Optimal control of influenza pandemics: The role of antiviral treatment and isolation

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Abstract

The implementation of control measures during a *pandemic* must be carefully assessed particularly in the case of a fast transmitting disease like influenza in resource-limited situations. Optimal control strategies that rely on the use of antiviral treatment or isolation strategies can reduce the number of clinical cases. A model for the transmission dynamics model of influenza that incorporates hospitalizations is used to evaluate the impact of isolation and/or antiviral drug delivery in unlimited and resource limited scenarios. Five pre-selected control strategies for influenza pandemics involving antiviral treatment and isolation are evaluated under the "unlimited" resource assumption. We explore scenarios that required the identification of "optimal" policies under resource limited situations. Naturally, the implementation of antiviral treatment at the start of a pandemic tends to reduce the magnitude of the epidemic peak often resulting on less localized increases in the number secondary cases over the outbreak's time horizon. In other words, controls' timing and intensity can reduce the pressures placed on the health care infrastructure during peak epidemic times. The role of isolation strategies as a component of pandemic mitigation policies particularly when the access to antiviral resources is limited, is highlighted. Identifying the

best use of stockpiles for the effective treatment of infectious individuals under limited resources is addressed in this manuscript. The limited resources scenario was approached initially from a constrained optimization problem perspective but its implementation turned out to be less effective than those generated by empirically based *solutions*. The best empirical solution turned out to be the one that follows the optimal solution (under the unlimited resources scenario) until the system runs out of resources.

1 Introduction

The emergence of novel influenza strains with unquantified transmission potential, is a source of concern. The identification, evaluation, and implementation of effective preventive and response protocols must be systematically explored as a component of pandemic mitigation response plans. The effective and fast implementation of strategies capable of containing influenza pandemics at their epicenter is critical due to influenza's characteristic short generation intervals [8, 10, 22, 23] and the fact that the timely implementation of mitigation strategies can reduce morbidity and mortality [11, 14]. Virulence, here defined in terms of case fatality rates in the population, should also be assessed [21] and the results considered in the preparation of preparedness plans that deal with the best allocation of antiviral medications. The evaluation of these policies is even more important when the antiviral drug supplies are insufficient [3, 25]. The scheduling of additional interventions measures including the distribution of non-pharmaceutical tools (e.g., face masks) and/or the availability of pharmaceutical devices (ventilators) in synchrony with the timing, duration and the geographical distribution and clustering of school closures are but some of the challenges faced by public health officials [11, 25].

The lack of *enough* pharmaceutical resources to protect the majority of the population at risk of becoming infected with this new strain of H1N1 has become even more troublesome as secondary pandemic waves of A (H1N1) hit the Northern Hemisphere. The world's limited production capacity to produce antiviral drugs and vaccines particularly the new H1N1 vaccine that the world is eager, some would say desperate to buy, raises concerns at multiple levels [13, 16, 19, 31]. The fact that the biggest stockpiles of antiviral drugs (and H1N1 vaccine) are in the hands of the haves rather than the have-nots but one of the outcomes of competition for global resources in the time of crises. In fact, there is a clear hierarchy, countries like Mexico and India, with the capacity of producing antiviral drugs at a large scale but not doing so yet, must confront pandemic challenges that thrive in areas of high population density and limited access to quality health care. Supplies will not meet the demand of

those who face the biggest risk in developing nations. Poor nations are in a different boat as they are extremely unlikely to get timely access to minimally adequate drug stockpiles, equipment or vaccine supplies. In fact, without the efforts of the WHO a large number of countries would have no access at all.

The task of identifying "optimal' control strategies that minimize the impact of influenza pandemics through the judicious use of a limited antiviral drug supply in combination with isolation, is the focus of this manuscript. A differential equations mathematical model previously calibrated with data from the 1918 Geneva influenza pandemic [7] provides the baseline scenario used to evaluate an array of alterantives based on the use of distribution of antiviral drugs and the isolation of hospitalized patients. Optimal control theory [12, 20, 28], with a history of successful applications in biological, medical and industrial problems [4, 6, 18, 29], is used in this setting. Identifying the optimal stockpile needed to provide effective treatment to infectious individuals reducing the impact of the pandemic at the *population* level under various scenarions is the driver of this project. The limited resources scenario can be approached from a constrained optimization problem perspective. However, such an approach turned out to be less effective than those generated by empirically based *solutions*. The best solution among those tested, turned out to be the solution that implemented the optimal solution, under the unlimited resources scenario, until the system ran out of resources.

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; The results of numerical simulations for five scenarios are collected and compared in Section 3; 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 modeled parametrized scenarios based on data for the 1918 influenza pandemic in Geneva, Switzerland [7]. Strategies or policies, modeled by the functions $u_i(t)$ (i=1,2,3) that control (hopefully reduce) the number of clinical cases and hospitalizations over a prescribed finite time horizon are identified under various strategic schemes. The 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 [7]:

$$\begin{cases} \dot{S}(t) &= -\beta S(t)[I(t) + (1-\epsilon_3 u_3(t))J(t) + qA(t)]/N(t) \\ \dot{E}(t) &= \beta S(t)[I(t) + (1-\epsilon_3 u_3(t))J(t) + qA(t)]/N(t) - kE(t) \\ \dot{A}(t) &= k(1-\rho)E(t) - \gamma_1 A(t) \\ \dot{I}(t) &= k\rho E(t) - (\alpha + \gamma_1 + \epsilon_1 u_1(t))I(t) \\ \dot{J}(t) &= \alpha I(t) - (\gamma_2 + \delta + \epsilon_2 u_2(t))J(t) \\ \dot{R}(t) &= \gamma_1(A(t) + I(t)) + \gamma_2 J(t) + \epsilon_1 u_1(t) I(t) + \epsilon_2 u_2(t) J(t) \\ \dot{D}(t) &= \delta J(t) \end{cases} \tag{1}$$

Susceptible individuals become infected at the rate $\beta(I(t) + J(t) + qA(t))/N(t)$ where β is the transmission rate, and q ($0 < q <= 1$) accounts for the potential reduction in transmissibility among individuals in the asymptomatic class (A). The total population size at time t is given by $N(t) = S(t) + E(t) + I(t) + A(t) + J(t) + R(t)$. Homogeneous mixing between individuals is assumed, therefore, the fraction $(I(t) + J(t) + qA(t))/N(t)$ is interpreted as the "probability" of a contact with an infectious individual. A constant proportion ρ ($0 < \rho < 1$) of latent individuals (E) progress at rate k to the clinically infectious class (I) while the rest $(1-\rho)k$ progresses from E to the asymptomatic partially infectious class (A). Asymptomatic cases progress to the recovered class at the rate γ_1 while clinically infectious individuals (class I) are hospitalized (reported) at the rate α or recover without being diagnosed at the rate γ_1. Hospitalized individuals (reported) recover at the rate γ_2 or die at the rate δ. The control functions, $u_1(t)$, $u_2(t)$ and $u_3(t)$ are ***Lebesque*** integrable functions, bounded in $[0, 1]$. The controlling effort $u_1(t)$ models the fraction of clinically infectious cases treated with antivirals per unit of time while the control $u_2(t)$ models the fraction of individuals getting antiviral treatments at hospitals per unit of time. It is assumed that both controls have constant antiviral efficacy, $\epsilon_1 = \epsilon_2$, incorporated in the model as $\epsilon_1 u_1(t)$ and $\epsilon_2 u_2(t)$. The isolation control, $(1 - \epsilon_3 u_3(t))$, models the effort required in preventing or limiting the interactions between J and S individuals, that is, the impact of isolation in hospital settings under the efficacy ϵ_3, a constant. Control variables near 1 ($u_1(t) \approx 1$ and $u_2(t) \approx 1$) denote almost full effort and model the situation where almost every infectious or hospitalized individual gets antiviral treatment. The term $\epsilon_3 u_3(t) \approx 1$ corresponds to the situation when contacts between susceptible and hospitalized individuals are nearly perfectly avoided (they are prevented through effective isolation). The efficacy of these controls can be modified by varying the efficacy

constant ϵ_i (i=1,2,3). For example, smaller ϵ_i (i=1,2) means lower antiviral efficacy while smaller ϵ_3 implies less efficient isolation strategies in hospitals (possibly due, for example, to shortage of hospital wards).

The dynamics of Model (1) in the absence of controls, is characterized by the basic reproduction number $\mathcal{R}_0$, a measure of the number of secondary cases generated by an infectious case when introduced in a completely susceptible population. Under no controls ($u_i(t)$=0, i=1,2,3), the reproduction number of Model (1) is

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

This number captures the contributions of three terms in (2): secondary infected cases generated by infectious (I), hospitalized (J), and asymptomatic (A), respectively. Further discussions on the basic reproduction number are found in [7].

The above descriptions and assumptions leads to a system of nonlinear differential equations, that incorporates three controls within a model already parametrized for the transmission dynamics of influenza in 1918. The objective functional $\mathcal{F}$ is used to formulate the optimization problem of interest, namely, that of identifying the most effective strategies over the admissible set of $(u_1(t), u_2(t), u_3(t))$. The overall objective is to minimize the number of clinically infectious and hospitalized individuals over a finite time interval $[0, T]$ at minimal cost. The objective functional $\mathcal{F}$ is given by the expression:

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

The control efforts are assumed to be nonlinear. We choose (as it is customary) to model the control effects using a linear combination of quadratic terms, $u_i^2(t)$ (i=1,2,3), where the coefficients, C_1, C_2, W_i (i=1, 2, 3) are weight constants. The weights, constant over the pre-selected finite time horizon, are a measure of the relative cost of the interventions over a finite time horizon. The optimal control problem hence becomes that of finding optimal functions, $(u_1^*(t), u_2^*(t), u_3^*(t))$, such that

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

where $\Omega = \{(u_1(t), u_2(t), u_3(t)) \in L^1(0,T) \| 0 \leq u_1(t), u_2(t), u_3(t) \leq 1, t \in [0,T]\}$ subject to the state equations given by (1) with initial conditions. Pontryagin's Maximum Principle is used to solve this optimal

control problem, the derivation of the necessary conditions are given in Appendix A.

Five different strategies are considered optimal solutions computed within each strategy, solutions that are later compared. The pre-selection of these strategies comes from our effort to test the use of single policies and the implementation of integrated public policies that involve the weighing of more than one strategy. Although the approach can be used to test various other options, here we only look at the following five alternatives:

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

Strategy 5 is from the implementation of the optimal solutions of Equations (1-4) (Further details are given in Appendix B). The results of numerical simulations under scenarios that involve the use of a single policy or policies that combine antiviral and isolation controls are computed by the following numerical procedures. All five strategies are implemented from the solutions of the associated optimality system consisting of a system of nonlinear ordinary differential equations that involve state and adjoint equations (see Appendix A and B). The iterative process used to solve this system is as follows: First, the state equations are solved using a forward method with given initial conditions for the state variables and the control functions (1); Secondly, the corresponding adjoint system is solved using a backward scheme with the Transversality Conditions (8, 9), all collected in Appendix A; thirdly, a convex combination of previously and currently computed controls are used to generate updated controls using the Optimality Equations (10) found in Appendix A; 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 these baseline values are used throughout the manuscript unless otherwise indicated.

3 Numerical Results

In this section, numerical results are presented based on the implementation of the strategies listed in Section 2 for two cases: the case when an unlimited amount of antiviral medications is discussed in Section 3.1 and the case when only a limited antiviral stockpile is available are discussed in Section 3.3. Sensitivity analyses on some parameters in the state system (1) are carried out in Section 3.2 but we only report on the results that pertain to the unlimited antiviral resources case.

3.1 Implications of treatments and interventions

We evaluate the impact of optimal antiviral treatments and isolation strategies for the dynamics of influenza pandemics of various degrees of transmissibility as measured by the basic reproduction number $\mathcal{R}_0$ under the assumption that we have access to unlimited antiviral drug supplies. The basic reproduction number $\mathcal{R}_0$ is assumed to be in the range of 1.5-4. This is not a capricious decision but based on recent estimates [7, 9]. The graphs of four optimal controls under strategies 1, 2, 3, and 5 are illustrated in Figure 1, the parameter values used are collected in Table 1 for $\mathcal{R}_0$=3.5. Controls, $u_1(t)$ and $u_2(t)$ model efforts of antiviral treatments on the clinically infectious and hospitalized individuals, respectively. The control, $u_3(t)$, increases the negative impact of the isolation of hospitalized cases on the generation of secondary cases. The top left three graphs (A, B, and C) in Figure 1 show the optimal control functions computed for Strategies 1, 2, and 3 (single control strategies). Three control efforts implementing Strategy 5 are illustrated in three graphs (D, E, and F). In general, higher reproduction numbers ($\mathcal{R}_0 > 2.5$), generate quickly growing epidemics characterized by high epidemic peaks. The graphs (G, H, and I) compare the impact of each strategy on states solutions with and without controls. Specifically, these graphs collect 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 the result as those under Strategy 1). Black dotted epidemic curves (under no interventions) are shown to distinguish them from those arising via optimal strategies. Strategy 5 (blue solid curve) shows significant reductions (about 90% compared to no intervention) in all three epidemics while Strategy 1 (red dashed-dotted curve) and 3 (green curve) generate relatively low reductions (about 30% compared to no intervention). Strategy 1 generates slightly better reductions than Strategy 3, due to hospitalization delays which in turn result in delayed isolations. Optimal strategies based on single controls (Strategies 1 to 3) require the implementation of intensive efforts at the beginning of an outbreak (A, B, and

C) followed by sudden reductions (most likely the result high depletion levels of susceptibility in the population which reflects directly in the size of the epidemic peaks–compare with Strategy 5). The use of integrated control strategies (4 or 5) require a high level effort at the beginning that must be maintained for larger periods of time than would be the case for policies based on Strategy 1 or 3. These intense efforts are followed by smooth reductions throughout the rest of the epidemic outbreak (D, E, and F).

In fact, it is not surprising to see that 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 use of full efforts (never effective enough) at the beginning of the pandemic, efforts that must be maintained for a short period of time in the case of Strategies 1, 2 or 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. In the case of Strategy 5 (integrated control policy), the shape of the optimal controls differ *because* the simultaneous implementation of multiple controls while incapable of eliminating the possibility of an outbreak still reduces the magnitude of influenza epidemic peak distributing the cases of infection and hospitalization over a broader window in time. Distributing the influenza case load burden over a longer window in time is a desirable outcome given the limited hospital bed capacity.

The case of low $\mathcal{R}_0's$ ($\mathcal{R}_0 < 2.5$ with the parameters used in this study) is handled optimally via the implementation of full efforts (control near 1) followed by a smooth effort reduction over the remaining epidemic outbreak (compare Figure 1 for $\mathcal{R}_0 = 3.5$ with Figure 2 for $\mathcal{R}_0 = 1.7$). The need to use controls over a long window in time is in retrospect obvious because 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 $\mathcal{R}_0$ values (for example, $\mathcal{R}_0$=1.7 in Figure 2). However, the panels in Figure 1 (G, H, and I) show that the use of optimal controls will not prevent epidemic outbreaks (see the rise in the number of infectious for $\mathcal{R}_0 = 3.5$) even under Strategy 5. Consequently, generating reliable estimates of $\mathcal{R}_0$ as early as possible will help assess the degree of effectiveness of single or integrated optimal control policies. Further, it helps to know in advanced, from a political perspective, the limitations of even optimal policies in the presence of highly and fast transmissible communicable diseases like influenza.

The impact of optimal Strategies 1-5 is presented in terms of the cumulative number of clinical cases as a function of $\mathcal{R}_0$ in Figure 3. Figure 3A collects comparisons of the cumulative number of clinical cases from the

scenario without interventions to those under Strategies $1-5$ as a function of $\mathcal{R}_0$; the black dot curve corresponds to the no interventions case; Strategy 3 corresponds to the red square curve. Strategy 1 (blue circle curve) supports slightly higher reductions than Strategy 2 (green triangle curve), that is, it can be more effective to use antiviral treatments for clinically infectious individuals than for diagnosed cases when the availability of antiviral resources is not an issue. Combined control strategies (Strategies 4 and 5) generate significant reductions in clinically infectious cases when compared to those generated with single controls.

As a way to quantify the resources that would be needed to achieve the optimal solution, the total number of antiviral treatments used for each of the strategies was calculated. Strategies 4 and 5 turned out to be quite efficient when $\mathcal{R}_0$ is between 1.5 and 2.5 (low to moderate pandemic level) but a lot less efficient for values of $\mathcal{R}_0$ in the range 2.5 to 4 (high pandemic level). Figure 3B collects the cumulative number of antiviral doses for Strategies 1, 2, 4, and 5. Strategy 1 (blue circled curve) uses about the same amount of antiviral doses as Strategy 2 (green triangle curve) for the selected ranges of $\mathcal{R}_0$. A sudden increase takes place in the case 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. As expected, Strategy 5 (diamond curve, antiviral treatments combining with the isolation strategy) uses considerably less antiviral resources for the entire pre-selected range of $\mathcal{R}_0$ values highlighting the role of effective isolation strategies.

We also measure the effectiveness of each strategy by the percentage reduction $(\%)$ in the cumulative number of clinically infectious cases *relative* to the no intervention scenarios. Figure 3C illustrates this reduction $(\%)$ as a function of $\mathcal{R}_0$. It is computed as the relative difference between the outcome without interventions versus the outcomes under Strategies $1-5$. Figure 3C shows high reductions for lower reproduction reproductive numbers regardless of the strategy. In fact, the five strategies show more than 75% reductions at $\mathcal{R}_0 = 1.5$) but as $\mathcal{R}_0$ increases the benefits decrease under all strategies. Nevertheless, Strategies 4 and 5 generate improvements over the entire range of $\mathcal{R}_0$. Specifically, Strategy 5 shows a near 90% reduction for $\mathcal{R}_0$ values up to $\mathcal{R}_0$=3 while maintaining 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. Figure 4 collects the cumulative number of clinical cases as a function of $\mathcal{R}_0$ for strategies 1, 2, 4, and 5. Antiviral treatment is initiated in our 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 case). As expected all strategies are most effective when applied at $t = 0$ days. Delays in the availability of antiviral treatment leads to significant increases in the number of clinically infectious cases for all strategies relative to the scenario of no interventions. Strategy 5 outperforms all selected strategies, it is highly efficient for the range $\mathcal{R}_0 = 1.5 - 3$ if implemented at $t = 0$ days. The range of $\mathcal{R}_0$ where optimal controls are effective, gets smaller as the time of the start of antiviral treatment increases. For example, the analyses (simulations) of the outcomes when the start date for the use of antiviral treatment is $t = 30$ days after the pandemic onset show that there is no efficient control strategy in this case, a situation that may be faced in various communities around the world.

3.2 Sensitivity analyses on parameters

The role of changes in model parameters is investigated through 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 efficacy for antiviral treatments and isolation strategies (parameters ϵ_1, ϵ_2, ϵ_3) are assessed. Figures 5-8 provide a glance of the impact of varying these parameters in terms of the cumulative number of clinically infectious cases in the case of no interventions versus those generated when controls are in place.

Effect of weight constant on controls. In this work, five different strategies are compared using five different objective functionals (given in Appendix B). The weight constants for all five strategies have been explored using different weight constants but we did not include all the results here because the results are not too sensitive for large range values in the weights. We illustrate this lack of sensitivity to weight changes for selected cases. One can generate several treatments and interventions using different weight constants on the controls namely, W_1, W_2, and W_3. Figure 5 shows the comparison of results implementing Strategy 1 using different weight constants on the control $u_1(t)$ ($W_1 = 0.1, 1, 50, 100, 1000$ and no control for $R_0 = 2.0$). Reasonable values of weight constant lie between 1-100. However, using $W_1 = 1$ leads to almost maximum controls throughout the whole time. Figure 6 shows the cumulative clinical cases (under all strategies and no interventions) 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, respectively. The general shapes of the curves are similar with *slight* changes in magnitude. As we increase the weight constants, thereby

increasing the cost of treatments and isolation efforts, the overall number of clinical cases also increase due to reductions in the intensity of implementation of interventions (see Figure 6).

We carried out a sensitivity analysis on W_3 fixing W_1= W_2=50 for Strategy 5 (not included here). It is assumed that the cost of antiviral treatment in the I- and J- classes is the same (fixing W_1=W_2=50 from the previous simulations). As W_3 increases, the cost of the control u_3 increases leading to a larger number of I- and J- individuals. Differences in the cumulative number of the I- and J-individuals are not significant when W_3 is in the range of 1,50, and 100. Also, we carried out a sensitivity analysis on the weights (C_1 and C_2) for Strategy 5 (not given here). This sensitivity analysis is carried out by varying the costs (C_2) on the J-class while keeping the cost on the I-class fixed to C_1=1. We found that the effects of these changes on the cumulative number of individuals in the I- and J- classes are not very significant when C_2 varies between 1 and 100.

Effect of the proportion of clinical infections. Three values of the proportion of clinical infections, ρ=0.25, ρ=0.5, and ρ=0.75 are used to illustrate the impact of this parameter on the cumulative number of clinical cases as functions of $\mathcal{R}_0$. A larger value of ρ indicates a higher number of clinically infectious individuals for all strategies. In Figure 7, the overall profile of the graphs are very similar with *significant* changes in magnitude. Larger values of ρ give larger cumulative numbers of clinical cases a result that can be observed in the three graphs, from left to right in Figure 7. The cumulative number of clinical cases using ρ=0.5 is twice the number of that using ρ=0.25. Similarly, ρ=0.75 gives almost twice the cumulative number of clinical cases corresponding to the case when ρ=0.5.

Effect of the relative infectiousness of the asymptomatic class. The relative infectiousness of the asymptomatic class, q, has been varied from 0.003 to 0.3. Figure 8 shows the cumulative clinical cases as functions of $\mathcal{R}_0$ for three different values of q. The value q=0.003 indicates low transmissibility from the asymptomatic cases while q=0.3 indicates that asymptomatic cases are 30% as infectious as clinical cases. Clearly, using the low value of q=0.003 gives us better controls on the cumulative number of clinical cases. On the other hand using the higher relative infectiousness of q=0.3 means that the force of infection becomes large so quickly that there is not enough time to implement controls and consequently, a large number of clinical cases are generated. The three graphs in Figure 8 are for higher values of q, from left to right. An increasing number of clinical cases is observed under all strategies, as q increases. For q=0.3, for example, there is a sudden increase after $\mathcal{R}_0 = 2$ even for Strategy 5 (diamond curve).

Effect of control efficacy. The efficacy of antiviral treatments and isolation is varied in the range 0.25-0.75. ϵ_1 and 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. Figure 9 illustrates the results for ranges of values for the three 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 ϵ_1= ϵ_2=$\epsilon_3 = 0.75$, Strategies $1-5$ generate significant reductions up to $\mathcal{R}_0 = 2$. Strategy 5 (diamond curve) generates a dramatic reduction even for higher $\mathcal{R}_0$ levels. The performance of Strategies $1-5$ with respect to each other vary as antiviral and isolation efficacies change. These observations are collected in the right graph of Figure 9. We see that high isolation efficacy levels result in the the strategy of isolating infectious individuals in hospitals outperforming the strategy that focuses on antiviral treatment of hospitalized individuals.

3.3 Suboptimal strategies with limited antiviral stockpiles

The expected number of antiviral courses available for pandemic control is limited particularly in the developing world. Experimenting with scenarios that account for the existence of a limited stockpile of antiviral resources can be carried out in the framework introduced in this paper. Hence, we consider the existence of a limited amount of antiviral resources, let's say 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 on the availability of antiviral resources as shown in Section 3.1. First, Suboptimal Strategy 1 or SS1 (maximal effort) is based on the implementation of the optimal antiviral treatment profile (under no antiviral drug limits). SS1 is the optimal solution in a subinterval $[0, T^*]$ where T^* less than or equal to T, jumping to zero at T^* when the 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 pre-slelcted fixed fraction of the antiviral treatment profile in the implementation of the full optimal control policy. This fraction is computed under the assumption that it will be applied at a fixed constant rate over $[0, T]$. The isolation strategy (Strategy 3) in the limited resources scenarios is taken as the one generated by $\epsilon_3 u_3$ in the optimal control with unlimited resources (over $[0, T]$).

The limited resources scenario was approached initially from a constrained optimization problem perspective but its implementation turned out to be less effective than those generated by empirically based *solutions*. For example, putting a limit on antiviral drugs in Strategy 4 or 5 requires the use of the following isoperimetric constraint, $\int_0^T u_1(t)I(t) + u_2(t)J(t)dt \leq B$ in our optimal control formulation, where B is the maximum number of antiviral doses. This isoperimetric approach leads to a reformulation with boundary conditions given in terms of inequalities in the Adjoint system. We tried this approach, and surprisingly, we found that it actually leads to an *optimal* solution with a substantially larger number of individuals in the I- and J- classes than those generated from the implementation of our *suboptimal* solution (especially when $\mathcal{R}_0 \leq 2$). Hence, our suboptimal approach leads to a more effective public health policy.

Figure 10 shows the results generated under the full optimal control and the results generated via these two suboptimal approaches (SS1 and SS2) for Strategy 1. The full optimal strategy uses 28% antiviral coverage for $\mathcal{R}_0$=3. Figure 10A compares the number of daily clinical cases using the full optimal (solid curve), suboptimal 1 (dotted curve) and suboptimal 2 (dashed-dotted curve). Figure 10B illustrates each antiviral 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; the suboptimal control 1 (a maximal effort) takes maximum usage at the beginning of epidemics while the suboptimal control 2 (a distributed effort) uses 22% of the full optimal control. The effective reproduction number is given by the following expression:

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

Note that the time-dependent fraction of susceptible individuals in the population, $S(t)/N(t)$ is taken into account in (5). We evaluate the effective reproduction number over time in the presence of controls. The comparative curves of the effective reproduction numbers as a function of time are in Figure 10C which includes the optimal (unlimited antiviral coverage) and the two suboptimal strategies (limited antiviral coverage). Interestingly, after the antiviral resources have ran out, a secondary increase in the daily number of clinical cases, reflected in the effective reproduction number under suboptimal strategy 1 (dotted curve in A and C), is observed. This jump is consistent with other reports [17]. However, as pointed out in [24], under the constraint of a limited antiviral stockpile, SS1 reduces the epidemic peak size and delays its timing of occurrence, not the same result under SS2. Naturally, intensive antiviral treatments (maximal efforts) as early in the epidemic outbreak as possible is more

efficient. The simulation results show that both maximal and distributed efforts yield essentially the same attack rates in the population.

We now investigate the impact of varying the antiviral coverage on the cumulative number of clinically infectious individuals. Results obtained using suboptimal Method 1 are given in Figures 11-12. Figure 11 shows the cumulative number of clinical cases as a function of $\mathcal{R}_0$ for three different antiviral coverage levels, namely 10%, 20% and 30%. The overall results are similar to those obtained using unlimited antiviral resources when $R_0 < 2.5$. Figure 11AB 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 $\mathcal{R}_0 > 2.5$. It is worth noting that Strategy 3 (isolation) is slightly more efficient than Strategies, 1 2, and 4, (antiviral treatments) for higher reproduction numbers due to limited antiviral resources (A, B). Using a high antiviral coverage of 30%, Figure 11C shows almost the same results to those obtained without limited antiviral supplies. This highlights the importance of effectively implementing an isolation strategy in the face of limited or no antiviral resources in reducing the total number of clinical cases.

We quantify the reduction in the number of clinical cases provided by the different strategies with respect to the baseline scenario of no interventions using a limited antiviral stockpile. Figure 12 summarizes this relative reduction as a function of $\mathcal{R}_0$ and antiviral coverage. Higher relative reductions can be observed in lower reproduction numbers and higher antiviral coverages (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 antiviral coverage decreases), reductions decrease for all strategies. However, the use of Strategies 4 and 5 still generate excellent reductions (90%) up to $\mathcal{R}_0$ values in the range of 2-2.5.

4 Discussion

Mitigating the impact and spread of the ongoing influenza A (H1N1) pandemic is on the minds of every newscaster, government official, aspiring politician, public health officials as well as billions of individuals around the world. The rate of growth/spread of influenza A(H1N1) news has even surpassed the rapid deployment of this new strain of influenza A around the world [15]. Further, the rather unusual age-dependent patterns of spread, morbidity and mortality that have been observed around just about everywhere add to the levels of uncertainty that are inherently common to the emergence and/or re-emergence of communicable diseases [27].

Issues being confronted in the face this health emergencies include the fact that not all clinical cases are diagnosed during the outbreak. Hence, we cannot properly assess the magnitude of the problem. Further even when diagnosis is possible, it is not handled over time scales that are fast enough to stop the global spread of influenza. Medical services, even in the wealthiest of nations, do not have the capability of responding instantly with high degree of effectiveness to influenza pandemics. All systems must deal with the negative impact of time delays that arise at many levels including those linked to the lag between symptoms onset and diagnosis. Unfortunately, the impact of delays in diagnosis and in the implementation of intervention like isolation or antiviral drug treatment has consequences that go well beyond the health of particular individuals or groups of individuals. These delays can and often do have global impact. Mathematical models provide viable quick, cheap and effective ways of exploring and evaluating the consequences of local decisions on disease dynamics at higher levels of organization. Questions that need to be addressed as interventions are scaled up from the individual to the population level include: What is the impact of the timing of interventions on 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, if policies do not work well, Is it due to the timing of intervention put in place? Or will highly transmissible diseases easily derail the potential effectiveness of optimal strategies put in place rather quickly?

Estimating the basic reproductive number, $\mathcal{R}_0$, according to the analysis in this manuscript, is the first and a necessary step in the process of assessing the likelihood that control measures will make a difference. Current data suggest that the range of estimated values for the basic reproductive number ($\mathcal{R}_0$) for this pandemic is within a reasonable range. That is, the timely implementation of optimal control measures can make a difference. However, the fact that not all countries have sufficient antiviral drug stockpiles or sufficiently adequate isolation facilities means that the distance between theory and practice is still huge. Further, the fact that the distribution of H1N1-vaccines will be distributed (in countries that are lucky enough that have it) over long periods of time and that the supplies will not be evenly distributed at a global scale means that its impact (not assessed in this manuscript) will not be nearly as effective as it could have been.

From this study, nevertheless, some patterns emerge. Simulation model results suggest that the treatment of clinical cases in a community (that must select among the strategies proposes in this paper) is better off if it provides antiviral treatment exclusively to diagnosed individuals. Model simulations also show that the use of integrated

mitigation/intervention policies is better than single policies. In fact, model simulations based on reasonable "pandemic" $\mathcal{R}_0$ values show that the use of integrated mitigation policies are *far superior* quantitatively speaking than the use of single policies. The difference in effectiveness is quite sensitive to the timing of initiation. They are far superior if put in place early in the outbreak. 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 observation may be of critical importance to policy makers and government officials. These 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. Further, the development of real time surveillance methods is critically important since the timing of interventions is the most sensitive factor when it comes down to stopping the spread of influenza [5, 34].

High values of the basic reproduction number ($\mathcal{R}_0$) are bad news and require the placement of control efforts as soon as possible. On the other hand outbreaks generated by low values of $\mathcal{R}_0$ may respond to control measures that are not delivered immediately. Obviously, the sooner policies are implemented in any case the better chance that we have to stop or mitigate the impact of an outbreak.

We have also identified some patterns in the delivery of optimal control strategies. The use of optimal strategies based on single controls (Strategies $1 - 3$) demand intensive efforts at the beginning of the epidemics that are shifted suddenly to zero. On the other hand, the use of integrated mitigation strategies (Strategies 4 or 5) demand a high level of effort at the beginning followed by a smoothly reduced efforts over the course of the epidemic outbreak. The use of single strategies, particularly when $\mathcal{R}_0$ is large, does not manage prevent large epidemic peaks (a nightmare for health care facilities if symptoms are severe). In this case, the susceptible population is brought below the critical mass needed to sustain an outbreak rather quickly. The simultaneous implementation of multiple strategies reduce the number of secondary infections more effectively when compared to single-control policies. The use of integrated control approaches manages to maintain the susceptible population above the critical mass needed to sustain an outbreak for a "long" period of time. The availability of a viable pool of susceptible individuals means that the need for controls remain since there are still infections to prevent. The use of an isolation strategy with high levels of efficacy is more effective than the use of a strategy that provides antiviral treatment to hospitalized individuals.

What about the case when there are not enough resources? In response to this challenge, we introduce/define maximal and distributed effort approaches under the constraint of limited antiviral resources. We found under both of these two protocols maximal and distributed) that intensive antiviral treatments at the beginning of epidemics reduces the epidemic peak and delays its timing. Our numerical simulations show that the epidemic impact is dramatically reduced with increases in the amount of antiviral resources available particularly if their delivery is carried out in combination with our isolation strategy in hospital settings. Strategy 5 is the best strategy (among the proposed five) and it is quite effective for the entire range of $\mathcal{R}_0$ values, antiviral coverage levels (0-30$\%$), and the start of antiviral treatments (0-30 days).

The impact of antiviral treatments on the emergence of antiviral resistance, not addressed here, has been explored and remains a matter of great concern [1, 2, 24, 26, 33]. It has been shown, for example, that the use of single antiviral treatment when combined with a second drug is very effective at controlling antiviral resistance [24, 33]. However, there is significant uncertainty associated with the timing of emergence of antiviral resistance influenza strains [30, 32]. Our study did not account for the potential emergence of antiviral resistant strains in the population. This is a serious concern since these drugs that are likely to available in large numbers all over world. The measures that restrict their prescription or controls its use are highly variable. Hence, resistance is likely to emerge rather quickly somewhere in the world. The viability of these resistant strains will determine the danger that they pose all communities.

In this manuscript, we have focused on identifying the significant benefits that come with the implementation of influenza mitigation policies that combine pharmaceutical and non-pharmaceutical interventions even in the context of *limited resources*. We showed that influenza pandemic mitigation is possible as long as the disease does not come with a very large basic reproductive number ($\mathcal{R}_0$). However, mitigation is only possible if the timing of interventions is "fast" enough as long as the policy involves the use of more than one intervention plan. These plans should be carried out simultaneously. No plan is possible unless minimal resources are available. This is an unlikely possibility given the inequities of our world. The HIV/AIDS pandemic has shown the role of international health disparities way too effectively.

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 equation (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 $\Omega = \{(u_1(t), u_2(t), u_3(t)) \in L^1(0,T) \| 0 \leq u_1(t), u_2(t), u_3(t) \leq 1, t \in [0,T]\}$ 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 [12]. The necessary conditions that optimal solutions must satisfy are derived from Pontryagin's Maximum Principle [28]. This principle converts the System (1)-(4) into the problem of minimizing the Hamiltonian H given by

$$\begin{aligned} H &= C_1 I + C_2 J + \frac{W_1}{2}{u_1}^2(t) + \frac{W_2}{2}{u_2}^2(t) + \frac{W_3}{2}{u_3}^2(t) \\ &+ \lambda_1(t)\{\mu N - \beta S[I + (1-\epsilon_3 u_3(t))J + qA]/N\} \\ &+ \lambda_2(t)\{\beta S[I + (1-\epsilon_3 u_3(t))J + qA]/N - kE\} \\ &+ \lambda_3(t)\{k(1-\rho)E - \gamma_1 A\} \\ &+ \lambda_4(t)\{k\rho E - (\alpha + \gamma_1 + \epsilon_1 u_1(t))I\} \\ &+ \lambda_5(t)\{\alpha I - (\gamma_2 + \delta + \epsilon_2 u_2(t))J\} \end{aligned} \tag{7}$$

From this Hamiltonian and Pontryagin's Maximum Principle [28], 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

$$\begin{aligned}
\dot{\lambda}_1(t) &= (\lambda_1(t) - \lambda_2(t))(\beta[I + (1-\epsilon_3 u_3(t))J + qA]/N) \\
\dot{\lambda}_2(t) &= \lambda_2(t)k - \lambda_3(t)k(1-\rho) - \lambda_4(t)k\rho \\
\dot{\lambda}_3(t) &= \lambda_1(t)(\beta q S/N) - \lambda_2(t)(\beta q S/N) + \lambda_3(t)\gamma_1, \\
\dot{\lambda}_4(t) &= -C_1 + \lambda_1(t)(\beta S/N) - \lambda_2(t)(\beta S/N) \\
&+ \lambda_4(t)(\alpha + \gamma_1 + \epsilon_1 u_1(t)) - \lambda_5(t)\alpha, \\
\dot{\lambda}_5(t) &= -C_2 + \lambda_1(t)(\beta(1-\epsilon_3 u_3(t))S/N) - \lambda_2(t)(\beta(1-\epsilon_3 u_3(t))S/N) \\
&+ \lambda_5(t)(\delta + \gamma_2 + \epsilon_2 u_2(t)),
\end{aligned} \tag{8}$$

with the transversality conditions,

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

Furthermore,

$$\begin{aligned}
u_1^*(t) &= min\{max\{0, \epsilon_1 I \frac{\lambda_4}{W_1}\}, 1\}, \\
u_2^*(t) &= min\{max\{0, \epsilon_2 J \frac{\lambda_5}{W_2}\}, 1\}, \\
u_3^*(t) &= min\{max\{0, \epsilon_3 JS \frac{\lambda_2 - \lambda_1}{NW_3}\}, 1\}.
\end{aligned} \tag{10}$$

Proof The existence of optimal controls follows from Corollary 4.1 of [12] 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. The following can be derived from the Pontryagin's Maximum Principle [28]:

$$\frac{d\lambda_1(t)}{dt} = -\frac{\partial H}{\partial S},\ \frac{d\lambda_2(t)}{dt} = -\frac{\partial H}{\partial E},\ \frac{d\lambda_3(t)}{dt} = -\frac{\partial H}{\partial A},$$
$$\frac{d\lambda_4(t)}{dt} = -\frac{\partial H}{\partial I},\ \frac{d\lambda_5(t)}{dt} = -\frac{\partial H}{\partial J}$$

with $\lambda_i(T) = 0$ for $i = 1, \cdots, 5$ 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:

$$\frac{\partial H}{\partial u_1} = W_1 u_1 + \epsilon_1 I(-\lambda_4) = 0 \text{ at } u_1 = u_1^*,$$

$$\frac{\partial H}{\partial u_2} = W_2 u_2 + \epsilon_2 J(-\lambda_5) = 0 \text{ at } u_2 = u_2^*,$$

$$\frac{\partial H}{\partial u_3} = W_3 u_3 + (\lambda_1 - \lambda_2)\epsilon_3 J \frac{S}{N} = 0 \text{ at } u_3 = u_3^*,$$

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

$$u_1^* = \epsilon_1 I \frac{\lambda_4}{W_1}, u_2^* = \epsilon_2 J \frac{\lambda_5}{W_2}, \text{ and } u_3^* = \epsilon_3 JS \frac{\lambda_2 - \lambda_1}{NW_3}.$$

By using the bounds $0 \leq u_1(t), u_2(t), u_3(t) \leq 1$, we have the properties (10).

Appendix B

Five strategies and corresponding objective functionals in Section 2 are given: Strategies $1 - 5$ use the objective functionals (11), (12), (13), (14), and (15), respectively. The derivation of necessary conditions can be done in a straightforward way (shown for Strategy 5 in Appendix A).

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

- Strategy 5: Two antiviral treatment controls on clinically infectious cases and hospitalizations together with isolation control ($u_1(t)$, $u_2(t)$, and $u_3(t)$)

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

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

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

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

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

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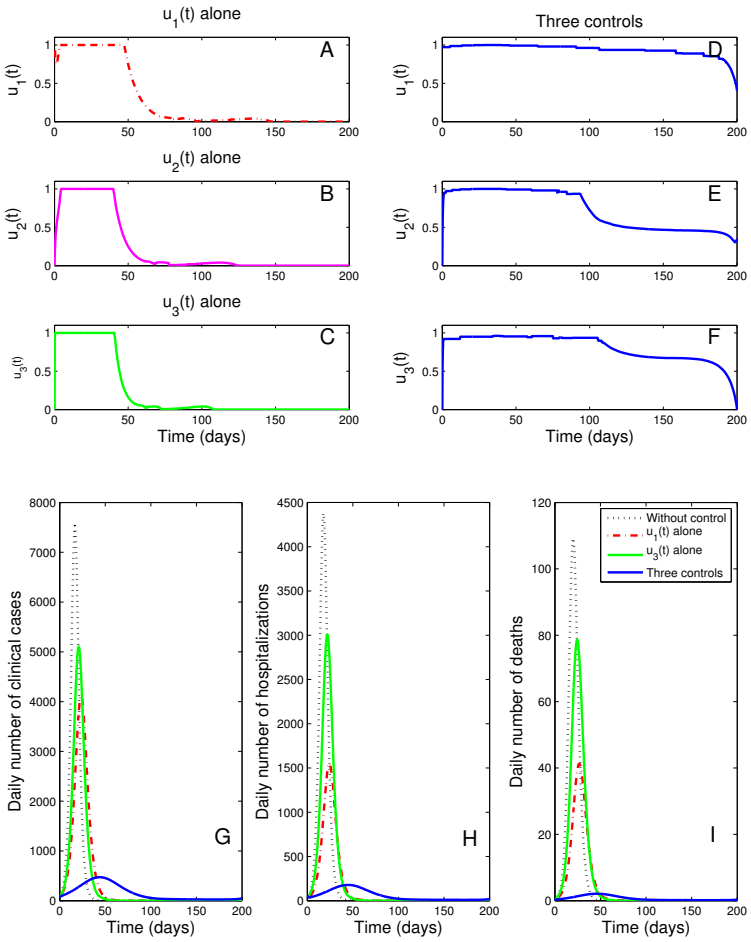

Figure 1: A, B, and C show the optimal control functions as a function of time computed for Strategies 1, 2, and 3 using only *one* control function, respectively. Three optimal control functions implemented in combination as a function of time define Strategy 5 and the results are collected in three graphs (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 curves in G, H, I) shows significant reductions in all state solutions. Parameter values are given in Table 1 and $\mathcal{R}_0$=3.5.

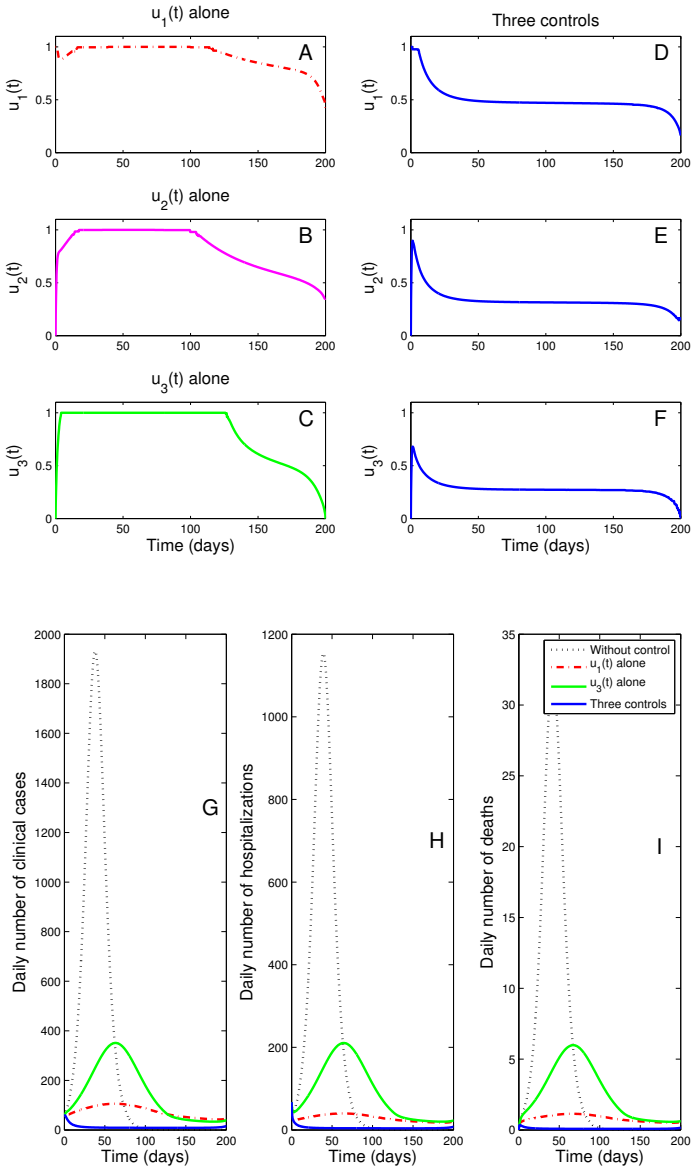

Figure 2: A, B, and C show the optimal control functions as a function of time computed for Strategies 1, 2, and 3 using only one control function, respectively. Three optimal control functions implemented in combination as a function of time are illustrated using Strategy 5 in three graphs (D, E, and 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 and using Strategies 1, 3, and 5. Optimal Strategy 5 (blue curves in G, H, I) shows significant reductions in all state solutions. Parameter values are given in Table 1 and $\mathcal{R}_0$=1.7.

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

Parameter	Description	Value	Reference
β	Transmission rate (days^{-1})	$1.03 - 2.75$	[7]
ρ	Proportion of clinical infections	0.5	[7]
q	Relative infectiousness of the asymptomatic class	0.003	[7]
k	Rate of progression to infectious (days^{-1})	0.53	[**?**]
δ	Mortality rate (days^{-1})	0.01	[**?**]
μ	Birth and natural death rate (days^{-1})	$1/(60*365)$	[**?**]
γ_1	Recovery rate (days^{-1}) for infectious class (days^{-1})	0.34	[7]
γ_2	Recovery rate for hospitalized class (days^{-1})	0.34	-
α	Diagnostic rate (days^{-1})	0.51	[7]
ϵ_1	Efficacy of antiviral treatment of clinically infectious	0.5	[22]
ϵ_2	Efficacy of antiviral treatment of hospitalizations	0.5	[22]
ϵ_3	Efficacy of isolation	0.5	-
$S(0)$	Initial number of susceptible individuals	174673	[7]
$E(0)$	Initial number of exposed individuals	207	[7]
$I(0)$	Initial number of infectious individuals	132	[7]
T	The simulated time (days)	200	-
C_i	Weight constant on I and J (i=1,2)	1	-
W_i	Weight constant on controls (i=1,2,3)	50	-

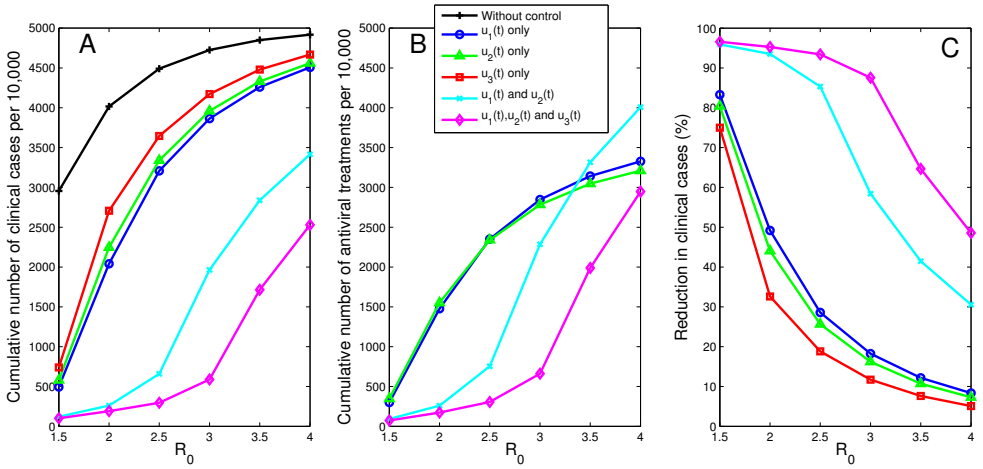

Figure 3: A: the cumulative number of clinical cases under no control and the cumulative number of clinical cases under Strategies $1-5$ as a function of $\mathcal{R}_0$. B: the cumulative number of antiviral treatment used for Strategies 1, 2, 4, and 5. C: the reduction in terms of the relative difference 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% at a higher $\mathcal{R}_0$=3-4.

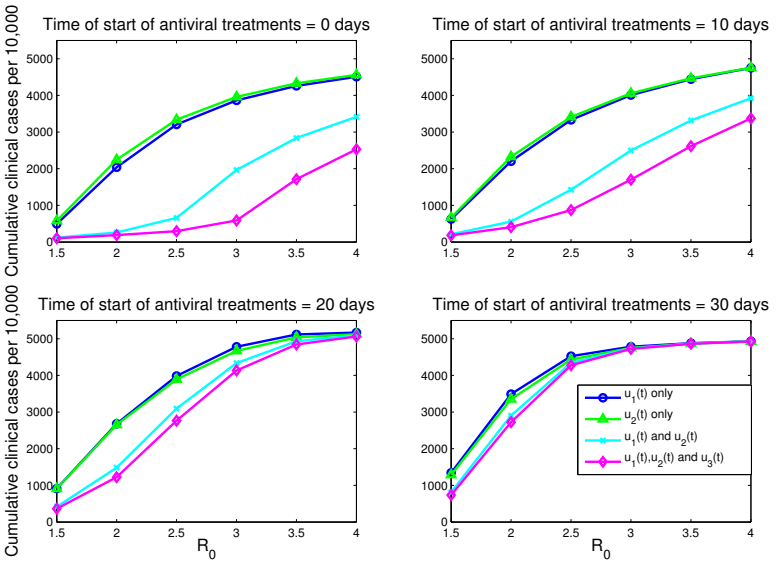

Figure 4: The cumulative number of clinical cases are shown as a function of $\mathcal{R}_0$ for Strategies 1, 2, 4, and 5. Antiviral treatment starts at $0, 10, 20, 30$ days after the pandemic onset. All strategies are most effective when they are applied at 0 days of epidemic onset. Strategy 5 outperforms other strategies as varying time of start of antiviral treatment for entire range of $\mathcal{R}_0$.

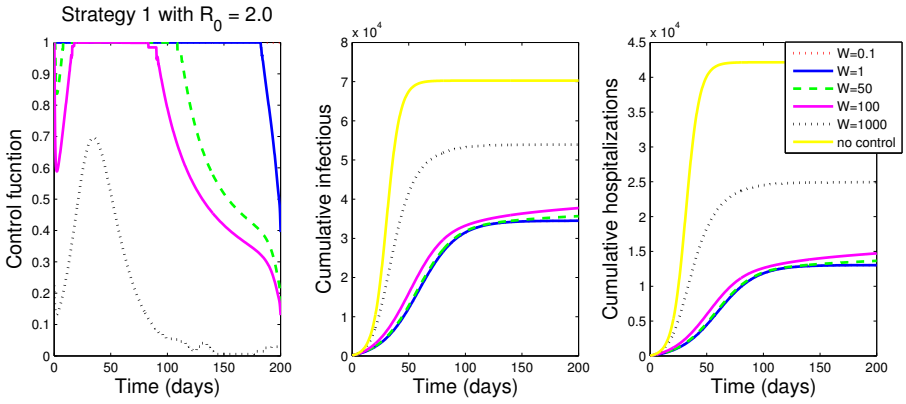

Figure 5: The comparison of results implementing Strategy 1 using different weight constants on the control ($W_1 = 0.1, 1, 50, 100, 1000$ and no control for $R_0 = 2.0$). Three graphs show the optimal control, the corresponding cumulative number of clinical and hospitalized cases, respectively (from left to right).

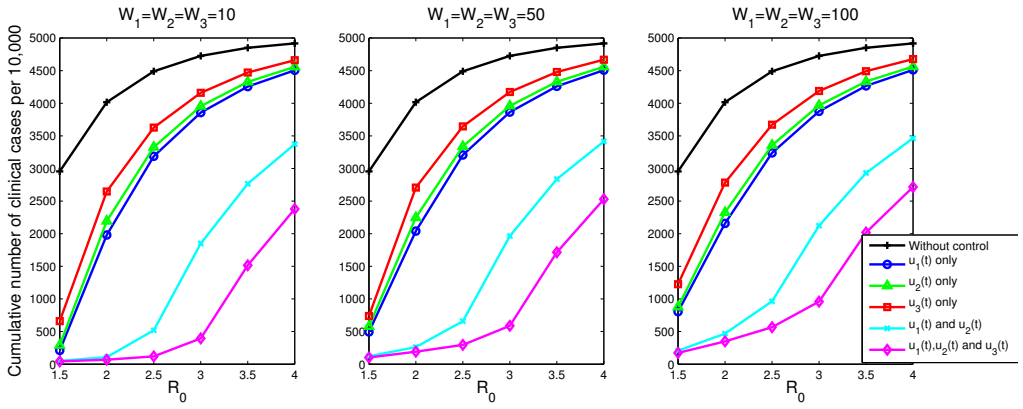

Figure 6: The cumulative clinical cases are plotted as functions of $\mathcal{R}_0$ for three different values of weight constants, W_1= W_2=W_3=10, W_1= W_2=W_3=50, and W_1= W_2=W_3=100. The general shapes of the curves are very similar with slight changes in magnitude. As we increase weight constants,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

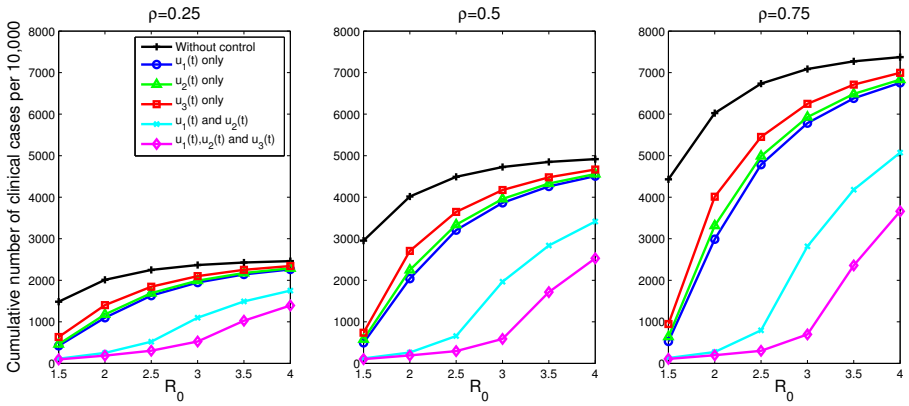

Figure 7: The cumulative clinical cases are plotted as functions of $\mathcal{R}_0$ for three different values of the proportion of clinical infections, ρ=0.25, ρ=0.5, and ρ=0.75. The overall profile of the graphs are very similar with significant changes in magnitude. Larger values of ρ lead to larger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

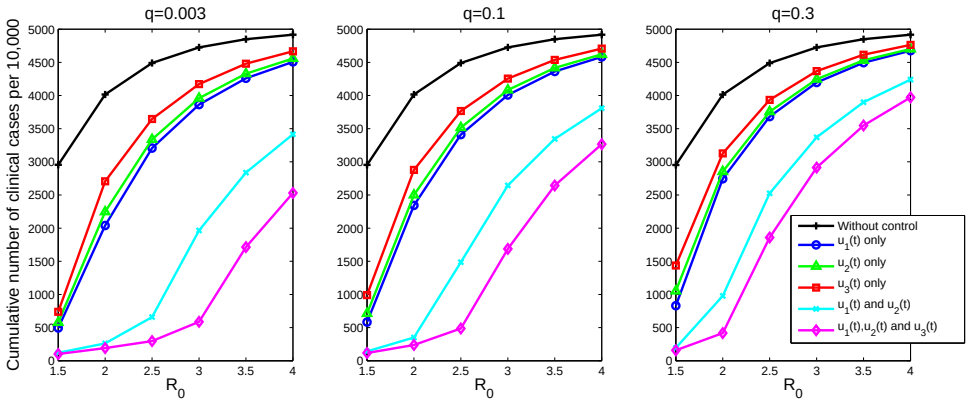

Figure 8: The cumulative clinical cases are plotted as functions of $\mathcal{R}_0$ for three different values of the relative infectiousness of asymptomatic cases, q=0.003, q=0.1, and q=0.3. The value q=0.003 indicates low relative transmissibility from asymptomatic cases while q=0.3 indicates that asymptomatic individuals are just 30% as infectious as clinical cases. Clearly, using the low value of q=0.003 gives us better controls on the cumulative clinical cases and on the other hand using q=0.3, the force of infection becomes larger quickly leading to a larger number of clinical cases.

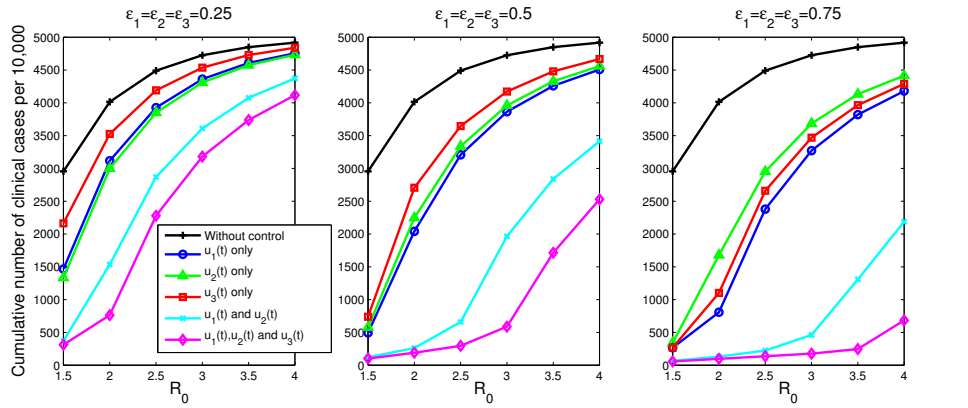

Figure 9: The cumulative clinical cases are plotted as functions of $\mathcal{R}_0$ for three different values of efficacy, ϵ_1= ϵ_2=ϵ_3=0.25, ϵ_1=ϵ_2=ϵ_3=0.5, and ϵ_1=ϵ_2=ϵ_3=0.75. Efficacy, ϵ_1 and ϵ_2 indicate the capacity for antiviral treatment effect while ϵ_3 represents the efficacy of the isolation strategy. Note that using ϵ_1=ϵ_2=ϵ_3=0.75, Strategy 5 (diamond curve) gives a dramatic reduction even at higher $\mathcal{R}_0$.

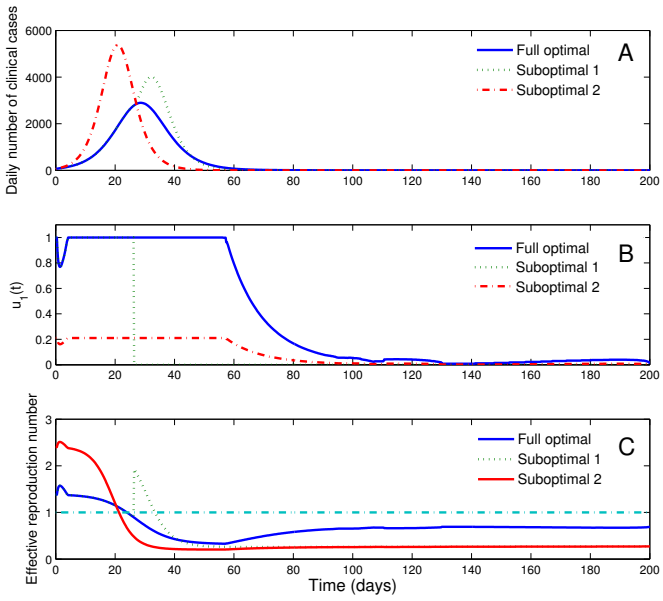

Figure 10: A: The number of daily clinical cases are compared using Strategy 1 for the full optimal and corresponding two suboptimal methods. B: antiviral controls as a function of time are plotted for the full optimal and corresponding two suboptimal methods. The full optimal and two suboptimal controls use 28% and 15% of antiviral coverage of total population size, respectively; the suboptimal control 1 is taking its maximum usage at the beginning of epidemics while the suboptimal control 2 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.

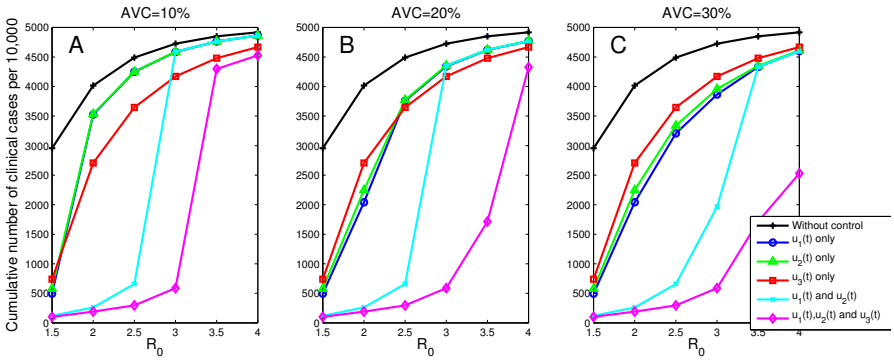

Figure 11: The cumulative number of clinical cases are compared as a function of $\mathcal{R}_0$ for three different antiviral coverages, 10 %, 20 % and 30 %. The overall results are similar from the results without a limited antiviral stockpile when $\mathcal{R}_0 < 2.5$. A and B with less antiviral coverage show significant increases in number of clinically infectious using Strategy 4 ($u_1(t)$ and $u_2(t)$) when higher $\mathcal{R}_0$ >2.5. Note that strategy 3 (isolation) is more efficient than Strategies, 1 2, and 4, (antiviral treatments) in the range of higher reproduction numbers due tolimited antiviral resources (A, B).

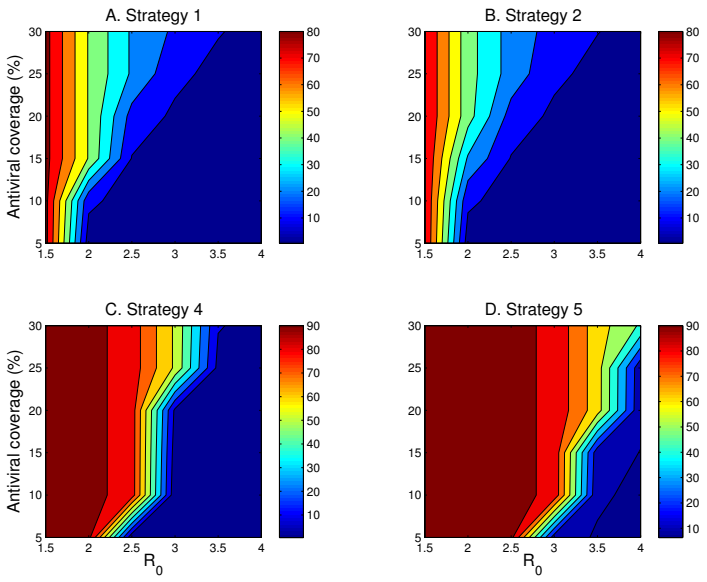

Figure 12: The relative difference of cumulative clinical cases (%) between the baseline scenario of no interventions and Strategies 1, 2, 4, and 5 plotted as a function of $\mathcal{R}_0$ and antiviral coverage (5-30%). Strategies 4 and 5 maintain excellent reductions event for high $\mathcal{R}_0$ values while Strategies 1 and 2 show a reduction efficiency of 80% around $\mathcal{R}_0$=1.5.