.

morbidity and mortality? Are there substantial quantitative differences that emerge from the use of single versus integrated control intervention strategies? Are there quick and effective ways of assessing the potential "severity" or transmissibility of an emergent disease? Furthermore, when policies do not seem to be working well, is the situation due just to the timing of interventions put in place? Can some transmissible diseases easily derail the potential effectiveness of optimal strategies even if they are effectively implemented? Or how can developing or poor nations cope with health emergencies?

Estimating the basic reproductive number, $\mathcal{R}_0$ is a first step in the process of assessing the potential impact of control interventions. Current data suggest that the range of estimated values for the basic reproductive number ($\mathcal{R}_0$) for the ongoing H1N1 pandemic is within a reasonable range and consequently, the timely implementation of optimal control measures could make a difference. The distance between theory and practice however is still huge. Many affected nations lack access to sufficient antiviral drug stockpiles or adequate isolation facilities. The delays in the distribution of minimally adequate H1N1pdm influenza vaccine levels (in countries lucky enough to have the funds to purchase them) mean that their impact cannot be very effective. Fortunately, the apparent "mildness" of this pandemic has accidentally reduced the impact of global inequities.

Some patterns emerge from our analyses. Simulation results suggest that the treatment of clinical cases in a community (that must select among the strategies proposes in this paper) provides larger reductions in the pandemic attack rate than focusing antiviral resources on hospitalized individuals. Model simulations for reasonable "pandemic" $\mathcal{R}_0$ values show that the use of integrated mitigation policies is *far superior* quantitatively speaking than the use of single policies albeit. On the other hand, there is not much that can be done to mitigate the impact of an influenza pandemic when $\mathcal{R}_0 > 2$. This last observation may be of critical importance to policy makers and government officials (they should not promise what cannot be delivered). Decision makers should routinely use estimates of $\mathcal{R}_0$ to assess the expected impact of planned mitigation efforts.

It is abundantly clear that putting in place an effective isolation strategy is rather effective particularly if antiviral medications are limited or scarce. The development of real time surveillance methods is therefore critically important since the timing of interventions is the most sensitive factor for stopping the spread of influenza (Bettencourt et al., 2007; Zeng et al., 2007). The implementation of alternative cost effective measures is essential if we are to deal effectively with global health threats of this nature. A recent article (Tracht et al., 2010) highlights the tremendous impact that the systematic use of face masks can have in reducing pandemic spread.

High values of the basic reproduction number ($\mathcal{R}_0$) are bad news because the need for the *immediate* implementation of control efforts becomes our "only" hope. Outbreaks associated with relative low values of $\mathcal{R}_0$ on the other hand are extremely likely to respond to control measures that are delivered within "reasonable" time windows. Obviously, the sooner a control policy is implemented in either case the better.

We have identified patterns in the delivery of optimal control strategies. The use of single controls (Strategies 1–3) demand intensive maximal sustained efforts (optimal control) at the beginning of epidemics. The use of integrated mitigation strategies (Strategies 4 or 5) require a high level effort at the beginning followed by a smoothly reduced control effort over the course of the epidemic outbreak. The use of single strategies, particularly when $\mathcal{R}_0$ is large, does not manage to prevent large epidemic peaks (a nightmare for health care facilities if symptoms are severe). When $\mathcal{R}_0$ is large, susceptible populations must be

brought below the critical mass needed to sustain an outbreak *rather quickly*. The simultaneous implementation of multiple strategies is more effective at reducing the number of secondary infections than the use of single-control policies. Integrated control approaches help maintain the susceptible population below the critical mass needed to sustain an outbreak for "longer" windows in time, hence reducing the likelihood of huge epidemic peaks. The availability of a viable pool of susceptible individuals over longer windows in time mean that controls remain viable since there are still infections to prevent. The use of isolation strategies with high levels of efficacy is more effective in reducing transmission rates than the use of strategies that provide antiviral treatment to hospitalized individuals.

The development of policies when the resources are limited benefitted from our study of the "unlimited" resource scenarios. Two "suboptimal" strategies were proposed and their impact explored under the five pre-selected strategies. We found that under both of these protocols (maximal and distributed) intensive antiviral treatments implemented at the beginning of an epidemic manage to reduce the magnitude while delaying the epidemic peak. Simulations show that the impact of the epidemic is dramatically reduced as the amount of antiviral resources available increases particularly if the delivery of such antiviral drugs is carried out in combination with an isolation strategy in hospital settings.

The impact of antiviral treatment on the emergence of antiviral resistance, not addressed here, has been explored and remains a matter of great concern (Arinaminpathy and McLean, 2008; Arino et al., 2009; McCaw et al., 2008; Moghadas et al., 2008; Wu et al., 2009). It has been shown, for example, that the use of a single type of antiviral treatment in combination with a second drug is quite effective in reducing antiviral resistance levels (McCaw et al., 2008; Wu et al., 2009) in some cases. However, significant levels of uncertainty associated with the timing of emergence of antiviral resistance for specific influenza strains remain (Sepkowitz, 2009; Weinstock and Zuccotti, 2009).

The focus of this study has been on identifying the benefits that come with the implementation of pandemic influenza mitigation policies that combine pharmaceutical and non-pharmaceutical interventions in the context of unlimited and *limited* resources. Efforts to mitigate the impact of an influenza pandemic can be successful specially if the basic reproductive number ($\mathcal{R}_0$) is not an outlier. Mitigation is possible if the timing of interventions is "fast" enough and if the policy involves the use of more than one intervention strategy—an integrated management approach. No plan is plausible unless minimal resources are available. The effects of early interventions in any nation provides benefits to the world. The first case of influenza H1N1most likely arrived in Japan on May 9, 2009 with multiple intervention strategies put in place on May 16, 2009. The fast response of Mexican officials and the sharing of information and knowledge across the world certainly helped to activate and increase the levels of preparedness in the Southern Hemisphere where the novel pandemic virus arrived a few months later but it also helped Japan and other countries where it arrived just a few weeks after it was reported in Mexico.

Acknowledgements

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Appendix A

The goal is to minimize the number of clinically infectious and hospitalized individuals over a finite time interval $[0,T]$ at a minimal cost of efforts during the course of a single influenza epidemic outbreak. The objective functional $\mathcal{F}$ is defined in Eq. (3). Our problem is to find optimal controls, $(u_1^*(t), u_2^*(t), u_3^*(t))$, such that

$$\mathcal{F}(u_1^*(t),u_2^*(t),u_3^*(t)) = \min_{\Omega}\mathcal{F}(u_1(t),u_2(t),u_3(t)) \tag{6}$$

where $\Omega = \{(u_1(t),u_2(t),u_3(t)) \in (L^2(0,T))^3 \| 0 \le u_1(t),u_2(t),u_3(t) \le 1, t \in [0,T]\}$ subject to the state equations (1) with initial conditions. Given the criterion (3) and the regularity of the system of equations (1), the existence of optimal controls is guaranteed by standard results in control theory (Fleming and Rishel, 1975). The necessary conditions that optimal solutions must satisfy are derived from Pontryagin's Maximum Principle (Pontryagin et al., 1962). This principle converts the problem (6) into the problem of minimizing the Hamiltonian H given by

$$\begin{aligned} H = {} & C_1 I + C_2 J + \frac{W_1}{2}u_1^2(t) + \frac{W_2}{2}u_2^2(t) + \frac{W_3}{2}u_3^2(t) \\ & + \lambda_1(t)\{-\beta S[I+(1-\varepsilon_3 u_3(t))J + qA]/N\} \\ & + \lambda_2(t)\{\beta S[I+(1-\varepsilon_3 u_3(t))J + qA]/N - kE\} \\ & + \lambda_3(t)\{k(1-\rho)E - \gamma_1 A\} + \lambda_4(t)\{k\rho E - (\alpha+\gamma_1+\varepsilon_1 u_1(t))I\} \\ & + \lambda_5(t)\{\alpha I - (\gamma_2+\delta+\varepsilon_2 u_2(t))J\} \end{aligned} \tag{7}$$

From this Hamiltonian and Pontryagin's Maximum Principle (Pontryagin et al., 1962), we obtain

Theorem 1. *There exist optimal controls* $(u_1^*(t), u_2^*(t), u_3^*(t))$ *and corresponding solutions,* S^*, E^*, A^*, I^*, J^*, R^*, *and* D^* *that minimizes* $\mathcal{F}(u_1(t),u_2(t),u_3(t))$ *over* Ω. *In order for the above statement to be true, it is necessary that there exist continuous functions* $\lambda_i(t)$ *such that*

$$\begin{aligned} \dot{\lambda}_1(t) &= (\lambda_1(t)-\lambda_2(t))(\beta[I+(1-\varepsilon_3 u_3(t))J+qA]/N), \\ \dot{\lambda}_2(t) &= \lambda_2(t)k - \lambda_3(t)k(1-\rho) - \lambda_4(t)k\rho, \\ \dot{\lambda}_3(t) &= \lambda_1(t)(\beta qS/N) - \lambda_2(t)(\beta qS/N) + \lambda_3(t)\gamma_1, \\ \dot{\lambda}_4(t) &= -C_1 + \lambda_1(t)(\beta S/N) - \lambda_2(t)(\beta S/N) + \lambda_4(t)(\alpha+\gamma_1+\varepsilon_1 u_1(t)) - \lambda_5(t)\alpha, \\ \dot{\lambda}_5(t) &= -C_2 + \lambda_1(t)(\beta(1-\varepsilon_3 u_3(t))S/N) - \lambda_2(t)(\beta(1-\varepsilon_3 u_3(t))S/N) \\ &\quad + \lambda_5(t)(\delta+\gamma_2+\varepsilon_2 u_2(t)), \end{aligned} \tag{8}$$

with the transversality conditions,

$$\lambda_i(T) = 0, \quad i = 1,\ldots,5. \tag{9}$$

Furthermore,

$$\begin{aligned} u_1^*(t) &= \min\left\{\max\left\{0, \varepsilon_1 I\frac{\lambda_4}{W_1}\right\}, 1\right\}, \\ u_2^*(t) &= \min\left\{\max\left\{0, \varepsilon_2 J\frac{\lambda_5}{W_2}\right\}, 1\right\}, \\ u_3^*(t) &= \min\left\{\max\left\{0, \varepsilon_3 JS\frac{\lambda_2-\lambda_1}{NW_3}\right\}, 1\right\}. \end{aligned} \tag{10}$$

Proof. The existence of optimal controls follows from Corollary 4.1 of Fleming and Rishel (1975) since the integrand of J is a convex function of (u_1, u_2, u_3) and the state system satisfies the *Lipshitz* property with respect to the state variables since state solutions are L^∞ bounded. The following can be derived from the

Pontryagin's Maximum Principle (Pontryagin et al., 1962):

$$\frac{d\lambda_1(t)}{dt} = -\frac{\partial H}{\partial S}, \quad \frac{d\lambda_2(t)}{dt} = -\frac{\partial H}{\partial E}, \quad \frac{d\lambda_3(t)}{dt} = -\frac{\partial H}{\partial A},$$

$$\frac{d\lambda_4(t)}{dt} = -\frac{\partial H}{\partial I}, \quad \frac{d\lambda_5(t)}{dt} = -\frac{\partial H}{\partial J}$$

with $\lambda_i(T)=0$ for $i=1,\ldots,5$ evaluated at the optimal controls and corresponding states, which results in the Adjoint System (8). The Hamiltonian H is minimized with respect to the controls at the optimal controls, so we differentiate H with respect to u_1, u_2, and u_3 on the set Ω, respectively, giving the following optimality conditions:

$$\frac{\partial H}{\partial u_1} = W_1 u_1 + \varepsilon_1 I(-\lambda_4) = 0 \quad \text{at } u_1 = u_1^*,$$

$$\frac{\partial H}{\partial u_2} = W_2 u_2 + \varepsilon_2 J(-\lambda_5) = 0 \quad \text{at } u_2 = u_2^*,$$

$$\frac{\partial H}{\partial u_3} = W_3 u_3 + (\lambda_1 - \lambda_2)\varepsilon_3 J\frac{S}{N} = 0 \quad \text{at } u_3 = u_3^*,$$

Solving for u_1^*, u_2^*, and u_3^* we obtain

$$u_1^* = \varepsilon_1 I\frac{\lambda_4}{W_1}, \quad u_2^* = \varepsilon_2 J\frac{\lambda_5}{W_2}, \quad \text{and} \quad u_3^* = \varepsilon_3 JS\frac{\lambda_2-\lambda_1}{NW_3}.$$

By standard variation arguments with the control bounds, we obtain the properties (10).

Appendix B

Five strategies and corresponding objective functionals in Section 2 are given: Strategies 1–5 use the objective functionals (11)–(15), respectively.

- Strategy 1: Antiviral treatment control on clinically infectious cases (control $u_1(t)$ alone).
- Strategy 2: Antiviral treatment control on hospitalizations (control $u_2(t)$ alone).
- Strategy 3: Isolation control on hospitalizations (control $u_3(t)$ alone).
- Strategy 4: Two antiviral treatment controls on clinically infectious cases and hospitalizations (controls $u_1(t)$ and $u_2(t)$).
- Strategy 5: Two antiviral treatment controls on clinically infectious cases and hospitalizations together with isolation control (controls $u_1(t)$, $u_2(t)$, and $u_3(t)$).

$$\mathcal{F}(u_1(t)) = \int_0^T \left[I(t) + \frac{W_1}{2}u_1^2(t)\right] dt. \tag{11}$$

$$\mathcal{F}(u_2(t)) = \int_0^T \left[J(t) + \frac{W_2}{2}u_2^2(t)\right] dt. \tag{12}$$

$$\mathcal{F}(u_3(t)) = \int_0^T \left[J(t) + \frac{W_3}{2}u_3^2(t)\right] dt. \tag{13}$$

$$\mathcal{F}(u_1(t),u_2(t)) = \int_0^T \left[C_1 I(t) + C_2 J(t) + \frac{W_1}{2}u_1^2(t) + \frac{W_2}{2}u_2^2(t)\right] dt. \tag{14}$$

$$\mathcal{F}(u_1(t),u_2(t),u_3(t)) = \int_0^T \left[C_1 I(t) + C_2 J(t) + \frac{W_1}{2}u_1^2(t) + \frac{W_2}{2}u_2^2(t) + \frac{W_3}{2}u_3^2(t)\right] dt. \tag{15}$$

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