

## **COST-EFFECTIVENESS ANALYSIS OF VACCINATION AND SELF-ISOLATION IN CASE OF H1N1**

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### **ABSTRACT**

In this research, we have conducted a cost-effectiveness analysis to examine the relative importance of vaccination and self-isolation, with respect to the current H1N1 outbreak. We have developed a continuous-time simulation model for the spread of H1N1 which allows for three types of interventions: antiviral prophylaxis and treatment, vaccination, and self-isolation and mandatory quarantine. The optimization model consists of two decision variables: vaccination fraction and self-isolation fraction among infectives. By considering the relative marginal costs associated with each of these decision variables, we have a linear objective function representing the total relative cost for each control policy. We have also considered upper bound constraints for maximum number of individuals under treatment (which is related to surge capacity) and percentage of infected individuals (which determines the attack rate). We have used grid search to obtain insight into the model, find the feasible region, and conduct the cost-effectiveness analysis.

### **1 INTRODUCTION**

#### **1.1 Research Question and Methodology**

Epidemiologists warn that the next pandemic influenza could infect 33% of the population and kill millions (Gibbs and Soares 2005). According to the Centers for Disease Control and Prevention (CDC), there will be up to \$71.3-165.5 billion economic impact on the United States Economy and the World Health Organization (WHO) estimates that 2-7.4 million people might die (Ekici, Keskinocak, and Swann 2008). Hence, preparing for a potential influenza pandemic should receive high priority from governments at all levels (local, state, federal), non-governmental organizations (NGOs), and companies. Also it is essential that considerable research be devoted to study different aspects of influenza pandemics scientifically.

According to the Department of Health and Human Services (HHS), development of efficient and effective pandemic mitigation strategies is a complicated systems issue that requires immediate attention (HHS pandemic influenza plan. 2007). As a matter of fact, there are always limitations on the implementation of the counter measures. For example, even after a new virus subtype is identified, it may take up to

six months to produce a potent vaccine in sufficient quantity (Fedson and Hant 2003). If the emerging virus belongs to a known subtype, available vaccine doses may not be adequate for the entire population; nor may be antiviral drugs. In addition, the government budget is always an inevitable limitation. Thus, the government dollars should be spent on the most effective interventions. These issues bring another important decision factor into the picture: “cost” of different interventions. Regarding the modeling approach to examine different interventions in case of influenza, the Institute Of Medicine (IOM) recommends that “future modeling efforts incorporate broader outcome measures, beyond influenza-related outcomes, to include the costs and benefits of intervention strategies” (Committee on Modeling Community Containment for Pandemic Influenza 2006). Considering both “effectiveness” and “cost” of an intervention leads us to “cost-effectiveness” analysis; which is currently widely used to compare different mitigation policies and find the “best” one.

Two of the most common ways to control an outbreak are vaccination and isolation. There is a cost associated with each of these interventions. The question is “which one is more effective and less costly?” Therefore the research question is: “*which one is more cost-effective?*” We have used a modeling approach to answer this question.

In this research, we have developed a compartmental continuous-time simulation model for the spread of H1N1 to conduct a cost-effectiveness analysis to examine the relative importance of vaccination and self-isolation, two common measures for controlling the spread of infectious diseases. The simulation model allows for three types of interventions: antiviral prophylaxis and treatment, vaccination, and self-isolation and mandatory quarantine.

To have a realistic estimation of the model parameters and validate the model, we need a target population, since the model parameters (such as contact rate) vary from a region and a population to another. We have considered the North Carolina State University (NCSU) undergraduate students as our target population. In this research, we have taken advantage of the cooperation of the NCSU Student Health Services Medical Director, who verified the merit of the model and suggested very helpful modifications to the structure of our model. Thus our model is now validated from this expert’s view.

The cost associated with each control policy is reflected in the objective function. By considering the relative marginal costs associated with each of the decision variables (i.e. vaccination fraction and self-isolation fraction) we have a linear objective function representing the total relative cost for each control policy.

It is not acceptable if a large portion of the population become infective, since the surge capacity is limited. In addition, if an outbreak is so widespread and the attack rate is so high, the people would panic which may result in a real public catastrophe. Also, a large outbreak would have severe negative impacts on the economy. Therefore, the outbreak should be in some way “controlled”. We may define the control of an epidemic as keeping the total number of infectives below a fixed value and keeping the number of infectives at any one time below another fixed value (Hethcote and Waltman 1973). As a result, we have considered two upper bound constraints for the maximum number of individuals under treatment (which is related to surge capacity), and percentage of total infective individuals (which determines the attack rate).

Our model, which is actually a system of differential equations, was too complicated to be solved analytically; therefore, we decided to use computer simulation to find the solution. We have used Arena as the simulation software. We have used a grid search to obtain some insight into the model and also to find a “good” feasible solution. Furthermore, we have used the grid search results to conduct a cost-effectiveness analysis on different control policies and to find the most cost-effective one.

We hope that the results of this research help the health care officials in their decision making process about implementing several interventions and taking appropriate and on-time counter measures.

## 1.2 Literature Review

Some of the efforts in modeling the pandemic outbreak have focused on developing statistical models to examine the statistical aspects of the outbreak (Cauchemez et al. 2004; Longini and Koopman 1982). On

the other hand, some other researchers have focused on the virus spread dynamics and transitions between disease phases. These efforts resulted in several mathematical models which are usually represented in a system of differential equations (Arino et al. 2006; Cahill et al. 2005).

In addition to statistical and mathematical models, simulation-based models (both agent-based models (which track each individual) and event-based models (which are driven by infection events)) have been developed to model the disease spread and also examine the impacts of different interventions, including antiviral prophylaxis and treatment, vaccination and isolation (Das and Savachkin 2008; Ferguson et al. 2006; Glass, Beyeler, and Min 2006). Some of these models integrate different types of interventions seeking synergetic strategies. A good example of such models is the network model of MIDAS (Models of Infectious Diseases Agent Study) which used three independent simulation models to examine different interventions in 2006-07 (Halloran et al. 2008). These models were used to simulate large-scale pandemic influenza spread for rural areas of Asia (Longini et al. 2005), U.S. and U.K. (Germann et al. 2006), and the city of Chicago (Eubank et al. 2004).

One popular way to model the progression of an infectious disease through a population is via detailed simulation modeling building on transportation planning models and social networks (Christley et al. 2005; Ferguson et al. 2005). Longini et al. (Longini et al. 2005) use a simulation model with social networks to address the possible spread of influenza in Southeast Asia. Wu et al. (Wu et al. 2006), building from the Hong Kong SARS experience, use simulation modeling to demonstrate the effectiveness of even partial voluntary “household-based” social controls such as self-isolation and quarantine. Ekici et al. (Ekici, Keskinocak, and Swann 2008) use a simulation based spread model with heterogeneous mixing to study the logistics side of the problem, specifically, food distribution logistics during the pandemic influenza. Finally, Yarmand et al. (Yarmand, Ivy, and Roberts 2010) have used a compartmental simulation model to analyze different interventions in case of an H1N1 outbreak.

Since the beginning of the recent H1N1 outbreak, several researchers and health institutions have turned their attention to this novel influenza. In some research, the disease transmission dynamics have been analyzed (Fraser et al. 2009; Madhav 2009). Also there have been some efforts to estimate the disease parameters and characteristics, especially the basic reproduction number and the horizontal incidence (Nishiura, Wilson, and Baker 2009).

Some of the guidelines and research have focused on specific interventions. Those models seeking synergetic strategies by integrating different interventions deal with a type of resource allocation problem and do not *directly* compare the effectiveness of two specific interventions. Furthermore, “cost” is a fairly recently considered factor in assessing different interventions. Also, social distancing, which may be very effective in mitigating the diseases spread, has sometimes been ignored in the disease spread models. We have incorporated both cost and social distancing measures in our model, in addition to vaccination and antiviral prophylaxis and treatment, which altogether create a comprehensive framework for the disease spread.

To the best of our knowledge, our work is the first one which focuses on comparing two specific interventions and examines not only the *relative effectiveness* of vaccination and self isolation (by grid search) but also the *relative cost-effectiveness* of these two interventions by incorporating relative marginal costs in a fairly uncomplicated way and by using the grid search results to calculate the Average Cost-Effectiveness Ratio (ACEV). Furthermore, the methodology introduced in our research can be used for comparing any two particular interventions (for example, vaccination and antiviral prophylaxis).

## 2 MODELING

### 2.1 Simulation Model

In a compartmental model, the disease is assumed to have several progress stages. Individuals move between these stages with specific rates (i.e. each individual can only be in one compartment at a time). It is assumed that all individuals in each of the compartments have similar characteristics in that all are in the same stage of the disease progress, and as soon as an individual enters a compartment, there is no differ-

ence between him/her and other individuals in that compartment; this assumption is referred to as the “homogeneity assumption”.

Most of the rates in a compartmental model have a similar form. They are a function of the current compartment population and the mean waiting time of an individual in that compartment before moving to the next compartment, which we denote by  $n_i$  and  $\tau_{ij}$  for the original compartment  $i$  and the destination compartment  $j$ , respectively. Also denote by  $\Delta(i, j)$  the transfer from compartment  $i$  to  $j$  (i.e. number of individuals transferred from compartment  $i$  to  $j$ ). Then the general form of the transfer rate from compartment  $i$  to  $j$  (denoted by  $r_{ij}$ ) would be

$$r_{ij} = \frac{d\Delta(i, j)}{dt} = n_i * \frac{1}{\tau_{ij}}$$

The disease characteristics in the context of infectiousness are reflected in the “horizontal incidence”, which is one of the rates. This rate determines the number of individuals who get infected per unit of time. Denote by  $f_I(t)$  and  $f_S(t)$  the infectious and susceptible fractions at time  $t$ , respectively. Also denote by  $N(t)$  the total population size at time  $t$ . If  $\beta$  is the average number of adequate contacts (i.e., contacts sufficient for transmission) of a person per unit time, then  $\beta f_I$  is the average number of contacts with infectives per unit time of one susceptible, and  $\beta N f_I f_S$  is the number of new cases per unit time due to the  $N f_S$  susceptibles. As a result, if we denote the horizontal incidence at time  $t$  by  $H(t)$ , then we have  $H(t) = \beta N(t) f_I(t) f_S(t)$ .

This form of the horizontal incidence is called the standard incidence, because it is formulated from the basic principles above (Hethcote 2000).

The model we have developed in this research is an extension of the SEIR model for H1N1 with three types of interventions (vaccination, antiviral prophylaxis and antiviral treatment, and self-isolation and mandatory quarantine). The transfer diagram for this model is presented in Figure 1. Our time horizon is 5 months. Note that due to the relatively short time horizon, zero birth and death rates have been considered in our model.

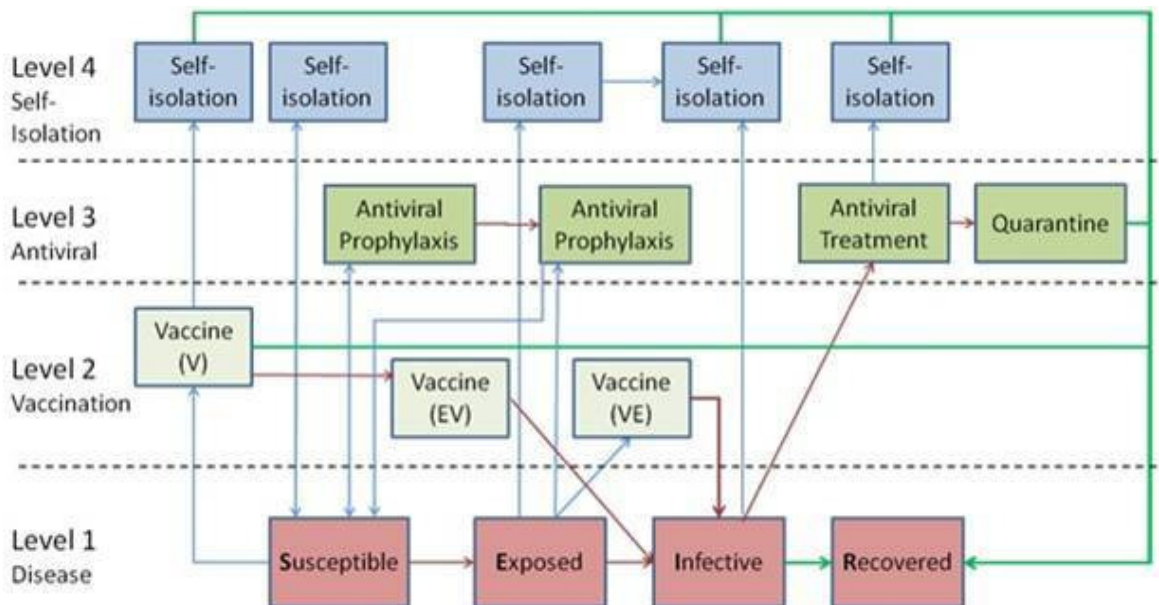


Figure 1: Transfer diagram for the spread model of H1N1.

Each red arrow refers to exposure or infection while each green arrow refers to returning to the healthy condition through recovery. Also each blue arrow refers to one of the interventions. We can di-

vide the transfer diagram into four levels as indicated in Figure 1. The first level, which appears at the bottom, includes the disease progress stages (compartments S for Susceptible, E for Exposed, I for Infective and R for Recovered). The susceptible compartment contains those individuals who do not have any type of immunity to H1N1 and can become infected. When there is an adequate contact of a susceptible with an infective so that transmission occurs, then the susceptible enters the exposed compartment of those in the latent period, who are infected but not yet infectious. After the latent period ends, the individual enters the infective compartment of infectives, who are infectious in the sense that they are capable of transmitting the infection. When the infectious period ends, the individual enters the recovered compartment consisting of those with permanent infection-acquired immunity.

The second level includes vaccination related compartments. If a susceptible receives vaccine, then he/she is transferred from the susceptible compartment to the vaccine compartment (V). After receiving the vaccine, it takes a while until the vaccine becomes effective. This period is called “vaccine effectiveness period”. It is possible that an exposed individual gets the vaccine, since the exposed individual has not developed any symptoms yet and therefore cannot be distinguished from a susceptible.

The third level includes antiviral related compartments (antiviral prophylaxis and treatment, and also mandatory quarantine). Although quite rare, both susceptible and exposed individuals may take antiviral prophylaxis for a certain period called “prophylaxis period” to prevent becoming infective and developing symptoms. For example, a susceptible individual may take antiviral prophylaxis to prevent transmission from an infective roommate. Antiviral prophylaxis is effective in preventing exposure (becoming infected) with a certain probability called Antiviral Effectiveness for Susceptibles (AVEs). Therefore some susceptible individuals who take the antiviral prophylaxis might still become infected. Antiviral drugs may also be used for treatment and recovery of those infective individuals with H1N1-related complications.

The fourth level, which is on the top of the transfer diagram, consists of self-isolation compartments. Individuals may decide to go to the self-isolation after receiving the vaccine. These individuals would be transferred to the recovered compartment after the end of the self-isolation period.

The model is basically a first-order system of 16 differential equations which altogether describe the dynamics of the disease spread and is numerically integrated by Arena.

## **2.2 Model Parameters**

Disease-related data may vary from region to region and also from age to age. As a result, it is required that we define a target population and then gather data for that particular target population in a specific area. As indicated previously, our target population in this research is the NCSU undergraduate students. Therefore, the data we gather should sufficiently match the specifications of this target population.

Due to lack of accurate data, we decided to use expert opinion as a validation for our model. Therefore we asked the NCSU Student Health Services Medical Director to examine our model structure and make suggestions. Those suggestions were incorporated into the final structure.

The model is deterministic and we used the values in the literature for the parameters. We have a number of parameters in this model. The parameters fall in four different groups:

- Parameters associated with the disease.
- Parameters associated with the interventions (including the two decision variables).
- Parameters associated with the target population demography.
- Parameters associated with the simulation runs.

## **2.3 Optimization Model**

We have considered two control measures: vaccination and self-isolation for infective individuals. Any control policy will result in a different set of outcomes. Of importance to us are three particular outcomes: cost, maximum number of individuals under treatment, and percentage of total infective individuals. The optimization model has two decision variables: vaccination fraction and self-isolation fraction among in-

fectives denoted by  $p_1$  and  $p_2$ , respectively. The objective function is the linear summation of the relative costs of vaccination and self-isolation by considering the relative marginal costs, associated with each of the decision variables (the costs of a 1% increase in the vaccination and self-isolation fraction) denoted by  $c_1$  and  $c_2$ , respectively. Clearly as long as  $cost\ ratio = \frac{c_1}{c_2}$  is constant, the optimal solution does not change. Since we will compare the minimum relative total cost for different cost ratios, we have normalized the relative marginal costs by considering the additional condition  $c_1 + c_2 = 1$ .

The constraints consist of two upper bound constraints for maximum number of individuals under treatment (which is related to surge capacity), and percentage of total infective individuals (attack rate) with upper bounds  $U_1$  and  $U_2$ , respectively. Therefore, the optimization model would be

$$\begin{aligned}
 &min \quad z = c_1 p_1 + c_2 p_2 \\
 &subject\ to: \\
 &max(Under\ Treatment) \leq U_1 \\
 &\% Total\ Infectives \leq U_2 \\
 &0 \leq p_1, p_2 \leq 1
 \end{aligned}$$

where  $c_1, c_2, U_1$  and  $U_2$  are determined by the modeler so that:

$$\begin{aligned}
 &0 \leq U_1 \leq Total\ Population \\
 &0 \leq U_2 \leq 1 \\
 &c_1 + c_2 = 1.
 \end{aligned}$$

### 3 RESULTS AND ANALYSIS

We have used grid search to obtain insight into the model and find “near optimal” feasible solutions. Also we have used the grid search results to conduct the cost-effectiveness analysis.

The optimization model has several parameters which should be determined by the modeler. The values for the optimization model parameters we have considered in this research are presented in Table 1.

Table 1: Optimization model parameters and their values.

Parameter	Value for Grid Search and Cost-Effectiveness Analysis	Parameter	Value for Grid Search and Cost-Effectiveness Analysis
$cost\ ratio$ $(c_1/c_2)$	1	$U_1$	200
$c_1$	0.5	$U_2$	0.05
$c_2$	0.5	Total Population	23087

#### 3.1 Grid Search

Our results show that in the region in which  $p_1, p_2 \leq 0.5$ , the performance measures are very sensitive to changes in the value of  $p_1$  and  $p_2$ . It makes sense, since the effectiveness of interventions is reasonably higher in lower levels. Therefore, we have conducted the grid search in the region  $p_1, p_2 \leq 0.5$  with time steps equal to 0.05. The associated numerical results have been presented in Tables 2-4.

Table 2: Relative cost for different control policies  $(p_1, p_2) \in [0, 0.5]$ .

Relative Cost		Vaccination Fraction (p1)										
		0.00	0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50
Self-isolation Fraction (p2)	0.00	0.000	0.025	0.050	0.075	0.100	0.125	0.150	0.175	0.200	0.225	0.250
	0.05	0.025	0.050	0.075	0.100	0.125	0.150	0.175	0.200	0.225	0.250	0.275
	0.10	0.050	0.075	0.100	0.125	0.150	0.175	0.200	0.225	0.250	0.275	0.300
	0.15	0.075	0.100	0.125	0.150	0.175	0.200	0.225	0.250	0.275	0.300	0.325
	0.20	0.100	0.125	0.150	0.175	0.200	0.225	0.250	0.275	0.300	0.325	0.350
	0.25	0.125	0.150	0.175	0.200	0.225	0.250	0.275	0.300	0.325	0.350	0.375
	0.30	0.150	0.175	0.200	0.225	0.250	0.275	0.300	0.325	0.350	0.375	0.400
	0.35	0.175	0.200	0.225	0.250	0.275	0.300	0.325	0.350	0.375	0.400	0.425
	0.40	0.200	0.225	0.250	0.275	0.300	0.325	0.350	0.375	0.400	0.425	0.450
	0.45	0.225	0.250	0.275	0.300	0.325	0.350	0.375	0.400	0.425	0.450	0.475
0.50	0.250	0.275	0.300	0.325	0.350	0.375	0.400	0.425	0.450	0.475	0.500	

Table 3: Percent of total infective individuals for different control policies  $(p_1, p_2) \in [0, 0.5]$ .

Percent of Infectives		Vaccination Fraction (p1)										
		0.00	0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50
Self-isolation Fraction (p2)	0.00	88.84	58.26	42.66	34.04	28.86	25.51	23.21	21.55	20.30	19.33	18.56
	0.05	85.70	51.61	35.80	27.75	23.17	20.30	18.37	17.00	15.97	15.19	14.56
	0.10	82.18	44.25	28.93	21.88	18.09	15.78	14.26	13.18	12.38	11.77	11.29
	0.15	78.22	36.51	22.57	16.83	13.88	12.12	10.97	10.16	9.56	9.11	8.75
	0.20	73.78	28.88	17.15	12.77	10.58	9.30	8.45	7.86	7.42	7.09	6.82
	0.25	68.86	21.97	12.85	9.67	8.10	7.18	6.57	6.14	5.83	5.58	5.39
	0.30	63.43	16.23	9.61	7.38	6.27	5.61	5.18	4.87	4.64	4.46	4.31
	0.35	57.51	11.83	7.25	5.70	4.93	4.46	4.14	3.92	3.75	3.61	3.51
	0.40	51.09	8.63	5.55	4.48	3.93	3.59	3.37	3.20	3.07	2.98	2.90
	0.45	44.15	6.39	4.32	3.58	3.19	2.95	2.78	2.65	2.56	2.49	2.43
0.50	36.63	4.82	3.44	2.91	2.63	2.45	2.33	2.23	2.16	2.11	2.06	

Table 4: Maximum number of individuals under treatment for different control policies  $(p_1, p_2) \in [0, 0.5]$ .

Maximum Treatment		Vaccination Fraction (p1) - Total population: 23087										
		0.00	0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50
Self-isolation Fraction (p2)	0.00	2047	1473	1141	941	814	727	666	621	586	559	537
	0.05	1615	1071	793	641	548	488	446	415	391	373	359
	0.10	1273	762	541	431	368	327	300	279	264	252	243
	0.15	998	529	364	289	248	222	204	191	181	174	168
	0.20	776	358	243	195	169	153	142	133	127	122	118
	0.25	595	237	163	133	118	107	101	95	91	88	86
	0.30	449	156	111	93	84	78	73	70	67	65	64
	0.35	330	103	77	67	61	57	55	53	51	50	49
	0.40	236	69	55	49	46	43	42	40	39	39	38
	0.45	161	48	40	37	35	34	33	32	31	31	30
0.50	105	34	30	29	27	27	26	26	25	25	24	

The results show that the best solution is  $(p_1, p_2) = (0.1, 0.45)$  with the associated relative cost of 0.275. Note that in Table 2, there are four feasible solutions with the same minimum cost of 0.275. We have picked  $(p_1, p_2) = (0.1, 0.45)$  by comparing the associated percent of infectives, which seems to be more important than the maximum number of individuals under treatment, since the former is the binding constraint. If we compare the columns and rows of Tables 3 and 4, it is observed that in low levels of vac-

ination and self-isolation, vaccination is more effective in improving both performance measures. For instance, when the self-isolation fraction is equal to zero (i.e.  $p_2 = 0$ ), the maximum number of individuals under treatment and percent of infectives are decreased from 2047 to 1473 and from 88.84 to 58.26, respectively as the vaccination fraction is increased from zero to 0.05 (i.e.  $p_1 = 0.05$ ). Compared with the case that vaccination fraction is equal to zero (i.e.  $p_1 = 0$ ) and self-isolation fraction is increased from zero to 0.05 (i.e.  $p_2 = 0.05$ ), these results show that in low levels of interventions, vaccination is more effective than self-isolation in improving both performance measures. By a similar comparison in high levels of interventions, and in particular in the feasible region, we observe that in high levels of interventions, self-isolation is more effective than vaccination in improving both performance measures. This conclusion becomes more evident by noting the contours of the percent of infective individuals in Figure 2.

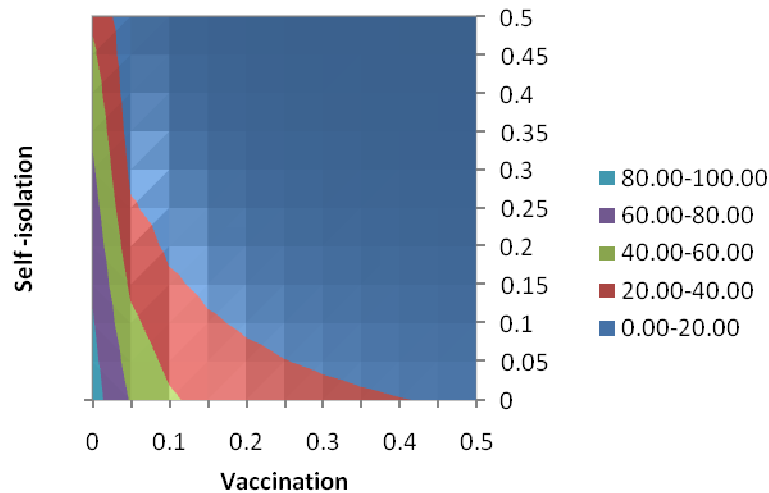


Figure 2: Percent of infective individuals for different control policies  $(p_1, p_2) \in [0, 0.5]$ .

Figure 2 clearly demonstrates that in low (high) levels of interventions, the percent of infectives is more sensitive to changes in the vaccination (self-isolation) fraction than self-isolation (vaccination) fraction.

### 3.2 Cost-Effectiveness Analysis

We conducted a cost-effectiveness analysis using the grid search results. We have used the Average Cost Effectiveness Ratio (ACER), which is widely used in the field of health services, to compare different control policies. We have already defined the cost as the linear summation of the relative marginal costs of vaccination and self-isolation. In other words, we have

$$\text{cost of policy } (p_1, p_2) = c_1 p_1 + c_2 p_2.$$

For the effect of the policy  $(p_1, p_2)$ , we consider the “percent of protected population”, which we define as the percent of population who has never become infective (has never become sick and developed symptoms). The percent of protected population is related to the percent of total infectives as follows

$$\text{effect} = \text{percent of protected population} = 100 - \text{percent of total infectives}.$$

It is reasonable to base the *effect* on the percent of total infectives, since this is the *binding* constraint (note that the feasible region in Table 3 is a subset of the feasible region in Table 4) and also logically seems to be more important than the other performance measure, maximum number of individuals under treatment.



The cost-effectiveness ratio for different control policies  $(p_1, p_2) \in [0, 0.5]$  is calculated and presented in Table 5.

Table 5: Cost-effectiveness ratio for different control policies  $(p_1, p_2) \in [0, 0.5]$ .

Cost-Eff. Ratio ( $\times 10^{-2}$ )	Vaccination Fraction ( $p_1$ )											
	0.00	0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50	
Self-isolation Fraction ( $p_2$ )	0.00	0.0000	0.0599	0.0872	0.1137	0.1406	0.1678	0.1953	0.2231	0.2509	0.2789	0.3070
	0.05	0.1748	0.1033	0.1168	0.1384	0.1627	0.1882	0.2144	0.2410	0.2678	0.2948	0.3219
	0.10	0.2806	0.1345	0.1407	0.1600	0.1831	0.2078	0.2333	0.2592	0.2853	0.3117	0.3382
	0.15	0.3444	0.1575	0.1614	0.1804	0.2032	0.2276	0.2527	0.2783	0.3041	0.3301	0.3562
	0.20	0.3814	0.1758	0.1811	0.2006	0.2237	0.2481	0.2731	0.2985	0.3240	0.3498	0.3756
	0.25	0.4014	0.1922	0.2008	0.2214	0.2448	0.2693	0.2943	0.3196	0.3451	0.3707	0.3964
	0.30	0.4102	0.2089	0.2213	0.2429	0.2667	0.2913	0.3164	0.3416	0.3670	0.3925	0.4180
	0.35	0.4119	0.2268	0.2426	0.2651	0.2893	0.3140	0.3390	0.3643	0.3896	0.4150	0.4405
	0.40	0.4089	0.2463	0.2647	0.2879	0.3123	0.3371	0.3622	0.3874	0.4127	0.4381	0.4634
	0.45	0.4029	0.2671	<b>0.2874</b>	0.3111	0.3357	0.3606	0.3857	0.4109	0.4362	0.4615	0.4868
	0.50	0.3945	0.2889	0.3107	0.3347	0.3595	0.3844	0.4095	0.4347	0.4599	0.4852	0.5105

Note that the most cost-effective control policy is the same as the best policy we found by grid search, which is  $(p_1, p_2) = (0.10, 0.45)$ .

One interesting result is that by comparing the symmetric policies in the feasible region (i.e. by comparing policies  $(a, b)$  and  $(b, a)$ ), we observe that the policy in which the self-isolation fraction is higher than the vaccination fraction is incrementally more cost-effective. For instance, consider the policy  $(p_1, p_2) = (0.35, 0.35)$ . Now, if the vaccination fraction is increased by 0.05, then the resulting policy,  $(p_1, p_2) = (0.40, 0.35)$ , has the cost-effectiveness ratio equal to 0.3896. But if the self-isolation fraction is increased by 0.05, then the resulting policy,  $(p_1, p_2) = (0.35, 0.40)$ , has the cost-effectiveness ratio equal to 0.3874. Therefore, if we are to make a decision about increasing one of the vaccination or self-isolation fractions, our model suggests that we increase the self-isolation fraction, since it is incrementally more cost-effective. An important point is that this conclusion is only valid in the feasible region, since by a similar analysis we observe that vaccination is incrementally more cost-effective in the *infeasible* low levels of interventions.

#### 4 CONCLUSION AND FUTURE DIRECTIONS

In this research, we developed a simulation model for the spread of H1N1. Also we developed an optimization model which seeks the least expensive feasible control policy regarding vaccination and self-isolation fractions. We conducted grid search to find a "near optimal" policy. The grid search results revealed that *while in low levels of interventions, vaccination is more effective than self-isolation in improving the performance measures, self-isolation is more effective in relatively high levels of interventions.* Then we used grid search results to conduct a cost-effectiveness analysis to conclude that while the most cost-effective policy is a combination of both vaccination and self-isolation, self-isolation is incrementally more cost-effective than vaccination in the feasible region.

Therefore, the public health officials should concentrate on vaccination at the beginning of an outbreak, and after a while, if the outbreak was not contained and the disease continued to spread, they should promote self-isolation as a more effective intervention.

Although our model is fairly comprehensive regarding different types of interventions we have incorporated into the model (vaccination, antiviral prophylaxis and treatment, and isolation and mandatory quarantine), it still can be improved to reflect the reality more accurately. For instance, although we really

dealt with a “nearly” homogeneous population (undergraduate students of the NC State University, all in a similar age group and with similar social behavior), the model can be more general by incorporating non-homogeneity into the model. Another future direction may be introducing a methodology to estimate the key model parameters (e.g. contact rate and infectious period) with or without data. Also the analysis would be more comprehensive if we use different values for cost ratio for the grid search and cost-effectiveness analysis. We can define the "effect" in a different way as well. For instance, instead of the percent of the protected population, we can define it as the gap between the attack rate and its maximum acceptable level (which is currently 5%). Furthermore, a more rigorous model would be obtained by considering other costs, such as prophylaxis and treatment costs, which may affect the results of our analysis.

As a final point, note the model we have developed can be used for comparing any two interventions. For instance, with the same methodology, one can compare the effectiveness or cost-effectiveness of vaccination versus antiviral prophylaxis. Also one can examine different isolation policies. For example, the effectiveness and also cost-effectiveness of self-isolation of infectives through promoting self-isolation versus general isolation strategies, such as school closure and limiting social gatherings may be examined and compared.

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*Yarmand, Ivy, Roberts, Bengtson and Bengtson*

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