Proceedings of the 2014 Winter Simulation Conference
A. Tolk, S. Y. Diallo, I. O. Ryzhov, L. Yilmaz, S. Buckley, and J. A. Miller, eds.

EVALUATING THE IMPACTS OF VACCINATION, ANTIVIRAL TREATMENT AND SCHOOL CLOSURE ON H1N1 INFLUENZA EPIDEMIC

Junhai Cao

Department of Automation

Beijing Technology and Business University
Beijing, 100048, CHINA

Feng Yang
Zongyu Geng
Xiaofei Shi

Industrial and Management Systems Engineering Department
West Virginia University
Morgantown, WV 26506, USA

ABSTRACT

Multi-objective simulation optimization was performed to synergistically investigate the cost and benefits of the most commonly-used strategies for H1N1 epidemic mitigation: vaccination, antiviral treatment, and school closure. By simultaneously considering the three intervention strategies, this study leads to findings that supplement those in the existing work, and provides additional insights regarding intervention decision making. Specifically, our investigation suggests that different vaccine prioritization strategies, the age-based vs. ACIP (Advisory Committee on Immunization Practices) recommendation, be implemented depending on vaccine availability; individual school closure policies are favored over their global counterparts, at least when both vaccination and antiviral treatment are implemented with relatively plentiful medicine supply. The trade-offs of cost and benefits of the intervention strategies were investigated, and can be used to support relevant decision making.

1 INTRODUCTION

Influenza is a serious public health problem that causes severe illness and death in high risk populations. To prevent an epidemic, a wide range of mitigation strategies have been investigated including vaccine allocation, use of antiviral, school closure policies, etc. In the current literature, agent-based simulation models (ABM) have been developed and served as an effective and popular method to investigate the mitigation effects of different intervention policies (Haber et al. 2007, Lee et al. 2010, Lee et al. 2010, Brown et al. 2011). However, the existing work is typically restricted to a small set of decision variables concerning a certain intervention aspect. For instance, Lee et al. (2010) compared the impacts of different vaccine prioritization policies when vaccine is in limited supply; Brown et al. (2011) evaluated various school closure policies specified by different closure lengths. These work focused on limited scenarios generated by varying one or two selected decision variables, evaluated those scenarios through ABM, and derived insights as to the main effects of the selected variables. Hence, they do not allow for the investigation of the potential interacting effects of mitigation policies (for example, the interacting effects of vaccine prioritization policies and the vaccine supply quantity), and neither are they adequate for the exploration of optimal policies concerning a range of mitigation strategies.

In light of the discussions above, an effort was made in this paper to simultaneously consider a large number of decision variables that specify three intervention aspects: vaccination, antiviral treatment, and school closure policies. The stochastic ABM developed through the Models of Infectious Disease Agent Study (University of Pittsburgh MIDAS National Center of Excellence 2009) was adopted as the scenario evaluation tool for H1N1. The ABM has been extended in this work to track a range of performance

metrics including attack/death rate of the disease, infections, years of life lost, productivity losses, and the total cost incurred. Clearly, there are trade-offs between the intervention benefits and costs.

To explore the solutions in the large decision space while balancing the benefits and costs of invention strategies, we adapted a genetic algorithm (GA)-based multi-objective simulation optimization method. The Pareto frontier of the non-dominated solutions obtained was further investigated, and used to derive interesting insights regarding the intervention policies.

2 METHODS

2.1 Agent-Based Simulation Model

FRED (Grefenstette, J. et al. 2013), the stochastic ABM available at the website of Framework for Reconstructing Epidemiological Dynamics (University of Pittsburgh Public Health Dynamics Laboratory 2013), was used in this simulation study. The ABM includes explicit representations of the county's population with each agent (virtual person) possessing a set of sociodemographic characteristics and daily behaviors (e.g., age, gender, employment status, school assignments for students, and work location assignments for employed adults); provides a range of parameters to characterize a disease (e.g., the basic reproductive rate); and has a range of built-in actions for epidemic mitigation. Detailed model structure of the ABM can be found from FRED User Guide (Grefenstette, John et al. 2013).

In this work, the ABM simulates the H1N1 influenza spread within Allegheny County, Pennsylvania, with a population of 1,164,779 individuals, 524,584 households, 532 schools and 48,703 work places. Based on the data from H1N1 2009 influenza epidemic in the U.S. (2009-2010), the reproductive rate of H1N1 is set as 1.8 (White et al. 2009), and the simulation length is set as 180 days to reflect the length of the epidemic season (Germann et al. 2006).

2.2 Intervention Strategies and Decision Variables

Figure 1 provides an overview of the intervention strategies considered in this work. A total of 15 decision variables are used to define the vaccine, antiviral and school closure policies, and to specify a scenario of the combination strategies. As detailed in the rest of this subsection, a range of experimental values are selected for each variable to investigate the variables' quantitative impacts, which leads to 10,459,400 alternative policy combinations.

2.2.1 Vaccines

Vaccination is the principal preventive strategy to prevent an outbreak of influenza epidemic and to reduce the disease burden of infectious diseases. Large quantities of vaccines were produced and distributed to all over the world to prevent the outbreak of influenza such as H1N1 and H5N1. How do the vaccine availability and prioritization affect the effectiveness of vaccination to mitigate an influenza epidemic? The vaccination plan and policies are specified by seven variables (V1)-(V7) in this work.

(V1) enable_vaccination: It is a Boolean variable, which can be either 0 or 1. A value of 0 corresponds to no implementation of vaccination strategies at all; and when (V1) is equal to 0, the variables (V2)-(V7) play no part in the simulation model. When (V1) takes a value of 1, the variables (V2)-(V7) come into play and their settings specify a vaccination plan to be implemented.

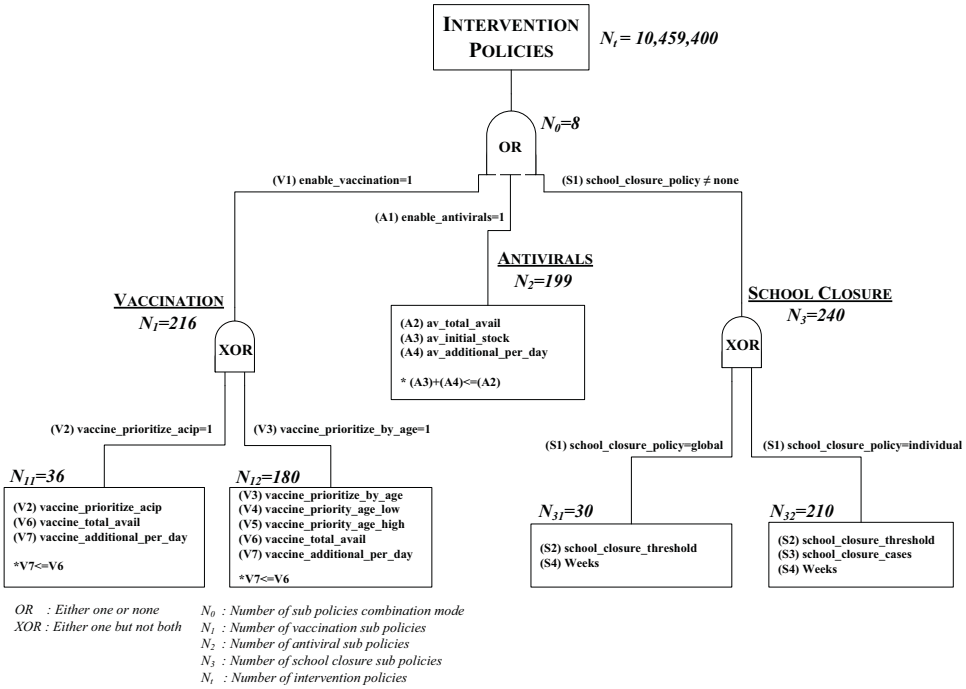

Figure 1: The intervention strategies and decision variables.

(V2) vaccine_prioritize_acip and (V3) vaccine_prioritize_by_age: The variable pair (V2, V3) is a two-dimensional Boolean vector, which could be either (1, 0) or (0, 1) corresponding to different types of vaccine prioritization policies detailed as follows.

- If (V2, V3) is set as (1, 0), then the ACIP vaccine prioritization policy is adopted. ACIP refers to the vaccine prioritization recommended by the Advisory Committee on Immunization Practices (ACIP) on July 29, 2009. By adopting the ACIP, the following groups of people have higher priority to receive the influenza vaccine (Lee et al. 2010): pregnant women, household contacts and caregivers for children younger than 6 months of age, healthcare and emergency medical services personnel, all people from 6 months through 24 years of age, and persons aged 25 through 64 years who have health conditions associated with higher risk of medical complications from influenza. The ACIP recommendation is primarily based on occupational risk of vulnerable populations.
- If (V2, V3) is set as (0, 1), then the age-based prioritization policy is employed. The age-based policy requires dividing the population into several age groups. In this work, five age groups (Medlock et al. 2009) are considered: (i) 0-5 years of age, (ii) 6-24 years of age, (iii) 25-44 years of age, (iv) 45-64 years of age, and (v) 65 years old and above. An age-based policy is defined by a selected age group with priority over other groups, and the selected group is specified by the variable pair (V4, V5) as below.

(V4) vaccine_priority_age_low and (V5) vaccine_priority_age_high: These two variables (V4, V5) specify the lower and upper bound of the priority age group. Based on the five age groups (i)-(v) considered, (V4, V5) can take values (0, 5), (6, 24), (25, 44), (45, 64) and (65, 120) assuming that 120 is the highest possible age.

(V6) vaccine_total_avail: It is the total amount of vaccine that will be made available during the influenza season. Timely production and delivery of sufficient vaccine still remains a challenge, and the variable (V6) constrains the maximum number of people that can be vaccinated. According to Fedson (2003), the doses of influenza vaccine distributed in North America is about 26.5% of the population.

Thus, in our exploration, (V6) is allowed to range from 5% to 20% of the population size. The population of Allegheny County, PA is about 1.2 millions, so the experimental value of (V6) is set as: 60,000, 80,000, 100,000, 150,000, 200,000, and 250,000.

(V7) vaccine_additional_per_day: This variable represents the additional daily supply of vaccines. It is required that (V7) is less than or equal to (V6). Starting from the first day of the simulated influenza season, the additional amount of (V7) will be made available on each day until the total planned vaccine supply (V6) has been reached. Given (V6), the variable (V7) largely determines the vaccine availability over the time. We allow (V7) to take the following values: 1,000, 2,000, 4,000, 6,000, 8,000, and 10,000 subjecting to the constraint (V7) ≤ (V6). For instance, if (V6)=100,000 and (V7)=6,000, then from day 1 until day 16, an additional daily supply of 6,000 will be provided; and on day 17, the leftover supply, which is equal to 100,000-6,000×16=4,000 will be added to the stock.

In FRED, it takes a default value of 14 days for the vaccines to take effects after being administered.

2.2.2 Antiviral

Antiviral drugs are a class of medication used specifically for treating viral infections, and hence antiviral policies are for treatment as opposed to prevention of the disease. In an influenza epidemic, the availability of antiviral drugs is a major concern, besides the effectiveness of the drugs (Moss et al. 2011). The following four variables are used to specify an antiviral policy.

(A1) enable_antivirals: It is a Boolean variable, which can be either 0 or 1. A value of 0 corresponds to no implementation of antiviral strategies at all; and when (A1) is equal to 0, the variables (A2)-(A4) play no part in the simulation model. When (A1) takes a value of 1, the variables (A2)-(A4) come into play and their settings specify an antiviral strategy to be implemented.

(A2) av_total_avail: It is the total amount of antiviral doses that will be made available in the epidemic season. A range of values have been selected for (A2): 10,000, 50,000, 100,000, 200,000, 300,000 and 400,000.

(A3) av_initial_stock: It is the initial stock of antivirals with healthcare agencies and hospitals at the beginning of epidemic season. The experimental values of (A3) are set as: 1,000, 5,000, 10,000, 20,000, 30,000, and 40, 000, with (A3) ≤ (A2).

(A4) av_additional_per_day: It is the daily antiviral doses added to supply, from the first day of the influenza season until the total planned amount (A2) has been reached. For instance, if (A2)=50,000, (A3)=5,000 and (A4)=20,000, then at the very beginning, an initial stock of 5,000 antiviral doses will be available; from day 1 until day 2, an additional daily supply of 20,000 doses will be provided; on day 3, the leftover supply, which is equal to 50,000-5,000-20,000×2=5,000 will be added to the stock. In this work, the variable (A4) is allowed to be 1,000, 5,000, 10,000, 20,000, 30,000 and 40,000, subjecting to the constraint: (A3) + (A4) ≤ (A2).

2.2.3 School Closure

As an indirect intervention strategy, school closure has been debated and questioned (Cowling et al. 2008, Cauchemez et al. 2009, Koonin et al. 2009). It has been noted that school closure could be very costly and perhaps not worthwhile, whereas at the same time, transmission among school children is also considered to be a primary mode of disease propagation (Germann et al. 2006, Haber et al. 2007). In this work, four decision variables are associated with school closure policies.

(S1) school_closure_policy: This variable is used to set the type of school closure policy, and it can be any of the three categories: none, global, and individual. When (S1) is set as "none", school closure policy is disabled, and the variables (S2)-(S4) play no part in the simulation model. When (S1) is set as "global", the global school closure policy is adopted and specified by the variables (S2) and (S4) below. When (S1) is set as "individual", the individual school closure policy is employed and specified by the variable (S2), (S3) and (S4), as will be seen.

(S2) school_closure_threshold: When the global school closure policy is employed, (S2) is the threshold attack rate (defined later in Section 2.3), above which all schools are to be closed. In Lee et al. (2010), a threshold of 1% is used, which means closure of all schools once the attack rate of the population being considered exceeds 1%. Herein, we allow (S3) to vary over the range of [0.5%, 1.5%], and take the following values: 0.5%, 0.7%, 0.9%, 1.1%, 1.3%, and 1.5%.

(S3) school_closure_cases: Under the individual school closure policy, a school will be closed if the number of infection cases at that individual school reaches the threshold (S3) or the global attack rate reaches threshold (S2). As in Brown et al. (2011), (S3) is set to range from 1 to 30, with experimental values: 1, 5, 10, 15, 20, 25, and 30.

(S4) Weeks: It is the duration of school closure once a closure has been triggered. Following Brown et al. (2011), (S4) ranges within [1, 8] weeks, and takes the following values in our work: 1, 2, 4, 6, and 8 weeks.

2.3 Performance Metrics

We have extended FRED to evaluate the five most commonly-used performance metrics (Cropper et al. 1994, Medlock et al. 2009, Perlroth et al. 2010, Milne et al. 2013) for each scenario specified by a combination of the intervention policies (i.e., a setting of the decision variables). These performance metrics are described as follows.

(1) ATTACK RATE (AR): An attack rate is the proportion of a well-defined population that develops illness over a specific period of time (Goodman et al. 1996), where the numerator is the number of new cases that occurred during that period and the denominator is the size of the population at risk (i.e., the individuals with a probability of acquiring the disease in the area considered). Attack rate is an important indicator used to aid in marshalling resources for delivery of medical care as well as production of vaccines and/or anti-viral and anti-bacterial medicines (Glaser 1995).

(2) DEATHS: Deaths is the outcome indicator that counts the number of deaths during an epidemic. Since deaths news tends to have severe mental and psychological effects on people, which may lead to people's psychological panic and even social chaos, the number of deaths is always one of primary indicators for epidemic severity (Medlock et al. 2009). A disease-associated death results in substantial social and economic losses.

(3) INFECTIONS: The total number of infections in an epidemic is the major factor that determines the medical cost and productivity loss (Medlock et al. 2009).

(4) YEAS OF LIFE LOST (YLL): YLL measures the total number of life years lost due to premature death (Medlock et al. 2009). The definition of premature death varies in studies, and in this work, YLL are calculated following the 2008 US Life Expectancy data (USCB 2012). YLL measures health loss from early death, taking into account the age that death occurred.

(5) TOTAL COST: The total cost seeks to quantify the economic and social losses incurred in an epidemic. Figure 2 illustrates the breakdown of the total cost, which can be divided into two parts: the intervention cost, and the infection cost. (i) The intervention cost includes the cost to implement the intervention policies: the manufacturing and delivery cost of vaccines/antivirals, the cost accounting for the productivity loss of teachers, and students school missed cost (including student daily cost and parents' productivity loss due to missing work), etc. (ii) The infection cost includes the cost triggered by disease infections, for which we consider two types of infected populations: the asymptomatic population that does not incur any infection cost yet (while being at increased risk for becoming symptomatic), and the symptomatic population. The cost incurred by symptomatically infected individuals is divided into two categories: death cost, and non-death cost caused by inpatients, outpatients and those who only need over-the-counter drugs. In each category, a patient incurs a cost of treatment depending on his/her age, vaccine condition, and a cost of productivity loss due to absenteeism. The cost parameters are given in Table 1.

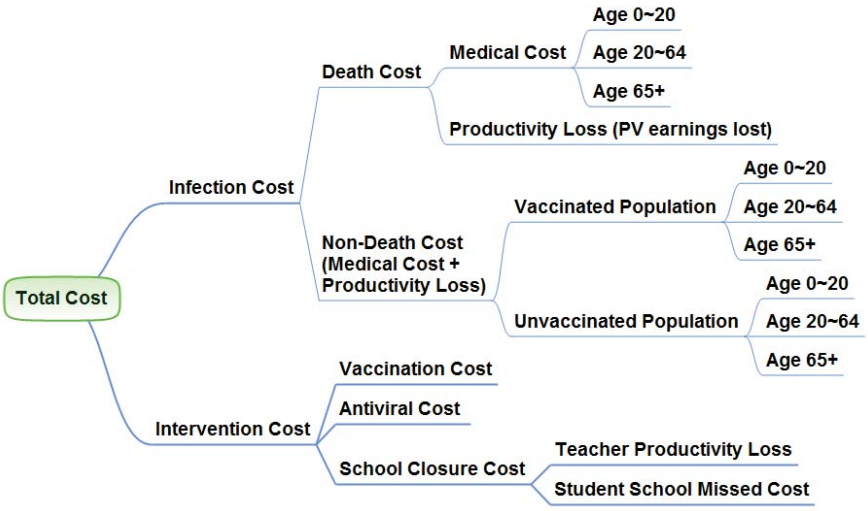

Figure 2: The breakdown of total cost.

Table 1: Cost parameters.

Cost	Values(1)		Source
Vaccination cost (per dose)(2)	$37.26		(Medlock et al. 2009)
Antiviral cost (per course)(3)	$134.30		(Smith et al. 2002)
Medical cost(4) (per death)	age 0-19	$3435	(Meltzer et al. 1999, Medlock et al. 2009)
	age 20-64	$7605	(Meltzer et al. 1999, Medlock et al. 2009)
	age 65+	$8309	(Meltzer et al. 1999, Medlock et al. 2009)
PV(5) earnings lost (per death)	age 0-19	$1016101	(Meltzer et al. 1999, Medlock et al. 2009)
	age 20-64	$1037673	(Meltzer et al. 1999, Medlock et al. 2009)
	age 65+	$65837	(Meltzer et al. 1999, Medlock et al. 2009)
Non-death cost(6) (per infection) (vaccinated)	age 0-19	$309.24	(Meltzer et al. 1999, Medlock et al. 2009)
	age 20-64	$377.42	(Meltzer et al. 1999, Medlock et al. 2009)
	age 65+	$517.46	(Meltzer et al. 1999, Medlock et al. 2009)
Non-death cost (per infection) (unvaccinated)	age 0-19	$330.28	(Meltzer et al. 1999, Medlock et al. 2009)
	age 20-64	$418.02	(Meltzer et al. 1999, Medlock et al. 2009)
	age 65+	$557.97	(Meltzer et al. 1999, Medlock et al. 2009)
Teacher productivity loss (per day) (2009 US Dollars)(7)	$208		(Perlroth et al. 2010)
Student school missed cost (per student per day) (2009 US Dollars)(8)	$19.22		(Perlroth et al. 2010, Milne et al. 2013)

The following further explains the cost metrics shown in table 1:

1) All costs are adjusted to 1995 U.S. dollars using Current to Real Dollars Converter (Casais 2013).
2) Vaccination cost includes cost of the vaccine, cost of loss of productivity, and cost of side effects.
3) Antiviral cost includes cost of testing and treatment, and cost of antiviral drugs.
4) Medical cost includes cost of hospitalization, outpatient visits, and loss of productivity.
5) PV (average present value), using a 3% discount rate, of expected future lifetime earnings and housekeeping services, weighted by age and gender and adjusted to 1995 dollars (Meltzer et al. 1999).

6) Non-death cost includes medical cost, cost of loss of productivity.
7) Teacher productivity loss adopts the median daily wage rate of 2009.
8) Student school missed cost includes student daily cost and parents' productivity loss.

2.4 Simulation Optimization

The ultimate goal is to find the intervention policies that lead to the best performance while minimizing the total cost involved. The performance of the intervention policies is typically measured in terms of the first four metrics described in Section 2.3: AR, DEATHS, INFECTIONS and YLL. These indicators are correlated with each other while emphasizing different aspects of epidemic severity, and since AR is most-widely used in the existing literature, we set "minimizing AR" as the performance objective of the optimization. The evaluation of TOTAL COST is also detailed in Section 2.3, and the cost objective is of course to minimize the total cost incurred for the epidemic. Hence, a multi-objective optimization problem is formulated as: "Minimize both AR and TOTAL COST with respect to the intervention policies specified by the decision variables (V1)-(V7), (A1)-(A4), (S1)-(S4)."

With the decision variables (along with their possible settings) presented in Section 2.2, there are totally 10,459,400 scenarios of different intervention policies. It takes about 3 minutes to complete a single simulation run by a 16-core Dell workstation. In light of the computational burden, a GA algorithm is adapted to search for the Pareto frontier of the multi-objective optimization problem.

As shown in Figure 1, with the experimental settings in Section 2.2, there are a total of 216 candidate vaccination policies, 199 candidate antiviral policies, and 240 candidate school closure policies. A policy combination of the three intervention strategies is encoded as a 24-bit genetic string in the GA.

The GA framework of our simulation optimization is given in Figure 3. The algorithm starts with the random generation of an initial population of candidate policies. For each candidate in the current population, simulation experiments are carried out to evaluate the performance and cost objectives associated with that candidate; 10 simulation replications are obtained for each candidate policy using different random streams; and the simulation length of each replication is 180 days. The fitness evaluation is performed by using the Pareto-ranking method proposed by Goldberg (1989). The Pareto-ranking method explicitly utilizes the Pareto dominance rule to rank candidates, and assigns a fitness value to each candidate based on its ranking in the current population. Here, all our objectives are supposed to be minimized. Following the fitness evaluation, a roulette selection, crossover, and mutation are carried out to reproduce a new population of candidates for further evaluation and reproduction.

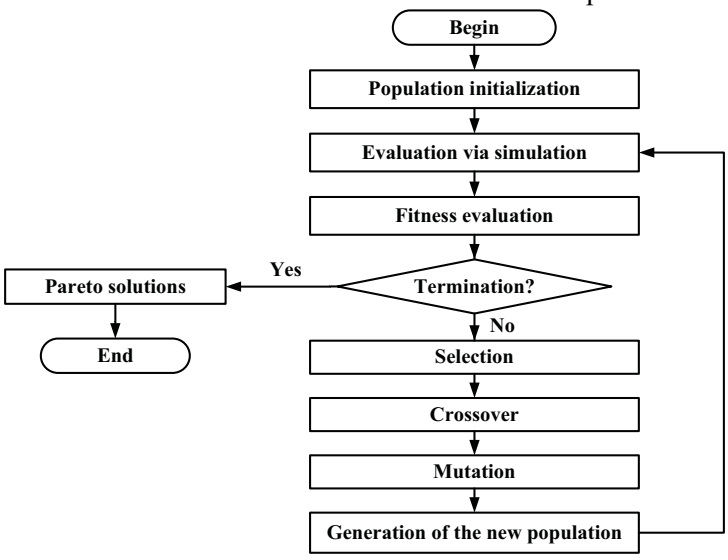

Figure 3: The GA Workflow.

The GA algorithm was implemented in python, and integrated with the simulation model in C++ programming language. For each candidate solution generated by GA in python, the corresponding parameter settings are written in a text file, which serves as input to the simulation model in C++; and the simulation results are sent back to the GA in a text file as well.

3 RESULTS AND DISCUSSIONS

In the GA-based simulation optimization, 4950 candidate policies were evaluated, and their corresponding objective values, AR and TOTAL COST, are represented as dots in Figure 4. The dotted curve depicts the Pareto frontier of solutions, and a total of 82 intervention policies lie on the frontier. For each Pareto solution/policy, its pair of AR and school closure cost is plotted as times symbols in Figure 4. In addition, the (AR, vaccination cost) pair is depicted as a square, and (AR, antiviral cost) as a cross; the vaccination and antiviral costs are very low compared to the school closure cost, and the squares and crosses both lie along the bottom of Figure 4.

As examples, the three Pareto solutions/policies (marked as Pu, Pm and Pd in Figure 4) are given in Table 3, and their five performance metrics are also provided. As can be seen from Table 2, AR is positively correlated with DEATHS, INFECTIONS, and YLL. The simulation optimization results support the following findings.

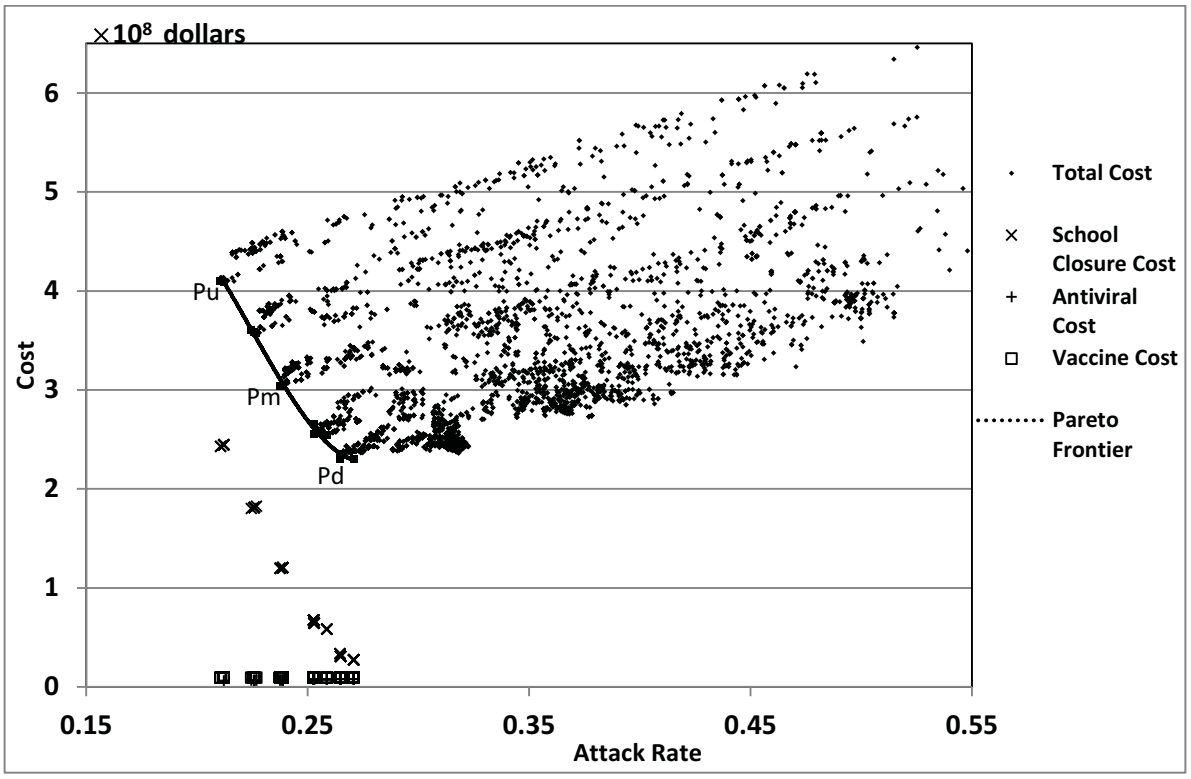

Figure 4: Solutions resulting from the simulation optimization.

3.1 Vaccination

This study confirms that vaccination has significant impacts on mitigating a H1N1 epidemic. All the policies included in the Pareto frontier call for a maximum total quantity of available vaccines by setting (V6) vaccine_total_avail at its maximum 250,000.

When vaccine supply is relatively plentiful (with the available vaccine quantity being more than 20% of the population as in these Pareto solutions), the age-based vaccine prioritization (with the priority group being the one from 6 to 24 years of age) is favored over the ACIP recommendation. This complements the findings of Lee et al. (2010): the ACIP prioritization should be adhered to when vaccine is in limited supply. By examining the GA candidate solutions with the minimum vaccine supply (with available vaccine quantity being 5% of the population), we also confirmed the superiority of ACIP in time of vaccine scarcity.

Table 2: Three selected Pareto policies.

Pareto Policies	**Decision Variables**	**Outcomes**				
		AR (%)	**Deaths**	**Infections**	**YLL**	**Total Cost($)**
Pu	V1=1,V2=0,V3=1,V4=6, V5=24,V6=250000, V7=10000, A1=1,A2=400000, A3=10000,A4=40000, S1= individual,S2=0.5, S3=5,S4=8	21.073	52	245,497	2,109	410,002,827
Pm	V1=1,V2=0,V3=1,V4=6, V5=24,V6=250000, V7=8000, A1=1,A2=400000, A3=40000,A4=20000, S1= individual,S2=0.5, S3=5,S4=4	23.757	56	276,749	2,274	304,102,767
Pd	V1=1,V2=0,V3=1,V4=6, V5=24,V6=250000, V7=10000, A1=1,A2=400000, A3=40000,A4=30000, S1=individual,S2=0.5, S3=1,S4=1	26.497	58	308,663	2,314	230,418,943

3.2 School closure

The cost and benefits of school closure are reflected in Figure 4. Compared to vaccination and antiviral strategies, the cost of school closure is very high, which is a cause for debate whether school closure is worthwhile (Brown et al. 2011).

All the Pareto solutions adopt the individual school closure policy, which is consistent with the CDC recommendation (WHO 2009) that school closures should be implemented at the discretion of local authorities based on local considerations. Lee et al. (2010) was not able to show any significant differences between individual and global closure policies, at least partly because that in their work, the impacts of different school closure policies were evaluated with all the other intervention policies fixed at certain levels, levels different from those in our Pareto solutions.

The individual school closure policies involved in these Pareto solutions vary in terms of their thresholds for closure (i.e., the values for the variable (S3) school_closure_cases) and their closure periods (i.e., the values for the variable (S4) Week). As illustrated in Table 3, the Pareto solutions are similar in terms of the vaccination and antiviral treatment policies. Hence, the times symbols in Figure 4

for school closure cost vs. AR indicates: The individual closure parameters, (S3) school_closure_cases and (S4) Week, affect both the school closure cost and the AR performance. This finding is again not given by Lee et al. (2010), who claim that AR is not sensitive to such variables. The trade-offs between cost and benefits are displayed in Figure 4, and can be employed for decision making regarding school closures.

3.3 Antiviral Policies

For each of the Pareto solutions, a large quantity of antiviral drugs is utilized with the variable (A2) av_total_avail being in its highest allowed value. As vaccination, antiviral strategies are relatively cost-effective, and hence tend to be pushed to its upper limit in the optimization iteration.

4 SUMMARY

A GA-based simulation optimization method was employed to explore the large decision space spanned by the decision variables for three types of intervention strategies: vaccination, antiviral treatment, and school closure. Our investigation suggests that different vaccine prioritization strategies be implemented depending on the vaccine availability: Age-based priority (with the group from 6 to 24 years of age being the priority group) is favored when vaccine supply is plentiful; and the ACIP is preferred in time of vaccine shortage. As far as school closure strategies are concerned, individual school closure policies appear to work better than their global counterparts, at least when both vaccination and antiviral treatment are both implemented with relatively plentiful medicine supply. In addition, the threshold and duration variables used to specify an individual closure policy tend to affect its cost and resulting benefits, the trade-offs of which have been graphically illustrated and can be used to support decision making.

The simulation optimization approach adopted here can be adapted to investigate the intervention strategies of other epidemics, provided that a high-fidelity simulation model is available. Through the case of H1N1 in this work, the potential of simulation optimization has been illustrated. In our immediate next-stage exploration, a number of tasks are to be performed: improving the optimization heuristics by taking into account the stochastic nature of the simulation outputs (e.g., cost); improving the cost analysis model embedded in the simulation for a more realistic cost evaluation; performing further and more thorough analysis to confirm or derive insights, based on simulation optimization results.

ACKNOWLEDGMENTS

This research was supported by National Science Foundation Grant CMMI-1068131.

REFERENCES

Brown, S. T., Tai, J. H., Bailey, R. R., Cooley, P. C., Wheaton, W. D., Potter, M. A., Voorhees, R. E., LeJeune, M., Grefenstette, J. J., Burke, D. S., McGlone, S. M. and Lee, B. Y. 2011. "Would school closure for the 2009 H1N1 influenza epidemic have been worth the cost?: a computational simulation of Pennsylvania." *BMC Public Health* 11: 353-363.

Eduardo Casais. 2013. "Current to Real Dollars Converter." Accessed April 20, 2014. http://stats.areppim.com/calc/calc_usdlrxdeflator.php.

Cauchemez, S., Ferguson, N. M., Wachtel, C., Tegnell, A., Saour, G., Duncan, B. and Nicoll, A. 2009. "Closure of schools during an influenza pandemic." *Lancet Infect Dis* 9: 473-481.

Cowling, B. J., Lau, E. H., Lam, C. L., Cheng, C. K., Kovar, J., Chan, K. H., Peiris, J. S. and Leung, G. M. 2008. "Effects of school closures, 2008 winter influenza season, Hong Kong." *Emerg Infect Dis* 14: 1660-1662.

Cropper, M. L., Aydede, S. K. and Portney, P. R. 1994. "Preferences for Life Saving Programs: How the Public Discounts Time and Age." *Journal of Risk and Uncertainty* 8: 243-265.

University of Pittsburgh MIDAS National Center of Excellence. 2009. "Models of Infectious Disease Agent Study." https://www.midas.pitt.edu/.

Fedson, D. S. 2003. "Pandemic influenza and the global vaccine supply." *Clin Infect Dis* 36: 1552-1561.

Germann, T. C., Kadau, K., Longini, I. M., Jr. and Macken, C. A. 2006. "Mitigation strategies for pandemic influenza in the United States." *Proc Natl Acad Sci U S A* 103: 5935-5940.

Glaser, A. N. 1995. *High-Yield Biostatistics.* Baltimore: Williams & Wilkins.

Goldberg, D. E. 1989. *Genetic Algorithms in Search, Optimization and Machine Learning.* New York: Addison-Wesley Longman Publishing Co., Inc.

Goodman, R. and Peavy, J. 1996. *Describing epidemiologic data.* New York: Oxford University Press.

Grefenstette, J., Brown, S. T., Rosenfeld, R., DePasse, J., Stone, N. T., Cooley, P. C., Wheaton, W. D., Fyshe, A., Galloway, D. D., Sriram, A., Guclu, H., Abraham, T. and Burke, D. S. 2013. "FRED (a Framework for Reconstructing Epidemic Dynamics): an open-source software system for modeling infectious diseases and control strategies using census-based populations." *BMC Public Health* 13: 940.

Grefenstette, J., DePasse, J., Galloway, D., Weng, Y.-T., Burke, D., Rosenfeld, R., Fyshe, A., Sriram, A., Tischuk, C., Brown, S., Stone, N., Cooley, P. and Wheaton, B. 2013. "FRED User's Guide." University of Pittsburgh, Pittsburgh.

Haber, M. J., Shay, D. K., Davis, X. M., Patel, R., Jin, X., Weintraub, E., Orenstein, E. and Thompson, W. W. 2007. "Effectiveness of interventions to reduce contact rates during a simulated influenza pandemic." *Emerg Infect Dis* 13: 581-589.

Koonin, L. M. and Cetron, M. S. 2009. "School closure to reduce influenza transmission." *Emerg Infect Dis* 15: 137-138, author reply 138.

University of Pittsburgh Public Health Dynamics Laboratory. 2013. "FRED (Framework for Reconstructing Epidemic Dynamics)." Accessed Feb 17, 2014. http://fred.publichealth.pitt.edu/index.php.

Lee, B. Y., Brown, S. T., Cooley, P., Potter, M. A., Wheaton, W. D., Voorhees, R. E., Stebbins, S., Grefenstette, J. J., Zimmer, S. M., Zimmerman, R. K., Assi, T. M., Bailey, R. R., Wagener, D. K. and Burke, D. S. 2010. "Simulating school closure strategies to mitigate an influenza epidemic." *J Public Health Manag Pract* 16: 252-261.

Lee, B. Y., Brown, S. T., Korch, G. W., Cooley, P. C., Zimmerman, R. K., Wheaton, W. D., Zimmer, S. M., Grefenstette, J. J., Bailey, R. R., Assi, T. M. and Burke, D. S. 2010. "A computer simulation of vaccine prioritization, allocation, and rationing during the 2009 H1N1 influenza pandemic." *Vaccine* 28: 4875-4879.

Medlock, J. and Galvani, A. P. 2009. "Optimizing influenza vaccine distribution." *Science* 325: 1705-1708.

Meltzer, M. I., Cox, N. J. and Fukuda, K. 1999. "The economic impact of pandemic influenza in the United States: priorities for intervention." *Emerg Infect Dis* 5: 659-671.

Milne, G. J., Halder, N. and Kelso, J. K. 2013. "The cost effectiveness of pandemic influenza interventions: a pandemic severity based analysis." *PLoS One* 8: e61504.

Moss, R., McCaw, J. M. and McVernon, J. 2011. "Diagnosis and antiviral intervention strategies for mitigating an influenza epidemic." *PLoS One* 6: e14505.

Perlroth, D. J., Glass, R. J., Davey, V. J., Cannon, D., Garber, A. M. and Owens, D. K. 2010. "Health outcomes and costs of community mitigation strategies for an influenza pandemic in the United States." *Clin Infect Dis* 50: 165-174.

Smith, K. J. and Roberts, M. S. 2002. "Cost-effectiveness of Newer Treatment Strategies for Influenza." *Theamerican Journal of Medicine* 113: 300-307.

USCB. 2012. "Expectation of Life at Birth, 1970 to 2008, and Projections,2010 to 2020." U.S. Census Bureau, Washington, DC.

White, L. F., Wallinga, J., Finelli, L., Reed, C., Riley, S., Lipsitch, M. and Pagano, M. 2009. "Estimation of the reproductive number and the serial interval in early phase of the 2009 influenza A/H1N1 pandemic in the USA." *Influenza Other Respir Viruses* 3: 267-76.

WHO. 2009. "Human infection with new influenza A (H1N1) virus: WHO consultation on suspension of classes and restriction of mass gatherings to mitigate the impact of epidemics caused by influenza A (H1N1)." *Wkly Epidemiol Rec* 84: 269-280.

AUTHOR BIOGRAPHIES

JUNHAI CAO is an Associate Professor of Beijing Technology and Business University, and visiting scholar at West Virginia University. He received his Ph.D. degree from School of Automation at Beijing Institute of Technology. His research field is Complex Systems Modeling and Simulation, Reliability Engineering, and Systems Engineering. His email address is: jhcao@163.com.

FENG YANG is an Associate Professor in the Department of Industrial and Management Systems Engineering at West Virginia University. She received her Ph.D. degree from the Department of Industrial Engineering and Management Sciences at Northwestern University. Her research interests include computer simulation, applied statistics, and applications in manufacturing and service industry. Her email address and web page are: feng.yang@mail.wvu.edu and http://www2.statler.wvu.edu/~yang/.

ZONGYU GENG is a Ph.D. candidate in the Department of Industrial and Management Systems Engineering at West Virginia University. His research has been focused on the development of new statistical methods for the efficient calibration of sensors. His email address is zygeng@gmail.com.

XIAOFEI SHI is a M.S. student in the Department of Industrial and Management Systems Engineering at West Virginia University. His email address is xashi@mix.wvu.edu.