Selecting Non-Pharmaceutical Interventions for Influenza

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Abstract

Models of influenza transmission have focused on the ability of vaccination, anti-viral therapy and social distancing strategies to mitigate epidemics. Influenza transmission, however, may also be interrupted by hygiene interventions such as frequent hand washing and wearing masks or respirators. We apply a model of influenza disease transmission that incorporates hygiene and social distancing interventions. The model describes population mixing as a Poisson process, and the probability of infection upon contact between an infectious and susceptible person is parameterized by p. While social distancing interventions modify contact rates in the population, hygiene interventions modify p. Public health decision making involves trade-offs, and we introduce an objective function which considers the direct costs of interventions and new infections to determine the optimum intervention type (social distancing versus hygiene intervention) and population compliance for epidemic mitigation. Significant simplifications have been made in these models. However, we demonstrate that the method is feasible, provides plausible results, and is sensitive to the selection of model parameters. Specifically, we show that the optimum combination of non-pharmaceutical interventions depends upon the probability of infection, intervention compliance, and duration of infectiousness. Means by which realism can be increased in the method are discussed.

Keywords

hygiene interventions, social distancing, disease transmission model, cost-benefit, intervention compliance

1. Introduction

Influenza pandemics remain a threat to the public's health. Influenza prevention and mitigation strategies include pharmaceutical interventions (e.g., vaccination and anti-viral medications) and non-pharmaceutical interventions (NPI). NPI include increased social distancing and hygiene interventions. While social distancing interventions seek to reduce the frequency of contact between infectious and susceptible persons, hygiene interventions seek to reduce the probability of influenza transmission upon contact through frequent hand washing, surface disinfection, the use of respiratory protection, and the use of cough/sneeze etiquette. These hygiene interventions reduce the density of virus in the environment, so as to interrupt potential routes of transmission.

Disease transmission modeling has focused on pharmaceutical interventions and social distancing; [1–4] with limited exploration of the potential role of hygiene interventions.[5–7] NPI, however, become particularly important in influenza management when pharmaceutical interventions are unavailable, ineffective, or have incomplete coverage.[8–10]

The lack of emphasis on hygiene interventions may be driven by the perception that hygiene interventions are less powerful than pharmaceutical and social distancing interventions because their effectiveness requires (i) that the intervention interrupt a dominant route of transmission, which has remained uncertain for influenza;[11–13] and (ii) that individuals comply with the interventions over the course of days and weeks, which is unlikely to be complete.[14–16]

Hygiene intervention modeling to date has been limited in scope, but has demonstrated that increased mask efficiency and compliance decrease the effective reproductive number in the context of homogenous well-mixed population model[6] and a heterogeneous (mask use or no mask use) four-compartment (SEIR) epidemic model.[7] Tracht et al.[7] found that early introduction of masks during the epidemic, and mask use by both infectious and susceptible persons reduced the number of cases.

On a larger geospatial scale, Kernéis et al.[5] considered the effects of mask use and isolation in conjunction with pharmaceutical interventions using a global transportation network model with city-level four-compartment (SEIR) models. These investigators found mask efficacy, coverage and date of introduction to be more strongly correlated with epidemic features (e.g., total number of cases and epidemic duration) than isolation in the context of a fast, massive pandemic ($R_\circ = 4.9$); but neither efficacy or coverage of masks or isolation were correlated with epidemic features in the context of a long-lasting pandemic ($R_\circ = 1.8$). Notably, NPI interventions were not consistently less correlated with epidemic features than pharmaceutical interventions.[(5)] While these results suggest that NPI may be useful for some types of pandemics, their interpretation for public health decision making is difficult. In particular, the use of broad uniform probability distributions for intervention features, such as mask and isolation efficacy (0–1 for masks, 0.2–0.7 for isolation) and intervention coverage in the population (0.001–1), extend beyond the feasible range and may therefore exaggerate the correlations. But more importantly, as pointed out by Kernéis et al.,[(5)] correlations between input variables (the interventions) and output variables (epidemic features) do not provide information about the significance of impact on the epidemic.

Overall, there remains a need to understand the potential impact of NPI for influenza prevention and epidemic mitigation, particularly in terms and conditions accessible to public health decision makers. The long-term objective of this research is to identify conditions under which NPI, particularly hygiene and social distancing interventions, are effective for the mitigation of influenza epidemics, if any. We frame our objective in terms of health and financial costs, as both criteria are used to develop policy recommendations for interventions. The purpose of this study is to illustrate our methodological approach. As a result, the analyses presented use simple representations of the population and cost structures. Future work will increase the realism in these structures, and consider more than two interventions simultaneously.

The specific mathematical model used is an extension of that of Larson,[17] which emphasized the role of social distancing in disease transmission among a heterogeneous population. The approach utilizes high- and low-activity groups; considers individuals to be susceptible, infectious or recovered; and enables a physical interpretation for the probability of infection upon contact to describe disease dynamics. The later feature is important from our perspective because we can define a range of physically plausible values for the probability of infection that reflect (i) the effectiveness of hygiene interventions, and (ii) the influence of viral factors on emission, environmental survival and transport, and infectivity.[13,18] We extend Larson's model by incorporating the effect of hygiene interventions on the probability of infection during contact, and compare the impact of two NPI simultaneously. We specifically consider the hygiene intervention of mask use, and the social distancing intervention of reduced contact rates in the high-activity group, but the method can incorporate other interventions, such as hand washing and heterogeneity in contact rate reduction.

Each NPI has a different effectiveness for epidemic mitigation, and also a different cost. Policy makers consider many factors in the recommendation of interventions, including: efficacy, compliance, and direct and indirect costs. To begin to inform this decision-making process, we present an optimization strategy to select some combination of NPIs which minimize financial costs of an epidemic. In this analysis, the levels of intervention compliance that minimizes cost and the number of infections are identified, along with the levels of intervention compliance that impact epidemic dynamics and changes in the total cost.

2. Methods

2.1. Disease Transmission Model I

The approach described by Larson[(17)] is applied in the context of a heterogenous population divided into two groups, with high and low social activity. Given the emphasis here on illustration of the modeling approach, the age structure of the population, and the influence of age on social activity is not included. We assume that each activity group is homogenous, and that there is no difference between the two groups with regard to biological susceptibility to infection.

Social contacts that could result in effective influenza transmission are assumed to occur between two people according to a homogenous Poisson process. The high- and low-activity groups have respectively λ_H and λ_L social contacts per person per day on average. The two groups interact, such that an individual in the high-activity group, for example, has a total of λ_H contacts per day which can occur with persons in either activity group. Initially (day 0), the high-activity group includes n_H individuals, and the low-activity group includes n_L individuals. Initially, in the population there are $(n_H\lambda_H + n_L\lambda_L)/2$ interactions, on average.

We assume that upon infection on day i, a susceptible person becomes infectious on day $i+1$, and is no longer able to transmit the disease, e.g. recovered, at the beginning of day $i+2$. The model can easily be extended to a longer period of infectiousness (as in model II), or a period of infectiousness with reduced contacts due to isolation at home. On day $i = 1, 2, \ldots, D$, $n_H^I(i)$ persons in the high-activity group are infectious, and $n_H^S(i)$ are susceptible. We define similarly, for the low-activity group, $n_L^I(i)$ and $n_L^S(i)$. All susceptible people on day i become infectious or remain susceptible on day $i+1$:

$$n_H^S(i) = n_H^S(i+1) + n_H^I(i+1), \tag{1}$$

$$n_L^S(i) = n_L^S(i+1) + n_L^I(i+1). \tag{2}$$

The probability that a susceptible person becomes infected upon a random interaction with an infectious person is given by parameter p. This constant parameter represents a weighted average infection likelihood over the range of all possible social contacts.

The probability that the next interaction of a randomly selected person is with an infectious person is equal to the proportion of contacts in the population on day i which involve an infectious person:

$$\beta(i) = \frac{\lambda_H n_H^I(i) + \lambda_L n_L^I(i)}{\lambda_H n_H + \lambda_L n_L}. \tag{3}$$

The denominator in Equation 3 is the number of contacts in the total population. This expression differs from that used by Larson,[17] who permanently removed persons from the population upon infection. The approach of Larson[17] is not physically reasonable when the number infected during the epidemic is large because the population available for contacts decreases, and approaches zero. Given a constant contact rate, the effect is to increase the intensity of contacts, which in the extreme, is not physically reasonable.

On day i the number of contacts between a person in the high-activity group and an infectious person in either activity group is a Poisson random variable, with expectation $E[C_H(i)] = \lambda_H \beta(i)$. The probability of infection conditional upon $C_H(i)$ is $1-(1-p)^{C_H(i)}$, such that the unconditional probability of infection across all possible values of $C_H(i)$ is:

$$p_H^S(i) = 1 - \exp[-\lambda_H \beta(i) p]. \tag{4}$$

Similarly, for persons in the low-activity group, the probability that a random susceptible person becomes infected on day i is:

$$p_L^S(i) = 1 - \exp[-\lambda_L \beta(i) p]. \tag{5}$$

On day $i+1$, the number of newly infectious persons is the product of the probability of infection on day i and the number of susceptible persons on day i:

$$\begin{aligned} n_H^I(i+1) &= p_H^S(i) n_H^S(i), \quad (6) \\ n_H^I(i+1) &= p_L^S(i) n_H^S(i). \quad (7) \end{aligned}$$

The computations repeat for each of the D days. The total number of infections can then be computed as:

$$N^I = \sum_{i=1}^{D} n_H^I(i) + n_L^I(i). \quad (8)$$

Social distancing interventions reduce the contact rates λ_H and/or λ_L. Here we consider social distancing to reduce λ_H by quantity λ_d, where $0 < \lambda_d < \lambda_H$. The contact rate decreases more with stronger social distancing interventions, such as closing additional public places, schools or offices.

Hygiene interventions reduce the probability of infection p, by interrupting one or more routes of disease transmission between persons. Here, we consider hygiene interventions to reduce p by the quantity p_h, where $0 < p_h < p$. The infection probability decreases more with more effective hygiene interventions.

The reproductive number, $R_\circ$, equal to the number of new infections created by the average infectious person on day 1, is computed:

$$R_\circ = \frac{p_H^S(1)[n_H - n_H^I(1)] + p_L^S(1)[n_L - n_L^I(1)]}{n_H^I(1) + n_L^I(1)}. \quad (9)$$

Hygiene interventions impact $R_\circ$ through the parameter p in the definition of $p_H^S(1)$ and

$p_L^S(1)$ (Equations 4 and 5); while social distancing interventions impact $R_\circ$ through the parameter λ_H and/or λ_L in the definition of $p_H^S(1)$, $p_L^S(1)$ and $\beta(1)$ (Equations refeqn: beta–5).

2.2. Disease Transmission Model II

Disease transmission model II extends model I to better reflect the duration of incubation (non-infectious and infectious) and symptomatic infection (infectious). Specifically, upon infection persons move deterministically through 6 states, each of duration 1 day: 1) asymptomatic but not infectious, 2) asymptomatic and infectious, and 3–6) symptomatic and infectious. This progression was selected to align with natural history of influenza described by Longini et al.[19] The number of persons in each of the 6 states on day i is denoted $n_H^A(i)$, $n_H^{I1}(i)$, $n_H^{I2}(i)$, $n_H^{I3}(i)$, $n_H^{I4}(i)$, $n_H^{I5}(i)$ for the high-activity group, respectively; and similarly for the low-activity group. This means: $n_H^{I1}(i+1) = n_H^A(i)$, $n_H^{I2}(i+1) = n_H^{I1}(i)$, etc. Analogously to Equation 3, the probability that the next interaction of a randomly selected person is with an infectious person on day i is:

$$\beta(i) = \frac{\lambda_H\left(\sum_{j=1}^{5} n_H^{Ij}(i)\right) + \lambda_L\left(\sum_{j=1}^{5} n_L^{Ij}(i)\right)}{\lambda_H n_H + \lambda_L n_L} \tag{10}$$

The probabilities that a random susceptible person becomes infected on day i is as defined in Equations 4–5, but that person enters the state n_H^A or n_L^A rather than n_H^I or n_L^I, as specified in Equations 6–7. The total number of new infections on day i is

$$N^{new}(i) = n_H^A(i) + n_L^A(i), \tag{11}$$

while the total number infected on day i is

$$N^I(i) = n_H^A(i) + \sum_{j=1}^{5} n_H^{Ij}(i) + n_L^A(i) + \sum_{j=1}^{5} n_L^{Ij}(i). \tag{12}$$

For this model we assume that persons are equally infectious on days 2–6 and retain the activity level of their group.

2.3. Optimization Model

The optimum combination of NPI is one which minimizes an objective function that takes into account both the financial costs of implementing each NPI and the social costs of the epidemic. The goal is to select the compliance levels for hygiene ($C_h \in (0, 1]$) and social distancing ($C_d \in (0, 1]$) interventions so as to minimize the total cost. The optimization problem is formulated as:

$$\min_{C_d, C_h}\left(C_d c_d + C_h c_h + N^I c_I\right) \tag{13}$$

where c_d and c_h are the costs per unit compliance of the social distancing and hygiene interventions, respectively, and c_I is the cost of each infection. For this analysis, these costs are assumed to be fixed, and independent of, respectively intervention effectiveness and N^I.

2.4. Implementation & Parameters

2.4.1. Population

We consider a population of 100,000 individuals, with a 30:70 split between the high- and low-activity groups: $n_H = 30,000$ and $n_L = 70,000$ (Table 1). There are no specific demographic features of the population. On day 1, we assume that 0.05% of the individuals are infectious, such that $n_H^I(1) = 15$, $n_H^S(1) = 29,985$, $n_L^I(1) = 35$, and $n_L^S(1) = 69,965$. Sensitivity to the initial population split between social activity groups was explored using two cases: (i) $n_H = n_L = 50,000$, and (ii) $n_H = 20,000$ and $n_L = 80,000$.

2.4.2. Contact Rates

Among European 20–29 year olds, the mean (standard deviation) of number of contacts is 13.57 (10.60) per day.[20] Assuming the contact rate is normally distributed, we equate the high-activity group contact rate with $\lambda_H = 26.4$ day^{-1} (87th percentile). The population-weighted average contact rate is 13.57 when the low-activity group contact rate is $\lambda_L = 8.07$ day^{-1} (30th percentile). In contrast, Tracht et al.[7] assumed a rate of 16 contacts per day for the entire population. Sensitivity to contract rates was explored using two cases: (i) $\lambda_H = 35.0$ day^{-1} and $\lambda_L = 8.07$ day^{-1} and (ii) $\lambda_H = 26.4$ day^{-1} and $\lambda_L = 4$ day^{-1}.

We assume that the effective contact rate in the high-activity group equals 50% of the baseline contact rate when complying with the intervention, denoted $f_d = 0.5$ (Table 1). The intervention is modeled for the duration of the epidemic. Sensitivity of predictions to f_d was explored using $f_d = \{0.3, 0.7\}$, where compliance with the intervention yields contact rates equal to 30% and 70% of the baseline rate for the high-activity group. Note that the overall population size and density affect the reduction in contact rate due to compliance with the social distancing intervention. For example, social distancing is likely to have a higher impact when people are spread out over a larger area and where social settings like school represent a relatively unique opportunity for contact. School closures in a crowded urban area, however, may not prevent social contacts with infectious persons as effectively since numerous contacts occur outside of schools. The reduction in contact rates should then be set taking into account the characteristics of the population under consideration.

On the population level, the reduction in λ_H by λ_d is a function of compliance with the distancing intervention, C_d. For $C_d \in [0, 1]$, equal to the decimal fraction of compliance, the average contact rate in the high-activity group is:

$$\lambda_{H,avg} = \lambda_H(1 - C_d) + f_d\lambda_H C_d = \lambda_H - C_d(\lambda_H - f_d\lambda_H) = \lambda_H - \lambda_d \tag{14}$$

for $f_d > 0$, and where $\lambda_d = C_d\lambda_H(1 - f_d)$.

2.4.3. *Infection Probability*

Mechanistic models suggest that for a relatively high-intensity, 15 min contact, the probability of infection varies several orders of magnitude, $p \in [10^{-7}, 10^{-1}]$.[18] These values of p used a dose-response function based on human infectivity studies with strains of seasonal influenza that had been maintained in the laboratory. For pandemic influenza, p could take even higher values due to increased viral infectivity, and absence of residual immunity due to prior exposure to or vaccination against similar viruses.[21] Respirators or masks reduce the inhaled dose of virus to a fraction f_h of the inhaled dose without respirator use. For small p, p is proportional to dose, such that when a respirator or mask is worn, the probability of infection is approximately pf_h.

We consider the NPI of wearing a respirator. N95 filtering facepiece respirators have an assigned protection factor (APF) of 10,[22] which means that the contaminant concentration in air inside the respiratory is one-tenth that in the outside air, $f_h = 0.10$. While research studies have found N95 filtering facepiece respirators to perform better than the APF,[23] use of the APF is required in the United States for respirator selection in occupational settings by OSHA (29 CFR 1910.134). Respirators interrupt exposures via other routes, by preventing the deposition of virus-laden droplets on the mucous membranes of the nose and mouth via droplet spray and contact. Therefore, the reduction in risk may be greater than expected from f_h, but effectiveness may be decreased because users are untrained in how to wear a respirator, duration of use may decrease compliance, and some users may substitute surgical or cloth masks which have lower protection factors.[24,26] As a result, we assume $f_h = 0.5$, corresponding to an assigned protection factor of 2. Sensitivity of predictions to f_h was explored using $f_h = \{0.3, 0.7\}$, for which the probability of infection equals 30% and 70% of the baseline value of p. The values for f_h equal the range of mask efficacy values used by Brienen et al.[6]

The hygiene intervention was applied for the duration of the epidemic (90 days). In accordance with the finding of Tracht et al.[7] that early introduction of mask use reduced the number of infections, we considered respirator use to begin on epidemic day 0, when 0.05% of the population is infected.

On the population level, the reduction in p by p_h is a function of compliance with respirator use, C_h. For $C_h \in (0, 1]$, the average probability of infection for the population is:

$$p_{avg} = p(1 - C_h) + pf_hC_h = p - C_h(p - pf_h) = p - p_h \tag{15}$$

for $f_h > 0$, and where $p_h = C_hp(1 - f_h)$.

The values of $p = 0.10$ and $p = 0.12$ were selected for use in disease transmission model I because they yield $R_\circ$ equal to 1.36 and 1.63, respectively, under baseline (no intervention) conditions (Table 2), which are similar to $R_\circ$ values observed for seasonal and 2009 H1N1 influenza epidemics.[26,27] Due to the prolonged presence of infectious persons in the population in disease transmission model II, smaller values of p are necessary to achieve observed $R_\circ$ values. The values $p = 0.028$ and $p = 0.034$ were selected for use in model II because they yield $R_\circ$ equal to 1.36 and and 1.66, respectively, under baseline conditions (Table 2).

2.4.4. *Social Distancing Costs*

There are many direct and indirect costs to social distancing interventions. As a starting point we consider only the costs associated with lost work productivity. A day of lost work is valued at \$180 per day.[28] We assume that reduced contacts equate to a 10% decrease in productivity, costing, \$18 per day.

We assume that social distancing is observed for the duration of the epidemic. Each fractional increase in compliance, $C_d \in (0, 1]$, with the social distancing intervention corresponds to $C_h n_H$ people with reduced productivity. The intervention cost per unit compliance, is c_d =\$18 per day per person $\times$ 90 days $\times n_H$ persons. Thus c_d= \$ 48.6×10^6 for $n_H = 30,000$, and c_d= \$ 32.4×10^6 and c_d= \$ 81.0×10^6 when $n_H = 20,000$ and $n_H = 50,000$, respectively.

In certain cases, social distancing intervention costs may grow exponentially, rather than linearly with compliance. This can be due to the expense of obtaining compliance from reluctant individuals or to the increasing financial impact of compliance. For instance, closure of schools or of public transportation would incur a cost that grows rapidly with compliance. To explore the sensitivity of the optimization problem to the functional form of costs, we defined the intervention cost as an exponential function of compliance with social distancing, and allowed the cost to vary based with n_H. For $n_H = 30,000$, the cost is \$ $10^6 \times \exp(5 \times C_d)$. For $n_H = 20,000$ and $n_H = 50,000$, the constant changes proportionally to n_H, such that the costs equal \$ $6.67 \times 10^5 \times \exp(5 \times C_d)$ and \$ $1.67 \times 10^6 \times \exp(5 \times C_d)$, respectively. The value of this cost function surpasses the linear costs for C_d >71%. The constants were selected to provide similar costs to the linear function for low compliance, and higher costs relative to the linear function for high compliance.

2.4.5. Hygiene Intervention Costs

The respirator considered for the hygiene intervention — an N95 filtering facepiece — can be purchased at hardware stores. At Lowe's hardware in Chicago, IL a package of 20 N95 filtering facepiece respirators costs $20. In the occupational setting, use of N95 filtering facepiece respirators requires a medical evaluation and fit-testing, which incur substantial costs. However, the general public wears these respirators without such evaluations and testing. While we therefore assume that no fit-testing occurs, we assume that the costs of the respirators increase 3-fold due to distribution and supply issues, to $3 per respirator.

We assume that respirator use is observed for the duration of the epidemic, expected to be 90 days. Each incremental increase δ in compliance with respirator use corresponds to δn individuals (where $n = n_L + n_H = 100,000$), who use 1 respirator per day for $D = 90$ days, such that the cost per unit compliance is c_h = \$3 each $\times n$ persons $\times$ 90 days = \$27 $\times 10^6$.

2.4.6. Infection Costs

Based on the analysis of Molinari et al.,[29] we assume: (i) 100% of infected persons lose 3 days of work, with a cost of $180 per day, (ii) 40% of infected persons seek outpatient care, costing $260 per person, (iii) 4% of infected persons are hospitalized, costing $24,000 per person, and (iv) 1% of infected persons die, costing \$80,000 per person. These data indicate the average cost of an infection to be \$2,400: $c_I = \$2,400$.

2.3.7. Optimization Function

The problem of selecting the compliance levels so as to minimize the epidemic and intervention costs is written in Equation 13. The total number of infections N^I depends on both compliance levels as compliance affects the spread of the epidemics, so we use numerical simulation to determine the total cost as a function of both C_d and C_h using Matlab. We simulate the dynamics of the epidemics by evaluating the number of infectious individuals in each subgroup using disease transmission model I (Equations 3–7) or model II (Equation 10); and evaluate the total number of new infections using Equation 8 or 12. Standard built-in optimization functions may then solve the optimization function.

3. Results

3.1. Disease Transmission Model

The basic epidemic features of disease transmission models I and II are summarized in Table 2 for baseline conditions and intervention compliance equal to 0% or 50%. In both models the hygiene intervention applied singly results in fewer infections and lower $R_\circ$ than the social distancing intervention applied singly. Increasing p increases $R_\circ$ and the total number of infections. The influence of the interventions on $R_\circ$ is similar in both models, though more individuals are infected in model II than in model I for the same R_o value.

For baseline conditions, the total number of infections is minimized by maximizing compliance with both interventions applied jointly for both disease transmission models (Figure 1 and S1). Even though the effectiveness of each intervention is equal ($f_h = f_d = 0.5$), the hygiene intervention yields fewer infections for a given level of compliance than the social distancing. This may be due, in part, to the application of the hygiene intervention to both activity groups, while the social distancing intervention is applied only the high-activity group. When social distancing is applied singly, the rate at which increased compliance decreases the number of infections decreases for larger values of p in both model I and II. This makes sense because if the probability of infection upon contact is high, then fewer contacts are needed, on average, to infect susceptible persons, such that reducing contact rates will have less influence on the epidemic. In Model II, this phenomenon is more apparent because infectious persons remain infectious in the population for five days, rather than one day, increasing the proportion of contacts among susceptible persons with infectious persons.

Increasing the effectiveness of the intervention (smaller values of f_h and f_d) increases the rate at which the number of infections decreases with increasing compliance (Figures 2 and S2). Figure 3 considers the event that social distancing is more effective (intervention compliance yields a high-activity contact rate equal to $0.3\lambda_H$ for $f_d = 0.3$) than the hygiene intervention (intervention compliance yields a probability of infection upon contact equal to 0.7p for $f_h = 0.7$): The asymmetry in intervention effectiveness is apparent, favoring compliance with social distancing over the hygiene intervention to decrease the total number of infections. The rate at which the number of infections decreases increases dramatically when compliance with the social distancing intervention exceeds 40% and 70% in models I and II, respectively, when applied singly. The opposite event is shown in Figure S3, where compliance with the hygiene intervention is favored relative to social distancing owing to the greater effectiveness of the hygiene intervention relative to the social distancing intervention ($f_d = 0.7$, $f_h = 0.3$).

Increasing the number of persons in the high-activity group increases the total number of infections in the population in both models I and II. Results for $n_H = 50,000$ are shown in Figure S4. For $n_H = \{20,000, 30,000, 50,000\}$ absent interventions, model I with $p = 0.10$ predicts 43%, 54% and 67% of the population to be infected, respectively. For all values of n_H, absent interventions, model II with $p = 0.028$ predicts 63%, 70%, 80% of the population to be infected, respectively. Increasing n_H decreases the effectiveness of both interventions applied singly and jointly (Figure S4), indicated by the higher number of total infections relative to the baseline cases.

Increasing the contact rate in the high-activity group from $\lambda_H = 26.8$ day^{-1} to $\lambda_H = 35$ day^{-1} increases the total number of infections slightly in model I, and decreases the number of infections prevented by the interventions applied singly and jointly (Figure S5). The influence on model II is smaller, likely owing to the high number of infections and small impact of the interventions in this model (Figure S5). Decreasing the contact rate in the low activity group from $\lambda_L = 8.07$ day^{-1} to $\lambda_L = 4$ day^{-1} has little impact on the number of infections, and on the number of infections prevented by the interventions in models I and II (data not shown).

For all combinations of input parameters, the total number of infections are minimized by maximum compliance with the interventions, applied jointly (Table 3).

3.2. Optimization of Intervention Strategies

Epidemic costs of disease transmission models I and II are summarized in Table 2 for baseline conditions and intervention compliance equal to 0% or 50%. Intervention compliance that minimizes total cost are presented in Table 3. For these baseline conditions, total cost increases with increasing probability of infection in both models, and is higher for model II than model I. When intervention costs are linear with compliance, peak total cost occurs in the absence of interventions for model I; while peak total cost occurs when the social distancing intervention is applied singly with approximately 50% compliance in model II. When social distancing intervention costs are exponential with compliance, high total cost is associated with application of social distancing in the absence of the hygiene intervention in both models.

Considering disease transmission model I with baseline conditions, the surface of total cost as a function of compliance is depicted in Figure 4 for $p = 0.10$ and Figure S6 for $p = 0.12$. When intervention costs are a linear function of compliance, the total cost is minimized (\$$2.8 \times 10^7$) for $p = 0.10$ when the hygiene intervention is applied singly with 100% compliance; and is minimized (\$4.3 $\times$ 10^7) for $p = 0.12$ when the hygiene and social distancing interventions are jointly applied with 100% and 26% compliance, respectively. Inspection of Figures 4(a) and S6(a) indicates that less compliance with the hygiene intervention does not dramatically increase total cost as long as social distancing is applied jointly. When social distancing intervention costs are an exponential function of compliance, the total cost is minimized (\$2.8$\times$$10^7$) for $p = 0.10$ when the hygiene and social distancing interventions are jointly applied with 84% and 26% compliance, respectively; and is minimized (\$3.3$\times$$10^7$) for $p = 0.12$ when the when the hygiene and social distancing interventions are jointly applied with 100% and 30% compliance, respectively. Inspection of Figures 4(b) and S6(b) indicates that small decreases in compliance with the hygiene intervention increase costs more rapidly than similar increases in compliance with the social distancing intervention. In the exponential cost scenario, the range of intervention compliance in which costs are minimized is small relative to the linear cost scenario.

Considering the disease transmission model II with baseline conditions, the surface of total cost as a function of compliance is depicted in Figure 5 for $p = 0.028$ and Figure S7 for $p = 0.034$. When intervention costs are a linear function of compliance, the total cost is minimized (\$3.7 $\times$ 10^7) for $p = 0.028$ when the hygiene and social distancing interventions are jointly applied with 100% and 37% compliance, respectively; and is minimized (\$6.4 $\times$ 10^7) for $p = 0.034$ when the hygiene and social distancing interventions are jointly applied with 100% and 66% compliance, respectively. Inspection of Figures 5(a) and S7(a) indicates that increasing social distancing compliance singly has little impact on the total cost, but total cost increases rapidly when compliance with the hygiene intervention decreases, unless companied by increased social distancing compliance. When social distancing intervention costs are an exponential function of compliance, the total cost is minimized ($\$4.9 \times 10^7$) for $p = 0.028$ when the hygiene and social distancing interventions are jointly applied with 100% and 33% compliance, respectively; and is minimized ($\$5.6 \times 10^7$) for $p = 0.034$ when the when the hygiene and social distancing interventions are jointly applied with 100% and 59% compliance, respectively. Inspection of Figures 5(b) and S7(b) indicates that the total cost in model II respond similarly to that in model I for the exponential increase social distancing costs with intervention compliance. However, in the model II, change in the total cost, particularly with compliance with the hygiene intervention when social distancing compliance is low, and is modest relative to the order of magnitude change observed in model I.

The total costs for various levels of intervention effectiveness, $f_h = \{0.3, 0.7\}$ and $f_d = \{0.3, 0.7\}$, are depicted in Figures 6 and S8–S14 for disease transmission model I ($p = 0.10$) and model II ($p = 0.028$). For both models, when intervention effectiveness increases ($f_h = f_d = 0.3$), the total cost decreases more rapidly as compliance increases from 0, such that total cost is minimized with lower intervention compliance (Figures S8 and S12). As in the baseline case, however, high compliance with social distancing does not lower the total cost regardless of whether social distancing intervention costs increase linearly or exponentially with compliance. When intervention effectiveness decreases ($f_h = f_d = 0.7$), the magnitude of change in total cost over the range of compliance decreases for both models (Figures S9 and S13); and the minimal total cost in model II is an order of magnitude higher than baseline conditions (Table 3). In this scenario, for both models I and II, when social distancing intervention costs are an exponential function of compliance, the total cost is higher when the social distancing intervention has a high compliance rate ($C_d > 0.8$) than when no interventions are applied. When hygiene interventions are more effective than social distancing ($f_h < f_d$), the total cost has similar contours to that for baseline conditions in both models. However, when social distancing interventions are more effective than hygiene interventions ($f_h > f_d$) and social distancing intervention costs are an exponential function of compliance, then total cost is minimized for a narrow range of social distancing compliance, that widens slightly as hygiene compliance increases (Figure 6).

Increasing the initial number of persons in the high-activity group (Figures S16–S17), and increasing the high-activity group contact rate (Figures S18–S19) increase the total cost in the absence of interventions. Responses to these changes are similar for both models I and II, and for linear and exponential increases in social distancing intervention costs when compared to the total cost for the respective baseline conditions. Essentially, these changes decrease the rate at which total cost decrease with increasing compliance, such that total cost is minimized by higher compliance levels than in the baseline conditions. Decreasing the low-activity group contact rate has small influence on the total cost (data not shown).

The duration of intervention utilization was assumed to be 90 days for all simulations, such that the total cost of interventions was independent of the epidemic duration. We explored the impact of calculating intervention costs based on the duration of the epidemic, where the duration of the epidemic was defined as time between intervention initiation and the number of new infections was $\leqslant 0.05\%$ of the total population. The cost-benefit optimization surfaces were indistinguishable from those attained assuming interventions costs were incurred over 90 days for model I. This indicates that the costs of the infections drive the optimization of the objective function specified by Equation 13.

Overall, these results indicate that while the magnitude of total cost varies between disease transmission models I and II, the total cost respond similarly to model inputs, including to changes in: intervention compliance, intervention effectiveness, contact rates, and initial subgroup populations. While application of the hygiene intervention singly did not minimize infections or total cost in all scenarios, the intervention is less sensitive than social distancing: Total cost declined more consistently with increasing compliance and had shallower slopes near points of minimization than was often seen with social distancing interventions. Not shown, is that further increase in p extends the patterns observed; increasing the total cost and decreasing the rate of cost reduction with increasing intervention compliance.

4. Discussion

This research presents a method by which the effect of hygiene and social distancing interventions on influenza epidemic dynamics can be compared; and an optimization strategy for the selection of these non-pharmaceutical interventions (NPI) taking implementation costs into account. We have illustrated that the method is feasible, sensitive to the duration of infectiousness, and sensitive to the selection of model parameters. Specifically, we demonstrated that the severity of the epidemic measured by the total number of infections and the optimal intervention strategy will depend upon the probability of infection (p), duration of infectiousness (models I and II), intervention compliance (C_d and C_h), intervention costs (c_d and c_h), and intervention effectiveness (f_d and f_h). Notably, the response of total cost to changes in p, C_d, C_h, f_d and f_h relative to baseline conditions were similar for disease transmission models I and II. These preliminary findings support refinement of the model to incorporate a more realistic population structure and more representative cost estimates; so as to enable informative exploration of the roles of NPI in influenza epidemic mitigation.

NPI may significantly impact influenza epidemics. Social distancing, in the form of school closures, was associated with a 29–37% reduction in influenza A/H1N1 transmission in Mexico.[27] Epidemiological investigations have been less conclusive with regards to the impact on hygiene interventions on influenza transmission,[16,30,31] but there is biological and physical plausibility for the ability of hygiene interventions to reduce infection risk. Recommended hygiene interventions such as frequent hand washing, surface disinfection, the use of respiratory protection, and the use of cough/sneeze etiquette are intended to reduce the density of virus along potential routes of transmission, thereby reducing virus exposure and infection risk. Social distancing interventions decrease the likelihood of environmental contamination by infectious persons, and likelihood of susceptible persons contacting infectious persons and contaminated environments. Individuals use NPI as a result of education, and concerns about influenza transmission.[31–33]

In this work we have specifically modeled the use of respirators to reduce the inhalation of virus in the environment, and like other investigators we have found that respirator (or mask) use can influence influenza epidemics.[5–7] The approach we have taken, however, is appropriate to other hygiene interventions. We propose in future work to calculate p for selected contact scenarios, such as what has been done for a person attending a bed-ridden infectious patient:[13,18] Different hygiene interventions can be directly incorporated into the contact scenario model to estimate p', the probability of infection given the intervention. Using the nomenclature herein, we could then estimate f_h based on the relative magnitudes of p and p'. Similarly, new knowledge or hypotheses about influenza transmission processes and strain-specific variation in infectivity and disease severity can be incorporated into calculation of p and p'. Alternatively, agent-based models of disease transmission[35,36] may be modified to meet this objective.

Model II extended the duration of infectiousness from 1 day in model I to five days, including one day of asymptomatic virus shedding to reflect the average duration of influenza infectiousness; but retains the activity level of infectious persons. This is unrealistic in the sense that individuals infected with influenza may be more likely to curtail social contacts, owing to affects of their illness, than susceptible or recovered individuals. Given the results presented herein, we expect that selectively reducing the contact rate for infectious persons would decrease the total number of infections, and would increase the effect of social distancing compliance. It is important to observe that total cost estimated with model II responded to changes in input parameters similarly to model I, suggesting that insights into epidemic mitigation may be obtained through relatively simple representations of the natural history of influenza.

Given the intent of illustrating a methodological approach, many important determinants of epidemic dynamics and costs have been excluded from the results presented herein. This is a stylized model that captures the essential trade-offs between NPI in a health- and cost-conscious environment. Our goal is to provide a tractable computational method that can be adapted to the needs of a specific decision-making framework. Complexity and realism must be balanced with interpretability and objectives. The complex influenza transmission model applied by Kernéis et al.,[5] for example, identified an important phenomenon — that the influence of interventions on epidemic features may vary between pandemic types, but the results do not identify the magnitude of impact from NPI, nor identify conditions under which NPI, alone or in combination, are effective for the mitigation of influenza epidemics.

With regard to the disease transmission model, for example, the population was defined with two strata — a high- and a low-activity group — but the modeling framework can be extended to more heterogeneous populations with age- and/or location-specific contact patterns. In addition, we assumed that the probability of infection, intervention effectiveness and compliance are constant over the duration of the epidemic, and uniform.

In fact, all of these factors vary, and are influenced by the size of the epidemic, disease severity, and personal lifestyle and beliefs.[34] Variability in these model parameters can be addressed by allowing them to vary across population strata, within population strata, and to change over time. Such variability requires the development of probability density functions for each parameter, or conditioning on epidemic features. For example, variability in p and p_h can be determined by using a mathematical model to estimate the probability of influenza transmission from person to person for selected, representative contact scenarios.[13,18] In contrast, observational data is available about contract rates and community population networks.[20,37,38]

With regard to the optimization model, only direct costs related to health outcomes and lost work productivity were included to the development of a cost function that is linear with intervention compliance. The optimization function, however, can be readily extended to include additional direct costs and indirect costs, such as costs resulting from: health policy implementation, social disruption, loss of quality of life, and/or lost life. Alternative expressions for the optimization function can also be defined that consider, for example, the likely event that intervention costs increase non-linearly with compliance due to the high programmatic costs associated with achieving high levels of compliance. We approximated this by a cost function that was exponential in compliance with the social distancing intervention, and showed that this changes the optimum combination of interventions.

The model presented herein has not directly considered the cost of severity. Severity of disease can be incorporated by increasing the costs associated with infection. Severity of the epidemic can be incorporated by increasing the cost of infection as the total number of infection increases.

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Variable	Value	Description
Disease Transmission Model		
D	90 day	Duration of epidemic simulation
n_H	30,000	Total population in high-activity group
n_L	70,000	Total population in low-activity group, $n_L = 100,000 - n_H$
$n_H^I(1)$	15	Number of infectious persons in high-activity group on day 1, $n_H^I(1) = 0.0005 \times n_H$
$n_L^I(1)$	35	Number of infectious persons in low-activity group on day 1, $n_L^I(1) = 0.0005 \times n_L$
$n_H^S(1)$	29,985	Number of susceptible persons in high-activity group on day 1
$n_L^S(1)$	69,965	Number of susceptible persons in low-activity group on day 1
p	{0.10, 0.12}	Probability of infection upon contact between infectious and susceptible persons, model I
p	{0.028, 0.034}	Probability of infection upon contact between infectious and susceptible persons, model II
λ_H	26.4 day^{-1}	Contact rate for persons in high-activity group
λ_L	8.07 day^{-1}	Contact rate for persons in low-activity group
C_d	(0,1]	Compliance rate for social distancing intervention
C_h	(0,1]	Compliance rate for hygiene intervention
f_d	0.5	Effectiveness of social distancing invention, proportional reduction in λ_H
f_h	0.5	Effectiveness of hygiene intervention, proportional reduction in p
Optimization Model: Linear Costs		
c_d	\$48.6$\times10^6$	Social distancing intervention cost per unit change compliance
c_h	\$27$\times10^6$	Hygiene intervention cost per unit change in compliance
c_I	\$2,400	Average cost of an infection

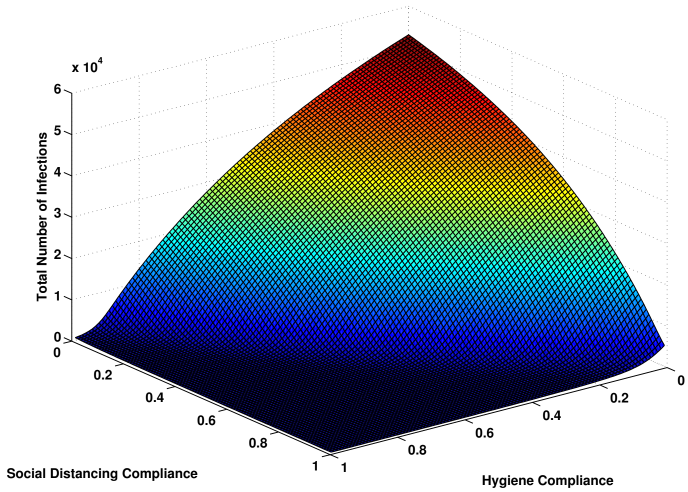
Table 1: Disease transmission and optimization model baseline parameters defined.

Intervention	$R_\circ$	$N^I \times 10^3$	Linear $\$ \times 10^7$	Exponential $\$ \times 10^7$	$R_\circ$	$N^I \times 10^3$	Linear $\$ \times 10^7\$$	Exponential $\times 10^7$
	Disease Transmission Model I							
	$p = 0.10$				$p = 0.12$			
No intervention	1.36	53	13	13	1.63	63	15	15
Hygiene only	1.02	34	9.4	9.5	1.22	47	13	13
Social distancing only	1.16	40	12	11	1.39	54	15	14
Both interventions	0.87	9.4	6.0	4.7	1.04	30	11	9.7
	Disease Transmission Model I							
	$p = 0.028$				$p = 0.034$			
No intervention	1.36	70	17	17	1.66	78	19	19
Hygiene only	1.03	56	15	15	1.25	66	17	17
Social distancing only	1.15	65	18	17	1.39	75	20	19
Both interventions	0.86	43	14	13	1.05	59	18	17

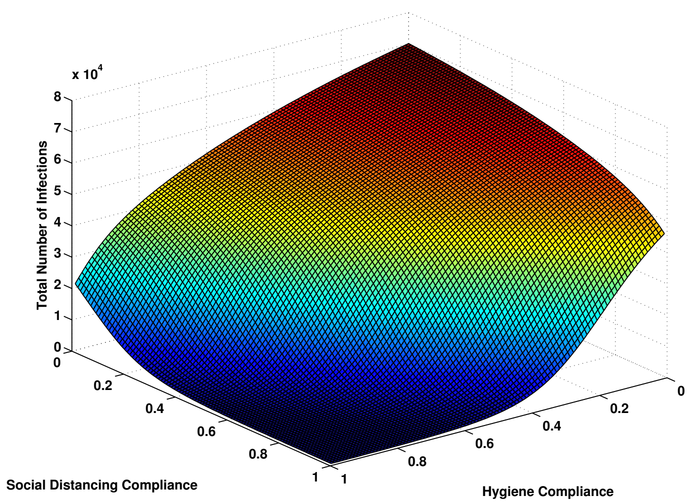
Table 2: Reproductive number ($R_\circ$), total number of infections (N^I), and total cost ($) calculated with and without NPI interventions at 50% compliance ($C_d = C_h = 0.5$) applied singly and jointly, under baseline conditions for social distancing costs as a linear and exponential function of compliance.

Input Parameters	Minimized Total Infections			Minimzied Total Costs					
				Linear Cost			Exponential Cost		
	C_d	C_h	N^I	C_d	C_h	$\$ \times 10^7$	C_d	C_h	$\$ \times 10^7$
Disease Transmission Model I									
Baseline, $p = 0.10$	1.0	1.0	100	0	1.0	2.8	0.26	0.84	2.8
Baseline, $p = 0.12$	1.0	1.0	127	0.26	1.0	2.3	0.30	1.0	3.3
$f_d = f_h = 0.3$	1.0	1.0	67	0	0.71	2.1	0.28	0.53	2.0
$f_d = f_h = 0.7$	1.0	1.0	605	0.79	1.0	7.7	0.59	1.0	7.1
$f_d = 0.3$, $f_h = 0.7$	1.0	1.0	115	0.77	0	4.0	0.51	0.68	3.5
$f_d = 0.7$, $f_h = 0.3$	1.0	1.0	79	0	0.71	2.1	0.04	0.70	2.2
$\lambda_H = 35.0$ day^{-1}	1.0	1.0	127	0.44	1.0	5.1	0.44	1.0	3.9
$\lambda_L = 4.0$ day^{-1}	1.0	1.0	83	0.07	1.0	3.3	0.28	0.88	3.0
$n_H = 20,000$	1.0	1.0	95	0	0.82	2.4	0.36	0.58	2.2
$n_H = 50,000$	1.0	1.0	113	0.23	1.0	4.1	0.25	1.0	3.5
Disease Transmission Model II									
Baseline, $p = 0.028$	1.0	1.0	99	0.37	1.0	3.7	0.33	1.0	4.9
Baseline, $p = 0.034$	1.0	1.0	257	0.66	1.0	6.4	0.59	1.0	5.6
$f_d = f_h = 0.3$	1.0	1.0	53	0.26	1.0	4.4	0.32	1.0	3.4
$f_d = f_h = 0.7$	1.0	1.0	22,700	1.0	1.0	13	0.45	1.0	15
$f_d = 0.3$, $f_h = 0.7$	1.0	1.0	21	1.0	0.89	2.5	0.19	0.80	2.6
$f_d = 0.7$, $f_h = 0.3$	1.0	1.0	45	0	0.90	2.5	1.0	0.89	2.6
$\lambda_H = 35.0$ day^{-1}	1.0	1.0	275	0.76	1.0	6.8	0.66	1.0	6.8
$\lambda_L = 4.0$ day^{-1}	1.0	1.0	58	0.41	1.0	5.2	0.43	1.0	3.9
$n_H = 20,000$	1.0	1.0	80	0.05	1.0	3.6	0.29	0.95	3.1
$n_H = 50,000$	1.0	1.0	151	0.60	1.0	6.1	0.51	1.0	6.0

Table 3: Social distancing intervention decimal fraction compliance, C_d, and hygiene intervention decimal fraction compliance, C_h, that minimize the total number of infections and total costs when social distancing intervention costs increase linearly or exponentially with compliance. Unless otherwise specified, all implementations of model I use $p = 0.10$ and all implementations of model II use $p = 0.028$. Input parameters reflect changes relative to baseline parameters (Table 1).

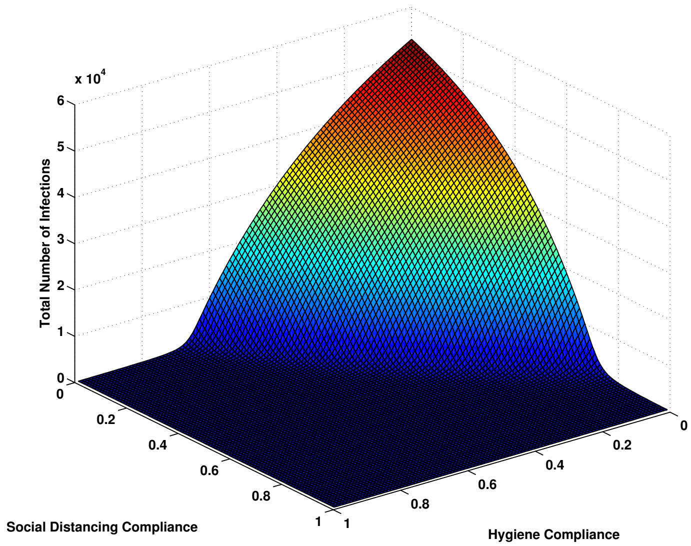


(a) Model I, $p = 0.10$

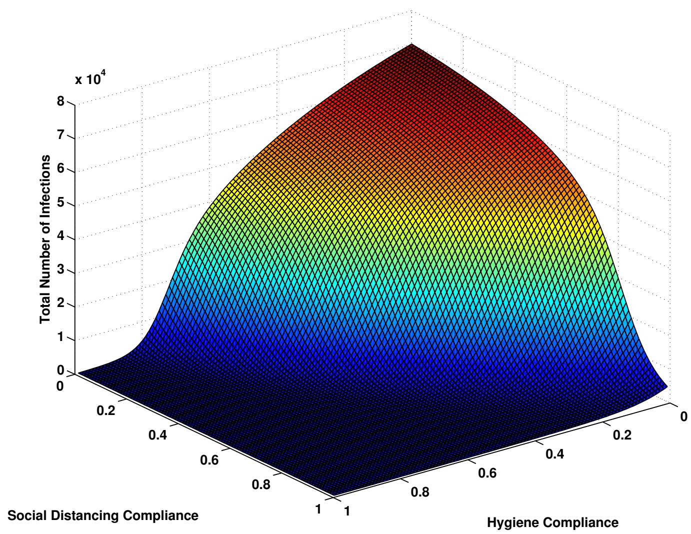


(b) Model II, $p = 0.028$

Figure 1: Total number of infections as a function of compliance for the lower probability of infection values in disease transmission models I and II.

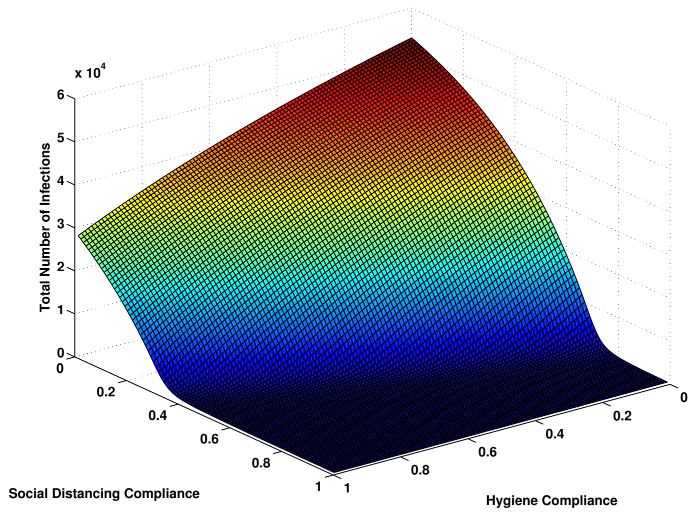


(a) Model I, $p = 0.10$

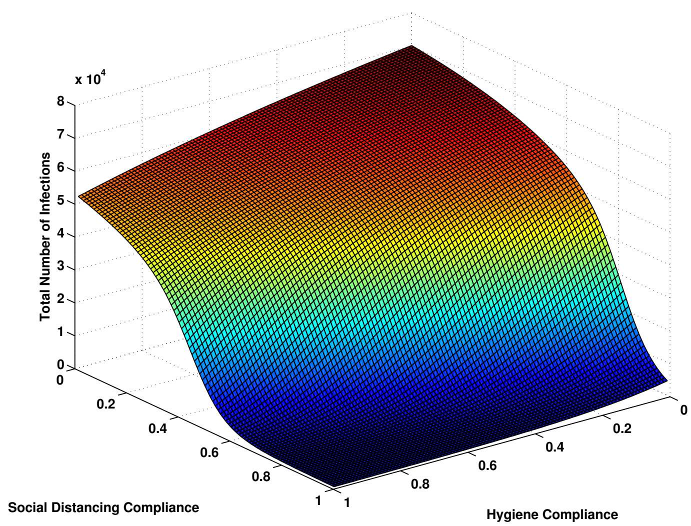


(b) Model II, $p = 0.028$

Figure 2: Total number of infections as a function of compliance given 30% probability of infection for respirator use ($f_h = 0.3$) and 30% contact rate in the high-activity group ($f_d = 0.3$) for disease transmission models I and II.

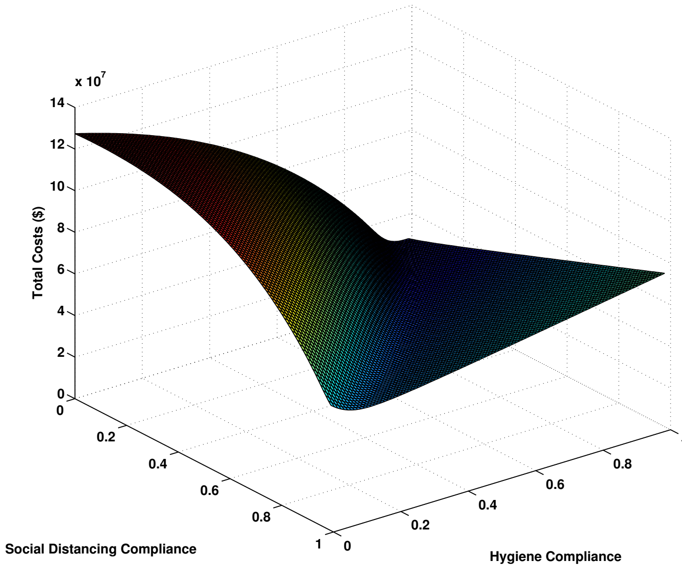


(a) Model I

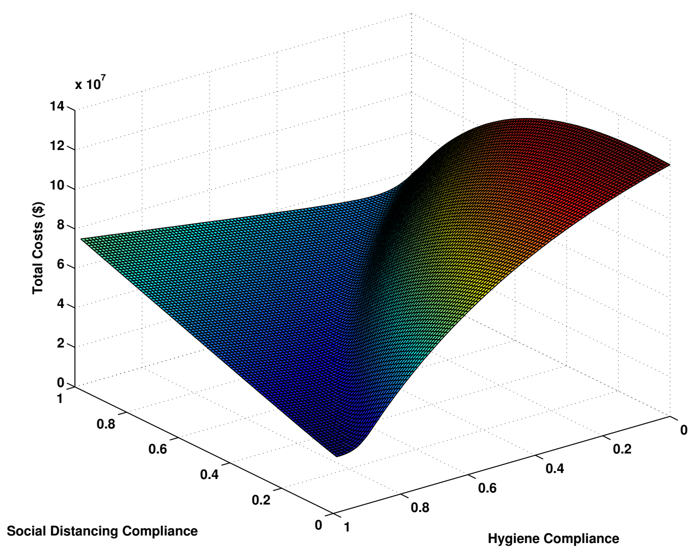


(b) Model II

Figure 3: Total number of infections as a function of compliance given 70% probability of infection for respirator use ($f_h = 0.7$) and 30% contact rate in the high-activity group ($f_d = 0.3$) for disease transmission models I ($p = 0.10$) and II ($p = 0.028$).

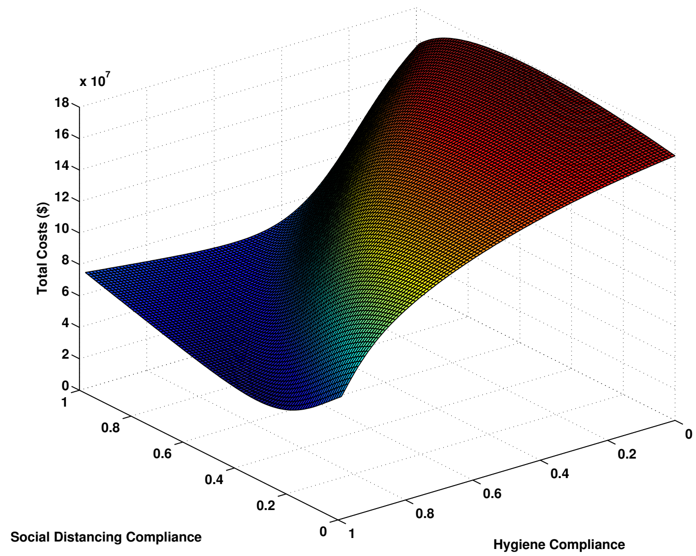


(a) Linear Cost

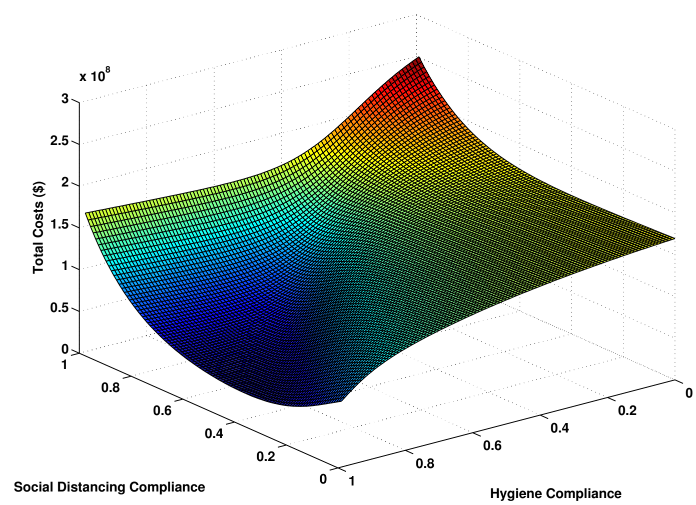


(b) Exponential Cost

Figure 4: Total costs as a function of compliance given linear costs as a function of intervention compliance for both interventions, compared to exponential costs for social distancing intervention compliance in disease transmission model I with baseline conditions and $p = 0.10$.

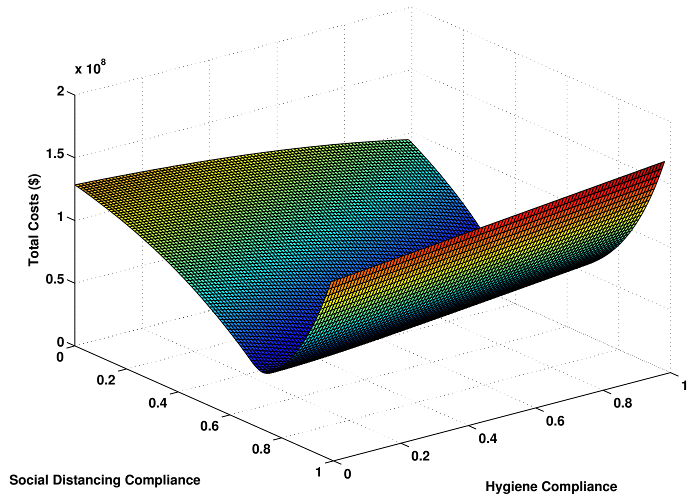


(a) Linear Cost

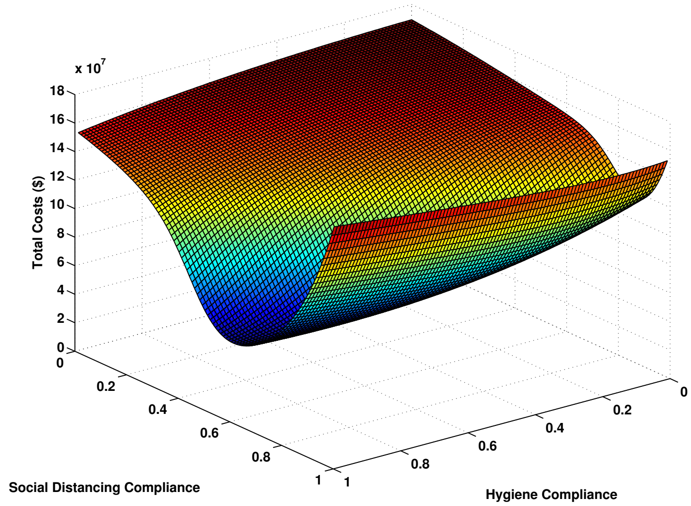


(b) Exponential Cost

Figure 5: Total costs as a function of compliance given linear costs as a function of intervention compliance for both interventions, compared to exponential costs for social distancing intervention compliance in disease transmission model II with baseline conditions and $p = 0.028$.



(a) Model I



(b) Model II

Figure 6: Total costs as a function of compliance given exponential costs of social distancing intervention compliance in disease transmission models I ($p = 0.10$) and II ($p = 0.028$) with decreased effectiveness of social distancing, $f_d = 0.3$, and increased effectiveness of the hygiene intervention, $f_h = 0.7$.

Figure Captions

Figure 1. Total number of infections as a function of compliance for the lower probability of infection values in disease transmission models I and II.

Figure 2. Total number of infections as a function of compliance given 30% probability of infection for respirator use ($f_h = 0.3$) and 30% contact rate in the high-activity group ($f_d = 0.3$) for disease transmission models I and II.

Figure 3. Total number of infections as a function of compliance given 70% probability of infection for respirator use ($f_h = 0.7$) and 30% contact rate in the high-activity group ($f_d = 0.3$) for disease transmission models I ($p = 0.10$) and II ($p = 0.028$).

Figure 4. Total costs as a function of compliance given linear costs as a function of intervention compliance for both interventions, compared to exponential costs for social distancing intervention compliance in disease transmission model I with baseline conditions and $p = 0.10$.

Figure 5. Total costs as a function of compliance given linear costs as a function of intervention compliance for both interventions, compared to exponential costs for social distancing intervention compliance in disease transmission model II with baseline conditions and $p = 0.028$.

Figure 6. Total costs as a function of compliance given exponential costs of social distancing intervention compliance in disease transmission models I ($p = 0.10$) and II ($p = 0.028$) with decreased effectiveness of social distancing, $f_d = 0.3$, and increased effectiveness of the hygiene intervention, $f_h = 0.7$.